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REVIEW

Genetic Factors of Diabetes

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Abstract Monogenic diabetes is a rare genetic type of diabetes caused by pancreatic β-cells dysfunction. All subtypes of monogenic diabetes are recognized in the pediatric population. They include maturity onset diabetes of the young, permanent neonatal diabetes mellitus and rare syndromic forms of diabetes. An early and proper diagnosis allows to implement an optimal treatment, leads to improved metabolic control and amelioration of related disabilities as well as increases the quality of life of the patients.

Keywords Monogenic diabetes · MODY · PNDM

Abbreviations

AS	Alström syndrome
DEND	Developmental delay, epilepsy and neonatal diabetes syndrome
GCK	Glucokinase
HNF1A	Hepatocyte nuclear factor-1-alpha
HNF1B	Hepatocyte nuclear factor-1-beta
HNF4A	Hepatocyte nuclear factor-4-alpha
i-DEND	Intermediate developmental delay, epilepsy and neonatal diabetes syndrome
MODY	Maturity onset diabetes of the young
NGS	Next-generation sequencing
PDX1	Pancreas/duodenum homeobox protein
PNDM	Permanent neonatal diabetes mellitus
WFS	Wolfram syndrome

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Introduction

Monogenic diabetes is a rare disease caused by single gene mutations and includes maturity onset diabetes of the young (MODY), permanent neonatal diabetes mellitus (PNDM) and syndromic forms of diabetes (Rubio-Cabezas et al. 2014).

MODY Diabetes

MODY is a clinically heterogeneous group of non–insulin dependent diabetes characterized by autosomal dominant inheritance, and an early age of onset, usually occurring prior to 25 years of age (Fajans et al. 2001). Currently, defects in thirteen genes are known to cause MODY, but the most common forms are caused by mutations in six of them: hepatocyte nuclear factor-1-alpha (*HNF1A*), hepatocyte nuclear factor-4-alpha (*HNF4A*), pancreas/duodenum homeobox protein-1 (*PDX1*), hepatocyte nuclear factor-1-beta (*HNF1B*), *BETA2/Neurod1* and glucokinase (*GCK*) (Bonnefond et al. 2012; Bowman et al. 2012; Siddiqui et al. 2015).

Mutations in the gene encoding transcription factor *HNF1A* are the most common cause of MODY in adult patients. Those mutations cause progressive β-cell dysfunction and hyperglycemia, and contribute to a considerable risk of microvascular and macrovascular complications (Colclough et al. 2013; Schwitzgebel 2014). Carriers of the mutations in the *HNF1A* gene displayed high sensitivity to treatment with sulfonylureas (Pearson et al. 2003).

The *GCK*-MODY subtype, responsible for the majority of MODY cases in a pediatric population, has been

associated with the presence of mutations in the *GCK* gene (Fendler et al. 2012; Gandica et al. 2015; Haliloglu et al. 2016). The *GCK* gene encodes the enzyme which plays a crucial role in the regulation of insulin secretion from β cells and hepatic glucose metabolism. The heterozygous inactivating mutations in the *GCK* gene lead to mild, asymptomatic, non-progressive fasting hyperglycaemia that does not result in long-term diabetes-related complication and does not require treatment (Osbak et al. 2009). A suitable diagnosis of the *GCK*-MODY diabetes allows to stop administering insulin injections and use a diet alone (Borowiec et al. 2012). In the Human Gene Mutation Database (HGMD), 765 mutations in the *GCK* gene have been described.

PNDM Diabetes

A complete deficiency of glucokinase activity, which results from recessive *GCK* gene mutations, causes a rare, isolated form of PNDM. Homozygous or compound heterozygous *GCK* gene mutations cause severe hyperglycemia and require insulin treatment soon after birth (Njolstad et al. 2001, 2003). PNDM is characterized by an onset of hyperglycemia. It occurs within the first six months of life and does not go into remission. The clinical course can be non-syndromic, as it happens in the case of mutations in *GCK* gene, or can be accompanied by additional features (Naylor et al. 2011).

The most common causes of PNDM are heterozygous activating mutations in the β-cell ATP-sensitive potassium channel (KATP) genes *KCNJ11* and *ABCC8* (Ellard et al. 2007). They account for about 50% of all PNDM cases. KATP channels play a central role in glucose-stimulated insulin secretion from pancreatic β cells. When plasma glucose level is low, potassium channels are open because of the low cytosolic ATP/ADP ratio that maintains the membrane potential hyperpolarized, which prevents calcium entry through voltage-gated calcium channels and insulin secretion. Glucose metabolism leads to an increase in the ratio of cytosolic ATP/ADP. ATP binds to the Kir6.2 subunit of the KATP channels, initiating channels closure, membrane depolarization and insulin secretion (Lang and Light 2010).

Activating mutations in *KCNJ11* and *ABCC8* genes cause diabetes by reducing the sensitivity of the KATP channel to ATP (Babenko et al. 2006; Gloyn et al. 2004).

The majority of patients with *KCNJ11* mutations have isolated diabetes but approximately 20% demonstrate some more neurodevelopmental impairments, such as developmental delay, motor weakness and epilepsy described as DEND syndrome. A milder clinical picture, consisting of neonatal diabetes with developmental delay and/or muscle weakness without epilepsy, is more common and known as intermediate DEND (i-DEND) syndrome. There is a strong genotype–phenotype correlation with the functional severity of the mutations in the *KCNJ11* gene, connected with differences in clinical phenotype (Hattersley and Ashcroft 2005). Although, mutations at the same residue can cause different functional effects (Shimomura et al. 2006).

An identification of the *KCNJ11* and *ABCC8* mutations has important therapeutic implications. Carriers of the mutations can switch from insulin injections to oral sulfonylurea, which results in improved glycemic control (Sagen et al. 2004). However, it has been shown that the use of sulfonylurea in patients with i-DEND syndrome, caused by *KCNJ11* mutations, not only improves metabolic control but also alleviates neurological disabilities (Mlynarski et al. 2007; Fendler et al. 2013). The patient with mutation His46Leu in the *KCNJ11* described by Młynarski et al. (2007) revealed a marked motor and mental developmental amelioration after switching from insulin to sulfonylurea (glibenclamide). Imaging studies confirm improvement in the cerebellar perfusion after implementation of a sulfonylurea treatment.

Among patients with an isolated form of PNDM, 20% have heterozygous mutations in the gene encoding insulin (*INS*). The majority of them are de novo in origin. Carriers of *INS* mutations are usually diagnosed at older age, whereas those with *KCNJ11* and *ABCC8* mutations and are diagnosed not later than within the first 6 months of life (Stoy et al. 2007). However, recessive mutations in *INS* causing PNDM have also been identified (Garin et al. 2010). Heterozygous mutations in the *INS* lead to the synthesis of structurally abnormal proinsulin. The mutations are located in crucial regions of the proinsulin molecule and prevent proper proinsulin folding. An abnormally folded proinsulin molecule may induce an unfolded protein response and undergo degradation in the endoplasmic reticulum, leading to severe endoplasmic reticulum stress and cell death by apoptosis (Stoy et al. 2007). In comparison to carriers of *KCNJ11* and *ABCC8* mutations, patients with *INS* mutations can be currently treated only with insulin, because there is no specific treatment for them (Stoy et al. 2010).

Syndromic Diabetes

Particularly, a pediatric population is affected by very rare and very severe genetic disorders, related to diabetes. Wolfram, Alström and Bardet–Biedl (WABB) syndromes are an autosomal recessive multi-systemic diseases requiring multidisciplinary medical care. Due to being rare and highly complex WABB syndromes are often misdiagnosed, diagnosed too late or not diagnosed at all. To

improve the diagnosis and treatment of patients with WABB syndromes, a multi-center project, called the Euro-WABB, was created (Farmer et al. 2013).

Alström Syndrome

Alström syndrome (AS) is a single gene form of early onset obesity, retinal dystrophy leading to blindness and type 2 diabetes caused by mutations in the *ALMS1* gene. Other clinical features, typical for to AS syndrome, include sensorineural hearing loss, dilated cardiomyopathy, insulin resistance with hyperinsulinemia, hepatic and renal dysfunction, hypertension, hypothyroidism, hyperlipidemia, hypogonadism, urological abnormalities, short stature in adulthood and bone–skeletal anomalies (Marshall et al. 2007a). The prevalence of AS patients is less than one per million in general population (Marshall et al. 2007b). The life span of patients with AS rarely exceeds 40 years. There is also no specific treatment for such patients; therefore, an early diagnosis and medical intervention can prevent progression of the disease and improve the quality of life of patients (Marshall et al. 2007a).

Wolfram Syndrome

Wolfram syndrome (WFS) is a rare form of diabetes mellitus, diabetes insipidus, optic nerve atrophy, hearing loss and neurodegeneration caused by recessive mutations in the wolframin gene (*WFS1*) (Cryns et al. 2003). So far there are no reliable data about the prevalence of the Wolfram syndrome. One of the publications reveals that the prevalence of Wolfram syndrome among Polish children with diabetes is about 0.12% (Zmyslowska et al. 2014).

Lack of effective treatments makes the current WFS prognosis poor. The average life expectancy of patients is approximately 30 years. Causes of death include central respiratory failure and renal failure secondary to infection (Barrett and Bundey 1997). However, there are attempts to establish new therapeutic approaches for patients with WFS. One of them is a drug repurposing strategy, which means that drugs currently approved by the United States Food and Drug Administration (FDA), the European Commission and the European Medicines Agency (EMA) can be adapted so that they can be administered to WFS patients (Urano 2016).

Bardet–Biedl Syndrome

Bardet–Biedl syndrome (BBS) is a very rare, multisystem disorder characterized by progressive retinal degeneration, central obesity, mental retardation, renal anomalies, polydactyly, and hypogenitalism. In addition, metabolic defects, cardiovascular anomalies, speech deficiency, hearing loss, hypertension, hepatic defects and high incidence of diabetes mellitus can occur. BBS is a genetically heterogeneous disease with 19 genes identified until now (Khan et al. 2016).

Prevalence and Diagnosis of Monogenic Diabetes

The most recent systematic population screening in UK pediatric clinics revealed that the prevalence of monogenic diabetes, affecting patients under the age of 20, is 2.5% (Shepherd et al. 2016).

In the Polish pediatric population, the prevalence of monogenic diabetes is estimated to be 3.1–4.2% (Fendler et al. 2012). Monogenic forms of diabetes are often misdiagnosed as type 1 or type 2 diabetes. Therefore, a proper monogenic diabetes classification is crucial to initiate an appropriate treatment and genetic counseling, as well as to make predictions with regards to the course of the disease and long-term complications (Amed and Oram 2016; Kleinberger and Pollin 2015). So far, more than 30 genes have appeared to be related to monogenic diabetes development (Alkorta-Aranburu et al. 2014).

However, still 11–39% patients are clinically suspected to suffer from monogenic diseases but without identified molecular causes (Edghill et al. 2010; Vaxillaire and Froguel 2009). Although, the Sanger sequencing is still a gold standard in diagnostics of monogenic diabetes, the development of a new sequencing technology, i.e., NGS (next-generation sequencing), significantly improves genetic testing and the definition of new genes involved in the development of the disease (Ellard et al. 2013; Philippe et al. 2015).

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