Review

Overview of Clinical Genetics of Diabetes Mellitus

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Review

Overview of Clinical Genetics of Diabetes Mellitus

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Abstract

Diabetes mellitus is characterized by elevated blood sugar due to absolute or relative insulin deficiency. Diabetes is broadly classified into 2 major forms: type 1 diabetes mellitus (T1D) and type 2 diabetes mellitus (T2D). It is known also that other categories of diabetes exist, and this includes gestational diabetes, monogenic causes, rare syndromes, and iatrogenic causes. Most cases of T1D and T2D are polygenic with environmental triggers. T1D often results from autoimmune destruction of pancreatic beta cells leading to absolute insulin deficiency. T2D is associated with obesity, insulin resistance with relative insulin deficiency. Genetic studies have focused on the identification of loci associated with increased susceptibility to diabetes. Early studies showed linkage between T1D and several HLA susceptibility loci on chromosome 6. The HLA haplotypes DR3 (DQb1*201) and/or DR4 (DQb1*302) are susceptibility alleles and the DR2 (DQb1*602) is considered a protective allele for development of T1D. Genome-wide association studies (GWAS) have identified more than 100 HLA- and non-HLA loci that increase susceptibility to T1D; many of these loci have small effects to the phenotype and are relevant to autoimmunity. Some of the notable genes for T1D are INS, PTPN22, CTLA4. Regarding T2D risk, thousands of gene variants that are common and contribute small effects have also been identified through GWAS, but the rarer variants may confer significant risk to an individual's risk. The usefulness of individual variants for genetic counseling in diabetes has been limited in the clinical setting in the past until the development of polygenic risk scores (PRS) and partitioned polygenic risk scores (PPRS) statistics derived from GWAS. PRS and PPRS are statistical methods that combine multiple disease-modifying variants obtained from GWAS to predict and classify diabetes. These scores use the cumulative effect of hundreds to millions of variants generated from GWAS to compute an individual's relative risk. Currently more than 100 variants for T1D and over 1000 variants for T2D are utilized in risk analysis of diabetes. Continued investment in global consortia such as the Type 1 Diabetic Genetics Consortium (T1DGC), National Institute of Diabetes and Kidney Diseases (NIDDK), and the Wellcome Trust Case-Control Consortium (WTCCC) in genetic variant mapping will help identify genes involved in pathophysiologic pathways involved in insulin secretion and signaling, and provide insight into new targets for prediction, prevention and treatment of diabetes. Monogenic diabetes comprises several clinical dysglycemic disorders that include neonatal diabetes, maturity-onset diabetes of the young (MODY), and several genetic syndromes that have diabetes either as an associated finding and/or complication. Some of the monogenic diabetes gene variants have incomplete penetrance and variable expressivity leading to different ages of onset and variable presentation even within the same family. Hence some patients with these conditions have been previously diagnosed as having T1D or T2D. Monogenic disorders follow Mendelian inheritance patterns so genetic counseling is relatively straightforward. Counseling for forms of diabetes due to maternally inherited mitochondrial cytopathies such MELAS and Kearne-Sayres syndrome are not straight-forward due to heteroplasmy. Clearer definition of diabetes phenotypes, development of powerful statistical methodologies, use of next-generation sequencing applications to interrogate the genome, incorporation of epigenetic mechanisms and accurate

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curation of gene variants, will help us realize application of genomic medicine and inform diabetes care.

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1. Introduction

Diabetes mellitus is a clinical condition characterized by chronic hyperglycemia due to either absolute or relative insulin deficiency. Diabetes is associated with a high morbidity and mortality from end-organ damage [1]. The American Diabetes Association Expert Panel defines diabetes as blood glucose level greater than 126 mg/dL and/or a glucose tolerance test with a 2-hour peak blood glucose level of 200 mg/dl in the absence of symptoms or a random blood glucose level greater than 200 mg/dL in the presence of symptoms such as polyuria, polydipsia, polyphagia with weight loss. [2]. Diabetes occurs worldwide and the World Health Organization reports that about 830 million people have the disease with most affected persons living in low- and middle-income countries [3]. In 2022, it was estimated that about 14% of adults aged 18 and above were living with diabetes, which is double the 1990 rate [4] The International Federation of Diabetes Atlas (2025) reports that 1 in 9 adults ages 20 to 79 have diabetes [5] In the United States of America, it is estimated that 97.6 million adults ages 18 years and older in 2021 had prediabetes and 1.2 million are diagnosed with diabetes every year [4]. Thus, diabetes is a major healthcare burden in all countries [4].

Diabetes mellitus is a genetically heterogeneous group of disorders [1,6–9]. Diabetes can be broadly classified into different categories of which types 1 and 2 diabetes are the most common. Type 1 diabetes (T1D) results from destruction of pancreatic beta cells because of autoimmune or other causes, leading to absolute insulin deficiency. Type 2 diabetes (T2D) is associated with insulin resistance, often due to obesity, and failure of pancreatic beta cells to produce sufficient amounts of insulin [1,6–8]. Relative insulin insufficiency in T2D is caused by intrinsic insulin secretory defect and beta cell glucotoxicity and lipotoxicity [10,11]. T2D may occur in normal weight individuals, and "lean type 2 diabetes" is thought to occur in 10 to 20% of people with T2D [12]

T1D and T2D are described as complex disorders in that different environmental factors interact with some genetic factors to cause the disorders. Some of the environmental factors include diet, obesity, infections and physical activity [1,13]. T1D and T2D are heritable conditions with a heritability estimated to be over 50% [1]. Evidence for the high heritability is based on the finding of familial aggregation and twin studies [1,14–17]. Decades ago, diabetes mellitus used to be regarded as the "geneticist's nightmare" since elucidating the genetic etiologies was difficult to unravel. Genetic analysis was hampered by differences in the diagnosis of affected individuals, age of onset, high prevalence of the disease in the population and gene-environment interaction [1,15,18]. Progress in gene mapping techniques and statistical genetics methodologies have helped in our understanding of risk assessment to affected family members to some extent. Methodologies used included candidate gene approaches that utilized sibpair linkage analysis, transmission disequilibrium test, etc. [1,15,18–22]. Hypothesis free testing using genome-wide association studies (GWAS) has enabled interrogation of the genome using single nucleotide variants (SNV) or single nucleotide polymorphisms (SNPs) [22–24].

A polygenic risk score (PRS) is a statistical estimate of an individual's genetic susceptibility to developing a complex disorder such as diabetes [25,26]. It is calculated by considering the cumulative effects of multiple genetic variants (SNV or SNPs) identified through GWAS that have been associated or linked to the disease in large population studies. A higher PRS indicates a higher genetic susceptibility to a disease. PRS have been calculated for different populations, and it does not fully account for the complex interaction between genetic and environmental factors [25,26].

Partitioned polygenic risk scores (PPRS) provide estimates about the extent to which different pathophysiologic processes contribute to risk and provide insight into underlying molecular

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heterogeneity of the disorder [26] PRS and PPRS are providing new insights into tissue and cell-specific pathways in our understanding of the etiology of diabetes mellitus [27,28]. GWAS conducted on thousands of subjects with T1D and T2D have been able to overcome clinical heterogeneity and have yielded large number of genetic susceptibility variants for T1D and T2D [27,29]. PRS and PPRS can identify individuals with higher risk of T1D and T2D than those in the general population. The original PRS and PPRS were developed using European GWAS data, but multi-ancestry models have been developed [28,30].

Other causes of diabetes include pregnancy-induced (gestational) diabetes, single gene defects (monogenic diabetes), diseases of the exocrine pancreas, endocrinopathies (Cushing syndrome, Polycystic Ovarian Syndrome, acromegaly, hyperthyroidism), surgical excision of pancreas, trauma, drugs or environmental chemical exposures, infections, and rare genetic syndromes [1,8]. A subset of this category called type 3C diabetes (pancreatogenic diabetes) is caused by chronic pancreatitis of varying etiologies, pancreatic cancer, surgery, trauma, cystic fibrosis, hemochromatosis, maple syrup urine disease, familial lipoprotein lipase deficiency, homocystinuria and some of the organic acidemias [8].

Monogenic diabetes comprises several clinical dysglycemic disorders that include neonatal diabetes, maturity-onset diabetes of the young (MODY), and several genetic syndromes that have diabetes either as an associated finding and/or complication [31] Some patients diagnosed with T2D may in fact have monogenic diabetes. The monogenic diabetes genes may have incomplete penetrance and variable expressivity leading to different ages of onset and variable presentation even within the same family [1,31–33]. Monogenic diabetes and diabetes associated with genetic syndromes tend to follow Mendelian inheritance patterns, so counseling may be straightforward [1,31–33]. Counseling for forms of diabetes due to maternally inherited mitochondrial cytopathies are not straight-forward because of heteroplasmy.

This review describes the clinical genetics of diabetes mellitus and discusses genetic counseling strategies for polygenic and Mendelian forms of the diabetes mellitus.

2. Type 1 Diabetes (T1D)

T1D is an autoimmune disorder culminating in progressive destruction of pancreatic islet beta cells leading to profound insulin deficiency. Age of onset of T1D is from childhood through adulthood and symptoms include polyuria, polydipsia, polyphagia weight loss, hyperglycemia and ketosis. Classic symptoms occur after destruction of 80 to 90% of insulin-secreting islet cells [8,29]. Glutamic acid decarboxylase (GAD) antibodies and ZnT8 testing help with diagnosis [8,29]. There is heterogeneity of the clinical and immunological features of T1D based on age of onset. Childhood T1D is usually characterized by sudden onset and ketosis and affected individuals tend to have HLA-DRB1*04-DQA1*0301-DQB1*0302 alleles and a high frequency of insulin and IA-2 autoantibodies [8,29,34]. On the other hand, the adult form of T1D, also called latent autoimmune diabetes (LADA), is slowly progressive and is initially non-insulin dependent but later requires insulin treatment. LADA is characterized by the presence of glutamic acid decarboxylase-65 (GAD65) autoantibodies and/or islet cell antibodies [8,34,35]. T1D is a polygenic disease, and genetic factors may account for about 35% of the susceptibility to the disorder based on concordance between monozygotic twins [1,13]. Other studies suggest that about 50% of the risk of T1D is due to genetic factors [1,8]. Heritability of T1D is estimated to be about 50 to 80% [13–15]. Early evidence of the high heritability of T1D came from familial aggregation and twin studies. The concordance rate of T1D among monozygotic (MZ) twins who share 100% of their genes in common is estimated as 30 to 70%, and the risk is highest if the MZ twins are diagnosed at a younger age. Dizygotic twins on the other hand share on average 50% of their genes in common and their concordance rate is much lower, at 6 to10% [1]. Also, the risk for T1D among first degree relatives is significantly higher than for unrelated individuals in the general population. The closer a person is to the affected individual (proband) the greater the risk (first degree relatives like parents and siblings have higher risk) and this risk diminish rapidly with distant relationships (second, third degree relatives, etc.) [1].

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Environmental triggers such as viral infections have been implicated in T1D. Other possible environmental factors include early diet such as cow's milk introduction and gut microbiome that can affect the immune system, and early infant obesity [1,13]. The HLA haplotypes DR3 (DQb1*201) and/or DR4 (DQb1*302) on chromosome 6 are susceptibility alleles and the DR2 (DQb1*602) is considered a protective allele for development of T1D [1,19,20]. Genome-wide association studies (GWAS) have identified more than 100 HLA- and non-HLA loci that increase susceptibility to T1D. (29) It has however been well established that a significant portion of the genetic risk for T1D is encoded in the HLA locus with a few notable genes, INS, PTPN22, CTLA4 that make moderate contributions to risk [29,31]. The remaining loci identified to date, though each on its own contributes modestly to T1D, the aggregate seems to increase risk based on PRS studies.

3. Type 2 Diabetes (T2D)

T2D results from insulin resistance and insufficient insulin production. T2D accounts for about 90% of all cases of diabetes mellitus. T2D prevalence is increased with obesity, consumption of obesogenic diet, sedentary lifestyle, stress and aging. The increasing frequency of T2D mainly driven by obesity epidemic makes it a worldwide epidemic [35]. T2D is a heterogeneous polygenic disorder with environmental modifiers. Disease usually occurs from childhood to adulthood and there is endogenous insulin production. In genetically susceptible individuals, there is a slow progression from euglycemia to hyperglycemia, largely due to a combination of insulin resistance and defects in insulin secretion. Initially insulin production increases to offset insulin resistance, but eventually there is relative insulin deficiency. The progressive pathogenesis of T2D depends on an interaction between genetic and environmental factors involved in both the initiation and progression of the disease. Phenotypic features include chronic hyperglycemia, relative insulin deficiency, insulin resistance, obesity and acanthosis nigricans. The complications of chronic hyperglycemia include nephropathy, neuropathy, retinopathy and cardiovascular compromise. Hyperglycemia in T2D can often be controlled by diet or oral hypoglycemic agents but exogenous insulin may be required. Heritability of T2D is estimated between 25 to 70% and evidence of genetics contribution comes from studies that showed high prevalence in certain racial groups, familial aggregation, familial transmission patterns, higher concordance among MZ twins than in DZ twins and a high sibling risk ratio of 3.5 [1,7,13,14,22]. Early reports suggested racial differences with Pima Indians (Akimel O'odham) having a higher incidence than other racial groups but further studies comparing ancestral group in Mexico showed that lifestyle changes associated with Westernization play a major role in the global epidemic of T2D [37,38].

Several gene loci associated with insulin resistance and defects in insulin secretion have been identified [1,7,36]. Many of these genes identified to date confer modest risk to T2D and yield inconsistent results in replication studies. For instance, the initial candidate genes, peroxisome-proliferation activated receptor gamma (PPARG), Caplain 10 (CAPN10) and pancreatic beta-cell inwardly rectifying potassium channel Kir 6.2 (KCNJ11) identified among many reported association studies failed to replicate in other studies. Non-coding variants in or near the transcription factor 2, hepatic (TCF2 also known as HNF1B) and Wolfram syndrome 1 (WFS1) genes have shown strong association with T2D. Severe pathogenic variants in these genes are known to cause rare genetic syndromes that have diabetes as associated findings. [1,39,40]. The gene locus transcription factor 7-like-2 gene (TCF7L2) has however been consistently replicated in diverse populations in Europe, Africa and Asia is considered the strongest common genetic association with T2D in most ethnicities [41–46]. Common variants identified by progressive GWAS reportedly explain 20% of the heritability in T2D suggesting there is "missing heritability" that must be accounted for low heritability estimate. This may be explained in part by rare variants that are not detected by current analytic methods, sample size considerations, intronic or intergenic variant [47,48] Other factors predisposing to T2D may be gene-gene interactions, epigenetic factors related to intrauterine environment, diet, exercise and other lifestyle exposures, copy number variations, noncoding RNAs that affect gene-environment interactions and gene-environment interactions [1,36]. The establishment of global

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consortia and biobanks has catalyzed the performance of large-scale genomic studies that has resulted in identification of thousands of loci associated with T2D. Next-generation sequencing may identify rare variants with large effects, but these may be ancestry-specific [47–49]. Use of common and rare genetic modifiers in multi-ancestry populations may help improve T2D PRS.

4. Monogenic Diabetes Mellitus

Monogenic diabetes comprises several clinical dysglycemic disorders that include neonatal diabetes, maturity-onset diabetes of the young (MODY), and several rare genetic syndromes that have diabetes either as an associated finding and/or complication [32,33]. Monogenic diabetes gene(s) may have incomplete penetrance and variable expressivity leading to different ages of onset and variable presentation even in the same family. These may have led to some patients labelled as having T2D. Monogenic diabetes is mostly caused by impaired development or function of pancreatic beta cells resulting in defective insulin secretion in the absence of obesity. Most patients with MODY or neonatal diabetes have autosomal dominant inheritance. Autosomal and X-linked recessive inheritance account for the remainder. With the advent of next-generation sequencing, several subtypes of monogenic diabetes have been identified with many of the pathogenic variants identified in the GCK and HNF1A genes. (49)

(i) Maturity-onset diabetes of the young (MODY)

MODY is the most common form of monogenic diabetes and may account for 0.5 to 5% of all patients diagnosed with non-autoimmune diabetes in European cohorts [1,49]. Although MODY has been typically described in Europeans, it has been reported in other racial groups [1,49]. MODY was first described as a mild and asymptomatic form of diabetes that was observed in non-obese children, adolescents and young adults with improvement in blood glucose levels with sulfonylureas therapy [50]. A clinical diagnosis of MODY can be suspected in an individual with early onset diabetes in adolescence or young adult typically under 35 years of age, features of atypical for T1D or T2D, mild but stable fasting hyperglycemia that does not progress or respond appreciably to drug therapy, extreme sensitivity to sulfonylureas, personal of family history of neonatal diabetes or neonatal hypoglycemia and extra-pancreatic features. [1] There are pathogenic variants in at least 14 genes that cause MODY; these include GCK, HNF1A, HNF4A, HNF1B, INS, NEUR01, PDX1, PAX4, ABCC8, KCNJ11, CEL, BLK and APPL1. The four most common genes are that cause MODY are GCK (MODY2), HNF1A (MODY3), HNF4A (MODY1), and HNF1B (MODY5). MODY is generally inherited in an autosomal dominant fashion but de novo variants do occur. Biallelic pathogenic variants in GCK and PDX1 causes PNDM [51–54].

(ii) Neonatal diabetes mellitus (NDM)

Neonatal diabetes mellitus (NDM) is relatively rare with a prevalence of 1 in 95,000 to 1 in 400,000 [55]. About 50 to 60% of NDM cases have transient hyperglycemia and 40-50% have persistent hyperglycemia [55–57]. NDM has been reported in all ethnic groups and there is no gender predilection. This group of disorders are caused by gene variants that results in glucose intolerance with or without pancreatic degeneration [1,55–57].

Transient neonatal diabetes mellitus (TNDM) is genetically heterogeneous. Hyperglycemia presents in the neonatal period with remission during infancy but can reoccur during the teenage years. Treatment often starts with intravenous insulin to correct hyperglycemia and dehydration, and long-term treatment with subcutaneous insulin injection or insulin pump. Approximately 50% of cases do not require insulin and are treated with sulfonylurea. Clinical manifestations include severe intrauterine growth restriction, hyperglycemia beginning in the first few weeks of life, dehydration, congenital anomalies and some dysmorphic features such as facial dysmorphism, macroglossia, umbilical hernia, deafness and neurologic dysfunction [57]. Ketoacidosis is rare in TNDM. About 20% of patients have developmental delay and seizures [57]. Heterozygous pathogenic variants in the KCNJ11 and ABCC8 genes on 11p15.1 and alterations in 6q24 region either due to paternal uniparental disomy (UPD6) partial duplication of paternal origin, maternal imprinting defects (maternal hypomethylation), or biallelic ZFP57 pathogenic variants cause TNDM [57]. In 6q24-

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transient neonatal diabetes mellitus, there is overexpression of the pleomorphic adenoma gene-like1 (PLAGL1/ZAC) and hydatidiform mole-associated and imprinted transcript (HYMA1) genes that result in functional beta cell defect [53]. 6q24_TNDM caused by paternal UPD6 is typically de novo; paternal 6q24 duplication could be de novo event, inherited from a father in a dominant fashion or inherited as a complex chromosomal rearrangement.

Permanent neonatal diabetes mellitus (PNDM) has onset is in the first 6 months of life and insulin deficiency is partial or complete. Clinical presentation includes hyperglycemia, ketosis, glycosuria, ketonuria, polyuria, severe dehydration and history of intrauterine growth restriction. Pathogenic variants in the ABCC8 and INS inherited in autosomal dominant or autosomal recessive fashion cause some cases of PNDM; heterozygous pathogenic variants in GATA6, HNF1B, and KCNJ11 cause autosomal dominant PNDM and EIF2AK3, GCK, GLIS3, MNX1, NEUROD1, NKX2-2, PDX1, PTF1A, RFX6, SLC2A2 and SLC19A2 autosomal recessive genes that cause PNDM. Consideration should be given to infants with PNDM and extra-pancreatic features. These syndromic disorders are inherited in autosomal dominant, autosomal recessive or X-linked recessive fashion and gene panels or genomic sequencing will help unravel the diagnosis. Most individuals with autosomal dominant PNDM caused by heterozygous pathogenic variants in the ABCC8, INS and KCNJ11 are de novo. (55,56,58)

5. Gestational Diabetes

Gestational diabetes mellitus (GDM) presents as newly developing hyperglycemia in pregnant women with no previous history of diabetes. GDM affects 9% of pregnancies worldwide and is typically diagnosed at 24-28 weeks of pregnancy. GDM is increasing globally due to obesity and older maternal age, and sedentary lifestyle [59,60]. The pathogenesis of GDM is explained by the failure of pancreatic beta cells to produce enough insulin to meet the metabolic demands of pregnancy. During pregnancy, insulin resistance develops in response to placental hormones which leads to an increased production of insulin by pancreatic beta cells. The hyperinsulinemia of pregnancy plays a vital role in promoting glucose uptake by skeletal muscle and adipose tissue and suppressing glucose production by the liver. Hyperinsulinemia also promotes lipogenesis and increases energy storage in adipose tissue. GDM occurs when maternal beta cells cannot adapt to the metabolic requirements of the mother and fetus associated with pregnancy. GDM is associated with a higher risk of fetal macrosomia, premature birth, hypoglycemia at birth, shoulder dystocia and difficult delivery due to shoulder dystocia. The infant of a mother with GDM also has a higher risk of obesity, T2D, and CVD [59].

GDM is heterogeneous disorder: diabetes resolves in some patients while other patients progress to T2D [59]. Some patients diagnosed with GDM may likely have T1D based on evidence that there is an increased prevalence of the HLA-DR3/DR4 antigens among these women compared to racially matched pregnant women without diabetes [60]. Also, evidence suggests that approximately a third of these women with gestational have anti-islet cell antibodies [61].

6. Genetic Syndromes Associated with Diabetes Mellitus

Numerous syndromes are associated with diabetes mellitus, and the genetic etiologies are well documented [1,62,63]; these include single gene disorders, chromosomal aberrations and some triple repeat expansion disorders. Common clinical manifestations of syndromic diabetes include seizures, sensorineural hearing loss, ataxia, vision loss and developmental abnormalities. Some of the known chromosome disorders associated with diabetes mellitus include Down syndrome, Klinefelter syndrome, Turner syndrome and Prader-Willi syndrome. Some of the single gene disorders associated with diabetes mellitus, though individually rare, are numerous and some are listed in Table 1. Notable ones include Wolfram syndrome (DIDMOAD – diabetes insipidus, insulin-deficient diabetes mellitus, optic nerve atrophy and deafness), IPEX syndrome, Rabson-Mendenhall syndrome, Alstrom syndrome, Wolcott-Rallison syndrome, etc. Repeat expansion disorders such as

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Friedreich's ataxia, Huntington disease and myotonic dystrophy do have high rates of diabetes mellitus. Glycogen storage disease type1, acute intermittent porphyria, cystic fibrosis and hemochromatosis have increased rates of diabetes mellitus [1,8,63].

The development of affordable high throughput next generation sequencing techniques using exome and genome sequencing platforms, development of powerful statistical tools and computational software will help identify the gene involved in many rare syndromes that has diabetes as associated findings and by so doing study common variants in these genes that may help identify loci involved in diabetes [64].

Table of selected genetic syndromes associated with diabetes mellitus

Syndromes	Types of DM	Pattern of inheritance	Genes
Wolfram syndrome (DIDMOAD)	Type 1	AR	WFS1
Alstrom syndrome	IGT – Type 2	AR	ALMS1
Wolcott-Rallison syndrome	Type 1	AR	EIF2AK3
Bardet-Biedl syndrome	IGT – Type 2	AR (could be oligogenic)	Several genes (at least 26)
Berardinelli-Seip congenital lipodystrophy	IR – Type 2	AR/AD	AGPAT2 BSCL2
Woodhouse Sakati syndrome	Type 2	AR	DCAF17
H syndrome	Type 1	AR	SLC29A3
Primrose syndrome	IGT – Type 2	AD (de novo in all cases)	ZBTB20
Schmidt syndrome	Type 1	AR/AD/polygenic	
Johanson-Blizzard syndrome	Type 1	AR	UBR1
Laron dwarfism II	Type 2	AR	GHR
Hereditary pancreatitis	IGT – Type 1	AD	PRSS1, SPINK1, CFTR
Ataxia telangiectasia	Type 2	AR	ATM
Stiff Person syndrome	Type 1	AD/Multifactorial (mostly sporadic)	Unknown
Cockayne syndrome	IGT	AR	ERCC6, ERCC8
Werner syndrome	Type 2	AR	RECQL2
IPEX syndrome	Type 1 (Congenital)	XR	FOXP3
Leprechaunism	IR	AR	INSR
Rabson-Mendenhall syndrome	IR	AR	INSR
Bloom syndrome	Type 2	AR	RECQL3/BLM
Mulvihill-Smith syndrome	Type 1	AR	Unknown
Roussy-Levy syndrome	Type 2	AD	PMP22, MPZ
Ramon syndrome	Type 1	AR	Unknown
Prader-Willi syndrome	Type 2	15q abnormality (deletion, UPD, imprinting defect	Contiguous gene deletion, imprinting defect including SNRPN
Hereditary panhypopituitarism	Type 2	AR/XR	PROP1, SOX3
Congenital malabsorptive diarrhea type 4	Type 1	AR	NEUROG3

DM, diabetes mellitus; AR, autosomal recessive; AD, autosomal dominant; XR, X-linked recessive; IGT, impaired glucose tolerance; IR, insulin resistant; UPD, uniparental disomy.

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7. Mitochondrial Disorders and Diabetes

Primary mitochondrial disorders arise because of mitochondrial respiratory chain dysfunction, and they affect tissues and organs that are highly dependent on aerobic respiration [66]. They are a heterogeneous group of disorders that are caused by pathogenic variants in genes encoding the mitochondrial respiratory chain and related proteins. Mitochondrial disorders that involve nuclear gene are inherited in a Mendelian fashion (nDNA) whereas maternally inherited disorders are inherited strictly from the maternal line (mtDNA). mtDNA-related disorders are clinically heterogeneous because of mitochondrial heteroplasmy, and/or modifying genes and environmental influences. Individuals with mitochondrial disorders may present with symptoms involving several organ systems, in particular, organs that require a lot of energy for function. Common clinical symptoms include neurologic dysfunction, myopathy and/or cardiomyopathy, hearing loss, gastrointestinal disorders, renal tubular dysfunction, hematological disorders, ophthalmological abnormalities and T2D and pancreatic beta-cell dysfunction. T2D in mitochondrial disorders may progress rapidly to require insulin therapy. Some patients develop GAD and islet cell antibodies creating confusion with late-onset T1D [1,8].

Mitochondrial disorders associated with diabetes mellitus include Kearne-Sayres syndrome, mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS), maternally inherited diabetes and deafness (MIDD) and Pearson syndrome. MELAS and MIDD are due to maternally inherited pathogenic variants in the t-RNA gene. Pearson syndrome and KSS are usually sporadic and caused by large deletions in the mtDNA [67–69].

MELAS is caused by maternally inherited pathogenic variants in the t-RNA gene; a common pathogenic variant is A3243G. Affected individuals may present with stroke-like episodes, encephalopathy with seizures, myopathy, hearing loss, peripheral neuropathy, short stature, and lactic acidosis and the find of ragged red fibers on muscle biopsy. Signs and symptoms occur between ages 2 and 40 years. Patients may die young due to severity of neurologic dysfunction [67].

Kearne-Sayres syndrome is a progressive multisystem disorder that begins before age 20 years. Patients present with chronic progressive ophthalmoplegia, pigmentary retinopathy and cardiac conduction defects. Neurologic dysfunction, hearing loss, endocrinopathies, growth failure and other body systems dysfunction occur. The disorder is caused by a single large-scale mitochondrial tRNA deletion [69].

Maternally inherited diabetes and deafness is the most common mitochondrial disorder without major neurologic dysfunction of myopathy. It is caused by pathogenic variants in the mitochondrial tRNA; the A3243G variant is commonest. Other variants described include the A8296G and T3721C variants and a 10.4Kb deletion [67–69].

Pearson syndrome is usually sporadic and is the result of a deletion in the tRNA gene. Individuals present with sideroblastic anemia, pancytopenia, pancreatic exocrine insufficiency, renal tubular defect, growth failure and early death in most cases [69].

8. Metabolic Disorders with Erroneous Diabetes Mellitus Diagnosis

Some inborn errors of metabolism (metabolic disorders) may erroneously be diagnosed as diabetes mellitus. Some of these disorders present with severe ketoacidosis and hyperglycemia during metabolic decompensation. Hyperammonemia may be present in some cases. Some of these disorders include the organic acidemias – propionic, methylmalonic, and isovaleric acidemias, beta-ketothiolase deficiency (3-oxo-thiolase deficiency), 3-methylglutaconic aciduria and congenital disorders of glycosylation (CDG). However, CDG typically does not have the ketoacidosis hallmark of the organic acidemias. Recurrent pancreatitis in maple syrup urine disease can result hyperglycemia [70–72].

Comprehensive biochemical genetics work-up and metabolic gene panel testing will help with diagnosis and appropriate management.

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9. Conclusions

Diabetes mellitus is a common condition seen in all populations. Family studies have shown that there is genetic susceptibility to T1D and T2D, but the causative genes have eluded researchers. GWAS has identified several gene loci that increase susceptibility to T1D and T2D. Use of PRS and PPRS have enabled risk assessment in susceptible families. Monogenic diabetes mellitus is inherited in Mendelian fashion, and they include neonatal diabetes, several types of MODY, trinucleotide repeat expansion disorders, mitochondrial cytopathies, chromosomal syndromes and rare genetic syndromes with diabetes as associated findings. Some metabolic disorders have biochemical findings that cause erroneous diagnosis of diabetes. Clearer definition of diabetes phenotype, development of powerful statistical methodologies, use of next-generation sequencing applications to interrogate the genome, incorporation of epigenetic mechanisms and accurate curation of gene variants will help us realize application of genomic medicine and inform diabetes care.

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