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Genetics of Diabetes Mellitus

Haseena Sait, Shubha R Phadke

Department of Medical Genetics, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

Correspondence to: Dr Shubha R Phadke *Email:* shubharaophadke@gmail.com

Abstract

Diabetes mellitus is a chronic metabolic disease with a rising trend of cases globally. While majority are polygenic in origin, monogenic forms account for 1-5 % of cases. Increased recognition of monogenic types is the outcome of a wider availability of molecular tests. With recent studies showing misdiagnosis of monogenic forms as type 1 or type 2 diabetes, it is crucial to clinically suspect these types with clinical and family history and to decide regarding the need for molecular tests. This article briefly describes the genetic aspects of various types of diabetes, systematic approach to a patient with diabetes and genetic counselling regarding the recurrence risks for both monogenic and polygenic forms of diabetes.

Introduction

Diabetes mellitus (DM) is a metabolic disorder that is characterized by high blood sugar levels due to insulin deficiency, insulin resistance, or both. There is an increase in the global prevalence of diabetes among adults over 18 years of age from 4.7% in 1980 to 8.5% in 2014 (Sarwar et al., 2010). The prevalence of diabetes in India is around 11.8% according to the National Diabetes and Diabetic Retinopathy Survey report in 2019. DM affects all age groups and is an example of etiological heterogeneity. Diabetes causes significant morbidity and is the leading cause for blindness, renal failure, myocardial infarction, stroke and lower limb amputation.

According to the recent classification by WHO (2019), DM is grossly divided into type 1, type 2, hybrid forms, monogenic diabetes and diabetes in pregnancy. Type 1 and type 2 DM have polygenic inheritance with a significant environmental contribution to disease causation. While most cases of diabetes are of multifactorial etiology, a small percentage of cases are monogenic in origin. This group includes neonatal diabetes, maturity-onset diabetes of young (MODY) and rare monogenic syndromes with genotyping being most relevant in such patients. Genetic etiology is important to tailor therapy and to prevent misdiagnosis of subtypes. The risk of recurrence as well as the issues in genetic counselling vary depending on the etiology.

While predicting risk of recurrence is usually straightforward for monogenic diabetes, such prediction for type 1 and type 2 DM is difficult but empirical risks can be provided based on family history and other biochemical markers. In this article, the genetic aspects and genetic counselling for this common disease are discussed, specifically highlighting the heterogeneous nature of this disease.

Genetics of type 1 DM

Type 1 DM accounts for 5-10% of diabetes cases and results from autoimmune destruction of pancreatic β-cells leading to insulin deficiency. Insulin autoantibodies (glutamic acid decarboxylase (GAD65), islet antigen-2, ZnT8 transporter) can be detected in the blood of about 85-90% of individuals (American Diabetes Association, 2014). Type 1 DM can also present at a later age and is known as 'slowly evolving, immune-mediated diabetes of adults' previously known as 'latent autoimmune diabetes of adulthood' (LADA). The major genetic contributor to type 1 DM susceptibility is the allelic variation in the HLA region with some haplotypes having odds ratios (OR) as high as 11 (Erlich et al., 2008). Studies have identified various susceptibility and protective alleles at HLA DP, DR-DQ loci (Varney et al., 2010). Though genetic testing is not considered to be a useful clinical tool in predicting the risk of recurrence in type 1 DM, evaluation of these alleles can be useful in identifying pre-symptomatic individuals at risk.

Table 1 Common syndromes associated with DM.

Subset	Syndromes
Chromosomal disorders	Down syndrome, Klinefelter syndrome, Turner syndrome
Triplet Repeat Disorders	Huntington disease, Friedreich ataxia, Myotonic dystrophy
Obesity associated syndromes	Bardet-Biedel syndrome, Prader-Willi syndrome, Alstrom syndrome
Others	Wolfram syndrome

Genetics of type 2 DM

Type 2 DM represents 90-95% cases of diabetes and is caused by insulin resistance and relative insulin deficiency. Non-pregnant diabetes, non-auto immune diabetes and diabetes with no specific etiology fall into this category. Genome-wide association studies (GWAS) have identified over 70 loci associated with type 2 DM (Morris et al., 2012). Though majority of these loci were identified in individuals of European ancestry, studies conducted in the Asian population have confirmed the associations of these genetic variants with the risk of Type 2 DM in Asian populations (Qi et al., 2015). P12A polymorphism (rs1801282) in *PPARG* and E23K (rs5219) polymorphism in *KCNJ11* are few of the initial polymorphisms found to be strongly linked to Type 2 DM in these populations.

Genetics of monogenic diabetes

Monogenic diabetes is a grossly under-recognised condition and can occur due to a defect in pancreatic β-cell function or insulin action. It can be grossly divided into monogenic defects causing pancreatic β-cell dysfunction {MODY, neonatal DM (permanent and transient)}, defects causing insulin resistance, and other syndromes associated with DM (Table 1).

- Monogenic defects causing pancreatic -cell dysfunction:

1. ***MODY:*** Maturity-onset diabetes of young (MODY) is the most common type of monogenic diabetes and is inherited in an autosomal dominant fashion. The various genes involved are *HNF4A* (MODY 1), *GCK* (MODY 2), *HNF1A* (MODY 3), *IPF1* (MODY 4), *HNF1B* (MODY 5), *NEUROD1* (MODY 6), *KLF11* (MODY 7), *CEL* (MODY 8), *PAX4* (MODY 9), *INS* (MODY 10), *BLK* (MODY 11), *ABCC8* (MODY 12) and *KCNJ11* (MODY 13). Identification of these genes is crucial not only for genetic counseling but also for planning the treatment and for screening other organs. For example, MODY is easily misdiagnosed as type 1 DM. It is important to differentiate it from type 1 DM as those caused by defects in *HNF1A* and *KCNJ11* gene respond to low or high dose sulfonylureas respectively instead of insulin. *HNF1B* mutations often cause renal cysts, and hyperechoic kidneys in the fetus is a presentation of *HNF1B* sequence variations or whole gene deletion (Vasileiou et al., 2019). In addition to heterozygous sequence variation in *HNF1B* gene, an approximate 1.3 Mb deletion at chromosome 17q12, which includes the entire *HNF1B* gene is a cause of DM with renal cysts and variable degree of neurodevelopmental abnormalities.

2. ***Neonatal DM (NDM)***: It is the second most common monogenic type of DM which usually manifests in infants under 6 months of age. Rare occurrence in infants up to 12 months of age has also been reported (Rubio-Cabezas & Ellard, 2013). Infants with insulin-dependent hyperglycemia, with blood glucose persistently greater than 250 mg/dL, lasting for more than 7-10 days without an alternative etiology should undergo genetic testing for neonatal DM.

NDM can be classified into transient (TNDM) and permanent forms. Approximately 50% of cases are transient in nature and the diabetes resolves on its own. The most common cause for TNDM is overexpression of the chromosome region 6q24. Although hyperglycaemia remits in TNDM patients by the age of 18 months, a relapse of diabetes occurs in 50% of the patients, usually during adolescence or early adulthood (Mackay & Temple, 2010). On the other hand, permanent NDM most often results from gain of function mutations in *KCNJ11* or *ABCC8* gene.

Table 2 Common genes and associated features of neonatal diabetes mellitus.

NDM		Genetic cause	Mode of inheritance	Pathogenesis	Associated features	Treatment
Transient		Overexpression of chromosome 6q24 • Paternal UPD • Paternal duplication • Maternal hypomethylation	• Sporadic • AD • Sporadic	Overexpression of *ZAC1* and *HYMA1* on chromosome 6 causes delayed maturation of the pancreatic islets and β-cells	IUGR, Cardiac abnormalities	Insulin
		KCNJ11, *ABCC8* (*KCNJ11* encodes K_{ATP} channel subunits KIR6.2, *ABCC8* encodes Sulfonylurea receptor)	Sporadic /AD	Mutation results in prolonged opening of potassium channel and hampering of insulin release	None	Insulin Sulfonylureas
		HNF-1B *	AD	Reduced pancreatic β cell mass	Pancreatic exocrine dysfunction, renal cysts/ hyperechoic kidneys	Insulin
Permanent	Non syndromic	*KCNJ11, ABCC8*	Sporadic /AD	Same as above	Developmental delay, epilepsy (DEND syndrome)	Insulin Sulfonylureas
		INS	AD	Pancreatic β-cell apoptosis	IUGR	Insulin
		GCK #	AR	Affects glucose phosphorylation and blocks ATP production; causes reduction of insulin secretion	IUGR	Insulin
		IPF1	AR	Marked pancreatic exocrine and endocrine failure due to pancreatic agenesis	Cerebellar hypoplasia, cardiac septal defects	Insulin
	Syndromic	*EIF2AK3*	AR	Pancreatic β-cell apoptosis	Wolcott- Rallison syndrome	Insulin
		FOXP3	X linked	Pancreatic β-cell apoptosis	IPEX syndrome	Insulin
		SLC2A2	AR	Reduced pancreatic β-cell function	Fanconi- Bickel syndrome	Insulin
		SLC19A2	AR	Reduced pancreatic β-cell function	TRMA syndrome	Insulin (Thiamine rarely)
		MTLL1	Mitochondrial	Reduced pancreatic β-cell function	MIDD syndrome	Insulin

NDM: Neonatal diabetes mellitus; UPD: Uniparental disomy; AD: Autosomal Dominant; AR: Autosomal Recessive; ZAC-1: zinc finger, apoptosis, and cell cycle; HYMA1: ([Fe] hydrogenase subunit HymA); IUGR: Intrauterine growth restriction; INS: Insulin; GCK: Glucokinase; IPF1: Insulin promoter factor 1; EIF2AK3: Eukaryotic translation initiation factor; IPEX- Immuno dysregulation, polyendocrinopathy, enteropathy, X-linked; TRMA: Thiamine-responsive megaloblastic anemia; MIDD- Maternally inherited diabetes and deafness.
*Also implicated in MODY-4, #Also implicated in MODY-2

These can be successfully treated with high doses of sulfonylureas unlike other NDM which require treatment with insulin. The most common genes and associated features involved in NDM are described in Table 2.

- Monogenic causes of insulin resistance: They are less common than monogenic β-cell defects. They typically present with features of insulin resistance in the absence of obesity, including hyperinsulinemia, acanthosis nigricans or virilization. Diabetes only develops when the β-cells fail to compensate for the insulin resistance. The common genes and syndromes associated with insulin resistance are listed in Table 3.

Gestational Diabetes Mellitus (GDM)

Type 2 DM can remain undiagnosed and can be recognised initially during pregnancy. It is essential to distinguish between GDM and type 2 DM in pregnancy as the latter is associated with a higher incidence of fetal malformations like caudal regression syndrome, congenital heart defects, renal anomalies etc. Family history of GDM and type 2 DM can act as a guide to predict risk of GDM. Women diagnosed with GDM are also at a significant risk for developing type 2 DM later in life.

Identification of monogenic diabetes has very significant relevance in pregnancy. Hyperglycemia in pregnancy is invariably always labelled as GDM but some of these patients may harbour mutation in the *GCK* (glucokinase) gene and identification of these women is important as the management differs substantially. Glucose-lowering agents are generally not required in *GCK*-associated MODY in normal individuals as the hyperglycemia is usually subclinical. Pregnancy is an exception where the requirement of treatment for *GCK*-associated MODY in pregnant woman depends on fetal inheritance of the *GCK* mutation. If the fetus inherits a maternal *GCK* mutation, then treatment of maternal hyperglycemia is not indicated as these fetuses have a similarly elevated glucose set-point as their mother and can have normal birth weight. On the other hand, treatment of maternal hyperglycemia is required in those fetuses who do not inherit *GCK* mutation, as they have a higher risk of developing macrosomia. When the fetal genotype is unknown, it can be indirectly inferred from monitoring serial fetal growth and an accelerated fetal growth would indicate that the fetus is probably not carrying the *GCK* mutation, warranting strict control of maternal hyperglycemia (Rudland, 2019).

Approach to a patient with DM

The common situation for counselling in genetic clinics pertaining to DM arises when a pregnant diabetic mother consults to know the impact of diabetes on her fetus. Apart from that situation, very rarely counseling is sought for family or personal history of DM. An exception to this situation arises when the diagnosis of DM is made in a young individual where family members are anxious about recurrence in the offspring and in the siblings of the affected child. Due to increasing incidence of the disease, increasing list of genes and susceptible loci and studies showing monogenic diabetes being misdiagnosed as type 1 or 2 DM (Pihoker et al., 2013), it is important to make an accurate and timely diagnosis for appropriate genetic counselling regarding the optimal therapy. Though the risk of recurrence is negligible in majority of cases, counselling in the rare types of autosomal recessive, X-linked and syndromic DM is vital as parents can opt for prenatal testing after establishing molecular diagnosis in the index patient.

- History taking: The following points are pertinent:

  - The age of onset; Table 4 enumerates the age-wise distribution of different types of DM and a few key points to differentiate one type from the other.
  - Type of intervention required and response to those medications
  - Associated visual or hearing impairment
  - Birth history including birth weight and birth defects
  - Detailed development history
  - Three-generation family history

While examining the patient, special attention should be given to look for presence of dysmorphic features, obesity, distribution of fat, signs of hyperinsulinemia and multisystem involvement like anemia, deafness, renal cyst and neurocognitive abnormalities. For example, Thiamine-responsive megaloblastic anemia (TRMA)

Table 3 Monogenic defects causing insulin resistance.

Gene	Inheritance	Disease	Phenotype
INSR	AR	Rabson-Mendenhall syndrome	Extreme insulin resistance, dysmorphism, severe intrauterine retardation and early mortality
INSR	AR	Leprechaunism (Donohue syndrome)	
INSR	AR	Type A insulin resistance	Milder form, manifestation after puberty
LMNA	AD	Familial partial lipodystrophy	Limb lipoatrophy in adult life, hyperlipidemia and insulin-resistant diabetes
PPARG			Partial lipodystrophy, severe insulin resistance, early onset Type 2 DM and hypertension
AGPAT2	AR	Congenital generalized lipodystrophy	Lipoatrophy, acanthosis nigricans, hepatomegaly, acromegaloid features, cardiomyopathy and global development delay.
BSCL2			

AD- Autosomal dominant, AR- Autosomal Recessive

Table 4 Age-wise distribution of different types of diabetes mellitus (*Adopted from WHO's manual on classification of Diabetes mellitus 2019*).

Age of onset	Type of DM	Others
<6 months (sometimes up to 1 year)	Neonatal DM	Genetic testing to distinguish transient from permanent
6 months – 10 years	Type 1 DM Neonatal DM	Thin individuals; positive autoantibodies confirm Type 1 DM
10-25 years	Type 1 DM Type 2 DM Monogenic DM	Overweight or obesity; acanthosis nigricans; strong family history of type 2 DM; undetectable islet autoantibodies and elevated or normal C-peptide distinguishes type 2 from type 1 DM. Strong family history suggesting AD pattern; undetectable islet autoantibodies; marked sensitivity to sulfonylureas; presence of extrapancrearic features like renal anomalies suggest MODY.
25-50 years	Type 2 DM Slowly evolving immune mediated DM (10%) (previously LADA) Type 1 DM (5%)	Thin individuals; presence of autoantibodies (especially GAD); initial response to sulfonylureas and later requiring insulin suggests LADA.
>50 years	Type 2 DM Slowly evolving immune mediated DM	

DM: Diabetes mellitus; GAD: glutamic acid decarboxylase; LADA: latent autoimmune diabetes of adulthood

is a rare disorder which may present with severe anemia responding to thiamine. Presence of macrocytosis and deafness may be a clue for this disorder. Diabetes may sometimes manifest later and may need evaluation.

After obtaining necessary information and baseline investigations like autoantibodies profile if available, one can ascertain the type of DM and can decide whether to proceed with genetic testing. Molecular testing is indicated in monogenic forms of diabetes. This should be followed by discussion regarding the risk of recurrence in subsequent pregnancies and options for prenatal testing.

- Genetic counseling regarding recurrence risk:

For monogenic disorders, counseling regarding recurrence risk in autosomal recessive and X-linked disorders is quite straight forward once the molecular diagnosis is established. However, rare autosomal dominant disorders pose significant challenge in counselling as the genetic evidence on penetrance of these genes is weak (Misra & Owen, 2018). Counselling for the recurrence risks of Type 1 and type 2 DM on the other hand is complex. Empiric risks can be used based on the family history and the community prevalence of the disease but these have their own limitations.

Type 1 DM: Previous studies have reported that younger age at diagnosis, young-onset diabetes of parents, male gender, and an older parental age at delivery increased the risk of type 1 DM in siblings. Younger age at diagnosis in the index patient is the strongest predictor of the risk of type 1 diabetes in siblings (Gillespie, 2002). Information on autoantibody status and levels, HLA-conferred disease susceptibility, and insulin secretion and sensitivity are also useful in predicting the occurrence of disease in siblings. The cumulative risk of type 1 diabetes up to ages 10, 20, 30, 40 and 50 years in brothers and sisters of patients with childhood-onset diabetes is 1.5 per cent, 4.1 per cent, 5.5 per cent, 6.4 per cent, and 6.9 per cent, respectively (Harjutsalo et al., 2005).

Type 2 DM: Study based on disease-gene frequency model and the community-based prevalence data suggested a sibling recurrence ratio of 1.8–2.5 (Busfield, 2002). The life-time risk of developing the disease in offspring of one parent with type 2 DM is around 40%, greater if the mother is affected, and the risk rises to 70% if both the parents are affected (Ridderstrale & Groop, 2009). Thus, the empirical recurrence risks for first-degree relatives of type 2 DM are higher than those for type 1 DM. The increased risk of recurrence highlights the need for change in lifestyle and surveillance for early diagnosis. In addition to genetic contribution to DM, it has become obvious that the renal and retinal complications of DM also have genetic susceptibility and are currently an important research subject (Mishra et al., 2016). Though genetic variations are known for susceptibility to type 1 and 2 DM and are being explored in ongoing research works, genetic testing including HLA studies are currently not indicated in clinical settings.

To conclude, DM is a chronic debilitating illness with diverse etiologies. While type 1 and type 2 DM are well known and have a multifactorial inheritance, other monogenic forms of diabetes are often misdiagnosed as type 1 or 2 DM or remain underdiagnosed. Correct diagnosis with the help of molecular testing will aid in proper management and appropriate genetic counseling.

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