Monogenic Forms of Diabetes Mellitus and Maturity Onset Diabetes of Young (MODY)

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V Mohan, Ami Ritesh Sanghvi

CHAPTER OUTLINE

INTRODUCTION

In the etiology of type 2 diabetes mellitus, both genetic and environmental factors play a role. The inheritance of classic type 2 diabetes is now known to be polygenic with multiple genes located on several chromosomes. There is also evidence for gene-gene interactions and gene-environmental interactions which makes study of its genetics extremely complex. In contrast, there are some monogenic forms of diabetes where the inheritance is fairly straightforward and this chapter reviews these forms of diabetes.

DEFINITION OF MONOGENIC FORMS OF DIABETES

There are types of diabetes which are characterised by single gene defects. Although they are collectively known as monogenic form of diabetes, there are several subtypes described in the literature and Table 1 lists some of these types. The most well-known monogenic form of diabetes is Maturity Onset Diabetes of Young (MODY) and this will be considered in detail first while the other monogenic forms of diabetes will be briefly discussed later.

MATURITY ONSET DIABETES OF YOUNG (MODY)

The term Maturity Onset Diabetes of Young (MODY) was first introduced by Tattersall and Fajans[1] in their classic report published in 1975 to denote a unique non insulin dependent form of juvenile onset diabetes. However, forms of juvenile onset diabetes that differ from what is recognized today as type 1 or insulin dependent diabetes mellitus have been recognized since the pre-insulin era, when Joslin first

Table 1. Sub-types of Monogenic Forms of Diabetes

1. Maturity Onset Diabetes of Young (MODY)
2. Maternally Inherited Diabetes and Deafness (MIDD) Ballinger Wallace syndrome
3. Myopathy Encephalopathy, Lactic Acidosis and Stroke like Episodes (MELAS)
4. Wolfram Syndrome
5. Friedreich's Ataxia
6. Paerson Marrow Pancreas Syndrome
7. Kearns Sayre syndrome
8. Rotig Syndrome
9. Myoclonus Epilepsy with Ragged Red Fibres (MERRF)
10. Others: 40 other mutations in the insulin receptor gene have been described but they are all rare.

reported on the features of four patients who were diagnosed with diabetes in their teens but survived for many years without insulin therapy.[2] Tattersall[3] has recently reviewed the history of non insulin dependent forms of juvenile diabetes, whose glucose metabolism was normalized with sulphonylureas. This chapter will deal with the current status of MODY worldwide and specifically highlight the published studies on MODY in India.

DEFINITION OF MODY

Tattersall and Fajans[1] first laid down the diagnostic criteria for MODY as follows:

1. Onset of diabetes below 25 years of age.
2. Absence of ketosis
3. Control of diabetes without insulin for atleast 2 (later modified to 5) years after diagnosis.
4. Autosomal dominant inheritance including vertical transmission of diabetes through at least three generations.

DISTRIBUTION AND PREVALENCE

Families with MODY have been reported from several countries including United Kingdom[4], Denmark[5], France[6] and Germany.[7] A recent PubMed search on MODY carried out by us showed that there are atleast 68 published references on MODY. However, it was Fajans from Michigan, Ann Arbor in USA who has contributed extensively to studies on MODY[8-10] and can truly be called as the "Father of MODY".

In the 1980s, it was realized that if the original definition of MODY was used, the prevalence of this condition was more common in some ethnic groups like Asian Indians.[11-13] Mohan et al[11] found that 4.8% of all type 2 diabetic patients seen at a tertiary diabetes centre at Chennai (formerly Madras) had age at diagnosis below 25 years. When he classified these patients based on family history, there were three subgroups: 27% of had definite autosomal dominant inheritance including three generation transmission

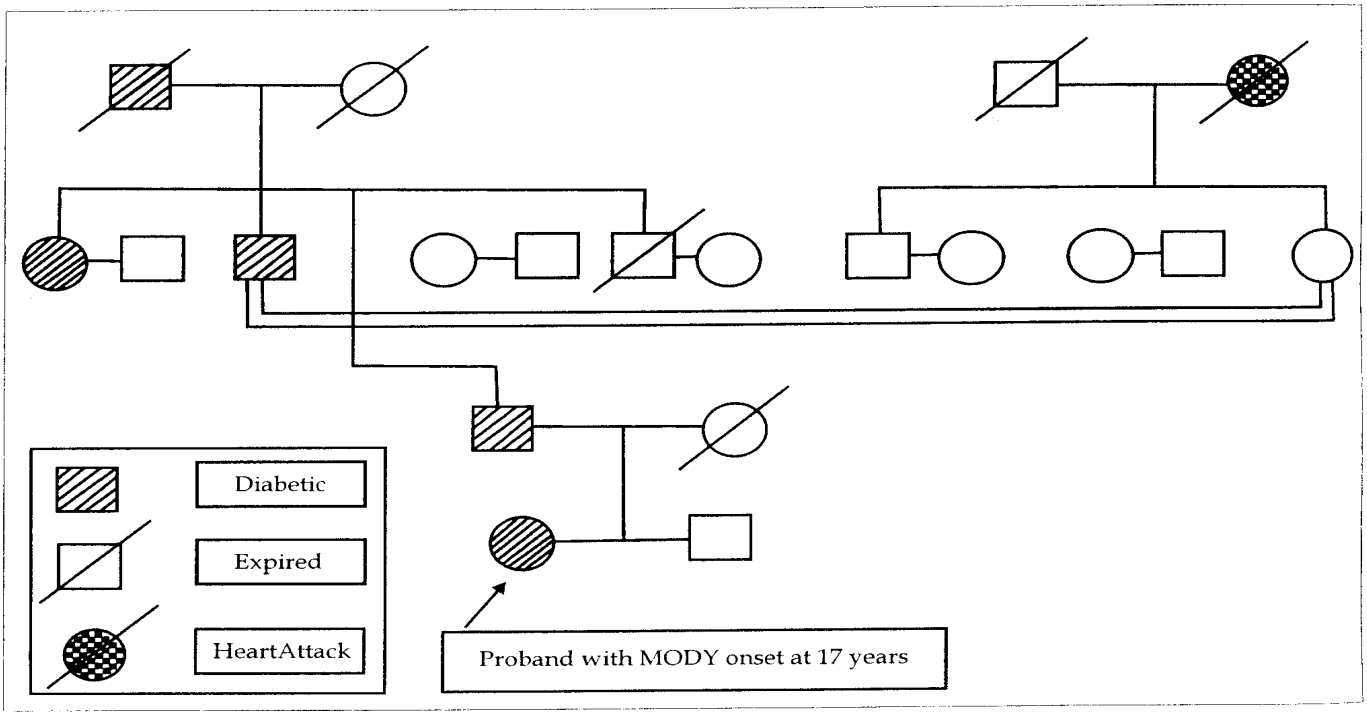

Fig. 1. The pedigree of a typical MODY patient seen at our centre

of diabetes and could be called MODY; in another 53%, the mode of inheritance was probably autosomal dominant as one of the parents had diabetes while there was no history of diabetes in grand parents although it is possible that some of them could have had diabetes but had not known about it as they had not been tested. In the remaining 20% of patients, there was no known family history of diabetes although the fact again remains that if the parents and grand parents had been tested, some of them could have had diabetes. Another problem is that due to the well-known phenomenon of "anticipation", people in subsequent generations develop diabetes earlier and thus we often find the proband presenting with MODY and only a few years later the parents test positive for diabetes. However, on follow-up some of these "sporadic" cases ultimately turned out to behave like type 1 diabetes and hence it is possible that they had Latent Autosomal Diabetes of Adult (LADA) type diabetes. The thumb rule therefore is to diagnose type 2 diabetes or MODY in a youth onset patient only if atleast one of the parents has diabetes. In Jialal's series from South Africa[13], an age of onset below 35 years was used and he called these patients as Non-Insulin Dependent Diabetes of Youth (or NIDDY) and hence the prevalence figures quoted by him are strictly not comparable with other series of MODY. Finally, clinic based figures are subject to referral biases and hence the prevalence figures quoted above do not have much significance. There are virtually no population based figures on the prevalence of MODY in developing countries and such studies are urgently needed. Figure 1 shows the pedigree of a typical MODY patient from our centre.

MODY has to be distinguished from another subgroup of type 2 diabetes mellitus called 'Early Onset type 2 diabetes' described by O'Rahilly et al[14] which usually appears in the age group of 25-40 years. They differ genetically from MODY and are characterized by a very high prevalence of diabetes and glucose intolerance in both the parents (92%) and among siblings (69%). This suggests that these subjects may inherit a diabetic gene or genes from both parents compatible with a "double gene" dose. Table 2 shows the distinguishing features between MODY and early onset type 2 diabetes.

Table 2. Distinguishing Clinical Characteristics of MODY and Early Onset Type 2 Diabetes

Characteristics	MODY	Early Onset Type 2 diabetes
Mode of inheritance	Monogenic, autosomal dominant	Polygenic (gene-gene and gene-environment interactions)
Age at onset	Childhood, adolescence, or young adulthood (usually <25 yr) Peak: 15-20yrs	Early adulthood (usually 25-40yr), occasionally adolescence (if person in obese)
Penetrance	80 – 95 %	Variable (possible 10-40%)
Pedigree	Usually multigenerational	Rarely multigenerational
Percentage of parents abnormal	50%	>90%
Percentage of siblings abnormal	50%	68%
Body Habitus	Usually non obese	Usually obese
Metabolic syndrome (diabetes, insulin resistance, hypertension, hypertriglyceridemia)	Usually absent	Usually present
Clinical course	Slow Progression	Progressive

PATHOGENESIS OF MODY

The pathogenesis of MODY shows some differences from that of the common garden variety type 2 DM. Patients with MODY show reduced secretion of insulin in response to an oral glucose load[15] but hyperinsulinemia has been described in a few families.[16] Fajans et al[16] reported that the insulin response declines with increasing duration of diabetes. Insulin resistance was assessed by Mohan et al[17] using euglycemic clamp studies, in matched groups of MODY, classical type 2 DM and non-diabetic control subjects. The results indicated that despite their younger age, patients with MODY were more insulin resistant than the patients with classical type 2 DM.

GENETICS OF MODY

After the early clinical description by Tattersall and Fajans, MODY was largely ignored, forgotten or at best considered as a rare academic curiosity. In fact,

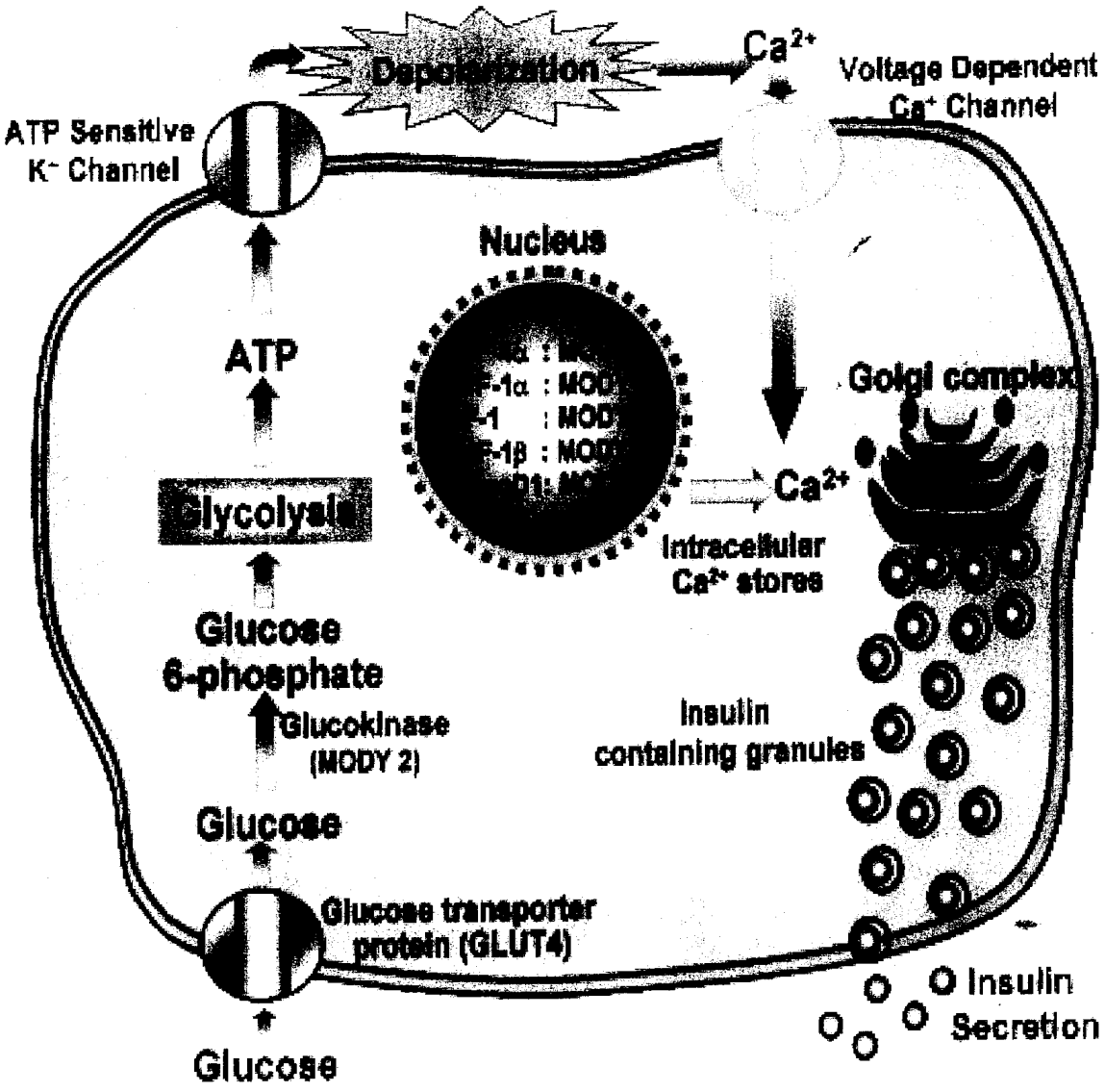

Fig. 2. Pathogenesis of different types of MODY showing site for the gene defects

Table 3. Clinical Phenotypes associated with Various MODY Subtypes

MODY Type	Gene and Chromosomal region	Clinical features of Heterozygous state	Molecular Basis	Treatment	Clinical features of Homozygous state
MODY 1	HNF – 4α 20q 12q 13	Diabetes, macrovascular complications (in many cases), reductions in serum concentration of triglycerides, apolipoproteins AII and CIII and Lp (α)	Abnormal regulation of gene transcription in beta cells, leading to a defect in metabolic signalling of insulin secretion, beta cell mass or both	Oral hypoglycemic agents, insulin	
MODY 2	Glucokinase 7p 15	Impaired fasting glucose, impaired glucose tolerance, mild diabetes, normal proinsulin to insulin ratio in serum	Defect in sensitivity of beta cells to glucose due to reduced glucose phosphorylation; defect in hepatic storage of glucose as glycogen	Diet and exercise	Permanent neonatal diabetes, requiring insulin treatment
MODY 3	HNF – 1α 12q24	Diabetes, microvascular complications (in many cases), renal glycosuria, increased sensitivity to sulphonylurea drugs, increased proinsulin to insulin ratio in serum	Abnormal regulation of gene transcription in beta cells, leading to a defect in metabolic signalling of insulin secretion, beta cell mass, or both	Oral hypoglycemic agents, insulin	
MODY 4	IPF-1 13q 12	Diabetes	Abnormal transcriptional regulation of beta cell development and function	Oral hypoglycemic agents, insulin	Pancreatic agenesis and neonatal diabetes, requiring insulin treatment
MODY 5	HNF – 1β 17q 12q 21	Diabetes, renal cysts and other abnormalities of renal development; progressive non-diabetic renal dysfunction, leading to chronic renal insufficiency and failure; internal genital abnormalities (in female carriers)	Abnormal transcriptional regulation of beta cell, leading to it in metabolic signalling of insulin secretion, beta cell . mass or both	Insulin	
MODY 6	Neuro D1 or BETA 2 2q 32	Diabetes	Abnormal transcriptional regulation of beta cell development and function	Insulin	

many textbooks and classifications of diabetes even dropped MODY completely. However, when the first gene for MODY was discovered[18], there was a resurgence of interest in the field. Indeed, finding the gene mutation in this disorder, provided new insights into the physiology of glucose homeostasis itself. Till date, six distinct MODY subtype have been identified based on specific gene defects and all are monogenic forms of diabetes. These genes are Glucokinase (GK), Hepatocyte nuclear factor (HNF 1α, HNF-4 α and HNF-1β), insulin promoter factor (IPF1) and NEURO D1/Beta 2. GK is an enzyme responsible for glucose phosphorylation whereas HNF-1α, IPF1, HNF-1β and Neuro D1 are all transcription factors. All these genes are expressed in the beta cell. Figure 2 shows the location of the gene defects within the beta cell. Two of these genes (GK and HNF-1α) account for the majority of cases (upto 70-80% of all MODY cases), whereas mutations of the other four genes are quite rare.

CLINICAL FEATURES OF MODY SUBTYPES

Glucokinase MODY (MODY 2)

Mutations in the glucokinase gene cause a rather mild form of diabetes. Hyperglycemia is often diagnosed during childhood, but fasting blood glucose values do not usually exceed 130 mg%. Most patients have impaired glucose tolerance rather than overt diabetes.[18] Accordingly, fasting insulin values are usually normal, but insulin secretion cannot be sustained during a prolonged hyperglycemic stimulus. Many individuals have good glycemic control without the need for insulin or oral agents and the occurrence of diabetic complications is rare.[19]

Transcription factor MODY (MODY 1, 3 and 5)

Diabetes associated with mutations in HNF-1α, HNF-4α and HNF-1β is generally more severe. About 60 to 70% of mutation carriers are diagnosed with diabetes before age 25 and the rest between ages 25 and 60. A small proportion of them may remain free of diabetes for their whole life (non-penetrants). The insulin response to a glucose load is severely impaired and peak insulin levels rarely exceed 20-30μU/ml.[20] About 50% of patients need insulin therapy.[21] Diabetic complications are common in this type of MODY. MODY-5 (HNF-1β) is often associated with renal abnormalities.

Insulin promotor factor (MODY 4)

This form of MODY is rare and very few families have been described in the world. In IPF1 mutation, the diabetes is milder and is diagnosed at a slightly older age than MODY due to HNF mutations.

Neuro D1 (MODY 6)

Of the two families of NEURO D1 mutations described in the literature, one has a phenotype resembling that of MODY due to HNF-1α mutations, while the other phenotype was similar to type 2 diabetes. Table 3 summarizes the MODY related genes and the clinical phenotypes associated with various mutations.

DO MUTATIONS IN MODY GENES AFFECT OTHER TISSUES BESIDES β CELLS?

With the exception of IPF-1, all MODY genes are expressed in other tissues beside the pancreas. Glucokinase is expressed in the liver; HNF-1α and HNF-4α in the liver, kidney, stomach and intestine. HNF-1β is also expressed in lung, ovary and NEURO D1 in the brain, lung and eye. In the case of HNF-1α mutations, the main extrapancreatic abnormality appears to be a lowering of the renal threshold for glucose and other proximal tubular defects (eg. aminoaciduria).[22-24] HNF-4 α mutations are associated with mild abnormalities of hepatic origin such as decreased levels of circulating apolipoproteins and triglycerides. The manifestation of renal dysfunction are variable and include renal cysts, ranging from isolated lesions to multicystic kidneys, proteinuria and chronic renal failure.

CLINICAL STUDIES ON MODY IN INDIA

Insulin secretion in MODY

Considerable heterogeneity has been described with respect to insulin responses to an oral glucose load in MODY.[10] Mohan et al[25] performed simultaneous studies of insulin and C-peptide responses to glucose load in subjects with MODY and matched groups of controls (non-diabetic subjects). It was found that C-peptide responses to glucose load were lower in MODY, thereby providing evidence for decreased beta cell function in MODY. The insulin responses were varied with some patients having normal responses and other low responses. This suggested that there could be an additional defects in the peripheral metabolism of insulin, most likely at the hepatic level with defects in hepatic extraction of insulin.

Insulin secretion in offspring of MODY

Defective pancreatic beta cell secretion is a well established feature of MODY. If the defect precedes

the onset of diabetes, it could be used as an early marker of diabetes in MODY families. Mohan et al[26] studied offspring of MODY at a stage when they had normal glucose tests and looked at insulin and C-peptide responses to glucose load. It was found that decreased C-peptide responses to glucose load was identifiable even years before the onset of clinical diabetes in MODY families.

Vascular complication in MODY

Typical microvascular and macrovascular complications have been reported to occur with relatively high frequency in many Caucasian MODY families reported by Fajans[27], while most members of families with MODY seen by Tattersall escaped significant complications.[4] This suggests that there could be heterogeneity in susceptibility to vascular disease even within MODY.[27]

In order to settle the controversy, Mohan et al[11] took up a large study to look at vascular complications in south Indians with MODY in Chennai, India. Even among those with definite autosomal inheritence, in patients with known duration of diabetes of greater than 15 years, non-proliferative diabetic retinopathy was found in 25% and proliferative retinopathy in 6% of the patients. In addition, nephropathy was present in 6%, ischemic heart disease in 6% and neuropathy in 31% of patients. These figures are similar to the complications seen in our type 2 diabetic patients.[28-35] Thus, MODY patients seen in south India are not protected from vascular complications.

We now know that the severity and prognosis of MODY varies depending on the specific subtype of MODY. Some forms like glucokinase MODY (MODY 2) are less susceptible while others like HNF1α (MODY 3) are prone to vascular complications like type 2 diabetes. This could also be related to the fact that the former is characterized by a milder, and the latter, a more severe form, of diabetes (see clinical features of MODY subtypes).

MODY GENES IN SOUTH INDIANS

The prevalence and nature of mutations in the HNF-1α gene (MODY 3) was studied by Radha et al[36] in unrelated south Indian patients with a clinical diagnosis of MODY. It was found that only 6-8% of MODY in south Indian subjects are caused by mutations in the HNF-1α gene. This is in contrast to most of the populations studied where mutations in the HNF1α (MODY 3) is a common cause of MODY.

Yet another study from our centre by Anuradha et al[37] estimated the prevalence of Ala98Val polymorphism of the HNF1α gene in five groups of Asian Indian diabetic patients including MODY, very early onset type 2 diabetes (<25yrs without family history), early-onset type 2 diabetes (age between 26-40yrs), late-onset type 2 diabetes (>40yrs), type 1 diabetic patients and a control group of normal glucose tolerant subjects. The frequency of the Val allele was significantly higher in MODY patients and in patients with very early and early onset diabetes. The mean age at onset of the Val/Val group was 5.2 years younger than that in the Ala/Val group, which in turn was 5.8 years younger than in the Ala/Ala group as shown in the figure. This was clearly reflected in the frequency of the Val allele increasing with decreasing age at onset of type 2 diabetes. The significant finding of the study is that the Val allele is associated with MODY and with earlier age at onset of type 2 diabetes. This is the first report on the genetics of MODY from India and also the first showing an association of this polymorphism with the disease. The Valine polymorphism could probably prove as one of the genetic markers for detection of earlier age at onset of type 2 diabetes in our population.

PREVENTION OF MODY

MODY is one type of diabetes with a tremendous potential for prevention of diabetes. As it is a monogenic form of diabetes, one can screen for these mutations relatively easily. Secondly, being an autosomal dominant disorder, one can predict that 50% of the offspring would be affected if one of the parents has the disease. By modifying environmental factors, eg. prevention of obesity by diet and exercise one could prevent, or atleast postpone, the clinical manifestation of the disease. Preliminary evidence suggests that subjects with HNF-1α mutations who are normoglycemic have a lower body mass index (BMI) than those with diabetes. This suggests that by staying slim they could delay the onset of MODY. If further studies confirm these findings, at risk individuals can be offered genetic counselling and a mutation test and then advised active lifestyle modification and thereby help to prevent diabetes in those who are genetically predisposed.

OTHER MONOGENIC FORMS OF DIABETES

Mitochondrial Diabetes

a. MIDD (Maternally Inherited Diabetes and Deafness) Ballinger Wallace Syndrome

This is due to mitochondrial mutations and also has a dominant inheritance pattern. It is a subtype of

diabetes characterized by maternal inheritance of diabetes and neurosensory deafness caused by variation in the mitochondrial tRNA gene at position 3243. It accounts for 0.5–3% of diabetes and highest prevalence has been reported from in Japan.[38]

b. **MELAS (Myopathy Encephalopathy, Lactic Acidosis and Stroke like episodes)**

This is caused by the same mutations as in MIDD. The heterogeneity in the phenotype is the result of chance differences in the tissue distribution of mutated mitochondria during development.

c. **Variants**

Other variants within the mitochondrial genome have also been described to be associated with type 2 diabetes.

CLINICAL FEATURES

Patients with mitochondrial diabetes have the following features.

- They are Non obese
- The onset of diabetes is early in life
- Due to progressive beta cell loss, need insulin earlier.
- May have features of neurological and occular deficits as seen in other mitochondrial disorders.

RARER FORMS OF MONOGENIC DIABETES

a. ***Wolfram Syndrome:*** It is a rare recessive disorder caused due to mutations in WFS1 gene, characterized by combination of familial juvenile onset diabetes mellitus, optic atrophy, diabetes insipidus and deafness.

b. ***Friedrich's Ataxia:*** This is an autosomal recessive condition due to mitochondrial dysfunction caused by deficiency of FRDA gene encoding frataxin which leads to ataxia. It is associated with hypertrophic cardiomyopathy, blindness, deafness and diabetes mellitus.

c. ***Pearson Marrow Pancreas Syndrome***: It is due to the deletion of large portion of mitochondrial DNA and characterised by type 1 diabetes mellitus, anaemia, exocrine pancreatic dysfunction and failure to thrive.

d. ***Kearns Sayre Syndrome:*** It is also due to deletion of portions of mitochondrial DNA manifesting with diabetes mellitus, ophthalmoplegia, cardiomyopathy and retinal degeneration.

e. ***Rotig Syndrome***: This is caused by deletion of variable portion of mitochondrial DNA. These patients present with diabetes mellitus and diarrhea and also have tubulopathy, cerebellar ataxia, myopathy, skin abnormality and deafness.

f. **MERRF (Myoclonus Epilepsy with Ragged Red Fibres)**: This is a neuromuscular disorder caused by point mutation at nucleotide 8344 at tRNA (Lys) gene of mitochondrial DNA characterized by mitochondrial myopathy and progressive myoclonus epilepsy.

g. **Others:** In addition, about 40 other mutations in the insulin receptor gene have also been described, many of which can cause diabetes, but these are all extremely rare conditions.

CONCLUSION

MODY and other forms of autosomal dominant diabetes are classical genetic models for the study of the etiology of type 2 diabetes. During the last decade, the study of these monogenic syndromes has led to the identification of several genes that were not previously suspected to play a role in glucose metabolism. It is anticipated that many more genes involved in insulin secretion or action will be identified by studying these forms of diabetes.

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