GENETIC SPECTRUM OF NEONATAL DIABETES

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ABSTRACT

Neonatal diabetes (ND) appears during the first months of life and is caused by a single gene mutation. It is heterogenous and very different compared to other forms of multi-factorial or polygenic diabetes. Clinically, this form is extremely severe, however, early genetic diagnosis is pivotal for successful therapy. A large palette of genes is demonstrated to be a cause of ND, however, the mechanisms of permanent hyperglycemia are different. This review will give an overview of more frequent genetic mutations causing ND, including the function of the mutated genes and the specific therapy for certain sub-forms.

Keywords: Classification; Mutations; Neonatal diabetes (ND); Syndromes.

INTRODUCTION

Most of the patients with diabetes mellitus (DM) in childhood suffer from DM type 1 (DMT1) that is of auto-immune etiology [1,2]. This form of diabetes appears after the first 6 months of life, and reaches the highest incidence in the 9-14 years age group, with the rising incidence in the age group before 4 years of age [3]. The persisting hyper-glycemia is due to autoimmune destruction of insulin producing β-cells in the endocrine pancreas leading to insulin deficiency. It is considered a polygenic disease involving mostly DQ and DR human leukocyte antigen (HLA) genes conferring susceptibility or resistance toward the disease [4-8]. Diabetes mellitus type 1 accounts for more than 95.0% of cases in childhood [7,9,10]. During the last few decades, obesity in childhood has caused increase of DM type 2 (DMT2) in children, which is induced by

an interplay of genetic and environmental factors. Genetic factors involved in DMT2 are still not precisely elucidated. A number of different gene polymorphisms affecting β-cell function causes impaired insulin secretion or insulin resistance [11,12]. The prevalence of DMT2 in childhood and adolescence varies in different countries, reaching up to 30.0% of all cases with DM in regions with the highest childhood obesity rates [1].

Monogenic diabetes (MD) caused by mutations of a single gene is a separate form of DM with a distinct etiology, clinical presentation, therapy and outcome. Monogenic diabetes is a heterogenous group of sub-forms of diabetes caused by mutations in different, highly penetrant genes that are pivotal for pancreas development, sensing of the level of glucose for insulin secretion, cellular metabolism, cell membrane depolarization control, or insulin synthesis/excretion [13-19]. Monogenic diabetes is not common, but it does account for 1.0-6.0% of pediatric diabetes cases [20].

Generally, based upon the detected mutation, timing of presentation, and affected genes, MD can be classified as follows [19]: *1)* neonatal diabetes (ND) (occurring before 6 months), *2)* syndromic ND associated with extra pancreatic features, and *3)* autosomal dominant familial hyperglycemia or diabetes or maturity onset diabetes of the young (MODY). This review will give an overview of mutations causing diabetes in the neonatal period that includes ND and syndromic diabetes.

Genes Involved in Monogenic Diabetes. Mutations in about 40 different genes are recognized as a cause of MD. These encompass genes involved in different processes that could compromise insulin secretion and action such as: reduction of β-cell number or pancreatic aplasia, impaired β-cell development, glucose sensing or metabolism, failure to depolarize cellular membrane and expulsion of insulin in circulation, failure of insulin synthesis, increased destruction of β-cells including immune-based

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destruction, increased apoptosis, and endoplasmatic reticulum stress, as well as other mechanisms that need to be elucidated [21-23]. Each of these steps in insulin secretion and action is under the control of a particular gene [19,24] (Tables 1 and 2).

Most of the recent molecular analyses in MD have been performed by Sanger sequencing using specific primers, or targeted next generation sequencing (NGS) of involved exons and searching for multiple gene mutations [25-28]. We have reviewed most of the recent guidelines for the diagnosis and treatment of all forms of ND, as well as numerous original articles describing characterizations of ND caused by different mutations.

Neonatal Diabetes. Although the neonatal period encompasses only the first 4 weeks of postnatal life, the term ND, by convention, is used for the DM that appears in neonates and infants up to 6 months of age, although some forms might appear up to 9-12 months of age [20,24]. It was first described in 1852 and has been reported since then in different countries and ethnicities around the world

[24,28-33]. If the hyperglycemia appears in the infant of 6-12 months, the distinction of the ND form early onset of DMT1 is necessary [34]. However, most of the patients do not display autoimmunity at this early age and belong to the monogenic "neonatal diabetes" [35]. The MODY mutations are present at birth, and they cause the appearance of diabetes later in life. Neonatal diabetes is rare, it appears, according to different authors, in one case per 100,000, 300,000 or even per 500,000 live births [19,23,36,37]. It can be classified as: transient ND mellitus (TNDM), and permanent ND mellitus (PNDM) [19,24,34,38,41]. Aguillar-Bryan *et al.* [24] have collected more than 195 patients from different studies and calculated that TNDM is more frequent, affecting 57.0% (111/ 195) of all neonates with ND.

Transient Neonatal Diabetes Mellitus. Transient ND mellitus appears in the first days or weeks after birth, usually in newborns with intrauterine growth retardation (IUGR). After introduction of low doses of insulin therapy, it resolves, usually approximately up to 4 months of age,

Table 1. Gene mutations in transient neonatal diabetes mellitus.

Mechanism of β-Cell Dysfunction	Gene Mutation	Chromosome Locus	Inheritance	Additional Features	Therapy
Reduced β-cell development	*ZAC* (*IPLAG1*)/ *HYMA1*	6q24	imprinting; AD	macroglossia; umbilical hernia	insulin
	ZEP57	6p22.1	AR		insulin
	HNF1B	17q21.3	AD	pancreatic hypoplasia; renal cysts	
Failure to depolarize membrane	*KCNJ11*[a] (Kir6.2)	11p15.1	AD; *de novo*	low birth weight; developmental delay; DEND	sulfonylurea
Failure to close KATP channel	*ABCC8*[a] (*SUR1*)	11p15.1	AD; AR; *de novo*	low birth weight	sulfonylurea
Abnormal β-cell function	*INS*[a] (proinsulin)	11p15.5	AR	low birth weight	insulin

AD: autosomal dominant; AR: autosomal recessive; DEND: developmental delay, epilepsy, DM; KATP: ATP-dependent potassium channel.

[a] These mutations can also be found in permanent neonatal diabetes mellitus.

Table 2. Gene mutations in permanent neonatal diabetes mellitus.

Mechanism of β-Cell Dysfunction	Gene Mutation	Chromosome Locus	Inheritance	Additional Features	Therapy
Failure to depolarize membrane	*KCNJ11* (Kir6.2)	11p15.1	AD; *de novo*	low birth weight; developmental delay; DEND	sulfonylurea
Failure to close KATP channel	*ABCC8* (*SUR1*)	11p15.1	*de novo*; AD; AR	low birth weight	sulfonylurea
Abnormal β-cell function	*INS* (proinsulin)	11p15.5	*de novo*; AD; AR	low birthweight	insulin
Abnormal glucose sensing	*GCK*	7p15-13	AR		
Abnormal pancreatic development	*PDX1*	13.q12.1	AR	pancreatic afenesis steatorrhea	

AD: autosomal dominant; AR: autosomal recessive; DEND: developmental delay, epilepsy, DM.

Table 3. Mutations in syndromic neonatal diabetes mellitus.

Mechanism	Gene Mutation	Chromosome Locus	Inheritance	Additional Features
Fanconi-Bickel syndrome	*SCL2A2* (*GLUT2*)	3q26.1-26.3	AR	hypergalatosemia; liver dysfunction
Roger syndrome	*SCL19A2*	1q23.3	AR	thiamine-responsive megaloblastic anemia; sensorinueral deafness
Abnormal pancreatic development	*RFX6*	6q22.1	AR	intestinal atresia + bladder agenesis
	GATA6	18q11-q11.2	AD	pancreatic agenesis; heart defects; biliary abnormalities
	GATA4	8p23.1	AD	pancreatic agenesis + heart defects
	GLIS3	9p24.3-p23	AR	congenital hypothyridism; glaucoma; hepatic fibrosis; renal cysts
	NEURG3	10q21.3	AR	malabsorbtive diarrhea
	NEUROD1	2q32	AR	cerebellar hypoplasia; visual impairment; deafness
	PAX6	11.p13	AR	microphtalmia; brain malformations
	MNX1	7q36.3	AR	developmental delay; sacral agenesis; imperforate anus
	MNX2-2	20p11.22	AR	developmental delay; hypotonia; short stature; deafness
	PTF1	10.p12.2	AR	pancreatic hypoplasia; cerebellar hypoplasia
Destruction of β-cells				
Wolcott-Rallison syndrome	*EIF2AK3*	2p11.2	*de novo* or AD	skeletal dysplasia; liver dysfunction
	IER3IP1	18q21.2	AR	microcephaly; lisencephaly; enceph-alopathy
IPEX syndrome	*FOXP3*	Xp11.23-p13.3	X-linked; recessive	autoimmune enteropathy; autoimmune hypothyroidism; eczema
Wolfram syndrome (DIDMOAD)[a]	*WFS1*	4p16.1	AR	optic atrophy; DM; DI
	WFS1	4p16.1	AD	congenital cataracts; deafness

AR: autosomal recessive; AD: autosomal dominant.

[a] Also known as Wolfram syndrome (see text).

but its duration could be extended up to 18 months [35-38]. However, during adolescence or in the young adult period, relapses can occur in about 50.0% of patients, when it resembles DMT2 [36-38]. Genes involved in TNDM are provided in Table 1.

The genetic origin of TNDM has been established for approximately 90.0% of patients with TNDM. The major genetic change causing the disease is abnormal imprinting at chromosome 6q24, which appears in approximately 70.0% of patients with TNDM [36,39,40-43]. Usually, for this chromosome region, only alleles inherited from the father are expressed, whereas mother's alleles are imprinted. Overexpression of paternal genes in this region can happen through uniparental isodisomy or inheritance of the duplication of the region from the father [44,45]. On the other hand, defects in maternal methylation of the 6q24 region can cause activation of the maternal alleles [46,47]. The methylation defect might be inherited or can appear sporadically. The 6q24 region is rich in imprinted genes. Only a few of them have been studied in detail, such as the *ZAC* and *HYMA1* genes. The regulator of the methylation of this chromosome region is the *ZFP57* gene. ZAC (zinc finger protein that regulates apoptosis and cell cycle arrest) is a multifunctional transcription factor and coactivator of p53 and coactivator or corepressor of some nuclear hormone receptors [48]. *ZAC* has been described as a tumor suppressor gene and its overexpression in cell lines has shown decreased rate of cell replication, increased apoptosis and cell mitosis G1 arrest [49]. Thus, when over-expressed, it would reduce growth of the β-cell mass, possibly through increase of the peroxisome proliferator-activated receptor γ (PPARγ) expression, which is an in-sulin sensitizer, during embryogenesis and slow down the β-cell proliferation. The function of *HYMAI* (hydatiform mole-associated and imprinted also called *PLAGL1*) has still to be elucidated. These methylation defects have the following effects: decreased cell replication, increased apoptosis, delayed maturation of pancreatic islets, and

decreased β-cell mass that cause impaired insulin secretion *in utero* and after birth. DNA multiple methylation defects can also appear and they are usually caused by mutation in the *ZFP57* gene when TNDM is only a part of the complex clinical picture [49]. Most of these facts have been confirmed in the mouse model [50].

Approximately 30.0% of children with TNDM have additional features such as umbilical hernia or macroglossia [43]. Insulin therapy is necessary, however, the dose is quickly tapered-down and not necessary after 12 weeks [19]. The relapse is usually common during puberty, it appears in 50.0-60.0% of patients and is presented as DMT2. Due to some residual degree of endogenous insulin secretion, many patients are successfully treated with sulfonylurea [51,52]. If the cause of the disease is duplication of the parental 6q24 region, the genetic risk for future children should be discussed with the family.

Transient ND mellitus can also be caused by mutations of the *ABCC8* and *KCNJ11* genes, and their function will be discussed with PNDM, as these two mutations can cause both TNDM and PNDM. Transient ND mellitus has rarely been described in association with HNF1 β mutations, causing pancreatic hypoplasia and associated prenatal cystic kidney [53], autosomal recessive insulin gene mutations [54], or homozygous glucokinase (GCK) mutation inherited from both parents in consanguineous families (Table 1). These genes and their mutations will be discussed in the section on PNDM.

Permanent Neonatal Diabetes Mellitus. Permanent ND mellitus has a very similar clinical presentation as TNDM, and can be distinguished only on the basis of the gene mutations, especially in hyperglycemic children with a low birth weight [55]. This diabetes is permanent, remission does not occur. About 10 genes are involved in the etiology of PNDM causing abnormal pancreatic development, increased apoptosis, reduction of β-cell mass and β-cell dysfunction. However, the most common mutations are in the *KCNJ11* and *ABCC8* genes, which account for approximately 30.0% of all PNDM cases, *INS* gene mutations accounting for 12.0%, and glucokinase (*GCK* gene) mutations. All of these genes are involved in glucose sensing and insulin secretion [19,24,55-57]. The function of these genes has been elucidated in Table 2 (Figure 1).

Channelopathies. *KCNJ11* and *ABCC8* gene mutations are responsible for approximately 40.0% of permanent or transient hyperglycemia (NDM) cases [56,58]. Most of them (approximately 60.0%) occur *de novo*. They act through increase of activity of ATP-sensitive potassium channels located on the β-cell membrane [35,59,60]. Glucose enters the cell facilitated by the Glut1 transporter, and the enzyme glucokinase (GCK) converts it to glucose-6-phosphate that is then transferred into mitochondria.

There, increased metabolic activity induces an increase of ATP/ADP ratio that results in a closure of the membrane K_{ATP} channel. As a result, the β-cell membrane gets depolarized, followed by influx of Ca^{++} into the cell, which triggers insulin secretion and expulsion from the β-cell [57,59] (Figure 1). The K_{ATP} channel is a key component of the glucose stimulated insulin secretion pathway. It is composed of four Kir6.2 subunits that compose the K+ conducting pore encoded by the *KCNJ11* gene. Four SUR1 regulatory subunits encoded by the *ABCC8* gene are located at the external site of the pore and regulate the channel activity. Dominant activating mutations in *KCNJ11* or *ABCC8* cause a permanently opened K_{ATP} channel, irrespective of the glucose level, which decreases the channel sensitivity toward ATP, disables the membrane depolarization and prevents insulin secretion causing NDM [57-59]. More than 205 different mutations of the *KCNJ11* and 748 of the *ABCC8* genes have been reported [59-65] Many additional polymorphisms with significance to be elucidated also have been referred [65]. Mutations in the *KCNJ11* gene are usually located at the N or C terminus below the plasma membrane, around the inhibitory ATP binding site, and they reduce affinity for ATP. The *ABCC8* gene mutations, on the other hand, are located throughout the entire molecule, however, the mechanism of the channel activation is poorly understood although it has been suggested that SUR1 acts to antagonize the Mg-dependent stimulatory action on Kir6.2 [61,64]. Mutations could be point mutations, *e.g.* missense, nonsense, frameshift, splicing mutations and deletions [65]. Depending upon the mutations, different numbers of permanently opened K_{ATP} channels and their different sensitivity for flux of ATP occurs, thus causing PNDM or TNDM. A complex interplay between Kir6.2 and SUR1 subunits, also involving
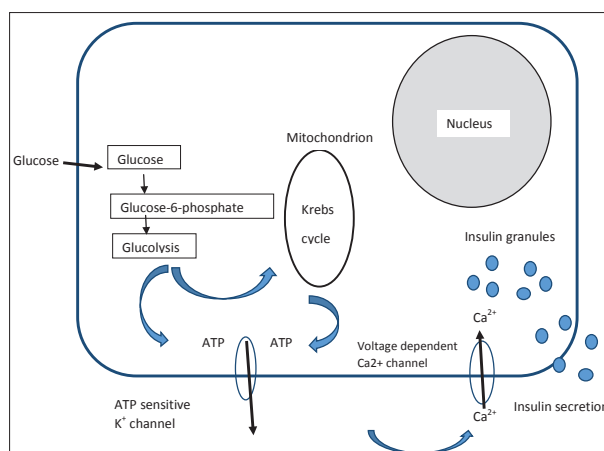

Figure1. Normal insulin secretion process after glucose enters the β-cell is presented. *KCNJ11* and *ABCC8* gene mutations influence the ATP channel causing inability of insulin expulsion.

Mg++ has been described [66]. *KCNJ11* and *SUR1* gene mutations occur *de novo* in 80.0% of patients without family history, causing isolated PNDM. The remaining cases are familial, and they are always dominantly transferred. *KCNJ11* gene mutations cause PNDM in 90.0% of patients who carry it, whereas the *ABCC8* gene mutations causes PNDM in less than 40.0% of patients. The remaining 10.0% and >60.0% of mutations, respectively cause TNDM [65]. Both *KCNJ11* and *ABCC8* genes are located on chromosome 11p, 4.5 kb apart. *KCNJ11* encodes for the 390-amino acid Kir6.2 protein, and *ABCC8* consists of 39 exons. It encodes for the SUR1 (sulphonyl-urea receptor) protein that consists of 1582 amino acids [65].

Permanent ND mellitus due to *KCNJ11* and *ABCC8* gene mutations usually have an acute clinical presentation in neonates at the age from several days of age up to 26 weeks after birth, who are born with a lower birth weight, but not as low as in TNDM [67]. Extreme hyperglycemia, severe dehydration, ketoacidosis hypoinsulinemia, and immediate insulin dependency are the common set of symptoms [19,24,68]. However, milder forms have been described in certain mutations [24,60]. Due to the confirmed expression of K_{ATP} channels in muscle cells and neurons, approximately 20.0-30.0% of patients have associated neurological features, which are usually associated with certain mutations such as V59M or R210 C of the *KCNJ11* gene [65,69-72]. Some of the children have PNDM, muscle weakness and hypotonia associated with epilepsy when this is termed DEND (developmental delay, epilepsy, ND) syndrome [71]. Others have different level of developmental delay, lower IQ, may have attention deficit hyperactivity disorder (ADHD), autism, anxiety, hypotonia, muscule weakness, balance problems, learning disabilities, and are termed iDEND (intrremediate DEND) syndrome. The V59M mutation has mostly been blamed for iDEND. In general, patients have lower academic achievements [72-74]. There are some data confirming that mutations that increase channel activity less than 15-fold are associated with both PNDM and TNDM, whereas, if the channel activity is more than 15-fold higher, DEND syndrome occurs [24]. Breakthrough in the treatment of children with PNDM occurred when sulfonylurea was shown to be a successful therapy that normalizes the function of the K_{ATP} channel [75,76] but also improves, to some extent, the developmental issues if given early enough [77]. Beyond 90.0% of patients with PNDM can be transferred from insulin to sulfonylurea and treated long-term with careful tapering of the doses that provides a very stable, long-term glycemic control [76,78]. However, in the review by Aguilar-Bryan and Bryan [24], 22 different *KCNJ11* gene mutations had a good response to sulfonylurea, whereas seven did not, whereas 20 *ABCC8*

gene mutations had a good response *vs.* three mutations where the response did not occur. In the patients who did not react favorably to sulfonylurea, therapy with insulin was necessary [24]. Therefore, genetic testing is mandatory for individualized treatment, improved outcome, and a better quality of life (QoL) [58,79-81].

Insulin gene mutations. Dominant mutations of the insulin gene (*INS*) are the second most frequent cause of PNDM [82,83]. Mutated genes usually appear *de novo* in 80.0% of cases, and cause disturbances in the folding of the proinsulin and/or insulin protein that becomes nonfunctional, but additionally causes endoplasmic reticulum stress due to protein accumulation inducing apoptosis of the β-cell [56]. No other tissues or organs are affected. A significant portion of mutations are *de novo*, usually dominant, and affect the disulfide bonds in the insulin molecule [84]. Diabetes is typically insulin-deficient, affected newborns have a low birth weight, hyperglycemia usually occurs during the second month of life. It can occasionally appear after the age of 6 months, and therefore, in all babies with negative anti β-cell antibodies, molecular testing for insulin gene mutations is necessary. Insulin gene mutations causing PNDM can also be recessive, causing delayed fetal growth, low birth weight, and severe early presentation after birth [82,83]. All newborns with a mutation of the insulin gene require insulin therapy.

Glucokinase mutations. Glucokinase is the enzyme that regulates adequate glucose-stimulated insulin secretion from the β-cell, and is termed a sensor for glucose [85]. In humans, the threshold of glycemia for insulin release is set to approximaltely 5 mmol/L. More than 200 mutations have been detected in the *GCK* gene. However, most of them being autosomal dominant mutations, if in heterozygous form, cause MODY2, *e.g.* mild hyperglycemia due to the inappropriate sensing of glucose level. They are usually detected later in childhood or during young adult life. However, several homozygous inactivating mutations are described in PNDM [86,87]. Recessive mutations, when in homozygous or compound homozygous states, cause complete lack of insulin secretion and PNDM, especially in consanguineous families. Parents usually have a history of low glucose tolerance or untreated mild diabetes. This form of diabetes accounts for only 2.0-3.0% of all patients with PNDM [88]. These neonates have low body mass due to insulin deficiency and are treated with insulin. Mutations of other genes causing ND are rare, and are given in Table 1.

Syndromic Neonatal Diabetes Mellitus. Syndromic ND mellitus (SNDM) should be considered after more common forms (K_{ATP} channelopathies) and other more frequent mutations are excluded. The number of genes discovered inducing SNDM is increasing with the newer molecular techniques. Most cases of SNDM belong to syn-

dromes with associated extra-pancreatic features affecting different organs or functions. All are very rare, some with only a few patients described. All require therapy with insulin, and other therapeutic procedures for associated problems. Major characteristics have been presented in Table 2. Only some will be mentioned briefly.

Eukaryotic initiation factor 2α kinase 3 (EIF2AK3) mutations in homozygotes or compound heterozygotes cause Wolcott-Rallison syndrome. It is the most common form of PNDM in consanguineous families. Clinical presentation is complex, and comprises additional features such as multiple epiphyseal dysplasia, growth retardation, occasionally associated with learning difficulties, epilepsy, hepatic and/or renal dysfunction, abnormalities of the cardiovascular system and dysfunction of the exocrine pancreas [89,90]. The location of this gene is at chromosome 2p12 and it is involved in the regulation of protein-folding in the endoplasmic reticulum [90,91]. If mutated, it causes endoplasmic stress and initiates apoptosis in many tissues including β-cells. About 20 different mutations have so far been reported, children present with ketoacidosis and insulin therapy is mandatory [24,91,92].

Mutations in the *WFS1* gene cause Wolfram syndrome. It is a very complex syndrome, also known as DIDMOAD, symptoms consisting of DM, diabetes insipidus, optic atrophy, deafness as well as neurodegeneration. It appears in 1:160,000-1:770,000 individuals. Although, on average it appears at 6 years of age, neonatal cases have been described with insulin-dependence, and additional features during childhood. The β-cell degeneration due to irregular folding of the protein wolframin, induces endoplasmic stress in different organs [93-95]. Mutations can be autosomal recessive, however, several dominant mutations have also been described [96]. Insulin therapy is mandatory, however, it should be accompanied by a complex involvement of ophtalmologists, nephrologists, otolaryngologists and neurologists. Life-span is shortened [97].

Immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome is caused by mutations of the fork-head box protein 3 (*FOXP3*) gene located on the short arm of the X chromosome (Xp11.23). It encodes FOXP3 protein that is crucial for the function of regulatory T-cells, thus the diabetes is of an autoimmune nature and general disorder of immunity. More than 70 different mutations have been described. The most common mutation is the substitution of the Pro339 by alanine or other amino acids [98]. Clinical presentation involves enteropathy, autoimmune diabetes, immunodeficiency, severe infections; 65.0% of patients survive. Treatment with immunosuppressive agents is recommended [99].

Utility of Testing for Neonatal Diabetes. Having in mind all previously mentioned forms of PNDM, and

many others that are extremely rare, there is a reasonable algorithm of testing that should be performed when NDM occurs. The first approach is to test for 6q24 abnormalities which cause 68.0% of TNDM. If it is negative, further testing for the *KCNJ11* gene should follow (10.0% of patients with NDM carry it), and if it is normal, tests for *ABCC8* gene mutations should be performed, as they are the cause of ND in 9.0% of patients. Novel methods provide simultaneous testing for many genes involved in monogenic diabetes including both NDM and MODY. Targeted NGS has been successfully applied [26] as well as the combination of NGS and methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA), assay for the detection of both transient and permanent NDM [100].

Molecular diagnosis of NDM is of the utmost importance as it provides the appropriate selection of therapy [77-79], which is in concordance with precision medicine [101]. It is also economically valuable as it provides the opportunity for transfer to oral therapy in certain patients [102,103], improving the QoL, and decreasing the cost of treatment [104]. On the other hand, knowing the molecular mechanisms of hyperglycemia provides new research for novel therapies [105], and gives insight into the mechanisms of more common forms of diabetes [106].

Conclusions. Neonatal diabetes is monogenic, and genetically polymorphic. Due to the severity of onset, danger of an unfavorable outcome and uncertain future, NDM should be genetically characterized as soon as possible through international platforms for countries with funding problems for genetic testing. The importance of this testing is providing a precise diagnosis, precision medicine, individual therapy and best possible outcome. However, genetic diagnosis has also taught endocrinologists of many physiological pathways in the β-cell function, genetic control of glucose homeostasis and interplay of involved genes in control of other organs.

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