

Maturity-onset Diabetes of the Young (MODY) Genes: Literature Review

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Abstract The aim of this article is to give brief introduction about MODY, its different types and to provide a review of the Genetic Screening and Linkage analysis techniques by analyzing the key properties and advance studies presented throughout the particular bibliography, how different MODY genes have been discovered in different populations. The full text articles related to almost all the MODY genes are downloaded. These papers are critically reviewed. The impact of diverse methodology, advantages and limitations of each of the techniques are described. This paper helps us to understand the potency and weak points of different techniques of Linkage analysis and Genetic Screening in argument by highlighting the strengths and weaknesses of these techniques.

Keywords MODY- Maturity-Onset Diabetes of the Young, DM-Diabetes Mellitus

1. Introduction

In humans, diseases are caused either by some microorganisms or due to some mutations in the chromosomes. The diseases which are caused by microorganisms are not inherited (except some viral diseases). But the diseases which are caused by the mutations at gene level are normally heritable and may become lethal. Genetic Disorders arise when one or both copies of a specific gene undergo an alteration known as mutation. Defective genes may also be inherited intact from the parents. Currently about 4,000 genetic disorders are known, with more being discovered.

MODY is the term that relies on the elderly classification of diabetes into juvenile-onset and maturity-onset diabetes. An etiology-based classification for diabetes has been revised and introduced by both the American Diabetes Association (ADA) and the World Health Organization (WHO). The group of "Genetic defect in B-cell function" has now included MODY as its part with its sub classification according to the gene involved Martine et al. (2008). Tattersall (U.K.) and Fajan (U.S.A.) first described MODY in 1974 Tattersal (1975), after taking into account a group of young people with diabetes who were treated without insulin 2 years or more after diagnosis. Since the 1970s there has been great interest in MODY as it is a genetic form of diabetes. MODY is an ancestral form of early-onset type2 diabetes. It is a monogenic form of diabetes mellitus

inherited in autosomal dominant mode (Anna, et al. (2001) and Owen, et al. (2001)). It is primarily an outcome of impaired B-Cells of pancreas (Anna, et al. (2001) and Owen, et al. (2001)). MODY is not a single entity but represents genetic, metabolic, and clinical heterogeneity Costa1, et al. (2000).

MODY generally develops in middle age, and mainly coupled with primarily scantiness of insulin secretion Vaxillaire, et al. (2006).

As MODY is a monogenic form of diabetes, most monogenic diabetes genes are fundamentally B-cell genes. A key outcome has been that the immense mass of genes where mutations cause early-onset diabetes have condensed B-cell function rather than improved insulin confrontation.

Till 2009 eight discrete MODY genes have been acknowledged Maciej, et al. (2009). These are the genes including HNF4A, encoding hepatocyte nuclear factor 4 Alpha Yamagata, et al. (1996), GCK, encoding glucokinase Froguel, et al. (1993), HNF1A, encoding hepatocyte nuclear factor 1 Alpha Yamagata, et al. (1996), IPF1, encoding insulin promoter factor 1 Stoffers, et al. (1997), HN F1B, encoding hepatocyte nuclear factor 1 Beta Horikawa, et al. (1997), NEUROD1, encoding neurogenic differentiation 1 Malecki, et al. (1999) and KLF11, encoding for kruppel-like factor 11 Neve, et al. (2005) and now four further genes have been exposed that cause MODY. These genes are PAX4, encoding, Paired Domain gene 4 (OMIM 612225), CEL, encoding carboxyl-ester lipase Raeder, et al. (2006), INS, encoding, Insulin (OMIM 176730) and BLK, encoding, Tyrosine kinase B-Lymphocyte. (OMIM 191305)

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2. Overview

Molecular genetic studies of MODY families have demonstrated that this clause is not a solo unit but is a clinically and hereditarily heterogeneous syndrome Martine, et al. (2008). Mutations, deletions, or other anomalies in at least eleven genes are a root for the bulk of the MODY cases R.Pearson, et al. (2006). These MODY genes encode the enzymes glucokinase (GCK (MODY 2)) that is liable for the early processing of glucose in the B-cell (Doria, et al. (2000) and Sung, et al. (2004)) and copious transcription factors that modulate the expression of numerous genes concerned with the demarcation and utility of B-cells (Doria, et al. (2000) and Sung, et al. (2004)).

The first MODY gene to be documented was glucokinase (GCK) Froguel, et al. (1992) and Hattersley, et al. (1992), followed by hepatocyte nuclear factors HNF1A (TCF1), HNF4A Yamagata, et al. (1996) and others.

The table 1 shows the genetic cataloging and detached phenotypes of the MODY subtypes.

3. Different Subtypes of Mody

HNF4A SUBTYPE (OMIM 125850)

MODY type 1 is caused by mutation in Hepatocyte Nuclear Factor 4 alpha (HNF4A) gene. This gene is also known as NR2A1 (nuclear receptor subfamily 2, group A, member 1). It is a nuclear receptor encoded by HNF4A gene

(Chartier, et al. (1994) and Argyrokastritis, et al. (1997)). This gene is located on chromosome 20. HNF4A is responsible for the regulation of hepatic and pancreatic β cell gene expression (Sladek, et al. (1990) and Kuo, et al. (1992)). Heterozygous mutation in human HNF4A gene results in progressive decrease in insulin production Yamagata, et al. (1996).

Heterozygous mutations in HNF4A are considered a rare source of MODY compared with MODY2/ GCK and MODY3/HNF1A mutations (Matschinsky (2005) and Pearson, et al. (2005). HNF4-A belongs to the steroid/thyroid hormone receptor super family. This gene plays a role in development of the liver, kidney, and intestines. HNF4A mutations are associated with an increase in birth weight and macrosomia and thus can be viewed as a novel cause of neonatal hypoglycemia Pearson, et al. (2007).

GCK SUBTYPE (OMIM 125851)

Glucokinase (GCK) is also called hexokinase IV or D. Heterozygous mutations of the glucokinase gene (GCK) result in MODY type 2 Froguel, et al. (1994). This gene maps to chromosome 7. It is the most common form of MODY Matschinsky, et al. (1990). Unlike other MODY subtypes, the pathophysiology involves impaired glucose sensing by the pancreatic β cells, resulting in mild non-progressive hyperglycemia (5.5 – 8 m mol/L) that is often asymptomatic Ohn, et al. (2009).

Table 1. Genetic classification and clinical phenotypes of the MODY subtypes.

Type	Gene Name	OMIM	Locus	Gene Function	Primary defect
MODY 1	Hepatocyte nuclear factor 4 α (HNF4A)	125850	20q	Transcription factor (Nuclear factor)	Pancreas
MODY 2	Glucokinase (GCK)	125851	7p15-p13	Hexokinase IV	Pancreas/Liver
MODY 3	Hepatocyte nuclear factor 1 α (HNF1A)	600496	12q24.2	Transcription factor (Homeodomain)	Pancreas/Kidney
MODY 4	Insulin promoter factor-1 (IPF-1)	606392	13q12.1	Transcription factor (Homeodomain)	Pancreas
MODY 5	Hepatocyte nuclear factor 1 β (HNF1B)	137920	17q12	Transcription factor (Homeodomain)	Kidney/Pancreas
MODY 6	Neurogenic differentiation 1 (NEUROD1)	606394	2q	Transcription factor(bHLH)	Pancreas
MODY 7	Kruppel-like factor 11 (KLF11)	610508	2p25	Transforming Growth Factor-Beta-Inducible-early Growth response 2.	Pancreas
MODY 8	Bile salt dependent lipase (CELL)	609812	9q34.3	The endocrine cells of pancreas synthesize insulin and are involved in the pathogenesis of diabetes mellitus and exocrine cells are involved in the pathogenesis of pancreatic malabsorption.	Pancreas
MODY 9	Paired Domain gene 4 (PAX4)	612225	7q32	Transcription Factor (Paired Domain gene 4)	Pancreas
MODY 10	Insulin (INS)	176730	11p15.5.	Beta cells of the islets of Langerhans	NF-kappa-B
MODY 11	Tyrosine kinase, B-Lymphocyte specific	191305	8p23-p22	Tyrosine kinase (B lymphocytes)	MIN6 beta cells

GCK acts as a candidate gene in MODY patients and families, more than 150 different mutations have been shown to cause MODY2 Fajans, et al. (2001). Compared with other subtypes of MODY, a lower prevalence of microvascular complications (retinopathy and proteinuria) was observed in MODY2 diabetic patients (Vaxillaire and Froguel (2006)). GCK mutations in the fetus, result in reduced birth weight, probably by affecting insulin-mediated fetal growth, whereas maternal GCK mutations indirectly increase the birth weight by enhancing fetal insulin secretion as a consequence of maternal hyperglycemia during fetal life (Hattersley, et al. (1998) and Velho, et al. (2000)).

HNF1A/TCF1 SUBTYPE (OMIM 600496)

Hepatocyte Nuclear Factor 1 alpha gene (HNF1A) accounts for a great part of the MODY type 3. This gene is located on chromosome 12 Velho, et al. (1996). This gene is linked to a defect in the nuclear transcription factors. Patients with HNF1A mutations develop diabetes after the first decade, and it is preceded by abnormal glucose-induced insulin secretion Stride, et al. (2005). Like type 1 MODY, it is also characterized by a progressive reduction in insulin secretion. This may require insulin and develop vascular complications for over time patients Velho, et al. (1996).

The penetrance of MODY 3 is high, although it is dependent on age, so that the probability of being diagnosed with diabetes increases steadily between 10 and 40 yr of age (Pearson, et al. (2001) and Matschinsky (2005)). MODY3 is a more severe form of diabetes, often evolving toward insulin dependency, and microvascular complications of diabetes are observed in MODY3 as in later onset diabetes (Vaxillaire and Froguel (2006)).

IPF1/PDX1 SUBTYPE (OMIM 606392)

PDX1 gene (Pancreatic and duodenal homeobox 1) is also known as insulin promoter factor 1 (IPF1). It is a transcription factor necessary for pancreatic development and β -cell maturation. Insulin Promoter Factor 1 (IPF1) is an orphan homeodomain protein and has been described as a master switch for both endocrine and exocrine function of pancreas. MODY Type 4 is caused by mutation in IPF1 gene present on chromosome 13 (Stoffers, et al. (1997) and Maestro, et al. (2007)).

PDX1 acts as a major transcriptional regulator of endocrine pancreas-specific genes in adults, such as the preproinsulin, glucose transporter-2 and GCK genes in B-cells, and the somatostatin gene in B-cells Martine, et al. (2008).

TCF2/HNF1B SUBTYPE (OMIM 137920)

MODY Type 5 is caused by mutation in Hepatocyte nuclear factor 1 beta (HNF1B) gene located on chromosome 17. It is a rare form of MODY that is associated with kidney disease. Hnf-1B plays a major role in kidney development and nephron differentiation and is also a critical regulator of a transcriptional network that controls the specification, growth, and differentiation of the embryonic pancreas (Haumaitre, et al. (2005) and Lindner, et al. (1999)).

Mutations in TCF2/HNF-1B are responsible for severe kidney disease, which may appear before the impairment of glucose tolerance Chantelot, et al. (2004). This has been recognized as a discrete clinical syndrome, called RCAD (renal cysts and diabetes syndrome) (Chantelot, et al. (2004) and Poulin, et al. (1997)).

NEUROD1 SUBTYPE (OMIM 606394)

Neurogenic Differentiation factor 1 (NEUROD1) is also called β 2 Naya, et al. (1997). It is a transcription factor of the NeuroD-type and encoded by the human gene NEUROD1. It is a member of the NeuroD family of basic-helix-loop-helix (bHLH) transcription factors and plays an important role in the development of the pancreas and the nervous system Martine, et al. (2008). Mutation in transcription factor NEUROD1 results in MODY6 Fajans, et al. (2001).

This gene is involved in neuronal differentiation and development of pancreas morphology Naya, et al. (1997).

KLF11 SUBTYPE (OMIM 610508)

Krueppel-like factor 11 is a protein that in humans is encoded by the KLF11 gene (Cook, et al. (1998) and Scohy, et al. 2001)). MODY7 is caused by mutations in the KLF11 gene. This gene maps to chromosome 2. KLF 11 regulates exocrine cells growth and behaves like a tumour suppressor for pancreatic malignancy Neve, et al. (2005).

CEL SUBTYPE (OMIM 609812)

Carboxyl-ester lipase gene (CEL) gene controls both exocrine and endocrine function of the pancreas. MODY8 is caused by mutation in CEL gene on chromosome 9. It is caused by frameshift deletions in the variable number of tandem repeats (VNTR) of the carboxyl-ester lipase gene.

PAX4 SUBTYPE (OMIM 612225)

Paired box gene 4 is also known as PAX4. It is a protein which in humans is encoded by the PAX4 gene (Matsushita, et al. (1998) and Inoue, et al. (1998)). MODY9 is caused by mutations in the PAX4 gene. This gene is located on chromosome 7. This gene is a member of the paired box (PAX) family of transcription factors. Members of this gene family typically contain a paired box domain, an octapeptide, and a paired-type homeodomain. These genes play critical roles during fetal development and cancer growth. The paired box gene 4 is involved in pancreatic islet development.

INS SUBTYPE (OMIM 176730)

Insulin is a hormone that is central to regulating energy and glucose metabolism in the body. Insulin causes cells in the liver, muscle, and fat tissue to take up glucose from the blood, storing it as glycogen in the liver and muscle. The proinsulin precursor of insulin is encoded by the INS gene Bell, et al. (1980).

MODY type 10 is caused by mutation in INS (PROINSULIN) gene. This gene is located on chromosome 11p15.5. It primarily defects NF-kappa-B Dandona, et al. (2001).

BLK SUBTYPE (OMIM 191305)

Tyrosine-protein kinase BLK is also known as B lymphocyte kinase. It is an enzyme that in humans is encoded by the BLK gene Drebin, et al. (1995). MODY type 11 is caused by mutation in BLK gene. This gene maps on chromosome 8p23-p22. It primarily defects MIN6 beta cells. This gene is a member of the SRC family of protooncogenes and on the basis of its preferential expression in B-lymphoid cells, it is concluded that it functions in a signal transducing pathway specific to this lineage Dymecki, et al. (1990).

The true relative prevalence of the eleven distinct MODY subtypes is unknown and varies substantially in different populations. The table below shows the distribution or prevalence of eleven subtypes of MODY.

Table 2. Distribution or prevalence of eleven MODY subtypes

MODY Subtype	Prevalence	Reference
MODY1	2-5%	Pruhova, et al. (2003)
MODY2	7-41%	Barrio, et al. (2002)
MODY3	11-63%	Pruhova, et al. (2003)
MODY4	2%	McCarthy, et al. (2008)
MODY5	2%	Mark, et al. (2008)
MODY6	1%	McCarthy, et al. (2008)
MODY7		
MODY8		
MODY9		
MODY10		
MODY11		

4. Literature Review

Genetic studies are contributing much in establishing the linkage association for genetic disorders and have been employed widely in identification of diseased genes. Different types of MODY have been discovered in European populations but still MODY is misdiagnosed as T2DM. MODY genes are named as MODY 1 to MODY 11 according to the year they have recognized in MODY patients. The table below shows the eleven subtypes of MODY, their gene name and the year they were recognized.

The primary objective of this chapter is to review the literature on the methodologies of the planned research area. This chapter will aid to gain background knowledge of the proposed research topic. It will confer the work that has been done up till now related to genetic screening and linkage analysis by different scientists/biologists. A thorough survey on preprocessing methodologies will facilitate us to not only compare and contrast the previous work but also with the proposed work. We will find out the problems in the area of interest that have already been investigated. Further, we will identify the potential sources of information for conducting

the detailed research on proposed work.

Table 3. Eleven MODY subtypes and year of recognition

MODY SUBTYPES (Year)	GENE NAME
MODY1 (1991)	HNF-4a
MODY2 (1993)	Glucokinase
MODY3 (1996)	HNF-1a
MODY4 (1997)	IPF-1 (PDX-1)
MODY5 (1997)	HNF-1b
MODY6 (1999)	Neuro-D1 / BETA-2
MODY7 (2005)	KLF11
MODY8 (2006)	CEL
MODY9 (OMIM 61225)	PAX4
MODY10 (OMM 176730)	INS
MODY11 (OMM 191350)	BLK

4.1. Review of Linkage Analysis/Genetic Screening Methodologies

Although there has been significant amount of research in the area of Diabetes and particularly on Maturity-onset diabetes of the young. But the work that is most related to the current research study with respect to methodologies is as follows:

Fajans (1989) performed the linkage analysis of a family that consists of 360 members spanning 6 generations and 74 members with diabetes, including those with MODY. This family had been studied prospectively since 1958. Linkage studies showed that the gene responsible for MODY in this family is tightly linked to 20q12-q13.1. This gene that maps to this chromosome is known as HNF1A. However, Fajans did not screen the HNF1A for detection of new mutation.

Similarly Froguel, (1992) also did linkage analysis on 16 French families with maturity-onset diabetes of the young and found that the linkage of the disease with GCK. There was statistically significant evidence of genetic heterogeneity, with an estimated 45 to 95% of the 16 families showing linkage to glucokinase. Because glucokinase is a key enzyme of blood glucose homeostasis, the results suggested a pathogenetic connection.

The demonstration by Fajans (1989), that the gene for HNF1A is the site of mutations causing MODY3 prompted Yamagata, et al. (1996) to screen the gene for HNF4A for a mutation. Yamagata, et al. (1996) verified a gln268-to-ter mutation in the gene encoding hepatocyte nuclear factor-4-alpha in a multigenerational family, in which type I maturity-onset diabetes of the young was first defined. HNF-4-alpha is most highly expressed in liver, kidney, and intestine. It is also expressed in pancreatic islets and insulinoma cells. It is a key regulator of hepatic gene expression and is a major activator of HNF-1-alpha (TCF1), which in turn activates the expression of a large number of liver-specific genes, including those involved in glucose, cholesterol, and fatty acid metabolism. This shows that these genes are somehow linked to each other. This association of genes will be determined through association rule mining techniques.

Vixillaire, et al., (1997) examined 10 unrelated Caucasian families in whom MODY cosegregated with markers for

MODY3 and found 10 different mutations in the TCF1 gene, all of which cosegregated with diabetes. In these families, they found no obvious relationships between the nature of the mutations observed (i.e., frame shift, nonsense, or missense), or their location in the gene, with clinical features of diabetes (e.g., age at onset, severity). Vixillaire research is limited to only affected members of MODY. He did not study the normal member to differentiate the wild and mutant genes in these families.

Costa, et al. (2000) investigate the frequencies of the major MODY subtypes in a panel of Spanish families. They also assessed the phenotypic difference in patients with different MODY subtypes. He concluded that mutations in MODY2 (GCK) and MODY 3 (HNF1A) genes contribute much in causing MODY in majority of the cases of Spanish MODY families. They wind up the results with the knowledge that the relative frequencies of MODY genes are in agreement with already reported prevalence of these genes in European populations.

Hansen, et al. (2000) examined 200 Danish patients with late-onset type II diabetes and 44 Danish and Italian MODY patients for mutations in the IPF1 gene by SSCP and heteroduplex analysis. In the patients with late-onset type II diabetes, they identified a noncoding G insertion/deletion polymorphism at nucleotide -108, a silent gly54-to-gly substitution, and the rare D76N variant. Moreover, a Danish MODY patient carried an ala140-to-thr (A140T) variant. Neither the D76N nor the A140T variant segregated with diabetes, and their transcriptional activation of the human insulin promoter expressed *in vitro* was indistinguishable from that of wild type.

Johansen, et al. (2005) examined the prevalence and nature of mutations in the 3 common MODY genes HNF4A, GCK, and TCF1 (HNF1A) through genetic screening in Danish patients with a clinical diagnosis of MODY and determined metabolic differences in probands with and without mutations in HNF4A, GCK, and TCF1. They identified 29 different mutations in 38 MODY families. Their findings suggested a relative prevalence of 3% of MODY1 (2 different mutations in 2 families), 10% of MODY2 (7 in 8), and 36% of MODY3 (21 in 28) among Danish kindred clinically diagnosed as MODY.

Pinterove, et al. (2007) screened the GCK gene that was known to cause MODY 2 in Froguel (1992). He examined the 92 Czech probands fulfilling classic MODY criteria and identified 15 different missense mutations in 27 (29%) patients; the mutations were not found in 50 unrelated healthy Czech individuals. Pinterove, et al. (2007) concluded that mutations in GCK are a common cause of MODY in the Czech population.

Pakistan is a developing country and not free from health burden threatened by MODY. It is even more difficult to diagnose and classify MODY in the country as no genetic research has been done so far. The prospective basis of above mentioned work done on linkage analysis and genetic screening of MODY will help us to conduct detailed research on linkage analysis and genetic screening of MODY in Pakistani population.

The summary of the methodologies adopted by different researchers that did examination on MODY patients and their experimental results are briefly shown in the table 4:

Table 4. Summary of Preprocessing Methodologies of linkage analysis and Genetic screening

Authors	Genes concerned	Methodology	Experimental results
Fajans et al., [1]	All 11 reported MODY genes.	Linkage analysis	Linkage studies showed that the gene responsible for MODY in the examined family is tightly linked to HNF1-Alpha.
Froguel et al., [2]	Linkage with all MODY genes.	Linkage analysis	Found linkage of the MODY disease with GCK gene.
Yamagata et al., [3]	HNF4-Alpha	Genetic screening	Demonstrate a gln268-to-ter mutation in the gene encoding HNF4-Alpha.
Vixillaire et al., [4]	TCF1 gene	Linkage analysis using micro satellite markers for TCF1 gene	Found 10 different mutations in the TCF1 gene and found
Hansen et al., [5]	IPF1 gene	Genetic screening using SSCP and heteroduplex analysis	Identified a noncoding G insertion/deletion polymorphism at nucleotide -108, a silent gly54-to-gly substitution, and the rare D76N variant in Late-onset type II diabetes patients and an ala140-to-thr mutation in IPF1 gene in MODY patients.
Costa et al., [6]	Major MODY genes that are involved MODY1, MODY2, MODY3 and MODY4	Screening for mutations in MODY genes and statistical analysis	Found that the prevalence of MODY genes is same as previously reported and that GCK and HNF1-Alpha genes account for the majority of cases in Spanish families diagnosed with MODY.
Johansen et al., [7]	HNF4-Alpha, GCK and TCF1	Genetic screening	Identified 29 different mutations in 38 MODY families. Also suggest a relative prevalence of 3% of MODY1, 10% of MODY2 and 36% of MODY3.
Pinterove et al., [8]	GCK gene	Screening of GCK gene	Identified 15 different missense mutations in 29% patients of 92 Czech probands.

6. Discussion

In this chapter we have discussed the work that has been done so far in the context of genetic screening and association extraction. Till now eleven genes contributing to MODY have been discovered in European population. These genes have been screened and linked in different populations by different scientists and researchers to find out new diseased gene location on chromosomal loci.

7. Summary

This section describes the key points of this review article.

i. This article is a literature review of Genetic screening and linkage analysis of MODY genes, an application of Bioinformatics, for the discovery of new diseased genes and mutations.

ii. This article will help the researchers and scientists to carry out research in this context to detect new genes in different populations.

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Both the authors contributed equally in this review article.

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