Molecular Characterization of Genes Associated with Maturity Onset Diabetes in Young (MODY)

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FINAL APPROVAL

It is certified that we have read the thesis submitted by Ibrar Rafique and we judge that this project is of sufficient standard to warrant its acceptance by the International Islamic University, Islamabad, in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Biotechnology.

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DEDICATION

This work is dedicated to my respected parents Haji Muhammad Rafique and Kulsom Akhter (late); they are always the source of inspiration for my studies.

DECLARATION

It is certified that work is done on this Ph.D.The biotechnology research thesis entitled "Molecular Characterization of Genes Associated with Maturity Onset Diabetes in Young (MODY)" is purely conducted by me. All the material is prepared by myself and has not been copied from anywhere; however, some tests and figures have been used which are properly referenced.

Date _____

Ibrar Rafique

Contents

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LIST OF ABBREVIATIONS

Acronym	Abbreviation
ABCC8	ATP-binding cassette transporter subfamily C member 8
APPL1	Adaptor protein, phosphor-tyrosine interaction
BIDE	Baqai Institute of Diabetology and Endocrinology
BWA	Burrows-Wheeler Alignment
BLK	lymphocyte kinase
BMI	Body Mass Index
CEL	Carboxyl ester lipase
DNA	Deoxyribonucleic acid
DPP4	Dipeptidyl peptidase 4
ELISA	Enzyme linked immunosorbent assay
GAD-65	Glutamic acid decarboxylase
GLP-1	Glucagon like peptide
GATK	Genome analysis toolkit
GCK	Glucokinase
HNF4a	Hepatocyte nuclear factor 4 alpha
HNF1a	Hepatocyte nuclear factor 1 alpha
HNF1B	Hepatocyte nuclear factor 1 alpha
HLA	Human leukocyte antigen
HbA1c	Hemoglobin A1c
INS	Insulin gene
KCNJ11	Potassium inwardly rectifying channel subfamily J member 11
KLF11	Kruppel like factor
MLPA	Multiplex ligation-dependant probe amplification
MODY	Maturity Onset Diabetes of the Young

NDSP	National Diabetes Survey of Pakistan
NEUROD1	Neurogenic differentiation factor 1
OMIM	Online Mendelian inheritance in Man
PDX1	Insulin promoter factor 1
PAX 4	Paired box gene 4
RFX6	Regulatory factor 6
SUR1	Sulphonylurea receptor
SIFT	Sorting intolerant from tolerant
WFS1	Wolfram syndrome
ZnT8A	Zinc transporter protein (ZnT8)

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ABSTRACT

Maturity onset diabetes of the Young (MODY) is the monogenic form of diabetes. MODY comprises 1-2% of all the diabetes cases. Its diagnosis carries paramount importance as most of MODY types have different treatment pattern. Therefore it is important to know the MODY types for appropriate treatment. Diabetes is huge public health burden in our country. The National Survey (2016-17) from Pakistan revealed every fourth adult person as diabetic in the population. As there was a scarcity of data on MODY from Pakistan, therefore there is dire need to determine its genetic etiology.

Systematic review of literature was conducted on 239 full-text studies, which idenitified 1017 causal variants for MODY. These variants were validated by softwares like Variant Validator, Intervar, and GnomAD.

A total of 191 participants, identified as suspected cases of MODY, in the data fom National Diabetes Survey and Diabetes Clinics located in two major cities (Lahore and Karachi) of Pakistan. Patients diagnosed with diabetes before 25 years of age were included in the study. The probability for MODY was determined by the online MODY probability calculator. Glutamate Decarboxylase (GAD-65) ELISA tests were performed on the serum samples to exclude autoimmune type 1 diabetes. Thirty five (35) GAD-65 negative patient's with clinical characteristics of low BMI, low HbA1c were selected for exome sequencing. The exome sequencing of 35 patients identified 37 variants. Including twelve heterozygous variants identified in nine genes i.e. *HNF1a, KLF11, RFX6, BLK, ABCC8, HNF1B, INSR, WFS1, ZBTB20*. The five variants in MODY genes were novel i.e. *HNF1a* (c.C169A, p.L57M), *KLF11* (c.G401C, p.G134A), *HNF1b* (c.C1058T, p.S353L), *ABCC8* (c.G814A, p.A272T) and *BLK*

(c.G94C, p.D32H) and one variant in *HNF1a* gene i.e. c.526+1G>A was already reported in literature

The six novel variants were found in other than known MODY genes i.e. *RFX6* (c.G919A, p.E307K) and (c.T1212A, p.H404Q), *WFS1* (c.G478A, p.E160K) and (c.G517A, p.E173K), *INSR* (c.G3921C, p.M1307I) and *ZBTB20* (c.G1049A, p.R350H). These genes are not reported for MODY pathogenicity.

In view of *WFS1* gene reports in MODY, Sanger sequencing of this gene was performed in 18 patients. *WFS1* gene analysis by Sanger sequencing identified a novel variant (c.G2416C:p.A806P) and a reported (c.C1037T:p.P346L) variant.

Further studies recruiting more patients will provide more insight into MODY causing variants in developing countries like Pakistan. Better diagnosis will result in accurate treatment of the disease and will improve the quality of life in patients.

Publications:

Following articles have been published from thesis

1. Rafique I, SaqibMAN, Mir A, Naeem M.Maturity Onset Diabetes of the Young – An Overview of Common Types. A Review. Romanian Journal of Diabetes Nutrition and Metabolic Diseases | Volume 25: Issue 2,2018, 209-213
2. Rafique I, Saqib MAN, Fawwad A, Zubaida B, Naeem M, Mir A, Basit A. Genetic characterization of suspected MODY patients in Pakistan by next generation sequencing - A pilot study. *Int J Diabetes Dev Ctries* (2021). https://doi.org/10.1007/s13410-021-00926-8. Published 10 February 2021.

3. Rafique I, Mir A, Saqib MAN, Naeem M, Marchand L, Polychronakos C. Causal Variants in Maturity Onset Diabetes of the Young (MODY) – A systematic review. Revision submitted in BMC Endocrine Disorders (BEND-D-20-00808R1)
4. Rafique I, Mir A, Siddiqui S, Saqib MAN, Marchand L, Fawwad A, Naeem M, Adnan M, Basit A, Polychronakos C. Comprehensive genetic screening reveals wide spectrum of genetic variants in MODY genes among Pakistani population. Revisions submitted in Pediatric Diabetes Journal (PDI-21-O-0034).

CHAPTER 1

INTRODUCTION

1. INTRODUCTION

1.1 Diabetes

Diabetes is an increasing public health burden globally both in developed and developing countries. It is a chronic disease that resulted due to either inability of the body to produce insulin or cannot use it properly which ultimately leads to the increased glucose level in the body. The insulin is a hormone produced by the pancreas, an organ located near to the stomach (Shepherd *et al.*, 2016; Urakami, 2019).

1.2 Prevalence of Diabetes

Diabetes has a huge burden worldwide, according to an estimate by International Diabetes Federation in 2015, there were 415 million people with diabetes among adults (20-79 years) and 5 million deaths were attributed to this deadly disease with 673 billion US dollars health expenditure(Ogurtsova *et al.*, 2017).The risk factors include genetics, a sedentary lifestyle, smoking, and an unhealthy diet(Yuan *et al.*, 2019; Zheng *et al.*, 2018). Diabetes is responsible for micro-vascular and macro-vascular complications leading to premature deaths globally in general and developing countries in particular (Bennett *et al.*, 2015; "Global Report on Diabetes," 2016).

In Pakistan,the first National Diabetes Survey was conducted in 1994-98 showing the prevalence of diabetes as 8.7%("Global Report on Diabetes," 2016; Shera *et al.*, 2010; Shera *et al.*, 1999; Shera *et al.*, 1995; Shera *et al.*, 1999). There were other local small-scale studies conducted showingan increase in diabetes over time (Zafar *et al.*, 2011; Zafar *et al.*, 2016). In 2016, the 2nd National Diabetes Survey was conducted all over the

country showed the weighted prevalence of 26.4% among adults(Basit *et al.*, 2018) These figures were alarming as indicating every fourth adult as diabetic.

1.3 Classification of Diabetes mellitus

Diabetes mellitus is a group of diseases having hyperglycemia due to defects in insulin action or insulin secretion or both. The symptoms varied with the duration and type of diabetes. The diabetes mellitus has been classified into the following types(Kharroubi *et al.*, 2015)

1.3.1 Type 2 diabetes mellitus

1.3.2 Type 1 diabetes mellitus

1.3.3 Gestational Diabetes

1.3.4 Monogenic Diabetes

1.3.1Type 2 Diabetes mellitus

Type 2 diabetes is more prevalent as 90% of the cases belonged to this type. The risk factors include overweight/obesity, a sedentary lifestyle, and less healthy food (Kraemer *et al.*, 2014). It is recommended that overweight children and adults must be regularly screened for diabetes (Reinehr, 2013). In this type, insulin resistance increases the demand for insulin from beta cells of the pancreas that could not be met due to defects in beta cells. This transforms some of the patients from independent to dependent on insulin (Halban *et al.*, 2014).

The disease begins with mild symptoms therefore might take years to diagnose. Its diagnosis usually delays in countries where there is no culture of routine check-up without symptoms. This resulted in developing complications of diabetes that are long

term in nature. The manifestations of insulin resistance include hypertension, nephropathy, and dyslipidemia. (Kraemer *et al.*, 2014; Reinehr, 2013)

1.3.2Type 1 Diabetes mellitus

Type 1 diabetes is more prevalent among children and adolescents. About 80-90% of type 1 diabetes are in children and adolescents (Craig *et al.*, 2009; Dabelea *et al.*, 2014).The destruction of pancreatic beta cells is responsible for the disease. The pancreatic beta cells are destroyed by the autoimmune response of humoral B cell and T cell-mediated inflammatory response(Devendra *et al.*, 2004). The autoantibodies' presence is an important indication for type 1 diabetes. These antibodies include Glutamic Acid Decarboxylase (GAD 65), autoantibodies to insulin (IAA), zinc transporter protein (ZnT8A), and islet cell autoantibodies. These antibodies can be detected in the serum of the patient. This type of diabetes has also a strong HLA association with DQ and DR genes (Couper *et al.*, 2009; Vermeulen *et al.*, 2011). The symptoms of type 1 diabetes included polyuria, feeling more tiredness, lack of energy, slow healing of wounds, recurrent infections, and blurred vision. In children, the symptoms can be worse than in adults (Katsarou *et al.*, 2017). This type of diabetes makesa patient more vulnerable to other autoimmune disorders like Addison's disease, Hashimoto's thyroiditis, Graves disease, hepatitis, and others. In this type, usually, there is a complete dependence on insulin(Kawasaki, 2014).

1.3.3 Gestational Diabetes

The hyperglycemia in pregnancy is called gestational diabetes mellitus. It increasesthe risk of adverse outcomes in the mother, fetus, and newborn. In pregnancy, hyperglycemia

increased the risk of preterm birth, caesarian birth, preeclampsia, and macrosomia i.e. birth weight more than 4.5 kg (Metzger *et al.*, 2008). The important risk factors for gestational diabetes were the age of the pregnancy, family history of diabetes, personal history of gestational diabetes, and lack of physical activity (Zhang *et al.*, 2016).

1.3.4 Monogenic Diabetes

Monogenic diabetes is due to a single gene defect results in disruption of beta cells function or reduce the number of beta cells. Monogenic diabetes consists of two types; neonatal diabetes and Maturity onset diabetes of the young (MODY). The symptoms of neonatal diabetes appear before six months of age while MODY occurs before the 25 years of age (Craig *et al.*, 2009).

1.3.5 Maturity Onset Diabetes of the Young

The MODY is an autosomal dominant form of diabetes. According to NCBI, there are fourteen subtypes of MODY depending on the type of gene involved. The following are the known 14 genes involved as shown in table 1.1(Urakami, 2019).

Table 1.1: Reported sub-types of MODY and genes

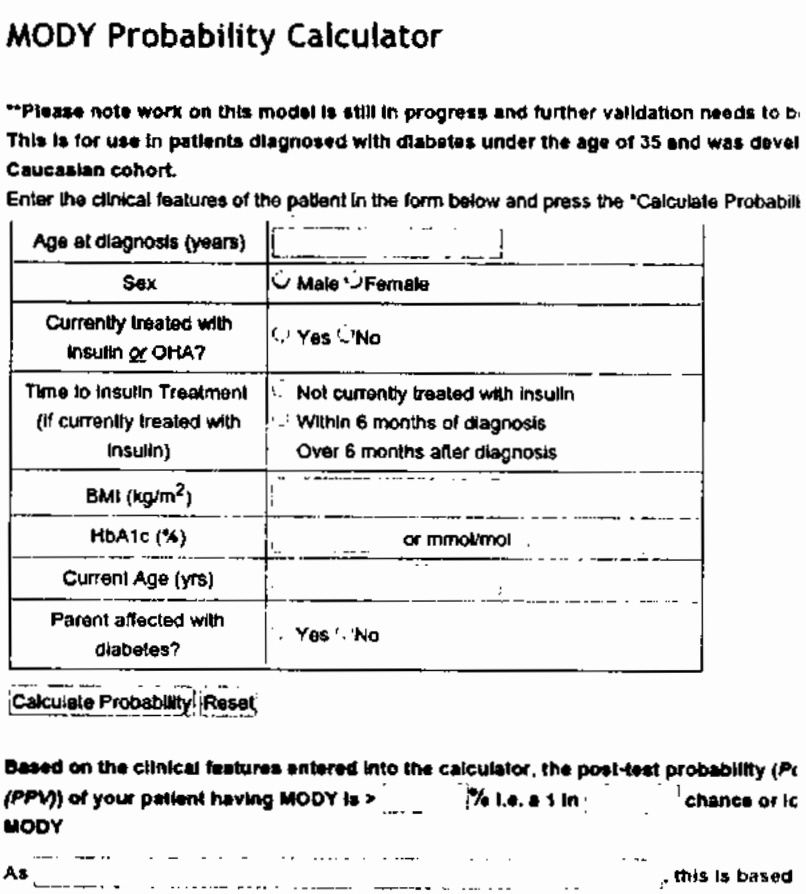
S.No	Type	Gene Involved
1.	MODY 1	*HNF4a*
2.	MODY 2	*GCK*
3.	MODY 3	*HNF1a*
4.	MODY 4	*PDX1*
5.	MODY 5	*HNF1B*
6.	MODY 6	*NEUROD1*
7.	MODY 7	*KLF11*
8.	MODY 8	*CEL*
9.	MODY 9	*PAX 4*
10.	MODY 10	*INS*
11.	MODY 11	*BLK*
12.	MODY 12	*ABCC8*
13.	MODY 13	*KCNJ11*
14.	MODY 14	*APPL1*

1.4 Diagnosis of MODY

The diagnosis for the MODY is challenging as it is generally misdiagnosed as type 1 or type 2 diabetes and the symptoms overlap with each other (A. T. Hattersley *et al.*, 2018; Thanabalasingham *et al.*, 2012).The MODY is different from type 1 diabetes as there is autoimmunity of pancreatic β cell involved in type1 diabetes In the case of MODY, diabetes remained well controlled with no or low insulin for five years (A. T. Hattersley *et al.*, 2018). It differentiates from type 2 diabetes in obesity as it is more prevalent in type 2 and MODY patients are generally lean(Urakami *et al.*, 2013). The accurate diagnosis of MODY and identification of its subtype is by genetic testing. The suspected cases having hyperglycemia, non-obese, absence of β-cellautoimmunity, and strong family history must be recommended for genetic testing (A. T. Hattersley *et al.*, 2018).

Genetic testing is available worldwide for the diagnosis of MODY to facilitate predictive treatment and prognosis. The already known MODY genes can be directly sequenced by using Sanger sequencing, targeted next-generation sequencing, and whole-exome sequencing (Szopa *et al.*, 2015). Traditionally, the Sanger sequencing was used for the three common genes that were involved in MODY but now a days, the targeted panel is available for confirmation of MODY in all known genes. In recent studies, whole-exome sequencing was used for the identification of new genes associated with the MODY (S. Johansson *et al.*, 2012; Johnson *et al.*, 2018).The diagnosis of the MODY carries significant importance as it alters the pattern of treatment. Most common algorithms developed for the prediction of MODY by Shields et al available online (Shields *et al.*,

2012). The probability calculator needs information about the age of onset of the disease, current age, HbA1c values, treatment information, BMI, and family history. Based on this information, the calculator determined the probability score for MODY (Figure 1.1).



MODY Probability Calculator

**"Please note work on this model is still in progress and further validation needs to b
This is for use in patients diagnosed with diabetes under the age of 35 and was devel
Caucasian cohort.**

Enter the clinical features of the patient in the form below and press the "Calculate Probabili

Age at diagnosis (years)	
Sex	Male Female
Currently treated with insulin *or* OHA?	Yes No
Time to Insulin Treatment (if currently treated with insulin)	Not currently treated with insulin Within 6 months of diagnosis Over 6 months after diagnosis
BMI (kg/m^2)	
HbA1c (%)	or mmol/mol
Current Age (yrs)	
Parent affected with diabetes?	Yes No

Calculate Probability Reset

**Based on the clinical features entered into the calculator, the post-test probability (*P
(PPV)*) of your patient having MODY is > % i.e. a 1 in chance or lc
MODY**

As , this is based

Figure 1.1: MODY probability calculator available at https://www.diabetesgenes.org/mody-probability-calculator/

1.5 Prevalence of MODY

The MODY is generally misclassified as type 1 diabetes or type 2 diabetes. In a study from the United Kingdom, it is reported that 80% of the MODY cases were misdiagnosed as type 1 or type 2 diabetes cases (Shields *et al.*, 2010). Its frequency was reported to be 1-2% in developed countries(Firdous *et al.*, 2018). In Canada, its incidence was reported as 0.4 cases per 100,000 among children and youth (Amed *et al.*, 2010). In the United States, its prevalence was reported as more than 2.1/100,000 individuals of less than 20 years of age. Its prevalence was also reported from India as well(Mohan *et al.*, 1985).

1.6 Sub-types of MODY

1.6.1 MODY 1 (*HNF4a*)

The MODY 1 type is relatively not common among all types. It accounts for almost 5% of the MODY cases (Pearson *et al.*, 2005). The gene involved is hepatocyte nuclear factor 4 alpha on chromosome 20 and plays an important role in expression in the pancreas, liver, and the kidney and regulates the transport and metabolism of glucose(Sladek *et al.*, 1990). It usually appears before the age of 25 years (McDonald *et al.*, 2013). It results in progressive insulin deficiency in young adults however in neonates; it results in hyper-insulinemic hypoglycemia (Pingul *et al.*, 2011). This type may also be involved in triglyceride metabolism like low levels of triglycerides and high-density lipoproteins (Lehto *et al.*, 1999).

The patients of MODY 1 can be treated with a controlled diet alone at the beginning (Stride *et al.*, 2002). Most patients will experience beta cell deterioration over time therefore needs pharmacological treatment. These patients can be treated with sulphonylurea and maintain good glycemic control. The dose of sulphonylurea should be low in the beginning to avoid hypoglycemia(Fajans *et al.*, 1993). These patients can be treated with a glucagon-like peptide (GLP-1) agonist which has the same glucose-lowering effect assulphonylurea with less risk for hypoglycemia(Ostoft *et al.*, 2014).

1.6.2 MODY 2 (*GCK*)

The glucokinase (GCK) enzyme plays an important role in glucose metabolism. It converts glucose to glucose-6-phosphate by adding phosphate from ATP in hepatocytes and pancreatic beta cells. This enzyme acts as a glucose sensor and play role in the release of insulin according to the glucose concentration. The mutations in the GCK gene resulted in a low rate of phosphorylation and threshold for the release of insulin-regulated at the upper level. By this, low insulin is released as compared to the required. As this gene is expressed in the liver so patients having a mutation in the GCK gene also have low storage of hepatic glycogen. In this type, there is mild hyperglycemia which is usually asymptomatic, and a modest increase in HbA1c. Microvascular and macrovascular complications are rarely associated with this type(Stride *et al.*, 2002; Velho *et al.*, 1997).

As hyperglycemia is mild therefore most of the time, it remains undetected throughout life or detected when checked for other routine investigations. It is important to detect GCK MODY because the patient may be unnecessarily put to treatment by considering as type 1 or type 2 diabetes patients (Feigerlova *et al.*, 2006). In a study from the Czech

Republic, almost 43% were found to have GCK MODY among non-obese children and adolescents (Feigerlova *et al.*, 2006). In the United Kingdom, 32% of all the MODY cases were of this type (Kavvoura *et al.*, 2012). Most of the time, it is detected during hyperglycemiascreening in schools. It is common in those countries where the school-based screening is conducted (Codner *et al.*, 2009; Estalella *et al.*, 2007).

Its identification in pregnancy carries vital importance. In the case of an affected mother, if a baby does not inherit the mutation, there will be an increased risk of macrosomia due to an increase in the risk of insulin from fetal cells as a response to maternal hyperglycemia (Spyer *et al.*, 2001). If baby inherits the same mutation as of mother then there will be normal weight, If baby inherits the mutation from his father, it will be at risk of low weight (almost 500g less weight) due to the release of less insulin (A. T. Hattersley *et al.*, 1998). It has been reported in a review that MODY 2 was common in Italy, Canada, Brazil, Czech Republic, United Kingdom, Spain, and Korea (Rafique I, 2018).

1.6.3 MODY 3 (*HNF1a*)

The *HNF1a*gene (transcription factor) is expressed in the kidney, liver, intestine, and beta cells of the pancreas. This *HNF1a* constitutes the network with other transcription factors and played a role in gene expression during embryonic development. In mature beta cells, these transcription factors regulate insulin expression and played role in the development, proliferation, and death of beta cells (McDonald *et al.*, 2013).

The genetic mutations in *HNF1a* altered the gene expression for proteins that are involved in glucose transport and metabolism (H. Wang *et al.*, 1998). It was proposed

that due to increased apoptosis and less proliferation of beta cells resulted in a decline in beta cells function (Hagenfeldt-Johansson *et al.*, 2001). It has been reported that about 63% of carriers developed diabetes by the age of 25, 79% by the age of 35, and about 96% by the age of 55 years (Shepherd *et al.*, 2001).

The diabetes was developed in mice with *HNF1a* knock out due to defective insulin secretion (Dukes *et al.*, 1998; Pontoglio *et al.*, 1998). This type of MODY is prevalent in Europe, America, and Asian countries (Rafique I, 2018). The MODY 3 appear in early adulthood by the age of 25 years. The patient tends to be normal glycemic control by birth, slim and normal sensitivity to insulin (Harries *et al.*, 2006). The disease develops due to a progressive decline in insulin secretion. It has been reported to be associated with microvascular and macrovascular complications. The frequency of complications was similar to type 2 diabetes (Isomaa *et al.*, 1998). The patients also develop glycosuria due to a low renal threshold for glucose (Pontoglio *et al.*, 2000).

For treatment, oral hypoglycemic agent sulphonylurea is generally recommended for MODY type 3. It has been reported that patients of HNF1a showed five times better response to sulphonylurea than metformin standard treatment while in type 2 diabetes both drugs have the same efficacy. Better glycemic control was observed with sulphonylurea instead of insulin therapy. As a result of this finding, most of the patients have successfully shifted to sulphonylurea from insulin therapy without any effect on glycemic control (Pearson *et al.*, 2003; Shepherd *et al.*, 2003).

1.6.4 MODY 4 (*PDX1*)

It is a rare form of MODY. The gene *PDX1* encodes the transcription factors having a role in the expression of insulin cells and the development of ß cells (Gragnoli *et al.*, 2005). The literature review showed 13 variants described for MODY 4 type. It was first reported in 1997 (Stoffers *et al.*, 1997).

1.6.5 MODY 5 *(HNF1b)*

The transcription factor *HNF1b* is expressed in the liver, kidney, genital tract, and pancreas (Urakami, 2019). Its clinical features are different from *HNF1a* and *HNF4a* MODY as it is characterized by both insulin resistance and ß cell dysfunction. The insulin therapy is required as there is not sensitivity to sulphonylurea (Pearson *et al.*, 2004). It can be diagnosed in ages from 0-61 years. In most cases, there is a deletion of the entire gene. Therefore, for diagnosing this type, methods also include the detection of whole gene deletion. There was also a report of denovo mutations in this type so it can be in patients without a family history (Bellanne-Chantelot *et al.*, 2005; Yorifuji *et al.*, 2004). Newborn babies with the mutation in this gene usually have a low birth weight due to less secretion of insulin in utero (Edghill *et al.*, 2006). The extrapancreatic manifestations associated with this type are renal cysts and kidney disease (Edghill *et al.*, 2008). The clinical features that differentiate this type from others are renal diseases with increased creatinine, raised liver enzymes, and hyperuricemia (Urakami, 2019).

1.6.6 MODY 6 (*NEUROD1*)

Neurogenic differentiation factor 1 (*NEUROD1*) has an important role in neuronal and pancreatic development. It is expressed in neurons and pancreas (Naya *et al.*, 1997). The

heterozygous mutation in this gene causes MODY while homozygous resulted in neonatal diabetes. Many studies have been reported with mutations in *NEUROD1* gene (Rubio-Cabezas *et al.*, 2010).

1.6.7 MODY 7 (*KLF11*)

The Kruppel like factor gene encodes the zinc finger transcription factors and is located in chromosome 2. It plays an important role in the functioning of ß cells. Mutation in this gene is responsible for the dysfunction of ß cells due to modulating the expression of free radical scavengers (Neve *et al.*, 2005).

1.6.8 MODY 8 (*CEL*)

The gene *CEL* encodes the lipase stimulated by the bile salt. This enzyme is the part of pancreatic juice and helps in the digestion of fats and cholesterol (Hui *et al.*, 2002). This juice played an important role in the digestion of milk and dietary esters in new-borns. The heterozygous mutations causing MODY 8 have been reported in the literature (Raeder *et al.*, 2006; Torsvik *et al.*, 2010).

1.6.9 MODY 9 (*PAX4*)

The *PAX 4* (Paired box gene 4) is a transcription factor on chromosome 7 and play an important role in the development and function of ß cells (Biason-Lauber *et al.*, 2005). The mutations in this gene have been reported from Thailand (Plengvidhya *et al.*, 2007).

1.6.10 MODY 10 (*INS*)

The gene *INS* encodes the precursors for insulin and is located on chromosome 11 (Dandona *et al.*, 2001). The mutations in this gene is responsible for the disruption of

disulfide bonds leading to a severe defect in the folding of proteins and apoptosis of ß cells. The age of onset of disease in this type varies (Ivarsson *et al.*, 2008).

1.6.11 MODY 11 (*BLK*)

The *BLK* (B -lymphocyte kinase) is a tyrosine kinase expressed in ß cells of the pancreas where it promotes the synthesis of insulin. Decreased activity of this gene resulted in a reduced quantity of insulin content and ß cells become less responsive to glucose leading to a decrease in insulin secretion and diabetes (Borowiec *et al.*, 2009).

1.6.12 MODY 12 (*ABCC8*)

The ATP-binding cassette transporter subfamily C member 8 (*ABCC8*) encodes the sulphonylurea receptor (SUR1) which is the important component of ATP-sensitive potassium channel across the membrane of ß cells. It mediates the regulation of sugar level in the blood. The mutations in this gene cause MODY which is responsive to sulphonylurea (Bowman *et al.*, 2012).

1.6.13 MODY 13 (*KCNJ11*)

This gene encodes the subunit for the potassium ATP channel expressed in ß cells of the pancreas (Liu *et al.*, 2013). The age of onset for this type and severity varies (Yorifuji *et al.*, 2005). Mutations in this gene have been reported from different countries (Massa *et al.*, 2005).

1.6.14 MODY 14 (*APPL1*)

The gene *APPL1* was identified to be involved in MODY in 2015. It is adaptor protein, phosphor-tyrosine interaction, pH domain, and leucine zipper containing 1 (*APPL1*). It is

an anchor protein that has interaction with lots of other proteins including those involved in the signaling pathway of insulin (Prudente *et al.*, 2015).

1.7 *WFS1* gene

The mutations in *WFS1* gene are responsible for wolfram syndrome. This is a rare genetic disorder having symptoms ranging from mild to severe characterized by juvenile diabetes, optic atrophy, neurodegeneration, and hearing loss. Currently, there is no treatment available to halt or reverse the progression of this disease. (D. Abreu *et al.*, 2019). The prevalence is estimated to be 1 in 500,000 persons worldwide. Wolfram Syndrome is an autosomal recessive disease.The WFS1 gene has eight exons and most of the mutations reported so far were on exon 8. The function of the gene is to regulate endoplasmic reticulum homeostasis (Pallotta *et al.*, 2019).

The symptoms of the disease usually started to appear in early childhood with diabetes mellitus at the age of 06 years and optic nerve atrophy at 10 years ago. In the next two decades, deafness, sleep apnea, and diabetes inspidiousdevelop (Urano, 2016). Wolfram syndrome is the Endoplasmic reticulum (ER) disorder. As the ER plays a role in the folding of proteins. The pathogenic variants of the WFS1 gene induce ER stress in the cells disturbing the calcium homeostasis and lipid biosynthesis (Fonseca *et al.*, 2010). Also, urinary tract problems were presented in wolfram syndrome patients affecting about 90% of the patients. More than half of patients develop neurological manifestations (Barrett *et al.*, 1995).

Although the clinical symptoms are important for the diagnosis of Wolfram syndrome the genetic test is used to confirm the diagnosis of this syndrome (Inoue *et al.*, 1998). A

review reported 178 mutations in the *WFS1* gene. These mutations were distributed throughout the protein without any major hotspot (de Heredia *et al.*, 2013)

1.8 Aims and objectives

The study aimed to understand the genetic etiology involved in the early onset of diabetes in the Pakistani population with following objectives:

- To determine the genetic variants responsible for MODY in Pakistani diabetic patients among already known genes
- To identify new genes causing Maturity Onset Diabetes of the Young in Diabetic patients from Pakistan
- To study the demographic and clinical variability in the Maturity Onset diabetes of the Young cases

1.9 Rationale of the study

Diabetes is a major public health burden around the globe. The National Survey conducted in 2016-17 reported that every fourth adult is diabetic in Pakistan. The diabetes is also associated with complications which put an extra burden on expenditure as well as resulted in economic burden.

Being a developing country, Pakistan has a poor health care system with very low facilities at primary and secondary health units. The other social factors like illiteracy, poor socio-economic conditions further aggravate the situation. Diagnosis and screening are pivotal in treatment and providing a better outcome. Proper timely diagnosis will help in preventing the complications of the disease.

For better diagnosis and treatment, there is a need for collaborative efforts including identification of MODY, its genetic diagnosis, and genetic counseling. There is a lack of comprehensive studies on MODY cases from Pakistan. Its diagnosis carried vital importance as it alters the treatment pattern. The treatment for different types of MODY varies. Therefore it is extremely important to have genetic variant data on MODY from Pakistan.

Chapter 2

Materials and Methods

2. MATERIALS AND METHODS

2.1 Ethical Approval

The study was conducted as per the Helsinki declaration. The Ethical Clearance has been taken from the Institutional Bioethics Committee of International Islamic University, Institutional Bioethics Committee of Pakistan Health Research Council, Ethical Review Board of Pakistan Institute of Medical Sciences, Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad.

2.2 Consent filling

The participants were briefed about the objectives of the study and written informed consent was taken from all participants prior to enrolment. In case of participants less than 18 years, consent was obtained from parents/guardian.

2.3 Sample population

A total of 191 participants were enrolled in the study. The participants were identified from National Diabetes Survey and Diabetes Clinicis located at Lahore (Diabetes Clinic I) and Karachi (Diabetes Clinic II) as per study inclusion criteria. The demographic and clinical information was taken from the patients and filled on a pre-designed questionnaire. Information related to the onset of disease, treatment were noted from the patients. The height and weight were measured for the calculation of BMI.

2.4 Enrolment of participants

The patients were enrolled with following inclusion criteria

2.4.1 Inclusion criteria

a. Diabetic if they fulfill any one of the following criteria a) having HbA1C > 6.5% (48 mmol/mol), b) fasting glucose level >126 mg/dl or plasma glucose after two hours glucose load >200 mg/dl
b. The onset of the disease was less than 25 years of age.

2.4.2 MODY probability Calculator

The online available MODY probability calculator was used to determine the probability of MODY in the study participants. The information like current age, age at diagnosis, HbA1c, family history and BMI were entered in software for calculation of the score.

2.5 Blood Sampling

The 5cc blood sample was obtained from the participants in 10ml vacutainer tubes (K2 EDTA tubes) by using 5cc syringe (BD 0.8mm). Separate 5cc blood samples in plain vacutainer tubes (BD)was taken for serum preparation. The serum and whole blood was stored at -80^{o}C

2.6 Serum Extraction

The whole blood was collected in 5cc vacutainer tubes and left for 30 minutes. The samples were centrifuged (100-2000 xg) for 10 minutes and clot was removed. The

serum (liquid component) was transferred by Pasteur pipette into clean tube. The serum was stored at -80°C for ELISA testing.

2.7 DNA Extraction

The extraction of DNA was carried out by two methods

- Kit by Promega Corporation
- Kit by Qiagen

2.7.1 DNA extraction by Kit (Promega Corporation)

The DNA was extracted by using four steps. Whole blood (300ul) was used for the extraction. First step was the lysis of red blood and white blood cells. Second step was the lysis of nuclei by using nuclei lysis solution. Third step involve the removal of cellular proteins by adding protein precipitation solution (salt precipitation method). Fourth step was desaltation and concentrating the DNA by adding isoprpanol (DNA rehydration solution).

2.7.2 DNA extraction by Kit (Qiagen)

The DNA extraction by Qiagen Kit is based on the principle of selective binding properties of silica membranes. First step was the lysis of cells by using lysis buffer. Then the sample loaded into the QIAmpa spin columns supplied with the kit. The DNA bound to the silica membranes and the contaminants were removed in multiple washing steps. The DNA was eluted in low salt buffer.

2.8 Biochemical tests

Following biochemical test were carried out to rule out the presence of autoimmune type 1 diabetes

2.8.1 Fasting C-peptide test

The c-peptide was performed by two step immunoassay method using serum samples. Firstly, assay diluents, antihuman c-peptide coated microparticles were combined with the sample. The c-peptide in the sample combines to the antihuman c-peptide microparticles and formed antigen-antibody complex. Second step involves the addition of conjugate (c-peptide acridinium labeled) to form a reactin mixture. After wash cycle, trigger solutions were added to the reaction mixtures. The chemiluminescent reaction was measured by relative light units.

2.8.2 GAD-65 ELISA

The GAD-65 ELISA was performed by using KRONUS Glutamic Acid Decarboxylase Antibody (GADAb) ELISA assay kit. This was used to determine the GAD-65 antibody in serum samples.

The ELISA strips were coated with GAD_{65} The GAD antibodies forms the bridge between GAD_{65} coated on the wells and liquid GAD_{65}biotin. This bound GAD_{65}biotinwas quantitated by adding streptavidin peroxidase and TMB (chromogenic substrate). The absorbance was read at 450 nm. The abosorbance of each well was directly proportional to the amount of GAD-65 antibodies present in the sample. The

antibody concentrations of the sample and the controls were interpolated with the help of semi-log graph.

2.9 Exome Sequencing

First step in exome sequencing was the library preparation. The DNA was sheared into small fragments and mixed with biotinylated RNA library baits and hybridization buffer. Then targeted regions were slected by using magnetic sreptavidin beads. Then it was washed, amplified and loaded on the sequencer. Suquencing process utilized four nucleotides having reversible fluorophore and termination properties. Each sequencing cycle took place in presence of all four nucleotides leading to more accuracy. The Illumina platform sequencer was used for the sequencing.

2.10 Raw Exome data filteration

The fastq files were aligned for map referencing using Burrows-Wheeler Alignment (BWA) tool. The duplications were marked using the PICARD tool. The variant calling and filtering were done by using the Genome analysis toolkit (GATK). Finally, the variant annotation was conducted by SnpEff. The analysis was mainly focused on non-synonymous coding variants, splice sites affecting variants, and frameshift indels as these were likely to be pathogenic. The analysis was conducted with preference to heterozygous variants located on already known 14 genes of MODY. The genetic variants were filtered according to the frequency reported in databases. The pathogenicity was assessed by different computational tools like SIFT LRT, Mutation Taster,

FATHMM, PROVEAN, Mutation assessor, MetaSVM, Meta LR, M-CAP and Fathmm-MKL.

2.11 Pathogenicity estimation

The missense variant was selected as pathogenic if majority of 10 algorithem predicted the variant as disease causing and PP3 by ACMG/AMP (American College of Medical Genetics and Genomics and the Association for Molecular Pathology).The PP3 was defined as multiple lines of computational evidence supports a deleterious effect on the gene or gene product.

2.12 Sanger Sequencing

The genomic DNA was amplified using Poylmerase Chain Reaction (PCR) with forward and reverse primers for exon-8 of *WFS1* gene. The oligonucleotide primers were designed by Primer 3 software. The primers used for the confirmation of splice site variant i.e. c.526+1G>A of *HNF1a* gene were (Forward primer GGGCTCCATAACTGCTTTCA and reverse primer CCTTTCCATCTACCTGTCTGTG) with annealing temperature of 60^0C. The reagents i.e. dNTPS, $MgCl_2$ solution, DNA polymerase, forward and reverse primers were used which were stored at -20^oC. Initialy PCR was optimized by using different annealing temperatures and $MgCl_2$ concentrations.

The PCR products were visualized on 1.5% agarose gel using Horizontal Gel electrophoresis system. The PCR products were then subjected to Sanger sequencing. The Sanger sequencing was analyzed by ChromasPro software. The chromatogram analysis

was carried out by aligning the chromatograms of other samples and comparing them against each other.

The variants found were interpretated and analyzed by using databases dbSNP, PubMed, Clinvar, HGMD (Human Genome Mutation Database) and ExAC (Exome Aggregation Consortium).

Chapter 3

Results

3 Results

The results chapter comprised of two sections i.e. i) systematic review and ii) original research.

3.1 Systematic Review

A systematic review of the literature was conducted to enlist all the causal variants reported in the literature for MODY. The reviews were available on diagnostics, types, and guidelines for treatment but a review on causal variants was lacking therefore this review was carried out.

3.1.1 Search Strategy

PubMed database was used for this review. The literature was searched and articles were included until 01 December 2019. Different combinations of search terms were used for search strategy, as follows: Maturity Onset Diabetes of the Young OR Monogenic diabetes AND MODY OR *ABCC8* OR APPL1 OR *BLK* OR *CEL* OR *GCK* OR *HNF1A* OR *HNF1B* OR *HNF4A* OR *INS* OR *KCNJ11* OR *KLF11* OR *NEUROD1* OR *PAX4* OR *PDX1*. The initial screening was done by reviewing the titles and abstracts. Those found relevant were accessed for full text. The articles were then reviewed as per the inclusion criteria.

3.1.2 Study Selection

The studies were selected based onthe following inclusion criteria:

i) The study identified MODY cases i.e. which was young onset, non-autoimmune, non-insulin resistance non-neonatal and non-syndromic

ii) Identified a novel pathogenic variant

iii) Published in English Language (studies published in other languages but with an abstract in English, and describing novel variants were also included in the analysis).

iv) The studies from all geographical locations were included, irrespective of year of publication.

The exclusion criteria were reviews, commentaries, and already reported variants (Figure 3.1) and details of excluded full-text studies are described in supplementary table 1.

3.1.3 Data Extraction

The studies fulfilling the inclusion criteria were reviewed and information from these studies was tabulated. Data including author name, country of origin, publication year, variant, a gene involved, and methodology used to identify the variant was taken. Only those novel variants which were pathogenic, likely pathogenic or uncertain significance, and having an impact on protein structure (software prediction) as reported by the authors were included. The benign, likely benign were excluded. The ClinVar database of NCBI (https://www.ncbi.nlm.nih.gov/clinvar/) was also searched for variants in the 14 known genes involved in MODY, which were also included even if not reported in the literature.

The variants were validated by using variant validator (https://variantvalidator.org/) and accession numbers were provided in the supplementary table. The ACMG criteria were assessed by the software "Intervar". The variants were also confirmed from the Human Gene Mutation Database (HGMD) and the PMID number of the articles were retrieved and mentioned in supplementary table 2.

3.1.4 Systematic Review Findings

A total of 1647 results were retrieved after literature searching. After reviewing their titles and abstracts, full articles were retrieved for 326 citations. After the final review, 87 studies were excluded resulting in 239 studies to be included in the analysis. The reasons for exclusion were reviews, no variants reported in the study, and no novel variants. A summary is presented in figure 3.2 and the details are in supplementary table 1.

The most frequently reported mutated gene was *GCK*, followed by *HNF1a* (Figure 3.3). When analyzing the methods employed for identifying the variants causing MODY, a majority (76%) used traditional Sanger sequencing while 11% used whole-exome sequencing (Figure 3.4).

The whole-exome sequencing and targeted next-generation sequencing were reported from studies from 2012 onwards till 2019. These techniques have played a major role in identifying new MODY types. The variants in *PDX1, INS, ABCC8, KCNJ11, NEUROD1, KLF11, BLK,* and *APPL1* were identified through targeted next-generation sequencing or whole-exome sequencing. Significantly more (65%) studies were conducted in 2011-2019 as compared to 23.5% in 2001-2010 and 11.5% in 1990-2000.

When analyzing according to the countries, variants in MODY genes were reported from almost every region of the world. The largest number of variants was found from the French population followed by Italy, Japan, and the United States of America (Figure 3.5).

A total of 1017 variants were identified through a literature review in 14 known genes and attached as supplementary table 2. A total of 94 pathogenic variants were

identified from ClinVar and 20 among them were already in the list and were therefore excluded. The list of those 74 variants is attached as supplementary table 3.

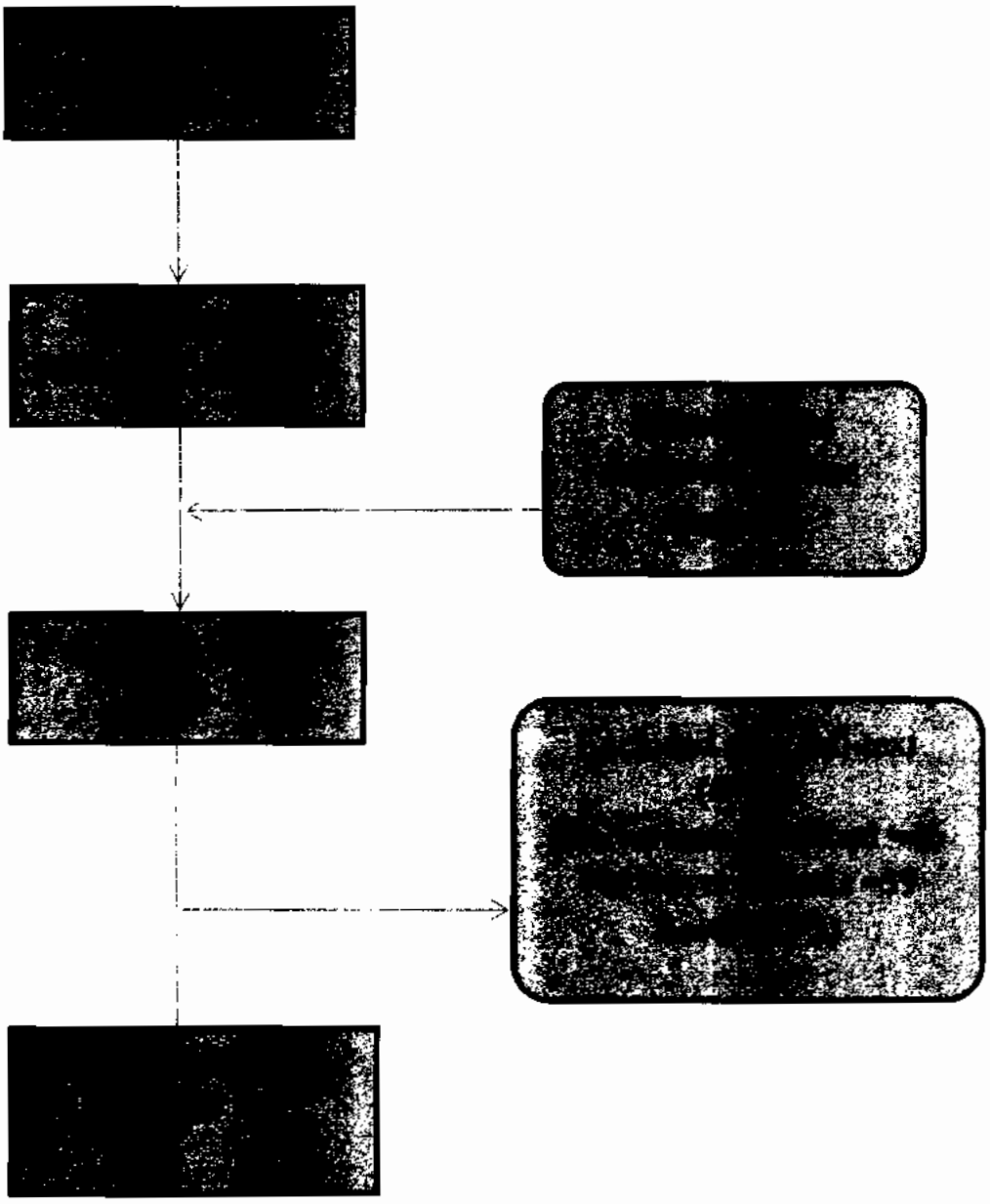


Figure 3-1: Flow chart showing the steps for a systematic review of the literature

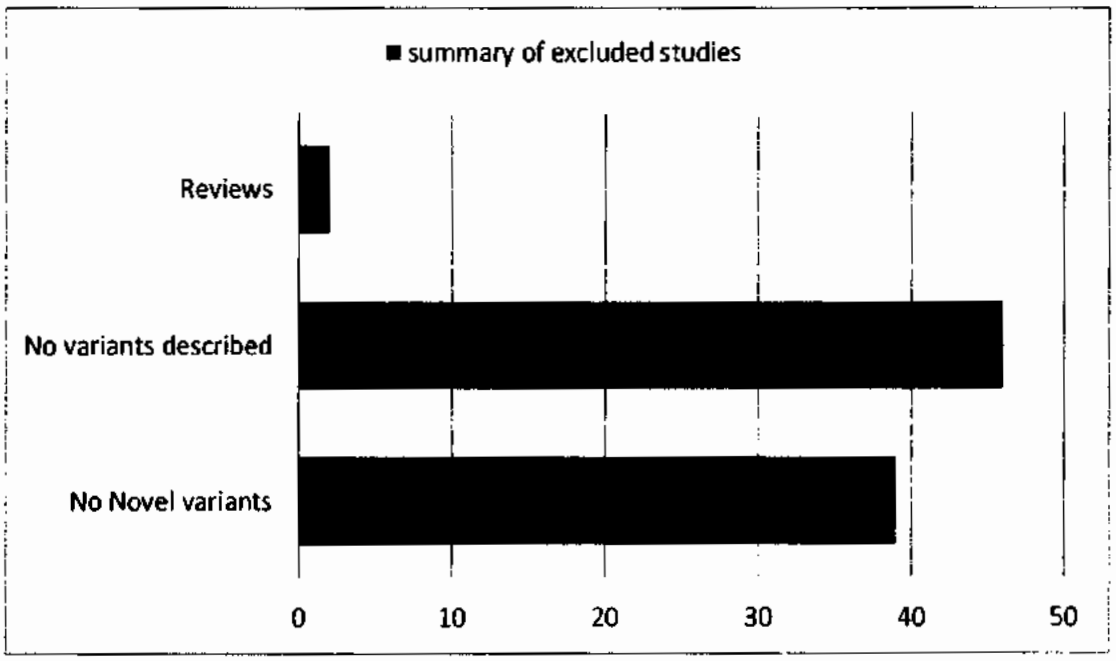


Figure 3-2: Detail-wise breakup of excluded studies from review with reasons

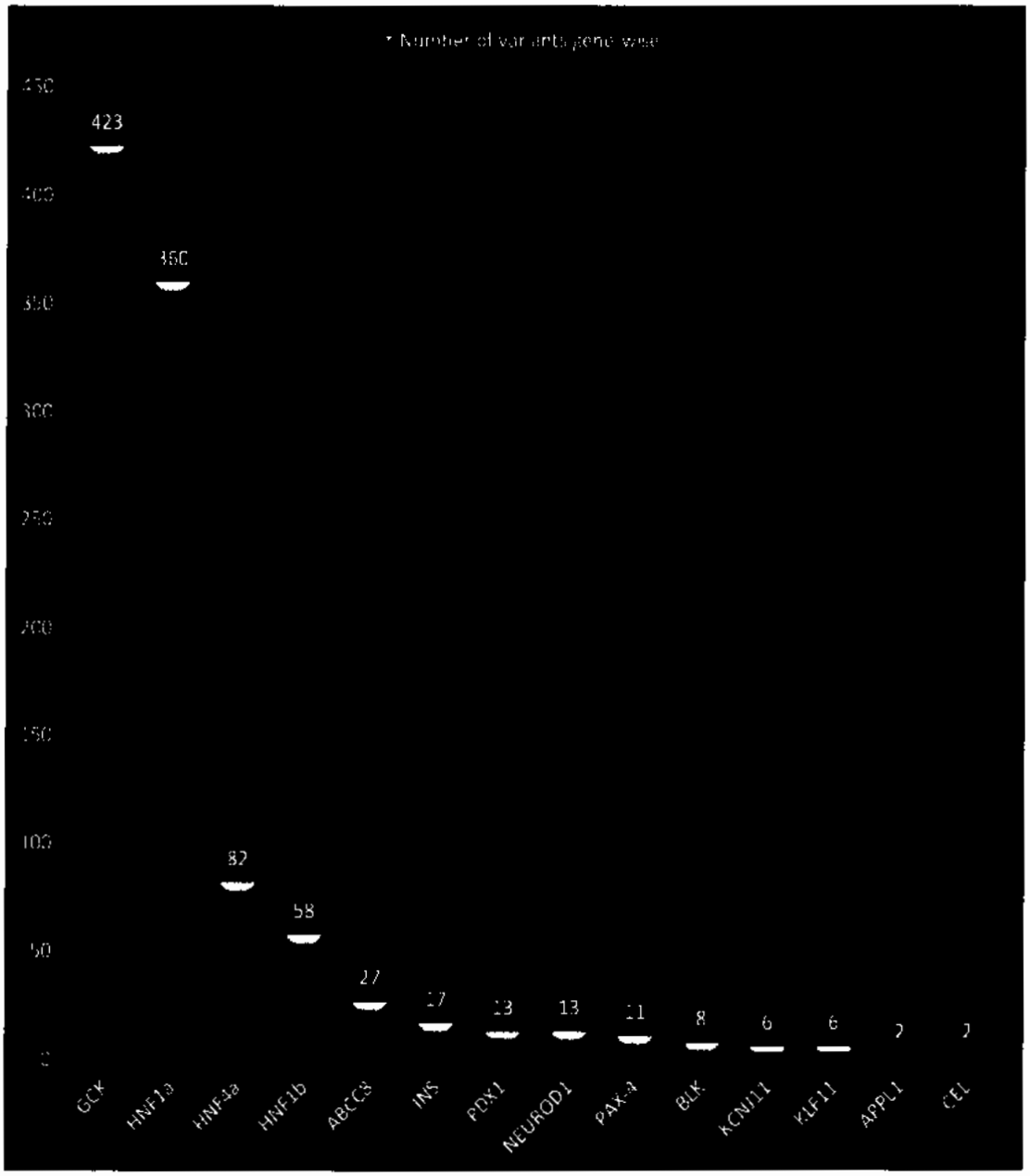


Figure 3-3: Number of gene-wise variants reported in literature. X-axis showing the name of the gene while the y-axis presenting the number of reported variants in literature.

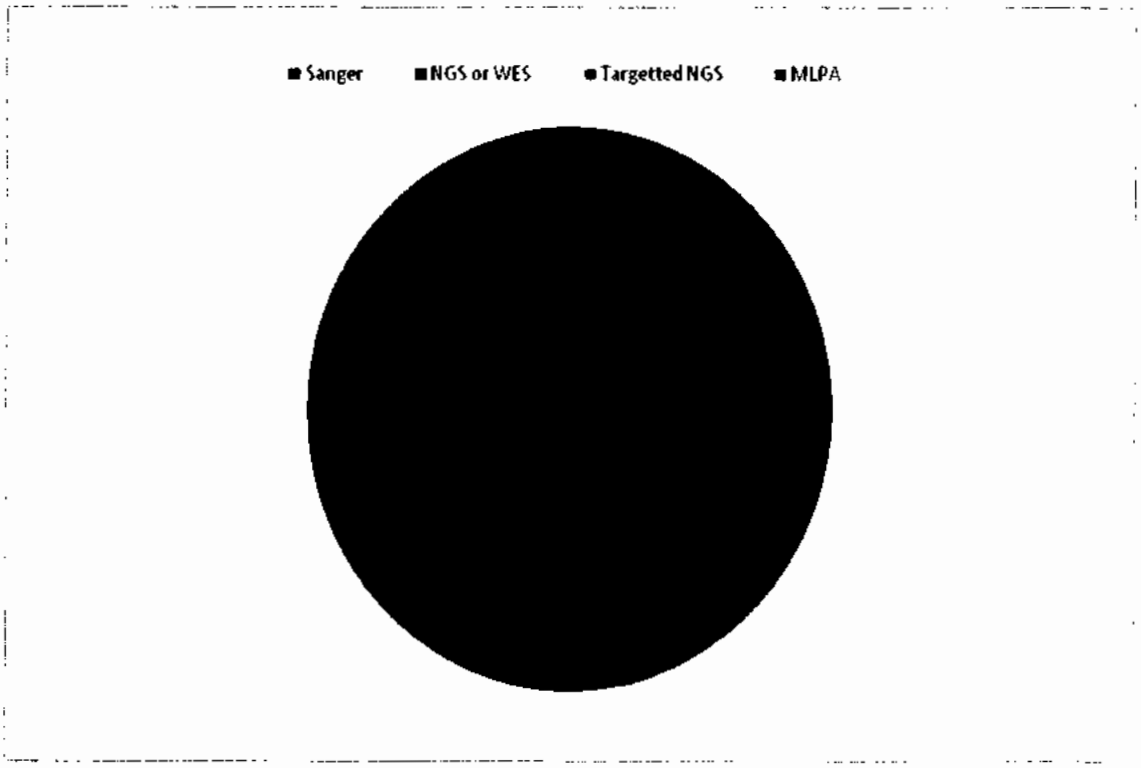


Figure 3-4: Percentage of methods used for reported variants in MODY

Figure 3-5: Graph showing Country-wise number of causal variants reported in the literature. The number of variants is presented on the x-axis while countries are shown on Y-axis

3.2 Research Findings

The search study was conducted to enroll patients from the National diabetes survey (2016-17) of Pakistan and Diabetes Clinics located in Lahore (Diabetes Clinic I) and Karachi (Diabetes Clinic II) within Pakistan to identify diabetes in youth (Figure 3.6)

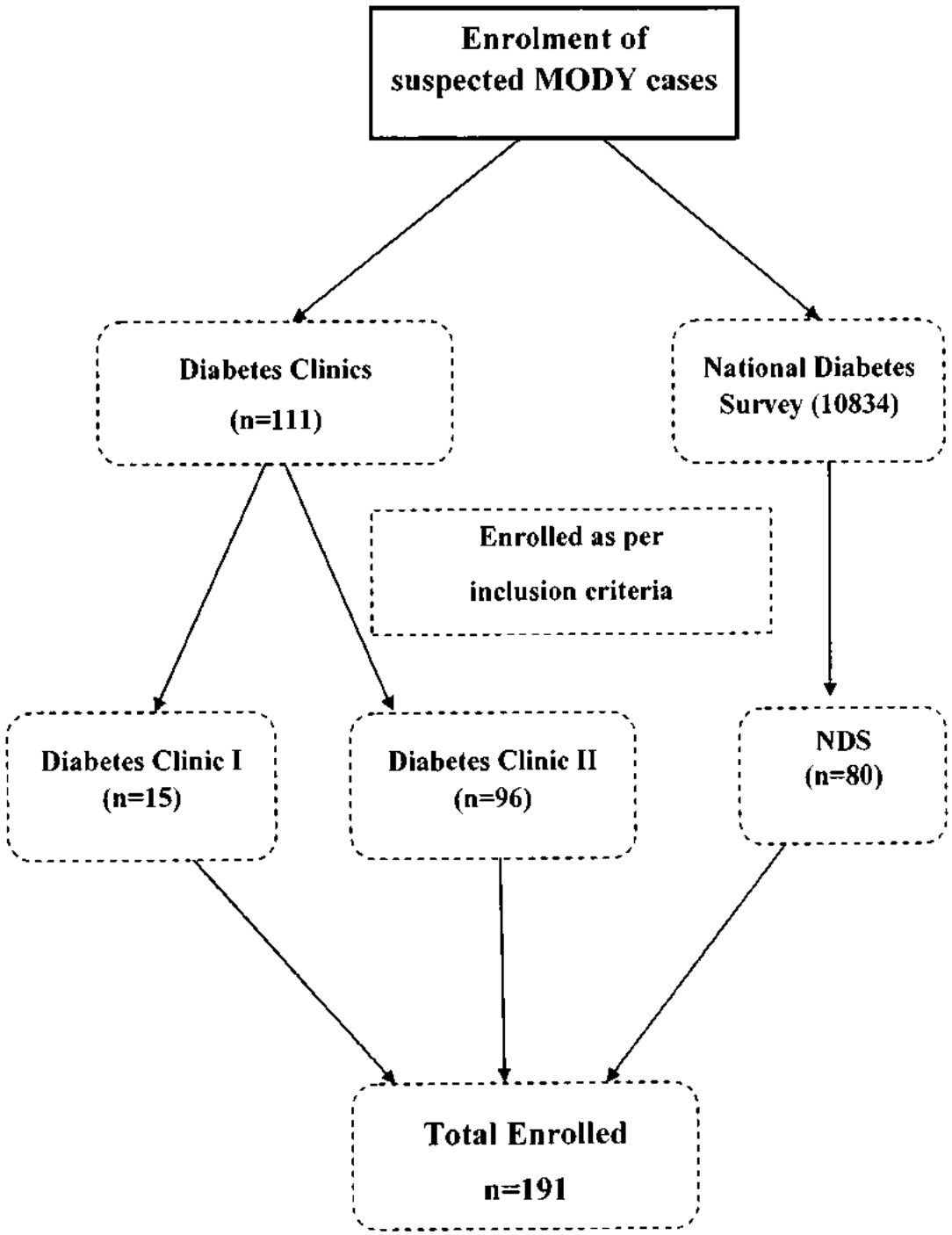


Figure 3-6: Schematic presentation of patient enrolment

3.2.3 Characteristics of the study participants:

In National Diabetes Survey, data of 80 participants is presented in Table 3.3. The median age was 24 years, 62% females, average BMI was 28 kg/m^2 and mean HbA1c was 6.2. When the MODY score was calculated, it was observed that 16 cases (20%) were having a probability score of more than 75%. In most of the cases (58%) the score was zero or could not be calculated due to missing information on some variables. (Table 3.4)

Based on probability score, patients were classified into two groups . One group of patients (Group 1) had MODY score >75 whereas the second group (Group 2) having a score of <75. The groups were compared for variables i.e. age, height, weight, BMI, and HbA1c as presented in Table 3.5. The HbA1c and BMI were significantly low in group 1 as compared to group 2.

Patients with high probability score were processed for ELISA testing of GAD-65. Among 34 patients, 10 were positive and 24 were negative. The GAD-65 positive indicates that patients were suffering from autoimmune type 1 diabetes (Figure 3.7)

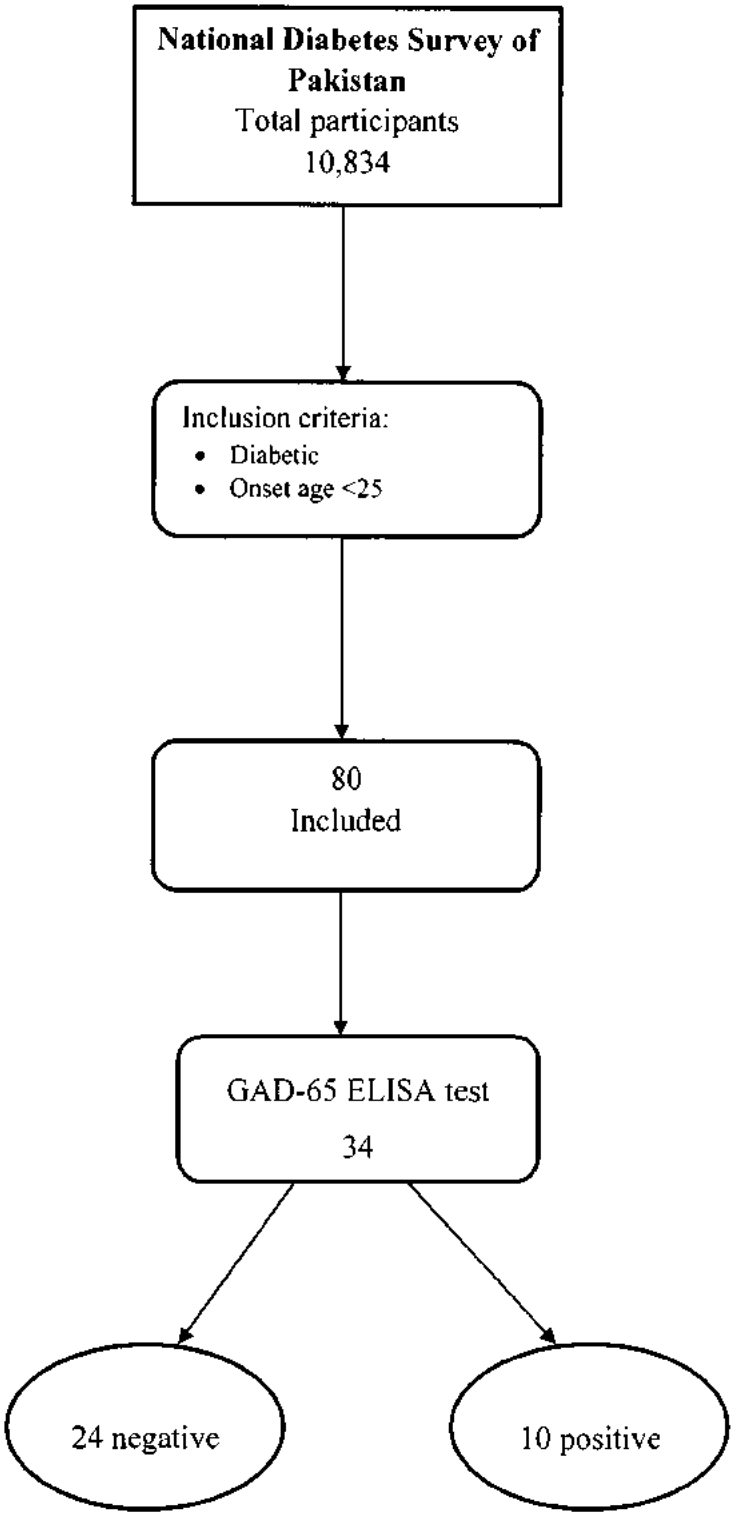


Figure 3-7: Selection of participants from National Diabetes Survey

Table 3.2: Demographic Characteristics of the participants of the National Diabetes Survey

S.No	Description	Frequency
1.	Median age (years)	24
2.	Average GTT Fasting (mg/dl)	169
3.	Male	37.5%
4.	Female	62.5%
5.	Getting treatment	6.25%
6.	BMI (kg/m^2)	28
7.	Average Systolic and Diastolic Blood Pressure (mmHg)	119/80
8.	HbA1c (%)	6.4

Table 3.3: MODY probability score of the study participants

S.No	Description	Number	Percentage (%)
1.	Probability Score >75	16	20
2.	Probability Score = 1-74	17	21.25
3.	Probability Score = 0	47	58.75
	Body Mass Index (BMI)	**Number**	**BMI (kg/m^2)**
4.	BMI <25kg/m^2	38	47.5
5.	BMI 25-29.9 kg/m^2	19	23.7
6.	BMI >30 kg/m^2	12	15

Table 3.4: Comparison of variables between Group 1 (high score) and Group 2 (low score) in study participants:

	Total (n=80)	Group 1 (n=17) P>75%	Group 2 (n=16) P<75%	P-Value
Age (years)	24.00±5.97	24.20±7.60	29.30±8.80	0.985
Age at diagnosis (years)	23.10±1.67	23.18±1.33	23.19±1.36	0.085
Duration of diabetes (years)	10.25±9.18	11.10±10.20	13.20±6.00	0.535
Fasting glucose (mg/dl)	168.20±68.63	151.80±59.40	231.70±84.20	0.004*
Random glucose (mg/dl)	215.53±89.99	250.10±94.50	275.60±58.0	0.354
Height (cm)	158.98±9.92	162.36±11.67	156.59±8.20	0.131
Weight (kg)	62.45±15.13	62.56±14.83	73.44±13.49	0.035
Waist circumference (cm)	88.91±15.92	87.87±14.00	97.27±14.14	0.064
Hip circumference (cm)	92.90±19.61	86.34±22.13	98.66±15.33	0.075
Systolic blood pressure (mmHg)	118.65±17.04	122.40±20.70	121.40±14.10	0.876
Diastolic blood pressure (mmHg)	79.73±11.98	82.90±14.40	80.80±6.90	0.585
Hemoglobin A1c (%)	6.37±2.15	6.21±1.99	9.14±1.71	<0.001
Body Mass Index (kg/m^2)	24.65±5.77	23.54±3.93	29.30±4.07	<0.001

3.2.4 Enrolment from Diabetes Clinics

The patients were enrolled from two main cities i.e. Diabetes Clinic I and Diabetes Clinic II. From Diabetes Clinic I, fifteen patients mean current age of 26.06 years ranging from 16-48 years while the mean age of diagnosis was 23 years. The mean Body Mass Index was 21.5 kg/m^2. The low BMI is indicative of a patient having more probability for having Maturity Onset diabetes of the Young (MODY)

The mean systolic blood pressure was 113.57 mmHg and diastolic blood pressure was 77.14 mmHg. The mean value for fasting blood sugar level was 239.26 mg/dl. The Hba1c level was ranging from 6% to 11% with a mean value of 8.27%.(Table 3.6 & 3.7)

Fasting c-peptide test results showed that 66.8% have normal fasting c-peptide levels. 26.6% have high value while 6.6% have values below the normal fasting c-peptide. The low fasting c-peptide is indicative of type-1 diabetes. Among the total, 73% of patients have a MODY score of more than 75. The GAD-65 ELISA testing was performed. (Figure 3.8)

Table 3.5: Demographic characteristics of the participants registered at Diabetes Clinic I

Description	Mean	Range	Standard Deviation
Age (years)	26.06	16-48	8.05
Age at Diagnosis (years)	23.07	16-30	4.0
Height (cms)	157.7	146-178	10.69
Weight (Kg)	53.6	42-80	11.53
BMI (kg/m^2)	21.5	15.5-31.10	3.93
Systolic Blood pressure (mmHg)	113.57	100-140	12.15
Diastolic Blood pressure (mmHg)	77.14	70-90	7.26
Fasting sugar level (mg/dl)	239.26	130.0 - 375.0	70.55
HbA1c (%)	8.27	6-11	1.59
Fasting C-peptide (ng/ml)	1.703	0.16-3.83	0.97

Table 3.6: Clinical description of the participants registered at Diabetes Clinic I

Description	Sub-headings	Percentage
Fasting C-peptide	Normal fasting C-peptide level	66.8%
	Above Normal	26.6%
	Below normal	6.6%
MODY Probability Score	More than 75%	73.3%
	Less than 75%	26.7%
How come to know about the diabetes	Antenatal screening	20.1
	Loss of weight	40.1
	Polyuria	13.4
	Pain	13.4
	Regular check-up	6.7
Taking treatment	Yes	40
	No	60
Type of treatment	Oral hypoglycemic agent (OHA)	26.7
	OHA and insulin	13.3

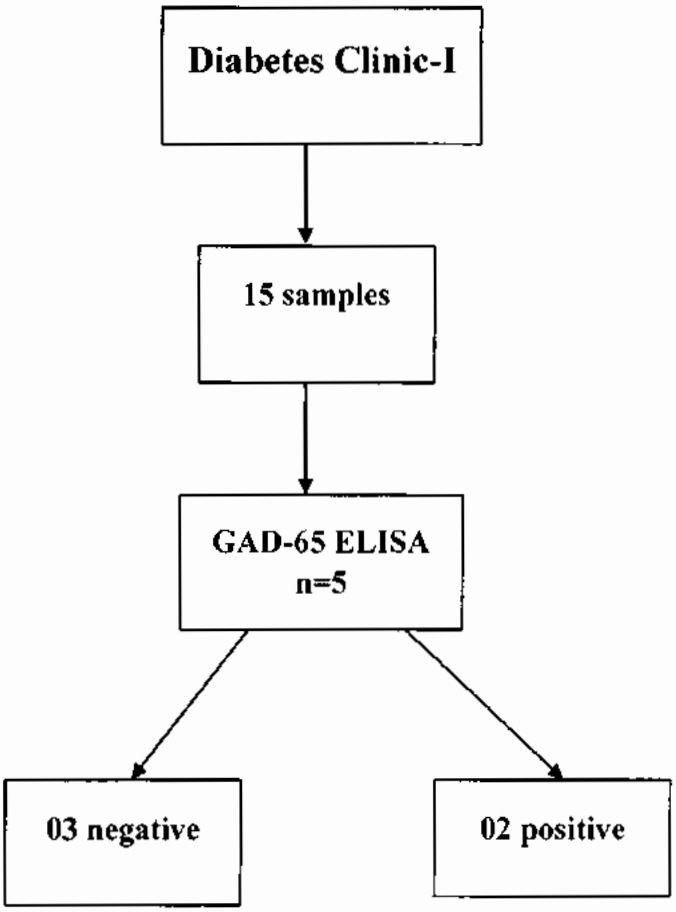


Figure 3-8: Summary chart of sampling details of patient enrolment at Diabetes Clinic I

From Diabetes Clinic II, 96 patients were enrolled. Their mean current age was 26.2 years while the age of onset of the disease was 16.5 years. Among all, 51 (53.1%) were males while 45 (46.8%) were females. Mean height was 161.4 cm, weight was 64.2 kg and BMI was 24.3 kg/m^2. The majority of the cases (95.8%) were having a family history of diabetes. Of the total, 93.75% were taking treatment (both oral and insulin injections) for diabetes and 68% were taking insulin as treatment. About 25% of the patients have a probability score of more than 75%. The Glutamate decarboxylase (GAD-65) test was performed on the patient's serum samples. Out of the total, 15 patients were GAD-65 negative having values less than 4 IU/ml. The samples were analyzed for having a high probability, family history, BMI, and HbA1c level (Figure 3.9).

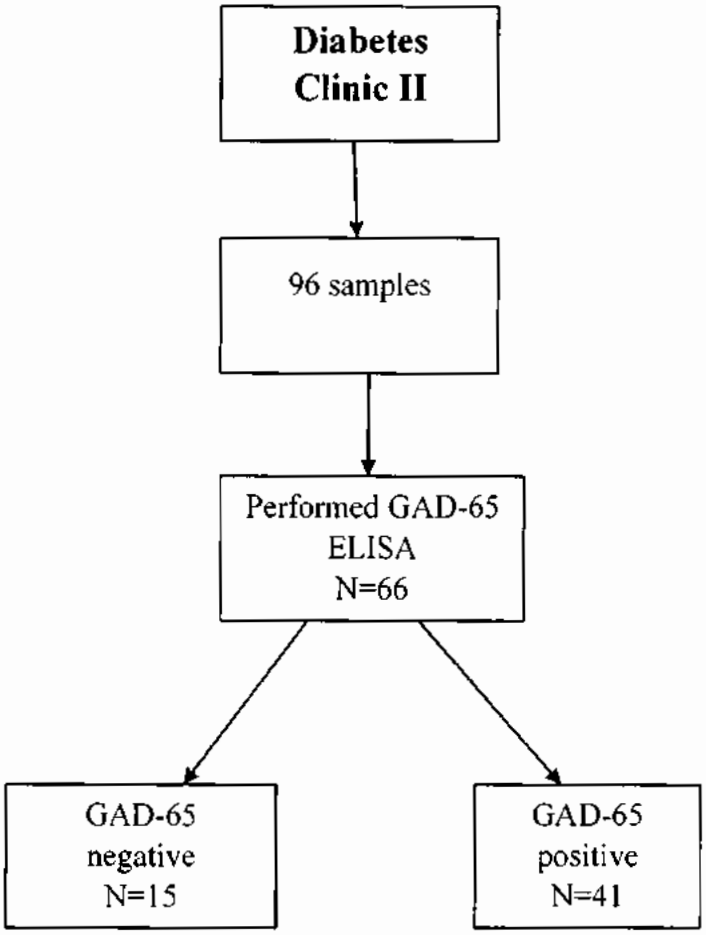


Figure 3-9: Summarized chart of sampling details of patient enrolment at Diabetes Clinic II

3.2.5 Selection for exome sequencing

All the GAD-65 negative samples were reviewed for clinical features like low BMI, parental family history, and moderately high HbA1c and further processed for exome sequencing. A total of 35 samples were shortlisted for exome sequencing. (Figure 3.10)

The detailed demographic features of the participants selected for exome sequencing are described in Table 3.8. Genderwise distributions identified 19 males and 16 females in total. Maternal diabetes history was positive in 23 patients while 12 had positive paternal diabetes history. The GAD-65 test was negative in 19 patients. Among all the patients, 21 patients were having BMI well below 25 indicating that they were lean indicating the important characteristic of MODY. The age for onset of diabetes was below 25 years in all patients.

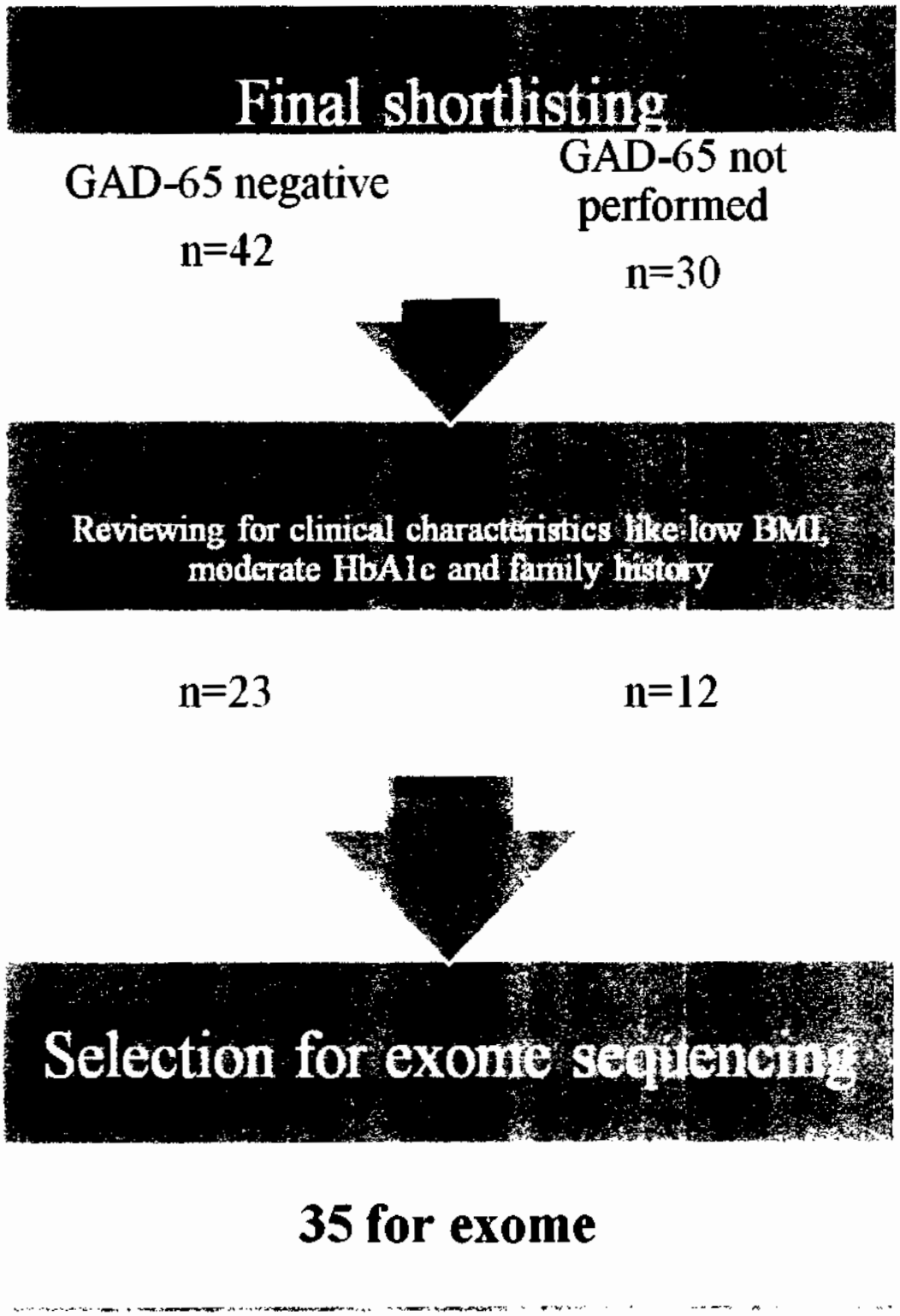


Figure 3-10: Selection of patients for exome sequencing

Table 3.7: Demographic characteristics of the participants selected for exome sequencing

S.No	Patient ID	Age	Gender	FBS mg/dl (Hba1C)	Mother affected	Father affected	BMI	GAD 65
1.	471	25	Male	237	NA	NA	22	Negative
2.	612	25	Female	119 (9.2)	Yes	Yes	22	Negative
3.	705	23	Male	148 (5.4)	NA	NA	26	Negative
4.	830	21	Female	7.2	NA	NA	NA	Negative
5.	P-4	25	Male	173 (7.5)	No	Yes	27	NA
6.	P-5	24	Male	149 (6.10)	No	No	16	NA
7.	P-9	20	Male	159 (6.20)	No	No	20	NA
8.	P-12	16	Male	290(10.8)	Yes	Yes	19	Negative
9.	P-13	23	Female	279(8.4)	Yes	No	22	Negative
10.	P33530	25	Male	NA	Yes	No	22	Negative
11.	P43614	18	female	NA	Yes	Yes	21	Negative

S.No	Patient ID	Age	Gender	FBS mg/dl (Hba1C)	Mother affected	Father affected	BMI	GAD 65
12.	P83936	18	female	NA	Yes	Yes	26	Negative
13.	P-17	15	female	NA	Yes	No	19	Negative
14.	P68	13	Male	6.8	Yes	No	NA	NA
15.	P69	18	Male	7.6	Yes	No	NA	NA
16.	P71	12	Male	7.10	No	Yes	14	NA
17.	P78	20	Female	10.10	Yes	Yes	26	NA
18.	P79	19	Male	9.8	Yes	No	31	NA
19.	P87	25	Male	6.10	Yes	No	31	NA
20.	P90	4	Female	8.20	Yes	No	24	NA
21.	M46	17	Male	6.5	Yes	No	24.2	Negative
22.	M54	15	Female	13.6	No	Yes	24.87	Negative
23.	M64	21	Female	12	Yes	No	22.3	Negative
24.	M13	13	Female	8.1	No	Yes	29.3	Negative
25.	M6	17	Male	8.2	Yes	No	24.6	Negative

S.No	Patient ID	Age	Gender	FBS mg/dl (Hba1C)	Mother affected	Father affected	BMI	GAD 65
26.	M15	15	Female	7.4	No	Yes	18.3	Positive
27.	M24	12	Male	8.1	Yes	No	26.9	Positive
28.	91	14	Male	12	Yes	No	20.32	NA
29.	92	16	female	9.7	No	Yes	25.4	NA
30.	88	21	female	9.6	No	Yes	26.96	NA
31.	85	3	Male	9.4	Yes	No	17.94	NA
32.	86	18	female	6.6	Yes	No	28	NA
33.	84669	25	male	NA	Yes	No	20	Negative
34.	08	25	Male	7.8	Yes	No	24	Negative
35.	66103	14	Female	NA	Yes	No	24.5	NA

3.2.6 Exome Sequencing

The exome sequencing was carried out from Macrogen, Korea, and Quebec Genome Centre, Canada and FastQ file format raw data was obtained.

3.2.7 Bioinformatics analysis

FastQ files were processed according to Genome analysis tool kit (GATK). The reads were mapped to human reference genome GRCh37 using Burrows-Wheeler alignment (BWA-MEM). The duplicate alignments were marked and removed by using the PICARD tool and then indel realignment and base quality score recalibration were done. The gVCFs were generated with GATK haplotype and joint variant calling was done. The variants with low map read (DP<20) and low genotype quality (GQ<20) were discarded. Annovar was used to annotate the variants. The UTR, synonymous, and intronic (unless splicing) variants were discarded by standard ES filtering procedure to focus on protein-altering ones. These variants were filtered for frequency in three public databases (Exome Aggregation Consortium, 1000 genomes, and gnomAD). For dominant genes, the Maximal allele frequency cutoff was 0.0001 in any population while it was 0.005 for recessive genes. The missense variants were selected only if predicted disease-causing by the majority of 10 algorithms (PP3 by ACMG/AMP). Details of design and analysis are presented in figure 3.11.

3.2.8 Description of variants

A total of 36,732 variants were filtered from 35 patient's exome data according to the criteria mentioned in figure 2.12. A list of 37 variants was identified in genes which were further shortlisted and screened according to cut off frequency and resulted in 12 variants.

Among the total 37 variants, 4 were from *KLF11* gene, 1 in *APPL1* gene, two in *ZBTB20*, three in *WFS1* gene, three in *RFX6* gene, two in *BLK* gene, three in *GATA4* gene, three in *CEL* gene, one in *INS-IGF2*, six in *HNF1a*, one in *PDX1*, three in *INSR* gene, one in *NKX2-2*, one in *HNF1b*, one in *HNF4a*, one in *ABCC8* and one in *GCK*.

Among the variants, 21 were found to be in known 14 MODY genes while others variants were found in genes other than known for MODY but functionally involved in diabetes. Of the total, 27 variants were missense while 10 variants were either duplication, frameshift, or splice variations. The SIFT score prediction was damaging for 12 variants. The 16 variants were supposed to be disease-causing as predicted by the mutation taster prediction software. The 17 variants have uncertain significance according to Intervar interpretation.

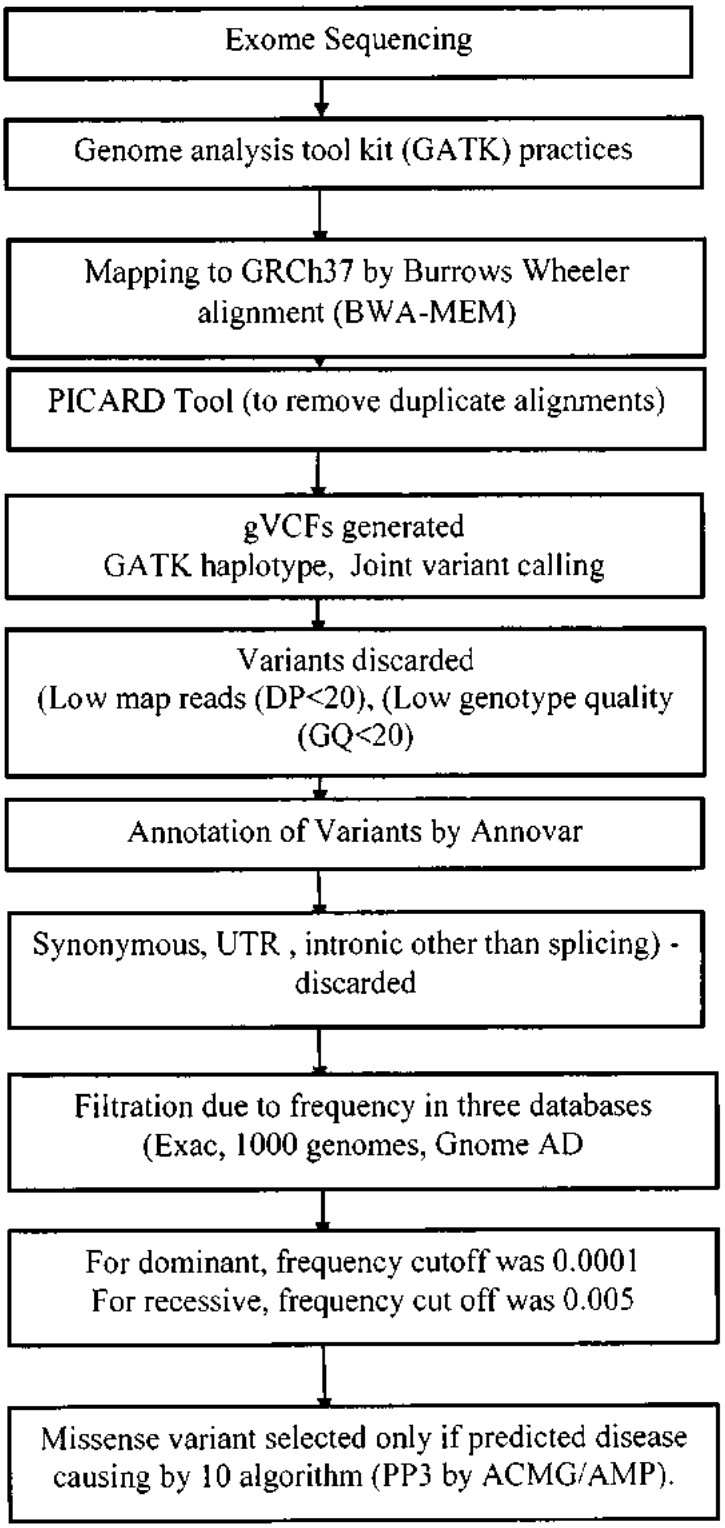


Figure 3-11: Bioinformatics analysis and steps in filtering variants

Table 3.8: Details of variants identified through exome sequencing

S.No	Patient ID	Gene name	cDNA change, amino acid change	SIFT (score, prediction)		Mutation taster (score, prediction)		Intervar
1.	471	*APPL1*	c.A200G, p.E67G	0.088	T	1	D	VUS*
2.	612	*HNF1a*	c.C169A, p.L57M	0.081	T	1	D	VUS
3.	705	*HNF1a*	c.865dupC, p.G288f	.	.	.	.	.
4.	P83936	*HNF1a*	c.865dupC, p.G288fs	.	.	.	.	.
5.	P-4	*HNF1a*	c.865dupC, p.G288fs	.	.	.	.	.
6.	P69	*HNF1a*	c.865dupC, p.G288fs	.	.	.	.	.
7.	M6	*HNF1a*	c.526+1G>A	-	-	-	-	-
8.	705	*KLF11*	c.G401C, p.G134A	0.78	T	1	N	VUS
9.	P-4	*KLF11*	c.G1331A, p.R444Q	0	D	1	D	VUS
10.	P43614	*KLF11*	c.C731T, p.P244L	0.182	T	1	D	LB
11.	M54	*KLF11*	c.*96dupA	-	-	-	-	-
12.	830	*RFX6*	c.G919A, p.E307K	0.267	T	1	D	VUS
13.	P-9	*RFX6*	c.C1927T, p.P643S	0.001	D	1	D	VUS

S.No	Patient ID	Gene name	cDNA change, amino acid change	SIFT (score, prediction)		Mutation taster (score, prediction)		Intervar
14.	P68	*RFX6*	c.T1212A,p.H404Q	0.668	T	0.687	D	VUS
15.	P-4	*WFS1*	c.G2380A, p.E794K	0.087	T	1	D	VUS
16.	P-17	*WFS1*	c.G478A, p.E160K	0.341	T	0.705	N	VUS
17.	P-17	*WFS1*	c.G517A, p.E173K	0.023	D	1	D	VUS
18.	P-12	*CEL*	c.A1622G, p.Y541C	0.001	D	0.683	N	LB**
19.	P43614	*CEL*	c.2168_2200del p.723_734del	.	.	.	.	.
20.	M64	*CEL*	c.1235C>T,p.Thr412Ile	0.008	D	1.0	D	-
21.	P-5	*BLK*	c.G94C, p.D32H	0.171	T	1	N	VUS
22.	P78	*BLK*	c.G500A, p.R167Q	0.001	D	1	D	LB
23.	P-5	*GATA4*	c.G1273A, p.D425N	0.001	D	1	A	B
24.	P68	*GATA4*	c.C1040T, p.A347V	0.133	T	1	N	LB
25.	P90	*GATA4*	c.C1067G, p.T356S	1	T	0.978	N	B
26.	P33530	*PDX1*	c.G670A,p.E224K	0.007	D	0.989	A	LB

S.No	Patient ID	Gene name	cDNA change, amino acid change	SIFT (score, prediction)		Mutation taster (score, prediction)		Intervar
27.	P-9	*ABCC8*	c.G814A, p.A272T	0.31	T	0.558	N	VUS
28.	P-13	*INS-IGF2*	c.T362C, p.I121T	0	D	1	N	LB
29.	P43614	*INSR*	c.G3957C, p.M1319I	0.104	T	1	D	VUS
30.	P87	*INSR*	c.G607A, p.G203R	0.02	D	1	D	VUS
31.	M15, M54,M 64	*INSR*	c.653-5_653-4delTC	-	-	-	-	-
32.	P-9	*HNF1B*	c.C1058T, p.S353L	.	.	1	D	VUS
33.	P69	*HNF4A*	c.933_935del, p.311_312del	.	.	.	.	.
34.	P71	*ZBTB20*	c.G1318A, p.E440K	0.005	D	1	D	B
35.	P87	*ZBTB20*	c.G1049A, p.R350H	0.038	D	0.993	D	VUS
36.	M15	*GCK*	c.-45G>A	-	-	-	-	-
37.	P79	*NKX2-2*	c.C677T, p.A226V	0.057	T	0.999	D	VUS

*VUS, Variant of Uncertain Significance, **LB, likely benign, ***B, Benign

The above mentioned variants in table 3.9 were further analyzed based on low frequencies and Clinvar predictions. Only twelve (12) variants were selected and details of these are given in table 3.10. Among these 12 variants, six variants are from already known MODY genes (*HNF1a, KLF11, BLK, ABCC8*, and *HNF1b*) and six variants were from other genes i.e. *RFX6, INSR, WFS1*, and *ZBTB20* genes. The functions of these genes are mentioned in table 3.11. The variant i.e. c.526+1G>A in *HNF1a* gene was confirmed in M6 patient (Figure 3.12).

Table 3.9: Variants selected based on frequency and pathogenicity

S.No	Patient ID	Position	Gene	cDNA change	Amino acid change	Max Frequency	Prediction of pathogenicity	Inter Var
1.	612	12; 1416740	*HNF1a*	c.C169A	p.L57M	0	T, NA, D,D, N. L, D,D,D,D	VUS
2.	705	2; 10187916	*KLF11*	c.G401C	p.G134A	0	T, ,N,N,T,N, N,T,T,T,N	VUS
3.	830	6;117237424	*RFX6*	c.G919A	p.E307K	0.0001	T,D,D,T,N, N, T,T,D,D	VUS
4.	P-5	8; 11400827	*BLK*	c.G94C	p.D32H	0.0003	T,N,N,T,N, N, T,T,T, N	VUS
5.	P-9	11; 7483138	*ABCC8*	c.G814A	p.A272T	0.0002	T,N,N,D,N, . L, T, D, D. D	VUS
6.	P-9	17; 6070581	*HNF1b*	c.C1136T	p.S379L	0.00003	NA, D. D, NA, NA, L, D,D,D,D	VUS
7.	43614	19; 7117259	*INSR*	c.G3921C	p.M1307I	0.0008	T,N,D.T.N, L, T. T, D,D	VUS
8.	P-17	4; 629294	*WFS1*	:c.G478A	p.E160K	0	T,N,N,D,N, ,	VUS

S.No	Patient ID	Position	Gene	cDNA change	Amino acid change	Max Frequency	Prediction of pathogenicity	InterVar
		1					M, D,D,D,D	
9.	P-17	4; 6292980	*WFS1*	c.G517A	p.E173K	0	D,D,D,D,D, M, T,T, D, D	VUS
10.	P-68	6; 117241502	*RFX6*	c.T1212A	p.H404Q	0.0001	T,D,D,T,N, L, T,T,T, D	VUS
11.	P-87	3; 114069876	*ZBTB20*	c.G1049A	p.R350H	0	D,D,D,T,N, N, T,T,T,D	VUS
12.	M6	12;121426836	*HNF1a*	c.526+1G>A	-	-	-	-

* SIFT, LRT, Mutation taster, FATHMM, PROVEAN, Mutation Assessor, MetaSVM, MetaLR, M-CAP, fathmm-MKL_codingare mentioned in sequence. D, deleterious; T tolerated for SIFT, LRT, MetaSVM, MetaLR_pred, M-Cap prediction, FATHMM. N is neutral for LRT and Provean. For mutation assessor. H: high; M: medium; L: low; N: neutral

Table 3.10: Functions of other than known MODY genes identified in this study

S.No	Gene Name	OMIM	Functions
1.	*RFX6*	* 612659	Direct islet cells differentiation
2.	*INSR*	* 147670	Instruct making protein Insulin receptor
3.	*WFS1*	* 606201	Encodes transmembrane protein located in the endoplasmic reticulum and expressed in the pancreas and insulinoma beta-cell lines.
4.	*ZBTB20*	* 606025	Acts as a transcriptional repressor and played role in glucose homeostasis

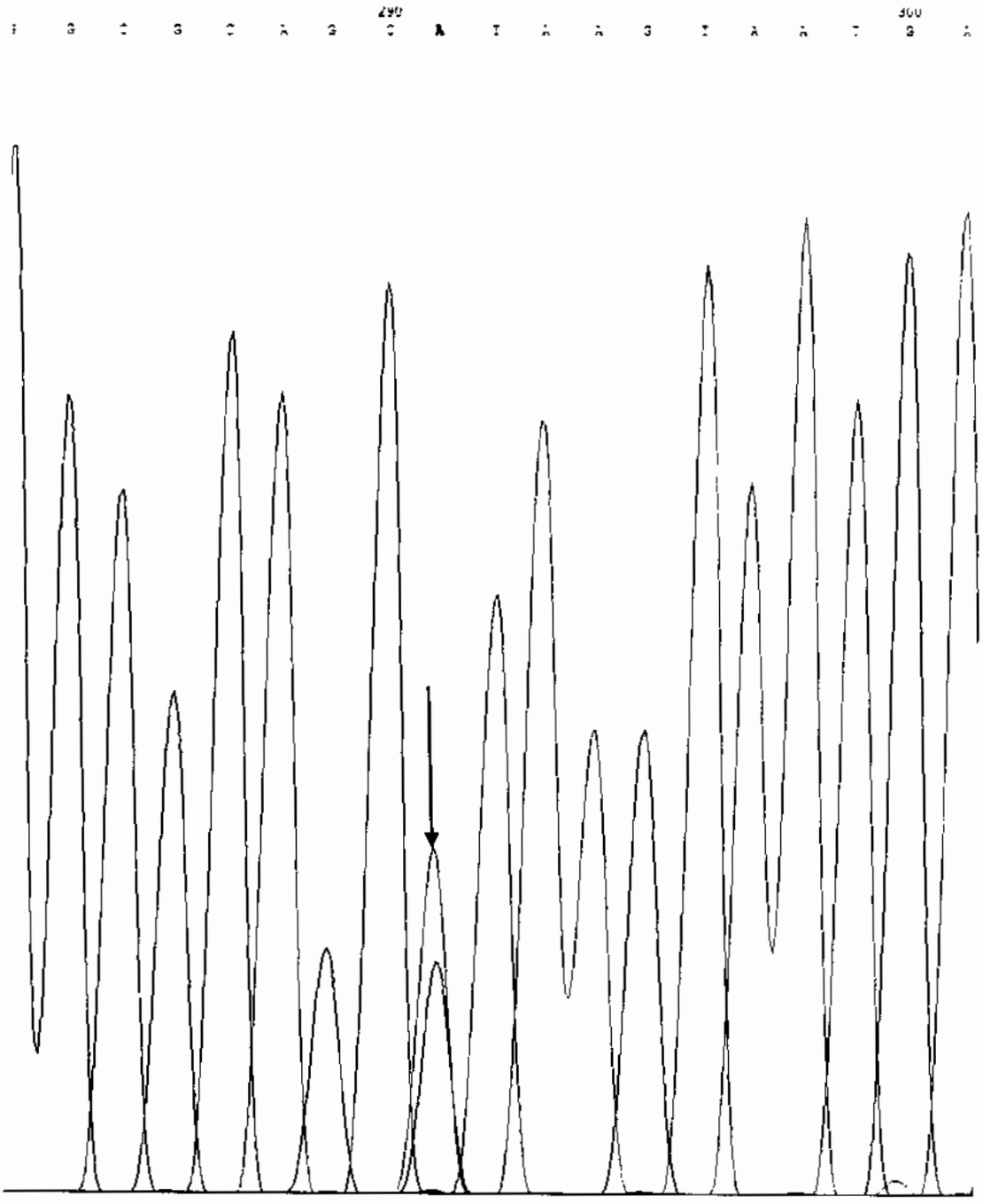


Figure 3-12: Heterozygous variant c.526+1G>A (splice site variant) in the HNF1a gene (patient ID-M6) and confirmed by Sanger sequencing.

3.3 *WFS1* gene sequencing

Among the samples collected from Diabetes Clinic II, there were 30 samples where GAD-65 could not be performed. These samples were reviewed carefully for clinical characteristics that were more relevant to MODY clinical features like low BMI and family history. These samples were processed for Sanger sequencing of exon 8 in *WFS1* gene (Table 3.12).

Two missense homozygous recessive mutations were identified in the *WFS1* gene. One of the homozygous recessive variants was c.G2416C:p.A806P identified inpatient (ID-96). This variant was not reported in Clinvar. The variant was identified in females who had developed diabetes at the age of 05 years. The pathogenicity predictions of SIFT and LRT were deleterious and Polyphen HDIV and HVAR were probably damaging. The mutation taster predicted disease-causing and mutation assessor as a medium. The details are presented in Table 3.13 & 3.14 and Figure 3.13.

The second homozygous recessive variant was c.C1037T:p.P346L identified in a patient ID-93. This missense low frequency variant is deleterious by SIFT and LRT software predict while polyphenol HDIV and polyphen HVAR predicted i.e. probably damaging and mutation taster as disease-causing. The details are presented in Table 3.15 & 3.16 and Figure 3.14.

Table 3.11: Clinical features of the participants undergoing Sanger sequencing of exon-8 of WFS1 gene

S.No	Patient ID number	Onset age of diabetes (years)	Gender	BMI (kg/m^2)	Family History
1.	P-43614	18	Female	21.2	Father affected
2.	P-11906	25	Female	29.98	Mother affected
3.	P-19008	19	Male	32.4	Mother affected
4.	P-48103	25	Male	28.3	Mother affected
5.	P-66103	14	Female	24.5	Mother affected
6.	P-33530	25	Male	22.2	NA
7.	P-26688 (55)	25	Female	39	Both affected
8.	P-67636 (17)	15	Female	19.3	NA
9.	P-83936	18	Female	26.0	Both affected
10.	P-84669	25	Male	20	Mother affected
11.	P-85	03	Male	17.9	Mother affected
12.	P-90	04	Female	24	Mother affected
13.	P-91	14	Male	20.3	Mother affected
14.	P-92	16	Female	25.4	Father affected
15.	P-71	12	Male	14	Father affected

16.	P-86	18	Female	28	Mother affected
17.	P-93	08	Female	28	Father affected
18.	P-96	05	Female	14.86	Father affected

Table 3.12: Summary Card for recessive missense variant c.G2416C:p.A806P in WFS1 identified in Patient (ID-96)

S.No	Features	Values
1.	Patient ID	96
2.	Gene	*WFS1*
3.	Type of mutation	Missense Variant
4.	Position	chr4:6302211 (GRCh38.p12)
5.	Alleles	G>C
6.	SNP	rs762075088
7.	Frequency:	C=0.00001 (2/247186, GnomAD_exome) C=0.00001 (1/117622, ExAC)

Table 3.14: Pathogenicity predictions for homozygous recessive variant c.G2416C, p.A806P in WFS1 identified in patient (ID-96)

S.No	Softwares	score	Converted ranked score	prediction	Interpretation
1.	SIFT	0.004	0.654	D	Deleterious
2.	Polyphen HDIV	1	0.899	D	Probably damaging
3.	Polyphen HVAR	0.99	0.916	D	Probably damaging
4.	LRT	0	0.843	D	Deleterious
5.	Mutation Taster	1	0.81	D	Disease causing
6.	Mutation assessor	2.51	0.734	M	Medium
7.	FATHMM	-3.55	0.948	D	Deleterious

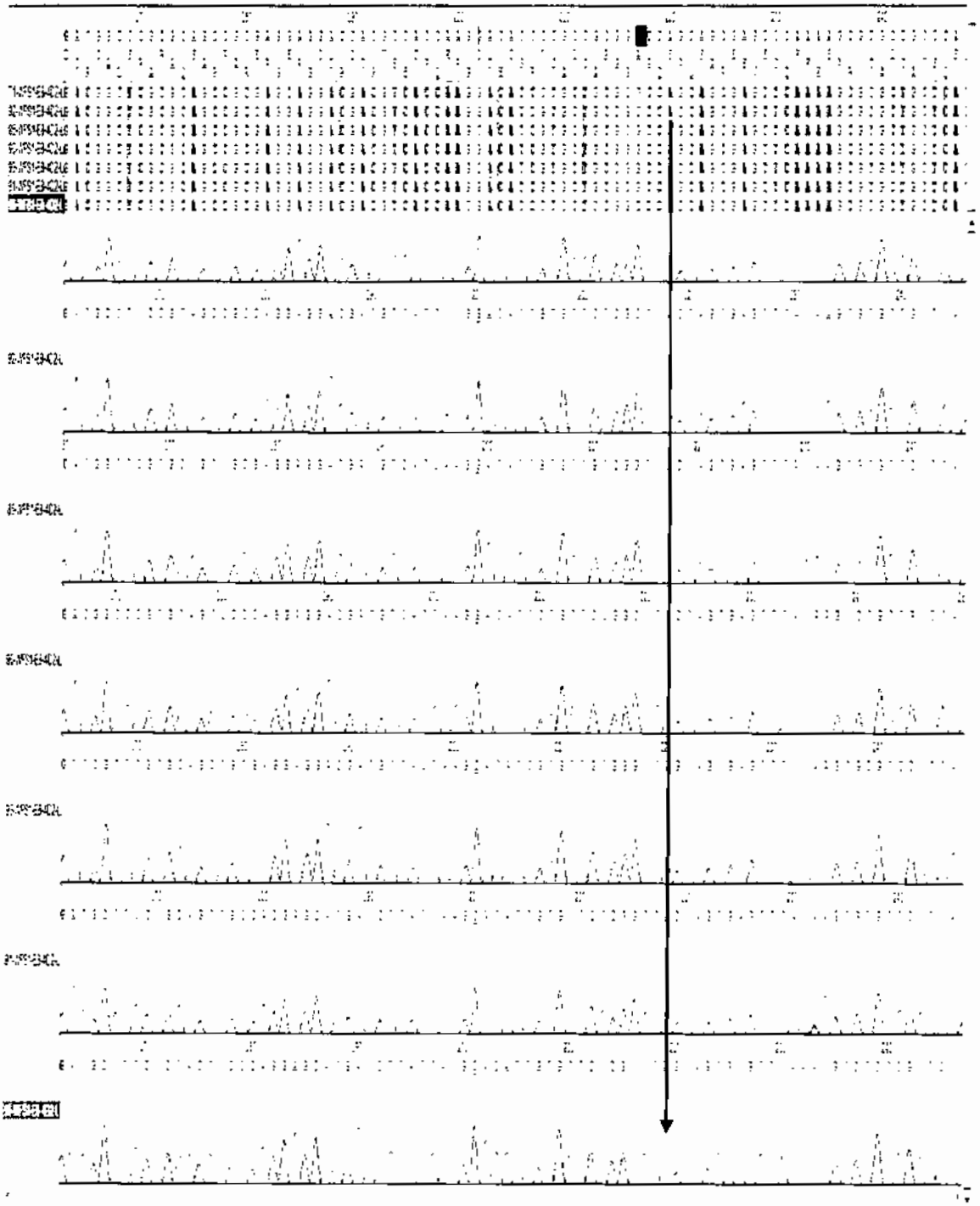


Figure 3-13: Sanger sequencing of homozygous recessive variant c.G2416C:p.A806P in WFS1 gene (patient ID 96). The nucleotide G (black highlighted) changed to C in the last row. The peaks were compared with other samples processed for exon 8 sequencing ofWFS1. The arrow idicating the mutation.

Table 3.15: Summary Card of homozygous recessive variant c.C1037T:p.P346L in WFS1 identified in patient (ID-93)

S.No	Features	Values
1.	Patient ID	93
2.	Gene	*WFS1*
3.	Type of mutation	Missense
4.	Position	chr4:6300832 (GRCh38.p12)
5.	Alleles	C>T
6.	SNP	rs773900146
7.	Frequency:	T=0.00002 (5/251458, GnomAD_exome) T=0.00001 (1/125568, TOPMED) T=0.00002 (2/121406, ExAC) (- 1 less)

Table 3.16: Pathogenicity software predictions for homozygous recessive variant c.C1037T:p.P346L in WFS1 identified in patient (ID-93)

S.No	Softwares	Score	Converted ranked score	Prediction	Interpretation
1.	SIFT	0	0.912	D	Deleterious
2.	Polyphen HDIV	1	0.899	D	Probably damaging
3.	Polyphen HVAR	1	0.971	D	Probably damaging
4.	LRT	0	0.843	D	Deleterious
5.	Mutation Taster	1	0.81	D	Disease Causing
6.	Mutation Assessor	2.85	0.831	M	Medium
7.	FATHMM	-4.02	0.964	D	Deleterious

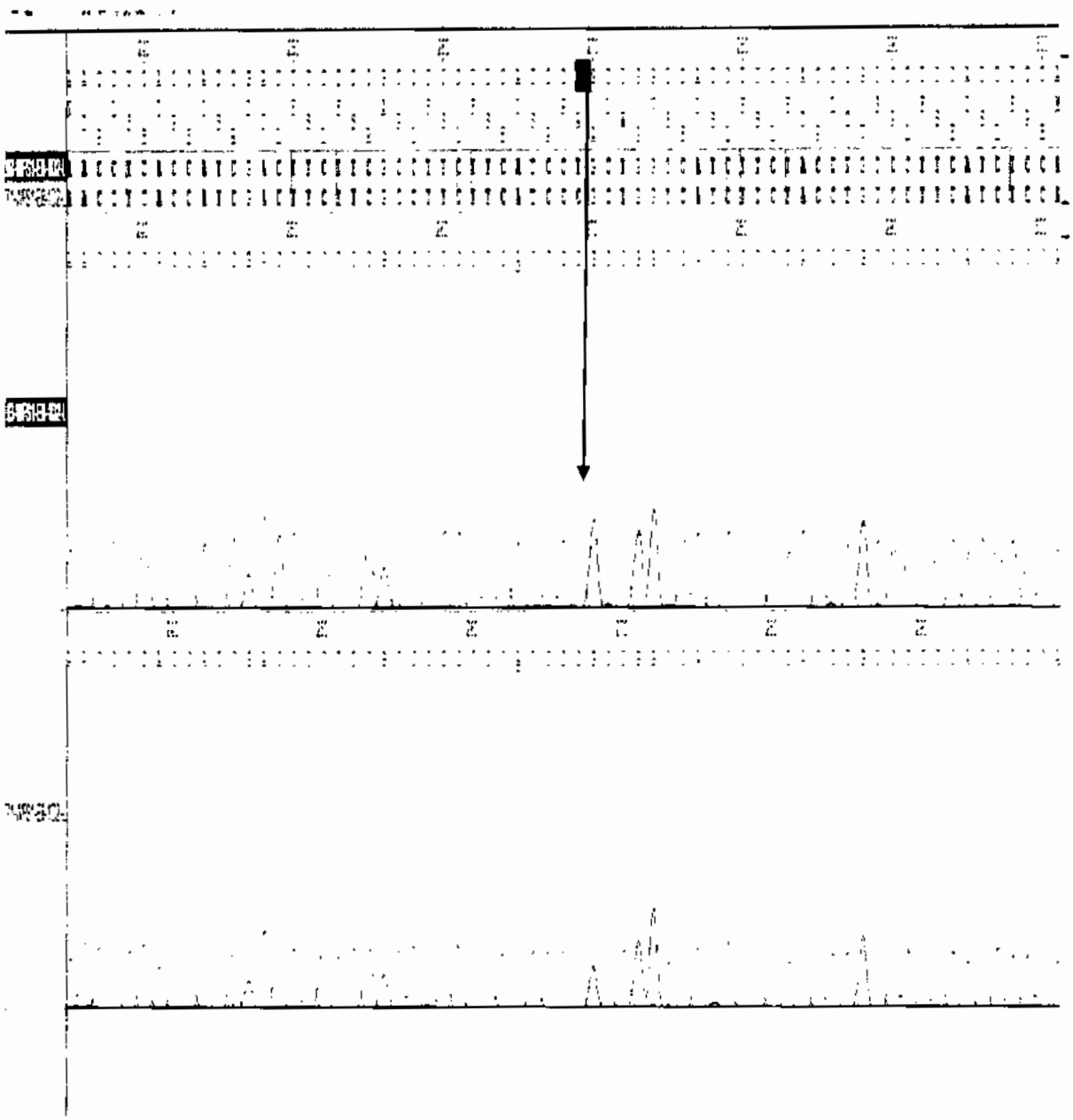


Figure 3-14: Chromatogram of homozygous recessive variant c.C1037T:p.P346L in WFS1 identified in a patient (P-93). The C nucleotide position (highlighted) changed to T and compared with other samples in figure. The arrow indicating the mutation.

Chapter 4

Discussion

4 Discussion

Comprehensive study on Maturity Onset diabetes of the Young (MODY) involving 191 participants from Paksiatn were designed. Clinical tests i.e. HbA1c, C-peptide and GAD-65 were performed for initial screening. Probability calculator was used to generate score and 35 indivdual samples were shortlisted for exome sequencing analysis. Sanger sequencing were performed in eighteen patients for causative variants in *WFS1*gene.

Exome analysis revealed 37 variants for the cause of the disease. Based on frequency and software predictions, 12 heterozygous variants were shortlisted as a pathogenic candidates for disease The five variants were found novel in i.e. *HNF1a* (c.C169A, p.L57M), *HNF1b* (c.C1058T, p.S353L), *ABCC8* (c.G814A, p.A272T), *BLK* (c.G94C, p.D32H), *KLF11* (c.G401C, p.G134A) and one was already reported in *HNF1a* c.526+1G>A.

Six novel variants were found in other than known MODY genes i.e. *RFX6* (c.G919A, p.E307K), *WFS1* (c.G478A, p.E160K), *WFS1* (c.G517A, p.E173K), *RFX6* (c.T1212A, p.H404Q), INSR (c.G3921C, p.M1307I) and *ZBTB20* (c.G1049A, p.R350H).

Sanger sequencing revealed two homozygous recessive variants i.e. (c.G2416C:p.A806P), (C1037T:p.P346L) in the *WFS1* gene. The *WFS1*gene is responsible for causing Wolfram syndrome however the clinical data of the patient is not supporting.

4.1Variants in Known MODY genes

4.1.1 Variants in *HNF1a* gene

The novel missense variant (c.C169A, p.L57M) was found in *HNF1a* gene in patient ID-612. The MODY 3 type was one of the most common forms of MODY and also known as *HNF1a*-MODY (Pavic *et al.*, 2018). The *HNF1a* gene expressed in beta cells of the pancreas and encodes members of transcription regulatory networks during embryonic development of the pancreas (Ferrer, 2002). During adult life, this *HNF1a* gene is expressed in the pancreas, liver, kidney, and gut (Harries *et al.*, 2006). The *HNF1a* binds to 106 genes in islets cells of the pancreas and 222 genes in the liver (Odom *et al.*, 2004). This also regulates the expression of glucose co-transporters which played role in reabsorbing glucose (Pontoglio *et al.*, 2000)

The heterozygous mutations in *HNF1a* genes resulted in the dysfunction of beta cells and progressive hyperglycemia with diabetes that is also associated with diabetic complications in later age (Kyithar *et al.*, 2011; Velho *et al.*, 1996). It has been reported that HDL cholesterol was higher in *HNF1a* patients as compared to normal and type 2 diabetic patients which can be used as a biomarker in the identification of *HNF1a* MODY (McDonald *et al.*, 2012).

The patients with *HNF1a* mutations respond well to a low dose of sulfonylurea (Pearson *et al.*, 2000) therefore it was suggested in the studies to change the treatment pattern from insulin to sulfonylurea (A. Hattersley *et al.*, 2009; Raile *et al.*, 2015). The use of therapy will also result in low rates of complications as reported in the literature with optimum glycaemic control (Bacon *et al.*, 2016). The prevalence of MODY 3 (*HNF1a*) was reported in the literature from 33% to 65% (Moises *et al.*, 2001). The quality of life among MODY 3 patients was significantly less affected as

compared to type 1 diabetic patients while it was more affected when compared to *GCK* MODY type (Szopa *et al.*, 2019). The *HNF1a* mutations have been reported from different countries including Ireland (Kyithar *et al.*, 2011), Turkey (Agladioglu *et al.*, 2016), Croatia (Pavic *et al.*, 2018). In different studies conducted globally, there was a majority of the MODY cases have mutations in the *GCK* gene like in Turkey (Agladioglu *et al.*, 2016). The MODY 3 (*HNF1a*) was more prevalent in Ukraine as compared to *GCK* MODY and other types (Globa *et al.*, 2017). In Tunisia, a study conducted on 23 subjects reported that the majority of the MODY types prevalent globally (*GCK, HN1a, HNF4a*) were not present in the Tunisian population (Ben Khelifa *et al.*, 2018).

The said variant c.C169A, p.L57M in*HNF1a* gene identified in a patient diagnosed with diabetes at 25 years of age having HbA1c 9.2% andBMI 22 kg/m^2 exhibiting the features of MODY 3. This variant was novel and not reported before in the literature.

The second identified variant in *HNF1a* gene is the splice donor variant i.e. c.526+1G>A in patient M6. The patient developed diabetes at the early age of 17 years with 24.6kg/m^2. This variant was already reported in different studies to be involved in the MODY type 3 (Fu *et al.*, 2020; Habeb *et al.*, 2011).

4.1.2 Variant in *KLF11* gene (MODY 7)

One novel variant was identified (c.G401C, p.G134A) in the *KLF11* gene in patient 705. The Kruppel like factor 11 is a transcription factor and negatively regulates the growth of exocrine cells (Neve *et al.*, 2005). These factors belong to the KLF family and their presence range from flies to humans and played role in the regulation of GC promoters (Lomberk *et al.*, 2005). The variants in *KLF11* gene are responsible for MODY 7 (Neve *et al.*, 2005). The *KLF11* is involved in insulin secretion as it was

reported in a study that *KLF11* knockout mice showed low serum insulin level as compared to wild type mice (Bonnefond *et al.*, 2011). In 2005, it was reported as the causative gene for the MODY (Neve *et al.*, 2005). The variants in this gene have been reported from France and Japan in different studies (Lomberk *et al.*, 2013; Ushijima *et al.*, 2019).

4.1.3 Variant in BLK gene

The novel variant identified in *BLK* gene i.e. c.G94C, p.D32H in patient P5. This type is named as MODY 11. The patient having this variant identified was of 24 years, diabetic and regularly taking oral drugs for hyperglycemia. His fasting c-peptide was 0.62ng/ml. This type was also found in a study from Norway (B. B. Johansson *et al.*, 2017), India (Doddabelavangala Mruthyunjaya *et al.*, 2017), Poland (Borowiec *et al.*, 2009), and Russia (Glotov *et al.*, 2019).

4.1.4 Variant in *ABCC8* gene

The novel variant i.e. c.G814A, p.A272T was identified in *ABCC8* gene in patient P9. The type of MODY caused by *ABCC8*is called as MODY 12. A study with bioinformatics assessment showed that patients with *ABBC8* gene exhibits better response to sulphonylurea (Song *et al.*, 2017). The variants were also reported from Turkey (Ozdemir *et al.*, 2018) and in United Kingdom by (Bowman *et al.*, 2012). The south Indian detailed study on 152 clinically diagnosed MODY patients reported that the *ABCC8* gene mutated in these cases at the second-highest number after *HNF1a* (Mohan *et al.*, 2018). Another study from Tunisia also reported three mutations in the *ABCC8* gene in 11 suspected patients for MODY (Dallali *et al.*, 2019). Variants in the *ABCC8* gene in MODY patients were also identified in a study from Brazil (de Santana *et al.*, 2019). The case report mentioned that sulphonylurea and

sodium/glucose co-transporter 2 inhibitors (SGLT2) can be considered as the best option for the treatment of MODY 12 (*ABCC8*) cases (Ovsyannikova *et al.*, 2016).

The *ABCC8* gene encodes the SUR1 (sulphonylurea receptor 1) and a component of the sodium-potassium channel in beta cells of the pancreas. This played a role in linking the cellular metabolism with the electrical activity of the membrane resulted in the secretion of insulin. The mutations in this gene cause the dysfunction inactivity of the sodium-potassium channel (Bowman *et al.*, 2012).

4.1.5 Variant in *HNF1b* gene

The novel variant (c.1136T, pS379L) was identified in the *HNF1b* gene in patient P9. This type was named as MODY 5. The hepatocyte nuclear factor 1 beta being the member of transcription factors played a role development of kidneys, pancreas, bile duct, and liver (Bellanne-Chantelot *et al.*, 2004; Edghill *et al.*, 2006). This MODY 5 type is rare among the MODY types and accounts for almost 2-6% of all diagnosed MODY (Horikawa *et al.*, 2014). This type was generally reported with dysfunction in the kidney like renal cysts (Omura *et al.*, 2019). It has been reported that complications of diabetes, cardiovascular diseases, chronic kidney disease stage 3-4, and end-stage renal diseases were most common among this type of MODY (Dubois-Laforgue *et al.*, 2017). Among all cases of *HNF1b*, around 40-50% of cases were due to mutations in the *HNF1b* gene while others were due to whole gene deletion (Bellanne-Chantelot *et al.*, 2005; Edghill *et al.*, 2008).The mutations in *HNF1b* were reported from Brazil (Dotto *et al.*, 2016; Dotto *et al.*, 2019), Korea (Kim *et al.*, 2014), Turkey (Ozsu *et al.*, 2018), Japan (Nagano *et al.*, 2019) and Greece (E. B. Tatsi *et al.*, 2020). The complications also include hypomagnesemia and coronary calcifications in this type (H. J. Li *et al.*, 2019).

4.2Variants in other than known MODY genes

4.2.1 Variants in RFX6

Two novel missense variants i.e c.G919A, p.E307K, and c.T1212A, p.H404Q were identified in the *RFX6* gene in patients 830 and P68 respectively. The regulatory factor 6 (RFX 6) gene has been reported to be associated with monogenic diabetes (Patel *et al.*, 2017). The RFX6 reported being involved in the development of the endocrine pancreas in humans and mice (Smith *et al.*, 2010; Taleb *et al.*, 2011). In a recessive manner, the *RFX6* caused Mitchell Riley syndrome which resulted in islet cell absence, diarrhea (Mitchell *et al.*, 2004). It has been reported that heterozygous RFX6 variants were associated with MODY in the Finnish population (Patel *et al.*, 2017). The variants from the same gene were reported in a case study from Japan to be involved in diabetes in pregnancy or early-onset diabetes (Akiba *et al.*, 2019). A comprehensive study from India found *RFX6* variants to be found in MODY patients (Mohan *et al.*, 2018). The dipeptidyl peptidase 4 (DPP4) inhibitors were reported to show the best results in treatment in this type of MODY (Artuso *et al.*, 2015).

4.2.2Variant in INSR gene

The novel missense variant c.G3957C, p.M1319I was identified in the *INSR* gene in patient 43614. The Insulin receptor (INSR) is a member of family tyrosine receptor kinases consisting of two subunits i.e. alpha subunit and a beta subunit. Its function is to mediate the action of insulin on target cells. The defect in this gene is responsible for insulin resistance (Seino *et al.*, 1989; Sesti *et al.*, 2001). The homozygous recessive mutations in the INSR gene caused the Donhue syndrome characterized by insulin resistance, coarse facial features, and enlarge genitalia in males while cystic ovaries in females (Qin *et al.*, 2017). This gene was reported to be involved in

diabetes in India (Bodhini *et al.*, 2012) and China (Zhu *et al.*, 2015). This gene had an association with type 2 diabetes in Iran (Khodaeian *et al.*, 2015) and Bangladesh (Parvin *et al.*, 2019).

4.2.3 Variants in the WFS1 gene

The two novel heterozygous variants were identified in the *WFS1* gene i.e. c.G478A, p.E160K, and c.G517A, p.E173K in patient P17. The Wolfram Syndrome (*WFS*) also known as Diabetes inspidus (DI), Diabetes mellitus (DM), Optic atrophy (OA), and deafness (D), collectively called (DIDMOAD). The minimum criteria for this disease were the onset of diabetes at a young age and optic atrophy(Chaussenot *et al.*, 2011). The protein product of this gene is called wolframin(Eiberg *et al.*, 2006). The wolfram syndrome can be caused by both heterozygous dominant and homozygous recessive manner. It has been reported that heterozygous variants in the WFS1 gene were also responsible for this syndrome (Eiberg *et al.*, 2006; Valero *et al.*, 2008)

The WFS1 mutations were reported from in Spanish families(Gomez-Zaera *et al.*, 2001), Italy (Rigoli *et al.*, 2013), French population (Giuliano *et al.*, 2005), Iran (Noorian *et al.*, 2016), United Kingdom (Hardy *et al.*, 1999), Brazil (Gasparin *et al.*, 2009).

4.3Homozygous recessive variants in WFS1gene by Sanger sequencing

In this study, two homozygous recessive variants were found in the *WFS1* gene. A novel variant c.G2416C:p.A806P identified in patient 96 is not available in Clinvar with damaging effect prediction. The second variant i.e. C1037T:p.P346L in the *WFS1* gene in patient 93 is rare and reported in two studies (Chaussenot *et al.*, 2011;

Ganie *et al.*, 2011). The study from Lebanon reported that *WFS1* mutations were found in 5.5% of the case of Juvenile onset diabetes (Zalloua *et al.*, 2008). The cases of Wolfram syndrome have been reported with various degree of severity in symptoms appearance (L. Hansen *et al.*, 2005)

The patient having a novel variant (c.G2416C:p.A806P) was examined by the physician and the clinical features were not indicative of Wolfram syndrome.

4.4 Conclusions

The current study identified a wide spectrum of genetic variants causing MODY in Pakistan. Globally prevalence of MODY genes in developed countries is not common in Pakistan. *WFS1* variants found in the study suggest the possibility of the gene involved in the early onset of diabetes in Pakistani patients.

4.5 Recommendations

Large-scale genetic studies on young adult diabetics need to be conducted in the Pakistani Population to identify the unknown gene variants involved in MODY. New variant detection will provide an insight into disease diagnosis and will help in the management of the disease. The diagnosis of the MODY is very important for appropriate and accurate treatment. The proper and timely diagnosis will ultimately improve the quality of life in diabetic patients.

Chapter 5

References

5 References

Abreu, D., & Urano, F. (2019). Current Landscape of Treatments for Wolfram Syndrome. *Trends Pharmacol Sci, 40*(10), 711-714. doi: 10.1016/j.tips.2019.07.011

Agladioglu, S. Y., Aycan, Z., Cetinkaya, S., Bas, V. N., Onder, A., Peltek Kendirci, H. N., . . . Ceylaner, S. (2016). Maturity onset diabetes of youth (MODY) in Turkish children: sequence analysis of 11 causative genes by next-generation sequencing. *J Pediatr Endocrinol Metab, 29*(4), 487-496. doi: 10.1515/jpem-2015-0039

Akiba, K., Ushijima, K., Fukami, M., & Hasegawa, Y. (2019). A heterozygous protein-truncating RFX6 variant in a family with childhood-onset, pregnancy-associated, and adult-onset diabetes. *Diabet Med*. doi: 10.1111/dme.13970

Al-Sheyab, F., Khamaiseh, E., Halaweh, M. A., & Khaul, R. W. (2009). Characterization of glucokinase polymorphisms associated with maturity-onset diabetes of the young (MODY2) in the Jordanian population. *Tsitol Genet, 43*(5), 58-63.

Amed, S., Dean, H. J., Panagiotopoulos, C., Sellers, E. A., Hadjiyannakis, S., Laubscher, T. A., . . . Hamilton, J. K. (2010). Type 2 diabetes, medication-induced diabetes, and monogenic diabetes in Canadian children: a prospective national surveillance study. *Diabetes Care, 33*(4), 786-791. doi: 10.2337/dc09-1013

Artuso, R., Provenzano, A., Mazzinghi, B., Giunti, L., Palazzo, V., Andreucci, E., . . . Giglio, S. (2015). Therapeutic implications of novel mutations of the RFX6 gene associated with early-onset diabetes. *Pharmacogenomics J, 15*(1), 49-54. doi: 10.1038/tpj.2014.37

Bacon, S., Kyithar, M. P., Rizvi, S. R., Donnelly, E., McCarthy, A., Burke, M., . . . Byrne, M. M. (2016). Successful maintenance on sulphonylurea therapy and low diabetes complication rates in a HNF1A-MODY cohort. *Diabet Med, 33*(7), 976-984. doi: 10.1111/dme.12992

Barrett, T. G., Bundey, S. E., & Macleod, A. F. (1995). Neurodegeneration and diabetes: UK nationwide study of Wolfram (DIDMOAD) syndrome. *Lancet, 346*(8988), 1458-1463. doi: 10.1016/s0140-6736(95)92473-6

Basit, A., Fawwad, A., Qureshi, H., & Shera, A. S. (2018). Prevalence of diabetes, pre-diabetes and associated risk factors: second National Diabetes Survey of Pakistan (NDSP), 2016-2017. *BMJ Open, 8*(8), e020961. doi: 10.1136/bmjopen-2017-020961

Bellanne-Chantelot, C., Chauveau, D., Gautier, J. F., Dubois-Laforgue, D., Clauin, S., Beaufils, S., . . . Timsit, J. (2004). Clinical spectrum associated with hepatocyte nuclear factor-1beta mutations. *Ann Intern Med, 140*(7), 510-517. doi: 10.7326/0003-4819-140-7-200404060-00009

Bellanne-Chantelot, C., Clauin, S., Chauveau, D., Collin, P., Daumont, M., Douillard, C., . . . Timsit, J. (2005). Large genomic rearrangements in the hepatocyte nuclear factor-1beta (TCF2) gene are the most frequent cause of maturity-onset diabetes of the young type 5. *Diabetes, 54*(11), 3126-3132. doi: 10.2337/diabetes.54.11.3126

Ben Khelifa, S., Martinez, R., Dandana, A., Khochtali, I., Ferchichi, S., & Castano, L. (2018). Maturity Onset Diabetes of the Young (MODY) in Tunisia: Low frequencies of GCK and HNF1A mutations. *Gene, 651*, 44-48. doi: 10.1016/j.gene.2018.01.081

Bennett, J. T., Vasta, V., Zhang, M., Narayanan, J., Gerrits, P., & Hahn, S. H. (2015). Molecular genetic testing of patients with monogenic diabetes and hyperinsulinism. *Mol Genet Metab, 114*(3), 451-458. doi: 10.1016/j.ymgme.2014.12.304

Biason-Lauber, A., Boehm, B., Lang-Muritano, M., Gauthier, B. R., Brun, T., Wollheim, C. B., & Schoenle, E. J. (2005). Association of childhood type 1 diabetes mellitus with a variant of PAX4: possible link to beta cell regenerative capacity. *Diabetologia, 48*(5), 900-905. doi: 10.1007/s00125-005-1723-5

Bodhini, D., Sandhiya, M., Ghosh, S., Majumder, P. P., Rao, M. R., Mohan, V., & Radha, V. (2012). Association of His1085His INSR gene polymorphism with type 2 diabetes in South Indians. *Diabetes Technol Ther, 14*(8), 696-700. doi: 10.1089/dia.2012.0009

Bonnefond, A., Lomberk, G., Buttar, N., Busiah, K., Vaillant, E., Lobbens, S., . . . Urrutia, R. (2011). Disruption of a novel Kruppel-like transcription factor p300-regulated pathway for insulin biosynthesis revealed by studies of the c.-331 INS mutation found in neonatal diabetes mellitus. *J Biol Chem, 286*(32), 28414-28424. doi: 10.1074/jbc.M110.215822

Borowiec, M., Liew, C. W., Thompson, R., Boonyasrisawat, W., Hu, J., Mlynarski, W. M., . . . Doria, A. (2009). Mutations at the BLK locus linked to maturity onset diabetes of the young and beta-cell dysfunction. *Proc Natl Acad Sci U S A, 106*(34), 14460-14465. doi: 10.1073/pnas.0906474106

Bowman, P., Flanagan, S. E., Edghill, E. L., Damhuis, A., Shepherd, M. H., Paisey, R., . . . Ellard, S. (2012). Heterozygous ABCC8 mutations are a cause of MODY. *Diabetologia, 55*(1), 123-127. doi: 10.1007/s00125-011-2319-x

Chaussenot, A., Bannwarth, S., Rouzier, C., Vialettes, B., Mkadem, S. A., Chabrol, B., . . . Paquis-Flucklinger, V. (2011). Neurologic features and genotype-phenotype correlation in Wolfram syndrome. *Ann Neurol, 69*(3), 501-508. doi: 10.1002/ana.22160

Codner, E., Rocha, A., Deng, L., Martinez-Aguayo, A., Godoy, C., Mericq, V., & Chung, W. K. (2009). Mild fasting hyperglycemia in children: high rate of glucokinase mutations and some risk of developing type 1 diabetes mellitus. *Pediatr Diabetes, 10*(6), 382-388. doi: 10.1111/j.1399-5448.2009.00499.x

Couper, J., & Donaghue, K. C. (2009). Phases of diabetes in children and adolescents. *Pediatr Diabetes, 10 Suppl 12*, 13-16. doi: 10.1111/j.1399-5448.2009.00574.x

Craig, M. E., Hattersley, A., & Donaghue, K. C. (2009). Definition, epidemiology and classification of diabetes in children and adolescents. *Pediatr Diabetes, 10 Suppl 12*, 3-12. doi: 10.1111/j.1399-5448.2009.00568.x

Dabelea, D., Mayer-Davis, E. J., Saydah, S., Imperatore, G., Linder, B., Divers, J., . . . Hamman, R. F. (2014). Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. *JAMA, 311*(17), 1778-1786. doi: 10.1001/jama.2014.3201

Dallali, H., Pezzilli, S., Hechmi, M., Sallem, O. K., Elouej, S., Jmel, H., . . . Kefi, R. (2019). Genetic characterization of suspected MODY patients in Tunisia by targeted next-generation sequencing. *Acta Diabetol, 56*(5), 515-523. doi: 10.1007/s00592-018-01283-5

Dandona, P., Aljada, A., Mohanty, P., Ghanim, H., Hamouda, W., Assian, E., & Ahmad, S. (2001). Insulin inhibits intranuclear nuclear factor kappaB and stimulates IkappaB in mononuclear cells in obese subjects: evidence for an

anti-inflammatory effect? *J Clin Endocrinol Metab, 86*(7), 3257-3265. doi: 10.1210/jcem.86.7.7623

de Heredia, M. L., Cleries, R., & Nunes, V. (2013). Genotypic classification of patients with Wolfram syndrome: insights into the natural history of the disease and correlation with phenotype. *Genet Med, 15*(7), 497-506. doi: 10.1038/gim.2012.180

de Santana, L. S., Caetano, L. A., Costa-Riquetto, A. D., Franco, P. C., Dotto, R. P., Reis, A. F., . . . Teles, M. G. (2019). Targeted sequencing identifies novel variants in common and rare MODY genes. *Mol Genet Genomic Med, 7*(12), e962. doi: 10.1002/mgg3.962

Devendra, D., Liu, E., & Eisenbarth, G. S. (2004). Type 1 diabetes: recent developments. *BMJ, 328*(7442), 750-754. doi: 10.1136/bmj.328.7442.750

Doddabelavangala Mruthyunjaya, M., Chapla, A., Hesarghatta Shyamasunder, A., Varghese, D., Varshney, M., Paul, J., . . . Thomas, N. (2017). Comprehensive Maturity Onset Diabetes of the Young (MODY) Gene Screening in Pregnant Women with Diabetes in India. *PLoS One, 12*(1), e0168656. doi: 10.1371/journal.pone.0168656

Dotto, R. P., Giuffrida, F. M., Franco, L., Mathez, A. L., Weinert, L. S., Silveiro, S. P., . . . Dias-da-Silva, M. R. (2016). Unexpected finding of a whole HNF1B gene deletion during the screening of rare MODY types in a series of Brazilian patients negative for GCK and HNF1A mutations. *Diabetes Res Clin Pract, 116*, 100-104. doi: 10.1016/j.diabres.2016.04.035

Dotto, R. P., Santana, L. S., Lindsey, S. C., Caetano, L. A., Franco, L. F., Moises, Rcms, . . . Reis, A. F. (2019). Searching for mutations in the HNF1B gene in a

Brazilian cohort with renal cysts and hyperglycemia. *Arch Endocrinol Metab, 63*(3), 250-257. doi: 10.20945/2359-3997000000138

Dubois-Laforgue, D., Cornu, E., Saint-Martin, C., Coste, J., Bellanne-Chantelot, C., Timsit, J., & Monogenic Diabetes Study Group of the Societe Francophone du, Diabete. (2017). Diabetes, Associated Clinical Spectrum, Long-term Prognosis, and Genotype/Phenotype Correlations in 201 Adult Patients With Hepatocyte Nuclear Factor 1B (HNF1B) Molecular Defects. *Diabetes Care, 40*(11), 1436-1443. doi: 10.2337/dc16-2462

Dukes, I. D., Sreenan, S., Roe, M. W., Levisetti, M., Zhou, Y. P., Ostrega, D., . . . Polonsky, K. S. (1998). Defective pancreatic beta-cell glycolytic signaling in hepatocyte nuclear factor-1alpha-deficient mice. *J Biol Chem, 273*(38), 24457-24464. doi: 10.1074/jbc.273.38.24457

Edghill, E. L., Bingham, C., Ellard, S., & Hattersley, A. T. (2006). Mutations in hepatocyte nuclear factor-1beta and their related phenotypes. *J Med Genet, 43*(1), 84-90. doi: 10.1136/jmg.2005.032854

Edghill, E. L., Bingham, C., Slingerland, A. S., Minton, J. A., Noordam, C., Ellard, S., & Hattersley, A. T. (2006). Hepatocyte nuclear factor-1 beta mutations cause neonatal diabetes and intrauterine growth retardation: support for a critical role of HNF-1beta in human pancreatic development. *Diabet Med, 23*(12), 1301-1306. doi: 10.1111/j.1464-5491.2006.01999.x

Edghill, E. L., Oram, R. A., Owens, M., Stals, K. L., Harries, L. W., Hattersley, A. T., . . . Bingham, C. (2008). Hepatocyte nuclear factor-1beta gene deletions--a common cause of renal disease. *Nephrol Dial Transplant, 23*(2), 627-635. doi: 10.1093/ndt/gfm603

Eiberg, H., Hansen, L., Kjer, B., Hansen, T., Pedersen, O., Bille, M., . . . Tranebjaerg, L. (2006). Autosomal dominant optic atrophy associated with hearing impairment and impaired glucose regulation caused by a missense mutation in the WFS1 gene. *J Med Genet, 43*(5), 435-440. doi: 10.1136/jmg.2005.034892

Estalella, I., Rica, I., Perez de Nanclares, G., Bilbao, J. R., Vazquez, J. A., San Pedro, J. I., . . . Castano, L. (2007). Mutations in GCK and HNF-1alpha explain the majority of cases with clinical diagnosis of MODY in Spain. *Clin Endocrinol (Oxf), 67*(4), 538-546. doi: 10.1111/j.1365-2265.2007.02921.x

Fajans, S. S., & Brown, M. B. (1993). Administration of sulfonylureas can increase glucose-induced insulin secretion for decades in patients with maturity-onset diabetes of the young. *Diabetes Care, 16*(9), 1254-1261. doi: 10.2337/diacare.16.9.1254

Feigerlova, E., Pruhova, S., Dittertova, L., Lebl, J., Pinterova, D., Kolostova, K., . . . Hansen, T. (2006). Aetiological heterogeneity of asymptomatic hyperglycaemia in children and adolescents. *Eur J Pediatr, 165*(7), 446-452. doi: 10.1007/s00431-006-0106-3

Ferrer, J. (2002). A genetic switch in pancreatic beta-cells: implications for differentiation and haploinsufficiency. *Diabetes, 51*(8), 2355-2362. doi: 10.2337/diabetes.51.8.2355

Firdous, P., Nissar, K., Ali, S., Ganai, B. A., Shabir, U., Hassan, T., & Masoodi, S. R. (2018). Genetic Testing of Maturity-Onset Diabetes of the Young Current Status and Future Perspectives. *Front Endocrinol (Lausanne), 9*, 253. doi: 10.3389/fendo.2018.00253

Fonseca, S. G., Ishigaki, S., Oslowski, C. M., Lu, S., Lipson, K. L., Ghosh, R., . . . Urano, F. (2010). Wolfram syndrome 1 gene negatively regulates ER stress

signaling in rodent and human cells. *J Clin Invest, 120*(3), 744-755. doi: 10.1172/JCI39678

Fu, J., Wang, T., Zhai, X., & Xiao, X. (2020). Primary hepatocellular adenoma due to biallelic HNF1A mutations and its co-occurrence with MODY 3: case-report and review of the literature. *Endocrine, 67*(3), 544-551. doi: 10.1007/s12020-019-02138-x

Ganie, M. A., Laway, B. A., Nisar, S., Wani, M. M., Khurana, M. L., Ahmad, F., . . . Tufail, S. (2011). Presentation and clinical course of Wolfram (DIDMOAD) syndrome from North India. *Diabet Med, 28*(11), 1337-1342. doi: 10.1111/j.1464-5491.2011.03377.x

Gasparin, M. R., Crispim, F., Paula, S. L., Freire, M. B., Dalbosco, I. S., Manna, T. D., . . . Moises, R. S. (2009). Identification of novel mutations of the WFS1 gene in Brazilian patients with Wolfram syndrome. *Eur J Endocrinol, 160*(2), 309-316. doi: 10.1530/EJE-08-0698

Giuliano, F., Bannwarth, S., Monnot, S., Cano, A., Chabrol, B., Vialettes, B., . . . French Group of, W. S. (2005). Wolfram syndrome in French population: characterization of novel mutations and polymorphisms in the WFS1 gene. *Hum Mutat, 25*(1), 99-100. doi: 10.1002/humu.9300

Globa, E., Zelinska, N., Elblova, L., Dusatkova, P., Cinek, O., Lebl, J., . . . Pruhova, S. (2017). MODY in Ukraine: genes, clinical phenotypes and treatment. *J Pediatr Endocrinol Metab, 30*(10), 1095-1103. doi: 10.1515/jpem-2017-0075

. Global Report on Diabetes. (2016): World Health Organization.

Glotov, O. S., Serebryakova, E. A., Turkunova, M. E., Efimova, O. A., Glotov, A. S., Barbitoff, Y. A., . . . Baranov, V. S. (2019). Wholeexome sequencing in Russian children with nontype 1 diabetes mellitus reveals a wide spectrum of

genetic variants in MODYrelated and unrelated genes. *Mol Med Rep, 20*(6), 4905-4914. doi: 10.3892/mmr.2019.10751

Gomez-Zaera, M., Strom, T. M., Rodriguez, B., Estivill, X., Meitinger, T., & Nunes, V. (2001). Presence of a major WFS1 mutation in Spanish Wolfram syndrome pedigrees. *Mol Genet Metab, 72*(1), 72-81. doi: 10.1006/mgme.2000.3107

Gragnoli, C., Stanojevic, V., Gorini, A., Von Preussenthal, G. M., Thomas, M. K., & Habener, J. F. (2005). IPF-1/MODY4 gene missense mutation in an Italian family with type 2 and gestational diabetes. *Metabolism, 54*(8), 983-988. doi: 10.1016/j.metabol.2005.01.037

Habeb, A. M., George, E. T., Mathew, V., & Hattersley, A. L. (2011). Response to oral gliclazide in a pre-pubertal child with hepatic nuclear factor-1 alpha maturity onset diabetes of the young. *Ann Saudi Med, 31*(2), 190-193. doi: 10.4103/0256-4947.75590

Hagenfeldt-Johansson, K. A., Herrera, P. L., Wang, H., Gjinovci, A., Ishihara, H., & Wollheim, C. B. (2001). Beta-cell-targeted expression of a dominant-negative hepatocyte nuclear factor-1 alpha induces a maturity-onset diabetes of the young (MODY)3-like phenotype in transgenic mice. *Endocrinology, 142*(12), 5311-5320. doi: 10.1210/endo.142.12.8592

Halban, P. A., Polonsky, K. S., Bowden, D. W., Hawkins, M. A., Ling, C., Mather, K. J., . . . Weir, G. C. (2014). beta-cell failure in type 2 diabetes: postulated mechanisms and prospects for prevention and treatment. *Diabetes Care, 37*(6), 1751-1758. doi: 10.2337/dc14-0396

Hansen, L., Eiberg, H., Barrett, T., Bek, T., Kjaersgaard, P., Tranebjaerg, L., & Rosenberg, T. (2005). Mutation analysis of the WFS1 gene in seven Danish

Wolfram syndrome families; four new mutations identified. *Eur J Hum Genet, 13*(12), 1275-1284. doi: 10.1038/sj.ejhg.5201491

Hardy, C., Khanim, F., Torres, R., Scott-Brown, M., Seller, A., Poulton, J., . . . Barrett, T. (1999). Clinical and molecular genetic analysis of 19 Wolfram syndrome kindreds demonstrating a wide spectrum of mutations in WFS1. *Am J Hum Genet, 65*(5), 1279-1290. doi: 10.1086/302609

Harries, L. W., Ellard, S., Stride, A., Morgan, N. G., & Hattersley, A. T. (2006). Isomers of the TCF1 gene encoding hepatocyte nuclear factor-1 alpha show differential expression in the pancreas and define the relationship between mutation position and clinical phenotype in monogenic diabetes. *Hum Mol Genet, 15*(14), 2216-2224. doi: 10.1093/hmg/ddl147

Hattersley, A., Bruining, J., Shield, J., Njolstad, P., & Donaghue, K. C. (2009). The diagnosis and management of monogenic diabetes in children and adolescents. *Pediatr Diabetes, 10 Suppl 12*, 33-42. doi: 10.1111/j.1399-5448.2009.00571.x

Hattersley, A. T., Beards, F., Ballantyne, E., Appleton, M., Harvey, R., & Ellard, S. (1998). Mutations in the glucokinase gene of the fetus result in reduced birth weight. *Nat Genet, 19*(3), 268-270. doi: 10.1038/953

Hattersley, A. T., Greeley, S. A. W., Polak, M., Rubio-Cabezas, O., Njolstad, P. R., Mlynarski, W., . . . Craig, M. E. (2018). ISPAD Clinical Practice Consensus Guidelines 2018: The diagnosis and management of monogenic diabetes in children and adolescents. *Pediatr Diabetes, 19 Suppl 27*, 47-63. doi: 10.1111/pedi.12772

Horikawa, Y., Enya, M., Fushimi, N., Fushimi, Y., & Takeda, J. (2014). Screening of diabetes of youth for hepatocyte nuclear factor 1 mutations: clinical phenotype of HNF1beta-related maturity-onset diabetes of the young and HNF1alpha-

related maturity-onset diabetes of the young in Japanese. *Diabet Med, 31*(6), 721-727. doi: 10.1111/dme.12416

Hui, D. Y., & Howles, P. N. (2002). Carboxyl ester lipase: structure-function relationship and physiological role in lipoprotein metabolism and atherosclerosis. *J Lipid Res, 43*(12), 2017-2030. doi: 10.1194/jlr.r200013-jlr200

Inoue, H., Tanizawa, Y., Wasson, J., Behn, P., Kalidas, K., Bernal-Mizrachi, E., . . . Permutt, M. A. (1998). A gene encoding a transmembrane protein is mutated in patients with diabetes mellitus and optic atrophy (Wolfram syndrome). *Nat Genet, 20*(2), 143-148. doi: 10.1038/2441

Isomaa, B., Henricsson, M., Lehto, M., Forsblom, C., Karanko, S., Sarelin, L., . . . Groop, L. (1998). Chronic diabetic complications in patients with MODY3 diabetes. *Diabetologia, 41*(4), 467-473. doi: 10.1007/s001250050931

Ivarsson, S. A., & Lernmark, A. (2008). Comment on: Edghill et al. (2008) Insulin mutation screening in 1,044 patients with diabetes: mutations in the INS gene are a common cause of neonatal diabetes but a rare cause of diabetes diagnosed in childhood or adulthood: Diabetes 57:1034-1042, 2008. *Diabetes, 57*(5), e9. doi: 10.2337/db08-0091

Johansson, B. B., Irgens, H. U., Molnes, J., Sztromwasser, P., Aukrust, I., Juliusson, P. B., . . . Njolstad, P. R. (2017). Targeted next-generation sequencing reveals MODY in up to 6.5% of antibody-negative diabetes cases listed in the Norwegian Childhood Diabetes Registry. *Diabetologia, 60*(4), 625-635. doi: 10.1007/s00125-016-4167-1

Johansson, S., Irgens, H., Chudasama, K. K., Molnes, J., Aerts, J., Roque, F. S., . . . Njolstad, P. R. (2012). Exome sequencing and genetic testing for MODY. *PLoS One, 7*(5), e38050. doi: 10.1371/journal.pone.0038050

Johnson, S. R., Leo, P. J., McInerney-Leo, A. M., Anderson, L. K., Marshall, M., McGown, I., . . . Duncan, E. L. (2018). Whole-exome sequencing for mutation detection in pediatric disorders of insulin secretion: Maturity onset diabetes of the young and congenital hyperinsulinism. *Pediatr Diabetes, 19*(4), 656-662. doi: 10.1111/pedi.12638

Katsarou, A., Gudbjornsdottir, S., Rawshani, A., Dabelea, D., Bonifacio, E., Anderson, B. J., . . . Lernmark, A. (2017). Type 1 diabetes mellitus. *Nat Rev Dis Primers, 3*, 17016. doi: 10.1038/nrdp.2017.16

Kavvoura, F. K., & Owen, K. R. (2012). Maturity onset diabetes of the young: clinical characteristics, diagnosis and management. *Pediatr Endocrinol Rev, 10*(2), 234-242.

Kawasaki, E. (2014). Type 1 diabetes and autoimmunity. *Clin Pediatr Endocrinol, 23*(4), 99-105. doi: 10.1297/cpe.23.99

Khalil, R., Al-Sheyab, F., Khamaiseh, E., Halaweh, M. A., & Abder-Rahman, H. A. (2009). Screening of mutations in the GCK gene in Jordanian maturity-onset diabetes of the young type 2 (MODY2) patients. *Genet Mol Res, 8*(2), 500-506. doi: 10.4238/vol8-2gmr597

Kharroubi, A. T., & Darwish, H. M. (2015). Diabetes mellitus: The epidemic of the century. *World J Diabetes, 6*(6), 850-867. doi: 10.4239/wjd.v6.i6.850

Khodaeian, M., Enayati, S., Tabatabaei-Malazy, O., & Amoli, M. M. (2015). Association between Genetic Variants and Diabetes Mellitus in Iranian

Populations: A Systematic Review of Observational Studies. *J Diabetes Res, 2015*, 585917. doi: 10.1155/2015/585917

Kim, E. K., Lee, J. S., Cheong, H. I., Chung, S. S., Kwak, S. H., & Park, K. S. (2014). Identification and Functional Characterization of P159L Mutation in HNF1B in a Family with Maturity-Onset Diabetes of the Young 5 (MODY5). *Genomics Inform, 12*(4), 240-246. doi: 10.5808/GI.2014.12.4.240

Kraemer, F. B., & Ginsberg, H. N. (2014). Gerald M. Reaven, MD: Demonstration of the central role of insulin resistance in type 2 diabetes and cardiovascular disease. *Diabetes Care, 37*(5), 1178-1181. doi: 10.2337/dc13-2668

Kyithar, M. P., Bacon, S., Pannu, K. K., Rizvi, S. R., Colclough, K., Ellard, S., & Byrne, M. M. (2011). Identification of HNF1A-MODY and HNF4A-MODY in Irish families: phenotypic characteristics and therapeutic implications. *Diabetes Metab, 37*(6), 512-519. doi: 10.1016/j.diabet.2011.04.002

Lehto, M., Bitzen, P. O., Isomaa, B., Wipemo, C., Wessman, Y., Forsblom, C., . . . Groop, L. (1999). Mutation in the HNF-4alpha gene affects insulin secretion and triglyceride metabolism. *Diabetes, 48*(2), 423-425. doi: 10.2337/diabetes.48.2.423

Li, H. J., Groden, C., Hoenig, M. P., Ray, E. C., Ferreira, C. R., Gahl, W., & Novacic, D. (2019). Case report: extreme coronary calcifications and hypomagnesemia in a patient with a 17q12 deletion involving HNF1B. *BMC Nephrol, 20*(1), 353. doi: 10.1186/s12882-019-1533-5

Liu, L., Nagashima, K., Yasuda, T., Liu, Y., Hu, H. R., He, G., . . . Xiang, K. (2013). Mutations in KCNJ11 are associated with the development of autosomal dominant, early-onset type 2 diabetes. *Diabetologia, 56*(12), 2609-2618. doi: 10.1007/s00125-013-3031-9

Lomberk, G., Grzenda, A., Mathison, A., Escande, C., Zhang, J. S., Calvo, E., . . . Urrutia, R. (2013). Kruppel-like factor 11 regulates the expression of metabolic genes via an evolutionarily conserved protein interaction domain functionally disrupted in maturity onset diabetes of the young. *J Biol Chem, 288*(24), 17745-17758. doi: 10.1074/jbc.M112.434670

Lomberk, G., & Urrutia, R. (2005). The family feud: turning off Sp1 by Sp1-like KLF proteins. *Biochem J, 392*(Pt 1), 1-11. doi: 10.1042/BJ20051234

Massa, O., Iafusco, D., D'Amato, E., Gloyn, A. L., Hattersley, A. T., Pasquino, B., . . . Barbetti, F. (2005). KCNJ11 activating mutations in Italian patients with permanent neonatal diabetes. *Hum Mutat, 25*(1), 22-27. doi: 10.1002/humu.20124

McDonald, T. J., & Ellard, S. (2013). Maturity onset diabetes of the young: identification and diagnosis. *Ann Clin Biochem, 50*(Pt 5), 403-415. doi: 10.1177/0004563213483458

McDonald, T. J., McEneny, J., Pearson, E. R., Thanabalasingham, G., Szopa, M., Shields, B. M., . . . Young, I. S. (2012). Lipoprotein composition in HNF1A-MODY: differentiating between HNF1A-MODY and type 2 diabetes. *Clin Chim Acta, 413*(9-10), 927-932. doi: 10.1016/j.cca.2012.02.005

Metzger, B. E., Lowe, L. P., Dyer, A. R., Trimble, E. R., Chaovarindr, U., Coustan, D. R., . . . Sacks, D. A. (2008). Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med, 358*(19), 1991-2002. doi: 10.1056/NEJMoa0707943

Mishra, G. D., McNaughton, S. A., Ball, K., Brown, W. J., Giles, G. G., & Dobson, A. J. (2010). Major dietary patterns of young and middle aged women: results from a prospective Australian cohort study. *Eur J Clin Nutr, 64*(10), 1125-1133. doi: 10.1038/ejcn.2010.121

Mitchell, J., Punthakee, Z., Lo, B., Bernard, C., Chong, K., Newman, C., . . . Polychronakos, C. (2004). Neonatal diabetes, with hypoplastic pancreas, intestinal atresia and gall bladder hypoplasia: search for the aetiology of a new autosomal recessive syndrome. *Diabetologia, 47*(12), 2160-2167. doi: 10.1007/s00125-004-1576-3

Mohan, V., Radha, V., Nguyen, T. T., Stawiski, E. W., Pahuja, K. B., Goldstein, L. D., . . . Peterson, A. S. (2018). Comprehensive genomic analysis identifies pathogenic variants in maturity-onset diabetes of the young (MODY) patients in South India. *BMC Med Genet, 19*(1), 22. doi: 10.1186/s12881-018-0528-6

Mohan, V., Ramachandran, A., Snehalatha, C., Mohan, R., Bharani, G., & Viswanathan, M. (1985). High prevalence of maturity-onset diabetes of the young (MODY) among Indians. *Diabetes Care, 8*(4), 371-374. doi: 10.2337/diacare.8.4.371

Moises, R. S., Reis, A. F., Morel, V., Chacra, A. R., Dib, S. A., Bellanne-Chantelot, C., & Velho, G. (2001). Prevalence of maturity-onset diabetes of the young mutations in Brazilian families with autosomal-dominant early-onset type 2 diabetes. *Diabetes Care, 24*(4), 786-788. doi: 10.2337/diacare.24.4.786

Nagano, C., Morisada, N., Nozu, K., Kamei, K., Tanaka, R., Kanda, S., . . . Iijima, K. (2019). Clinical characteristics of HNF1B-related disorders in a Japanese population. *Clin Exp Nephrol, 23*(9), 1119-1129. doi: 10.1007/s10157-019-01747-0

Naya, F. J., Huang, H. P., Qiu, Y., Mutoh, H., DeMayo, F. J., Leiter, A. B., & Tsai, M. J. (1997). Diabetes, defective pancreatic morphogenesis, and abnormal enteroendocrine differentiation in BETA2/neuroD-deficient mice. *Genes Dev, 11*(18), 2323-2334. doi: 10.1101/gad.11.18.2323

Neve, B., Fernandez-Zapico, M. E., Ashkenazi-Katalan, V., Dina, C., Hamid, Y. H., Joly, E., . . . Froguel, P. (2005). Role of transcription factor KLF11 and its diabetes-associated gene variants in pancreatic beta cell function. *Proc Natl Acad Sci U S A, 102*(13), 4807-4812. doi: 10.1073/pnas.0409177102

Noorian, S., Savad, S., & Mohammadi, D. S. (2016). A novel nonsense mutation in the WFS1 gene causes the Wolfram syndrome. *J Pediatr Endocrinol Metab, 29*(5), 607-609. doi: 10.1515/jpem-2015-0045

Odom, D. T., Zizlsperger, N., Gordon, D. B., Bell, G. W., Rinaldi, N. J., Murray, H. L., . . . Young, R. A. (2004). Control of pancreas and liver gene expression by HNF transcription factors. *Science, 303*(5662), 1378-1381. doi: 10.1126/science.1089769

Ogurtsova, K., da Rocha Fernandes, J. D., Huang, Y., Linnenkamp, U., Guariguata, L., Cho, N. H., . . . Makaroff, L. E. (2017). IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Res Clin Pract, 128*, 40-50. doi: 10.1016/j.diabres.2017.03.024

Omura, Y., Yagi, K., Honoki, H., Iwata, M., Enkaku, A., Takikawa, A., . . . Tobe, K. (2019). Clinical manifestations of a sporadic maturity-onset diabetes of the young (MODY) 5 with a whole deletion of HNF1B based on 17q12 microdeletion. *Endocr J, 66*(12), 1113-1116. doi: 10.1507/endocrj.EJ19-0020

Ostoft, S. H., Bagger, J. I., Hansen, T., Pedersen, O., Faber, J., Holst, J. J., . . . Vilsboll, T. (2014). Glucose-lowering effects and low risk of hypoglycemia in patients with maturity-onset diabetes of the young when treated with a GLP-1 receptor agonist: a double-blind, randomized, crossover trial. *Diabetes Care, 37*(7), 1797-1805. doi: 10.2337/dc13-3007

Ovsyannikova, A. K., Rymar, O. D., Shakhtshneider, E. V., Klimontov, V. V., Koroleva, E. A., Myakina, N. E., & Voevoda, M. I. (2016). ABCC8-Related Maturity-Onset Diabetes of the Young (MODY12): Clinical Features and Treatment Perspective. *Diabetes Ther, 7*(3), 591-600. doi: 10.1007/s13300-016-0192-9

Ozdemir, T. R., Kirbiyik, O., Dundar, B. N., Abaci, A., Kaya, O. O., Catli, G., . . . Erdogan, K. M. (2018). Targeted next generation sequencing in patients with maturity-onset diabetes of the young (MODY). *J Pediatr Endocrinol Metab, 31*(12), 1295-1304. doi: 10.1515/jpem-2018-0184

Ozsu, E., Cizmecioglu, F. M., Yesiltepe Mutlu, G., Yuksel, A. B., Caliskan, M., Yesilyurt, A., & Hatun, S. (2018). Maturity Onset Diabetes of the Young due to Glucokinase, HNF1-A, HNF1-B, and HNF4-A Mutations in a Cohort of Turkish Children Diagnosed as Type 1 Diabetes Mellitus. *Horm Res Paediatr, 90*(4), 257-265. doi: 10.1159/000494431

Pallotta, M. T., Tascini, G., Crispoldi, R., Orabona, C., Mondanelli, G., Grohmann, U., & Esposito, S. (2019). Wolfram syndrome, a rare neurodegenerative disease: from pathogenesis to future treatment perspectives. *J Transl Med, 17*(1), 238. doi: 10.1186/s12967-019-1993-1

Parvin, M., Jahan, F., Sarkar, P. K., Howlader, Z. H., Nabi, Ahmn, & Hosen, M. I. (2019). Functional Polymorphism Located in the microRNA Binding Site of the Insulin Receptor (INSR) Gene Confers Risk for Type 2 Diabetes Mellitus in the Bangladeshi Population. *Biochem Genet, 57*(1), 20-33. doi: 10.1007/s10528-018-9872-7

Patel, K. A., Kettunen, J., Laakso, M., Stancakova, A., Laver, T. W., Colclough, K., . . . Weedon, M. N. (2017). Heterozygous RFX6 protein truncating variants are

associated with MODY with reduced penetrance. *Nat Commun, 8*(1), 888. doi: 10.1038/s41467-017-00895-9

Pavic, T., Juszczak, A., Pape Medvidovic, E., Burrows, C., Sekerija, M., Bennett, A. J., . . . Owen, K. R. (2018). Maturity onset diabetes of the young due to HNF1A variants in Croatia. *Biochem Med (Zagreb), 28*(2), 020703. doi: 10.11613/BM.2018.020703

Pearson, E. R., Badman, M. K., Lockwood, C. R., Clark, P. M., Ellard, S., Bingham, C., & Hattersley, A. T. (2004). Contrasting diabetes phenotypes associated with hepatocyte nuclear factor-1alpha and -1beta mutations. *Diabetes Care, 27*(5), 1102-1107. doi: 10.2337/diacare.27.5.1102

Pearson, E. R., Liddell, W. G., Shepherd, M., Corrall, R. J., & Hattersley, A. T. (2000). Sensitivity to sulphonylureas in patients with hepatocyte nuclear factor-1alpha gene mutations: evidence for pharmacogenetics in diabetes. *Diabet Med, 17*(7), 543-545. doi: 10.1046/j.1464-5491.2000.00305.x

Pearson, E. R., Pruhova, S., Tack, C. J., Johansen, A., Castleden, H. A., Lumb, P. J., . . . Hattersley, A. T. (2005). Molecular genetics and phenotypic characteristics of MODY caused by hepatocyte nuclear factor 4alpha mutations in a large European collection. *Diabetologia, 48*(5), 878-885. doi: 10.1007/s00125-005-1738-y

Pearson, E. R., Starkey, B. J., Powell, R. J., Gribble, F. M., Clark, P. M., & Hattersley, A. T. (2003). Genetic cause of hyperglycaemia and response to treatment in diabetes. *Lancet, 362*(9392), 1275-1281. doi: 10.1016/S0140-6736(03)14571-0

Pingul, M. M., Hughes, N., Wu, A., Stanley, C. A., & Gruppuso, P. A. (2011). Hepatocyte nuclear factor 4alpha gene mutation associated with familial

neonatal hyperinsulinism and maturity-onset diabetes of the young. *J Pediatr, 158*(5), 852-854. doi: 10.1016/j.jpeds.2011.01.003

Plengvidhya, N., Kooptiwut, S., Songtawee, N., Doi, A., Furuta, H., Nishi, M., . . . Banchuin, N. (2007). PAX4 mutations in Thais with maturity onset diabetes of the young. *J Clin Endocrinol Metab, 92*(7), 2821-2826. doi: 10.1210/jc.2006-1927

Pontoglio, M., Prie, D., Cheret, C., Doyen, A., Leroy, C., Froguel, P., . . . Friedlander, G. (2000). HNF1alpha controls renal glucose reabsorption in mouse and man. *EMBO Rep, 1*(4), 359-365. doi: 10.1093/embo-reports/kvd071

Pontoglio, M., Sreenan, S., Roe, M., Pugh, W., Ostrega, D., Doyen, A., . . . Polonsky, K. S. (1998). Defective insulin secretion in hepatocyte nuclear factor 1alpha-deficient mice. *J Clin Invest, 101*(10), 2215-2222. doi: 10.1172/JCI2548

Prudente, S., Jungtrakoon, P., Marucci, A., Ludovico, O., Buranasupkajorn, P., Mazza, T., . . . Doria, A. (2015). Loss-of-Function Mutations in APPL1 in Familial Diabetes Mellitus. *Am J Hum Genet, 97*(1), 177-185. doi: 10.1016/j.ajhg.2015.05.011

Qin, L., Li, X., Hou, Q., Wang, H., Lou, G., Li, T., . . . Liao, S. (2017). Novel heterozygous mutations of the INSR gene in a familial case of Donohue syndrome. *Clin Chim Acta, 473*, 26-31. doi: 10.1016/j.cca.2017.08.007

Raeder, H., Johansson, S., Holm, P. I., Haldorsen, I. S., Mas, E., Sbarra, V., . . . Njolstad, P. R. (2006). Mutations in the CEL VNTR cause a syndrome of diabetes and pancreatic exocrine dysfunction. *Nat Genet, 38*(1), 54-62. doi: 10.1038/ng1708

Rafique I, Saqib MAN , Mir A , Naeem M,. (2018). MATURITY ONSET DIABETES OF THE YOUNG – AN OVERVIEW OF COMMON TYPES. A

REVIEW. *Rom J Diabetes NutrMetab Dis, 25*((2)), 209-213 doi: 10.2478/rjdnmd-2018-0024)

Raile, K., Schober, E., Konrad, K., Thon, A., Grulich-Henn, J., Meissner, T., . . . Mellitus, D. P. V. Initiative the German BMBF Competence Network Diabetes. (2015). Treatment of young patients with HNF1A mutations (HNF1A-MODY). *Diabet Med, 32*(4), 526-530. doi: 10.1111/dme.12662

Reinehr, T. (2013). Type 2 diabetes mellitus in children and adolescents. *World J Diabetes, 4*(6), 270-281. doi: 10.4239/wjd.v4.i6.270

Rigoli, L., Lombardo, F., Salzano, G., Di Bella, C., Messina, M. F., De Luca, F., & Iafusco, D. (2013). Identification of one novel causative mutation in exon 4 of WFS1 gene in two Italian siblings with classical DIDMOAD syndrome phenotype. *Gene, 526*(2), 487-489. doi: 10.1016/j.gene.2012.10.023

Rubio-Cabezas, O., Minton, J. A., Kantor, I., Williams, D., Ellard, S., & Hattersley, A. T. (2010). Homozygous mutations in NEUROD1 are responsible for a novel syndrome of permanent neonatal diabetes and neurological abnormalities. *Diabetes, 59*(9), 2326-2331. doi: 10.2337/db10-0011

Seino, S., Seino, M., Nishi, S., & Bell, G. I. (1989). Structure of the human insulin receptor gene and characterization of its promoter. *Proc Natl Acad Sci U S A, 86*(1), 114-118. doi: 10.1073/pnas.86.1.114

Sesti, G., Federici, M., Lauro, D., Sbraccia, P., & Lauro, R. (2001). Molecular mechanism of insulin resistance in type 2 diabetes mellitus: role of the insulin receptor variant forms. *Diabetes Metab Res Rev, 17*(5), 363-373. doi: 10.1002/dmrr.225

Shepherd, M., Ellis, I., Ahmad, A. M., Todd, P. J., Bowen-Jones, D., Mannion, G., . . . Hattersley, A. T. (2001). Predictive genetic testing in maturity-onset diabetes

of the young (MODY). *Diabet Med, 18*(5), 417-421. doi: 10.1046/j.1464-5491.2001.00447.x

Shepherd, M., Pearson, E. R., Houghton, J., Salt, G., Ellard, S., & Hattersley, A. T. (2003). No deterioration in glycemic control in HNF-1alpha maturity-onset diabetes of the young following transfer from long-term insulin to sulphonylureas. *Diabetes Care, 26*(11), 3191-3192. doi: 10.2337/diacare.26.11.3191-a

Shepherd, M., Shields, B., Hammersley, S., Hudson, M., McDonald, T. J., Colclough, K., . . . Hattersley, A. T. (2016). Systematic Population Screening, Using Biomarkers and Genetic Testing, Identifies 2.5% of the U.K. Pediatric Diabetes Population With Monogenic Diabetes. *Diabetes Care, 39*(11), 1879-1888. doi: 10.2337/dc16-0645

Shera, A. S., Basit, A., Fawwad, A., Hakeem, R., Ahmedani, M. Y., Hydrie, M. Z., & Khwaja, I. A. (2010). Pakistan National Diabetes Survey: prevalence of glucose intolerance and associated factors in the Punjab Province of Pakistan. *Prim Care Diabetes, 4*(2), 79-83. doi: 10.1016/j.pcd.2010.01.003

Shera, A. S., Rafique, G., Khawaja, I. A., Baqai, S., & King, H. (1999). Pakistan National Diabetes Survey: prevalence of glucose intolerance and associated factors in Baluchistan province. *Diabetes Res Clin Pract, 44*(1), 49-58.

Shera, A. S., Rafique, G., Khwaja, I. A., Ara, J., Baqai, S., & King, H. (1995). Pakistan national diabetes survey: prevalence of glucose intolerance and associated factors in Shikarpur, Sindh Province. *Diabet Med, 12*(12), 1116-1121.

Shera, A. S., Rafique, G., Khwaja, I. A., Baqai, S., Khan, I. A., & King, H. (1999). Pakistan National Diabetes Survey prevalence of glucose intolerance and

associated factors in North West at Frontier Province (NWFP) of Pakistan. *J Pak Med Assoc, 49*(9), 206-211.

Shields, B. M., Hicks, S., Shepherd, M. H., Colclough, K., Hattersley, A. T., & Ellard, S. (2010). Maturity-onset diabetes of the young (MODY): how many cases are we missing? *Diabetologia, 53*(12), 2504-2508. doi: 10.1007/s00125-010-1799-4

Shields, B. M., McDonald, T. J., Ellard, S., Campbell, M. J., Hyde, C., & Hattersley, A. T. (2012). The development and validation of a clinical prediction model to determine the probability of MODY in patients with young-onset diabetes. *Diabetologia, 55*(5), 1265-1272. doi: 10.1007/s00125-011-2418-8

Sladek, F. M., Zhong, W. M., Lai, E., & Darnell, J. E., Jr. (1990). Liver-enriched transcription factor HNF-4 is a novel member of the steroid hormone receptor superfamily. *Genes Dev, 4*(12B), 2353-2365. doi: 10.1101/gad.4.12b.2353

Smith, S. B., Qu, H. Q., Taleb, N., Kishimoto, N. Y., Scheel, D. W., Lu, Y., . . . German, M. S. (2010). Rfx6 directs islet formation and insulin production in mice and humans. *Nature, 463*(7282), 775-780. doi: 10.1038/nature08748

Song, J., Yang, Y., Mauvais-Jarvis, F., Wang, Y. P., & Niu, T. (2017). KCNJ11, ABCC8 and TCF7L2 polymorphisms and the response to sulfonylurea treatment in patients with type 2 diabetes: a bioinformatics assessment. *BMC Med Genet, 18*(1), 64. doi: 10.1186/s12881-017-0422-7

Spyer, G., Hattersley, A. T., Sykes, J. E., Sturley, R. H., & MacLeod, K. M. (2001). Influence of maternal and fetal glucokinase mutations in gestational diabetes. *Am J Obstet Gynecol, 185*(1), 240-241. doi: 10.1067/mob.2001.113127

Stoffers, D. A., Zinkin, N. T., Stanojevic, V., Clarke, W. L., & Habener, J. F. (1997). Pancreatic agenesis attributable to a single nucleotide deletion in the human

IPF1 gene coding sequence. *Nat Genet, 15*(1), 106-110. doi: 10.1038/ng0197-106

Stride, A., Vaxillaire, M., Tuomi, T., Barbetti, F., Njolstad, P. R., Hansen, T., . . . Hattersley, A. T. (2002). The genetic abnormality in the beta cell determines the response to an oral glucose load. *Diabetologia, 45*(3), 427-435. doi: 10.1007/s00125-001-0770-9

Szopa, M., Ludwig-Galezowska, A., Radkowski, P., Skupien, J., Zapala, B., Platek, T., . . . Malecki, M. T. (2015). Genetic testing for monogenic diabetes using targeted next-generation sequencing in patients with maturity-onset diabetes of the young. *Pol Arch Med Wewn, 125*(11), 845-851. doi: 10.20452/pamw.3164

Szopa, M., Matejko, B., Ucieklak, D., Uchman, A., Hohendorff, J., Mrozinska, S., . . . Malecki, M. T. (2019). Quality of life assessment in patients with HNF1A-MODY and GCK-MODY. *Endocrine, 64*(2), 246-253. doi: 10.1007/s12020-018-1812-0

Taleb, N., & Polychronakos, C. (2011). RFX6 is needed for the development and maintenance of the beta-cell phenotype. *Islets, 3*(5), 291-293. doi: 10.4161/isl.3.5.15944

Tatsi, E. B., Kanaka-Gantenbein, C., Scorilas, A., Chrousos, G. P., & Sertedaki, A. (2020). Next generation sequencing targeted gene panel in Greek MODY patients increases diagnostic accuracy. *Pediatr Diabetes, 21*(1), 28-39. doi: 10.1111/pedi.12931

Thanabalasingham, G., Pal, A., Selwood, M. P., Dudley, C., Fisher, K., Bingley, P. J., . . . Owen, K. R. (2012). Systematic assessment of etiology in adults with a clinical diagnosis of young-onset type 2 diabetes is a successful strategy for

identifying maturity-onset diabetes of the young. *Diabetes Care, 35*(6), 1206-1212. doi: 10.2337/dc11-1243

Torsvik, J., Johansson, S., Johansen, A., Ek, J., Minton, J., Raeder, H., . . . Njolstad, P. R. (2010). Mutations in the VNTR of the carboxyl-ester lipase gene (CEL) are a rare cause of monogenic diabetes. *Hum Genet, 127*(1), 55-64. doi: 10.1007/s00439-009-0740-8

Urakami, T. (2019). Maturity-onset diabetes of the young (MODY): current perspectives on diagnosis and treatment. *Diabetes Metab Syndr Obes, 12*, 1047-1056. doi: 10.2147/DMSO.S179793

Urakami, T., Kuwabara, R., Habu, M., Okuno, M., Suzuki, J., Takahashi, S., & Mugishima, H. (2013). Clinical characteristics of non-obese children with type 2 diabetes mellitus without involvement of beta-cell autoimmunity. *Diabetes Res Clin Pract, 99*(2), 105-111. doi: 10.1016/j.diabres.2012.11.021

Urano, F. (2016). Wolfram Syndrome: Diagnosis, Management, and Treatment. *Curr Diab Rep, 16*(1), 6. doi: 10.1007/s11892-015-0702-6

Ushijima, K., Narumi, S., Ogata, T., Yokota, I., Sugihara, S., Kaname, T., . . . Adolescent, Diabetes. (2019). KLF11 variant in a family clinically diagnosed with early childhood-onset type 1B diabetes. *Pediatr Diabetes, 20*(6), 712-719. doi: 10.1111/pedi.12868

Valero, R., Bannwarth, S., Roman, S., Paquis-Flucklinger, V., & Vialettes, B. (2008). Autosomal dominant transmission of diabetes and congenital hearing impairment secondary to a missense mutation in the WFS1 gene. *Diabet Med, 25*(6), 657-661. doi: 10.1111/j.1464-5491.2008.02448.x

Velho, G., Blanche, H., Vaxillaire, M., Bellanne-Chantelot, C., Pardini, V. C., Timsit, J., . . . Froguel, P. (1997). Identification of 14 new glucokinase mutations and

description of the clinical profile of 42 MODY-2 families. *Diabetologia, 40*(2), 217-224. doi: 10.1007/s001250050666

Velho, G., Vaxillaire, M., Boccio, V., Charpentier, G., & Froguel, P. (1996). Diabetes complications in NIDDM kindreds linked to the MODY3 locus on chromosome 12q. *Diabetes Care, 19*(9), 915-919. doi: 10.2337/diacare.19.9.915

Vermeulen, I., Weets, I., Asanghanwa, M., Ruige, J., Van Gaal, L., Mathieu, C., . . . Gorus, F. K. (2011). Contribution of antibodies against IA-2beta and zinc transporter 8 to classification of diabetes diagnosed under 40 years of age. *Diabetes Care, 34*(8), 1760-1765. doi: 10.2337/dc10-2268

Wang, H., Maechler, P., Hagenfeldt, K. A., & Wollheim, C. B. (1998). Dominant-negative suppression of HNF-1alpha function results in defective insulin gene transcription and impaired metabolism-secretion coupling in a pancreatic beta-cell line. *EMBO J, 17*(22), 6701-6713. doi: 10.1093/emboj/17.22.6701

Woodhouse, N. J., Elshafie, O. T., Al-Mamari, A. S., Mohammed, N. H., Al-Riyami, F., & Raeburn, S. (2010). Clinically-Defined Maturity Onset Diabetes of the Young in Omanis: Absence of the common Caucasian gene mutations. *Sultan Qaboos Univ Med J, 10*(1), 80-83.

Yorifuji, T., Kurokawa, K., Mamada, M., Imai, T., Kawai, M., Nishi, Y., . . . Nakahata, T. (2004). Neonatal diabetes mellitus and neonatal polycystic, dysplastic kidneys: Phenotypically discordant recurrence of a mutation in the hepatocyte nuclear factor-1beta gene due to germline mosaicism. *J Clin Endocrinol Metab, 89*(6), 2905-2908. doi: 10.1210/jc.2003-031828

Yorifuji, T., Nagashima, K., Kurokawa, K., Kawai, M., Oishi, M., Akazawa, Y., . . . Nakahata, T. (2005). The C42R mutation in the Kir6.2 (KCNJ11) gene as a

cause of transient neonatal diabetes, childhood diabetes, or later-onset, apparently type 2 diabetes mellitus. *J Clin Endocrinol Metab, 90*(6), 3174-3178. doi: 10.1210/jc.2005-0096

Yuan, S., & Larsson, S. C. (2019). A causal relationship between cigarette smoking and type 2 diabetes mellitus: A Mendelian randomization study. *Sci Rep, 9*(1), 19342. doi: 10.1038/s41598-019-56014-9

Zafar, J., Bhatti, F., Akhtar, N., Rasheed, U., Bashir, R., Humayun, S., . . . Umaimato. (2011). Prevalence and risk factors for diabetes mellitus in a selected urban population of a city in Punjab. *J Pak Med Assoc, 61*(1), 40-47.

Zafar, J., Nadeem, D., Khan, S. A., Jawad Abbasi, M. M., Aziz, F., & Saeed, S. (2016). Prevalence of diabetes and its correlates in urban population of Pakistan: A Cross-sectional survey. *J Pak Med Assoc, 66*(8), 922-927.

Zalloua, P. A., Azar, S. T., Delepine, M., Makhoul, N. J., Blanc, H., Sanyoura, M., . . . Julier, C. (2008). WFS1 mutations are frequent monogenic causes of juvenile-onset diabetes mellitus in Lebanon. *Hum Mol Genet, 17*(24), 4012-4021. doi: 10.1093/hmg/ddn304

Zhang, C., Rawal, S., & Chong, Y. S. (2016). Risk factors for gestational diabetes: is prevention possible? *Diabetologia, 59*(7), 1385-1390. doi: 10.1007/s00125-016-3979-3

Zhang, Y., Xie, Z., Zhou, L., Li, L., Zhang, H., Zhou, G., . . . Zhang, W. J. (2012). The zinc finger protein ZBTB20 regulates transcription of fructose-1,6-bisphosphatase 1 and beta cell function in mice. *Gastroenterology, 142*(7), 1571-1580 e1576. doi: 10.1053/j.gastro.2012.02.043

Zheng, Y., Ley, S. H., & Hu, F. B. (2018). Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat Rev Endocrinol, 14*(2), 88-98. doi: 10.1038/nrendo.2017.151

Zhu, A. N., Yang, X. X., Sun, M. Y., Zhang, Z. X., & Li, M. (2015). Associations between INSR and MTOR polymorphisms in type 2 diabetes mellitus and diabetic nephropathy in a Northeast Chinese Han population. *Genet Mol Res, 14*(1), 1808-1818. doi: 10.4238/2015.March.13.9

APPENDICES

APPENDICES

Appendix-I

CONSENT FORM

Project Information:

Name of Project: **Application of next-generation sequencing (NGS) in diabetes screening and Identification of maturity-onset diabetes in young**

Name of organization & donor: **Pakistan Health Research Council& International Islamic University, Islambad**

Purpose: The purpose is to identify the common variants/mutations in the genes responsible for MODY in Pakistani families/patients

Methods: Patient will be enrolled for having symptoms of diabetes and onset of age below 25 years Tests like an antibody to glutamic acid decarboxylase (GAD-Ab) by ELISA or fasting C-peptide shall be performed to rule out type I diabetes.

The DNA will be extracted and exome sequencing will be done.

Possible benefits: The patients will be informed about the gene involved in the disease and their physicians are also informed.

Financial Considerations: There will be no financial compensation for participation in this research.

Confidentiality: The information will not be kept confidential and will be used for research purposes only.

Refusal to participate: if you feel that participating as a respondent in the research will put you at hazard, you have full authority to refuse to participate or continue at any given time. Participation is completely voluntary and there is no obligation to answer/respond to any question, part of a question, or the study asa whole.

Further Information: if you would like to have more information about the study, you can contact the person/s given below for more information;

Name: Dr. Asif Mir, 051-9019736-2736

Ibrar Rafique, 051-9207386, 0334-9567202

Consent to participate in the study:

I have read/ I have been explained about the study (put the name) with possible hazards and refusal. I am voluntarily participating in the study without any coercion. I am assured it will not contradict any provincial or national regulation applicable or civil rights.

Name:

_____

Signature/Thumb Impression of participant:_____

Appendix-II

Questionnaire

Application of next generation sequencing (NGS) in diabetes screening and identification of maturity onset diabetes in young

(International Islamic University, Islamabad)

1. Name:_____
2. Current Age: _____years
3. **Age at Diagnosis_____years**
4. **Gender Male (1) Female (2)**
5. Ethnicity Punjab (1) Sindhi (2) Pathan (3) Urdu Speaking (4) Baluch(5) others (specify) (6)
6. Place of Residence:_____

_____

7. Telephone Number: _____
8. Education:

   Illiterate (1), Primary (2), Middle (3), Secondary (4), Graduation (5) Post graduation (6) Unknown (7)
9. Socio Economic Status: (As per income criteria) Low (1) Medium (2) High (3)
10. **Family History Of Diabetes: Yes (1); No (2)**

    Relation: Yes (1); No (2) Types of Diabetes: Type 1 (1); Type2 (2);Others, (please specify) (3)

(1) **Mother** _____

_____

(2) **Father** _____

_____

Siblings with Diabetes

(3) Male (n) ___ _____

_____

(4) Female (n) ___ _____

_____

Grand Parents

(5) Maternal _____

_____

(6) Paternal _____

_____

11. Information On Above Items Was Provided By

    Self (1) Family Member/Relative of Patient (2) Friend of Patient (3) Medical Records (4)

CLINICAL INFORMATION

12. Date of First Diagnosis ___DD ___ MM _____ YY

13. Duration of Diabetes _____Years ____months

14. Mode of presentation at the onset:

Osmotic (1) Weight Loss (2) Ketosis (3) Incidental (4) Others (5)

15. Height: _____ cm, Weight _____Kg, BMI _____,Waist _____cm

16. **BP:** Systolic (mm Hg) _____ Diastolic (mm Hg) _____

17. Currently treated with insulin or Oral Hypoglycemic Agent? Yes (1) No (2)

18. Time to Insulin Treatment (if currently treated with insulin)

- Not currently treated with insulin
- Within 6 months of diagnosis
- Over 6 months after diagnosis

19. Complications:

Present (1); Absent (2); Not Known (3) If (1); Specify Treatment

a) Retinopathy _____
b) Nephropathy _____
c) Neuropathy _____
d) Tuberculosis _____
e) Sepsis _____
f) Coronary Artery Disease _____
g) Stroke _____
h) Peripheral Vascular Disease _____
i) Any others Specify _____

20. Current Treatment

Insulin

(A) Type

Regular (1) Intermediate Acting (2) Pre-mixed (3) Long Acting Analogue (4) Short Acting Analogue (5) Pre-mixed Analogue (6)

(B) Regimen

TDS (1) OD (2) BD (3) Multidose (4) Pump (5)

21. **Oral hypoglycemic agents (OHA)**

Biguanides (1) Sulphonylureas (2) Glitazones (3) α-Glucosidase inhibitor (4) Meglitinide analogues (5) DPP IV inhibitor (6) Combination of insulin and OHA

22. Treatment for Other Co-Morbidities (e.g. Hypertension, Dyslipidemia and Coronary Artery Disease, Autoimmune thyroid disease, Celiac Disease)

Yes (1) No (2) If yes specify

_____

23. Diagnostic tests:

(a) Glycosylated Haemoglobin Hba1C(%) , _____

(b) **Urinary C-peptide creatinine ratio**(if available): _____

(c) **Fasting C-peptide test**: _____

(d) **Glutamte decarboxylase antibody test**: _____

(e) Fasting (pmol/ml): _____

Appendix-III

Supplementary table 1: Full-text studies excluded from the final analysis:

S. No	Reasons for exclusion	Number of studies
5	No novel variants	39
6	No variants described in 14 known MODY genes	46
7	Reviews	2
	Total	**87**

Reason for exclusion:

S.no	Excluded studies	Reason
1.	Early Onset of Liver Steatosis in a JapaneseGirl with Maturity-Onset Diabetes of theYoung Type 3 (MODY3) Nakamura A 2012 PMID: 22672869	No novel variant
2.	Pregnancy Complicated by Maternal MODY 3 andPaternal MODY 2 Diabetes and Subsequent RapidlyFalling Insulin Requirement Mikuscheva 2018 PMID 30356406	No novel variant
3.	Maturity-onset diabetes of the young type 5:a case report Bañares JJ 2011 PMID: 22233861	No variant described
4.	Using highly sensitive C-reactive protein measurement todiagnose MODY in a family with suspected type 2 diabetes Besser 2012, 22787179	No variant described
5.	HNF1A gene p.I27L is associated with earlyonset,maturity-onset diabetes of the young-like diabetes in Turkey Beysel S 2019, PMID: 31109344	Association studies
6.	GCK-MODY in the US National Monogenic Diabetes Registry: Frequently Misdiagnosed and Unnecessarily Treated Carmody 2016 PMID 27106716	No variant described
7.	Next-generation sequencing	No variant described

	identifiesmonogenic diabetes in 16% of patientswith late adolescence/adult-onset diabetes selected on a clinical basis: a crosssectional analysis Donath, 2019 PMID: 31291970	
8.	Hepatocyte nuclear factor 1-alpha mutation in normal glucose-tolerant subjects and early onset type 2diabetic patients Lim 2008, PMID: 19119252	No novel variant
9.	Diabetic ketoacidosis in the setting of HNF1A-maturity onset diabetes of the young Egan, PMID: 25837654	NO novel variant
10.	First UK survey of paediatric type 2 diabetes and MODY Ehtisham 2004, 15155395	No variant described
11.	Optimal Glycemic Control in a Patient WithHNF1A MODY With GLP-1 RA Monotherapy: Implications forFuture Therapy Fantasia, 2018, PMID: 31737858	No variant described
12.	Prevalence of monogenic diabetes amongst Polish children after a nationwide genetic screening campaign W. Fendler 2012, PMID: 22782286	No variant described
13.	An evolving spectrum of diabetes in a woman with GCK-MODY Garrahy 2019, PMID: 30608898	No novel variant
14.	Maturity-Onset Diabetes of the Young Caused by aBalanced Translocation Where the 20q12 Break PointResults in Disruption Upstream of the Coding Region ofHepatocyte Nuclear Factor-4_ (HNF4A) Gene Anna L. Gloyn 2002, PMID: 12086970	No variant described
15.	Assessment of Newly Proposed Clinical Criteria toIdentify HNF1A MODY in Patients with an Initial Diagnosis ofType 1 or Type 2 Diabetes Mellitus Grzanka 2016, PMID: 26942212	No variant described
16.	Exploring Phenotype-GenotypeCorrelations Using InterstitialGlucose Results in a Family With aGlucokinase Mutation Lunt 2018, PMID: 29944009	No variant described
17.	Low Frequencies of Autoimmunity-Associated PTPN22 Polymorphisms in MODY Patients, Including Those Transiently Expressing Islet	No variant described

	Cell Autoantibodies Heneberg 2015, PMID: 25896041	
18.	Assessing the phenotypic effects in the general population of rare variants in genes for a dominant mendelian form of diabetes Flannick2013, PMID: 24097065	No novel variant
19.	Identification of a Locus for Maturity-Onset Diabetes ofthe Young on Chromosome 8p23 Kim 2004, PMID: 15111509	No variant described
20.	Structural and Functional Study of theGlnB22-Insulin Mutant Responsible forMaturity-Onset Diabetes of the Young Kr̆ı´z̆kova´ 1 2014, PMID: 25423173	No novel variant
21.	Juvenile-Onset Diabetes and Congenital Cataract: "Double-Gene" Mutations Mimicking SyndromicDiabetes Presentation Lenfant 2017, PMID: 29112131	Not relevant
22.	Dysmorphic Features, Frontal Cerebral Cavernoma, andHyperglycemia in a Girl with a De Novo Deletion of 7.23 Mb in Region 7p13 p12.1 López 2017, PMID: 28387648	Syndromic
23.	Non-penetrance in a MODY 3 family with a mutation in the hepatic nuclear factor 1á gene: implications for predictive testing Miedzybrodzka, 1999, PMID: 10482964	No novel or causal variant
24.	Clinical and molecular characterization of maturity onset-diabetes of the young causedby hepatocyte nuclear factor-4 alpha mutation:red flags for prediction of the diagnosis Mohamed 2014, PMID: 25266181	No novel variant
25.	Functional Investigations of HNF1AIdentify Rare Variants as Risk Factors for Type 2 Diabetes in the GeneralPopulation Najmi 2017, PMID: 27899486	No variant described
26.	Low serum level of high-sensitivity C-reactive protein in a Japanese patient with maturityonsetdiabetes of the young type 3 (MODY3) Ohki 2014, PMID: 25411618	No novel variant
27.	Maturity Onset Diabetes of the Young due to Glucokinase, HNF1-A, HNF1-B, and HNF4-A Mutations in a Cohort of Turkish	No novel variant

	ChildrenDiagnosed as Type 1 Diabetes Mellitus Ozsu, 2018, PMID: 30481753	
28.	Heterozygous RFX6 protein truncating variants areassociated with MODY with reduced penetrance Patel 2017, PMID: 29026101	No variants described
29.	Maturity Onset Diabetes of the Young is Not Necessarily Associated with Autosoma Inheritance: Case Description of a De Novo HFN1A Mutation Salzano 2019, PMID: 31098941	No novel variant
30.	Genetic causes of maturity onset diabetes of the young may be less prevalent in American pregnant women recently diagnosed with diabetes mellitus than in previously studied European populations . Sewell 2015, PMID: 25012807	No variants described
31.	Digenic heterozygous HNF1A and HNF4A mutations in two siblings with childhood-onset diabetes Shankar 2013, PMID: 23551881	No novel variant
32.	A UK nationwide prospective study of treatment changein MODY: genetic subtype and clinical characteristics predict optimalglycaemic control after discontinuing insulin and metformin Shepherd 2018, PMID: 30229274	No variant described
33.	Can Biomarkers Help Target Maturity-Onset Diabetes of the Young Genetic Testing in Antibody-Negative Diabetes? Majidi 2018, PMID: 29355436	No variant described
34.	Expression of mutant mRNA and protein in pancreatic cells derived from MODY3- iPS cells Yabe 2019, PMID: 31145732	No variant described
35.	Novel Presentations of Congenital Hyperinsulinism due to Mutations in the MODY genes: HNF1A andHNF4A Stanescu 2012, PMID: 22802087	No novel variant
36.	In silico and in vitro analyses of the pathological relevance of the R258H mutation of hepatocyte nuclear factor 4a identified in maturity-onset diabetes of the young type 1 Sugawara 2019, PMID: 30325586	No novel variant
37.	Genetic testing for monogenic diabetes using targeted next-generation sequencing in patients with maturity-onset diabetes of	No variant described

	theyoung Szopa 2015, PMID: 26552609	
38.	Systematic Assessment of Etiology in Adults With a Clinical Diagnosis ofYoung-Onset Type 2 Diabetes Is aSuccessful Strategy for IdentifyingMaturity-Onset Diabetes of the Young THANABALASINGHAM, 2012, PMID: 22432108	No novel variant
39.	Letter to the Editor Identification of novel and recurrentglucokinase mutations in Belgian andLuxembourg maturity onset diabetesof the young patients Vits 2006, PMID: 16965331	No novel variant
40.	Bilateral Cataracts in a 6-year-old with New Onset Diabetes: A novel presentation of a known INS gene mutation Wasserman, 2016, PMID: 26530398	No novel variant
41.	Clinically-Defined Maturity Onset Diabetes of the Young in OmanisAbsence of the common Caucasian gene mutations Woodhouse 2010, PMID: 21509085	No variants
42.	Assessing the Pathogenicity, Penetrance, and Expressivity of Putative Disease-CausingVariants in a Population Setting Wright 2019, PMID: 30665703	No variants for MODY
43.	Studies of genetic variability of the hepatocyte nuclear factor-1α gene in an Indian maturity-onset diabetes of the young family Yang, 2016, PMID: 27148439	No pathogenic variants
44.	Like-Triple Diabetes as First Manifestation of MODY2 in anOverweight Teenager With TransientMultiple Antibodies Wedrychowicz 2014, PMID: 24652732	No variant described
45.	Absence of Islet Autoantibodies and Modestly Raised GlucoseValues at Diabetes DiagnosisShould Lead to Testing for MODY:Lessons From a 5-Year Pediatric Swedis National Cohort Study Carlsson 2019, PMID: 31704690	No variant described
46.	Linkage of maturity-onset diabetes of the young to theglucokinase gene - evidence of genetic heterogeneity Hattersley 1992, PMID: 8449303	No variant described
47.	Structure–function studies of HNF1A (MODY3) gene mutations in South	No novel variant

	Indianpatients with monogenic diabetes Balamurugan 2016, PMID: 26853433	
48.	Bioinformatic detection of copy number variation in HNF4Acausing maturity onset diabetes of the young Berberich 2019, PMID: 31309534	No variant described.
49.	The coexistence of type 1 diabetes, MODY2 and metabolicsyndrome in a young girl Calcaterra 2012, PMID: 21688019	No novel variant
50.	Exonic Duplication of the Hepatocyte Nuclear Factor-1_Gene (Transcription Factor 2, Hepatic) as a Cause ofMaturity Onset Diabetes of the Young Type 5 Carette 2007, PMID: 17440011	No variant described
51.	Research: Pregnancy An Irish National Diabetes in Pregnancy Audit aiming for best outcomes for women withdiabetes Egan 2019, PMID: 30710451	No variant described
52.	From Biology to Genes and BackAgain: Gene Discovery forMonogenic Forms of Beta-Cell Dysfunction in Diabetes De Franco 2016, PMID: 31479665	Review
53.	Identification of Twelve Novel Mutations in PatientsWith Classic and Variant Forms of Maple SyrupUrine Disease Henneke 2003, PMID: 14517957	No variant for MODY
54.	Molecular background and clinical characteristics of HNF1A MODYin a Polish population Skupien 2008, PMID: 18838325	No novel variant
55.	Whole-exome sequencing for mutation detection in pediatricdisorders of insulin secretion: Maturity onset diabetes of theyoung and congenital hyperinsulinism Johnson 2017, PMID: 29417725	No novel variant
56.	HNF1α Mutations Are Present in Half of Clinically Defined MODYPatients in South-Brazilian Individuals MARASCHIN 2008, PMID: 19169489	No novel variant
57.	A case of Type-1 diabetes mellitus formerly diagnosed asmaturity-onset diabetes of the young (MODY) carryingsuggestive MODY3 gene Miura 1997, PMID: 9483378	No variant described
58.	An analysis of the sequence of the BAD geneamong patients with maturity-onset diabetes	Not relevant gene

	Antosik 2017, PMID: 27935851	
59.	A Common Haplotype for the 677T Thermolabile Variant of the 5,10-MethylenetetrahydrofolateReductase Gene in Thrombophilic Patients and Controls Linnebank 2002, PMID: 12442281	No relevant variant
60.	High Prevalence of Rare Monogenic Forms of Obesityin Obese Guadeloupean Afro-Caribbean Children Foucan 2018, PMID: 29216354	No relevant variant described
61.	Monogenic diabetes prevalence among Polish children—Summary of 11 years-long nationwide geneti screeningprogram Małachowska 2018, PMID: 28436179	No variant described
62.	Onset of type 1 diabetes mellitus in two patients with maturity onset diabetesof the young Maltoni G, 2012, PMID: 21696527	Not relevant
63.	GCK-MODY diabetes as a protein misfolding disease: The mutationR275C promotes protein misfolding, self-association and cellulardegradation Negahdar M 2014, PMID: 24001579	No novel variant
64.	Meglitinide Analogues in Adolescent Patients WithHNF1A-MODY (MODY 3) Marianne Becker 2013, PMID: 24567025	No variant described
65.	High prevalence of glucokinase mutations in italian children with MODY. Influence on glucose tolerance, first phase insulin response, insulin sensitivity and BMI Massa 2001, PMID: 11508276	No novel variant
66.	Case Report An infant with combination gene mutations for Monogenic Diabetes of Youth (MODY) 2 and 4, presenting with Diabetes Mellitus Requiring Insulin (DMRI) at 8 months of age Odem 2009, PMID: 19515026	No novel variant
67.	A description of clinician reported diagnosis of type 2 diabetes and other non-type 1 diabete included in a large internationalmulticentered pediatric diabetes registry (SWEET) Pacaud 2016, PMID: 27748026	No variant described
68.	Short Report: Epidemiology	No novel variant

	Substantial proportion of MODY among multiplexfamilies participating in a Type diabetes prediction Petruzelkova 2015, PMID: 26641800	
69.	Prevalence of Maturity-OnsetDiabetes of theYoung Mutations inBrazilian FamiliesWith Autosomal-Dominant Early-Onset Type 2Diabetes Moises 2001, PMID: 11315851	No novel variant
70.	Dimerization defective MODY mutations of hepatocyte nuclear factor 4α Singh, 2019, PMID: 30648609	No variant described
71.	Screening of mutations in the GCK gene in Jordanian maturity-onset diabetes of the young type 2 (MODY2) patients Khalil, 2009, PMID: 19551638	No variant described
72.	Etiology of Early-Onset Type 2 Diabetes in Indians: IsletAutoimmunity and Mutations in Hepatocyte NuclearFactor 1_ and Mitochondrial Gene Ravi 2007, PMID: 17440016	No novel variant
73.	Phenotype, genotype and glycaemic variability in peoplewith activating mutations in the ABCC8 gene response toappropriate therapy Reilly 2019, PMID: 31562829	No variant described
74.	Diagnostic screening of NEUROD1(MODY6) in subjects with MODY or gestational diabetes mellitus Sagen 2005, PMID: 16026366	No novel variant
75.	A Prevalent Amino Acid Polymorphism at Codon 98 (Ala98Val) of the Hepatocyte Nuclear Factor-1 Is Associated With Maturity-Onset Diabetes of the Young and Younger Age at Onset of Type 2 Diabetes Younger Age at Onset of Type Diabetes in Asian Indians ANURADHA 2005, PMID: 16186275	No variant described
76.	Minigene splicing assessment of 20 novel synonymous andintronic glucokinase gene variants identified in patients withmaturity-onset diabetes of the young Tiulpakov 2019, PMID: 31529753	No variant described
77.	The unique clinical spectrum of maturity onsetdiabetes of the young type 3 Lebenthal 2017, PMID: 29107759	No novel variant
78.	Hepatocyte Nuclear Factor-1_ Gene Inactivation:	No novel variant

	Cosegregation between Liver Adenomatosis and Diabetes Phenotypes in Two Maturity-Onset Diabetes ofthe Young (MODY)3 Families REZNIK 2004, PMID: 15001650	
79.	Hepatocyte nuclear factor-α genetic mutation in a Chinese pedigree with maturity-onset diabetes of the young (MODY3) Zhang 2015, PMID: 26436572	No novel variant
80.	Mutation screening of the hepatocyte nuclear factor(HNF)-6 gene in Japanese subjects with diabetes mellitus Zhu 2001, PMID: 11323086	No variant described
81.	Heterozygous lys169Glu mutation of glucokinase gene in a Chinese family having glucokinas maturity-onset diabetes of the young (GCK-MODY) Zhou 2019, PMID: 31571622	No novel variant
82.	Variation in Maturity-Onset Diabetes of the Young Genes Influence Response to Interventions for Diabetes Prevention Billings 2017, PMID: 28453780	No variants described
83.	Molecular diagnosis of maturity onset diabetes of the young in India Nair 2013, PMID: 23869298	Review
84.	Familial early-onset diabetes is not a typical MODY in several Tunisian patients. Amara 2012, PMID: 23247789	No novel variant
85.	Davis TM, Makepeace AE, Ellard S, Colclough K, Peters K, The prevalence of monogenic diabetes in Australia: the Fremantle Diabetes Study Phase II. Davis 2017, PMID: 29020906	No novel variant
86.	Glucokinase diabetes in 103 families from a country-based study in the Czech Republic: geographically restricted distribution of two prevalent GCK mutations. Pruhova2010,PMID: 20337973	No novel variant
87.	Prevalence of diabetes in Australia: insights from the Fremantle Diabetes Study Phase II. Davis 2018, PMID: 29512259	No novel variant

Appendix-IV

Supplementary table 2:List of causal variants for MODY identified through literature review

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
1.	*GCK*	c.908G>T	p.Arg303Leu	NM_001354800.1 NP_001341729.1 (25921421)	NA	Greece	LP	2015	(Papadimitriou *et al.*, 2015)
2.	*GCK*	c.748C>T	p.Arg250Cys	NP_000153.1 (17204055)	NA	Serbia	VUS	2006	(Milenkovic *et al.*, 2008)
3.	*GCK*	c.182G>A	p.T61I	NP_000153.1 (8433729)	NA	Spain	VUS	2000	(Costa *et al.*, 2000)
4.	*GCK*	c.358C>T	p.A120T	?	NA	Spain	VUS		
5.	*GCK*	c.238delT	M238fsdelT	NP_000153.1	NA	Spain	-		
6.	*GCK*	c.226delinsAA	V226fsdelTinsAA	NP_000153.1	NA	Spain	-		
7.	*GCK*	c.intron418-7del11	S418–7del11	NP_000153.1	NA	Spain	-		
8.	*GCK*	c.76C>T,	p.Gln26Ter	NP_000153.1 (11508276)	NA	Brazil	VUS	2013	(Mota *et al.*, 2013)
9.	*GCK*	c.1012G>A	p.Q338X	NP_000153.1 (26226118)	NA	Turkey	P	2015	(Anik *et al.*, 2015)
10.	*GCK*	c.755G>C	p.C252S	NP_000153.1 (26226118)	NA	Turkey	VUS		
11.	*GCK*	c.257T>C	p.Val86Ala	NP_000153.1 (26226118)	NA	Turkey	VUS		
12.	*GCK*	c.43A>T	p.Lys15*	NM_001354800.1 NP_001341729	NA	Italy	P	2017	(Aloi *et al.*, 2017)

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				9.1 (23771925)					
13.	*GCK*	c.579G>T	p.Gly193Gly	NM_001354800.1 NP_001341729.1	NA	Italy	VUS		
14.	*GCK*	c.505A>G	p.Lys169Glu	NP_000153.1	NA	Italy	VUS		
15.	*GCK*	c.580-3C>A	-	NM_001354800.1 NP_001341729.1	NA	Italy	-		
16.	*GCK*	c.595G>A	p.Val199Met	NP_000153.1	NA	Italy	VUS		
17.	*GCK*	c.944T>C	p.Leu315Pro	NP_000153.1	NA	Italy	LP		
18.	*GCK*	c.1229G>T	p.Gly410Val	NP_000153.1	NA	Italy	LP		
19.	*GCK*	c.1103_1122_del19nt_	p.Arg368fs27*	NP_000153.1	NA	Italy	-		
20.	*GCK*	c.1322C>T	p.Ser441Leu	NP_000153.1	NA	Italy	LP		
21.	*GCK*	c.1226delA	p.D409VfsX21	NM_001354800.1 NP_001341729.1	NA	Canada		2016	(Brahm *et al.*, 2016)
22.	*GCK*	c.880_891delinsCATGGCGAGCTGGTGT	p.Gly294HisfsTer179)	NM_001354800.1 NP_001341729.1	NA	Argentina		2016	(Lopez *et al.*, 2016)
23.	*GCK*	c.895G>C	p.Gly299Arg	NM_001354800.1	NA	Argentina	LP		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				NP_001341729.1 (1303265)					
24.	*GCK*	c.260T>C	p.Val86Ala	NP_000153.1 (26226118)	NA	Turkey	VUS	2018	(Aykut *et al.*, 2018)
25.	*GCK*	c.313delC	p.His105ThrfsX11	NM_001354800.1 NP_001341729.1	NA	Turkey			
26.	*GCK*	c.349G>A	p.Gly117Ser	NP_000153.1	NA	Turkey	VUS		
27.	*GCK*	c.387C>A	p.Cys129X	NP_000153.1 (11508276)	NA	Turkey	P		
28.	*GCK*	c.390delC	p.Ser131ProfsX9	NM_001354800.1 NP_001341729.1	NA	Turkey			
29.	*GCK*	c.475A>G	p.Ile159Val	NM_001354800.1 NP_001341729.1 (21978167)	NA	Turkey	VUS		
30.	*GCK*	c.478G>C	p.Asp160His	NM_001354800.1 NP_001341729.1	NA	Turkey	LP		
31.	*GCK*	c.512T>C	p.Phe171Ser	NM_001354800.1 NP_001341729.1	NA	Turkey	VUS		
32.	*GCK*	c.686delG	p.Gly229AfsX65	NM_001354800.1 NP_001341729.1	NA	Turkey			

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
33.	*GCK*	c.713T>C	p.Met238Thr	NM_001354800.1 NP_001341729.1	NA	Turkey	VUS		
34.	*GCK*	c.819T>G	p. Tyr273X	NM_001354800.1 NP_001341729.1	NA	Turkey	LP		
35.	*GCK*	c.841T>G	p.Ser281Ala	NM_001354800.1 NP_001341729.1	NA	Turkey	VUS		
36.	*GCK*	c.950A>C	p.His317Pro	NM_001354800.1 NP_001341729.1	NA	Turkey	LP		
37.	*GCK*	c.1055T>C	p.Leu352Pro	NM_001354800.1 NP_001341729.1	NA	Turkey	VUS		
38.	*GCK*	c.1179_1192delGCGCGAGAGCCGCA	p.Glu395Glyfs*59	NM_001354800.1 NP_001341729.1	NA	Turkey			
39.	*GCK*	c.1222G>T	p.Val408Leu	NM_001354800.1 NP_001341729.1	NA	Turkey	VUS		
40.	*GCK*	c.1256T>G	p.Pfe419Cys	NM_001354800.1 NP_001341729.1 (19790256)	NA	Turkey	VUS		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
41.	*GCK*	c.1391_1392delGC		?	NA	Turkey			
42.	*GCK*	IVS8+1delG	g.51709_51709delG	?	NA	Turkey			
43.	*GCK*	c.208+3A>T		NM_001354800.1 NP_001341729.1	NA	Turkey			
44.	*GCK*	c.729delG	p.Val244TrpfsTer50	NM_001354800.1 NP_001341729.1	NA	Czech Republic		2010	(Bazalova *et al.*, 2010)
45.	*GCK*	c.1268T>A	p.Phe423Tyr	NM_001354800.1 NP_001341729.1 (19790256)	NA	Portugal	LP	2014	(Almeida *et al.*, 2014)
46.	*GCK*	c.718A>G	p.Asn240Asp	NM_001354800.1 NP_001341729.1 (24735133)	NA	Italy	VUS	2015	(Costantini *et al.*, 2015)
47.	*GCK*	c.757G>T	p.Val253Phe	NM_001354800.1 NP_001341729.1 (24735133)	NA	Italy	LP		
48.	*GCK*	c.872A>C	p.Lys291Thr	NM_001354800.1 NP_001341729.1 (24735133)	NA	Italy	VUS		
49.	*GCK*	c.1151C>T	p.Ala384Val	NM_001354800.1	NA	Italy	VUS		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				NP_001341729.1 (24735133)					
50.	*GCK*	c.175C>T	p.Pro59Ser	NM_001354800.1 NP_001341729.1 (22060211)	NA	Italy	LP	2013	(Delvecchio *et al*, 2013)
51.	*GCK*	c.49G>T	p.Glu17X	NM_001354800.1 NP_001341729.1 (22335469)	NA	Italy	P		
52.	*GCK*	c.1114G>T	p.Glu372X	NM_001354800.1 NP_001341729.1 (22335469)	NA	Italy	P		
53.	*GCK*	c.118G>A	p.Glu40Lys	NP_000153.1 (12627330)	NA	Czech Republic	LP	2012	(P. Dusatkova *et al.*, 2012)
54.	*GCK*	c.944T>A	p.Leu315His	NP_000153.1 (17204055)	NA	Czech Republic	LP		
55.	*GCK*	c.952G>A	p.Gly318Arg	NP_000153.1 (12627330)	NA	Czech Republic	LP		
56.	*GCK*	c.98T>C	p.Val33Ala	NP_000153.1 (18271687)	NA	Czech Republic	LP		
57.	*GCK*	c.605T>C	p.Met202Thr	NP_000153.1 (17937063)	NA	Israel		2007	(Stern *et al.*, 2007)
58.	*GCK*	c.616A>C	p.T206P	NP_000153.1	NA	Israel	LP		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				(17937063)					
59.	*GCK*	c.1113C>A	p.Cys371X	NP_000153.1		Greece		2020	(E. B. Tatsi *et al*, 2020)
60.	*GCK*	c.605T>C	p.Met202Thr	NM_001354800.1 NP_001341729.1 (17937063)	NA	Spain	LP	2007	(Estalella *et al.*, 2007)
61.	*GCK*	c.1258A>G	p.Lys420Glu	NM_001354800.1 NP_001341729.1 (17573900)	NA	Spain	VUS		
62.	*GCK*	96_98delAAG,	p.Lys32del	NP_000153.1	NA	Brazil		2013	(F. M. Giuffrida *et al.*, 2013)
63.	*GCK*	c.533G>C	p.Gly178Ala	NM_001354800.1 NP_001341729.1	NA	Brazil	LP	2017	(F. M. Giuffrida *et al*, 2013; F. M. A. Giuffrida *et al.*, 2017)
64.	*GCK*	c.227C>G	p.Ser76Cys	NM_001354800.1 NP_001341729.1 (21978167)	NA	Israel	VUS	2012	(Gozlan *et al.*, 2012)
65.	*GCK*	c.455T>C	p.Phe152Ser	NM_001354800.1 NP_001341729	NA	Israel	VUS		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				9.1 (21978167)					
66.	*GCK*	c.476T>A	p.Ile159Asn	NM_001354800.1 NP_001341729.1 (21978167)	NA	Israel	VUS		
67.	*GCK*	c.499T>C	p.Trp167Arg	NM_001354800.1 NP_001341729.1 (21978167)	NA	Israel	VUS		
68.	*GCK*	c.532G>T	p.Gly178Trp	NM_001354800.1 NP_001341729.1 (21978167)	NA	Israel	LP		
69.	*GCK*	c.820G>C	p.Asp274His	NM_001354800.1 NP_001341729.1 (21978167)	NA	Israel	VUS		
70.	*GCK*	c.567_568insTATC	p.Lys190fs197X	NM_001354800.1 NP_001341729.1	NA	Israel			
71.	*GCK*		p.Gly80Ser	NP_000153.1 (10694920)	NA	Italy		1998	(Guazzini *et al.*, 1998)
72.	*GCK*	c.661G>A	p.Glu221Lys	NP_000153.1 (10694920)	NA	Italy			
73.	*GCK*		p.Gly227Cys	NP_000153.1 (10694920)	NA	Italy			
74.	*GCK*	c.579+1G>C		NM_001354800.1	NA	Norway		2013	(Irgens *et al.*, 2013)

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				NP_001341729.1					
75.	*GCK*	c.556C>G	p.Arg186Gly	NM_001354800.1 NP_001341729.1 (24097065)	NA	Norway	VUS		
76.	*GCK*	c.227C>A	p.Ser76Tyr	NM_001354800.1 NP_001341729.1 (21978167)	NA	Norway	VUS		
77.	*GCK*	c.1175G>C	p.Arg392Pro	NM_001354800.1 NP_001341729.1 (24097065)	NA	Norway	LP		
78.	*GCK*	c.629T>A	p.Met210Lys	NM_001354800.1 NP_001341729.1 (11372010)	NA	Norway	LP		
79.	*GCK*	c.697T>C	p.Cys233Arg	NM_001354800.1 NP_001341729.1 (17573900)	NA	Norway	VUS		
80.	*GCK*	c.579+1G>C		NM_001354800.1 NP_001341729.1	NA	Norway			
81.	*GCK*	c.766G>A	p.Glu256Lys	NM_001354800.1 NP_001341729	NA	Norway	LP		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				9.1 (8446612)					
82.	*GCK*	c.706G>A	p.Glu237Lys	NP_000153.1 (15305805)	NA	Canada		2004 2003	(J. McKinney *et al.*, 2003; J. L. McKinney *et al.*, 2004)
83.	*GCK*	c.971T>C	p.Leu324Pro	NP_000153.1 (15305805)	NA	Canada			
84.	*GCK*	IVS3 - 8G>A		?	NA	Canada			
85.	*GCK*	c.349G>C	p.G117R	NM_001354800.1 NP_001341729.1	NA	USA		2015	(Bennett *et al.*, 2015)
86.	*GCK*	c.397T>C	p.F133L	NM_001354800.1 NP_001341729.1 (25555642)	NA	USA	VUS		
87.	*GCK*	c.601G>C	p.A201P	NM_001354800.1 NP_001341729.1 (25555642)	NA	USA	LP		
88.	*GCK*	c.883G>T	p.G295C	NM_001354800.1 NP_001341729.1 (25555642)	NA	USA	LP		
89.	*GCK*	c.951delC	p.H317Qfs*36	NM_001354800.1 NP_001341729.1 (25555642)	NA	USA			
90.	*GCK*	c.1113C>	p.C371*	NM_001354800	NA	USA			

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
		A		0.1 NP_00134172 9.1					
91.	*GCK*	c.1268T>C	p.F423S	NM_00135480 0.1 NP_00134172 9.1 (25555642)	NA	USA	VUS		
92.	*GCK*	c.464G>C	p.Arg155Thr	NP_000153.1 (19410318)	NA	Spain			
93.	*GCK*	c.764C>T	p.Thr255Ile	NP_000153.1 (19410318)	NA	Spain			
94.	*GCK*	c.995C>A	p.Thr332Lys	NP_000153.1 (19410318)	NA	Spain		2009	(Solera *et al* , 2009)
95.	*GCK*		p.His424Y	NP_000153.1 (19410318)		Spain			
96.	*GCK*		p.Arg449Ser	NP_000153.1 (19410318)		Spain			
97.	*GCK*		p.Tyr289X	NP_000153.1		Spain			
98.	*GCK*		p.Lys143del	NP_000153.1		Spain			
99.	*GCK*	c.571C>T	p.Arg191Trp	NP_000153.1 (10753050)		South Korea		2006	(Hwang *et al.*, 2006)
100.	*GCK*	c. 24G>A	p.Met8Ile	NM_00135480 0.1 NP_00134172 9.1 (15928245)		Denmark	VUS		
101.	*GCK*	c.365T>C	p.Leu122Pro	NM_00135480 0.1 NP_00134172 9.1 (15928245)		Denmark	VUS	2005	(Johansen *et al.*, 2005)
102.	*GCK*	c.533G>A	p.Gly178Glu	NM_00135480 0.1	NA	Denmark	LP		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				NP_001341729.1 (15928245)					
103.	*GCK*	c.617C>T	p.Thr206Met	NM_001354800.1 NP_001341729.1 (11508276)	NA	Denmark	VUS		
104.	*GCK*	c.1019+1G>A	-	NM_001354800.1 NP_001341729.1	NA	Denmark			
105.	*GCK*	c.1183G>T	p.Glu395Ter	NM_001354800.1 NP_001341729.1 (15928245)	NA	Denmark	P		
106.	*GCK*	c.1210-1211delAT		NP_000153.1		Denmark			
107.	*GCK*		p.Arg186X	NP_000153.1 (1360036)		France			
108.	*GCK*	c.626C>T	p.Ala209Val	NP_000153.1 (8168652)	3.97687052104957E-06	France		1994	(Hager *et al.*, 1994)
109.	*GCK*		p.Gly261Glu	NP_000153.1 (8168652)		France			
110.	*GCK*		p.Arg36Trp	NP_000153.1 (8168652)		France			
111.	*GCK*	c.835_836	p.Glu236Ala	NP_000153.1		Japan		200	(Kawakita

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
		del		NM_001354800.1 (24804978)				4	*et al*., 2014)
112.	*GCK*	c.864-2A>G		NM_001354800.1 NP_001341729.1		Japan			
113.	*GCK*	c.538A>C	p.Asn180His	NM_001354800.1 NP_001341729.1 (24804978)		Japan	VUS		
114.	*GCK*	c.635_637del	p.Ser212del	NM_001354800.1 NP_001341729.1		Japan			
115.	*GCK*	c.1055T>G	p.Leu352Arg	NM_001354800.1 NP_001341729.1 (24804978)	NA	Japan	VUS		
116.	*GCK*	c.707A>C	p.Glu236Ala	NM_001354800.1 NP_001341729.1 (24804978)	NA	Japan	VUS		
117.	*GCK*	c.1144-1149dup	p.C382_S383dup	NP_000153.1	NA	Japan			
118.	*GCK*	32insC(33)intron3		?	NA	Germany		2004	(Knebel *et al.*, 2004)
119.	*GCK*	39insC(40)intron3		?	NA	Germany			
120.	*GCK*	c.364C>A	p.Leu122Ile	NP_000153.1 (15216446)		Germany	LP		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
121.	*GCK*	c.72G>R		NP_000153.1 (10447526)		Sweden		1999	(Lehto *et al.*, 1999)
122.	*GCK*	IVS3 + 1G > A		?		Sweden			
123.	*GCK*	IVS3 ±2A > G		?		Sweden			
124.	*GCK*	133dupY125-D132	p.Leu45ProfsTer7	NM_001354800.1 NP_001341729.1		Sweden			
125.	*GCK*	c.1093G>A	p.Asp365Asn	NM_001354800.1 NP_001341729.1 (25174781)	NA	Brazil	VUS	2014	(Weinert *et al.*, 2014)
126.	*GCK*	c.242G>A	p.Gly81Asp	NM_001354800.1 NP_001341729.1 (20132997)	NA	Brazil	VUS		
127.	*GCK*	c.757G>C	p.Val253Leu	NM_001354800.1 NP_001341729.1 (25174781)	NA	Brazil	LP		
128.	*GCK*	c.571C>T	p.Arg191Trp	NP_000153.1 (10753050)	NA	Brazil	VUS	2012	(Caetano *et al.*, 2012)
129.	*GCK*	c.661G>A	p.Glu221Lys	NP_000153.1 (10694920)	NA	Brazil	LP		
130.	*GCK*	c.584T>C	p.Phe195Ser	NP_000153.1	NA	China		2018	(Liu *et al.*, 2018)
131.	*GCK*	c.632T>C	p.Met211Thr	NP_000153.1	3.97674400108	China			

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
					167E-06				
132.	*GCK*	c.665T>A	p.Val222Asp	NP_000153.1	NA	China			
133.	*GCK*	c.707A>G	p.Glu236Gly	NP_000153.1	NA	China			
134.	*GCK*	c.1373A>G	p.Lys458Arg	NP_000153.1	NA	China			
135.	*GCK*	c.46-15_46-11delnsGGGAGGG		?	NA	USA		2010	(Loomba-Albrecht *et al.*, 2010)
136.	*GCK*	c.45+1G>A		NM_001354800.1 NP_001341729.1	NA	Macedonia		2017	(Kocova *et al.*, 2017)
137.	*GCK*	c.895G>T	p.Gly299Cys	NP_000153.1 (1303265)	NA	UK		1992	(Stoffel *et al.*, 1992)
138.	*GCK*	c.483G>C	p.Lys161Asn	NM_001354800.1 NP_001341729.1 (12955723)	NA	Italy	VUS	2003	(Mantovani *et al.*, 2003)
139.	*GCK*	c.511T>C	p.Phe171Leu	NM_001354800.1 NP_001341729.1	NA	Italy	VUS		
140.	*GCK*	c.682A>G	p.Thr228Ala	NM_001354800.1 NP_001341729.1 (12955723)	NA	Italy	LP		
141.	*GCK*	c.683C>G	p.Thr228Arg	NM_001354800	NA	Italy	LP		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
			,	0.1 NP_00134172 9.1 (12955723)					
142.	*GCK*	c.772G>T	p.Gly258Cys	NM_00135480 0.1 NP_00134172 9.1 (12955723)	NA	Italy	VUS		
143.	*GCK*	c.1148C>A	p.Ser383Ter	NM_00135480 0.1 NP_00134172 9.1 (12955723)		Italy	P		
144.	*GCK*	c.1253+1G>T		NM_00135480 0.1 NP_00134172 9.1		Italy			
145.	*GCK*	c.1298_1309del12	p.Ser433_Ile436del	NP_000153.1		Italy			
146.	*GCK*	c.48_50delAGA,	p.Glu17del	NM_00135480 0.1 NP_00134172 9.1		Italy		2017 (Delvecchio *et al.*, 2017)	
147.	*GCK*	c.167A>G	p.Lys56Arg	NM_00135480 0.1 NP_00134172 9.1		Italy	VUS		
148.	*GCK*	c.208+1G		NM_00135480		Italy			

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
		>T		0.1 NP_00134172 9.1					
149.	*GCK*	c.457C>T	p.Pro153Ser	NM_00135480 0.1 NP_00134172 9.1		Italy	LP		
150.	*GCK*	c.466C>A	p.His156Asn	NM_00135480 0.1 NP_00134172 9.1		Italy	LP		
151.	*GCK*	c.475A>T	p.Ile159Phe	NM_00135480 0.1 NP_00134172 9.1		Italy	VUS		
152.	*GCK*	c.685G>T	p.Gly229Cys	NM_00135480 0.1 NP_00134172 9.1		Italy	VUS		
153.	*GCK*	c.688T>G	p.Cys230Gly	NM_00135480 0.1 NP_00134172 9.1		Italy	LP		
154.	*GCK*	c.763A>C	p.Thr255Pro	NM_00135480 0.1 NP_00134172 9.1		Italy	VUS		
155.	*GCK*	c.775_777 delGCC	p.Ala259del	NP_000153.1	NA	Italy			
156.	*GCK*	c.859C>T	p. Gln287Ter	NM_00135480 0.1 NP_00134172 9.1		Italy	P		
157.	*GCK*	c.925C>G	p.Leu309Val	NM_00135480	NA	Italy	VUS		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				0.1 NP_001341729.1					
158.	*GCK*	c.960_970del	p.Ala320del	NP_000153.1	NA	Italy			
159.	*GCK*	c.1019G>A	p.Ser340Asn	NM_001354800.1 NP_001341729.1	NA	Italy	VUS		
160.	*GCK*	c.1180C>A	p.Arg394Ser	NM_001354800.1 NP_001341729.1		Italy	VUS		
161.	*GCK*	c.1182insA	p.Arg394ins	NP_000153.1		Italy			
162.	*GCK*	c.1222G>A	p.Val408Met	NM_001354800.1 NP_001341729.1		Italy	VUS		
163.	*GCK*	c.1228C>G	p.Gly410Arg	NP_000153.1		Italy	VUS		
164.	*GCK*	c.1310C>T	p.Thr437Ile	NM_001354800.1 NP_001341729.1		Italy	VUS		
165.	*GCK*	c.1318G>A	p.Glu440Lys	NM_001354800.1 NP_001341729.1		Italy	VUS		
166.	*GCK*	c.1332_1333dupGC,	p.Gly444delins	NP_000153.1		Italy			
167.	*GCK*	c.676G>A	p.Val226Met	NP_000153.1 (9049484)		Canada	LP	2007	(Henderson *et al.*, 2007)

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
168.	*GCK*	c.185T>C	p.Val62Ala	NP_000153.1 (9736233)		Norway	LP	1998	(Henderson *et al.*, 2007; Njolstad *et al.*, 1998)
169.	*GCK*	c.509G>T	p.Gly170Val	NP_000153.1 (25372588)		Portugal	LP	2014	(Afonso *et al.*, 2014)
170.	*GCK*	c.980G>A	p.Arg327His	NP_000153.1 (18811724)		Thailand		2009	(Plengvidhya *et al.*, 2009)
171.	*GCK*	c.208+1G>A		NM_001354800.1 NP_001341729.1		Czech Republic		2010	(Pruhova *et al.*, 2010)
172.	*GCK*	c.242G>A	p.Gly81Asp	NM_001354800.1 NP_001341729.1 (20132997)		Czech Republic	VUS		
173.	*GCK*	c.370G>A,	p.Asp124Asn	NM_001354800.1 NP_001341729.1 (19790256)		Czech Republic	LP		
174.	*GCK*	c.540delT	p.Asn180fs	NM_001354800.1 NP_001341729.1		Czech Republic			
175.	*GCK*	c.579+1G>T		NM_001354800.1 NP_001341729.1	NA	Czech Republic			
176.	*GCK*	c.626C>A,	p.Thr209Lys	NM_001354800.1		Czech Repub	VUS		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				NP_001341729.1 (20337973)		lic			
177.	*GCK*	c.677T>A,	p.Val226Glu	NM_001354800.1 NP_001341729.1 (20337973)		Czech Republic	LP		
178.	*GCK*	c.730delG,	p.Val244fs	NM_001354800.1 NP_001341729.1		Czech Republic			
179.	*GCK*	c.829_830delinsAG,	p.Val277Arg	NM_001354800.1 NP_001341729.1		Czech Republic			
180.	*GCK*	c.864-1G>C		NM_001354800.1 NP_001341729.1 (20337973)		Czech Republic			
181.	*GCK*	c.1153G>T	p.Gly385Trp	NM_001354800.1 NP_001341729.1 (20337973)		Czech Republic	LP		
182.	*GCK*	c.1233_1238delCinsACCCCA,	p.Val412fs	NP_000153.1		Czech Republic			
183.	*GCK*	c.1334G>T	p.Glu442stop	NM_001354800.1 NP_001341729.1		Czech Republic	VUS		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				(20337973)					
184.	*GCK*		p. Leu77Arg	NP_000153.1 (27185633)		China		2016	(Q. Li *et al.*, 2016)
185.	*GCK*	c.323A>G	p.Tyr108Cys	NM_001354800.1 NP_001341729.1 (12050210)		Spain	VUS	2002	(Barrio *et al.*, 2002)
186.	*GCK*	c.563C>A +564T>A,	188A>E	NM_001354800.1 NP_001341729.1		Spain	LP		
187.	*GCK*	c.755G>A	p.Cys252Tyr	NM_001354800.1 NP_001341729.1 (12050210)		Spain	VUS		
188.	*GCK*	c.893T>A	p.Met298Lys	NM_001354800.1 NP_001341729.1 (12050210)		Spain	VUS		
189.	*GCK*	c.1106G>C	p.Arg369Pro	NM_001354800.1 NP_001341729.1 (12050210)		Spain	VUS		
190.	*GCK*	c.1148C>T	p.Ser383Leu	NM_001354800.1 NP_001341729.1 (11942313)		Spain	LP		
191.	*GCK*	c.1232C>T	p.Ser411Phe	NM_001354800.1		Spain	VUS		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				NP_001341729.1 (12050210)					
192.	*GCK*	c.-457C>T		NM_001354800.1 NP_001341729.1	0.000318	Tunisia		2018	(Ben Khelifa *et al.*, 2018)
193.	*GCK*	c.227C>A	p.Ser76Tyr	NP_000153.1 (18399931)		Norway		2008	(Sagen *et al.*, 2008)
194.	*GCK*	c.692A>G	p.Asn231Ser	NP_000153.1 (18399931)	NA	Norway			
195.	*GCK*	c.110T>C	p.Met37Thr	NM_001354800.1 NP_001341729.1		Brazil	VUS	2017	(Santana *et al.*, 2017)
196.	*GCK*	c.326delC	p.Ile110Serfs*6	NM_001354800.1 NP_001341729.1		Brazil			
197.	*GCK*	c.418A>G	p.Lys140Glu	NM_001354800.1 NP_001341729.1		Brazil	VUS		
198.	*GCK*	c.505A>G	p.Lys169Glu	NM_001354800.1 NP_001341729.1	NA	Brazil	VUS		
199.	*GCK*	c.580-3C>A		NM_001354800.1 NP_001341729.1		Brazil			
200.	*GCK*	c.749G>A	p.Arg250His	NM_001354800.1	NA	Brazil	VUS		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				NP_001341729.1					
201.	*GCK*	c.767A>C	p.Glu256Ala	NM_001354800.1 NP_001341729.1	NA	Brazil	VUS		
202.	*GCK*	c.791G>A	p.Gly264Asp	NM_001354800.1 NP_001341729.1	NA	Brazil	VUS		
203.	*GCK*	c.1106_1111dup,	p.Cys371Serfs*33	NM_001354800.1 NP_001341729.1	NA	Brazil			
204.	*GCK*	c.1135_1154del;1134_1135ins9,	p.His380GlyfsTer85	NM_001354800.1 NP_001341729.1	NA	Brazil			
205.	*GCK*	c.1226delA	p.Asp409Valfs*22	NM_001354800.1 NP_001341729.1	NA	Brazil			
206.	*GCK*	c.1247delA	p.His416Profs*15	NM_001354800.1 NP_001341729.1	NA	Brazil			
207.	*GCK*	c.745G > T	p.G249C	NM_001354800.1 NP_001341729.1 (19790256)	NA	Turkey	VUS	2016	(Agladioglu *et al.*, 2016)
208.	*GCK*	c.91A > T	p.Lys31Ter	NM_001354800.1 NP_001341729	NA	Turkey	P		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				9.1					
209.	*GCK*	c.943C > T	p.Leu315Phe	NM_001354800.1 NP_001341729.1 (16965331)	NA	Turkey	VUS		
210.	*GCK*	c.112C > T	p.Gln38Ter	NM_001354800.1 NP_001341729.1	NA	Turkey	P		
211.	*GCK*	c.214G > A	p.Gly72Arg	NM_001354800.1 NP_001341729.1 (10447526)	NA	Turkey	LP		
212.	*GCK*	c.379T > C	p.Ser127Pro	NM_001354800.1 NP_001341729.1	NA	Turkey	VUS		
213.	*GCK*	c. 1178T>C	p.Met393Thr	NM_001354800.1 NP_001341729.1 (19790256)	NA	Turkey	VUS		
214.	*GCK*	c.667G > A	p.Gly223Ser	NM_001354800.1 NP_001341729.1 (11508276)		Turkey	LP		
215.	*GCK*	c.658T > C	p.Cys220Arg	NM_001354800.1 NP_001341729.1 (24097065)		Turkey	LP		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
216.	*GCK*	c.616A > G	p.Thr206Ala	NM_001354800.1 NP_001341729.1 (24405491)	NA	India	LP	2014	(Kanthimathi *et al.*, 2014)
217.	*GCK*		p.His156fs	NP_000153.1	NA	Korea		2019	(Park *et al.*, 2019)
218.	*GCK*	c.490C>T	p.Leu164Phe	NP_000153.1 (18248649)		Korea			
219.	*GCK*	c.363+2T>C		NM_001354800.1 NP_001341729.1		Korea			
220.	*GCK*	c.1030G>T	p.Asp344Tyr	NM_001354800.1 NP_001341729.1 (27016322)		India	VUS	2016	(Jha *et al.*, 2016)
221.	*GCK*	c.151G>T	p.Glu51Ter	NM_001354800.1 NP_001341729.1		Turkey	P	2018	(Ozdemir *et al.*, 2018)
222.	*GCK*	c.1396T>A	p.*466R	(19790256)		Turkey	VUS		
223.	*GCK*	c.595G>A	p.Val199Met	NP_000153.1		Australia		2019	(Taylor *et al.*, 2019)
224.	*GCK*	c.206C>G	p.Ser69Stop	NM_001354800.1 NP_001341729.1 (23295287)		Brazil	P	2012	(DellaManna *et al.*, 2012)
225.	*GCK*	c.431_432delTGinsCT L144P	p.Leu144Pro	NM_001354800.1 NP_001341729.1		Germany		2005	(Toaima *et al.*, 2005)

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
226.	*GCK*	c.580-1G>A		NM_001354800.1 NP_001341729.1		Germany			
227.	*GCK*	c.891C>A	p.Tyr297Ter	NM_001354800.1 NP_001341729.1 (15841481)		Germany	P		
228.	*GCK*	c.1195G>T	p.Glu399Ter	NM_001354800.1 NP_001341729.1 (15841481)		Germany	P		
229.	*GCK*	c.1377delG	K459fsX610	NP_000153.1	NA	Germany			
230.	*GCK*	c.73G>C	p.Ala25Pro	?	NA	Germany	Uncertain		
231.	*GCK*	c.1155_1156insA	p.Leu386ThrfsTer86	NM_001354800.1 NP_001341729.1		Germany			
232.	*GCK*	c.1323delG	p.Glu442ArgfsTer22	NM_001354800.1 NP_001341729.1		Germany			
233.	*GCK*	c.157G>T	p.Ala53Ser	NP_000153.1		France		1997	(Velho *et al.*, 1997)
234.	*GCK*	c.239G>C	p.Gly80Ala	NP_000153.1 (9049484)		France			
235.	*GCK*	L122-1G>T		?	NA	France			
236.	*GCK*	c.410A>G	p.His137Arg	NP_000153.1	NA	Franc			

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				(9049484)		e			
237.	*GCK*	K161+1del10		?	NA	France			
238.	*GCK*	c.502A>C	p.Thr168Pro	NP_000153.1 (9049484)	NA	France			
239.	*GCK*		p.Arg186X	NP_000153.1		France	P		
240.	*GCK*	c.629T>C	p.Met210Thr	NP_000153.1 (9049484)	NA	France			
241.	*GCK*	c.637T>C	p.Cys213Arg	NP_000153.1 (9049484)	NA	France			
242.	*GCK*	c.676G>A	p.Val226Met	NP_000153.1 (9049484)	NA	France	LP		
243.	*GCK*		p.Glu248X	NP_000153.1 (9049484)		France			
244.	*GCK*	c.781G>A	p.Gly261Arg	NP_000153.1 1502186		France	LP		
245.	*GCK*	c.1007C>T	p.Ser336Leu	NP_000153.1 (9049484)		France			
246.	*GCK*	c.1079C>A	p.Ser360X	NP_000153.1 (9049484)		France			
247.	*GCK*	c.1099G>A	p.Val367Met	NP_000153.1 (9049484)		France			
248.	*GCK*	V401del1		NP_000153.1	NA	France			
249.	*GCK*	c.1257-20_1315del		NM_001354800.1 NP_001341729.1	NA	Korea		2018	(Y. K. Cho *et al.*, 2018)
250.	*GCK*	c.1084_1086del	p.Thr362del	NM_001354800.1 NP_001341729.1		China		2019	(Ming-Qiang *et al.*, 2019)
251.	*GCK*	c.1165del	p.V389Sfs*1	NM_001354800		China			

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
		G	39	0.1 NP_00134172 9.1					
252.	*GCK*	c.871A > T,	p.Lys291Ter	NM_00135480 0.1 NP_00134172 9.1		Germany		2017	(Bansal *et al.*, 2017)
253.	*GCK*	c.1340_1368del	p.Arg447LeufsTer15	NM_00135480 0.1 NP_00134172 9.1		Germany			
254.	*GCK*	c.863+1G >T		?	NA	Germany			
255.	*GCK*	c.484G>A ,	p.Gly162Ser	NM_00135480 0.1 NP_00134172 9.1 (19790256)	NA	Germany	VUS		
256.	*GCK*	c.952G>A	p.Gly318Arg	NM_00135480 0.1 NP_00134172 9.1 (12627330)		Germany	LP		
257.	*GCK*	c.617C>T	p.Thr206Met	NM_00135480 0.1 NP_00134172 9.1 (11508276)		Germany	VUS		
258.	*GCK*	c.238G>A	p.Gly80Ser	NM_00135480 0.1 NP_00134172 9.1 (10694920)		Germany	LP		
259.	*GCK*	c.1349C >	p.Ala450Val	NM_00135480	8.33	Germ	VUS		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
		T		0.1 NP_00134172 9.1 (22035297)	270838020481E-06	any			
260.	*GCK*	c.911T > C	p.Leu304Pro	NM_00135480 0.1 NP_00134172 9.1 (11942313)		Germany	LP		
261.	*GCK*	c.559G>T	p.Asp187Tyr	NM_00135480 0.1 NP_00134172 9.1 (17573900)		Germany	VUS		
262.	*GCK*	c.214G>A	p.Gly72Arg	NM_00135480 0.1 NP_00134172 9.1 (10447526)		Germany	LP		
263.	*GCK*	c.118G>A	p.Glu40Lys	NM_00135480 0.1 NP_00134172 9.1		Germany	LP		
264.	*GCK*	c.562G > A	p.Ala188Thr	NM_00135480 0.1 NP_00134172 9.1 (8314448)		Germany	VUS		
265.	*GCK*	c.640T>G	p.Tyr214Asp	NM_00135480 0.1 NP_00134172 9.1		Germany	VUS		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				(21348868)					
266.	*GCK*	c.131G > A	p.Gly44Asp	NM_001354800.1 NP_001341729.1 (12627330)	3.97702868233085E-06	Germany	LP		
267.	*GCK*	c.572G > A	p.Arg191Gln	NM_001354800.1 NP_001341729.1 (11508276)	NA	Germany	LP		
268.	*GCK*	c.787_801del	p.Ser263_Asp267del	NM_001354800.1 NP_001341729.1		Germany			
269.	*GCK*	c.544G>A	p.Val182Met	NM_001354800.1 NP_001341729.1 (8433729)		Germany	LP		
270.	*GCK*	c.706G>A	p.Glu236Lys	NM_001354800.1 NP_001341729.1 (19790256)	NA	Germany	LP		
271.	*GCK*	c.394G>A	p.Asp132Asn	NM_001354800.1 NP_001341729.1 (18382660)	NA	Germany	VUS		
272.	*GCK*	c.757G>A	p.Val253Ile	NM_001354800		Germ	LP		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
		,		0.1 NP_001341729.1		any			
273.	*GCK*	c.31G > A	p.Ala11Thr	NM_001354800.1 NP_001341729.1	0.0021	Germany	likely benign		
274.	*GCK*	c.35A>G	p.Lys12Arg	NM_001354800.1 NP_001341729.1	7.96996915621936E-06	Germany	VUS		
275.	*GCK*		p.Arg43His	NP_000153.1 (11942313)		UK		2012	(Beer *et al.*, 2012)
276.	*GCK*	c.203G>A	p.Gly68Asp	NP_000153.1 (19790256)		UK			
277.	*GCK*	c.208 + 3A>T		NM_001354800.1 NP_001341729.1	NA	Turkey		2016	(Haliloglu *et al.*, 2016)
278.	*GCK*	c.368T>C	p.Phe123Ser	NM_001354800.1 NP_001341729.1	NA	Turkey	VUS		
279.	*GCK*	c.173T>C	p.Leu58Pro	NM_001354800.1 NP_001341729.1		Turkey	VUS		
280.	*GCK*	c.1256T>G	p.Phe419Cys	NM_001354800.1 NP_001341729.1		Turkey			

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
281.	*GCK*	c.208+3A>T		NM_001354800.1 NP_001341729.1	NA	Turkey			
282.	*GCK*	c.452C>G	p.Ser151Cys	NM_001354800.1 NP_001341729.1	NA	Turkey			
283.	*GCK*	c.676G>A	p.Phe330Ser	NP_000153.1	NA	Germany		2011	(Bonfig *et al.*, 2011; Haliloglu *et al.*, 2016)
284.	*GCK*	c.120G>C	p.Glu40Asp	NP_000153.1 (22761713)	NA	Italy		2012	(Capuano *et al.*, 2012)
285.	*GCK*	c.460G>T	p.Val154Leu	NP_000153.1 (22761713)	NA	Italy			
286.	*GCK*	c.1339delC	p.Arg447Glyfs	NP_000153.1 (26587058)	NA	Italy			
287.	*GCK*	c.1373_1385del	p.Lys458_Cys461del	NP_000153.1	NA	Italy			
288.	*GCK*		p.Glu395_Arg397del	NP_000153.1	NA	Italy			
289.	*GCK*	c.580-2A>T		NM_001354800.1 NP_001341729.1	NA	Italy			
290.	*GCK*	c.431T>C	p.Leu144Pro	NM_001354800.1 NP_001341729	NA	USA	VUS	2016	(Chambers *et al.*, 2016)

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				9.1					
291.	*GCK*	c.460G>C	p.Val154Leu	NM_001354800.1 NP_001341729.1 (22761713)	NA	USA	VUS		
292.	*GCK*	c.605 T>C	p.Met202Thr	NM_001354800.1 NP_001341729.1 (17937063)	NA	USA	LP		
293.	*GCK*	c.1160C>A	p.Ala387Glu	NM_001354800.1 NP_001341729.1 (23771925)	NA	USA	LP		
294.	*GCK*	c.1265G>C	p.Arg422Pro	NM_001354800.1 NP_001341729.1	NA	USA	VUS		
295.	*GCK*	c.554T>A	p.Leu185Gln	NM_001354800.1 NP_001341729.1	NA	Brazil	VUS	2019	(de Santana *et al.*, 2019)
296.	*GCK*	c.1334 G>C	p.Ser445Thr	NM_001354800.1 NP_001341729.1	NA	China	VUS		
297.	*GCK*	c.1289_1294delTGACGC	p.Leu430_Thr431del	NM_001354800.1 NP_001341729.1	NA	China		2019	(Fu *et al.*, 2019)
298.	*GCK*	c.584 T>C	p.Phe195Ser	NM_001354800.1	NA	China	VUS		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				NP_001341729.1					
299.	*GCK*	c.30delC	p.Ala11ProfsTer6	NM_001354800.1 NP_001341729.1	NA	China			
300.	*GCK*		p.Gly71Cys	?	NA	UK		2009	(Gasperikova *et al.*, 2009)
301.	*GCK*	c.596T>C	p.Val199Ala	NM_001354800.1 NP_001341729.1	NA	Serbia		2019	(Komazec *et al.*, 2019)
302.	*GCK*	c.45G>A	p.Lys15=	NM_001354800.1 NP_001341729.1 (23771925)	NA	Italy			
303.	*GCK*	c.7G>A				Italy			
304.	*GCK*	c.451T>C	p.Ser151Pro	NM_001354800.1 NP_001341729.1 (19564454)	NA	Italy	VUS	2009	(Lorini *et al.*, 2009)
305.	*GCK*	c.483G>A	p.Lys161=	NM_001354800.1 NP_001341729.1 (12955723)	NA	Italy	VUS		
306.	*GCK*	c.613G>T	p.Asp205Tyr	NM_001354800.1 NP_001341729.1 (19564454)	NA	Italy	VUS		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
307.	*GCK*	c.749G>C	p.Arg250Pro	NM_001354800.1 NP_001341729.1 (19564454)	NA	Italy	LP		
308.	*GCK*	c.794A>T	p.Glu265Val	NM_001354800.1 NP_001341729.1 (19564454)	NA	Italy	VUS		
309.	*GCK*	c.805T>C	p.Phe269Leu	NM_001354800.1 NP_001341729.1 (19564454)	NA	Italy	VUS		
310.	*GCK*	c.827T>C	p.Leu276Pro	NM_001354800.1 NP_001341729.1 (19564454)	NA	Italy	VUS		
311.	*GCK*	c.865T>C	p.Tyr289His	NM_001354800.1 NP_001341729.1 (19564454)	NA	Italy	VUS		
312.	*GCK*	c.976A>C	p.Thr326Pro	NM_001354800.1 NP_001341729.1 (19564454)	NA	Italy	VUS		
313.	*GCK*	c.991G>A	p.Glu331Lys	NM_001354800.1 NP_001341729.1	NA	Italy	VUS		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				(19564454)					
314.	*GCK*	c.1019+5G>A		NM_001354800.1 NP_001341729.1	NA	Italy			
315.	*GCK*	c.1313T>A	p.Phe438Tyr	NM_001354800.1 NP_001341729.1 (19564454)	NA	Italy	VUS		
316.	*GCK*	33Val>Ala	p.Val33Ala	NP_000153.1 18271687	NA	Czech Republic		2008	(Lukasova *et al.*, 2008)
317.	*GCK gene*	1343G>A,	p.Gly448Asp	NM_001354800.1 NP_001341729.1	NA	USA	VUS	2018	(Estica *et al.*, 2018)
318.	*GCK*	259A>T	p.Ala259Thr	NP_000153.1 (9662401)	NA	UK		1998	(Matyka *et al.*, 1998)
319.	*GCK*	c.1010delA	p.Gln337ArgfsTer16	NM_001354800.1 NP_001341729.1	NA	Iran		2013	(Noorian *et al.*, 2013)
320.	*GCK*	c.44A>T	p.Lys15Met	NM_001354800.1 NP_001341729.1 (23771925)	NA	USA	VUS	2013	(Pihoker *et al.*, 2013)
321.	*GCK*	c.1265G>T	p.Arg422Leu	NM_001354800.1 NP_001341729.1 (23771925)	NA	USA			
322.	*GCK*		p.Gly299Ar	NP_000153.1	NA	USA	LP	201	(Gandica

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
			g	(1303265)				5	*et al.*, 2015)
323.	*GCK*		p.Val182Met	NP_000153.1 (8433729)		USA	LP		
324.	*GCK*	185Arg>Ter	p.Arg185Ter	?		USA			
325.	*GCK*	340Arg>Lys	p.Arg340Lys	?		USA			
326.	*GCK*	c.181T>G	p.Tyr61Asp	NM_001354800.1 NP_001341729.1		Brazil	VUS	2019	(Tarantino *et al*., 2019)
327.	*GCK*		p.Val62Ala	NP_000153.1 (9736233)		Norway		2006	(Sagen *et al.*, 2006)
328.	*GCK*		p.Gly72Arg	NP_000153.1 (10447526)		Norway			
329.	*GCK*		p.Lys146Arg	NP_000153.1 (16731834)		Norway			
330.	*GCK*		p.Ala208Thr	NP_000153.1 (16731834)		Norway			
331.	*GCK*		p.Met210Lys	NP_000153.1 (11372010)		Norway			
332.	*GCK*		p.Tyr215X	NP_000153.1 (10753050)		Norway			
333.	*GCK*		p.Ser263Pro	NP_000153.1 (12442280)		Norway			
334.	*GCK*		p.Glu339Gly	NP_000153.1 (16731834)		Norway			
335.	*GCK*		p.Arg377Cys	NP_000153.1 (16731834)		Norway			
336.	*GCK*		p.Ser453Leu	NP_000153.1 (14517956)		Norway	LP		
337.	*GCK*	IVS5 1G>C		?		Norway			
338.	*GCK*	203V>A	p.Val203Ala	NP_000153.1		Switz		200	(Schnyder

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				(8433729)		erland		5	*et al.*, 2005)
339.	*GCK*	c.244 A>G	p.Thr82Ala	NM_001354800.1 NP_001341729.1 (20587714)		Canada	VUS	2010	(Marks *et al.*, 2010)
340.	*GCK*	c.83delA	p.Glu28GlyfsTer3	NM_001354800.1 NP_001341729.1		Canada			
341.	*GCK*	c.1340G>A	p.Arg447Gln	NM_001354800.1 NP_001341729.1 (14517956)		UK	LP	2016	(Shepherd *et al.*, 2016)
342.	*GCK*	c.659G>A	p.Cys220Tyr	NM_001354800.1 NP_001341729.1 (22341229)		USA	LP	2012	(Shoemaker *et al.*, 2012)
343.	*GCK*		p.Glu70Asp	NP_000153.1 (18382660)		Italy		2008	(Tinto *et al.*, 2008)
344.	*GCK*		p.Phe123Leu	NP_000153.1 (18382660)		Italy			
345.	*GCK*		p.Asp132Asn	NP_000153.1		Italy			
346.	*GCK*		p.His137Asp	NP_000153.1 (18382660)		Italy			
347.	*GCK*		p.Gly162Asp	NP_000153.1 (18382660)		Italy			
348.	*GCK*		p.Thr168Ala	NP_000153.1 (18382660)		Italy			

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
349.	*GCK*		p.Arg392Ser	NP_000153.1 (18382660)		Italy			
350.	*GCK*		p.Glu290X	NP_000153.1 (18382660)		Italy			
351.	*GCK*		p.Gln106_Met107delinsLeu	NP_000153.1		Italy			
352.	*GCK*		p.Ile110N	NP_000153.1 22493702		Slovakia			
353.	*GCK*		p.Val200Ala	NP_000153.1 (22493702)		Slovakia			
354.	*GCK*		p.Asn204Asp	NP_000153.1 (22493702)		Slovakia			
355.	*GCK*		p.Gly258Arg	NP_000153.1 (22493702)		Slovakia			
356.	*GCK*		p.Phe419Ser	NP_000153.1 (22493702)		Slovakia		2012	(Valentinova *et al.*, 2012)
357.	*GCK*	c.580-A>C		NM_001354800.1 NP_001341729.1		Slovakia			
358.	*GCK*	c.1113–1114delGC		?		Slovakia			
359.	*GCK*	c.507G>C	p.Lys169Asn	NM_001354800.1 NP_001341729.1 (11508276)	NA	China	VUS	2019	(Z. Wang *et al.*, 2019)
360.	*GCK*	c.645C>A	p.Tyr215Ter	NM_001354800.1 NP_001341729.1 (10753050)	NA	China	P		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
361.	*GCK*	c.771G>A	p.Trp257Ter	NM_001354800.1 NP_001341729.1	NA	China	P		
362.	*GCK*	c.698G>A	p.Cys233Tyr	NM_001354800.1 NP_001341729.1 (24355479)	NA	NewZealand	Uncertain significance	2013	(Wheeler *et al.*, 2013)
363.	*GCK*	c.483+2T>A		NM_001354800.1 NP_001341729.1		China		2018	(X. Li *et al.*, 2018)
364.	*GCK*		p.Ser151del	NP_000153.1		China			
365.	*GCK*		p.Met57GlyfsX29	NP_000153.1		China			
366.	*GCK*		p.Val374_Ala377del	NP_000153.1		China			
367.	*HNF1a*		p.Val133Met	NP_001293108.2 (10754480)	NA	Spain		2000	(Costa *et al.*, 2000)
368.	*HNF1a*		p.Arg159Gln	NP_001293108.2 (9097962)	NA	Spain			
369.	*HNF1a*		p.Val259Asp	NP_001293108.2 (10754480)	NA	Spain			
370.	*HNF1a*	c.1-326del		?	NA	UK		2019	(Juszczak *et al.*, 2019)
371.	*HNF1a*	c.404delA	p.Asp135ValfsTer20	NM_001306179.1 NP_001293108	NA	UK			

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				8.1					
372.	*HNF1a*	c.685C>T*	p.Arg229Ter	NP_001293108.2 (9032114)	7.96355875513649E-06	UK	P		
373.	*HNF1a*	c.779C>T	p.Thr260Met	NP_001293108.2 NM_001306179.1 (9166684)	4.01174639343999E-06	UK	LP		
374.	*HNF1a*	c.872delC	p.Pro291GlnfsTer51	NM_001306179.1 NP_001293108.1 (23771925)	NA	UK			
375.	*HNF1a*	c.872dup	p.Gly292ArgfsTer25	NP_001293108.2 NM_001306179.1	NA	UK			
376.	*HNF1a*	c.1129delC	p.Leu377fs	NP_001293108.2 NM_001306179.1	NA	UK			
377.	*HNF1a*	c.1136_1137delCT†	p.Pro379ArgfsTer39	NM_001306179.1 NP_001293108.1	NA	UK			
378.	*HNF1a*	c.1136C>G	p.Pro379Arg	NP_001293108.2	3.99817	UK	VUS		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				NM_001306179.1 (15657605)	683136489E-06				
379.	*HNF1a*	c.723C>A	p.Cys241Ter	NP_001293108.2 NM_001306179.1 (26226118)	NA	Turkey	P	2015	(Anik *et al.*, 2015)
380.	*HNF1a*	c.707G>A	p.Cys236tyr	NP_001293108.2	NA	Canada	VUS	2016	(Brahm *et al.*, 2016)
381.	*HNF1a*	c.137_138insG	p.K46KfsX13	NP_001293108.2	NA	Canada			
382.	*HNF1a*	c.243_244insAG	p.T82RfsX73	NP_001293108.2	NA	Canada			
383.	*HNF1a*	c.1108-3delTAG			NA	Canada			
384.	*HNF1a*		p.Glu48Asp	NP_001293108.2 (21168233)	NA	Argentina		2011	(Lopez *et al.*, 2011)
385.	*HNF1a*	g.914fsinsGA				Argentina			
386.	*HNF1a*	g.2707C>G	p.Arg203Gly	NP_001293108.2 (21168233)	NA	Argentina			
387.	*HNF1a*	g.3430delC		?		Argentina			
388.	*HNF1a*		p.Gln463X	?		Argentina			
389.	*HNF1a*	g.4962+3insT		?		Argentina			
390.	*HNF1a*	g.1777-21c>t –		?		Argentina			

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
391.	*HNF1a*	g.3513+23g>t		?		Argentina			
392.	*HNF1a*	g.3482C>G	p.Pro308Pro	NP_001293108.2		Argentina			
393.	*HNF1a*	g.4962+68a>g		?		Argentina			
394.	*HNF1a*	c.802T>C	p.Phe268Leu	NP_001293108.2 NM_001306179.1 (20132997)	NA	Czech Republic	VUS	2010	(Bazalova *et al.*, 2010)
395.	*HNF1a*	c.871C>T	p.Pro291Ser	NP_001293108.2 NM_001306179.1 (20132997)	0.00023	Czech Republic	Likely benign		
396.	*HNF1a*	c.92G>A	p.Gly31Asp	NP_001293108.2 NM_001306179.1 (9754819)	0.000749	Netherland	LP	2009	(Beijers *et al.*, 2009)
397.	*HNF1A*	c.1501G>T	p.Ala501Ser	NM_001306179.1 NP_001293108.1 (25041077)	NA	India	VUS	2015	(Chapla *et al.*, 2015)
398.	*HNf1a*	c.	p.Arg54X	NP_001293108.2 (12547858)	NA	China		2015	(Fang *et al.*, 2015)
399.	*HNf1a*	c.92G>A	p.Gly31Asp	NP_001293108.2 (9754819)	0.00074	France		1998	(Chevre *et al.*, 1998)
400.	*HNf1a*	c.481G>A	p.Ala161Thr	NP_001293108.2	0.00009	France			

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				(9754819)	54				
401.	*HNf1a*		p.Arg200trp	NP_001293108.2 (9754819)	NA	France	VUS		
402.	*HNf1a*		p.Arg271Trp	NP_001293108.2 (9754819)	NA	France			
403.	*HNf1a*	IVS5nt+2T>A		?	NA	France			
404.	*HNF1a*	P175delll		?	NA	Israel		2007	(Stern *et al.*, 2007)
405.	*HNF1a*	c.17G>A	p.Ser6Asn	NP_001293108.2 NM_001306179.1 (18513305)	NA	Norway	VUS	2008	(Eide *et al.*, 2008)
406.	*HNF1A*		p.Asn402Tyr	NP_001293108.2	NA	Greece		2020	(E. B. Tatsi *et al.*, 2020)
407.	*HNF1a*		p.Ile414Gly	NP_001293108.2	NA	UK		2000	(Ellard *et al.*, 2000)
408.	*HNF1a*	c.1425insC	p.P475PfsX74	NP_001293108.2		Turkey			
409.	*HNF1a*	c.90_108delGGGTGAGCCGGGGCCCTACinsT	p.Gly31_Tyr36del	NM_001306179.1 NP_001293108.1		Turkey		2017	(Karaca *et al.*, 2017)
410.	*HNF1a*	c.-187C>A		NM_001306179.1 NP_001293108.1		Turkey	VUS		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
411.	*HNF 1a*	c.707G>A	p.Cys236Tyr	NP_001293108.2 NM_001306179.1	NA	Ukraine		2017	(Globa *et al.*, 2017)
412.	*HNF 1a*	c.1621C>T	p.Gln541*	NP_001293108.2 NM_001306179.1	NA	Ukraine	P		
413.	*HNF 1a*	c.326+4A>G		NM_001306179.1 NP_001293108.1		Ukraine			
414.	*HNF 1a*		p.Pro224Ser	NP_001293108.2 (15031772)	NA	Germany		2004	(Fehmann *et al.*, 2004)
415.	*HNF 1a*		p.Gln9X	NP_001293108.2 (22432108)	NA	Japan		2014	(Horikawa *et al.*, 2014)
416.	*HNF 1a*		p.Leu12His	NP_001293108.2 (9287053)	NA	Japan			
417.	*HNF 1a*		p.Ala15Asp	NP_001293108.2 (24905847)		Japan			
418.	*HNF 1a*		p.Arg54X	NP_001293108.2 (12547858)		Japan	VUS		
419.	*HNF 1a*		p.Arg131Trp	NP_001293108.2 (9166684)		Japan	VUS		
420.	*HNF 1a*		p.His143Asn	NP_001293108.2 (24905847)		Japan			
421.	*HNF*		p.Lys158As	NP_001293108	NA	Japan			

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
	1a		n	8.2 (10078571)					
422.	*HNF 1a*		p.Arg159Gln	NP_001293108.2 (9097962)		Japan	LP		
423.	*HNF 1a*	c.607C>T	p.Arg203Cys	NP_001293108.2 (10078571)	0.000000397	Japan	VUS		
424.	*HNF 1a*	c.685C>T	p.Arg229X	NP_001293108.2 (9032114)	7.96355875513649E-06	Japan			
425.	*HNF 1a*		p.Val233Leu	NP_001293108.2 (12488961)	NA	Japan			
426.	*HNF 1a*	c.716C>T	p.Ala239Val	NP_001293108.2 (12488961)	0.0001772	Japan	VUS		
427.	*HNF 1a*		p.Arg271Gly	NP_001293108.2 (12050210)	NA	Japan			
428.	*HNF 1a*		p.Arg271Trp	NP_001293108.2 (9754819)	NA	Japan	LP		
429.	*HNF 1a*		p.Met283Arg	NP_001293108.2 (24905847)	NA	Japan			
430.	*HNF 1a*		P291fsinsC	?	NA	Japan			
431.	*HNF*	c.1340C>	p.Pro447Leu	NP_001293108	0.00	Japan	LP		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
	1a	T		8.2 (8945470)	00120				
432.	*HNF 1a*		p.Pro499Leu	NP_001293108.2 (24905847)	NA	Japan			
433.	*HNF 1a*	c.686G>A	p.Arg229Gln	NP_001293108.2 NM_001306179.1 (9032114)	NA	Norway	LP		
434.	*HNF 1a*	c.1136_1137delCT	p.Pro379fs	NP_001293108.2 NM_001306179.1	NA	Norway			
435.	*HNF 1a*	c.872dupC	p.Gly292fs	NP_001293108.2 NM_001306179.1	NA	Norway			
436.	*HNF 1a*	c.686G>A	p.Arg229Gln	NP_001293108.2 NM_001306179.1 (9032114)	NA	Norway	LP	2013	(Irgens *et al.*, 2013)
437.	*HNF 1a*	c.391C>T	p.Arg131Trp	NP_001293108.2 NM_001306179.1 **(8945470)**	NA	Norway	VUS		
438.	*HNF 1a*	c.686G>A	p.Arg229Gln	NP_001293108.2 NM_001306179.1 **(23348805)**	NA	Norway	LP		
439.	*HNF*	c.1745A>	p.His582Arg	?	0.00	Norw	LP		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
	1a	G		(23348805)	00540	ay			
440.	*HNF 1a*	c.872dupC	p.Gly292fs	NP_001293108.2v NM_001306179.1	NA	Norway			
441.	*HNF 1a*	c.956-2A>G		NM_001306179.1 NP_001293108.1	NA	Norway			
442.	*HNF 1a*	c.1351A>G	p.Ser451Gly	NP_001293108.2 NM_001306179.1 23624530	NA	Norway	VUS		
443.	*HNF 1a*	c.666_668delGAA	p.Lys222del	NP_001293108.2 NM_001306179.1	NA	Norway			
444.	*HNF 1a*	c.593delA	p.Lys198fs	NP_001293108.2 NM_001306179.1	NA	Japan		2013	(Iwabuchi *et al.*, 2013)
445.	*HNF 1a*	IVS5-1delTAG		?	NA	Canada			
446.	*HNF 1a*	E275fsdelGAAG		NP_001293108.2	NA	Canada			
447.	*HNF 1a*		p.Phe268Ser	NP_001293108.2 (15305805)	NA	Canada		2004	(J. L. McKinney *et al.*, 2004)
448.	*HNF 1a*		p.Lys44fsdelC	NP_001293108.2	NA	Canada			
449.	*HNF*	c.768delC	p.Asn257Tfs	NM_001306179	NA	USA		201	(Bennett *et*

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
	1a		*85	9.1 NP_001293108.2				5	*al.*, 2015)
450.	*HNF 1a*		p.Tyr218Cys	NP_001293108.2 **(10872540)**	NA	China	VUS	2000	(Jap *et al.*, 2000)
451.	*HNF 1a*		P393fsdelC	?	NA	South Korea		2006	(Hwang *et al.*, 2006)
452.	*HNF 1a*	c.608G>A	p.Arg203His	NP_001293108.2 **(10588527)**	7.95804518578056E-06	Norway	LP	2017	(B. B. Johansson *et al.*, 2017)
453.	*HNF 1a*	c.1061C>T	p.Thr354Met	NP_001293108.2 **(11058894)**	0.000006365	Norway	VUS		
454.	*HNF 1a*	c.1640_1641del	p.Thr547ArgfsTer	?		Norway			
455.	*HNF 1a*	c.1739C>T	p.Pro580Leu	NM_001306179.1 NP_001293108.1	0.00001166	Norway	VUS		
456.	*HNF 1a*	c.539C>T	p.Ala180Val	NP_001293108.2 NM_001306179.1 **(24097065)**	NA	Norway	VUS	2017	(Sagen *et al.*, 2017)
457.	*HNF 1a*		p.Gln495X	NP_001293108.2 **(21224407)**	NA	germany		2013	(Iwen *et al.*, 2013)
458.	*HNF 1a*		p.Leu107Ile	NP_001293108.2		Sweden		1999	(Lehto *et al.*, 1999)

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				(10447526)					
459.	*HNF 1a*		p.Ser315fsinsA	NP_001293108.2		Sweden			
460.	*HNF 1a*		p.Gly375fsdelG	NP_001293108.2		Sweden			
461.	*HNF 1a*		p.Gly47Glu	NP_001293108.2 **(12574234)**		Norway			
462.	*HNF 1a*	T196fsdelCCAA		NP_001293108.2		Norway			
463.	*HNF 1a*	IVS3–1G>A		?		Norway			
464.	*HNF 1a*	c.766T>A	p.Ser256Thr	NP_001293108.2 **(12574234)**	0.000020900964	Norway			
465.	*HNF 1a*		p.Ala276Asp	NP_001293108.2 **(12574234)**		Norway	LP	2003	(Bjorkhaug *et al.*, 2003)
466.	*HNF 1a*		p.S445fsdelAG	NP_001293108.2		Norway			
467.	*HNF 1a*	c.1564A>G	p.Met522Val	NP_001293108.2 **(12574234)**	3.97933927050752E-06	Norway			
468.	*HNF 1a*	c.1592G>C	p.Ser531Thr	NP_001293108.2 **(12574234)**	0.000001990	Norway			
469.	*HNF 1a*	c.-154_-160TGGGGGT		?	NA	Spain		2013	(Lopez-Garrido *et al.*, 2013)

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
470.	*HNF1a*	c.368T > C	p.Leu123Pro	NP_001293108.2 **(18433912)**	NA	Serbia	VUS	2008	(Jesic *et al.*, 2008)
471.	*HNF1a*	c.392G>A	p.Arg131Gln	NP_001293108.2 **(8945470)**	0.000000397788 2	Japan	LP	2016	(Moritani *et al.*, 2016)
472.	*HNF1a*		p.Arg203Ser	NP_001293108.2 **(23348805)**	NA	Japan			
473.	*HNF1a*	c.226G>A	p.Asp76Asn	NP_001293108.2 NM_001306179.1	NA	Italy	VUS	2017	(Delvecchio *et al.*, 2017)
474.	*HNF1a*	c.1182insA	p.Pro394ins	NP_001293108.2	NA	Italy			
475.	*HNF1a*	c.1053delG	p.Ser352fs	NP_001293108.2 NM_001306179.1	NA	Ireland		2011	(Kyithar *et al.*, 2011)
476.	*HNF1a*	c.1276_1277insAGGT	p.Phe426X	NP_001293108.2	NA	Ireland			
477.	*HNF1a*		p.Arg229Gln	NP_001293108.2 **(9032114)**	NA	germany		1997	(Frayling *et al.*, 1997)
478.	*HNF1a*		p.Arg229X	NP_001293108.2 **(9032114)**	NA	germany	LP		
479.	*HNF1a*	c.241C>G		NP_001293108.2 **(9032114)**	NA	germany			
480.	*HNF*		p.Arg272His	NP_00129310	NA	germa	LP		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
	1a			8.2 **(9032114)**		ny			
481.	*HNF 1a*		P291fsinsC	NP_00129310 8.2	NA	germany			
482.	*HNF 1a*		p.Gln401fsdelC	NP_00129310 8.2	NA	germany			
483.	*HNF 1a*	c.1424C>T	p.Pro475Leu	NP_00129310 8.2	0.000052021	Thailand		2009	(Plengvidhya *et al.*, 2009)
484.	*HNF 1a*		p.Gly554fsX556	?	NA	Thailand			
485.	*HNF 1a*	c.811C>G	p.Arg271Gly	NP_00129310 8.2 **(18811724)**	NA	Spain	LP	2002	(Barrio *et al.*, 2002)
486.	*HNF 1a*		p.His153N	NM_001306179.1 NP_00129310 8.1 p.(Gly51=)	NA	Japan		2004	(Kitanaka *et al.*, 2004)
487.	*HNF 1a*	c.1558C>T	p.Gln520Ter	NP_00129310 8.2 NM_001306179.1		Brazil	P	2017	(Santana *et al.*, 2017)
488.	*HNF 1a*	c.1722_1740dup		?		Brazil			
489.	*HNF 1a*	c.1192C>T	p.Q398*	NP_00129310 8.2 NM_001306179.1 **(21224407)**		Turkey	P	2016	(Agladioglu *et al.*, 2016)
490.	*HNF 1a*		p.Arg272His	NP_00129310 8.2 **(9032114)**		Japan	LP	1997	(Yamada *et al.*, 1997)

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
491.	*HNF1a*	P291fsinsC		NP_001293108.2		Japan			
492.	*HNF1a*	c.1747C>G	p.Arg583Gly	? **(9313763)**	4.16347466942011E-06	Japan			
493.	*HNF1a*	c.415C>G	p.Leu139Val	NP_001293108.2 NM_001306179.1	NA	Korea	VUS	2016	(Kwak *et al.*, 2016)
494.	*HNF1a*	P291fsinsC		NP_001293108.2	NA	Tunisia		2016	(Khelifa *et al.*, 2016)
495.	*HNF1a*	c.1340C>T	p.Pro447Leu	NP_001293108.2 NM_001306179.1 **(8945470)**	0.00001120	USA	LP	2016	(Cantu *et al.*, 2016)
496.	*HNF1a*	619E>K	p.Glu619Lys	NP_001293108.2 **(9626139)**	NA	USA		1998	(Elbein *et al.*, 1998)
497.	*HNF1a*		p.Arg537Thr	? **(9626139)**		USA			
498.	*HNF1a*	c.712A>G	p.Arg238Gly	NP_001293108.2 NM_001306179.1		Turkey	VUS	2018	(Ozdemir *et al.*, 2018)
499.	*HNF1a*	c.1831_1838delCCG	p.H613Qfs*64	?		Turkey			

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
		GCCCA							
500.	*HNF 1a*	c.608G>A	p.Arg203His	NP_001293108.2 **(10588527)**	7.95804518578056E-06	Japan		1998	(Awata *et al.*, 1998)
501.	*HNF 1a*	c.481G>C	p.Ala161Pro	NM_001306179.1 NP_001293108.2 **(23517481)**		Greece	VUS	2013	(C. Tatsi *et al.*, 2013)
502.	*HNF 1a*	c.493T>C	p.Trp165Arg*	NP_001293108.2 NM_001306179.1 **(23517481)**		Greece	VUS		
503.	*HNF 1a*	c.682-684delGAG	p.Glu228del	NP_001293108.2		Greece			
504.	*HNF 1a*	c.1177delT	p.Ser393fs	NP_001293108.2 NM_001306179.1		Greece			
505.	*HNF 1a*	c.1201C>T	p.Gln401X	NP_001293108.2 **(23517481)**		Greece	P		
506.	*HNF 1a*	c.1331-1332 delAG	p.Ser445fs	NP_001293108.2	NA	Greece			
507.	*HNF 1a*		p.Pro379fsdelCT	NP_001293108.2	NA	UK		1997	(Frayling *et al.*, 1997)
508.	*HNF*		p.A443fsdel	NP_001293108	NA	UK			

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
	1a		CA	8.2					
509.	*HNF 1a*		p.Pro129T	NP_00129310 8.2 **(9075818)**	NA	UK			
510.	*HNF 1a*		p.Arg131Trp	NP_00129310 8.2 **(9166684)**		UK			
511.	*HNF 1a*	c.475C>T	p.Arg159Trp	NP_00129310 8.2 **(9754819)**	3.97807286238254E-06	UK	LP		
512.	*HNF 1a*		p.Pro519Leu	NP_00129310 8.2 **(9075818)**	NA	UK			
513.	*HNF 1a*		p.Thr620Ile	? **(9075818)**	NA	UK			
514.	*HNF 1a*		p.Ile128Asn	NP_00129310 8.2 **(9075819)**		USA			
515.	*HNF 1a*		p.His143Tyr	NP_00129310 8.2 **(9075819)**		USA			
516.	*HNF 1a*		p.Pro447Lys	NP_00129310 8.2 **(8945470)**		USA			
517.	*HNF 1a*		p.Pro379fsdelT	NP_00129310 8.2		USA			
518.	*HNF 1a*		p.Ala559fsinsA	?		USA			
519.	*HNF 1a*	c.-538G>C	p.Ala180Pro	NM_00130617 9.1		India	VUS	2009	(Radha *et al.*, 2009)

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				NP_001293108.1					
520.	*HNF1a*	c.340C>T	p.Arg114Cys	NP_001293108.2 NM_001306179.1 (19336507)	0.00001019	India	VUS		
521.	*HNF1a*	c.402C>T	p.Val134Val	NP_001293108.2 NM_001306179.1 (19336507)	0.00001019	India	Likely benign		
522.	*HNF1a*	c.511C>G	p.Arg171Gly	NP_001293108.2 NM_001306179.1 (19336507)		India	VUS		
523.	*HNF1a*	c.703G>C	p.Glu235Gln	NP_001293108.2 NM_001306179.1 (19336507)	3.98787685436273E-06	India	VUS		
524.	*HNF1a*	c.733G>A	p.Gly245Arg	NP_001293108.2 NM_001306179.1 (19336507)	NA	India	VUS		
525.	*HNF1a*	c.788G>A	p.Arg263His	NP_001293108.2 NM_001306179.1 (16917892)	NA	India	LP		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
526.	*HNF1a*	c.864_865insG	p.Pro289AlafsTer28	NM_001306179.1 NP_001293108.1	NA	China		2019	(X. Wang *et al.*, 2019)
527.	*HNF1a*	c.245C>T	p.Thr82Met	NP_001293108.2 NM_001306179.1 **(16834925)**	0.000483 6	China	VUS	2006	(Yang *et al.*, 2006)
528.	*HNF1a*	c.390G>T	p.Gln130His	NP_001293108.2 NM_001306179.1 **(16834925)**	NA	China	VUS		
529.	*HNF1a*		p.Pro353fsdelACGGGCCTGGAGC	?	NA	China			
530.	*HNF1a*	c.442C>T	p.Leu148Phe	NP_001293108.2	NA	Russia	VUS	2019	(Zubkova *et al.*, 2019)
531.	*HNF1a*		p.Ser6Arg	NP_001293108.2	NA	Russia		2018	(Ovsyannikova *et al.*, 2018)
532.	*HNF1a*	c.994delG	p.Glu332fs	NP_001293108.2	NA	Germany		2017	(Bansal *et al.*, 2017)
533.	*HNF1a*	c.955+1G>T		NM_001306179.1 NP_001293108.1	NA	Germany			
534.	*HNF1a*	c.1730_1733dupACCT	p.Gln579fs	?	NA	Germany			
535.	*HNF1a*	c.1A>C	p.Met1Leu	NM_001306179.1	NA	France	LP	2008	(Bellanne-Chantelot

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				NP_001293108.2 (18003757)					*et al.*, 2008)
536.	*HNF1a*	c.22C>A	p.Leu8Met	NP_001293108.2 NM_001306179.1 (18003757)	NA	France	VUS		
537.	*HNF1a*	c.41C>T	p.Ala14Val	NP_001293108.2 NM_001306179.1 (18003757)	NA	France	VUS		
538.	*HNF1a*	c.49C>G	p.Leu17Val	NP_001293108.2 NM_001306179.1 (18003757)	NA	France	VUS		
539.	*HNF1a*	c.50T>A	p.Leu17Gln	NP_001293108.2 NM_001306179.1	NA	France	VUS		
540.	*HNF1a*	c.59G>C	p.Gly20Ala	NP_001293108.2 NM_001306179.1 (18003757)	NA	France	LP		
541.	*HNF1a*	c.77T>C	p.Leu26Pro	NP_001293108.2 NM_001306179.1 (18003757)	NA	France	VUS		
542.	*HNF1a*	c.80T>C	p.Ile27Thr	NP_001293108.2	NA	France	VUS		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				NM_001306179.1 (18003757)					
543.	*HNF1a*	c.80T>G	p.Ile27Ser	NP_001293108.2 NM_001306179.1 (18003757)	NA	France	VUS		
544.	*HNF1a*	c.82C>T	p.Gln28X	NP_001293108.2 NM_001306179.1	NA	France	VUS		
545.	*HNF1a*	c.98C>T	p.Pro33Leu	NP_001293108.2 NM_001306179.1 (18003757)		France	VUS		
546.	*HNF1a*	c.202C>T	p.Arg68Trp	NP_001293108.2 NM_001306179.1 (18003757)	4.32271674101739E-06	France	VUS		
547.	*HNF1a*	c.206delG	p.Gly69fs	NP_001293108.2 NM_001306179.1	NA	France			
548.	*HNF1a*	c.217G>T	p.Glu73Ter	NP_001293108.2 NM_001306179.1 (18003757)	NA	France	VUS		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
549.	*HNF1a*	c.225C>A	p.Asp75Glu	NP_001293108.2 NM_001306179.1 **(18003757)**	4.25311115080681E-06	France	VUS		
550.	*HNF1a*	c.259A>T	p.Lys87X	NP_001293108.2 NM_001306179.1 **(18003757)**	NA	France	VUS		
551.	*HNF1a*	c.282_283insT	p.Glu95X	NP_001293108.2 NM_001306179.1	NA	France			
552.	*HNF1a*	c.319C>G	p.Leu107Val	NP_001293108.2 NM_001306179.1 **(18003757)**	NA	France	VUS		
553.	*HNF1a*	c.326delA	p.Gln109fs	NP_001293108.2 NM_001306179.1	NA	France			
554.	*HNF1a*	c.346G>A	p.Ala116Thr	NP_001293108.2 NM_001306179.1 **(18003757)**	NA	France	VUS		
555.	*HNF1a*	c.368T>G	p.Leu123Arg	NP_001293108.2 NM_001306179.1	NA	France	VUS		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				(18003757)					
556.	*HNF 1a*	c.396G>C	p.Glu132Asp	NP_001293108.2 NM_001306179.1 (18003757)	NA	France	VUS		
557.	*HNF 1a*	c.397G>T	p.Val133Leu	NP_001293108.2 NM_001306179.1 (18003757)	NA	France	VUS		
558.	*HNF 1a*	c.403G>A	p.Asp135Asn	NP_001293108.2 NM_001306179.1 (18003757)	NA	France	VUS		
559.	*HNF 1a*	c.410C>G	p.Thr137Ser	NP_001293108.2 NM_001306179.1 (18003757)	NA	France	VUS		
560.	*HNF 1a*	c.412G>A	p.Gly138Ser	NP_001293108.2 NM_001306179.1 (18003757)	NA	France	VUS		
561.	*HNF 1a*	c.427delC	p.His143fs	NP_001293108.2 NM_001306179.1	NA	France			
562.	*HNF 1a*	c.436_438dup	p.Gln146dup	NP_001293108.2 NM_001306179.1	NA	France			

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
563.	*HNF1a*	c.436C>T	p.Gln146X	NP_001293108.2 NM_001306179.1 (18003757)	NA	France	P		
564.	*HNF1a*	c.442C>A	p.Leu148Ile	NP_001293108.2 NM_001306179.1 (18003757)	NA	France	VUS		
565.	*HNF1a*	c.447C>G	p.Asn149Lys	NP_001293108.2 NM_001306179.1 (18003757)	NA	France	VUS		
566.	*HNF1a*	c.460A>G	p.Met154Val	NP_001293108.2 NM_001306179.1 (18003757)	NA	France	VUS		
567.	*HNF1a*	c.461T>C	p.Met154Thr	NP_001293108.2 NM_001306179.1 (18003757)	NA	France	VUS		
568.	*HNF1a*	c.461T>G	p.Met154Arg	NP_001293108.2 NM_001306179.1 (18003757)	NA	France	VUS		
569.	*HNF1a*	c.517G>A	p.Val173Met	NP_001293108.2 NM_001306179.1	NA	France	VUS		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				(18003757)					
570.	*HNF 1a*	c.521C>T	p.Ala174Val	NP_001293108.2 NM_001306179.1 **(18003757)**	0.000195	France	VUS		
571.	*HNF 1a*	c.523C>T	p.Gln175X	NP_001293108.2 NM_001306179.1 **(18003757)**		France	P		
572.	*HNF 1a*	c.526+1G>C		?		France			
573.	*HNF 1a*	c.526+5G>A		?		France			
574.	*HNF 1a*	c.586A>G	p.Thr196Ala	NP_001293108.2 NM_001306179.1 **(18003757)**	0.000265	France	VUS		
575.	*HNF 1a*	c.614delA	p.Lys205fs	NP_001293108.2 NM_001306179.1	NA	France			
576.	*HNF 1a*	c.620_621insG	p.Gly207fs	NP_001293108.2	NA	France			
577.	*HNF 1a*	c.650C>G	p.Ala217Gly	NP_001293108.2 NM_001306179.1 **(18003757)**	NA	France	VUS		
578.	*HNF 1a*	c.676A>G	p.Lys226Glu	NP_001293108.2	NA	France	VUS		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				NM_001306179.1 (18003757)					
579.	*HNF1a*	c.682_683insG	p.Glu228fs	NP_001293108.2 NM_001306179.1	NA	France			
580.	*HNF1a*	c.682G>A	p.Glu228Lys	NP_001293108.2 NM_001306179.1 (18003757)	NA	France	VUS		
581.	*HNF1a*	c.696_697insA	p.Val233fs	NP_001293108.2 NM_001306179.1	NA	France			
582.	*HNF1a*	c.704_705insA	p.Cys236fs	NP_001293108.2 NM_001306179.1	NA	France			
583.	*HNF1a*	c.711_713_6del	p.Arg238fs	NP_001293108.2	NA	France			
584.	*HNF1a*	c.713+1G>C		?	NA	France			
585.	*HNF1a*	c.715G>A	p.Ala239Thr	NP_001293108.2 NM_001306179.1 (18003757)	NA	France	VUS		
586.	*HNF1a*	c.722G>A	p.Cys241Tyr	NP_001293108.2 NM_001306179.1 (18003757)	NA	France	VUS		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
587.	*HNF1a*	c.732A>T	p.Arg244Ser	NP_001293108.2 NM_001306179.1 **(18003757)**	NA	France	VUS		
588.	*HNF1a*	c.732_733delAG	p.Ser247fs	NP_001293108.2 NM_001306179.1	NA	France			
589.	*HNF1a*	c.737T>G	p.Val246Gly	NP_001293108.2 NM_001306179.1 **(18003757)**	NA	France	VUS		
590.	*HNF1a*	c.746_747insC	p.Gln250fs	NP_001293108.2 NM_001306179.1	NA	France			
591.	*HNF1a*	c.763G>A	p.Gly255Ser	NP_001293108.2 NM_001306179.1 **(18003757)**	NA	France	VUS		
592.	*HNF1a*	c.785_786insT	p.Arg263fs	NP_001293108.2 NM_001306179.1	NA	France			
593.	*HNF1a*	c.790G>T	p.Val264Phe	NP_001293108.2 NM_001306179.1 **(18003757)**	NA	France	LP		
594.	*HNF1a*	c.798C>G	p.Asn266Lys	NP_001293108.2	NA	France	VUS		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				NM_001306179.1 (18003757)					
595.	*HNF1a*	c.814C>A	p.Arg272Ser	NP_001293108.2 NM_001306179.1 (18003757)	NA	France	LP		
596.	*HNF1a*	c.827C>G	p.Ala276Gly	NP_001293108.2 NM_001306179.1 (18003757)	7.14546013190519E-06	France	LP		
597.	*HNF1a*	c.842T>C	p.Leu281Pro	NP_001293108.2 NM_001306179.1 (18003757)		France	VUS		
598.	*HNF1a*	c.865C>T	p.Pro289Ser	NP_001293108.2 NM_001306179.1 (18003757)		France	VUS		
599.	*HNF1a*	c.871C>A	p.Pro291Thr	NP_001293108.2 NM_001306179.1 (18003757)	0.000001251	France	VUS		
600.	*HNF1a*	c.919delC	p.Leu307fs	NP_001293108.2 NM_001306179.1		France			

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
601.	*HNF1a*	c.923C>T	p.Pro308Leu	NP_001293108.2 NM_001306179.1 **18003757**	0.000028 1	France	VUS		
602.	*HNF1a*	c.955+2T>C		?		France			
603.	*HNF1a*	c.959_962dupTGCG	p.Tyr322fs	NP_001293108.2 NM_001306179.1		France			
604.	*HNF1a*	c.965A>G	p.Tyr322Cys	NP_001293108.2 NM_001306179.1 **18003757**	0.000145	France	VUS		
605.	*HNF1a*	c.966T>G	p.Tyr322X	NP_001293108.2 NM_001306179.1 **18003757**	NA	France	LP		
606.	*HNF1a*	c.970C>T	p.Gln324X	NP_001293108.2 NM_001306179.1 **18003757**	NA	France	P		
607.	*HNF1a*	c.984T>G	p.Ser328Arg	NP_001293108.2 NM_001306179.1 **18003757**	NA	France	VUS		
608.	*HNF1a*	c.1017delT	p.Leu341X	NP_001293108.2 NM_001306179	NA	France			

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				9.1					
609.	*HNF 1a*	c.1059_1060insC	p.Thr354fs	NP_001293108.2 NM_001306179.1	NA	France			
610.	*HNF 1a*	c.1080_1081dupCA	p.Ser361fs	NP_001293108.2 NM_001306179.1	NA	France			
611.	*HNF 1a*	c.1118C>G	p.Ala373Gly	NP_001293108.2 NM_001306179.1 **18003757**	NA	France	VUS		
612.	*HNF 1a*	c.1135C>A	p.Pro379Thr	NP_001293108.2 NM_001306179.1 **18003757**	0.000248	France	LP		
613.	*HNF 1a*	c.1135C>G	p.Pro379Ala	NP_001293108.2 NM_001306179.1 **18003757**	0.0001884769	France	LP		
614.	*HNF 1a*	c.1135C>T	p.Pro379Ser	NP_001293108.2 NM_001306179.1 **18003757**	0.000003598	France	LP		
615.	*HNF 1a*	c.1136delC	p.Pro379fs	NP_001293108.2 NM_001306179.1		France			
616.	*HNF*	c.1137_11	p.Val380fs	NP_00129310		Franc			

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
	1a	38insT		8.2 NM_00130617 9.1		e			
617.	*HNF 1a*	c.1165T>G	p.Leu389Val	NP_00129310 8.2 NM_00130617 9.1 18003757	0.00060 2	France	Likely benign		
618.	*HNF 1a*	c.1195C>T	p.Gln399X	NP_00129310 8.2 NM_00130617 9.1 18003757	NA	France	P		
619.	*HNF 1a*	c.1226C>A	p.Pro409His	NP_00129310 8.2 NM_00130617 9.1 18003757	7.96197 361401 944E-06	France	VUS		
620.	*HNF 1a*	c.1271C>T	p.Pro424Leu	NP_00129310 8.2 NM_00130617 9.1 18003757		France	VUS		
621.	*HNF 1a*	c.1502+2A>G		NM_00130617 9.1 NP_00129310 8.1		France			
622.	*HNF 1a*	c.1502+2A>T		NM_00130617 9.1		France			
623.	*HNF 1a*	c.1369_1383dup	p.Thr457_Pro461dup	NP_00129310 8.2 NP_00129310		France			

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				8.1					
624.	*HNF 1a*	c.1387C>T	p.Gln463X	NP_001293108.2 NM_001306179.1 **18003757**	NA	France	P		
625.	*HNF 1a*	c.1394C>T	p.Ser465Phe	NP_001293108.2 NM_001306179.1 **18003757**		France	VUS		
626.	*HNF 1a*	c.1400C>T	p.Pro467Leu	NP_001293108.2 NM_001306179.1 **18003757**	0.000001601	France	VUS		
627.	*HNF 1a*	c.1421_1422insA	p.Pro475fs	NP_001293108.2 NM_001306179.1		France			
628.	*HNF 1a*	c.1444_1445delAG	p.Ser482fs	NP_001293108.2 NM_001306179.1		France			
629.	*HNF 1a*	c.1465T>G	p.Phe489Val	NP_001293108.2 NM_001306179.1 **18003757**		France	VUS		
630.	*HNF 1a*	c.1495C>T	p.Pro499Ser	NP_001293108.2 NM_001306179.1 **18003757**		France	VUS		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
631.	*HNF1a*	c.1498C>A	p.His500Asn	NP_001293108.2 18003757	0.000063 6	France	VUS		
632.	*HNF1a*	c.1509C>A	p.Tyr503X	NP_001293108.2 NM_001306179.1 18003757		France	P		
633.	*HNF1a*	c.1513C>A	p.His505Asn	NP_001293108.2 NM_001306179.1 18003757	0.000079696	France	VUS		
634.	*HNF1a*	c.1522G>A	p.Glu508lys	NP_001293108.2 NM_001306179.1 18003757	0.000044 27	France	VUS		
635.	*HNF1a*	c.1537A>T	p.Thr513Ser	NP_001293108.2 NM_001306179.1 18003757	7.96463701166819E-06	France	VUS		
636.	*HNF1a*	c.1544C>A	p.Thr515Lys	NP_001293108.2 NM_001306179.1 18003757	0.000003582	France	VUS		
637.	*HNF1a*	c.1573A>T	p.Thr525Ser	NP_001293108.2 NM_001306179.1	0.000003 89	France	VUS		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				18003757					
638.	*HNF1a*	c.1574C>T	p.Thr525Ile	NP_001293108.2 NM_001306179.1 **18003757**	NA	France	VUS		
639.	*HNF1a*	c.1576G>A	p.Asp526Asn	NP_001293108.2 NM_001306179.1 **18003757**	0.000019	France	LP		
640.	*HNF1a*	c.1576G>T	p.Asp526Tyr	NP_001293108.2 NM_001306179.1 **18003757**	NA	France	LP		
641.	*HNF1a*	c.1587_1588insA	p.Asn529fs	NP_001293108.2 NM_001306179.1	NA	France			
642.	*HNF1a*	c.1611_1614delGCCC	p.Pro538fs	NP_001293108.2 NM_001306179.1	NA	France			
643.	*HNF1a*	c.1623+2T>C		?		France			
644.	*HNF1a*	c.1637A>G	p.Asp546Gly	? **18003757**		France	VUS		
645.	*HNF1a*	c.1663C>T	p.Leu555Phe	?	8.05892687329755E-	France	VUS		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
					06				
646.	*HNF1a*	c.1670_1685dup	p.His563GlnfsTer2	NM_001306179.1 NP_001293108.1	NA	France			
647.	*HNF1a*	c.1673_1674insC	p.Ala559fs	NM_001306179.1 NP_001293108.1	NA	France			
648.	*HNF1a*	c.1762C>T	p.Pro588Ser	? **18003757**	4.18154600118755E-06	France	VUS		
649.	*HNF1a*	c.1840_1841delAA	p.Asn614fs	?		France			
650.	*HNF1a*	c.1853_1854delTC	p.Ile618fs	?		France			
651.	*HNF1a*	c.1864_1890dup	p.Ile622_Ser630dup	NM_001306179.1 NP_001293108.1		France			
652.	*HNF1a*		p.Ala15Ala	NP_001293108.2		Brazil		2012	(Bonatto *et al.*, 2012)
653.	*HNF1a*		p.Gln141Gln	NP_001293108.2		Brazil			
654.	*HNF1a*	c.599G>A	p.Arg200Gln	NP_001293108.2 **9472859**	3.97873762612	USA	LP	2016	(Chambers *et al.*, 2016)

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
					598E-06				
655.	*HNF1a*	c.1136C>A	p.Pro379His	NP_001293108.2 NM_001306179.1 **15883474**	0.000005197	USA	VUS		
656.	*HNF1a*		p.Glu235Gly	NP_001293108.2 **21170474**		Spain		2011	(Galan *et al*., 2011)
657.	*HNF1a*	c-57-64delCACGCGGT		?		Spain			
658.	*HNF1a*	c.117_119delAAG	p.Lys39del	?		Russia		2019	(Glotov *et al*., 2019)
659.	*HNF1a*	c.1346_1347delCG	p.Ala449fs	?		Russia			
660.	*HNF1a*	c.868G>C	p.Glu290Gln	?		Russia	VUS		
661.	*HNF1a*	c.1253G>C	p.Ser418Thr	?		Russia			
662.	*HNF1a*	c.199G>T	p.Glu67*	?		Russia			
663.	*HNF1a*	c.485T>G	p.Leu162Arg	NP_001293108.2 NM_001306179.1		Russia	LP		
664.	*HNF1a*	c.526+1G>A		NM_001306179.1 NP_001293108.1		Saudi Arabia		2011	(Habeb *et al*., 2011)
665.	*HNF1a*	c.1761C>G	p.Pro588Ala	?		Germany	Likely	2016	(Knebel *et al*., 2016)

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
							benign		
666.	*HNF1a*	c.1765_1766delinsGCCCGfs86*	p.His589AlafsTer67	NM_001306179.1 NP_001293108.1		Germany			
667.	*HNf1a*		p.Arg363Cys	?		Italy		2009	(Lorini *et al.*, 2009)
668.	*HNF1a*		p.Cys49Gly	?		Iran		2018	(Moghbeli *et al.*, 2018)
669.	*HNF1a*		p.Trp113X	NP_001293108.2 **11692182**		Brazil		2011	(Nogaroto *et al.*, 2011)
670.	*HNF1a*		p.Gly292fs	NP_001293108.2		Malta		2019	(Pace *et al.*, 2019)
671.	*HNF1a*		p.Ser3Cys	NP_001293108.2		Croatia		2018	(Pavic *et al.*, 2018)
672.	*HNF1a*		p.Gly151Ser	NP_001293108.2		Croatia			
673.	*HNF1a*	c.155G>C	p.Gly52Ala	NP_001293108.2 NM_001306179.1 **23771925**	0.00027	USA	VUS	2013	(Pihoker *et al.*, 2013)
674.	*HNF1a*	c.725T>C	p.Ile242Thr	NP_001293108.2 NM_001306179.1 **23771925**	NA	USA	VUS		
675.	*HNF*	c.800G>C	p.trp267Ser	NP_001293108	NA	USA	VUS		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
	1a			8.2 NM_001306179.1 **23771925**					
676.	*HNF 1a*	c.872C>A	p.Pro291Q	NP_001293108.2 NM_001306179.1 **23771925**	0.000020919 1	USA	LP		
677.	*HNF 1a*	c.1124G>T	p.Gly375Val	NP_001293108.2 NM_001306179.1 **23771925**	4.00641025641025E-06	USA	VUS		
678.	*HNF 1a*	c.1504C>G	p.Lys502Val	NP_001293108.2 NM_001306179.1 **23771925**	NA	USA	VUS		
679.	*HNF 1a*	c.676delAAG	p.lys226del	NP_001293108.2	NA	USA			
680.	*HNF 1a*	c.607C>T	p.Arg203Cys	NP_001293108.2 **10078571**	0.000003978 9	Thailand		2019	(Plengvidhya *et al.*, 2019)
681.	*HNF 1a*	IVS1+1G>A		?	NA	USA		2015	(Gandica *et al.*, 2015)
682.	*HNF 1a*	c.734G>T	p.Gly245Val	NP_001293108.2 NM_001306179.1		UK	LP	2018	(Rama Chandran *et al.*, 2018)

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				(19336507)					
683.	*HNF1a*	c.398T>A	p.Val133Glu	NP_001293108.2 NM_001306179.1 (18003757)		Brazil	VUS	2019	(Tarantino *et al.*, 2019)
684.	*HNF1a*	c.1296_1297insC	p.Thr433Hisfs*116	NP_001293108.2 NM_001306179.1		Brazil			
685.	*HNF1a*	P291fsinsC c.872dup	p.Gly292ArgfsTer25	NP_001293108.2 NM_001306179.1		USA		2013	(Shankar *et al.*, 2013)
686.	*HNF1a*	c.1349dup	p.Asn450LysfsTer106	NM_001306179.1 NP_001293108.1		UK		2017	(Shields *et al.*, 2017)
687.	*HNF1a*	c.391C>T	p.Arg131Trp	NM_001306179.1 NP_001293108.1 **9166684**		UK	VUS		
688.	*HNF1a*	c.495G>C	p.Trp165Cys	NM_001306179.1 NP_001293108.1		UK	VUS		
689.	*HNF1a*	c.28A>C	p.Thr10Pro	NM_001306179.1 NP_001293108.1 (23348805)		UK	VUS		
690.	*HNF*	c.814C>T	p.Arg272Cy	NM_001306617		UK	LP		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
	1a	,	s	9.1 NP_001293108.1 23348805					
691.	*HNF 1a*	c.-258A>G		?		UK			
692.	*HNF 1a*	c.779 C>T	p.Thr260Met	NP_001293108.2 NM_001306179.1 9166684	4.01174639343999E-06	China	LP	2017	(Tang *et al.*, 2017)
693.	*HNF 1a*		p.Val264fs	NP_001293108.2		Spain		2019	(Urrutia *et al.*, 2019)
694.	*HNF 1a*	c.864delGinsCC	p.Gly292ArgfsX25	NP_001293108.2 NM_001306179.1		NewZealand		2013	(Wheeler *et al.*, 2013)
695.	*HNF 1a*		p.Gln243Glu	NP_001293108.2 (15657605)		China			
696.	*HNF 1a*	c.932C>A	p.Ala311Asp	NP_001293108.2	9.48964679534627E-06	China		2005	(Xu *et al.*, 2005)
697.	*HNF 1a*	c.1136C>G	p.Pro379Arg	NP_001293108.2	3.99817683136489	China			

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
					E-06				
698.	*HNF1a*		p.Pro488fsdelC	NP_001293108.2	NA	China			
699.	*HNF1a*	c.758G>A	p.Gly253Glu	NP_001293108.2 NM_001306179.1 (23348805)	NA	Iran	VUS	2019	(Mohammadi *et al.*, 2019)
700.	*HNF4a*	c.G25A	p.Asp9Asn	NP_000448.3	7.07108562377581E-06	Canada	VUS	2016	(Brahm *et al.*, 2016)
701.	*HNF4a*	Phe75fsdelT		?	NA	Denmark		1999	(Moller *et al.*, 1999)
702.	*HNF4a*	c.-1009G>C		?	NA	India	LP	2011	(Anuradha *et al.*, 2011)
703.	*HNF4a*	c.-129T>C		?	NA	India	Likely benign		
704.	*HNF4a*	c.-79C>T		?	NA	India	VUS		
705.	*HNF4a*	c.640C>T	p.His214Tyr	?	NA	Netherland	LP	2009	(Beijers *et al.*, 2009)
706.	*HNF4a*		p.Glu276Gln	?	NA	UK		1997	(Bulman *et al.*, 1997)
707.	*HNF4a*	c.811G>A	p.Asp271Asn	NM_001287182.1 NP_001274111	NA	India	LP	2015	(Chapla *et al.*, 2015)

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				1.1					
708.	*HNF 4a*	c.58A>C			NA	Italy	VUS	1997	(Gragnoli *et al.*, 1997)
709.	*HNF 4a*		p.Ala193Val	NP_001274113.1	NA	Israel		2007	(Stern *et al.*, 2007)
710.	*HNF 4A*		p.Glu285Lys	NP_000448.3	NA	Greece		2020	(E. B. Tatsi *et al.*, 2020)
711.	*HNF 4a*	c.572delT	p.Leu191fs	NP_001245284.1	NA	Ukraine		2017	(Globa *et al.*, 2017)
712.	*HNF 4a*		p.Arg127trp	NP_001245284.1	NA	Japan		1997	(Furuta *et al.*, 1997)
713.	*HNF 4a*	c.146A>G	p.His49Arg	NP_001025175.1	NA	USA	LP	2015	(Bennett *et al.*, 2015)
714.	*HNF 4a*	c.353G>A	p.Arg118Gln	NP_001025175.1 NM_001287182.1 (23348805)	NA	USA	VUS		
715.	*HNF 4a*	c.318_331del	p.Val108Gfs*11	NP_001025175.1	NA	USA			
716.	*HNF 4a*	c.878_881dup	p.Gln294Hfs*15	NP_001025175.1	NA	USA			
717.	*HNF 4a*	c.556>557GATinsGfs	p.Asp177fsinsG	?	NA	Denmark		2005	(Johansen *et al.*, 2005)
718.	*HNF 4a*	c.929GACGG3CAG	p.Arg301Gln	NP_001274112.1	NA	Denmark	LP		
719.	*HNF 4a*	c.734G>C	p.Arg245Pro	NP_001025175.1	NA	UK	LP	2019	(Apperley *et al.*, 2019)

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
720.	*HNF 4a*	c.426+1G>A		?	NA	Italy		2017	(Delvecchio *et al.*, 2017)
721.	*HNF 4a*	c.37A>T	p.Lys13*	?		USA		2019	(Sanyoura *et al.*, 2019)
722.	*HNF 4a*	c.295del	p.Trp99Glyfs*3	?		USA			
723.	*HNF 4a*	c.317_333del	p.Gln106Argfs*9	NP_001274112.1	NA	USA			
724.	*HNF 4a*	c.344dup	p.Met115Ilefs*6	NM_001287182.1 NP_001274111.1		USA			
725.	*HNF 4a*	c.848delAsn283Thrfs*11	p.Ile283ThrfsTer10	NM_001287182.1 NP_001274111.1		USA			
726.	*HNF 4a*	c.1082dupC	p.T362Hisfs*97	?		USA			
727.	*HNF 4a*	c.1113C>A	p.Cys371*	?		USA	LP		
728.	*HNF 4a*	c.2T>C	p.Met1	NP_000448.3 NM_001287182.1 (21683639)	3.977778803163137E-06	Ireland		2011	(Kyithar *et al.*, 2011)
729.	*HNF 4a*	c.868C>T	p.Arg290Cys	NP_001025175.1 (21683639)	NA	Ireland	LP		
730.	*HNF 4a*	c.842-2delA		?	NA	Spain		2002	(Barrio *et al.*, 2002)
731.	*HNF*		p.Met1Ile	NP_000448.3	NA	Korea		201	(Park *et*

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
	4a			(21683639)				9	*al.*, 2019)
732.	*HNF 4a*	c.956T>C ,	p.Leu319Pro	NP_000448.3 NM_001287182.1 (15830177)	NA	Korea	LP	2016	(Kwak *et al.*, 2016)
733.	*HNF 4a*	c.344G>A ,	p.Cys115tyr	NP_000448.3 NM_001287182.1	NA	Turkey	LP	2018	(Ozdemir *et al.*, 2018)
734.	*HNF 4a*	c.149C>T ,	p.Ala50Val	NP_000448.3 NM_001287182.1	0.000212	Turkey	VUS		
735.	*HNF 4a*	c.736+2T>A		?	NA	Turkey			
736.	*HNF 4a*	c.736G>A	p.Gly246Ser	NP_000448.3 NM_001287182.1	NA	Turkey	LP		
737.	*HNF 4a*	c.534_536 delGAA	p.lys179del	NP_849181.1	NA	Turkey			
738.	*HNF 4a*		p.Gln142His	NP_001025175.1	NA	Japan		2018	(Ushijima *et al.*, 2018)
739.	*HNF 4a*		p.Glu256Ala	NP_001025175.1	NA	Japan			
740.	*HNF 4a*		p.Arg331His	NP_000448.3	4.02197607728629E-06	China		2019	(X. Wang *et al.*, 2019)
741.	*HNF 4A*	c.317G>A	p.Met116Ile	?	NA	UK	LP	2014	(Arya *et al.*, 2014)
742.	*HNF 4a*	c.575_582 +10del		?	NA	USA		2016	(Chambers *et al.*, 2016)
743.	*HNF*	c.932G>A	p.Arg311His	NP_001025175	NA	USA	LP		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
	4a			5.1 (10768098)					
744.	*HNF 4a*	c.7A>G	p.Ser3Gly	NP_001025175.1	4.04226593259117E-06	Brazil	VUS	2019	(de Santana *et al.*, 2019)
745.	*HNF 4a*	c.145C>T	p.His49Tyr	NP_001025175.1	NA	Brazil	LP		
746.	*HNF 4a*		p.Arg80Gln		NA	Italy		2010	(Forlani *et al.*, 2010)
747.	*HNF 4a*		p.Val393Ile		NA	France		1998	(Hani *et al.*, 1998)
748.	*HNF 4a*		p. Arg244Gln		NA	Japan		2002	(Hara *et al.*, 2002)
749.	*HNF 4a*	c.266G>A	p.Arg89Gln	NP_000448.3	NA	Norway	LP	2012	(S. Johansson *et al.*, 2012)
750.	*HNF 4a*	c.200G>A	p.Arg67Gln	NP_001025175.1 (20705777)	NA	USA	LP	2019	(Gordon *et al.*, 2019)
751.	*HNF 4a*		p.Arg114Gln	NP_001245284.1	NA	UK		2016	(Laver *et al.*, 2016)
752.	*HNF 4a*		p.Arg154	?	NA	germany		1997	(Lindner *et al.*, 1997)
753.	*HNF 4a*	c.932G>A	p.Arg311His	NP_001025175.1 (10768098)	NA	Italy	LP	2014	(Delvecchio *et al.*, 2014)
754.	*HNF 4a*	c.503G>A	p.Arg168Gln	? (23771925)	NA	USA	LP	2013	(Pihoker *et al.*, 2013)

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
755.	*HNF 4a*	c.779T>C	p.Lys260Pro	? (23771925)	NA	USA	LP		
756.	*HNF 4a*	c.1183G>A	p.Val395Ile	NP_001245284.1 23771925	NA	USA	VUS		
757.	*HNF 4a*		p.Gly326arg		NA	Norway		2006	(Raeder *et al.*, 2006)
758.	*HNF 4a*		p.Thr339Ile		NA	Norway			
759.	*HNF 4a*		p.Trp340X		NA	Norway			
760.	*HNF 4a*		p.Arg127Trp	NP_001245284.1	NA	USA		2013	(Shankar *et al.*, 2013)
761.	*HNF 4a*	c.340C>T	p.Arg114Trp	NP_001025175.1 (9313765)	NA	UK	VUS	2016	(Shepherd *et al.*, 2016)
762.	*HNF 4a*	c.12G>A	p.Trp4Ter	NM_001287182.1 NP_001274111.1	NA	UK	P		
763.	*HNF 4a*	c.1064-5_1070del			NA	UK		2017	(Shields *et al.*, 2017)
764.	*HNF 4a*	c.-12G>A	p.Trp4Ter	NM_001287182.1 NP_001274111.1	NA	UK	P		
765.	*HNF 4a*		p.Val255Met		NA	Iran		2009	(Taghavi *et al.*, 2009)
766.	*HNF 1B*	c.274C>T	p.Leu92Phe	NM_000458.3 NP_000449.1 (25041077)	NA	India	VUS	2015	(Chapla *et al.*, 2015)

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
767.	*HNF 1b*		p.Arg112Pro	NP_000449.1 (15068978)	NA	France		2004	(Bellanne-Chantelot *et al.*, 2004)
768.	*HNF 1b*		p.Gln136Glu	NP_000449.1 (15068978)	NA	France			
769.	*HNF 1b*		p.lys164Gln	NP_000449.1 (15068978)	NA	France			
770.	*HNF 1b*		p.Arg165His	NP_000449.1 (15068978)	NA	France			
771.	*HNF 1b*		p.Arg181X	NP_000449.1 (15068978)	NA	France			
772.	*HNF 1b*		p.Arg182X	NA	NA	France			
773.	*HNF 1b*	IVS2IG3T			NA	France			
774.	*HNF 1b*		p.Arg295His	NP_000449.1 (15068978)	NA	France			
775.	*HNF 1b*	443 C>T	p.Cys443Thr	NP_000449.1	NA	Germany		2008	(Mayer *et al.*, 2008)
776.	*HNF 1b*		p.Ser148Leu	NP_000449.1 (15930087)	NA	Japan		2014	(Horikawa *et al.*, 2014)
777.	*HNF 1b*	354Q>X	p.Gln354X	NP_000449.1 (24905847)	NA	Japan			
778.	*HNF 1b*	c.393A>T	p.Gln131His	NP_000449.1 NM_000458.3 NP_000449.1	NA	Norway	VUS	2017	(B. B. Johansson *et al.*, 2017)
779.	*HNF 1b*	c.867C>G	p.Asn289Lys	NP_000449.1 NM_000458.3	NA	Norway	VUS		
780.	*HNF 1b*	c.883C>T	p.Arg295Cys	NP_000449.1 NM_000458.3 (16249435)	NA	Norway	VUS		
781.	*HNF*	c.1085C>	p.Ser362Phe	NM_000458.3	NA	Norw	VUS		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
	1b	T		NP_000449.1		ay			
782.	*HNF 1b*	c.124G>A	p.Gly42Arg	NA	NA	Norway			
783.	*HNF 1b*		p.A263fsinsGG	NP_000449.1	NA	Japan		2016	(Shimoda *et al.*, 2016)
784.	*HNF 1b*	c.727C>T	p.Gln243X	NP_000449.1 NM_000458.3	NA	USA	P	2013	(Thirumalai *et al.*, 2013)
785.	*HNF 1b*		p.Leu168Pro	NP_000449.1	NA	Japan		2018	(Ushijima *et al.*, 2018)
786.	*HNF 1b*	160M>V	p.Met160Val	NP_000449.1 (22034641)	NA	Australia		2014	(Wentworth *et al.*, 2014)
787.	*HNF 1b*	c.1007A>G	p.His336Arg	NP_000449.1 NM_000458.3 (16971658)	NA	China	VUS	2017	(Y. Wang *et al.*, 2017)
788.	*HNF 1b*	239G>E	p.Gly239Glu	NP_000449.1	NA	China		2017	(Luo *et al.*, 2017)
789.	*HNF 1b*	c.1005dupC	p.His336fs	NP_000449.1 NM_000458.3 (16971658)	NA	germany		2017	(Bansal *et al.*, 2017)
790.	*HNF 1b*	c.143delT	p.Leu48fs	NP_000449.1 NM_000458.3	NA	France		2005	(Bellanne-Chantelot *et al.*, 2005)
791.	*HNF 1b*	c.226G>T	p.Gly76Cys	NP_000449.1 NM_000458.3 (16249435)	0.00054998 4	France	LP		
792.	*HNF 1b*	c.406C>T	p.Gln136X	NP_000449.1 NM_000458.3 (16249435)	NA	France	P		
793.	*HNF 1b*	c.704G>A	p.Arg235Gln	NP_000449.1 NM_000458.3	NA	France	VUS		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				(16249435)					
794.	*HNF1b*	c.826G>A	p.Arg276Gly	NP_000449.1 (16249435)	NA	France	P		
795.	*HNF1b*	c.854G>A	p.Gly285Asp	NP_000449.1 NM_000458.3 (16249435)	NA	France	VUS		
796.	*HNF1b*	c.883CT	p.Arg295Cys	NP_000449.1 NM_000458.3 (16249435)	NA	France	VUS		
797.	*HNF1b*	c.1108G>A	p.Gly370Ser	NP_000449.1 (16249435)	0.000180	France	LP		
798.	*HNF1b*	c.1046–294_1206704del	p.Gly349_Met402del	NP_000449.1 XP_011523462.1	NA	France			
799.	*HNF1b*	c.1+1671del	p.Met1_Trp557del	NP_000449.1	NA	France			
800.	*HNF1b*	c207_211delCGCCA	p.His69GlnfsTer17	NM_000458.3 NP_000449.1	NA	Spain		2017	(Carrillo *et al*, 2017)
801.	*HNF1b*		p.Arg276X	NP_000449.1 (12161522)	NA	Japan		2007	(Fujimoto *et al.*, 2007)
802.	*HNF1b*	c.578T>C	p.Met193Thr	NM_000458.3 NP_000449.1	3.97845270017584E-06	Japan	VUS	2012	(Jo *et al*, 2012)
803.	*HNf1b*	c.434T>A	p.Leu145Gln	NP_000449.1 NM_000458.3	NA	japan	VUS	2018	(Kato *et al.*, 2018)

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
804.	*HNF 1b*		p.Pro159Leu	NP_000449.1 (20378641)	NA	Korea		2014	(Kim *et al.*, 2014)
805.	*HNF 1b*	c.1580G>A	p.Arg527Gln	NP_000449.1 NM_000458.3	0.000001590	Malta	VUS	2018	(Pace *et al.*, 2018)
806.	*HNF 1b*	c.1-*151+del			NA	UK		2016	(Shepherd *et al.*, 2016)
807.	*HNF 1b*	c.1-_1674+del			NA	UK		2017	(Shields *et al* . 2017)
808.	*HNF 1b*	c.77C>T			NA	China		2016	(Zhou *et al.*, 2016)
809.	*INS*	c.89T>G	p.Leu30Arg	NP_000198.1 NM_001291897.1		Canada	LP	2016	(Brahm *et al.*, 2016)
810.	*INS*	c.125T>C	pVal42Ala	NP_000198.1 NM_001291897.1		Italy	LP	2016	(Piccini *et al.*, 2016)
811.	*INS*	c.163C>T	p.Arg55Cys	NP_000198.1 NM_001291897.1 (18192540)		Norway	LP	2013	(Irgens *et al.*, 2013)
812.	*INS*	c.–331delC		?		USA		2015	(Bennett *et al.*, 2015)
813.	*INS*	c.265CNT	p.Arg89Cys	NM_001291897.1 NP_001278826.1 (17855560)		USA	LP		
814.	*INS*	c.4G>A	p.Ala2Thr	NP_000198.1	0.000003244084	china		2017	(Yan *et al.*, 2017)

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
					95				
815.	*INS*	c.277G>A	p.Glu93Lys	NP_000198.1 NM_001291897.1	NA	Australia		2018	(Johnson *et al.*, 2018)
816.	*INS*	c.233delA	p.Gln78fs	NP_000198.1 NM_001291897.1	NA	Czech Republic		2015	(L. Dusatkova *et al.*, 2015)
817.	*INS*		p.Gly32Ser	NP_000198.1 (17855560)	NA	Japan		2016	(Moritani *et al.*, 2016)
818.	*INS*		p.Gly75Cys	NP_000198.1	NA	Japan		2018	(Ushijima *et al.*, 2018)
819.	*INS*		p.Cys96Phe	NP_000198.1	NA	Japan			
820.	*INS*	c.212dupG	p.Gly73fs	NP_000198.1 NM_001291897.1	NA	China		2019	(Xiao *et al.*, 2019)
821.	*INS*	c.298T>G	p.Cys100Gly	NP_000198.1 NM_001291897.1	NA	China	LP	2019	(Ming-Qiang *et al.*, 2019)
822.	*INS*	c.17G>A	p.Arg6His	NP_000198.1 NM_001291897.1 (20007936)	0.000063850	Denmark	VUS	2010	(Boesgaard *et al.*, 2010)
823.	*INS*	c.65delC	p.Ala23GlnfsTer4	NP_000198.1 NM_001291897.1	NA	Brazil		2019	(de Santana *et al.*, 2019)
824.	*INS*	c.163C>T	p.Arg55Cys	NP_000198.1 NM_001291897.1 (18192540)	NA	Norway	LP	2008	(Molven *et al.*, 2008)
825.	*ABCC8*	c.3202T>A	p.Phe1068Ile	NP_001274103.1		UK	VUS	2019	(Cattoni *et al.*, 2019)

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
826.	*ABCC8*	c.2376delC	p.Phe793Serfs*71	NP_000343.2 NM_000352.4		Tunisia		2019	(Dallali *et al.*, 2019)
827.	*ABCC8*	c.4608+4A>G		NM_000352.4 NP_000343.2		Tunisia			
828.	*ABCC8*		p.Met1514Thr	NP_001274103.1		Greece		2020	(E. B. Tatsi *et al.*, 2020)
829.	*ABCC8*		p.Ser1386Phe	NP_001274103.1 (10204114)		Greece			
830.	*ABCC8*	c.1277A>G	p.Asn426Ser	NP_001274103.1 NM_000352.4	3.97649098529493E-06	USA	VUS	2015	(Bennett *et al.*, 2015)
831.	*ABCC8*	c.3545G>A	p.Arg1182Gln	NM_000352.4 NP_000343.2 (16885549)			LP		
832.	*ABCC8*	c.1608T>G	p.Phe536Leu	NP_001274103.1 NM_000352.4 (25555642)		USA	VUS		
833.	*ABCC8*	c.2422C>A,	p.Gln808Lys	NP_000343.2 NM_000352.4	0.00005302	USA	VUS		
834.	*ABCC8*	c.2506C>T c.4138_4140delinsCA	p.Arg836Ter p.Thr1380Glnfs*80	NM_000352.4 NP_000343.2		USA	P		
835.	*ABC*	c.4138_41	p.Thr1380Gl	NM_000352.4					

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
	C8	40delinsCA	nfsTer80	NP_000343.2					
836.	*ABCC8*	c.4543A>G	p.Thr1515Ala	NP_000343.2 NM_000352.4 (25555642)		USA	VUS		
837.	*ABCC8*	c.4169C>T	p.Ala1390Val	NP_000343.2 NM_000352.4 (21378087)		Australia	VUS	2018	(Johnson *et al.*, 2018)
838.	*ABCC8*	c.307C>T	p.His103Tyr	NP_001274103.1 NM_000352.4	0.000003558	Korea	VUS	2016	(Kwak *et al.*, 2016)
839.	*ABCC8*	c.221G>A	p.Arg74Gln	NP_001274103.1 NM_000352.4 (9618169)	0.000000079	Korea	VUS		
840.	*ABCC8*	c.1880A>G	p.His627Arg	NP_001274103.1 NM_000352.4	0.000001076	Russia	VUS	2019	(Zubkova *et al.*, 2019)
841.	*ABCC8*	c.4096G>A	p.Ala1366Thr	NP_000343.2 NM_000352.4 (22662265)		Norway	VUS	2012	(S. Johansson *et al.*, 2012)
842.	*ABCC8*	c.4058G>A	p.Arg1353His	NP_001274103.1		Greece	LP	2019	(Koufakis *et al.*, 2019)
843.	*ABCC8*	c.1819G>A	p.Val607Met	NP_001274103.1 NM_000352.4 (18025408)	8.00371372316755E-06	Japan	VUS	2018	(Shima *et al.*, 2018)
844.	*PDX*	c.164G>A	p.Gly55Asp	NP_000200.1	0.00	Turke		201	(Anik *et*

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
	1			(26226118)	013	y		5	*al.*, 2015)
845.	*PDX 1*	c.713_714 ins	p.L238 ins P	NP_000200.1		Canada		2016	(Brahm *et al.*, 2016)
846.	*PDX 1*	c.A571C	p.lys191Gln	NP_000200.1 NM_000209.3		Canada	LP		
847.	*PDX 1*	c.529G>A	p.Val177Met	NM_000209.3 NP_000200.1 (25041077)		India	VUS	2015	(Chapla *et al.*, 2015)
848.	*PDX 1*	c.670G>A,	p.Glu224Lys	NM_000209.3 NP_000200.1 (14764823)	0.00113 9	India	VUS		
849.	*PDX 1*	c.188delC	p.Pro63ArgfsTer60	NP_000200.1 NM_000209.3	0.00001446152 5	Brazil		2018	(Caetano *et al.*, 2018)
850.	*PDX 1*	c.664G>A	p.Glu222Lys	NP_000200.1 NM_000209.3	0.00001 83	Brazil	VUS	2019	(de Santana *et al.*, 2019)
851.	*PDX 1*	c.463C>A	p.Arg155Ser	NP_000200.1 NM_000209.3	0.00007458 1	China	VUS	2019	(Deng *et al.*, 2019)
852.	*PDX 1*	c.670 G>A	p.Glu224Lys	NP_000200.1 NM_000209.3 (14764823)	0.00113 9	India	VUS	2017	(Doddabelavangala Mruthyunjaya *et al.*, 2017)
853.	*PDX 1*	c.694G>A	p.Gly232Ser	NP_000200.1	0.00004 61	USA		2015	(Mangrum *et al.*, 2015)
854.	*NEUROD 1*	c.175 G>C	p.Glu59Gln	NM_002500.4 NP_002491.2 (25041077)	0.00004 34	India	VUS	2015	(Chapla *et al.*, 2015)

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
855.	*NEUROD1*	c.-162G>A		NM_002500.4 NP_002491.2	NA	India			
856.	*NEUROD1*	c.616_617insC,	p.His206ProfsTer38	NP_002491.2 NM_002500.4	NA	Japan		2018	(Horikawa *et al.*, 2018)
857.	*NEUROD1*	c.734delC	p.Pro245ArgfsTer17	NP_002491.2 NM_002500.4	NA	Japan			
858.	*NEUROD1*		p.Leu157Arg	NP_002491.2	NA	Japan			
859.	*NEUROD1*	c.616delC	p.His206ThrfsTer56	NP_002491.2 NM_002500.4	NA	Japan			
860.	*NEUROD1*	c.308G > C	p.Arg103Pro	NP_002491.2 NM_002500.4 (26773576)	NA	Poland		2016	(Szopa *et al.*, 2016)
861.	*NEUROD1*	c.1972G>A		?	NA	Thailand		2009	(Plengvidhya *et al.*, 2009)
862.	*NEUROD1*		p.Ala322Asn	NP_002491.2	NA	Thailand			
863.	*NEUROD1*	c.451T>C	p.Trp151Arg	NP_002491.2 NM_002500.4	0.000056 5	China	VUS	2019	(Ming-Qiang *et al.*, 2019)
864.	*NEUROD1*		p.Phe256Leufs*2	NP_002491.2	NA	Brazil		2019	(G. M. Abreu *et al.*, 2019)
865.	*NEUROD1*	c.693C>G	p.Tyr231Ter	NP_002491.2 NM_002500.4	NA	Brazil	VUS	2019	(de Santana *et al.*, 2019)

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
866.	*NEUROD1*	c.616dup	p.His206ProfsTer38	NM_002500.4 NP_002491.2	NA	UK		2017	(Shields *et al.*, 2017)
867.	*PAX4*	IVS7-1G>A		?	NA	Thailand		2016	(Sujjitjoon *et al.*, 2016)
868.	*PAX4*	c.92G>T	p.Arg31Leu	NM_006193.2 NP_006184.2 (25041077)	0.00041	Canada	VUS	2016	(Brahm *et al.*, 2016)
869.	*PAX4*	c.G290A	p.Arg97His	NM_006193.2 NP_006184.2	0.00003318	Canada	VUS		
870.	*PAX4*	c.92G>T	p.Arg31Leu	NM_006193.2 NP_006184.2 (25041077)	0.00041	India	VUS	2015	(Chapla *et al.*, 2015)
871.	*PAX4*	c.490C>T	p.Arg164Trp	? (17426099)	0.00004995	Thailand		2007	(Plengvidhya *et al.*, 2007)
872.	*PAX4*	c.574C>A	p.Arg192Ser	NM_006193.2 NP_006184.2	0.00027682	China	Likely benign	2019	(Ming-Qiang *et al.*, 2019)
873.	*PAX4*	c.92G>A	p.Arg31Gln	NM_006193.2 NP_006184.2	0.00034777	China	Likely benign		
874.	*PAX4*	c.377A>G	p.Asp126Gly	NM_006193.2 NP_006184.2	NA	Russia	VUS	2019	(Zubkova *et al.*, 2019)
875.	*PAX4*	c.55C>T	p.Arg19Trp	NM_006193.2 NP_006184.2	7.95646223863021E-	Russia	VUS		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
					06				
876.	*PAX4*	c.374-412 del 39			NA	Japan		2011	(Jo *et al.*, 2011)
877.	*PAX4*	c.593 C>T	p.Ala198Val	NM_006193.2 NP_006184.2	NA	Italy	VUS	2018	(Pezzilli *et al.*, 2018)
878.	*BLK*	c.809C>T	p.Thr270Met	NP_001706.2 NM_001715.2	0.00010 60	Canada	VUS	2016	(Brahm *et al.*, 2016)
879.	*BLK*	c.57G>A			NA	USA		2009	(Borowiec *et al.*, 2009)
880.	*BLK*	c.211G>A	p.Ala71Thr	NP_001706.2 (19667185)	0.01160 1	USA			
881.	*BLK*	Chr8:11,459,364 T>G			NA	USA			
882.	*BLK*	Chr8:11,459,531 G>T			NA	USA			
883.	*BLK*	Chr8:11,468,050 C>T			NA	USA			
884.	*BLK*	c.338T>G	p.Val113Gly	NP_001706.2 NM_001715.2	NA	Italy	VUS	2018	(Pezzilli *et al.*, 2018)
885.	*KCNJ11*	c.175G>A	p.Val59Met	NP_000516.3 NM_000525.3 (15115830)		Norway	VUS	2013	(Irgens *et al.*, 2013)
886.	*KCNJ11*	c.616C>T	p.Arg206Cys	NP_000516.3 NM_000525.3 (25555642)	0.00001 20	USA	VUS	2015	(Bennett *et al.*, 2015)
887.	*KCNJ11*	c.691G>C	p.Val231Leu	NP_000516.3 NM_000525.3 (27118464)		USA	VUS		
888.	*KCNJ11*	c.970G>A	p.Gly324Arg	NP_000516.3 NM_000525.3	0.00001	USA	VUS		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
				(27118464)	06				
889.	*KCNJ11*	c.85delC	p.Arg29AlafsTer101	NP_000516.3 NM_000525.3	NA	Australia		2019	(Johnson *et al.*, 2019)
890.	*KLF11*		p.His418Gln	NP_003588.1	NA	Japan		2019	(Ushijima *et al.*, 2019)
891.	*KLF11*	c.604G>A	p.Glu202Lys	NP_003588.1 NM_003597.4	NA	China	VUS	2019	(Ming-Qiang *et al.*, 2019)
892.	*KLF11*	c.686T>G	p.Val229Gly	NP_003588.1 NM_003597.4	NA	China	VUS		
893.	*KLF11*	c.14A>G	p.Asp5Gly	NP_003588.1 NM_003597.4	0.000060	China	VUS		
894.	*KLF11*	c.316A>C	p.Ile106Leu	NP_003588.1 NM_003597.4	3.99176100528509E-06	China	VUS		
895.	*APPL1*	c.1655T>A	p.Leu552Ter	NP_036228.1 NM_012096.2 (26073777)	NA	Italy	P	2015	(Prudente *et al.*, 2015)
896.	*APPL1*	c.280G>A	p.Asp94Asn	NP_036228.1 NM_012096.2 (15115830)	4.03222554656817E-06	Italy	VUS		

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
897.	*CEL*	c.1785delC	p.Val596CysfsTer111	NM_001807.4 NP_001798.2	NA	Norway	VUS	2013	(Irgens *et al.*, 2013)
898.	*HNF1a*	c.34C>T	p.Leu12Phe	NP_001293108.2 NM_000545.6 NP_000536.5 (15928245)	NA	Denmark	VUS	2005	(Johansen *et al.*, 2005)
899.	*HNF1a*	c.370C>T	p.Gln124Ter	NP_001293108.2 NP_000536.5 NM_000545.6 (15928245)	NA	Denmark	P		
900.	*HNF1a*	c.686G>C,	p.Arg229Pro	NP_001293108.2 NP_000536.5 NM_000545.6 (11058894)	NA	Denmark	LP		
901.	*HNF1a*	c.700G>T	p.Glu234Ter	NP_001293108.2 NM_000545.6 (11058894)		Denmark	P		
902.	*HNF1a*	c. 1636-1639delGACA GACACTdelGACAfs	p.Asp546Thr547fsdelGACA	NP_000536.6	NA	Denmark			
903.	*HNF1a*	c. 1767-1768insAGTG-insAfs	p.Val590fsinsA	NP_000536.6	NA	Denmark			
904.	*INS*	c.187+24		NM_00129189	NA	USA		201	(Carmody

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
		1G>A		7.1 NP_001278826.1				5	*et al.*, 2015)
905.	*HNF1b*	c.983delC	p.Pro328Leufs*48	NM_000458.3 NP_000449.1	NA	Brazil		2019	(Dotto *et al.*, 2019)
906.	*GCK*	c.92T>C	p.Leu31Pro	NM_033507.1 NP_277042.1	NA	Korea	LP	2017	(E. H. Cho *et al.*, 2017)
907.	*GCK*	c.1151C>T	p.Ser383Pro	NP_000153.1	NA	Korea	LP		
908.	*GCK*		p.Gly178Ala	NP_000153.1	NA	Brazil		2017	(Franco *et al.*, 2017)
909.	*HNF1a*	c.815G>A	p.Arg272His	NM_000545.6 NP_000536.5	NA	Netherland	VUS	2019	(Haring *et al.*, 2019)
910.	*HNF1b*	c.276C>T	p.Arg276X	NM_001165923.3 NP_001159395.1 (12161522)		Japan	Likely benign	2007	(Fujimoto *et al.*, 2007)
911.	*HNF1a*	Gly288fs*863_864insC	p.Pro289AlafsTer28	NM_000545.6 NP_000536.5		Denmark		2017	(Gjesing *et al.*, 2017)
912.	*HNf4a*	992G>A	p.Arg331His	NM_178849.2 NP_849180.1	4.021976077286 29E-06	Denmark	VUS		
913.	*HNf4a*	c.256C>T	p.Gln86X	NM_001287182.1 NP_001274111.1	NA	USA	P	2018	(Kleinberger *et al.*, 2018)

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
914.	*HNF4a*	c.9871003del17ins9	p.Leu330fs	NP_001245284.1	NA	UK		2008	(Kapoor *et al.*, 2008)
915.	*HNF4a*	c.264–21A>G				UK			
916.	*HNF4a*	c.48C>G	p.Tyr16X	NM_001287182.1 NP_001274111.1 (17407387)		UK	P		
917.	*HNf1a*		p.Pro611Leu	XP_024304936.1		India		2018	(Mohan *et al.*, 2018)
918.	*HNf1a*		p.Val648Ile	XP_024304936.1		India			
919.	*HNf1a*	c.1061C>T	p.Thr354Met	XP_024304936.1 (11058894)	0.000063636	India			
920.	*HNf1a*		p.Trp113*	XP_024304936.1 (11692182)	NA	India			
921.	*ABCC8*		p.lys1023Gln	NP_001274103.1		India			
922.	*ABCC8*	c.2912A>T	p.Glu971Val	NP_001274103.1	0.000000397	India			
923.	*ABCC8*		p.Ala1473Thr	NP_001274103.1		India			
924.	*ABCC8*		p.Gly1009Ser	NP_001274103.1		India			
925.	*ABCC8*		p.Asn781Ser	NP_001274103.1		India			
926.	*BLK*		p.Arg446Gl	NP_001706.2		India			

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
			y						
927.	*CEL*	c.294C>G	p.tyr98*	?	4.00936587869262E-06	India			
928.	*GCK*		p.Thr207Ala	NP_277042.1	NA	India			
929.	*HNF1b*	c.1306A>G	p.Thr436Ala	NP_000449.1	3.97630124458229E-06	India			
930.	*KCNJ11*	c.1084G>A	p.Ala362Thr	NP_000516.3	0.000023898	India			
931.	*KLF11*	c.1394G>A	p.Arg465His	NP_003588	0.000001193	India			
932.	*PDX1*		p.lys147Arg	NP_000200.1		India			
933.	*ABCC8*		p.Ala1457Thr	NP_000343.2 (12364426)		Russia		2016	(Ovsyannikova *et al.*, 2016)
934.	*HNF1b*	c.374T>C	p.Ile125Thr	NM_001165923.3 NP_001159395.1 (22432796)		France	VUS	2012	(Poitou *et al.*, 2012)
935.	*HNF*	c.544+1_		NM_00116592		Franc			

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
	1b	544+4del		3.3 NP_00115939 5.1		e			
936.	*HNF 1b*	c.698G>A	p.Arg233His	NM_000458.3 NP_000449.1 (22432796)		France	VUS		
937.	*HNF 4a*	c.268C>T	p.Gln268Ser			USA		1996	(Yamagata *et al.*, 1996)
938.	*GCK*		p.Val406Ala	NP_000153.1		Poland		2014	(Fendler *et al.*, 2014)
939.	*GCK*		p.Arg447Gln	NP_000153.1		Poland			
940.	*GCK*		p.Arg43Cys	NP_000153.1 (17573900)		Poland			
941.	*GCK*		p.Arg337Cys	?		Poland			
942.	*GCK*		p.Gly318Arg	NP_000153.1		Poland			
943.	*GCK*		p.Phe150fs	NP_000153.1		Poland			
944.	*GCK*		p.Arg186X	NP_000153.1		Poland			
945.	*GCK*		p.Gly318Arg	NP_000153.1 (12627330)	NA	Poland			
946.	*ABCC8*	c.1763C>T	p.Thr588Ile	NP_000343.2	NA	Finland	VUS	2016	(Huopio *et al.*, 2016)
947.	*GCK*	c.635_637delCCT	p.Ser212	NP_000153.1	NA	Finland			
948.	*GCK*	c.364-8T>G		NM_033508.1 NP_277043.1	NA	Iran		2019	(Yaghootkar *et al.*, 2019)
949.	*GCK*		p.Arg308lys	NP_000153.1	NA	India		2014	(Yellapu *et al.*,

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
									2014)
950.	*GCK*	c.1278_1286dup9,	p.Arg427_Leu429dup	NM_033508.2 NP_277043.1	NA	Japan		2012	(Yorifuji *et al.*, 2012)
951.	*GCK*	c.1142T>G	p.Met381Arg	NM_000162.4 NP_000153.1	NA	Japan	LP		
952.	*GCK*	c.175C>T	p.Pro59Ser	NM_000162.4 NP_000153.1 (22060211)	NA	Japan	LP		
953.	*GCK*	c.182A>G	p.Tyr61Cys	NM_000162.4 NP_000153.1 (22060211)	NA	Japan	VUS		
954.	*GCK*	c.576G>T	p.Gly193Trp	NM_033508.2 NP_277043.1 (24804978)	NA	Japan	VUS		
955.	*GCK*	c.500G>A	p.Trp167Ter	NM_000162.4 NP_000153.1 (24804978)	NA	Japan	P		
956.	*HNF1a*	c.1043T>C	p.Leu348Pro	NM_000545.6 NP_000536.5 (24804978)	NA	Japan	VUS		
957.	*HNF1a*	c.1054delT	p.Ser352ProfsTer12	NM_000545.6 NP_000536.5	NA	Japan			
958.	*HNF1b*	c.395A>C	p.His132Pro	NM_001165923.3 NP_001159395.1 (24804978)		Japan	VUS		
959.	*HNF4a*	c.915_916insT	p.Arg306SerfsTer37	NM_001287184.1 NP_001274113.1		Japan			

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
960.	*HNF4a*	c.970C>T	p.Arg324Cys	NP_00124528 4.1		Japan	LP		
961.	*GCK*	c.492_494 delTCT	p.Leu165del	NM_000162.4 NP_000153.1		Japan		2018	(Yorifuji *et al.*, 2018)
962.	*GCK*	c.533G>C	p.Gly178Ala	NM_000162.4 NP_000153.1		Japan	LP		
963.	*GCK*	c.538A>C	p.Asn180His	NM_000162.4 NP_000153.1		Japan	VUS		
964.	*GCK*	c.577G>T	p.Gly193Trp	NM_000162.4 NP_000153.1 (24804978)		Japan	VUS		
965.	*GCK*	c.671T>A	p.Met224Lys	NM_000162.4 NP_000153.1		Japan	VUS		
966.	*GCK*	c.707A>C	p.Glu236Ala	NM_000162.4 NP_000153.1		Japan	VUS		
967.	*GCK*	c.836_837 delAG	p.Glu279Efs	NM_000162.4 NP_000153.1		Japan			
968.	*GCK*	c.898G>T	p.Glu300*	NM_000162.4 NP_000153.1 (24804978)		Japan	P		
969.	*GCK*	c.1055T>G	p.Leu352Arg	NM_000162.4 NP_000153.1 (24804978)		Japan	VUS		
970.	*GCK*	c.1144_1149dupTGCTCG	p.Cys382_Ser383dup	NM_000162.4 NP_000153.1		Japan			
971.	*GCK*	c.1278_1286dupCGTGCGCAG	p.Ser426_Arg428dup	NM_000162.4 NP_000153.1		Japan			

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
972.	*GCK*	c.1340_1368del29	p.Arg447LeufsTer2	NM_000162.4 NP_000153.1		Japan			
973.	*HNF1a*	c.618G>A	p.Trp206Ter	NM_000545.6 NP_000536.5 (24642958)		Japan	P		
974.	*HNF1a*	c.752C>T	p.Ala251Val	NM_000545.6 NP_000536.5		Japan	VUS		
975.	*HNF1a*	c.778A>T	p.Thr260Ser	NM_000545.6 NP_000536.5		Japan	VUS		
976.	*HNF1a*	c.791T>C	p.Val264Ala	NM_000545.6 NP_000536.5		Japan	VUS		
977.	*HNF1b*	c.395A>C	p.His132Pro	NM_001165923.3 NP_001159395.1 (22060211)		Japan	VUS		
978.	*HNF4a*	c.146A>C	p.His49Pro	NM_001287184.1 NP_001274113.1		Japan	LP		
979.	*HNF4a*	c.426+1G>A		?		Japan			
980.	*HNF4a*	c.857T>A	p.Ile286Asn	NM_001287184.1 NP_001274113.1		Japan	LP		
981.	*HNF4a*	c.874C>T	p.Gln292*	NP_787110.2		Japan	P		
982.	*PDX1*	c.302C>T	p.Pro101Leu	NP_000200.1	0.000001536	India		2019	(Sahoo *et al.*, 2019)
983.	*GCK*	c.70G>A		NP_000153.1	NA	Franc	P	199	(Froguel *et*

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
						e		3	*al.*, 1993)
984.	*GCK*	c.98C>T		NP_000153.1	NA	France			
985.	*GCK*	c.161-15bpdeletion			NA	France			
986.	*GCK*	c.175G>A		NP_000153.1	NA	France	LP		
987.	*GCK*	c.182G>A		NP_000153.1		France	VUS		
988.	*GCK*	c.186C>T	p.Tyr62Tyr	NP_000153.1	0.000003537	France	Likely benign		
989.	*GCK*	c.203T>C		NP_000153.1	NA	France	VUS		
990.	*GCK*	c.227G>T				France			
991.	*GCK*	c.228C>T		NP_000153.1		France	Likely benign		
992.	*GCK*	c.261G>A		NP_000153.1		France	VUS		
993.	*GCK*	c.279G>T		NP_000153.1		France			
994.	*GCK*	c.300G>A		NP_000153.1		France	Likely benign		
995.	*GCK*	c.300G>C		NP_000153.1		France	VUS		
996.	*GCK*	c.309T>C		NP_000153.1		France			

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
997.	*GCK*	c.414A>G		NP_000153.1		France	Likely benign		
998.	*HNF1b*	heterozygous deletion				New Zealand		2017	(Mikusheva *et al.*, 2017)
999.	*HNF1b*	*HNF1b* deletion				USA		2019	(H. J. Li *et al.*, 2019)
1000	*GCK*	c.1116G>C	p.Glu372Asp	NP_000153.1	NA	Italy	VUS	2019	(Marucci *et al.*, 2019)
1001	*HNF1b*	*HNF1b* deletion				Japan		2019	(Omura *et al.*, 2019)
1002	*HNF1b*	*HNF1b* deletion				UK		2018	(Stiles *et al.*, 2018)
1003	*PDX1*	Pro63fsdelC		NP_000200.1		USA		2000	(Clocquet *et al.*, 2000)
1004	*HNF1b*	*HNF1b* deletion				UK		2013	(Edghill *et al.*, 2013)
1005	*GCK*	GCK exon2				UK		2007	(Ellard *et al.*, 2007)
1006	*HNF1a*	*Exon1*				UK			
1007	*HNF1a*	*Exon2-10*				UK			
1008	*HNF*	*Exon 1-10*				UK			

S. No	*Gene*	Nucleotide position	Protein position	Accession number (PMID number from HGMD)	Gnom freq	Country	Intervar	Pub. Year	Reference
	1a								
1009	*HNF 1b*	*HNF1b* deletion				Germany		2009	(Raile *et al.*, 2009)
1010	*HNF 1b*	*HNF1b* deletion				Germany		2018	(Roehlen *et al.*, 2018)
1011	*ABC C8*		p.Arg826Trp	NP_001274103.1		Argentina		2016	(Taberner *et al.*, 2016)
1012	*HNF 1a*	*HNF1α* ex2-3del mutation				New Zealand			(Willson *et al.*, 2013)
1013	*HNF 1a*	c.1512C>A	p.Ser504Arg	NM_000545.6 NP_000536.5	0.000000797	China			(M. Li *et al.*, 2020)
1014	*HNF 1a*	c.956-1G>C		NM_000545.6 NP_000536.5					
1015	*HNF 1a*	c.347C>T	p.Ala116Val	NM_000545.6 NP_000536.5 (11315828)	3.97946595566874E-06				
1016	*HNF 1a*	c.1192C>G	p.Gln398Glu	NM_000545.6 NP_000536.5					
1017	*HNF 1a*	c.1136C>A	p.Pro379His	NP_000536.6 (15883474)	0.0000051	Mexico			(Dominguez-Lopez *et al.*, 2005)

Related References:

Abreu, Tarantino, Cabello, Zembrzuski, da Fonseca, Rodacki, Zajdenverg, & Campos Junior. (2019). The first case of NEUROD1-MODY reported in Latin America. *Mol Genet Genomic Med, 7*(12), e989. doi: 10.1002/mgg3.989

Abreu, & Urano. (2019). Current Landscape of Treatments for Wolfram Syndrome. *Trends Pharmacol Sci, 40*(10), 711-714. doi: 10.1016/j.tips.2019.07.011

Afonso, Ferraria, Carvalho, & Castro. (2014). Maturity onset diabetes of young type 2 due to a novel de novo GKC mutation. [Case Reports]. *Arq Bras Endocrinol Metabol, 58*(7), 772-775. doi: 10.1590/0004-2730000003147

Agladioglu, Aycan, Cetinkaya, Bas, Onder, Peltek Kendirci, Dogan, & Ceylaner. (2016). Maturity onset diabetes of youth (MODY) in Turkish children: sequence analysis of 11 causative genes by next generation sequencing. *J Pediatr Endocrinol Metab, 29*(4), 487-496. doi: 10.1515/jpem-2015-0039

Akiba, Ushijima, Fukami, & Hasegawa. (2019). A heterozygous protein-truncating RFX6 variant in a family with childhood-onset, pregnancy-associated and adult-onset diabetes. *Diabet Med.* doi: 10.1111/dme.13970

Almeida, Silva, Garcia, Leite, Teles, & Campos. (2014). A novel genetic mutation in a Portuguese family with GCK-MODY. [Case Reports]. *J Pediatr Endocrinol Metab, 27*(1-2), 129-133. doi: 10.1515/jpem-2013-0056

Aloi, Salina, Minuto, Tallone, Lugani, Mascagni, Mazza, Cassanello, Maghnie, & d'Annunzio. (2017). Glucokinase mutations in pediatric patients with impaired fasting glucose. *Acta Diabetol, 54*(10), 913-923. doi: 10.1007/s00592-017-1021-y

Amed, Dean, Panagiotopoulos, Sellers, Hadjiyannakis, Laubscher, Dannenbaum, Shah, Booth, & Hamilton. (2010). Type 2 diabetes, medication-induced

diabetes, and monogenic diabetes in Canadian children: a prospective national surveillance study. [Research Support, Non-U.S. Gov't]. *Diabetes Care, 33*(4), 786-791. doi: 10.2337/dc09-1013

Anik, Catli, Abaci, Sari, Yesilkaya, Korkmaz, Demir, Altincik, Tuhan, Kizildag, Ozkan, Ceylaner, & Bober. (2015). Molecular diagnosis of maturity-onset diabetes of the young (MODY) in Turkish children by using targeted next-generation sequencing. *J Pediatr Endocrinol Metab, 28*(11-12), 1265-1271. doi: 10.1515/jpem-2014-0430

Anuradha, Radha, & Mohan. (2011). Association of novel variants in the hepatocyte nuclear factor 4A gene with maturity onset diabetes of the young and early onset type 2 diabetes. [Comparative Study

Research Support, Non-U.S. Gov't]. *Clin Genet, 80*(6), 541-549. doi: 10.1111/j.1399-0004.2010.01577.x

Apperley, Giri, Houghton, Flanagan, Didi, & Senniappan. (2019). A rare case of congenital hyperinsulinism (CHI) due to dual genetic aetiology involving HNF4A and ABCC8. [Case Reports]. *J Pediatr Endocrinol Metab, 32*(3), 301-304. doi: 10.1515/jpem-2018-0389

Artuso, Provenzano, Mazzinghi, Giunti, Palazzo, Andreucci, Blasetti, Chiuri, Gianiorio, Mandich, Monami, Mannucci, & Giglio. (2015). Therapeutic implications of novel mutations of the RFX6 gene associated with early-onset diabetes. *Pharmacogenomics J, 15*(1), 49-54. doi: 10.1038/tpj.2014.37

Arya, Rahman, Senniappan, Flanagan, Ellard, & Hussain. (2014). HNF4A mutation: switch from hyperinsulinaemic hypoglycaemia to maturity-onset diabetes of the young, and incretin response. [Case Reports

Research Support, Non-U.S. Gov't]. *Diabet Med, 31*(3), e11-15. doi: 10.1111/dme.12369

Awata, Kurihara, Inoue, Inoue, Takei, Ishii, Negishi, Namai, Kanazawa, Kuzuya, & Katayama. (1998). A novel missense mutation in the homeodomain of the hepatocyte nuclear factor-1alpha/maturity-onset diabetes of the young 3 in a Japanese early-onset type 2 diabetic patient and time-course of glucose-stimulated insulin secretion. [Case Reports

Letter]. *Diabetes Care, 21*(9), 1569-1571. doi: 10.2337/diacare.21.9.1569

Aykut, Karaca, Onay, Goksen, Cetinkalp, Eren, Ersoy, Cakir, Buyukinan, Kara, Anik, Kirel, Ozen, Atik, Darcan, & Ozkinay. (2018). Analysis of the GCK gene in 79 MODY type 2 patients: A multicenter Turkish study, mutation profile and description of twenty novel mutations. [Multicenter Study]. *Gene, 641*, 186-189. doi: 10.1016/j.gene.2017.10.057

Bacon, Kyithar, Rizvi, Donnelly, McCarthy, Burke, Colclough, Ellard, & Byrne. (2016). Successful maintenance on sulphonylurea therapy and low diabetes complication rates in a HNF1A-MODY cohort. *Diabet Med, 33*(7), 976-984. doi: 10.1111/dme.12992

Bansal, Gassenhuber, Phillips, Oliveira, Harbaugh, Villarasa, Topol, Seufferlein, & Boehm. (2017). Spectrum of mutations in monogenic diabetes genes identified from high-throughput DNA sequencing of 6888 individuals. *BMC Med, 15*(1), 213. doi: 10.1186/s12916-017-0977-3

Barrett, Bundey, & Macleod. (1995). Neurodegeneration and diabetes: UK nationwide study of Wolfram (DIDMOAD) syndrome. [Research Support, Non-U.S. Gov't]. *Lancet, 346*(8988), 1458-1463. doi: 10.1016/s0140-6736(95)92473-6

Barrio, Bellanne-Chantelot, Moreno, Morel, Calle, Alonso, & Mustieles. (2002). Nine novel mutations in maturity-onset diabetes of the young (MODY) candidate genes in 22 Spanish families. *J Clin Endocrinol Metab, 87*(6), 2532-2539. doi: 10.1210/jcem.87.6.8530

Basit, Fawwad, Qureshi, & Shera. (2018). Prevalence of diabetes, pre-diabetes and associated risk factors: second National Diabetes Survey of Pakistan (NDSP), 2016-2017. [Research Support, Non-U.S. Gov't]. *BMJ Open, 8*(8), e020961. doi: 10.1136/bmjopen-2017-020961

Bazalova, Rypackova, Broz, Brunerova, Polak, Rusavy, Treslova, & Andel. (2010). Three novel mutations in MODY and its phenotype in three different Czech families. [Research Support, Non-U.S. Gov't]. *Diabetes Res Clin Pract, 88*(2), 132-138. doi: 10.1016/j.diabres.2010.01.005

Beer, Osbak, van de Bunt, Tribble, Steele, Wensley, Edghill, Colcough, Barrett, Valentinova, Rundle, Raimondo, Grimsby, Ellard, & Gloyn. (2012). Insights into the pathogenicity of rare missense GCK variants from the identification and functional characterization of compound heterozygous and double mutations inherited in cis. [Research Support, Non-U.S. Gov't]. *Diabetes Care, 35*(7), 1482-1484. doi: 10.2337/dc11-2420

Beijers, Losekoot, Odink, & Bravenboer. (2009). Hepatocyte nuclear factor (HNF)1A and HNF4A substitution occurring simultaneously in a family with maturity-onset diabetes of the young. [Case Reports]. *Diabet Med, 26*(11), 1172-1174. doi: 10.1111/j.1464-5491.2009.02855.x

Bellanne-Chantelot, Carette, Riveline, Valero, Gautier, Larger, Reznik, Ducluzeau, Sola, Hartemann-Heurtier, Lecomte, Chaillous, Laloi-Michelin, Wilhem, Cuny, Duron, Guerci, Jeandidier, Mosnier-Pudar, Assayag, Dubois-Laforgue,

Velho, & Timsit. (2008). The type and the position of HNF1A mutation modulate age at diagnosis of diabetes in patients with maturity-onset diabetes of the young (MODY)-3. [Research Support, Non-U.S. Gov't]. *Diabetes, 57*(2), 503-508. doi: 10.2337/db07-0859

Bellanne-Chantelot, Chauveau, Gautier, Dubois-Laforgue, Clauin, Beaufils, Wilhelm, Boitard, Noel, Velho, & Timsit. (2004). Clinical spectrum associated with hepatocyte nuclear factor-1beta mutations. *Ann Intern Med, 140*(7), 510-517. doi: 10.7326/0003-4819-140-7-200404060-00009

Bellanne-Chantelot, Clauin, Chauveau, Collin, Daumont, Douillard, Dubois-Laforgue, Dusselier, Gautier, Jadoul, Laloi-Michelin, Jacquesson, Larger, Louis, Nicolino, Subra, Wilhem, Young, Velho, & Timsit. (2005). Large genomic rearrangements in the hepatocyte nuclear factor-1beta (TCF2) gene are the most frequent cause of maturity-onset diabetes of the young type 5. *Diabetes, 54*(11), 3126-3132. doi: 10.2337/diabetes.54.11.3126

Ben Khelifa, Martinez, Dandana, Khochtali, Ferchichi, & Castano. (2018). Maturity Onset Diabetes of the Young (MODY) in Tunisia: Low frequencies of GCK and HNF1A mutations. *Gene, 651*, 44-48. doi: 10.1016/j.gene.2018.01.081

Bennett, Vasta, Zhang, Narayanan, Gerrits, & Hahn. (2015). Molecular genetic testing of patients with monogenic diabetes and hyperinsulinism. [Research Support, N.I.H., Extramural]. *Mol Genet Metab, 114*(3), 451-458. doi: 10.1016/j.ymgme.2014.12.304

Biason-Lauber, Boehm, Lang-Muritano, Gauthier, Brun, Wollheim, & Schoenle. (2005). Association of childhood type 1 diabetes mellitus with a variant of PAX4: possible link to beta cell regenerative capacity. [Research Support,

Non-U.S. Gov't]. *Diabetologia, 48*(5), 900-905. doi: 10.1007/s00125-005-1723-5

Bjorkhaug, Sagen, Thorsby, Sovik, Molven, & Njolstad. (2003). Hepatocyte nuclear factor-1 alpha gene mutations and diabetes in Norway. [Research Support, Non-U.S. Gov't]. *J Clin Endocrinol Metab, 88*(2), 920-931. doi: 10.1210/jc.2002-020945

Bodhini, Sandhiya, Ghosh, Majumder, Rao, Mohan, & Radha. (2012). Association of His1085His INSR gene polymorphism with type 2 diabetes in South Indians. *Diabetes Technol Ther, 14*(8), 696-700. doi: 10.1089/dia.2012.0009

Boesgaard, Pruhova, Andersson, Cinek, Obermannova, Lauenborg, Damm, Bergholdt, Pociot, Pisinger, Barbetti, Lebl, Pedersen, & Hansen. (2010). Further evidence that mutations in INS can be a rare cause of Maturity-Onset Diabetes of the Young (MODY). [Research Support, Non-U.S. Gov't]. *BMC Med Genet, 11*, 42. doi: 10.1186/1471-2350-11-42

Bonatto, Nogaroto, Svidnicki, Milleo, Grassiolli, Almeida, Vicari, & Artoni. (2012). Variants of the HNF1alpha gene: A molecular approach concerning diabetic patients from southern Brazil. *Genet Mol Biol, 35*(4), 737-740. doi: 10.1590/S1415-47572012005000061

Bonfig, Hermanns, Warncke, Eder, Engelsberger, Burdach, Ziegler, & Lohse. (2011). GCK-MODY (MODY 2) Caused by a Novel p.Phe330Ser Mutation. [Case Reports]. *ISRN Pediatr, 2011*, 676549. doi: 10.5402/2011/676549

Bonnefond, Lomberk, Buttar, Busiah, Vaillant, Lobbens, Yengo, Dechaume, Mignot, Simon, Scharfmann, Neve, Tanyolac, Hodoglugil, Pattou, Cave, Iovanna, Stein, Polak, Vaxillaire, Froguel, & Urrutia. (2011). Disruption of a novel Kruppel-like transcription factor p300-regulated pathway for insulin

biosynthesis revealed by studies of the c.-331 INS mutation found in neonatal diabetes mellitus. *J Biol Chem, 286*(32), 28414-28424. doi: 10.1074/jbc.M110.215822

Borowiec, Liew, Thompson, Boonyasrisawat, Hu, Mlynarski, El Khattabi, Kim, Marselli, Rich, Krolewski, Bonner-Weir, Sharma, Sale, Mychaleckyj, Kulkarni, & Doria. (2009). Mutations at the BLK locus linked to maturity onset diabetes of the young and beta-cell dysfunction. [Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't]. *Proc Natl Acad Sci U S A, 106*(34), 14460-14465. doi: 10.1073/pnas.0906474106

Bowman, Flanagan, Edghill, Damhuis, Shepherd, Paisey, Hattersley, & Ellard. (2012). Heterozygous ABCC8 mutations are a cause of MODY. [Research Support, Non-U.S. Gov't]. *Diabetologia, 55*(1), 123-127. doi: 10.1007/s00125-011-2319-x

Brahm, Wang, Wang, McIntyre, Cao, Ban, & Hegele. (2016). Genetic Confirmation Rate in Clinically Suspected Maturity-Onset Diabetes of the Young. *Can J Diabetes, 40*(6), 555-560. doi: 10.1016/j.jcjd.2016.05.010

Bulman, Dronsfield, Frayling, Appleton, Bain, Ellard, & Hattersley. (1997). A missense mutation in the hepatocyte nuclear factor 4 alpha gene in a UK pedigree with maturity-onset diabetes of the young. [Case Reports

Research Support, Non-U.S. Gov't]. *Diabetologia, 40*(7), 859-862. doi: 10.1007/s001250050760

Caetano, Jorge, Malaquias, Trarbach, Queiroz, Nery, & Teles. (2012). Incidental mild hyperglycemia in children: two MODY 2 families identified in Brazilian subjects. [Case Reports

Research Support, Non-U.S. Gov't]. *Arq Bras Endocrinol Metabol, 56*(8), 519-524. doi: 10.1590/s0004-27302012000800010

Caetano, Santana, Costa-Riquetto, Lerario, Nery, Nogueira, Ortega, Rocha, Jorge, & Teles. (2018). PDX1 -MODY and dorsal pancreatic agenesis: New phenotype of a rare disease. [Research Support, Non-U.S. Gov't]. *Clin Genet, 93*(2), 382-386. doi: 10.1111/cge.13044

Cantu, Krier, & Hashemi. (2016). Hepatocyte Nuclear Factor 1alpha Mutation-associated MODY-3 and Familial Liver Adenomatosis. [Case Reports

Letter]. *J Clin Gastroenterol, 50*(2), 181-182. doi: 10.1097/MCG.0000000000000461

Capuano, Garcia-Herrero, Tinto, Carluccio, Capobianco, Coto, Cola, Iafusco, Franzese, Zagari, Navas, & Sacchetti. (2012). Glucokinase (GCK) mutations and their characterization in MODY2 children of southern Italy. [Research Support, Non-U.S. Gov't]. *PLoS One, 7*(6), e38906. doi: 10.1371/journal.pone.0038906

Carmody, Park, Ye, Perrone, Alkorta-Aranburu, Highland, Hanis, Philipson, Bell, & Greeley. (2015). Continued lessons from the INS gene: an intronic mutation causing diabetes through a novel mechanism. [Case Reports

Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't]. *J Med Genet, 52*(9), 612-616. doi: 10.1136/jmedgenet-2015-103220

Carrillo, Lomas, Pines, & Lamas. (2017). Long-lasting response to oral therapy in a young male with monogenic diabetes as part of HNF1B-related disease. *Endocrinol Diabetes Metab Case Rep, 2017*. doi: 10.1530/EDM-17-0052

Cattoni, Jackson, Bain, Houghton, & Wei. (2019). Phenotypic variability in two siblings with monogenic diabetes due to the same ABCC8 gene mutation. [Case Reports

Research Support, Non-U.S. Gov't]. *Pediatr Diabetes, 20*(4), 482-485. doi: 10.1111/pedi.12826

Chambers, Fouts, Dong, Colclough, Wang, Batish, Jaremko, Ellard, Hattersley, Klingensmith, & Steck. (2016). Characteristics of maturity onset diabetes of the young in a large diabetes center. [Research Support, Non-U.S. Gov't]. *Pediatr Diabetes, 17*(5), 360-367. doi: 10.1111/pedi.12289

Chapla, Mruthyunjaya, Asha, Varghese, Varshney, Vasan, Venkatesan, Nair, Mathai, Paul, & Thomas. (2015). Maturity onset diabetes of the young in India - a distinctive mutation pattern identified through targeted next-generation sequencing. [Research Support, Non-U.S. Gov't]. *Clin Endocrinol (Oxf), 82*(4), 533-542. doi: 10.1111/cen.12541

Chaussenot, Bannwarth, Rouzier, Vialettes, Mkadem, Chabrol, Cano, Labauge, & Paquis-Flucklinger. (2011). Neurologic features and genotype-phenotype correlation in Wolfram syndrome. [Research Support, Non-U.S. Gov't]. *Ann Neurol, 69*(3), 501-508. doi: 10.1002/ana.22160

Chevre, Hani, Boutin, Vaxillaire, Blanche, Vionnet, Pardini, Timsit, Larger, Charpentier, Beckers, Maes, Bellanne-Chantelot, Velho, & Froguel. (1998). Mutation screening in 18 Caucasian families suggest the existence of other MODY genes. [Research Support, Non-U.S. Gov't]. *Diabetologia, 41*(9), 1017-1023. doi: 10.1007/s001250051025

Cho, Cho, Choi, & Kim. (2018). Novel deletion mutation in the glucokinase gene from a korean man with GCK-MODY phenotype and situs inversus. [Case

Reports]. *Diabetes Res Clin Pract, 143*, 263-266. doi: 10.1016/j.diabres.2018.07.036

Cho, Min, Choi, Choi, & Kim. (2017). Identification of Maturity-Onset Diabetes of the Young Caused by Glucokinase Mutations Detected Using Whole-Exome Sequencing. *Endocrinol Metab (Seoul), 32*(2), 296-301. doi: 10.3803/EnM.2017.32.2.296

Clocquet, Egan, Stoffers, Muller, Wideman, Chin, Clarke, Hanks, Habener, & Elahi. (2000). Impaired insulin secretion and increased insulin sensitivity in familial maturity-onset diabetes of the young 4 (insulin promoter factor 1 gene). [Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, P.H.S.]. *Diabetes, 49*(11), 1856-1864. doi: 10.2337/diabetes.49.11.1856

Codner, Rocha, Deng, Martinez-Aguayo, Godoy, Mericq, & Chung. (2009). Mild fasting hyperglycemia in children: high rate of glucokinase mutations and some risk of developing type 1 diabetes mellitus. [Research Support, N.I.H., Extramural]. *Pediatr Diabetes, 10*(6), 382-388. doi: 10.1111/j.1399-5448.2009.00499.x

Costa, Bescos, Velho, Chevre, Vidal, Sesmilo, Bellanne-Chantelot, Froguel, Casamitjana, Rivera-Fillat, Gomis, & Conget. (2000). Genetic and clinical characterisation of maturity-onset diabetes of the young in Spanish families. [Research Support, Non-U.S. Gov't]. *Eur J Endocrinol, 142*(4), 380-386. doi: 10.1530/eje.0.1420380

Costantini, Malerba, Contreas, Corradi, Marin Vargas, Giorgetti, & Maffeis. (2015). Genetic and bioinformatics analysis of four novel GCK missense variants

detected in Caucasian families with GCK-MODY phenotype. *Clin Genet, 87*(5), 440-447. doi: 10.1111/cge.12406

Couper, & Donaghue. (2009). Phases of diabetes in children and adolescents. [Review]. *Pediatr Diabetes, 10 Suppl 12*, 13-16. doi: 10.1111/j.1399-5448.2009.00574.x

Craig, Hattersley, & Donaghue. (2009). Definition, epidemiology and classification of diabetes in children and adolescents. [Review]. *Pediatr Diabetes, 10 Suppl 12*, 3-12. doi: 10.1111/j.1399-5448.2009.00568.x

Dabelea, Mayer-Davis, Saydah, Imperatore, Linder, Divers, Bell, Badaru, Talton, Crume, Liese, Merchant, Lawrence, Reynolds, Dolan, Liu, & Hamman. (2014). Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. [Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, P.H.S.]. *JAMA, 311*(17), 1778-1786. doi: 10.1001/jama.2014.3201

Dallali, Pezzilli, Hechmi, Sallem, Elouej, Jmel, Ben Halima, Chargui, Gharbi, Mercuri, Alberico, Mazza, Bahlous, Ben Ahmed, Jamoussi, Abid, Trischitta, Abdelhak, Prudente, & Kefi. (2019). Genetic characterization of suspected MODY patients in Tunisia by targeted next-generation sequencing. *Acta Diabetol, 56*(5), 515-523. doi: 10.1007/s00592-018-01283-5

Dandona, Aljada, Mohanty, Ghanim, Hamouda, Assian, & Ahmad. (2001). Insulin inhibits intranuclear nuclear factor kappaB and stimulates IkappaB in mononuclear cells in obese subjects: evidence for an anti-inflammatory effect? [Research Support, Non-U.S. Gov't]. *J Clin Endocrinol Metab, 86*(7), 3257-3265. doi: 10.1210/jcem.86.7.7623

de Heredia, Cleries, & Nunes. (2013). Genotypic classification of patients with Wolfram syndrome: insights into the natural history of the disease and correlation with phenotype. [Research Support, Non-U.S. Gov't]. *Genet Med, 15*(7), 497-506. doi: 10.1038/gim.2012.180

de Santana, Caetano, Costa-Riquetto, Franco, Dotto, Reis, Weinert, Silveiro, Vendramini, do Prado, Abrahao, de Almeida, Tavares, Goncalves, Santomauro Junior, Halpern, Jorge, Nery, & Teles. (2019). Targeted sequencing identifies novel variants in common and rare MODY genes. *Mol Genet Genomic Med, 7*(12), e962. doi: 10.1002/mgg3.962

DellaManna, Silva, Chacra, Kunii, Rolim, Furuzawa, Maciel, & Reis. (2012). Clinical follow-up of two Brazilian subjects with glucokinase-MODY (MODY2) with description of a novel mutation. *Arq Bras Endocrinol Metabol, 56*(8), 490-495. doi: 10.1590/s0004-27302012000800005

Delvecchio, Di Paola, Mangiacotti, Sacco, Menzaghi, & Trischitta. (2014). Clinical heterogeneity of abnormal glucose homeostasis associated with the HNF4A R311H mutation. [Case Reports

Letter

Research Support, Non-U.S. Gov't]. *Ital J Pediatr, 40*, 58. doi: 10.1186/1824-7288-40-58

Delvecchio, Ludovico, Bellacchio, Stallone, Palladino, Mastroianno, Zelante, Sacco, Trischitta, & Carella. (2013). MODY type 2 P59S GCK mutant: founder effect in South of Italy. *Clin Genet, 83*(1), 83-87. doi: 10.1111/j.1399-0004.2012.01856.x

Delvecchio, Mozzillo, Salzano, Iafusco, Frontino, Patera, Rabbone, Cherubini, Grasso, Tinto, Giglio, Contreas, Di Paola, Salina, Cauvin, Tumini,

d'Annunzio, Iughetti, Mantovani, Maltoni, Toni, Marigliano, & Barbetti. (2017). Monogenic Diabetes Accounts for 6.3% of Cases Referred to 15 Italian Pediatric Diabetes Centers During 2007 to 2012. *J Clin Endocrinol Metab, 102*(6), 1826-1834. doi: 10.1210/jc.2016-2490

Deng, Xiao, Zhou, & Wang. (2019). First Case Report of Maturity-Onset Diabetes of the Young Type 4 Pedigree in a Chinese Family. [Case Reports]. *Front Endocrinol (Lausanne), 10*, 406. doi: 10.3389/fendo.2019.00406

Devendra, Liu, & Eisenbarth. (2004). Type 1 diabetes: recent developments. [Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, P.H.S.

Review]. *BMJ, 328*(7442), 750-754. doi: 10.1136/bmj.328.7442.750

Doddabelavangala Mruthyunjaya, Chapla, Hesarghatta Shyamasunder, Varghese, Varshney, Paul, Inbakumari, Christina, Varghese, Kuruvilla, T, Jose, Regi, Lionel, Jeyaseelan, Mathew, & Thomas. (2017). Comprehensive Maturity Onset Diabetes of the Young (MODY) Gene Screening in Pregnant Women with Diabetes in India. *PLoS One, 12*(1), e0168656. doi: 10.1371/journal.pone.0168656

Dominguez-Lopez, Miliar-Garcia, Segura-Kato, Riba, Esparza-Lopez, Ramirez-Jimenez, Rodriguez-Torres, Canizales-Quinteros, Cabrera-Vasquez, Fragoso-Ontiveros, Aguilar-Salinas, Altamirano-Bustamante, Calzada-Leon, Robles-Valdes, Bravo-Rios, & Tusie-Luna. (2005). Mutations in MODY genes are not common cause of early-onset type 2 diabetes in Mexican families. [Research Support, Non-U.S. Gov't]. *JOP, 6*(3), 238-245.

Dotto, Giuffrida, Franco, Mathez, Weinert, Silveiro, Sa, Reis, & Dias-da-Silva. (2016). Unexpected finding of a whole HNF1B gene deletion during the

screening of rare MODY types in a series of Brazilian patients negative for GCK and HNF1A mutations. *Diabetes Res Clin Pract, 116*, 100-104. doi: 10.1016/j.diabres.2016.04.035

Dotto, Santana, Lindsey, Caetano, Franco, Moises, Sa, Nishiura, Teles, Heilberg, Dias-da-Silva, Giuffrida, & Reis. (2019). Searching for mutations in the HNF1B gene in a Brazilian cohort with renal cysts and hyperglycemia. *Arch Endocrinol Metab, 63*(3), 250-257. doi: 10.20945/2359-3997000000138

Dubois-Laforgue, Cornu, Saint-Martin, Coste, Bellanne-Chantelot, Timsit, & Monogenic Diabetes Study Group of the Societe Francophone du. (2017). Diabetes, Associated Clinical Spectrum, Long-term Prognosis, and Genotype/Phenotype Correlations in 201 Adult Patients With Hepatocyte Nuclear Factor 1B (HNF1B) Molecular Defects. *Diabetes Care, 40*(11), 1436-1443. doi: 10.2337/dc16-2462

Dukes, Sreenan, Roe, Levisetti, Zhou, Ostrega, Bell, Pontoglio, Yaniv, Philipson, & Polonsky. (1998). Defective pancreatic beta-cell glycolytic signaling in hepatocyte nuclear factor-1alpha-deficient mice. [Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, P.H.S.]. *J Biol Chem, 273*(38), 24457-24464. doi: 10.1074/jbc.273.38.24457

Dusatkova, Dusatkova, Vosahlo, Vesela, Cinek, Lebl, & Pruhova. (2015). Frameshift mutations in the insulin gene leading to prolonged molecule of insulin in two families with Maturity-Onset Diabetes of the Young. [Case Reports

Research Support, Non-U.S. Gov't]. *Eur J Med Genet, 58*(4), 230-234. doi: 10.1016/j.ejmg.2015.02.004

Dusatkova, Pruhova, Borowiec, Vesela, Antosik, Lebl, Mlynarski, & Cinek. (2012). Ancestral mutations may cause a significant proportion of GCK-MODY. [Research Support, Non-U.S. Gov't]. *Pediatr Diabetes, 13*(6), 489-498. doi: 10.1111/j.1399-5448.2011.00845.x

Edghill, Bingham, Ellard, & Hattersley. (2006). Mutations in hepatocyte nuclear factor-1beta and their related phenotypes. *J Med Genet, 43*(1), 84-90. doi: 10.1136/jmg.2005.032854

Edghill, Bingham, Slingerland, Minton, Noordam, Ellard, & Hattersley. (2006). Hepatocyte nuclear factor-1 beta mutations cause neonatal diabetes and intrauterine growth retardation: support for a critical role of HNF-1beta in human pancreatic development. [Research Support, Non-U.S. Gov't]. *Diabet Med, 23*(12), 1301-1306. doi: 10.1111/j.1464-5491.2006.01999.x

Edghill, Oram, Owens, Stals, Harries, Hattersley, Ellard, & Bingham. (2008). Hepatocyte nuclear factor-1beta gene deletions--a common cause of renal disease. [Research Support, Non-U.S. Gov't]. *Nephrol Dial Transplant, 23*(2), 627-635. doi: 10.1093/ndt/gfm603

Edghill, Stals, Oram, Shepherd, Hattersley, & Ellard. (2013). HNF1B deletions in patients with young-onset diabetes but no known renal disease. [Research Support, N.I.H., Extramural]. *Diabet Med, 30*(1), 114-117. doi: 10.1111/j.1464-5491.2012.03709.x

Eiberg, Hansen, Kjer, Hansen, Pedersen, Bille, Rosenberg, & Tranebjaerg. (2006). Autosomal dominant optic atrophy associated with hearing impairment and impaired glucose regulation caused by a missense mutation in the WFS1 gene. *J Med Genet, 43*(5), 435-440. doi: 10.1136/jmg.2005.034892

Eide, Raeder, Johansson, Midthjell, Sovik, Njolstad, & Molven. (2008). Prevalence of HNF1A (MODY3) mutations in a Norwegian population (the HUNT2 Study). [Research Support, Non-U.S. Gov't]. *Diabet Med, 25*(7), 775-781. doi: 10.1111/j.1464-5491.2008.02459.x

Elbein, Teng, Yount, & Scroggin. (1998). Linkage and molecular scanning analyses of MODY3/hepatocyte nuclear factor-1 alpha gene in typical familial type 2 diabetes: evidence for novel mutations in exons 8 and 10. [Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, Non-P.H.S.

Research Support, U.S. Gov't, P.H.S.]. *J Clin Endocrinol Metab, 83*(6), 2059-2065. doi: 10.1210/jcem.83.6.4874

Ellard, Bulman, Frayling, Shepherd, & Hattersley. (2000). Proposed mechanism for a novel insertion/deletion frameshift mutation (I414G415ATCG-->CCA) in the hepatocyte nuclear factor 1 alpha (HNF-1 alpha) gene which causes maturity-onset diabetes of the young (MODY). *Hum Mutat, 16*(3), 273. doi: 10.1002/1098-1004(200009)16:3<273::AID-HUMU18>3.0.CO;2-Z

Ellard, Thomas, Edghill, Owens, Ambye, Cropper, Little, Strachan, Stride, Ersoy, Eiberg, Pedersen, Shepherd, Hansen, Harries, & Hattersley. (2007). Partial and whole gene deletion mutations of the GCK and HNF1A genes in maturity-onset diabetes of the young. [Research Support, Non-U.S. Gov't]. *Diabetologia, 50*(11), 2313-2317. doi: 10.1007/s00125-007-0798-6

Estalella, Rica, Perez de Nanclares, Bilbao, Vazquez, San Pedro, Busturia, & Castano. (2007). Mutations in GCK and HNF-1alpha explain the majority of cases with clinical diagnosis of MODY in Spain. [Multicenter Study

Research Support, Non-U.S. Gov't]. *Clin Endocrinol (Oxf), 67*(4), 538-546. doi: 10.1111/j.1365-2265.2007.02921.x

Estica, Seelenfreund, Durruty, & Briones. (2018). [Finding of a new mutation in a Chilean family with monogenic diabetes. Report of one case]. [Case Reports]. *Rev Med Chil, 146*(7), 929-932. doi: 10.4067/s0034-98872018000700929

Fajans, & Brown. (1993). Administration of sulfonylureas can increase glucose-induced insulin secretion for decades in patients with maturity-onset diabetes of the young. [Research Support, U.S. Gov't, P.H.S.]. *Diabetes Care, 16*(9), 1254-1261. doi: 10.2337/diacare.16.9.1254

Fang, Huang, Huang, Chen, Chen, & Hu. (2015). A novel nonsense mutation of the HNF1alpha in maturity-onset diabetes of the young type 3 in Asian population. [Case Reports

Research Support, Non-U.S. Gov't]. *Diabetes Res Clin Pract, 109*(2), e5-7. doi: 10.1016/j.diabres.2015.05.026

Fehmann, Gross, & Epe. (2004). A new mutation in the hepatocyte nuclear factor-1-alpha gene (P224S) in a newly discovered German family with maturity-onset diabetes of the young 3 (MODY 3). Family members carry additionally the homozygous I27L amino acid polymorphism in the HNF1 alpha gene. [Case Reports]. *Exp Clin Endocrinol Diabetes, 112*(2), 84-87. doi: 10.1055/s-2004-815755

Feigerlova, Pruhova, Dittertova, Lebl, Pinterova, Kolostova, Cerna, Pedersen, & Hansen. (2006). Aetiological heterogeneity of asymptomatic hyperglycaemia in children and adolescents. [Research Support, Non-U.S. Gov't]. *Eur J Pediatr, 165*(7), 446-452. doi: 10.1007/s00431-006-0106-3

Fendler, Malachowska, Baranowska-Jazwiecka, Borowiec, Wyka, Malecki, Jarosz-Chobot, Mysliwiec, & Mlynarski. (2014). Population-based estimates for double diabetes amongst people with glucokinase monogenic diabetes, GCK-MODY. [Letter

Research Support, Non-U.S. Gov't]. *Diabet Med, 31*(7), 881-883. doi: 10.1111/dme.12449

Ferrer. (2002). A genetic switch in pancreatic beta-cells: implications for differentiation and haploinsufficiency. *Diabetes, 51*(8), 2355-2362. doi: 10.2337/diabetes.51.8.2355

Firdous, Nissar, Ali, Ganai, Shabir, Hassan, & Masoodi. (2018). Genetic Testing of Maturity-Onset Diabetes of the Young Current Status and Future Perspectives. [Review]. *Front Endocrinol (Lausanne), 9*, 253. doi: 10.3389/fendo.2018.00253

Fonseca, Ishigaki, Oslowski, Lu, Lipson, Ghosh, Hayashi, Ishihara, Oka, Permutt, & Urano. (2010). Wolfram syndrome 1 gene negatively regulates ER stress signaling in rodent and human cells. [Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't]. *J Clin Invest, 120*(3), 744-755. doi: 10.1172/JCI39678

Forlani, Zucchini, Di Rocco, Di Luzio, Scipione, Marasco, Romeo, Marchesini, & Mantovani. (2010). Double heterozygous mutations involving both HNF1A/MODY3 and HNF4A/MODY1 genes: a case report. [Case Reports]. *Diabetes Care, 33*(11), 2336-2338. doi: 10.2337/dc10-0561

Franco, Peixoto-Barbosa, Dotto, Vieira, Dias-da-Silva, Reis, Giuffrida, & Reis. (2017). More than kin, less than kind: one family and the many faces of

diabetes in youth. [Case Reports]. *Arch Endocrinol Metab, 61*(6), 637-642. doi: 10.1590/2359-3997000000312

Frayling, Bulamn, Ellard, Appleton, Dronsfield, Mackie, Baird, Kaisaki, Yamagata, Bell, Bain, & Hattersley. (1997). Mutations in the hepatocyte nuclear factor-1alpha gene are a common cause of maturity-onset diabetes of the young in the U.K. [Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, P.H.S.]. *Diabetes, 46*(4), 720-725. doi: 10.2337/diab.46.4.720

Froguel, Zouali, Vionnet, Velho, Vaxillaire, Sun, Lesage, Stoffel, Takeda, Passa, & et al. (1993). Familial hyperglycemia due to mutations in glucokinase. Definition of a subtype of diabetes mellitus. [Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, P.H.S.]. *N Engl J Med, 328*(10), 697-702. doi: 10.1056/NEJM199303113281005

Fu, Wang, Liu, Wang, Li, & Xiao. (2019). Birthweight correlates with later metabolic abnormalities in Chinese patients with maturity-onset diabetes of the young type 2. [Research Support, Non-U.S. Gov't]. *Endocrine, 65*(1), 53-60. doi: 10.1007/s12020-019-01929-6

Fu, Wang, Zhai, & Xiao. (2020). Primary hepatocellular adenoma due to biallelic HNF1A mutations and its co-occurrence with MODY 3: case-report and review of the literature. *Endocrine, 67*(3), 544-551. doi: 10.1007/s12020-019-02138-x

Fujimoto, Sasaki, Hiki, Nemoto, Utsunomiya, Yokoo, Nakai, Ohashi, Hosoya, Eto, & Tajima. (2007). In vitro and pathological investigations of MODY5 with the R276X-HNF1beta (TCF2) mutation. [Case Reports

Research Support, Non-U.S. Gov't]. *Endocr J, 54*(5), 757-764. doi: 10.1507/endocrj.k07-051

Furuta, Iwasaki, Oda, Hinokio, Horikawa, Yamagata, Yano, Sugahiro, Ogata, Ohgawara, Omori, Iwamoto, & Bell. (1997). Organization and partial sequence of the hepatocyte nuclear factor-4 alpha/MODY1 gene and identification of a missense mutation, R127W, in a Japanese family with MODY. [Case Reports

Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, P.H.S.]. *Diabetes, 46*(10), 1652-1657. doi: 10.2337/diacare.46.10.1652

Galan, Garcia-Herrero, Azriel, Gargallo, Duran, Gorgojo, Andia, & Navas. (2011). Differential effects of HNF-1alpha mutations associated with familial young-onset diabetes on target gene regulation. [Research Support, Non-U.S. Gov't]. *Mol Med, 17*(3-4), 256-265. doi: 10.2119/molmed.2010.00097

Gandica, Chung, Deng, Goland, & Gallagher. (2015). Identifying monogenic diabetes in a pediatric cohort with presumed type 1 diabetes. [Research Support, N.I.H., Extramural]. *Pediatr Diabetes, 16*(3), 227-233. doi: 10.1111/pedi.12150

Ganie, Laway, Nisar, Wani, Khurana, Ahmad, Ahmed, Gupta, Ali, Shabir, Shadan, Ahmed, & Tufail. (2011). Presentation and clinical course of Wolfram (DIDMOAD) syndrome from North India. *Diabet Med, 28*(11), 1337-1342. doi: 10.1111/j.1464-5491.2011.03377.x

Gasparin, Crispim, Paula, Freire, Dalbosco, Manna, Salles, Gasparin, Guedes, Marcantonio, Gambini, Salim, & Moises. (2009). Identification of novel mutations of the WFS1 gene in Brazilian patients with Wolfram syndrome.

[Research Support, Non-U.S. Gov't]. *Eur J Endocrinol, 160*(2), 309-316. doi: 10.1530/EJE-08-0698

Gasperikova, Tribble, Stanik, Huckova, Misovicova, van de Bunt, Valentinova, Barrow, Barak, Dobransky, Bereczkova, Michalek, Wicks, Colclough, Knight, Ellard, Klimes, & Gloyn. (2009). Identification of a novel beta-cell glucokinase (GCK) promoter mutation (-71G>C) that modulates GCK gene expression through loss of allele-specific Sp1 binding causing mild fasting hyperglycemia in humans. [Research Support, Non-U.S. Gov't]. *Diabetes, 58*(8), 1929-1935. doi: 10.2337/db09-0070

Giuffrida, Calliari, Manna, Ferreira, Saddi-Rosa, Kunii, Furuzawa, Dias-da-Silva, & Reis. (2013). A novel glucokinase deletion (p.Lys32del) and five previously described mutations co-segregate with the phenotype of mild familial hyperglycaemia (MODY2) in Brazilian families. *Diabetes Res Clin Pract, 100*(2), e42-45. doi: 10.1016/j.diabres.2013.01.029

Giuffrida, Moises, Weinert, Calliari, Manna, Dotto, Franco, Caetano, Teles, Lima, Alves, Dib, Silveiro, Dias-da-Silva, & Reis. (2017). Maturity-onset diabetes of the young (MODY) in Brazil: Establishment of a national registry and appraisal of available genetic and clinical data. *Diabetes Res Clin Pract, 123*, 134-142. doi: 10.1016/j.diabres.2016.10.017

Giuliano, Bannwarth, Monnot, Cano, Chabrol, Vialettes, Delobel, Paquis-Flucklinger, & French Group of. (2005). Wolfram syndrome in French population: characterization of novel mutations and polymorphisms in the WFS1 gene. *Hum Mutat, 25*(1), 99-100. doi: 10.1002/humu.9300

Gjesing, Rui, Lauenborg, Have, Hollensted, Andersson, Grarup, Sun, Quan, Brandslund, Damm, Pedersen, Wang, & Hansen. (2017). High Prevalence of

Diabetes-Predisposing Variants in MODY Genes Among Danish Women With Gestational Diabetes Mellitus. *J Endocr Soc, 1*(6), 681-690. doi: 10.1210/js.2017-00040

Globa, Zelinska, Elblova, Dusatkova, Cinek, Lebl, Colclough, Ellard, & Pruhova. (2017). MODY in Ukraine: genes, clinical phenotypes and treatment. *J Pediatr Endocrinol Metab, 30*(10), 1095-1103. doi: 10.1515/jpem-2017-0075

. Global Report on Diabetes. (2016): World Health Organization.

Glotov, Serebryakova, Turkunova, Efimova, Glotov, Barbitoff, Nasykhova, Predeus, Polev, Fedyakov, Polyakova, Ivashchenko, Shved, Shabanova, Tiselko, Romanova, Sarana, Pendina, Scherbak, Musina, Petrovskaia-Kaminskaia, Lonishin, Ditkovskaya, Zhelenina Lcapital A, Tyrtova, Berseneva, Skitchenko, Suspitsin, Bashnina, & Baranov. (2019). Wholeexome sequencing in Russian children with nontype 1 diabetes mellitus reveals a wide spectrum of genetic variants in MODYrelated and unrelated genes. *Mol Med Rep, 20*(6), 4905-4914. doi: 10.3892/mmr.2019.10751

Gomez-Zaera, Strom, Rodriguez, Estivill, Meitinger, & Nunes. (2001). Presence of a major WFS1 mutation in Spanish Wolfram syndrome pedigrees. *Mol Genet Metab, 72*(1), 72-81. doi: 10.1006/mgme.2000.3107

Gordon, Yao, Siegel, & Stackpole. (2019). A Case of a 13-Year-Old Female With Maturity Onset Diabetes of the Young (MODY) Identified by School-Based Cardiovascular Screening. *Glob Pediatr Health, 6*, 2333794X19874215. doi: 10.1177/2333794X19874215

Gozlan, Tenenbaum, Shalitin, Lebenthal, Oron, Cohen, Phillip, & Gat-Yablonski. (2012). The glucokinase mutation p.T206P is common among MODY patients

of Jewish Ashkenazi descent. [Research Support, Non-U.S. Gov't]. *Pediatr Diabetes, 13*(6), e14-21. doi: 10.1111/j.1399-5448.2011.00822.x

Gragnoli, Lindner, Cockburn, Kaisaki, Gragnoli, Marozzi, & Bell. (1997). Maturity-onset diabetes of the young due to a mutation in the hepatocyte nuclear factor-4 alpha binding site in the promoter of the hepatocyte nuclear factor-1 alpha gene. [Case Reports

Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, P.H.S.]. *Diabetes, 46*(10), 1648-1651. doi: 10.2337/diacare.46.10.1648

Gragnoli, Stanojevic, Gorini, Von Preussenthal, Thomas, & Habener. (2005). IPF-1/MODY4 gene missense mutation in an Italian family with type 2 and gestational diabetes. [Research Support, N.I.H., Extramural

Research Support, U.S. Gov't, P.H.S.]. *Metabolism, 54*(8), 983-988. doi: 10.1016/j.metabol.2005.01.037

Guazzini, Gaffi, Mainieri, Multari, Cordera, Bertolini, Pozza, Meschi, & Barbetti. (1998). Three novel missense mutations in the glucokinase gene (G80S; E221K; G227C) in Italian subjects with maturity-onset diabetes of the young (MODY). Mutations in brief no. 162. Online. [Research Support, Non-U.S. Gov't]. *Hum Mutat, 12*(2), 136. doi: 10.1002/(SICI)1098-1004(1998)12:2<136::AID-HUMU11>3.0.CO;2-0

Habeb, George, Mathew, & Hattersley. (2011). Response to oral gliclazide in a pre-pubertal child with hepatic nuclear factor-1 alpha maturity onset diabetes of the young. [Case Reports]. *Ann Saudi Med, 31*(2), 190-193. doi: 10.4103/0256-4947.75590

Hagenfeldt-Johansson, Herrera, Wang, Gjinovci, Ishihara, & Wollheim. (2001). Beta-cell-targeted expression of a dominant-negative hepatocyte nuclear factor-1 alpha induces a maturity-onset diabetes of the young (MODY)3-like phenotype in transgenic mice. [Research Support, Non-U.S. Gov't]. *Endocrinology, 142*(12), 5311-5320. doi: 10.1210/endo.142.12.8592

Hager, Blanche, Sun, Vaxillaire, Poller, Cohen, Czernichow, Velho, Robert, Cohen, & et al. (1994). Six mutations in the glucokinase gene identified in MODY by using a nonradioactive sensitive screening technique. [Research Support, Non-U.S. Gov't]. *Diabetes, 43*(5), 730-733. doi: 10.2337/diab.43.5.730

Halban, Polonsky, Bowden, Hawkins, Ling, Mather, Powers, Rhodes, Sussel, & Weir. (2014). beta-cell failure in type 2 diabetes: postulated mechanisms and prospects for prevention and treatment. [Review]. *Diabetes Care, 37*(6), 1751-1758. doi: 10.2337/dc14-0396

Haliloglu, Hysenaj, Atay, Guran, Abali, Turan, Bereket, & Ellard. (2016). GCK gene mutations are a common cause of childhood-onset MODY (maturity-onset diabetes of the young) in Turkey. [Research Support, Non-U.S. Gov't]. *Clin Endocrinol (Oxf), 85*(3), 393-399. doi: 10.1111/cen.13121

Hani, Suaud, Boutin, Chevre, Durand, Philippi, Demenais, Vionnet, Furuta, Velho, Bell, Laine, & Froguel. (1998). A missense mutation in hepatocyte nuclear factor-4 alpha, resulting in a reduced transactivation activity, in human late-onset non-insulin-dependent diabetes mellitus. [Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, P.H.S.]. *J Clin Invest, 101*(3), 521-526. doi: 10.1172/JCI1403

Hansen, Eiberg, Barrett, Bek, Kjaersgaard, Tranebjaerg, & Rosenberg. (2005). Mutation analysis of the WFS1 gene in seven Danish Wolfram syndrome families; four new mutations identified. [Case Reports

Research Support, Non-U.S. Gov't]. *Eur J Hum Genet, 13*(12), 1275-1284. doi: 10.1038/sj.ejhg.5201491

Hansen, Eiberg, Rouard, Vaxillaire, Moller, Rasmussen, Fridberg, Urhammer, Holst, Almind, Echwald, Hansen, Bell, & Pedersen. (1997). Novel MODY3 mutations in the hepatocyte nuclear factor-1alpha gene: evidence for a hyperexcitability of pancreatic beta-cells to intravenous secretagogues in a glucose-tolerant carrier of a P447L mutation. [Research Support, Non-U.S. Gov't]. *Diabetes, 46*(4), 726-730. doi: 10.2337/diab.46.4.726

Hara, Noda, Waki, Tobe, Yamauchi, Kadowaki, Satou, Tsukamoto, Nagamatsu, Yamagata, Matsuzawa, Akanuma, Kimura, & Kadowaki. (2002). Maturity-onset diabetes of the young resulting from a novel mutation in the HNF-4alpha gene. [Case Reports]. *Intern Med, 41*(10), 848-852. doi: 10.2169/internalmedicine.41.848

Hardy, Khanim, Torres, Scott-Brown, Seller, Poulton, Collier, Kirk, Polymeropoulos, Latif, & Barrett. (1999). Clinical and molecular genetic analysis of 19 Wolfram syndrome kindreds demonstrating a wide spectrum of mutations in WFS1. [Research Support, Non-U.S. Gov't]. *Am J Hum Genet, 65*(5), 1279-1290. doi: 10.1086/302609

Haring, Vriesendorp, Klein Wassink-Ruiter, de Haas, Gouw, & de Meijer. (2019). Diagnosis of hepatocellular adenoma in men before onset of diabetes in HNF1A-MODY: Watch out for winkers. *Liver Int, 39*(11), 2042-2045. doi: 10.1111/liv.14235

Harries, Ellard, Stride, Morgan, & Hattersley. (2006). Isomers of the TCF1 gene encoding hepatocyte nuclear factor-1 alpha show differential expression in the pancreas and define the relationship between mutation position and clinical phenotype in monogenic diabetes. [Research Support, Non-U.S. Gov't]. *Hum Mol Genet, 15*(14), 2216-2224. doi: 10.1093/hmg/ddl147

Hattersley, Beards, Ballantyne, Appleton, Harvey, & Ellard. (1998). Mutations in the glucokinase gene of the fetus result in reduced birth weight. [Research Support, Non-U.S. Gov't]. *Nat Genet, 19*(3), 268-270. doi: 10.1038/953

Hattersley, Bruining, Shield, Njolstad, & Donaghue. (2009). The diagnosis and management of monogenic diabetes in children and adolescents. *Pediatr Diabetes, 10 Suppl 12*, 33-42. doi: 10.1111/j.1399-5448.2009.00571.x

Hattersley, Greeley, Polak, Rubio-Cabezas, Njolstad, Mlynarski, Castano, Carlsson, Raile, Chi, Ellard, & Craig. (2018). ISPAD Clinical Practice Consensus Guidelines 2018: The diagnosis and management of monogenic diabetes in children and adolescents. [Practice Guideline]. *Pediatr Diabetes, 19 Suppl 27*, 47-63. doi: 10.1111/pedi.12772

Henderson, Levy, Delvin, Losekoot, & Lambert. (2007). Prevalence and clinical phenotype of the p.Val226Met glucokinase gene mutation in French Canadians in Quebec, Canada. [Research Support, Non-U.S. Gov't]. *Mol Genet Metab, 90*(1), 87-92. doi: 10.1016/j.ymgme.2006.09.006

Horikawa, Enya, Fushimi, Fushimi, & Takeda. (2014). Screening of diabetes of youth for hepatocyte nuclear factor 1 mutations: clinical phenotype of HNF1beta-related maturity-onset diabetes of the young and HNF1alpha-related maturity-onset diabetes of the young in Japanese. [Research Support, Non-U.S. Gov't]. *Diabet Med, 31*(6), 721-727. doi: 10.1111/dme.12416

Horikawa, Enya, Mabe, Fukushima, Takubo, Ohashi, Ikeda, Hashimoto, Watada, & Takeda. (2018). NEUROD1-deficient diabetes (MODY6): Identification of the first cases in Japanese and the clinical features. [Research Support, Non-U.S. Gov't]. *Pediatr Diabetes, 19*(2), 236-242. doi: 10.1111/pedi.12553

Hui, & Howles. (2002). Carboxyl ester lipase: structure-function relationship and physiological role in lipoprotein metabolism and atherosclerosis. [Research Support, U.S. Gov't, P.H.S.

Review]. *J Lipid Res, 43*(12), 2017-2030. doi: 10.1194/jlr.r200013-jlr200

Huopio, Miettinen, Ilonen, Nykanen, Veijola, Keskinen, Nanto-Salonen, Vangipurapu, Raivo, Stancakova, Mannisto, Kuulasmaa, Knip, Otonkoski, & Laakso. (2016). Clinical, Genetic, and Biochemical Characteristics of Early-Onset Diabetes in the Finnish Population. [Research Support, Non-U.S. Gov't]. *J Clin Endocrinol Metab, 101*(8), 3018-3026. doi: 10.1210/jc.2015-4296

Hwang, Shin, Yang, Jung, & Huh. (2006). Genetic and clinical characteristics of Korean maturity-onset diabetes of the young (MODY) patients. [Research Support, Non-U.S. Gov't]. *Diabetes Res Clin Pract, 74*(1), 75-81. doi: 10.1016/j.diabres.2006.03.002

Inoue, Tanizawa, Wasson, Behn, Kalidas, Bernal-Mizrachi, Mueckler, Marshall, Donis-Keller, Crock, Rogers, Mikuni, Kumashiro, Higashi, Sobue, Oka, & Permutt. (1998). A gene encoding a transmembrane protein is mutated in patients with diabetes mellitus and optic atrophy (Wolfram syndrome). [Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, P.H.S.]. *Nat Genet, 20*(2), 143-148. doi: 10.1038/2441

Irgens, Molnes, Johansson, Ringdal, Skrivarhaug, Undlien, Sovik, Joner, Molven, & Njolstad. (2013). Prevalence of monogenic diabetes in the population-based Norwegian Childhood Diabetes Registry. [Research Support, Non-U.S. Gov't]. *Diabetologia, 56*(7), 1512-1519. doi: 10.1007/s00125-013-2916-y

Isomaa, Henricsson, Lehto, Forsblom, Karanko, Sarelin, Haggblom, & Groop. (1998). Chronic diabetic complications in patients with MODY3 diabetes. [Comparative Study

Research Support, Non-U.S. Gov't]. *Diabetologia, 41*(4), 467-473. doi: 10.1007/s001250050931

Ivarsson, & Lernmark. (2008). Comment on: Edghill et al. (2008) Insulin mutation screening in 1,044 patients with diabetes: mutations in the INS gene are a common cause of neonatal diabetes but a rare cause of diabetes diagnosed in childhood or adulthood: Diabetes 57:1034-1042, 2008. [Comment

Letter]. *Diabetes, 57*(5), e9. doi: 10.2337/db08-0091

Iwabuchi, Kamoda, Shinohara, & Sumazaki. (2013). Japanese boy with maturity-onset diabetes of the young type 3 who developed diabetes at 19 months old. *Pediatr Int, 55*(2), e32-34. doi: 10.1111/j.1442-200X.2012.03741.x

Iwen, Klein, Hubold, Lehnert, & Weitzel. (2013). Maturity-onset diabetes of the young and hepatic adenomatosis - characterisation of a new mutation. [Case Reports

Clinical Trial]. *Exp Clin Endocrinol Diabetes, 121*(6), 368-371. doi: 10.1055/s-0033-1341519

Jap, Wu, Chiou, & Kwok. (2000). A novel mutation in the hepatocyte nuclear factor-1alpha/MODY3 gene in Chinese subjects with early-onset Type 2 diabetes mellitus in Taiwan. [Case Reports

Research Support, Non-U.S. Gov't]. *Diabet Med, 17*(5), 390-393. doi: 10.1046/j.1464-5491.2000.00285.x

Jesic, Sajic, Jesic, Maringa, Micic, & Necic. (2008). A case of new mutation in maturity-onset diabetes of the young type 3 (MODY 3) responsive to a low dose of sulphonylurea. [Case Reports]. *Diabetes Res Clin Pract, 81*(1), e1-3. doi: 10.1016/j.diabres.2008.03.005

Jha, Siddiqui, Waghdhare, Dubey, Krishna, Subramanian, Dikshit, Ravikiran, & Bhargava. (2016). Identification of a novel glucokinase mutation in an Indian woman with GCK-MODY. [Case Reports

Letter]. *Lancet Diabetes Endocrinol, 4*(4), 302. doi: 10.1016/S2213-8587(16)00040-1

Jo, Endo, Ishizu, Nakamura, & Tajima. (2011). A novel PAX4 mutation in a Japanese patient with maturity-onset diabetes of the young. [Case Reports]. *Tohoku J Exp Med, 223*(2), 113-118. doi: 10.1620/tjem.223.113

Jo, Sano, Sudo, Matsunami, Kawamura, & Tajima. (2012). A Case of Novel Mutation of HNF1B in Maturity-onset Diabetes of the Young Type 5 (MODY5). [Case Reports]. *Clin Pediatr Endocrinol, 21*(3), 53-55. doi: 10.1297/cpe.21.53

Johansen, Ek, Mortensen, Pedersen, & Hansen. (2005). Half of clinically defined maturity-onset diabetes of the young patients in Denmark do not have mutations in HNF4A, GCK, and TCF1. [Research Support, Non-U.S. Gov't]. *J Clin Endocrinol Metab, 90*(8), 4607-4614. doi: 10.1210/jc.2005-0196

Johansson, Irgens, Chudasama, Molnes, Aerts, Roque, Jonassen, Levy, Lima, Knappskog, Bell, Molven, & Njolstad. (2012). Exome sequencing and genetic testing for MODY. [Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, P.H.S.]. *PLoS One, 7*(5), e38050. doi: 10.1371/journal.pone.0038050

Johansson, Irgens, Molnes, Sztromwasser, Aukrust, Juliusson, Sovik, Levy, Skrivarhaug, Joner, Molven, Johansson, & Njolstad. (2017). Targeted next-generation sequencing reveals MODY in up to 6.5% of antibody-negative diabetes cases listed in the Norwegian Childhood Diabetes Registry. *Diabetologia, 60*(4), 625-635. doi: 10.1007/s00125-016-4167-1

Johnson, Ellis, Leo, Anderson, Ganti, Harris, Curran, McInerney-Leo, Paramalingam, Song, Conwell, Harris, Jones, Brown, Davis, & Duncan. (2019). Comprehensive genetic screening: The prevalence of maturity-onset diabetes of the young gene variants in a population-based childhood diabetes cohort. [Research Support, Non-U.S. Gov't]. *Pediatr Diabetes, 20*(1), 57-64. doi: 10.1111/pedi.12766

Johnson, Leo, Conwell, Harris, Brown, & Duncan. (2018). Clinical usefulness of comprehensive genetic screening in maturity onset diabetes of the young (MODY): A novel ABCC8 mutation in a previously screened family. [Case Reports]. *J Diabetes, 10*(9), 764-767. doi: 10.1111/1753-0407.12778

Johnson, Leo, McInerney-Leo, Anderson, Marshall, McGown, Newell, Brown, Conwell, Harris, & Duncan. (2018). Whole-exome sequencing for mutation detection in pediatric disorders of insulin secretion: Maturity onset diabetes of the young and congenital hyperinsulinism. [Research Support, Non-U.S. Gov't]. *Pediatr Diabetes, 19*(4), 656-662. doi: 10.1111/pedi.12638

Johnson, McGown, Oppermann, Conwell, Harris, & Duncan. (2018). A novel INS mutation in a family with maturity-onset diabetes of the young: Variable insulin secretion and putative mechanisms. [Case Reports

Research Support, Non-U.S. Gov't]. *Pediatr Diabetes, 19*(5), 905-909. doi: 10.1111/pedi.12679

Juszczak, Pavic, Vuckovic, Bennett, Shah, Pape Medvidovic, Groves, Sekerija, Chandler, Burrows, Rojnic Putarek, Vucic Lovrencic, Cuca Knezevic, James, Gloyn, Lauc, McCarthy, Owen, & Gornik. (2019). Plasma Fucosylated Glycans and C-Reactive Protein as Biomarkers of HNF1A-MODY in Young Adult-Onset Nonautoimmune Diabetes. [Research Support, Non-U.S. Gov't]. *Diabetes Care, 42*(1), 17-26. doi: 10.2337/dc18-0422

Kanthimathi, Jahnavi, Balamurugan, Ranjani, Sonya, Goswami, Chowdhury, Mohan, & Radha. (2014). Glucokinase gene mutations (MODY 2) in Asian Indians. [Research Support, Non-U.S. Gov't]. *Diabetes Technol Ther, 16*(3), 180-185. doi: 10.1089/dia.2013.0244

Kapoor, Locke, Colclough, Wales, Conn, Hattersley, Ellard, & Hussain. (2008). Persistent hyperinsulinemic hypoglycemia and maturity-onset diabetes of the young due to heterozygous HNF4A mutations. [Case Reports

Research Support, Non-U.S. Gov't]. *Diabetes, 57*(6), 1659-1663. doi: 10.2337/db07-1657

Karaca, Onay, Cetinkalp, Aykut, Goksen, Ozen, Atik, Darcan, Tekin, & Ozkinay. (2017). The spectrum of HNF1A gene mutations in patients with MODY 3 phenotype and identification of three novel germline mutations in Turkish Population. *Diabetes Metab Syndr, 11 Suppl 1*, S491-S496. doi: 10.1016/j.dsx.2017.03.042

Kato, Tanaka, Muro, Jambaljav, Mori, Yonemitsu, Oki, & Inagaki. (2018). A Novel p.L145Q Mutation in the HNF1B Gene in a Case of Maturity-onset Diabetes of the Young Type 5 (MODY5). [Case Reports]. *Intern Med, 57*(14), 2035-2039. doi: 10.2169/internalmedicine.9692-17

Katsarou, Gudbjornsdottir, Rawshani, Dabelea, Bonifacio, Anderson, Jacobsen, Schatz, & Lernmark. (2017). Type 1 diabetes mellitus. [Review]. *Nat Rev Dis Primers, 3*, 17016. doi: 10.1038/nrdp.2017.16

Kavvoura, & Owen. (2012). Maturity onset diabetes of the young: clinical characteristics, diagnosis and management. [Review]. *Pediatr Endocrinol Rev, 10*(2), 234-242.

Kawakita, Hosokawa, Fujimaru, Tamagawa, Urakami, Takasawa, Moriya, Mizuno, Maruo, Takuwa, Nagasaka, Nishi, Yamamoto, Aizu, & Yorifuji. (2014). Molecular and clinical characterization of glucokinase maturity-onset diabetes of the young (GCK-MODY) in Japanese patients. [Research Support, Non-U.S. Gov't]. *Diabet Med, 31*(11), 1357-1362. doi: 10.1111/dme.12487

Kawasaki. (2014). Type 1 diabetes and autoimmunity. [Review]. *Clin Pediatr Endocrinol, 23*(4), 99-105. doi: 10.1297/cpe.23.99

Kharroubi, & Darwish. (2015). Diabetes mellitus: The epidemic of the century. [Review]. *World J Diabetes, 6*(6), 850-867. doi: 10.4239/wjd.v6.i6.850

Khelifa, Dendana, Barboura, Khochtali, Chahed, Ferchichi, & Miled. (2016). Successful switch from insulin to oral sulfonylurea therapy in HNF1A-MODY Tunisian patient with the P291fsinsC mutation. [Case Reports]. *Diabetes Res Clin Pract, 115*, 133-136. doi: 10.1016/j.diabres.2016.01.015

Khodaeian, Enayati, Tabatabaei-Malazy, & Amoli. (2015). Association between Genetic Variants and Diabetes Mellitus in Iranian Populations: A Systematic

Review of Observational Studies. *J Diabetes Res, 2015*, 585917. doi: 10.1155/2015/585917

Kim, Lee, Cheong, Chung, Kwak, & Park. (2014). Identification and Functional Characterization of P159L Mutation in HNF1B in a Family with Maturity-Onset Diabetes of the Young 5 (MODY5). *Genomics Inform, 12*(4), 240-246. doi: 10.5808/GI.2014.12.4.240

Kitanaka, Miki, Hayashi, & Igarashi. (2004). Promoter-specific repression of hepatocyte nuclear factor (HNF)-1 beta and HNF-1 alpha transcriptional activity by an HNF-1 beta missense mutant associated with Type 5 maturity-onset diabetes of the young with hepatic and biliary manifestations. [Case Reports

Research Support, Non-U.S. Gov't]. *J Clin Endocrinol Metab, 89*(3), 1369-1378. doi: 10.1210/jc.2003-031308

Kleinberger, Copeland, Gandica, Haymond, Levitsky, Linder, Shuldiner, Tollefsen, White, & Pollin. (2018). Monogenic diabetes in overweight and obese youth diagnosed with type 2 diabetes: the TODAY clinical trial. [Clinical Trial

Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't]. *Genet Med, 20*(6), 583-590. doi: 10.1038/gim.2017.150

Knebel, Jacob, Boxberg, Muller-Wieland, & Kotzka. (2004). A novel nonsense mutation in GCK exon 9 co-segregates with diabetes phenotype. [Case Reports

Research Support, Non-U.S. Gov't]. *Exp Clin Endocrinol Diabetes, 112*(6), 298-301. doi: 10.1055/s-2004-820967

Knebel, Mack, Haas, Herman-Friede, Lange, Schubert, Kotzka, & Muller-Wieland. (2016). Divergent phenotypes in siblings with identical novel mutations in the HNF-1alpha gene leading to maturity onset diabetes of the young type 3. [Case Reports]. *BMC Med Genet, 17*(1), 36. doi: 10.1186/s12881-016-0297-z

Kocova, Elblova, Pruhova, Lebl, & Dusatkova. (2017). Novel glucokinase gene mutation in the first Macedonian family tested for MODY. [Case Reports]. *Diabetes Res Clin Pract, 130*, 86-89. doi: 10.1016/j.diabres.2017.04.001

Komazec, Zdravkovic, Sajic, Jesic, Andjelkovic, Pavlovic, & Ugrin. (2019). The importance of combined NGS and MLPA genetic tests for differential diagnosis of maturity onset diabetes of the young. *Endokrynol Pol, 70*(1), 28-36. doi: 10.5603/EP.a2018.0064

Koufakis, Sertedaki, Tatsi, Trakatelli, Karras, Manthou, Kanaka-Gantenbein, & Kotsa. (2019). First Report of Diabetes Phenotype due to a Loss-of-Function ABCC8 Mutation Previously Known to Cause Congenital Hyperinsulinism. [Case Reports]. *Case Rep Genet, 2019*, 3654618. doi: 10.1155/2019/3654618

Kraemer, & Ginsberg. (2014). Gerald M. Reaven, MD: Demonstration of the central role of insulin resistance in type 2 diabetes and cardiovascular disease. [Biography

Historical Article

Portrait]. *Diabetes Care, 37*(5), 1178-1181. doi: 10.2337/dc13-2668

Kwak, Jung, Ahn, Park, Chae, Jung, Cho, Lee, Kim, & Park. (2016). Clinical whole exome sequencing in early onset diabetes patients. *Diabetes Res Clin Pract, 122*, 71-77. doi: 10.1016/j.diabres.2016.10.005

Kyithar, Bacon, Pannu, Rizvi, Colclough, Ellard, & Byrne. (2011). Identification of HNF1A-MODY and HNF4A-MODY in Irish families: phenotypic

characteristics and therapeutic implications. [Research Support, Non-U.S. Gov't]. *Diabetes Metab, 37*(6), 512-519. doi: 10.1016/j.diabet.2011.04.002

Laver, Colclough, Shepherd, Patel, Houghton, Dusatkova, Pruhova, Morris, Palmer, McCarthy, Ellard, Hattersley, & Weedon. (2016). The Common p.R114W HNF4A Mutation Causes a Distinct Clinical Subtype of Monogenic Diabetes. [Research Support, Non-U.S. Gov't]. *Diabetes, 65*(10), 3212-3217. doi: 10.2337/db16-0628

Lehto, Bitzen, Isomaa, Wipemo, Wessman, Forsblom, Tuomi, Taskinen, & Groop. (1999). Mutation in the HNF-4alpha gene affects insulin secretion and triglyceride metabolism. [Research Support, Non-U.S. Gov't]. *Diabetes, 48*(2), 423-425. doi: 10.2337/diabetes.48.2.423

Lehto, Wipemo, Ivarsson, Lindgren, Lipsanen-Nyman, Weng, Wibell, Widen, Tuomi, & Groop. (1999). High frequency of mutations in MODY and mitochondrial genes in Scandinavian patients with familial early-onset diabetes. [Multicenter Study

Research Support, Non-U.S. Gov't]. *Diabetologia, 42*(9), 1131-1137. doi: 10.1007/s001250051281

Li, Cao, Qiu, Lu, Gao, Liu, Yuan, Yang, & Yang. (2016). A three-step programmed method for the identification of causative gene mutations of maturity onset diabetes of the young (MODY). *Gene, 588*(2), 141-148. doi: 10.1016/j.gene.2016.05.021

Li, Groden, Hoenig, Ray, Ferreira, Gahl, & Novacic. (2019). Case report: extreme coronary calcifications and hypomagnesemia in a patient with a 17q12 deletion involving HNF1B. *BMC Nephrol, 20*(1), 353. doi: 10.1186/s12882-019-1533-5

Li, Ting, Sheng, Liang, Shao, Jiang, Xu, Lin, & Liu. (2018). Genetic and clinical characteristics of Chinese children with Glucokinase-maturity-onset diabetes of the young (GCK-MODY). [Research Support, Non-U.S. Gov't]. *BMC Pediatr, 18*(1), 101. doi: 10.1186/s12887-018-1060-8

Li, Wang, Xu, Chen, Fu, Gu, Shi, Zhang, Sun, Chen, Han, Li, Tang, Cai, Li, Yang, & Polychronakos. (2020). High Prevalence of a Monogenic Cause in Han Chinese Diagnosed With Type 1 Diabetes, Partly Driven by Nonsyndromic Recessive WFS1 Mutations. *Diabetes, 69*(1), 121-126. doi: 10.2337/db19-0510

Lindner, Gragnoli, Furuta, Cockburn, Petzold, Rietzsch, Weiss, Schulze, & Bell. (1997). Hepatic function in a family with a nonsense mutation (R154X) in the hepatocyte nuclear factor-4alpha/MODY1 gene. [Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, P.H.S.]. *J Clin Invest, 100*(6), 1400-1405. doi: 10.1172/JCI119660

Liu, Liu, Ge, Liu, Chen, Wang, Li, Yin, Zhang, Chen, Zhang, Jiang, Zhao, Yang, Zheng, Lu, Zhuang, & Jiang. (2018). Insights into pathogenesis of five novel GCK mutations identified in Chinese MODY patients. [Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't]. *Metabolism, 89*, 8-17. doi: 10.1016/j.metabol.2018.09.004

Liu, Nagashima, Yasuda, Liu, Hu, He, Feng, Zhao, Zhuang, Zheng, Friedman, & Xiang. (2013). Mutations in KCNJ11 are associated with the development of autosomal dominant, early-onset type 2 diabetes. [Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't]. *Diabetologia, 56*(12), 2609-2618. doi: 10.1007/s00125-013-3031-9

Lomberk, Grzenda, Mathison, Escande, Zhang, Calvo, Miller, Iovanna, Chini, Fernandez-Zapico, & Urrutia. (2013). Kruppel-like factor 11 regulates the expression of metabolic genes via an evolutionarily conserved protein interaction domain functionally disrupted in maturity onset diabetes of the young. *J Biol Chem, 288*(24), 17745-17758. doi: 10.1074/jbc.M112.434670

Lomberk, & Urrutia. (2005). The family feud: turning off Sp1 by Sp1-like KLF proteins. *Biochem J, 392*(Pt 1), 1-11. doi: 10.1042/BJ20051234

Loomba-Albrecht, Jame, & Bremer. (2010). A novel glucokinase gene mutation and its effect on glycemic/C-peptide fluctuations in a patient with maturity-onset diabetes of the young type 2. [Case Reports]. *Diabetes Res Clin Pract, 87*(3), e23-25. doi: 10.1016/j.diabres.2009.11.013

Lopez-Garrido, Herranz-Antolin, Alija-Merillas, Giralt, & Escribano. (2013). Co-inheritance of HNF1a and GCK mutations in a family with maturity-onset diabetes of the young (MODY): implications for genetic testing. [Research Support, Non-U.S. Gov't]. *Clin Endocrinol (Oxf), 79*(3), 342-347. doi: 10.1111/cen.12050

Lopez, de Dios, Chiesa, Perez, & Frechtel. (2016). Analysis of mutations in the glucokinase gene in people clinically characterized as MODY2 without a family history of diabetes. *Diabetes Res Clin Pract, 118*, 38-43. doi: 10.1016/j.diabres.2016.04.057

Lopez, Foscaldi, Perez, Rodriguez, Traversa, Puchulu, Bergada, & Frechtel. (2011). HNF1 alpha gene coding regions mutations screening, in a Caucasian

population clinically characterized as MODY from Argentina. *Diabetes Res Clin Pract, 91*(2), 208-212. doi: 10.1016/j.diabres.2010.11.024

Lorini, Klersy, d'Annunzio, Massa, Minuto, Iafusco, Bellanne-Chantelot, Frongia, Toni, Meschi, Cerutti, & Barbetti. (2009). Maturity-onset diabetes of the young in children with incidental hyperglycemia: a multicenter Italian study of 172 families. [Multicenter Study]. *Diabetes Care, 32*(10), 1864-1866. doi: 10.2337/dc08-2018

Lukasova, Vcelak, Vankova, Vejrazkova, Andelova, & Bendlova. (2008). Screening of mutations and polymorphisms in the glucokinase gene in Czech diabetic and healthy control populations. [Research Support, Non-U.S. Gov't]. *Physiol Res, 57 Suppl 1*, S99-108.

Luo, Dai, Li, Shan, & Wu. (2017). Hepatocyte nuclear factor 1beta maturity-onset diabetes of the young in a Chinese child presenting with hyperglycemic hyperosmolar state. *Acta Diabetol, 54*(10), 969-973. doi: 10.1007/s00592-017-1007-9

Mangrum, Rush, & Shivaswamy. (2015). Genetically Targeted Dipeptidyl Peptidase-4 Inhibitor Use in a Patient with a Novel Mutation of MODY type 4. [Case Reports]. *Clin Med Insights Endocrinol Diabetes, 8*, 83-86. doi: 10.4137/CMED.S31926

Mantovani, Salardi, Cerreta, Bastia, Cenci, Ragni, Zucchini, Parente, & Cicognani. (2003). Identification of eight novel glucokinase mutations in Italian children with maturity-onset diabetes of the young. [Research Support, Non-U.S. Gov't]. *Hum Mutat, 22*(4), 338. doi: 10.1002/humu.9179

Marks, & Couch. (2010). Identification of two new mutations in the glucokinase gene that result in maturity-onset diabetes of the young. [Case Reports

Letter]. *Diabetes Care, 33*(7), e94. doi: 10.2337/dc10-0685

Marucci, Biagini, Di Paola, Menzaghi, Fini, Castellana, Cardinale, Mazza, & Trischitta. (2019). Association of a homozygous GCK missense mutation with mild diabetes. *Mol Genet Genomic Med, 7*(7), e00728. doi: 10.1002/mgg3.728

Massa, Iafusco, D'Amato, Gloyn, Hattersley, Pasquino, Tonini, Dammacco, Zanette, Meschi, Porzio, Bottazzo, Crino, Lorini, Cerutti, Vanelli, & Barbetti. (2005). KCNJ11 activating mutations in Italian patients with permanent neonatal diabetes. [Research Support, Non-U.S. Gov't]. *Hum Mutat, 25*(1), 22-27. doi: 10.1002/humu.20124

Matyka, Beards, Appleton, Ellard, Hattersley, & Dunger. (1998). Genetic testing for maturity onset diabetes of the young in childhood hyperglycaemia. [Case Reports

Research Support, Non-U.S. Gov't]. *Arch Dis Child, 78*(6), 552-554. doi: 10.1136/adc.78.6.552

Mayer, Bottcher, Kovacs, Halbritter, & Stumvoll. (2008). Phenotype of a patient with a de novo mutation in the hepatocyte nuclear factor 1beta/maturity-onset diabetes of the young type 5 gene. [Case Reports

Research Support, Non-U.S. Gov't]. *Metabolism, 57*(3), 416-420. doi: 10.1016/j.metabol.2007.11.001

McDonald, & Ellard. (2013). Maturity onset diabetes of the young: identification and diagnosis. [Research Support, Non-U.S. Gov't

Review]. *Ann Clin Biochem, 50*(Pt 5), 403-415. doi: 10.1177/0004563213483458

McDonald, McEneny, Pearson, Thanabalasingham, Szopa, Shields, Ellard, Owen, Malecki, Hattersley, & Young. (2012). Lipoprotein composition in HNF1A-

MODY: differentiating between HNF1A-MODY and type 2 diabetes. *Clin Chim Acta, 413*(9-10), 927-932. doi: 10.1016/j.cca.2012.02.005

McKinney, Cao, Behme, Mahon, & Hegele. (2003). Maturity-onset diabetes of the young (MODY) mutation in type 2 diabetes and latent autoimmune diabetes of the adult. [Comment

Letter]. *Diabetes Care, 26*(12), 3358-3359. doi: 10.2337/diacare.26.12.3358-a

McKinney, Cao, Robinson, Metzger, Cummings, Riddell, Sanderson, Pacaud, Ho, & Hegele. (2004). Spectrum of HNF1A and GCK mutations in Canadian families with maturity-onset diabetes of the young (MODY). [Research Support, Non-U.S. Gov't]. *Clin Invest Med, 27*(3), 135-141.

Metzger, Lowe, Dyer, Trimble, Chaovarindr, Coustan, Hadden, McCance, Hod, McIntyre, Oats, Persson, Rogers, & Sacks. (2008). Hyperglycemia and adverse pregnancy outcomes. [Multicenter Study

Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't]. *N Engl J Med, 358*(19), 1991-2002. doi: 10.1056/NEJMoa0707943

Mikuscheva, McKenzie, & Mekhail. (2017). 21-Year-Old Pregnant Woman with MODY-5 Diabetes. [Case Reports]. *Case Rep Obstet Gynecol, 2017*, 6431531. doi: 10.1155/2017/6431531

Milenkovic, Zdravkovic, & Mitrovic. (2008). [Novel glucokinase mutation in a boy with maturity-onset diabetes of the young]. [Case Reports]. *Srp Arh Celok Lek, 136*(9-10), 542-544. doi: 10.2298/sarh0810542m

Ming-Qiang, Yang-Li, Ke, Wei, Jun-Fen, Chao-Chun, & Guan-Ping. (2019). Maturity onset diabetes of the young (MODY) in Chinese children: genes and clinical

phenotypes. *J Pediatr Endocrinol Metab, 32*(7), 759-765. doi: 10.1515/jpem-2018-0446

Mitchell, Punthakee, Lo, Bernard, Chong, Newman, Cartier, Desilets, Cutz, Hansen, Riley, & Polychronakos. (2004). Neonatal diabetes, with hypoplastic pancreas, intestinal atresia and gall bladder hypoplasia: search for the aetiology of a new autosomal recessive syndrome. *Diabetologia, 47*(12), 2160-2167. doi: 10.1007/s00125-004-1576-3

Moghbeli, Naghibzadeh, Ghahraman, Fatemi, Taghavi, Vakili, & Abbaszadegan. (2018). Mutations in HNF1A Gene are not a Common Cause of Familial Young-Onset Diabetes in Iran. *Indian J Clin Biochem, 33*(1), 91-95. doi: 10.1007/s12291-017-0648-3

Mohammadi, Eskandari, Sarmadi, Rahimi, Iraj, Hashemipour, Chaleshtori, & Tabatabaiefar. (2019). Genetic Study of Hepatocyte Nuclear Factor 1 Alpha Variants in Development of Early-Onset Diabetes Type 2 and Maturity-Onset Diabetes of the Young 3 in Iran. *Adv Biomed Res, 8*, 55. doi: 10.4103/abr.abr_54_19

Mohan, Radha, Nguyen, Stawiski, Pahuja, Goldstein, Tom, Anjana, Kong-Beltran, Bhangale, Jahnavi, Chandni, Gayathri, George, Zhang, Murugan, Phalke, Chaudhuri, Gupta, Zhang, Santhosh, Stinson, Modrusan, Ramprasad, Seshagiri, & Peterson. (2018). Comprehensive genomic analysis identifies pathogenic variants in maturity-onset diabetes of the young (MODY) patients in South India. *BMC Med Genet, 19*(1), 22. doi: 10.1186/s12881-018-0528-6

Mohan, Ramachandran, Snehalatha, Mohan, Bharani, & Viswanathan. (1985). High prevalence of maturity-onset diabetes of the young (MODY) among Indians. *Diabetes Care, 8*(4), 371-374. doi: 10.2337/diacare.8.4.371

Moises, Reis, Morel, Chacra, Dib, Bellanne-Chantelot, & Velho. (2001). Prevalence of maturity-onset diabetes of the young mutations in Brazilian families with autosomal-dominant early-onset type 2 diabetes. *Diabetes Care, 24*(4), 786-788. doi: 10.2337/diacare.24.4.786

Moller, Dalgaard, Ambye, Hansen, Schmitz, Hansen, & Pedersen. (1999). A novel Phe75fsdelT mutation in the hepatocyte nuclear factor-4alpha gene in a Danish pedigree with maturity-onset diabetes of the young. [Research Support, Non-U.S. Gov't]. *J Clin Endocrinol Metab, 84*(1), 367-369. doi: 10.1210/jcem.84.1.5396

Molven, Ringdal, Nordbo, Raeder, Stoy, Lipkind, Steiner, Philipson, Bergmann, Aarskog, Undlien, Joner, Sovik, Bell, & Njolstad. (2008). Mutations in the insulin gene can cause MODY and autoantibody-negative type 1 diabetes. [Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't]. *Diabetes, 57*(4), 1131-1135. doi: 10.2337/db07-1467

Moritani, Yokota, Horikawa, Urakami, Nishii, Kawamura, Kikuchi, Kikuchi, Ogata, Sugihara, & Amemiya. (2016). Identification of monogenic gene mutations in Japanese subjects diagnosed with type 1B diabetes between >5 and 15.1 years of age. [Comparative Study]. *J Pediatr Endocrinol Metab, 29*(9), 1047-1054. doi: 10.1515/jpem-2016-0030

Mota, Bruggemann, & Costa. (2013). MODY 2: mutation identification and molecular ancestry in a Brazilian family. [Clinical Trial

Research Support, Non-U.S. Gov't]. *Gene, 512*(2), 486-491. doi: 10.1016/j.gene.2012.10.013

Nagano, Morisada, Nozu, Kamei, Tanaka, Kanda, Shiona, Araki, Ohara, Matsumura, Kasahara, Mori, Seo, Miura, Washiyama, Sugimoto, Harada, Tazoe, Kourakata, Enseki, Aotani, Yamada, Sakakibara, Yamamura, Minamikawa, Ishikura, Ito, Hattori, & Iijima. (2019). Clinical characteristics of HNF1B-related disorders in a Japanese population. *Clin Exp Nephrol, 23*(9), 1119-1129. doi: 10.1007/s10157-019-01747-0

Naya, Huang, Qiu, Mutoh, DeMayo, Leiter, & Tsai. (1997). Diabetes, defective pancreatic morphogenesis, and abnormal enteroendocrine differentiation in BETA2/neuroD-deficient mice. [Research Support, U.S. Gov't, P.H.S.]. *Genes Dev, 11*(18), 2323-2334. doi: 10.1101/gad.11.18.2323

Neve, Fernandez-Zapico, Ashkenazi-Katalan, Dina, Hamid, Joly, Vaillant, Benmezroua, Durand, Bakaher, Delannoy, Vaxillaire, Cook, Dallinga-Thie, Jansen, Charles, Clement, Galan, Hercberg, Helbecque, Charpentier, Prentki, Hansen, Pedersen, Urrutia, Melloul, & Froguel. (2005). Role of transcription factor KLF11 and its diabetes-associated gene variants in pancreatic beta cell function. [Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, P.H.S.]. *Proc Natl Acad Sci U S A, 102*(13), 4807-4812. doi: 10.1073/pnas.0409177102

Njolstad, Cockburn, Bell, & Sovik. (1998). A missense mutation, Val62Ala, in the glucokinase gene in a Norwegian family with maturity-onset diabetes of the young. [Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, P.H.S.]. *Acta Paediatr, 87*(8), 853-856. doi: 10.1080/080352598750013626

Nogaroto, Svidnicki, Bonatto, Milleo, Almeida, Vicari, & Artoni. (2011). New HNF-1alpha nonsense mutation causes maturity-onset diabetes of the young type 3. [Research Support, Non-U.S. Gov't]. *Clinics (Sao Paulo), 66*(1), 167-168. doi: 10.1590/s1807-59322011000100029

Noorian, Savad, & Mohammadi. (2016). A novel nonsense mutation in the WFS1 gene causes the Wolfram syndrome. *J Pediatr Endocrinol Metab, 29*(5), 607-609. doi: 10.1515/jpem-2015-0045

Noorian, Sayarifard, Farhadi, Barbetti, & Rezaei. (2013). GCK Mutation in a Child with Maturity Onset Diabetes of the Young, Type 2. [Case Reports]. *Iran J Pediatr, 23*(2), 226-228.

Odom, Zizlsperger, Gordon, Bell, Rinaldi, Murray, Volkert, Schreiber, Rolfe, Gifford, Fraenkel, Bell, & Young. (2004). Control of pancreas and liver gene expression by HNF transcription factors. *Science, 303*(5662), 1378-1381. doi: 10.1126/science.1089769

Ogurtsova, da Rocha Fernandes, Huang, Linnenkamp, Guariguata, Cho, Cavan, Shaw, & Makaroff. (2017). IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. [Historical Article]. *Diabetes Res Clin Pract, 128*, 40-50. doi: 10.1016/j.diabres.2017.03.024

Omura, Yagi, Honoki, Iwata, Enkaku, Takikawa, Kuwano, Watanabe, Nishimura, Liu, Chujo, Fujisaka, Enya, Horikawa, & Tobe. (2019). Clinical manifestations of a sporadic maturity-onset diabetes of the young (MODY) 5 with a whole deletion of HNF1B based on 17q12 microdeletion. *Endocr J. 66*(12), 1113-1116. doi: 10.1507/endocrj.EJ19-0020

Ostoft, Bagger, Hansen, Pedersen, Faber, Holst, Knop, & Vilsboll. (2014). Glucose-lowering effects and low risk of hypoglycemia in patients with maturity-onset

diabetes of the young when treated with a GLP-1 receptor agonist: a double-blind, randomized, crossover trial. [Comparative Study

Randomized Controlled Trial]. *Diabetes Care, 37*(7), 1797-1805. doi: 10.2337/dc13-3007

Ovsyannikova, Rymar, Ivanoshchuk, Mikhailova, Shakhtshneider, Orlov, Malakhina, & Voevoda. (2018). A Case of Maturity Onset Diabetes of the Young (MODY3) in a Family with a Novel HNF1A Gene Mutation in Five Generations. *Diabetes Ther, 9*(1), 413-420. doi: 10.1007/s13300-017-0350-8

Ovsyannikova, Rymar, Shakhtshneider, Klimontov, Koroleva, Myakina, & Voevoda. (2016). ABCC8-Related Maturity-Onset Diabetes of the Young (MODY12): Clinical Features and Treatment Perspective. *Diabetes Ther, 7*(3), 591-600. doi: 10.1007/s13300-016-0192-9

Ozdemir, Kirbiyik, Dundar, Abaci, Kaya, Catli, Ozyilmaz, Acar, Koc, Guvenc, Kutbay, & Erdogan. (2018). Targeted next generation sequencing in patients with maturity-onset diabetes of the young (MODY). *J Pediatr Endocrinol Metab, 31*(12), 1295-1304. doi: 10.1515/jpem-2018-0184

Ozsu, Cizmecioglu, Yesiltepe Mutlu, Yuksel, Caliskan, Yesilyurt, & Hatun. (2018). Maturity Onset Diabetes of the Young due to Glucokinase, HNF1-A, HNF1-B, and HNF4-A Mutations in a Cohort of Turkish Children Diagnosed as Type 1 Diabetes Mellitus. *Horm Res Paediatr, 90*(4), 257-265. doi: 10.1159/000494431

Pace, Craus, Felice, & Vassallo. (2018). Case Report: Identification of an HNF1B p.Arg527Gln mutation in a Maltese patient with atypical early onset diabetes and diabetic nephropathy. [Case Reports]. *BMC Endocr Disord, 18*(1), 28. doi: 10.1186/s12902-018-0257-z

Pace, Rizzo, Abela, Gruppetta, Fava, Felice, & Vassallo. (2019). Identification of an HNF1A p.Gly292fs Frameshift Mutation Presenting as Diabetes During Pregnancy in a Maltese Family. [Case Reports]. *Clin Med Insights Case Rep, 12*, 1179547619831034. doi: 10.1177/1179547619831034

Pallotta, Tascini, Crispoldi, Orabona, Mondanelli, Grohmann, & Esposito. (2019). Wolfram syndrome, a rare neurodegenerative disease: from pathogenesis to future treatment perspectives. [Review]. *J Transl Med, 17*(1), 238. doi: 10.1186/s12967-019-1993-1

Papadimitriou, Willems, Bothou, Karpathios, & Papadimitriou. (2015). A novel heterozygous mutation in the glucokinase gene is responsible for an early-onset mild form of maturity-onset diabetes of the young, type 2. [Case Reports Letter]. *Diabetes Metab, 41*(4), 342-343. doi: 10.1016/j.diabet.2015.03.009

Park, Jang, Ahn, Kim, Jung, Cho, Lee, Shin, Chae, Choi, Jang, Bae, Won, Kim, Kim, Kwak, & Park. (2019). Identifying Pathogenic Variants of Monogenic Diabetes Using Targeted Panel Sequencing in an East Asian Population. *J Clin Endocrinol Metab*. doi: 10.1210/jc.2018-02397

Parvin, Jahan, Sarkar, Howlader, Nabi, & Hosen. (2019). Functional Polymorphism Located in the microRNA Binding Site of the Insulin Receptor (INSR) Gene Confers Risk for Type 2 Diabetes Mellitus in the Bangladeshi Population. *Biochem Genet, 57*(1), 20-33. doi: 10.1007/s10528-018-9872-7

Patel, Kettunen, Laakso, Stancakova, Laver, Colclough, Johnson, Abramowicz, Groop, Miettinen, Shepherd, Flanagan, Ellard, Inagaki, Hattersley, Tuomi, Cnop, & Weedon. (2017). Heterozygous RFX6 protein truncating variants are associated with MODY with reduced penetrance. *Nat Commun, 8*(1), 888. doi: 10.1038/s41467-017-00895-9

Pavic, Juszczak, Pape Medvidovic, Burrows, Sekerija, Bennett, Cuca Knezevic, Gloyn, Lauc, McCarthy, Gornik, & Owen. (2018). Maturity onset diabetes of the young due to HNF1A variants in Croatia. *Biochem Med (Zagreb), 28*(2), 020703. doi: 10.11613/BM.2018.020703

Pearson, Badman, Lockwood, Clark, Ellard, Bingham, & Hattersley. (2004). Contrasting diabetes phenotypes associated with hepatocyte nuclear factor-1alpha and -1beta mutations. [Research Support, Non-U.S. Gov't]. *Diabetes Care, 27*(5), 1102-1107. doi: 10.2337/diacare.27.5.1102

Pearson, Liddell, Shepherd, Corrall, & Hattersley. (2000). Sensitivity to sulphonylureas in patients with hepatocyte nuclear factor-1alpha gene mutations: evidence for pharmacogenetics in diabetes. *Diabet Med, 17*(7), 543-545. doi: 10.1046/j.1464-5491.2000.00305.x

Pearson, Pruhova, Tack, Johansen, Castleden, Lumb, Wierzbicki, Clark, Lebl, Pedersen, Ellard, Hansen, & Hattersley. (2005). Molecular genetics and phenotypic characteristics of MODY caused by hepatocyte nuclear factor 4alpha mutations in a large European collection. [Multicenter Study

Research Support, Non-U.S. Gov't]. *Diabetologia, 48*(5), 878-885. doi: 10.1007/s00125-005-1738-y

Pearson, Starkey, Powell, Gribble, Clark, & Hattersley. (2003). Genetic cause of hyperglycaemia and response to treatment in diabetes. [Clinical Trial

Comparative Study

Randomized Controlled Trial

Research Support, Non-U.S. Gov't]. *Lancet, 362*(9392), 1275-1281. doi: 10.1016/S0140-6736(03)14571-0

Pezzilli, Ludovico, Biagini, Mercuri, Alberico, Lauricella, Dallali, Capocefalo, Carella, Miccinilli, Piscitelli, Scarale, Mazza, Trischitta, & Prudente. (2018). Insights From Molecular Characterization of Adult Patients of Families With Multigenerational Diabetes. *Diabetes, 67*(1), 137-145. doi: 10.2337/db17-0867

Piccini, Artuso, Lenzi, Guasti, Braccesi, Barni, Casalini, Giglio, & Toni. (2016). Clinical and molecular characterization of a novel INS mutation identified in patients with MODY phenotype. *Eur J Med Genet, 59*(11), 590-595. doi: 10.1016/j.ejmg.2016.09.016

Pihoker, Gilliam, Ellard, Dabelea, Davis, Dolan, Greenbaum, Imperatore, Lawrence, Marcovina, Mayer-Davis, Rodriguez, Steck, Williams, & Hattersley. (2013). Prevalence, characteristics and clinical diagnosis of maturity onset diabetes of the young due to mutations in HNF1A, HNF4A, and glucokinase: results from the SEARCH for Diabetes in Youth. [Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, P.H.S.]. *J Clin Endocrinol Metab, 98*(10), 4055-4062. doi: 10.1210/jc.2013-1279

Pingul, Hughes, Wu, Stanley, & Gruppuso. (2011). Hepatocyte nuclear factor 4alpha gene mutation associated with familial neonatal hyperinsulinism and maturity-onset diabetes of the young. [Case Reports]. *J Pediatr, 158*(5), 852-854. doi: 10.1016/j.jpeds.2011.01.003

Plengvidhya, Boonyasrisawat, Chongjaroen, Jungtrakoon, Sriussadaporn, Vannaseang, Banchuin, & Yenchitsomanus. (2009). Mutations of maturity-onset diabetes of the young (MODY) genes in Thais with early-onset type 2 diabetes mellitus. [Research Support, Non-U.S. Gov't]. *Clin Endocrinol (Oxf), 70*(6), 847-853. doi: 10.1111/j.1365-2265.2008.03397.x

Plengvidhya, Kooptiwut, Songtawee, Doi, Furuta, Nishi, Nanjo, Tantibhedhyangkul, Boonyasrisawat, Yenchitsomanus, Doria, & Banchuin. (2007). PAX4 mutations in Thais with maturity onset diabetes of the young. [Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't]. *J Clin Endocrinol Metab, 92*(7), 2821-2826. doi: 10.1210/jc.2006-1927

Plengvidhya, Tangjittipokin, Teerawattanapong, Narkdontri, & Yenchitsomanus. (2019). HNF1A mutation in a Thai patient with maturity-onset diabetes of the young: A case report. [Case Reports]. *World J Diabetes, 10*(7), 414-420. doi: 10.4239/wjd.v10.i7.414

Poitou, Francois, Bellanne-Chantelot, Noel, Jacquet, Clauin, Beaudreuil, Damieri, Hebibi, Hammoudi, Benoit, Charpentier, & Durrbach. (2012). Maturity onset diabetes of the young: clinical characteristics and outcome after kidney and pancreas transplantation in MODY3 and RCAD patients: a single center experience. *Transpl Int, 25*(5), 564-572. doi: 10.1111/j.1432-2277.2012.01458.x

Pontoglio, Prie, Cheret, Doyen, Leroy, Froguel, Velho, Yaniv, & Friedlander. (2000). HNF1alpha controls renal glucose reabsorption in mouse and man. [Comparative Study

Research Support, Non-U.S. Gov't]. *EMBO Rep, 1*(4), 359-365. doi: 10.1093/embo-reports/kvd071

Pontoglio, Sreenan, Roe, Pugh, Ostrega, Doyen, Pick, Baldwin, Velho, Froguel, Levisetti, Bonner-Weir, Bell, Yaniv, & Polonsky. (1998). Defective insulin secretion in hepatocyte nuclear factor 1alpha-deficient mice. [Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, P.H.S.]. *J Clin Invest, 101*(10), 2215-2222. doi: 10.1172/JCI2548

Prudente, Jungtrakoon, Marucci, Ludovico, Buranasupkajorn, Mazza, Hastings, Milano, Morini, Mercuri, Bailetti, Mendonca, Alberico, Basile, Romani, Miccinilli, Pizzuti, Carella, Barbetti, Pascarella, Marchetti, Trischitta, Di Paola, & Doria. (2015). Loss-of-Function Mutations in APPL1 in Familial Diabetes Mellitus. [Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't]. *Am J Hum Genet, 97*(1), 177-185. doi: 10.1016/j.ajhg.2015.05.011

Pruhova, Dusatkova, Sumnik, Kolouskova, Pedersen, Hansen, Cinek, & Lebl. (2010). Glucokinase diabetes in 103 families from a country-based study in the Czech Republic: geographically restricted distribution of two prevalent GCK mutations. [Research Support, Non-U.S. Gov't]. *Pediatr Diabetes, 11*(8), 529-535. doi: 10.1111/j.1399-5448.2010.00646.x

Qin, Li, Hou, Wang, Lou, Li, Wang, Liu, Li, & Liao. (2017). Novel heterozygous mutations of the INSR gene in a familial case of Donohue syndrome. *Clin Chim Acta, 473*, 26-31. doi: 10.1016/j.cca.2017.08.007

Radha, Ek, Anuradha, Hansen, Pedersen, & Mohan. (2009). Identification of novel variants in the hepatocyte nuclear factor-1alpha gene in South Indian patients with maturity onset diabetes of young. [Research Support, Non-U.S. Gov't]. *J Clin Endocrinol Metab, 94*(6), 1959-1965. doi: 10.1210/jc.2008-2371

Raeder, Bjorkhaug, Johansson, Mangseth, Sagen, Hunting, Folling, Johansen, Bjorgaas, Paus, Sovik, Molven, & Njolstad. (2006). A hepatocyte nuclear factor-4 alpha gene (HNF4A) P2 promoter haplotype linked with late-onset diabetes: studies of HNF4A variants in the Norwegian MODY registry.

[Research Support, Non-U.S. Gov't]. *Diabetes, 55*(6), 1899-1903. doi: 10.2337/db05-1677

Raeder, Johansson, Holm, Haldorsen, Mas, Sbarra, Nermoen, Eide, Grevle, Bjorkhaug, Sagen, Aksnes, Sovik, Lombardo, Molven, & Njolstad. (2006). Mutations in the CEL VNTR cause a syndrome of diabetes and pancreatic exocrine dysfunction. [Research Support, Non-U.S. Gov't]. *Nat Genet, 38*(1), 54-62. doi: 10.1038/ng1708

Rafique I. (2018). MATURITY ONSET DIABETES OF THE YOUNG – AN OVERVIEW OF COMMON TYPES. A REVIEW. *Rom J Diabetes NutrMetab Dis, 25*((2)), 209-213 doi: 10.2478/rjdnmd-2018-0024)

Raile, Klopocki, Holder, Wessel, Galler, Deiss, Muller, Riebel, Horn, Maringa, Weber, Ullmann, & Gruters. (2009). Expanded clinical spectrum in hepatocyte nuclear factor 1b-maturity-onset diabetes of the young. *J Clin Endocrinol Metab, 94*(7), 2658-2664. doi: 10.1210/jc.2008-2189

Raile, Schober, Konrad, Thon, Grulich-Henn, Meissner, Wolfle, Scheuing, Holl, & Mellitus. (2015). Treatment of young patients with HNF1A mutations (HNF1A-MODY). *Diabet Med, 32*(4), 526-530. doi: 10.1111/dme.12662

Rama Chandran, Bhalshankar, Farhad Vasanwala, Zhao, Owen, & Su-Lyn Gardner. (2018). Traditional clinical criteria outperform high-sensitivity C-reactive protein for the screening of hepatic nuclear factor 1 alpha maturity-onset diabetes of the young among young Asians with diabetes. *Ther Adv Endocrinol Metab, 9*(9), 271-282. doi: 10.1177/2042018818776167

Reinehr. (2013). Type 2 diabetes mellitus in children and adolescents. [Review]. *World J Diabetes, 4*(6), 270-281. doi: 10.4239/wjd.v4.i6.270

Rigoli, Lombardo, Salzano, Di Bella, Messina, De Luca, & Iafusco. (2013). Identification of one novel causative mutation in exon 4 of WFS1 gene in two Italian siblings with classical DIDMOAD syndrome phenotype. *Gene, 526*(2), 487-489. doi: 10.1016/j.gene.2012.10.023

Roehlen, Hilger, Stock, Glaser, Guhl, Schmitt-Graeff, Seufert, & Laubner. (2018). 17q12 Deletion Syndrome as a Rare Cause for Diabetes Mellitus Type MODY5. [Case Reports

Review]. *J Clin Endocrinol Metab, 103*(10), 3601-3610. doi: 10.1210/jc.2018-00955

Rubio-Cabezas, Minton, Kantor, Williams, Ellard, & Hattersley. (2010). Homozygous mutations in NEUROD1 are responsible for a novel syndrome of permanent neonatal diabetes and neurological abnormalities. [Case Reports

Research Support, Non-U.S. Gov't]. *Diabetes, 59*(9), 2326-2331. doi: 10.2337/db10-0011

Sagen, Bjorkhaug, Haukanes, Grevle, Molnes, Nedrebo, Sovik, Njolstad, Johansson, & Molven. (2017). The HNF1A mutant Ala180Val: Clinical challenges in determining causality of a rare HNF1A variant in familial diabetes. *Diabetes Res Clin Pract, 133*, 142-149. doi: 10.1016/j.diabres.2017.08.001

Sagen, Bjorkhaug, Molnes, Raeder, Grevle, Sovik, Molven, & Njolstad. (2008). Diagnostic screening of MODY2/GCK mutations in the Norwegian MODY Registry. [Research Support, Non-U.S. Gov't]. *Pediatr Diabetes, 9*(5), 442-449. doi: 10.1111/j.1399-5448.2008.00399.x

Sagen, Odili, Bjorkhaug, Zelent, Buettger, Kwagh, Stanley, Dahl-Jorgensen, de Beaufort, Bell, Han, Grimsby, Taub, Molven, Sovik, Njolstad, & Matschinsky. (2006). From clinicogenetic studies of maturity-onset diabetes of the young to

unraveling complex mechanisms of glucokinase regulation. [Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't]. *Diabetes, 55*(6), 1713-1722. doi: 10.2337/db05-1513

Sahoo, Zaidi, Vipin, Chapla, Thomas, Yu, Asthana, & Bhatia. (2019). Heterogeneity in the aetiology of diabetes mellitus in young adults: A prospective study from north India. *Indian J Med Res, 149*(4), 479-488. doi: 10.4103/ijmr.IJMR_1004_17

Santana, Caetano, Costa-Riquetto, Quedas, Nery, Collett-Solberg, Boguszewski, Vendramini, Crisostomo, Floh, Zarabia, Kohara, Guastapaglia, Passone, Sewaybricker, Jorge, & Teles. (2017). Clinical application of ACMG-AMP guidelines in HNF1A and GCK variants in a cohort of MODY families. *Clin Genet, 92*(4), 388-396. doi: 10.1111/cge.12988

Sanyoura, Letourneau, Knight Johnson, Del Gaudio, Greeley, Philipson, & Naylor. (2019). GCK-MODY in the US Monogenic Diabetes Registry: Description of 27 unpublished variants. *Diabetes Res Clin Pract, 151*, 231-236. doi: 10.1016/j.diabres.2019.04.017

Schnyder, Mullis, Ellard, Hattersley, & Fluck. (2005). Genetic testing for glucokinase mutations in clinically selected patients with MODY: a worthwhile investment. [Case Reports]. *Swiss Med Wkly, 135*(23-24), 352-356. doi: 2005/23/smw-11030

Seino, Seino, Nishi, & Bell. (1989). Structure of the human insulin receptor gene and characterization of its promoter. *Proc Natl Acad Sci U S A, 86*(1), 114-118. doi: 10.1073/pnas.86.1.114

Sesti, Federici, Lauro, Sbraccia, & Lauro. (2001). Molecular mechanism of insulin resistance in type 2 diabetes mellitus: role of the insulin receptor variant forms. *Diabetes Metab Res Rev, 17*(5), 363-373. doi: 10.1002/dmrr.225

Shankar, Ellard, Standiford, Pihoker, Gilliam, Hattersley, & Dolan. (2013). Digenic heterozygous HNF1A and HNF4A mutations in two siblings with childhood-onset diabetes. [Case Reports

Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't]. *Pediatr Diabetes, 14*(7), 535-538. doi: 10.1111/pedi.12018

Shepherd, Ellis, Ahmad, Todd, Bowen-Jones, Mannion, Ellard, Sparkes, & Hattersley. (2001). Predictive genetic testing in maturity-onset diabetes of the young (MODY). [Case Reports

Research Support, Non-U.S. Gov't]. *Diabet Med, 18*(5), 417-421. doi: 10.1046/j.1464-5491.2001.00447.x

Shepherd, Pearson, Houghton, Salt, Ellard, & Hattersley. (2003). No deterioration in glycemic control in HNF-1alpha maturity-onset diabetes of the young following transfer from long-term insulin to sulphonylureas. [Clinical Trial

Letter

Research Support, Non-U.S. Gov't]. *Diabetes Care, 26*(11), 3191-3192. doi: 10.2337/diacare.26.11.3191-a

Shepherd, Shields, Hammersley, Hudson, McDonald, Colclough, Oram, Knight, Hyde, Cox, Mallam, Moudiotis, Smith, Fraser, Robertson, Greene, Ellard, Pearson, & Hattersley. (2016). Systematic Population Screening, Using Biomarkers and Genetic Testing, Identifies 2.5% of the U.K. Pediatric

Diabetes Population With Monogenic Diabetes. *Diabetes Care, 39*(11), 1879-1888. doi: 10.2337/dc16-0645

Shera, Basit, Fawwad, Hakeem, Ahmedani, Hydrie, & Khwaja. (2010). Pakistan National Diabetes Survey: prevalence of glucose intolerance and associated factors in the Punjab Province of Pakistan. *Prim Care Diabetes, 4*(2), 79-83. doi: 10.1016/j.pcd.2010.01.003

Shera, Rafique, Khawaja, Baqai, & King. (1999). Pakistan National Diabetes Survey: prevalence of glucose intolerance and associated factors in Baluchistan province. *Diabetes Res Clin Pract, 44*(1), 49-58. doi: 10.1016/s0168-8227(99)00017-0

Shera, Rafique, Khwaja, Ara, Baqai, & King. (1995). Pakistan national diabetes survey: prevalence of glucose intolerance and associated factors in Shikarpur, Sindh Province. [Comparative Study]. *Diabet Med, 12*(12), 1116-1121. doi: 10.1111/j.1464-5491.1995.tb00430.x

Shera, Rafique, Khwaja, Baqai, Khan, & King. (1999). Pakistan National Diabetes Survey prevalence of glucose intolerance and associated factors in North West at Frontier Province (NWFP) of Pakistan. *J Pak Med Assoc, 49*(9), 206-211.

Shields, Hicks, Shepherd, Colclough, Hattersley, & Ellard. (2010). Maturity-onset diabetes of the young (MODY): how many cases are we missing? [Evaluation Study

Research Support, Non-U.S. Gov't]. *Diabetologia, 53*(12), 2504-2508. doi: 10.1007/s00125-010-1799-4

Shields, McDonald, Ellard, Campbell, Hyde, & Hattersley. (2012). The development and validation of a clinical prediction model to determine the probability of

MODY in patients with young-onset diabetes. [Research Support, Non-U.S. Gov't

Validation Study]. *Diabetologia, 55*(5), 1265-1272. doi: 10.1007/s00125-011-2418-8

Shields, Shepherd, Hudson, McDonald, Colclough, Peters, Knight, Hyde, Ellard, Pearson, & Hattersley. (2017). Population-Based Assessment of a Biomarker-Based Screening Pathway to Aid Diagnosis of Monogenic Diabetes in Young-Onset Patients. *Diabetes Care, 40*(8), 1017-1025. doi: 10.2337/dc17-0224

Shima, Usuda, Futatani, Akahori, Kaneko, Yorifuji, & Takamura. (2018). Heterogeneous nature of diabetes in a family with a gain-of-function mutation in the ATP-binding cassette subfamily C member 8 (ABCC8) gene. [Case Reports]. *Endocr J, 65*(10), 1055-1059. doi: 10.1507/endocrj.EJ18-0054

Shimoda, Okada, Shimoyama, Kusano, & Yamada. (2016). Maturity onset diabetes of the young 5 accompanied by duodenal cysts. [Case Reports]. *J Diabetes, 8*(3), 448-449. doi: 10.1111/1753-0407.12367

Shoemaker, Zienkiewicz, & Moore. (2012). Clinical assessment of HNF1A and GCK variants and identification of a novel mutation causing MODY2. [Case Reports]. *Diabetes Res Clin Pract, 96*(2), e36-39. doi: 10.1016/j.diabres.2012.01.032

Sladek, Zhong, Lai, & Darnell. (1990). Liver-enriched transcription factor HNF-4 is a novel member of the steroid hormone receptor superfamily. [Comparative Study

Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, P.H.S.]. *Genes Dev, 4*(12B), 2353-2365. doi: 10.1101/gad.4.12b.2353

Smith, Qu, Taleb, Kishimoto, Scheel, Lu, Patch, Grabs, Wang, Lynn, Miyatsuka, Mitchell, Seerke, Desir, Vanden Eijnden, Abramowicz, Kacet, Weill, Renard, Gentile, Hansen, Dewar, Hattersley, Wang, Wilson, Johnson, Polychronakos, & German. (2010). Rfx6 directs islet formation and insulin production in mice and humans. *Nature, 463*(7282), 775-780. doi: 10.1038/nature08748

Solera, Arias, Aminoso, Gonzalez-Casado, Garre, Herranz, Villarroel, Cruz, Janez, Pallardo, & Gracia. (2009). Identification of eight new mutations in the GCK gene by DHPLC screening in a Spanish population. *Diabetes Res Clin Pract, 85*(1), 20-23. doi: 10.1016/j.diabres.2009.04.002

Song, Yang, Mauvais-Jarvis, Wang, & Niu. (2017). KCNJ11, ABCC8 and TCF7L2 polymorphisms and the response to sulfonylurea treatment in patients with type 2 diabetes: a bioinformatics assessment. *BMC Med Genet, 18*(1), 64. doi: 10.1186/s12881-017-0422-7

Spyer, Hattersley, Sykes, Sturley, & MacLeod. (2001). Influence of maternal and fetal glucokinase mutations in gestational diabetes. [Case Reports

Research Support, Non-U.S. Gov't]. *Am J Obstet Gynecol, 185*(1), 240-241. doi: 10.1067/mob.2001.113127

Stern, Strihan, Potievsky, Nimri, Shalitin, Cohen, Shehadeh, Weintrob, Phillip, & Gat-Yablonski. (2007). Four novel mutations, including the first gross deletion in TCF1, identified in HNF-4alpha, GCK and TCF1 in patients with MODY in Israel. [Multicenter Study

Research Support, Non-U.S. Gov't]. *J Pediatr Endocrinol Metab, 20*(8), 909-921. doi: 10.1515/jpem.2007.20.8.909

Stiles, Thuraisingham, Bockenhauer, Platts, Kumar, & Korbonits. (2018). De novo HNF1 homeobox B mutation as a cause for chronic, treatment-resistant

hypomagnesaemia. *Endocrinol Diabetes Metab Case Rep, 2018*. doi: 10.1530/EDM-17-0120

Stoffel, Patel, Lo, Hattersley, Lucassen, Page, Bell, Bell, Turner, & Wainscoat. (1992). Missense glucokinase mutation in maturity-onset diabetes of the young and mutation screening in late-onset diabetes. [Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, P.H.S.]. *Nat Genet, 2*(2), 153-156. doi: 10.1038/ng1092-153

Stoffers, Zinkin, Stanojevic, Clarke, & Habener. (1997). Pancreatic agenesis attributable to a single nucleotide deletion in the human IPF1 gene coding sequence. [Case Reports

Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, P.H.S.]. *Nat Genet, 15*(1), 106-110. doi: 10.1038/ng0197-106

Stride, Vaxillaire, Tuomi, Barbetti, Njolstad, Hansen, Costa, Conget, Pedersen, Sovik, Lorini, Groop, Froguel, & Hattersley. (2002). The genetic abnormality in the beta cell determines the response to an oral glucose load. [Multicenter Study

Research Support, Non-U.S. Gov't]. *Diabetologia, 45*(3), 427-435. doi: 10.1007/s00125-001-0770-9

Sujjitjoon, Kooptiwut, Chongjaroen, Tangjittipokin, Plengvidhya, & Yenchitsomanus. (2016). Aberrant mRNA splicing of paired box 4 (PAX4) IVS7-1G>A mutation causing maturity-onset diabetes of the young, type 9. [Research Support, Non-U.S. Gov't]. *Acta Diabetol, 53*(2), 205-216. doi: 10.1007/s00592-015-0760-x

Szopa, Ludwig-Galezowska, Radkowski, Skupien, Machlowska, Klupa, Wolkow, Borowiec, Mlynarski, & Malecki. (2016). A family with the Arg103Pro mutation in the NEUROD1 gene detected by next-generation sequencing - Clinical characteristics of mutation carriers. [Research Support, Non-U.S. Gov't]. *Eur J Med Genet, 59*(2), 75-79. doi: 10.1016/j.ejmg.2016.01.002

Szopa, Ludwig-Galezowska, Radkowski, Skupien, Zapala, Platek, Klupa, Kiec-Wilk, Borowiec, Mlynarski, Wolkow, & Malecki. (2015). Genetic testing for monogenic diabetes using targeted next-generation sequencing in patients with maturity-onset diabetes of the young. [Research Support, Non-U.S. Gov't]. *Pol Arch Med Wewn, 125*(11), 845-851. doi: 10.20452/pamw.3164

Szopa, Matejko, Ucieklak, Uchman, Hohendorff, Mrozinska, Glodzik, Zapala, Platek, Solecka, Sani, & Malecki. (2019). Quality of life assessment in patients with HNF1A-MODY and GCK-MODY. *Endocrine, 64*(2), 246-253. doi: 10.1007/s12020-018-1812-0

Taberner, Flanagan, Mackay, Ellard, Taverna, & Ferraro. (2016). Clinical and genetic features of Argentinian children with diabetes-onset before 12months of age: Successful transfer from insulin to oral sulfonylurea. *Diabetes Res Clin Pract, 117*, 104-110. doi: 10.1016/j.diabres.2016.04.005

Taghavi, Fatemi, Rafatpanah, Ganjali, Tavakolafshari, & Valizadeh. (2009). Mutations in the coding regions of the hepatocyte nuclear factor 4 alpha in Iranian families with maturity onset diabetes of the young. [Research Support, Non-U.S. Gov't]. *Cardiovasc Diabetol, 8*, 63. doi: 10.1186/1475-2840-8-63

Taleb, & Polychronakos. (2011). RFX6 is needed for the development and maintenance of the beta-cell phenotype. *Islets, 3*(5), 291-293. doi: 10.4161/isl.3.5.15944

Tang, Tang, Wang, Guo, Tang, Zhou, Tan, Liu, Zhou, & Zhou. (2017). Genetic diagnosis and treatment of a Chinese ketosis-prone MODY 3 family with depression. *Diabetol Metab Syndr, 9*, 5. doi: 10.1186/s13098-016-0198-5

Tarantino, Abreu, Fonseca, Kupfer, Pereira, Campos Junior, Zajdenverg, & Rodacki. (2019). MODY probability calculator for GCK and HNF1A screening in a multiethnic background population. *Arch Endocrinol Metab.* doi: 10.20945/2359-3997000000173

Tatsi, Kanaka-Gantenbein, Scorilas, Chrousos, & Sertedaki. (2020). Next generation sequencing targeted gene panel in Greek MODY patients increases diagnostic accuracy. *Pediatr Diabetes, 21*(1), 28-39. doi: 10.1111/pedi.12931

Tatsi, Kanaka-Gantenbein, Vazeou-Gerassimidi, Chrysis, Delis, Tentolouris, Dacou-Voutetakis, Chrousos, & Sertedaki. (2013). The spectrum of HNF1A gene mutations in Greek patients with MODY3: relative frequency and identification of seven novel germline mutations. [Research Support, Non-U.S. Gov't]. *Pediatr Diabetes, 14*(7), 526-534. doi: 10.1111/pedi.12032

Taylor, Mackie, Mogra, Pinner, Rajendran, & Ross. (2019). Caudal regression syndrome in a fetus of a glucokinase-maturity-onset diabetes of the young pregnancy. [Case Reports]. *Diabet Med, 36*(2), 252-255. doi: 10.1111/dme.13844

Thanabalasingham, Pal, Selwood, Dudley, Fisher, Bingley, Ellard, Farmer, McCarthy, & Owen. (2012). Systematic assessment of etiology in adults with a clinical diagnosis of young-onset type 2 diabetes is a successful strategy for identifying maturity-onset diabetes of the young. [Research Support, Non-U.S. Gov't]. *Diabetes Care, 35*(6), 1206-1212. doi: 10.2337/dc11-1243

Thirumalai, Holing, Brown, & Gilliam. (2013). A case of hepatocyte nuclear factor-1beta (TCF2) maturity onset diabetes of the young misdiagnosed as type 1 diabetes and treated unnecessarily with insulin. [Case Reports]. *J Diabetes, 5*(4), 462-464. doi: 10.1111/1753-0407.12043

Tinto, Zagari, Capuano, De Simone, Capobianco, Daniele, Giugliano, Spadaro, Franzese, & Sacchetti. (2008). Glucokinase gene mutations: structural and genotype-phenotype analyses in MODY children from South Italy. [Research Support, Non-U.S. Gov't]. *PLoS One, 3*(4), e1870. doi: 10.1371/journal.pone.0001870

Toaima, Nake, Wendenburg, Praedicow, Rohayem, Engel, Galler, Gahr, & Lee-Kirsch. (2005). Identification of novel GCK and HNF1A/TCF1 mutations and polymorphisms in German families with maturity-onset diabetes of the young (MODY). [Research Support, Non-U.S. Gov't]. *Hum Mutat, 25*(5), 503-504. doi: 10.1002/humu.9334

Torsvik, Johansson, Johansen, Ek, Minton, Raeder, Ellard, Hattersley, Pedersen, Hansen, Molven, & Njolstad. (2010). Mutations in the VNTR of the carboxyl-ester lipase gene (CEL) are a rare cause of monogenic diabetes. [Research Support, Non-U.S. Gov't]. *Hum Genet, 127*(1), 55-64. doi: 10.1007/s00439-009-0740-8

Urakami. (2019). Maturity-onset diabetes of the young (MODY): current perspectives on diagnosis and treatment. [Review]. *Diabetes Metab Syndr Obes, 12*, 1047-1056. doi: 10.2147/DMSO.S179793

Urakami, Kuwabara, Habu, Okuno, Suzuki, Takahashi, & Mugishima. (2013). Clinical characteristics of non-obese children with type 2 diabetes mellitus

without involvement of beta-cell autoimmunity. *Diabetes Res Clin Pract, 99*(2), 105-111. doi: 10.1016/j.diabres.2012.11.021

Urano. (2016). Wolfram Syndrome: Diagnosis, Management, and Treatment. [Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't

Review]. *Curr Diab Rep, 16*(1), 6. doi: 10.1007/s11892-015-0702-6

Urrutia, Martinez, Rica, Martinez de LaPiscina, Garcia-Castano, Aguayo, Calvo, & Castano. (2019). Negative autoimmunity in a Spanish pediatric cohort suspected of type 1 diabetes, could it be monogenic diabetes? [Research Support, Non-U.S. Gov't]. *PLoS One, 14*(7), e0220634. doi: 10.1371/journal.pone.0220634

Ushijima, Fukami, Ayabe, Narumi, Okuno, Nakamura, Takahashi, Ihara, Ohkubo, Tachikawa, Nakayama, Arai, Kikuchi, Kikuchi, Kawamura, Urakami, Hata, Nakabayashi, Matsubara, Amemiya, Ogata, Yokota, & Sugihara. (2018). Comprehensive screening for monogenic diabetes in 89 Japanese children with insulin-requiring antibody-negative type 1 diabetes. [Research Support, Non-U.S. Gov't]. *Pediatr Diabetes, 19*(2), 243-250. doi: 10.1111/pedi.12544

Ushijima, Narumi, Ogata, Yokota, Sugihara, Kaname, Horikawa, Matsubara, Fukami, & Kawamura. (2019). KLF11 variant in a family clinically diagnosed with early childhood-onset type 1B diabetes. [Case Reports

Research Support, Non-U.S. Gov't]. *Pediatr Diabetes, 20*(6), 712-719. doi: 10.1111/pedi.12868

Ushijima, Narumi, Ogata, Yokota, Sugihara, Kaname, Horikawa, Matsubara, Fukami, Kawamura, Japanese Study Group of Insulin Therapy for, & Adolescent.

(2019). KLF11 variant in a family clinically diagnosed with early childhood-onset type 1B diabetes. *Pediatr Diabetes, 20*(6), 712-719. doi: 10.1111/pedi.12868

Valentinova, Beer, Stanik, Tribble, van de Bunt, Huckova, Barrett, Klimes, Gasperikova, & Gloyn. (2012). Identification and functional characterisation of novel glucokinase mutations causing maturity-onset diabetes of the young in Slovakia. [Research Support, Non-U.S. Gov't]. *PLoS One, 7*(4), e34541. doi: 10.1371/journal.pone.0034541

Valero, Bannwarth, Roman, Paquis-Flucklinger, & Vialettes. (2008). Autosomal dominant transmission of diabetes and congenital hearing impairment secondary to a missense mutation in the WFS1 gene. *Diabet Med, 25*(6), 657-661. doi: 10.1111/j.1464-5491.2008.02448.x

Velho, Blanche, Vaxillaire, Bellanne-Chantelot, Pardini, Timsit, Passa, Deschamps, Robert, Weber, Marotta, Pilkis, Lipkind, Bell, & Froguel. (1997). Identification of 14 new glucokinase mutations and description of the clinical profile of 42 MODY-2 families. [Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, P.H.S.]. *Diabetologia, 40*(2), 217-224. doi: 10.1007/s001250050666

Velho, Vaxillaire, Boccio, Charpentier, & Froguel. (1996). Diabetes complications in NIDDM kindreds linked to the MODY3 locus on chromosome 12q. *Diabetes Care, 19*(9), 915-919. doi: 10.2337/diacare.19.9.915

Vermeulen, Weets, Asanghanwa, Ruige, Van Gaal, Mathieu, Keymeulen, Lampasona, Wenzlau, Hutton, Pipeleers, & Gorus. (2011). Contribution of antibodies against IA-2beta and zinc transporter 8 to classification of diabetes diagnosed under 40 years of age. [Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't]. *Diabetes Care, 34*(8), 1760-1765. doi: 10.2337/dc10-2268

Wang, Diao, Liu, Li, Zheng, Zhang, Yu, Zhang, Ping, & Xiao. (2019). Identification and functional analysis of GCK gene mutations in 12 Chinese families with hyperglycemia. *J Diabetes Investig, 10*(4), 963-971. doi: 10.1111/jdi.13001

Wang, Maechler, Hagenfeldt, & Wollheim. (1998). Dominant-negative suppression of HNF-1alpha function results in defective insulin gene transcription and impaired metabolism-secretion coupling in a pancreatic beta-cell line. [Research Support, Non-U.S. Gov't]. *EMBO J, 17*(22), 6701-6713. doi: 10.1093/emboj/17.22.6701

Wang, Wang, Yu, Zhang, Ping, Zhang, Xu, Feng, & Xiao. (2019). Screening of HNF1A and HNF4A mutation and clinical phenotype analysis in a large cohort of Chinese patients with maturity-onset diabetes of the young. *Acta Diabetol, 56*(3), 281-288. doi: 10.1007/s00592-018-1232-x

Wang, Zhao, Zhang, Yang, & Liu. (2017). A case of a novel mutation in HNF1beta-related maturity-onset diabetes of the young type 5 with diabetic kidney disease complication in a Chinese family. [Case Reports]. *J Diabetes Complications, 31*(7), 1243-1246. doi: 10.1016/j.jdiacomp.2016.11.011

Weinert, Silveiro, Giuffrida, Cunha, Bulcao, Calliari, Della Manna, Kunii, Dotto, Dias-da-Silva, & Reis. (2014). Three unreported glucokinase (GCK) missense mutations detected in the screening of thirty-two Brazilian kindreds for GCK and HNF1A-MODY. [Research Support, Non-U.S. Gov't]. *Diabetes Res Clin Pract, 106*(2), e44-48. doi: 10.1016/j.diabres.2014.08.006

Wentworth, Lukic, Bahlo, Finlay, Nguyen, Morahan, & Harrison. (2014). Maturity-onset diabetes of the young type 5 in a family with diabetes and mild kidney disease diagnosed by whole exome sequencing. [Case Reports

Research Support, Non-U.S. Gov't]. *Intern Med J, 44*(11), 1137-1140. doi: 10.1111/imj.12584

Wheeler, Patterson, Love, Prosser, Tomlinson, Taylor, & Manning. (2013). Frequency and genetic spectrum of maturity-onset diabetes of the young (MODY) in southern New Zealand. [Case Reports]. *J Diabetes Metab Disord, 12*(1), 46. doi: 10.1186/2251-6581-12-46

Willson, Godwin, Wiggins, Guilford, & McCall. (2013). Primary hepatocellular neoplasms in a MODY3 family with a novel HNF1A germline mutation. [Case Reports]. *J Hepatol, 59*(4), 904-907. doi: 10.1016/j.jhep.2013.05.024

Wolfram Syndrome.

Xiao, Liu, Xiao, Xie, Li, Zhou, Tang, Liu, & Zhou. (2019). Novel frameshift mutation in the insulin (INS) gene in a family with maturity onset diabetes of the young (MODY). [Case Reports]. *J Diabetes, 11*(1), 83-86. doi: 10.1111/1753-0407.12849

Xu, Dan, Chan, Wat, Tam, Tiu, Lee, Siu, Tsang, Fung, Chan, & Lam. (2005). Genetic and clinical characteristics of maturity-onset diabetes of the young in Chinese patients. [Comparative Study

Research Support, Non-U.S. Gov't]. *Eur J Hum Genet, 13*(4), 422-427. doi: 10.1038/sj.ejhg.5201347

Yaghootkar, Abbasi, Ghaemi, Rabbani, Wakeling, Eshraghi, Enayati, Vakili, Heidari, Patel, Sayarifard, Borhan-Dayani, McDonald, Ellard, Hattersley, Amoli, Vakili, & Colclough. (2019). Type 1 diabetes genetic risk score discriminates

between monogenic and Type 1 diabetes in children diagnosed at the age of <5 years in the Iranian population. [Research Support, Non-U.S. Gov't]. *Diabet Med, 36*(12), 1694-1702. doi: 10.1111/dme.14071

Yamada, Nishigori, Onda, Utsugi, Yanagawa, Maruyama, Onigata, Nagashima, Nagai, Morikawa, Takeuchi, & Takeda. (1997). Identification of mutations in the hepatocyte nuclear factor (HNF)-1 alpha gene in Japanese subjects with IDDM. [Research Support, Non-U.S. Gov't]. *Diabetes, 46*(10), 1643-1647. doi: 10.2337/diacare.46.10.1643

Yamagata, Oda, Kaisaki, Menzel, Furuta, Vaxillaire, Southam, Cox, Lathrop, Boriraj, Chen, Cox, Oda, Yano, Le Beau, Yamada, Nishigori, Takeda, Fajans, Hattersley, Iwasaki, Hansen, Pedersen, Polonsky, Bell, & et al. (1996). Mutations in the hepatocyte nuclear factor-1alpha gene in maturity-onset diabetes of the young (MODY3). [Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, P.H.S.]. *Nature, 384*(6608), 455-458. doi: 10.1038/384455a0

Yan, Jiang, Zhang, Xu, Zhou, Ren, Peng, Liu, Hu, & Jia. (2017). Whole-exome sequencing identifies a novel INS mutation causative of maturity-onset diabetes of the young 10. [Research Support, Non-U.S. Gov't]. *J Mol Cell Biol, 9*(5), 376-383. doi: 10.1093/jmcb/mjx039

Yang, Wu, Zheng, Lu, & Xiang. (2006). Identification of four novel mutations in the HNF-1A gene in Chinese early-onset and/or multiplex diabetes pedigrees. [Research Support, Non-U.S. Gov't]. *Chin Med J (Engl), 119*(13), 1072-1078.

Yellapu, Valasani, Pasupuleti, Gopal, Potukuchi Venkata Gurunadha Krishna, & Matcha. (2014). Identification and analysis of novel R308K mutation in glucokinase of type 2 diabetic patient and its kinetic correlation. [Research

Support, Non-U.S. Gov't]. *Biotechnol Appl Biochem, 61*(5), 572-581. doi: 10.1002/bab.1209

Yorifuji, Fujimaru, Hosokawa, Tamagawa, Shiozaki, Aizu, Jinno, Maruo, Nagasaka, Tajima, Kobayashi, & Urakami. (2012). Comprehensive molecular analysis of Japanese patients with pediatric-onset MODY-type diabetes mellitus. [Research Support, Non-U.S. Gov't]. *Pediatr Diabetes, 13*(1), 26-32. doi: 10.1111/j.1399-5448.2011.00827.x

Yorifuji, Higuchi, Kawakita, Hosokawa, Aoyama, Murakami, Kawae, Hatake, Nagasaka, & Tamagawa. (2018). Genetic basis of early-onset, maturity-onset diabetes of the young-like diabetes in Japan and features of patients without mutations in the major MODY genes: Dominance of maternal inheritance. [Research Support, Non-U.S. Gov't]. *Pediatr Diabetes, 19*(7), 1164-1172. doi: 10.1111/pedi.12714

Yorifuji, Kurokawa, Mamada, Imai, Kawai, Nishi, Shishido, Hasegawa, & Nakahata. (2004). Neonatal diabetes mellitus and neonatal polycystic, dysplastic kidneys: Phenotypically discordant recurrence of a mutation in the hepatocyte nuclear factor-1beta gene due to germline mosaicism. [Case Reports]. *J Clin Endocrinol Metab, 89*(6), 2905-2908. doi: 10.1210/jc.2003-031828

Yorifuji, Nagashima, Kurokawa, Kawai, Oishi, Akazawa, Hosokawa, Yamada, Inagaki, & Nakahata. (2005). The C42R mutation in the Kir6.2 (KCNJ11) gene as a cause of transient neonatal diabetes, childhood diabetes, or later-onset, apparently type 2 diabetes mellitus. [Case Reports]. *J Clin Endocrinol Metab, 90*(6), 3174-3178. doi: 10.1210/jc.2005-0096

Yuan, & Larsson. (2019). A causal relationship between cigarette smoking and type 2 diabetes mellitus: A Mendelian randomization study. *Sci Rep, 9*(1), 19342. doi: 10.1038/s41598-019-56014-9

Zafar, Bhatti, Akhtar, Rasheed, Bashir, Humayun, Waheed, Younus, Nazar, & Umaimato. (2011). Prevalence and risk factors for diabetes mellitus in a selected urban population of a city in Punjab. [Research Support, Non-U.S. Gov't]. *J Pak Med Assoc, 61*(1), 40-47.

Zafar, Nadeem, Khan, Jawad Abbasi, Aziz, & Saeed. (2016). Prevalence of diabetes and its correlates in urban population of Pakistan: A Cross-sectional survey. *J Pak Med Assoc, 66*(8), 922-927.

Zalloua, Azar, Delepine, Makhoul, Blanc, Sanyoura, Lavergne, Stankov, Lemainque, Baz, & Julier. (2008). WFS1 mutations are frequent monogenic causes of juvenile-onset diabetes mellitus in Lebanon. *Hum Mol Genet, 17*(24), 4012-4021. doi: 10.1093/hmg/ddn304

Zhang, Rawal, & Chong. (2016). Risk factors for gestational diabetes: is prevention possible? [Review

Research Support, N.I.H., Intramural]. *Diabetologia, 59*(7), 1385-1390. doi: 10.1007/s00125-016-3979-3

Zheng, Ley, & Hu. (2018). Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. [Research Support, Non-U.S. Gov't

Review]. *Nat Rev Endocrinol, 14*(2), 88-98. doi: 10.1038/nrendo.2017.151

Zhou, Wei, Guo, Zhu, Campbell, Li, Xu, Wang, Luan, Chen, & Chen. (2016). A Single Nucleotide Variant in HNF-1beta is Associated with Maturity-Onset Diabetes of the Young in a Large Chinese Family. *Iran J Public Health, 45*(2), 170-178.

Zhu, Yang, Sun, Zhang, & Li. (2015). Associations between INSR and MTOR polymorphisms in type 2 diabetes mellitus and diabetic nephropathy in a Northeast Chinese Han population. *Genet Mol Res, 14*(1), 1808-1818. doi: 10.4238/2015.March.13.9

Zubkova, Burumkulova, Plechanova, Petrukhin, Petrov, Vasilyev, Panov, Sorkina, Ulyatovskaya, Makretskaya, & Tiulpakov. (2019). High frequency of pathogenic and rare sequence variants in diabetes-related genes among Russian patients with diabetes in pregnancy. *Acta Diabetol, 56*(4), 413-420. doi: 10.1007/s00592-018-01282-6

Appendix V

Supplementary table 3:

Mutations retrieved from Clinvar that could not be identified in literature review:

S.No	DNA changes	Protein change	Accession number	Gene	Interpretation
1.	c.1253+2T>A		VCV000393449	GCK	Pathogenic
2.	c.1132G>A	p.Ala378Thr	VCV000016145	GCK	Pathogenic
3.	c.1031_1034dup	p.Lys346fs	VCV000802307	GCK	Pathogenic
4.	c.1016A>G	p.Glu339Gly	VCV000393450	GCK	Pathogenic
5.	c.1015G>A	p.Glu339Lys	VCV000039759	GCK	Pathogenic
6.	c.1003del	p.Val335fs	VCV000036166	GCK	Pathogenic
7.	c.944T>A	p.Leu315His	VCV000036266	GCK	Pathogenic
8.	c.941T>C	p.Leu314Pro	VCV000435305	GCK	Pathogenic
9.	c.835G>T	p.Glu279Ter	VCV000016132	GCK	Pathogenic
10.	c.793G>T	p.Glu265Ter	VCV000016139	GCK	Pathogenic
11.	c.781G>A	p.Gly261Arg	VCV000016135	GCK	Pathogenic
12.	c.775G>A	p.Ala259Thr	VCV000435302	GCK	Pathogenic
13.	c.683C>T	p.Thr228Met	VCV000016134	GCK	Pathogenic
14.	c.680-1G>A		VCV000393452	GCK	Pathogenic

S.No	DNA changes	Protein change	Accession number	Gene	Interpretation
15.	c.678_679+2del		VCV000435308	GCK	Pathogenic
16.	c.676G>A	p.Val226Met	VCV000036243	GCK	Pathogenic
17.	c.661G>A	p.Glu221Lys	VCV000036241	GCK	Pathogenic
18.	c.645C>G	p.Tyr215Ter	VCV000036238	GCK	Pathogenic
19.	c.571C>T	p.Arg191Trp	VCV000426122	GCK	Pathogenic
20.	c.449T>C	p.Phe150Ser	VCV000036218	GCK	Pathogenic
21.	c.391T>C	p.Ser131Pro	VCV000016138	GCK	Pathogenic
22.	c.317_333del	p.Gln106fs	VCV000211071	GCK	Pathogenic
23.	c.295del	p.Trp99fs	VCV000435304	GCK	Pathogenic
24.	c.291del	p.Gln98fs	VCV000590262	GCK	Pathogenic
25.	c.214G>A	p.Gly72Arg	VCV000036209	GCK	Pathogenic
26.	c.184G>A	p.Val62Met	VCV000419624	GCK	Pathogenic
27.	c.183C>A	p.Tyr61Ter	VCV000802309	GCK	Pathogenic
28.	c.148C>T	p.His50Tyr	VCV000631495	GCK	Pathogenic
29.	c.106C>T	p.Arg36Trp	VCV000431973	GCK	Pathogenic
30.	c.45+1G>T		VCV000619964	GCK	Pathogenic
31.	GCK, IVS4DS, 15-BP DEL		VCV000016137.1	GCK	Pathogenic
32.	c.130del	p.Leu44fs	VCV000036798	HNF1a	Pathogenic
33.	c.335C>T	p.Pro112Leu	VCV000014942	HNF1a	Pathogenic
34.	c.365A>G	p.Tyr122Cys	VCV000014930	HNF1a	Pathogenic

S.No	DNA changes	Protein change	Accession number	Gene	Interpretation
35.	c.476G>A	p.Arg159Gln	VCV000586792	HNF1a	Pathogenic
36.	c.694dup	p.Leu232fs	VCV000393456	HNF1a	Pathogenic
37.	c.714-1G>A		VCV000014941	HNF1a	Pathogenic
38.	c.815G>A	p.Arg272His	VCV000014931	HNF1a	Pathogenic
39.	c.864_897del	p.Pro290fs	VCV000585219	HNF1a	Pathogenic
40.	c.956-1G>C		VCV000617646	HNF1a	Pathogenic
41.	c.1328_1329CA	p.Gln444fs	VCV000617650	HNF1a	Pathogenic
42.	c.1359del	p.Ser454fs	VCV000435427.1	HNF1a	Pathogenic
43.	c.1592G>C	p.Ser531Thr	VCV000014947.1	HNF1a	Pathogenic
44.	c.1747C>G	p.Arg583Gly	VCV000014932	HNF1a	Pathogenic
45.	c.3039dup		VCV000438709	HNF1a	Pathogenic
46.	c.*2998G>A		VCV000014935	HNF1a	Pathogenic
47.	c.331C>T	p.Gln111Ter	VCV000009212	HNF1a	Pathogenic
48.	HNF1A, 2-BP DEL, AG		VCV000014946.1	HNF1a	Pathogenic
49.	HNF1A, 4-BP DEL		VCV000014944.1	HNF1a	Pathogenic
50.	HNF1A, 1-BP DEL, -119G, PROMOTER		VCV000014936.1	HNF1a	Pathogenic
51.	HNF1A, A-C, -58, PROMOTER		VCV000014933	HNF1a	Pathogenic

S.No	DNA changes	Protein change	Accession number	Gene	Interpretation
52.	HNF1A, 1-BP DEL		VCV000014929	HNF1a	Pathogenic
53.	c.253C>T	p.Arg85Trp	VCV000156152	HNF4a	Pathogenic
54.	c.331C>T	p.Gln111Ter	VCV000617653	HNF4a	Pathogenic
55.	c.487C>T	p.Arg163Ter	VCV000009211	HNF4a	Pathogenic
56.	c.493-1G>A		VCV000587398	HNF4a	Pathogenic
57.	c.648+1G>A		VCV000617652	HNF4a	Pathogenic
58.	c.649-2del		VCV000009215	HNF4a	Pathogenic
59.	c.829C>T	p.Gln277Ter	VCV000009210	HNF4a	Pathogenic
60.	c.1118T>G	p.Met373Arg	VCV000009216	HNF4a	Pathogenic
61.	HNF4A, 1-BP DEL, PHE75T		VCV000009214.1	HNF4a	Pathogenic
62.	c.137G>A	p.Arg46Gln	VCV000013391	INS	Pathogenic
63.	c.16C>T	p.Arg6Cys	VCV000013390	INS	Pathogenic
64.	c.533A>G	p.Glu178Gly	VCV000030124	PDX1	Pathogenic

S.No	DNA changes	Protein change	Accession number	Gene	Interpretation
65.	PDX1, 1-BP DEL,188C		VCV000008857.1	PDX1	Pathogenic
66.	c.309C>G	p.Arg103	VCV000218145	NEUROD1	Pathogenic
67.	c.772-1G>A		VCV000013794	PAX4	Pathogenic
68.	c.514C>T	p.Arg172Trp	VCV000013793.1	PAX4	Pathogenic
69.	c.*505G>T		VCV000059736	BLK	Pathogenic
70.	c.967dup	p.Asp323fs	VCV000478917	KCNJ11	Pathogenic
71.	c.124T>C	p.Cys42Arg	VCV000008676	KCNJ11	Pathogenic
72.	c.679G>A	p.Glu227Lys	VCV000158682	KCNJ11	Pathogenic
73.	c.1039G>T	p.Ala347Ser	VCV000006498	KLF11	Pathogenic
74.	CEL, 1-BP DEL, 1686T		VCV000017600.1	CEL	Pathogenic

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