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Permanent Neonatal Diabetes Mellitus

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Summary

Clinical characteristics

Permanent neonatal diabetes mellitus (PNDM) is characterized by the onset of hyperglycemia within the first six months of life (mean age: 7 weeks; range: birth to age 26 weeks). The diabetes mellitus is associated with partial or complete insulin deficiency. Clinical manifestations at the time of diagnosis include hyperglycemia, glycosuria, osmotic polyuria, severe dehydration, and history of intrauterine growth deficiency. Therapy with insulin and/or oral hypoglycemic medications (in some molecular causes of PNDM) can correct the hyperglycemia and result in dramatic catch-up growth. The course of PNDM varies by genotype.

Diagnosis/testing

The diagnosis of PNDM is established in an infant with diabetes mellitus diagnosed in the first six months of life that does not resolve over time. Molecular genetic testing is recommended, as identification of a specific molecular cause of PNMD can guide treatment.

Management

Targeted therapy: Oral sulfonylureas after initial management with insulin in those with *ABCC8*- or *KCNJ11*-related PNDM.

Supportive care: Rehydration and intravenous insulin infusion promptly after diagnosis; subcutaneous insulin therapy when the infant is stable and tolerating oral feedings; high caloric diet to achieve weight gain; developmental and educational support in those with *KCNJ11*-, *MNX1*-, *NEUROD1*-, or *NKX2-2*-related PNDM; anti-seizure medication as needed in those with DEND syndrome (*d*evelopmental delay, *e*pilepsy, and *n*eonatal *d*iabetes mellitus); pancreatic enzyme replacement therapy in those with exocrine pancreatic insufficiency.

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Surveillance: Frequent blood glucose monitoring; urinalysis for microalbuminuria and cystatin C measurement annually beginning at age ten years to screen for kidney manifestations of persistent hyperglycemia; ophthalmologic examination for retinopathy annually beginning at age ten years; developmental evaluation annually or as needed in those with *KCNJ11*-, *MNX1*-, *NEUROD1*-, or *NKX2-2*-related PNDM; neurology evaluation and EEG in those with *KCNJ11*-related DEND syndrome; evaluation of pancreatic exocrine function in those with symptoms of malabsorption; serum concentrations of fat-soluble vitamins every six months in those with known exocrine pancreatic insufficiency.

Agents/circumstances to avoid: In general, avoid rapid-acting insulin preparations (lispro and aspart) as well as short-acting (regular) insulin preparations (except as a continuous intravenous or subcutaneous infusion), as they may cause severe hypoglycemia in young children.

Evaluation of relatives at risk: Evaluate apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from surveillance and treatment of hyperglycemia.

Pregnancy management: Pregnant women with PNDM should be managed by an endocrinologist and maternal-fetal medicine specialist; high-resolution ultrasonography and fetal echocardiography should be offered during pregnancy to screen for congenital anomalies in the fetus.

Genetic counseling

The mode of inheritance of PNDM varies by gene: *ABCC8*- and *INS*-related PNDM are inherited in an autosomal dominant or an autosomal recessive manner; *GATA6*-, *HNF1B*-, and *KCNJ11*-related PNDM are inherited in an autosomal dominant manner; *EIF2AK3*-, *GCK*-, *GLIS3*-, *MNX1*-, *NEUROD1*-, *NKX2-2*-, *PDX1*-, *PTF1A*-, *RFX6*-, *SLC2A2*-, and *SLC19A2*-related PNDM are inherited in an autosomal recessive manner.

Autosomal dominant inheritance: The majority of individuals with autosomal dominant PNDM caused by a heterozygous pathogenic variant in *ABCC8*, *INS*, or *KCNJ11* have the disorder as the result of a *de novo* pathogenic variant. Each child of an individual with PNDM inherited in an autosomal dominant manner has a 50% chance of inheriting the PNDM-related pathogenic variant.

Autosomal recessive inheritance: The parents of an individual with PNDM caused by biallelic pathogenic variants are presumed to be heterozygous for a PNDM-related pathogenic variant. The heterozygous parents of a child with autosomal recessive PNDM may or may not have diabetes mellitus. If both parents are known to be heterozygous for a PNDM-related pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being heterozygous, and a 25% chance of inheriting neither of the familial pathogenic variants. The heterozygous sibs of a proband with autosomal recessive PNDM may or may not have diabetes mellitus. Heterozygote testing for at-risk relatives requires prior identification of the PNDM-related pathogenic variants in the family.

Once the PNDM-related pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing for PNDM are possible.

Diagnosis

Suggestive Findings

Permanent neonatal diabetes mellitus (PNDM) **should be suspected** in individuals with the following laboratory and radiographic features.

Laboratory features

- Persistent hyperglycemia (plasma glucose concentration >250mg/dL) in infants younger than age six months that lasts for longer than seven to ten days [Lemelman et al 2018]
- Features typical of diabetes mellitus (e.g., glucosuria, ketonuria, hyperketonemia)
- Low or undetectable plasma insulin and C peptide relative to the hyperglycemia
- Low fecal elastase and high stool fat in infants with pancreatic aplasia or hypoplasia due to pancreatic exocrine insufficiency [Greeley et al 2022]

Note: Measurement of hemoglobin A1c (HgA1c) is not suitable for diagnosing diabetes mellitus in infants younger than age six months because of the higher proportion of fetal hemoglobin compared to hemoglobin A.

Radiographic features. Pancreatic hypoplasia identified on ultrasound, CT, or MRI examination. Note: Visualization of the pancreas in neonates may be difficult.

Establishing the Diagnosis

The diagnosis of PNDM **is established** in an infant with diabetes mellitus diagnosed in the first six months of life that does not resolve over time. Molecular testing is recommended; identification of pathogenic (or likely pathogenic) variant(s) in one of the genes listed in Table 1 can guide treatment (see Management).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a variant(s) of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

A neonatal diabetes mellitus multigene panel that includes the genes in Table 1 and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests including DNA methylation analysis.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Permanent Neonatal Diabetes Mellitus

Gene [1, 2]	Proportion of PNDM Attributed to Pathogenic Variants in Gene [3]	MOI	Proportion of Pathogenic Variants [4] Identified by Method	
			Sequence analysis [5, 6]	Gene-targeted deletion/ duplication analysis [6, 7]
ABCC8	10%-15%	AD AR	100%	See footnote 8.
EIF2AK3	<10% [9]	AR	~97%	~3%
GATA6	~5%	AD	~90%	~10%
GCK	~5%	AR	100%	See footnote 8.
GLIS3	~5%	AR	~50%	~50%
HNF1B	<1%	AD	100%	See footnote 8.
INS	20%-25%	AD AR	>95%	<5%
KCNJ11	~25%	AD	100%	None reported [10]
MNX1	~1%	AR	100%	See footnote 8.
NEUROD1	~2%	AR	100%	None reported
NKX2-2	~1%	AR	100%	None reported
PDX1	~4%	AR	100%	None reported
PTF1A	<1%	AR	>90% [11]	<10%
RFX6	~5%	AR	100%	None reported
SLC2A2	<1%	AR	100%	See footnote 12.
SLC19A2	2%-3%	AR	100%	See footnote 8.

Table 1. continued from previous page.

Gene [1, 2]	Proportion of PNDM Attributed to Pathogenic Variants in Gene [3]	MOI	Proportion of Pathogenic Variants [4] Identified by Method	
			Sequence analysis [5, 6]	Gene-targeted deletion/ duplication analysis [6, 7]
Unknown [13]	<20% [14]	NA		

NA = not applicable; PNDM = permanent neonatal diabetes mellitus

1. Genes are listed in alphabetic order.

2. See Table A. Genes and Databases for chromosome locus and protein.

3. Flanagan et al [2014] and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]

4. See Molecular Genetics for information on variants detected in these genes.

5. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.

6. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]

7. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.

8. Large deletions/duplication have been reported in individuals with additional phenotypes (see Phenotype Correlations by Gene and Genetically Related Disorders). To date, large deletions/duplications have not been reported in individuals with isolated PNDM [Stenson et al 2020].

9. Biallelic *EIF2KA3* pathogenic variants are associated with Wolcott-Rallison syndrome. However, PNDM may be the first clinical manifestation, and therefore *EIF2KA3* should be considered in those presenting with apparently isolated PNDM.

10. Activating pathogenic variants in *KCNJ11* cause PNDM; deletion/duplication analysis is not expected to identify PNDM-related pathogenic variants in *KCNJ11*.

11. Analysis of *PTF1A* should include sequencing of the downstream enhancer, which accounts for >60% of PNDM-related pathogenic variants in this gene [Demirbilek et al 2020].

12. The 26-bp insertion and complex rearrangement in *SLC2A2* each reported in an individual with Fanconi-Bickel syndrome should be detectable by sequence analysis.

13. Relative hypomethylation within the 6q24 differentially methylated region (DMR) has been reported in one individual to date with PNDM [Cao et al 2017]. Findings reported in the individual included severe intrauterine growth restriction, hyperglycemia beginning in the neonatal period, and absence of ketoacidosis. 6q24 DMR relative hypomethylation is typically associated with transient neonatal diabetes mellitus (see Diabetes Mellitus, 6q24-Related Transient Neonatal).

14. De Franco et al [2015]

Clinical Characteristics

Clinical Description

Diabetes mellitus. Permanent neonatal diabetes mellitus (PNDM) is characterized by the onset of hyperglycemia within the first six months of life, with a mean age at diagnosis of seven weeks (range: birth to age 26 weeks) [Gloyn et al 2004b]. Clinical manifestations at diagnosis include intrauterine growth restriction (IUGR; a reflection of insulin deficiency in utero), hyperglycemia, glycosuria, osmotic polyuria, severe dehydration, and poor weight gain.

The diabetes mellitus is associated with partial or complete insulin deficiency. Therapy with insulin corrects the hyperglycemia and results in dramatic catch-up growth. Many individuals with *ABCC8*- or *KCNJ11*-related PNDM have improved glycemic control with sulfonylureas alone or combined with insulin treatment. Long-term follow-up studies of infants diagnosed with *ABCC8*- or *KCNJ11*-related PNDM showed that most individuals had good glycemic control on sulfonylureas with HgA1c averaging 5.9%-6.0% and minimal hypoglycemia with an average follow-up time of five to ten years [Bowman et al 2018, Warncke et al 2022].

Reports of microvascular complications vary among cohorts, with 4%-19% of affected individuals reported to have microalbuminuria and 6% reported to have retinopathy. There was no strong evidence that treatment with sulfonylureas was less effective over time, but there was a trend that later initiation of sulfonylurea treatment was associated with the need for combined treatment with insulin.

Phenotype Correlations by Gene

The course of PNDM is highly variable depending on the causative gene. Additional phenotypic features are associated with pathogenic variants in specific genes (see Table 2).

Table 2. Permanent Neonatal Diabetes Mellitus: Phenotypes by Gene

Gene [1]	DM Phenotype & Presenting Features	Additional Phenotypic Features
ABCC8	• Most diagnosed age <3 mos • Most have low birth weight, symptomatic hyperglycemia, & often DKA • Note: PNDM is the most common phenotype; TNDM is also reported.	None
EIF2AK3	• Most diagnosed age ≤6 mos (median: age 2.4 mos) • DKA at presentation is common. [2]	Skeletal abnormalities & liver dysfunction (Spondyloepiphyseal dysplasia w/DM [Wolcott-Rallison syndrome]), *EIF2AK3*-related)
GATA6	Severity of DM can vary from neonatal-lethal PNDM to adult-onset DM. [3]	Congenital heart anomalies, gallbladder agenesis, congenital diaphragmatic hernia
GCK	• IUGR • Insulin-requiring DM from 1st day of life • Hyperglycemia in both parents	None
GLIS3	• Low birth weight • Hyperglycemia typically presents shortly after birth.	Neonatal DM w/congenital hypothyroidism (OMIM 610199)
HNF1B	• PNDM severity is variable even among persons w/ same pathogenic variant. • Rare cause of PNDM or TNDM presenting w/ hyperglycemia at age <6 mos	• Pancreatic exocrine insufficiency [4] • Cystic renal disease / renal dysplasia
INS	• Median age at diagnosis is 9 wks • Persons present w/DKA or marked hyperglycemia. • Most newborns are small for gestational age. [5]	None
KCNJ11	• Most diagnosed age <3 mos • Most have low birth weight, symptomatic hyperglycemia, & often DKA • Treatment w/sulfonylureas corrects hyperglycemia & can prevent/improve neurologic manifestations (see Management). • Note: PNDM is the most common phenotype; TNDM is also reported.	• 20%-23% have DEND syndrome. • Neurologic manifestations also incl muscle weakness, ADHD, & sleep disorders. [6] • A milder form, intermediate DEND syndrome, presents w/less severe DD & w/o epilepsy.
MNX1	• Limited info reg DM phenotype exists; severity appears variable. • Low birth weight is common. [7]	• Neonatal DM, DD, sacral agenesis, & imperforate anus. [8] • Additional neurologic, skeletal, lung, & urologic congenital anomalies reported in 1 infant w/PNDM & biallelic *MNX1* pathogenic variants. [7]
NEUROD1	• Neonatal DM presenting at age <2 mos w/normal pancreatic size • Low birth weight is common. [9]	Neonatal DM, cerebellar hypoplasia, sensorineural deafness, & visual impairment [10]

Table 2. continued from previous page.

Gene [1]	DM Phenotype & Presenting Features	Additional Phenotypic Features
NKX2-2	• Neonatal DM presents in 1st few days of life. • History of low birth weight is common. [11]	PNDM, DD, hypotonia, short stature, deafness, & constipation [8]
PDX1	Pancreatic agenesis/hypoplasia w/more severe insulin deficiency than *ABCC8*-, *GCK*-, or *KCNJ11*-related PNDM w/low birth weight & younger age at diagnosis	• Pancreatic exocrine insufficiency [4] • Clinical manifestations are milder in persons w/hypomorphic pathogenic variants. [12]
PTF1A	• Pancreatic hypoplasia/agenesis w/PNDM onset typically age <1 mo • Low birth weight is common. [13]	Pancreatic exocrine insufficiency, [4] cerebellar hypoplasia/agenesis, dysmorphic facies, IUGR, & optic atrophy (OMIM 609069)
RFX6	• Pancreatic hypoplasia w/neonatal DM presenting w/in 1st few days of life • Low birth weight is common. [14]	• Mitchell-Riley syndrome (OMIM 615710) • PNDM w/hypoplastic or annular pancreas, pancreatic exocrine insufficiency, [4] intestinal atresia &/or malrotation, & gallbladder hypoplasia/agenesis
SLC2A2	• PNDM is less common than TNDM. • History of low birth weight is common. [15]	Fanconi-Bickel syndrome (tubular nephropathy & features of glycogen storage disease) can present w/ or w/o PNDM or other types of DM (OMIM 227810).
SLC19A2	• PNDM can respond to high-dose thiamine treatment in some persons. • History of low birth weight is common. [16]	Thiamine-responsive megaloblastic anemia syndrome & sensorineural deafness can present w/ or w/o PNDM or other types of DM.

ADHD = attention-deficit/hyperactivity disorder; DD = developmental delay; DEND = *d*evelopmental delay, *e*pilepsy, and *n*eonatal *d*iabetes mellitus; DKA = diabetic ketoacidosis; DM = diabetes mellitus; IUGR = intrauterine growth restriction; PNDM = permanent neonatal diabetes mellitus; TNDM = transient neonatal diabetes mellitus

1. Genes are listed in alphabetic order.
2. Welters et al [2020]
3. Yorifuji et al [2012]
4. Results in poor weight gain and loose, foul-smelling stools.
5. Støy et al [2007], Polak et al [2008]
6. Carmody et al [2016], Landmeier et al [2017]
7. Aly et al [2023]
8. Flanagan et al [2014]
9. Rubio-Cabezas et al [2010]
10. Rubio-Cabezas et al [2010], Demirbilek et al [2018], Horikawa & Enya [2019]
11. Auerbach et al [2020]
12. Nicolino et al [2010]
13. Demirbilek et al [2020]
14. Sansbury et al [2015]
15. Sansbury et al [2012]
16. Shaw-Smith et al [2012]

Genotype-Phenotype Correlations

No genotype-phenotype correlations for *EIF2AK3*, *GATA6*, *GCK*, *GLIS3*, *HNF1B*, *MNX1*, *NEUROD1*, *NKX2-2*, *PDX1*, *RFX6*, *SLC2A2*, or *SLC19A2* have been identified.

ABCC8. For neonatal diabetes caused by pathogenic variants in *ABCC8*, genotype-phenotype correlations are less distinct [Edghill et al 2010]. Children with neonatal diabetes associated with autosomal dominant *ABCC8* pathogenic variants may have a parent with the same *ABCC8* variant and type 2 diabetes, suggesting that the severity of the phenotype and age of onset of diabetes is variable among individuals with *ABCC8* pathogenic variants [Babenko et al 2006].

INS. The relationship between genotype and phenotype is beginning to emerge for neonatal diabetes mellitus caused by pathogenic variants in *INS*. The diabetes mellitus in persons who are homozygous or compound heterozygous for pathogenic variants in *INS* can be permanent or transient. The variants c.-366_343del, c.3G>A, c.3G>T, c.184C>T, c.-370-?186+?del (a 646-bp deletion), and c.*59A>G appear to be associated with PNDM, whereas the variants c.-218A>C and c.-331C>A or c.-331C>G have been identified in persons with both PNDM and TNDM as well as persons with childhood-onset monogenic diabetes, also called type 1b diabetes mellitus [Støy et al 2010] due to features including absence of evidence of beta cell autoimmunity, low serum C peptide, and insulin dependency.

KCNJ11. Some *KCNJ11* pathogenic variants are associated with TNDM; others are associated with PNDM; and two variants, p.Val252Ala and p.Arg201His, are associated with both disorders [Colombo et al 2005, Girard et al 2006]. Furthermore, functional studies have shown some overlap between the magnitude of the K_{ATP} channel currents in TNDM- and PNDM-associated pathogenic variants [Girard et al 2006, Ashcroft 2023].

The location of the *KCNJ11* pathogenic variant can partially predict the severity of the disease, i.e., isolated diabetes mellitus, intermediate DEND (*d*evelopmental delay, *e*pilepsy, and *n*eonatal *d*iabetes mellitus) syndrome, DEND syndrome; however, there are some exceptions. Studies have evaluated reduction in K_{ATP} channel ATP sensitivity and its effect on phenotype. Pathogenic variants in residues that lie within the putative ATP binding site (Arg50, Ile192, Leu164, Arg201, Phe333) or are located at the interfaces between Kir6.2 subunits (Phe35, Cys42, and Gu332) or between Kir6.2 and *SUR1* (Gly53) are associated with isolated diabetes mellitus. See Molecular Genetics.

The severity of PNDM along the spectrum of isolated diabetes mellitus, intermediate DEND syndrome, and DEND syndrome correlates with the genotype [Proks et al 2004]. *KCNJ11* variants that cause additional neurologic features occur at codons for amino acid residues that lie at some distance from the ATP binding site (Gln52, Gly53, Val59, Cys166, and Ile296) [Hattersley & Ashcroft 2005, Ashcroft 2023].

- Of 24 individuals with pathogenic variants at the arginine residue, Arg201, all but three had isolated PNDM.
- The p.Val59Met variant is associated with intermediate DEND syndrome.
- The following pathogenic variants associated with DEND syndrome are not found in less severely affected individuals: p.Gln52Arg, p.Val59Gly, p.Cys166Phe, p.Ile296Val [Gloyn et al 2006], p.Gly334Asp [Masia et al 2007], p.Ile167Leu [Shimomura et al 2007], p.Gly53Asp, p.Cys166Tyr, and p.Ile296Leu [Flanagan et al 2006].
- Improvement of the neurologic features of DEND syndrome with sulfonylurea treatment also appears to be genotype dependent: children with the variants p.Val59Met [Støy et al 2008, Mohamadi et al 2010] and p.Gly53Asp [Koster et al 2008] have been shown to respond to sulfonylureas.

PTF1A. Biallelic null variants are associated with pancreatic and cerebellar agenesis. Biallelic pathogenic variants involving the downstream enhancer region are associated with isolated pancreatic agenesis.

Penetrance

Reduced penetrance has been reported in *ABCC8*- and *KCNJ11*-related PNDM [Flanagan et al 2007]. Limited data is available regarding the penetrance for other molecular causes of PNDM [De Franco et al 2020c].

Nomenclature

Some individuals with "neonatal" diabetes mellitus may not be diagnosed until age three to six months; therefore it has been suggested that the term "diabetes mellitus of infancy" or "congenital diabetes" should replace the designation "neonatal diabetes mellitus" [Massa et al 2005, Greeley et al 2011].

Prevalence

The estimated incidence of neonatal diabetes mellitus ranges from 1:90,000 to 1:260,000 live births, 50% being PNDM [Kanakatti Shankar et al 2013, Zhang et al 2021].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with a germline pathogenic variant in *EIF2AK3*, *GLIS3*, *MNX1*, *NKX2-2*, *PTF1A*, or *SLC19A2*.

Other phenotypes associated with germline pathogenic variants in permanent neonatal diabetes mellitus-related genes are summarized in Table 3.

Table 3. Allelic Disorders

Gene	TNDM [1, 2]	MODY	Familial Hyperinsulinism	Type 2 DM [3, 4]	Other
ABCC8	+	+	+	+	
GATA6				+	Congenital heart disease, gall bladder agenesis, congenital diaphragmatic hernia
GCK		+	+	+	
HNF1B	+	+		+	Renal cysts and diabetes (RCAD) syndrome (OMIM 137920)
INS	+	+			
KCNJ11	+	+	+	+	
NEUROD1		+		+	
PDX1		+		+	
RFX6		+ [4]		+	
SLC2A2	+ [4]			+	

+ = associated phenotype; DM = diabetes mellitus; MODY = maturity-onset diabetes of the young; TNDM = transient neonatal diabetes mellitus
1. Greeley et al [2022]
2. See Differential Diagnosis.
3. OMIM 125853
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]

Differential Diagnosis

Permanent neonatal diabetes mellitus (PNDM) vs transient neonatal diabetes mellitus (TNDM). When diabetes mellitus is diagnosed in the neonatal period, it is difficult to determine if it is likely to be transient or permanent.

The most common causes of TNDM are 6q24-related TNDM and *ABCC8*- or *KCNJ11*-related TNDM.

- 6q24-related TNDM is caused by overexpression of the imprinted genes at 6q24 (*PLAGL1* and *HYMAI*). The cardinal features are severe intrauterine growth restriction, hyperglycemia that begins in the neonatal period in a term infant and resolves by age 18 months, dehydration, and absence of ketoacidosis. Macroglossia and umbilical hernia may be present. 6q24-related TNDM associated with a multilocus imprinting disturbance (MLID) can be associated with marked hypotonia, congenital heart disease, deafness, macroglossia, neurologic features including epilepsy, and renal malformations. Diabetes mellitus lasts on average three months but can last more than a year. Although insulin is usually required initially,

the need for insulin gradually declines over time. Intermittent episodes of hyperglycemia may occur in childhood, particularly during intercurrent illnesses. Diabetes mellitus may recur in adolescence or later in adulthood. Women who have had 6q24-related TNDM are at risk for relapse during pregnancy.

- Activating pathogenic variants in *ABCC8* and *KCNJ11* with less severe effects on beta cell K_{ATP} channel function have been found to cause TNDM that is similar to the biphasic course seen in 6q24-related TNDM. Typically, infants with *ABCC8*- or *KCNJ11*-related TNDM present before age six months, go into remission between ages six and 12 months, and are likely to relapse during adolescence or early adulthood [Gloyn et al 2005, Flanagan et al 2007, De Franco et al 2020c].

For infants with PNDM and extra-pancreatic features, consideration of syndromic PNDM may be appropriate (see Table 4).

Table 4. Syndromic Permanent Neonatal Diabetes Mellitus

Gene	Disorder	MOI	Distinctive Features (in addition to neonatal DM)
CNOT1	Holoprosencephaly ± pancreatic agenesis (OMIM 618500)	AD	• PNDM • Pancreatic agenesis • Holoprosencephaly • Gallbladder agenesis
CTLA4	Immune dysregulation w/autoimmunity, immunodeficiency, & lymphoproliferation (OMIM 616100)	AD	• PNDM • Lymphoproliferative syndrome • Enteropathy • Cytopenias • Thyroiditis
EIF2B1 [1]	Neonatal/early-onset DM & transient hepatic dysfunction	AD	• PNDM • Transient hepatitis
FOXP3	IPEX syndrome	XL	• Enteropathy • Dermatitis
GATA4	*GATA4*-related PNDM [2]	AD	• Pancreatic exocrine insufficiency/agenesis • Cardiac abnormalities
IER3IP1	Neonatal DM, microcephaly, lissencephaly, & epileptic encephalopathy (OMIM 614231)	AR	
IL2RA	Neonatal DM & immune dysfunction (OMIM 606367)	AR	• PNDM • Congenital hypothyroidism • Sepsis [3]
ITCH [4]	Neonatal DM & systemic autoimmunity	AR	• PNDM • Dysmorphic facies • Widespread autoimmunity
KCNMA1	Liang-Wang syndrome (OMIM 618729)	AD	
LRBA [5]	Common variable immunodeficiency 8 w/ autoimmunity (OMIM 614700)	AR	• PNDM • Enteropathy • Hypothyroidism • Hemolytic anemia
NEUROG3	Congenital malabsorptive diarrhea & neonatal DM (OMIM 610370)	AR	Congenital malabsorptive diarrhea
ONECUT1 [6]	Neonatal DM, non-autoimmune assoc w/pancreatic hypoplasia	AR	• PNDM • IUGR • Pancreatic hypoplasia • Gall bladder hypoplasia • Pancreatic exocrine insufficiency

Table 4. continued from previous page.

Gene	Disorder	MOI	Distinctive Features (in addition to neonatal DM)
PAX6	Neonatal DM w/brain malformations, microcephaly, & microphthalmia [7]	AR	• Brain malformations • Microcephaly • Microphthalmia
STAT3 [8]	Neonatal DM assoc w/autoimmunity & pancreatic hypoplasia	AR	• Leads to early activation of NEUROG3 & premature endocrine activations • Critical component of cytokine signaling
WFS1	Classic Wolfram syndrome (See *WFS1* Spectrum Disorder.)	AR	• Optic atrophy • DM & diabetes insipidus • Deafness
YIPF5 [9]	Microcephaly, epilepsy, & DM syndrome (OMIM 619278)	AR	

AD = autosomal dominant; AR = autosomal recessive; DM = diabetes mellitus; IUGR = intrauterine growth restriction; MOI = mode of inheritance; PNDM = permanent neonatal diabetes mellitus; XL = X-linked

1. Unfolded protein response and endoplasmic reticulum stress [De Franco et al 2020a]
2. D'Amato et al [2010], Shaw-Smith et al [2014]
3. Sri Nagesh et al [2016]
4. Johnson et al [2016]
5. Neonatal diabetes and beta cell destruction from autoimmunity [Johnson et al 2017]
6. Philippi et al [2021]
7. Yasuda et al [2002], Solomon et al [2009]
8. Flanagan et al [2014], Saarimäki-Vire et al [2017]
9. De Franco et al [2020b]

Management

No clinical practice guidelines for permanent neonatal diabetes mellitus (PNDM) have been published. General guidelines for treatment of neonatal diabetes are available in the ISPAD Clinical Guidelines for Permanent Neonatal Diabetes [Greeley et al 2022]. In the absence of published guidelines, the following recommendations are based on the authors' personal experience managing individuals with this disorder.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with PNDM, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Permanent Neonatal Diabetes Mellitus: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Diabetes mellitus	Pediatric endocrinology eval/referral for acute & long-term DM mgmt	
Kidney manifestations	Renal ultrasound for evidence of cystic kidney disease or dysplasia	In persons w/*HNF1B*-related PNDM
Developmental delay / Neurologic features of DEND syndrome	• Developmental eval • Neurology eval & EEG in those w/ suspected seizures	In those w/*KCNJ11*-, *MNX1*-, *NEUROD1*-, & *NKX2-2*-related PNDM
Exocrine pancreatic insufficiency	• Imaging of pancreas • Eval of pancreatic exocrine function (fecal elastase, serum concentrations of fat-soluble vitamins)	In those w/*HNF1B*-, *PDX1*-, *PTF1A*-, & *RFX6*-related PNDM

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
Genetic counseling	By genetics professionals [1]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of PNDM to facilitate medical & personal decision making
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement for parental support • Home nursing referral

DEND = *d*evelopmental delay, *e*pilepsy, and *n*eonatal *d*iabetes mellitus; DM = diabetes mellitus; MOI = mode of inheritance; PNDM = permanent neonatal diabetes mellitus
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Targeted Therapy

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

Oral sulfonylureas in those with *ABCC8- or KCNJ11*-related PNDM. Children with *ABCC8- or KCNJ11*-related PNDM can be transitioned to therapy with oral sulfonylureas after initial management with insulin. High doses of sulfonylureas are usually required (0.4-1.0 mg/kg/day of glibenclamide or 0.5-2.5 mg/kg/day of glyburid). Treatment transition protocols are available at www.diabetesgenes.org or in Greeley et al [2021]. Treatment with sulfonylureas in those with *ABCC8*- or *KCNJ11*-related PNDM is associated with improved glycemic control [Thurber et al 2015, Babiker et al 2016].

Note: Mild beneficial effect of oral sulfonylureas in persons with *GCK*-related PNDM has also been reported in some but not all individuals [Turkkahraman et al 2008, Hussain 2010, Oriola et al 2015, Tikhonovich et al 2022].

Supportive Care

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 6).

Table 6. Permanent Neonatal Diabetes Mellitus: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Dehydration & acute treatment of DM	Prompt rehydration & IV insulin infusion after diagnosis, particularly in infants w/ketoacidosis	
Long-term insulin therapy for DM	**Insulin therapy.** Subcutaneous insulin when infant is stable & tolerating oral feedings. Few data on the most appropriate insulin preparations for young infants are available.	Long-term insulin therapy is required except in those w/*ABCC8*- or *KCNJ11*-related PNDM (see Targeted Therapy). • In general, rapid-acting (lispro, aspart) & short-acting preparations should be avoided as they may cause

Table 6. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
	• Longer-acting preparations w/no significant peak-of-action effect (e.g., glargine, detemir) may work better in small infants. • Some centers recommend continuous subcutaneous insulin infusion for young infants as a safer, more physiologic, & more accurate way of administering insulin. Long-term complications of hyperglycemia can be significantly reduced by maintaining blood glucose concentrations w/in a target range of 70-180 mg/dL for >70% of the day & by maintaining a HbA1c <7.0%. These goals must be balanced w/risks assoc w/prolonged periods of hypoglycemia, esp in children who are age <6 yrs who may be unable to communicate symptoms of hypoglycemia. [1]	severe hypoglycemic events (except when used as a continuous IV or subcutaneous infusion). • Intermediate-acting preparations (neutral protamine hagedorn) tend to have shorter duration of action in infants, possibly because of smaller dose size or higher subcutaneous blood flow.
	In persons w/very low insulin requirements, diluted insulin (5 or 10 U/mL) may be more appropriate if used w/caution.	Use extreme caution w/diluted insulin preparation to avoid dose errors.
Poor weight gain	High caloric intake to achieve weight gain	
Development	Developmental & educational support	In those w/*KCNJ11*-, *MNX1*-, *NEUROD1*-, & *NKX2-2*-related PNDM
Seizures	Anti-seizure medication (in addition to sulfonylureas) as needed for those w/persistent seizures	In those w/*KCNJ11*-related DEND syndrome
Exocrine pancreatic insufficiency	Pancreatic enzyme replacement therapy	In those w/*HNF1B*-, *PDX1*-, *PTF1A*-, & *RFX6*-related PNDM

DEND = *d*evelopmental delay, *e*pilepsy, and *n*eonatal *d*iabetes mellitus; DM = diabetes mellitus; HbA1c = hemoglobin A1c; IV = intravenous; PNDM = permanent neonatal diabetes mellitus
1. In 2020 the American Diabetes Association revised the HbA1c target to be individualized for children who are not able to express symptoms of hypoglycemia [American Diabetes Association Professional Practice Committee 2022].

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 7 are recommended.

Table 7. Permanent Neonatal Diabetes Mellitus: Recommended Surveillance

System/Concern	Evaluation	Frequency
Diabetes mellitus	Blood glucose concentrations to avoid acute complications such as diabetic ketoacidosis & hypoglycemia	• Frequent monitoring in hospital immediately following diagnosis • Lifelong monitoring (≥4x/day or w/ continuous glucose monitor) after stabilization on treatment
Kidney manifestations	• Urinalysis for microalbuminuria • Measurement of cystatin C in blood	Annually beginning at age 10 yrs to screen for kidney manifestations of persistent hyperglycemia
Ocular manifestations of DM	Ophthalmologic exam to assess for retinopathy	Annually beginning at age 10 yrs
Development	Developmental eval	Annually or as needed in those w/*KCNJ11*-, *MNX1*-, *NEUROD1*-, & *NKX2-2*-related PNDM

Table 7. continued from previous page.

System/Concern	Evaluation	Frequency
Seizures	Neurology eval & EEG	As needed in those w/*KCNJ11*-related DEND syndrome
Exocrine pancreatic insufficiency	Eval of pancreatic exocrine function (fecal elastase, serum concentrations of fat-soluble vitamins)	As needed in those w/symptoms of malabsorption
	Serum concentrations of fat-soluble vitamins	Every 6 mos in those w/known exocrine pancreatic insufficiency

DEND = *d*evelopmental delay, *e*pilepsy, and *n*eonatal *d*iabetes mellitus; DM = diabetes mellitus; PNDM = permanent neonatal diabetes mellitus

Agents/Circumstances to Avoid

In general, rapid-acting insulin preparations (lispro and aspart) as well as short-acting (regular) insulin preparations should be avoided (except when used as a continuous intravenous or subcutaneous infusion), as they may cause severe hypoglycemic events in young children.

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from surveillance and treatment of hyperglycemia. (Hyperglycemia may be asymptomatic.) Evaluations can include:

- Molecular genetic testing if the pathogenic variant(s) in the family are known;
- Screening with HbA1c or fasting or post-prandial glucose levels may be used to assess for abnormalities in glycemic control if the pathogenic variant(s) in the family are not known. Rarely an oral glucose tolerance test is needed. Continuous glucose monitors to track glucose patterns in relatives of individuals with monogenic forms of diabetes have been used.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Pregnant women with PNDM should be managed by an endocrinologist and maternal-fetal medicine specialist. Management should conform to the guidelines for treatment of other forms of diabetes during gestation [American Diabetes Association Professional Practice Committee 2022]. Glycemic control during gestation is important to prevent complications in the mother, fetal overgrowth, and congenital anomalies due to maternal hypo- and hyperglycemia. High-resolution ultrasonography and fetal echocardiography should be offered during pregnancy to screen for congenital anomalies in the fetus.

Until recently, insulin was the mainstay of therapy for diabetes during pregnancy. Although there have been reports supporting the safety and efficacy of glyburide in the treatment of diabetes during pregnancy [Moretti et al 2008], a recent meta-analysis found that glyburide was associated with an increased risk of neonatal hypoglycemia [Guo et al 2019].

Therapies Under Investigation

Search ClinicalTrials.gov in the and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

The mode of inheritance of permanent neonatal diabetes mellitus (PNDM) varies by gene (see Table 8).

Table 8. Permanent Neonatal Diabetes Mellitus: Mode of Inheritance

Gene	Mode of Inheritance
ABCC8	AD, AR
EIF2AK3	AR
GATA6	AD
GCK	AR
GLIS3	AR
HNF1B	AD
INS	AD, AR
KCNJ11	AD
MNX1	AR
NEUROD1	AR
NKX2-2	AR
PDX1	AR
PTF1A	AR
RFX6	AR
SLC2A2	AR
SLC19A2	AR

AD = autosomal dominant; AR = autosomal recessive

If an individual has a specific genetic syndrome associated with PNDM (e.g., Wolcott-Rallison syndrome or thiamine-responsive megaloblastic anemia syndrome), counseling for that condition is indicated.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- The majority of individuals with autosomal dominant PNDM caused by a heterozygous pathogenic variant in *ABCC8*, *INS*, or *KCNJ11* have the disorder as the result of a *de novo* pathogenic variant:
  - Most reported individuals with autosomal dominant *ABCC8*-related PNDM have the disorder as the result of a *de novo* pathogenic variant [Patch et al 2007].
  - Approximately 73% of individuals with *INS*-related PNDM [Nishi & Nanjo 2011] and 90% of individuals with *KCNJ11*-related PNDM [Greeley et al 2022] have the disorder as the result of a *de novo* pathogenic variant.

- Some individuals with autosomal dominant PNDM have the disorder as the result of a pathogenic variant inherited from a parent.
  - Children with autosomal dominant *ABCC8*-related PNDM may have a parent diagnosed with type 2 diabetes mellitus who is heterozygous for the same *ABCC8* pathogenic variant [Babenko et al 2006].
  - Children with autosomal dominant *INS*-related PNDM may have a parent with the same *INS* pathogenic variant and a history of type 2 diabetes mellitus diagnosed in adulthood (although the expected phenotype in a heterozygous parent would be PNDM) [Støy et al 2007].
- Recommendations for the evaluation of parents of a proband who appears to be the only affected family member (i.e., a simplex case) include molecular genetic testing (if a molecular diagnosis has been established in the proband) and clinical testing for diabetes mellitus including screening HbA1c, blood glucose monitoring, or oral glucose tolerance testing.
- If a molecular diagnosis has been established in the proband, the pathogenic variant found in the proband is not identified in either parent, and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant;
  - The proband inherited a pathogenic variant from a parent with gonadal (or somatic and gonadal) mosaicism. Gonadal mosaicism for a pathogenic variant in *KCNJ11* has been reported [Gloyn et al 2004a, Edghill et al 2007]; the overall incidence of gonadal mosaicism is unknown. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ (gonadal) cells only.
- Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of failure by health care professionals to recognize the disorder in affected family members, reduced penetrance (*ABCC8*- and *KCNJ11*-related PNDM), and/or a milder phenotypic presentation. Therefore, an apparently negative family history cannot be confirmed until appropriate clinical and molecular evaluations have been performed.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the PNDM-related pathogenic variant identified in the proband, the risk to the sibs is 50%.
- If a molecular diagnosis has been established in the proband and the PNDM-related pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is slightly greater than that of the general population because of the possibility of parental gonadal mosaicism [Gloyn et al 2004a, Edghill et al 2007].
- If the parents are clinically unaffected but their genetic status is unknown, the risk to the sibs of a proband appears to be low but increased over that of the general population because of the possibility of reduced penetrance in a heterozygous parent and the possibility of parental gonadal mosaicism.

Offspring of a proband. Each child of an individual with PNDM inherited in an autosomal dominant manner has a 50% chance of inheriting the PNDM-related pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected and/or is known to have the PNDM-related pathogenic variant, the parent's family members may be at risk.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of a child with PNDM caused by biallelic pathogenic variants are presumed to be heterozygous for a PNDM-related pathogenic variant.
- Recommendations for the evaluation of parents of a proband include molecular genetic testing (if a molecular diagnosis has been established in the proband) and clinical testing for diabetes mellitus including screening HbA1c, blood glucose monitoring, or oral glucose tolerance testing.
- The heterozygous parents of a child with autosomal recessive PNDM may or may not have diabetes mellitus (see Genotype-Phenotype Correlations).
  - In 43% of individuals with *ABCC8*-related PNDM, the condition is inherited in an autosomal recessive manner from unaffected parents with heterozygous pathogenic variants [Patch et al 2007].
  - *INS*-related PNDM has also been reported to be inherited in an autosomal recessive manner from unaffected parents [Garin et al 2010]. Heterozygous parents with pathogenic variants in *INS* that are associated with autosomal recessive PNDM may have adult-onset diabetes mellitus [Raile et al 2011].
  - Individuals who are heterozygous for a pathogenic variant in *GCK* or *PDX1* may have milder forms of diabetes mellitus (*GCK*- or *PDX1*-related maturity-onset diabetes of the young [MODY], respectively).

Sibs of a proband

- If both parents are known to be heterozygous for a PNDM-related pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being heterozygous, and a 25% chance of inheriting neither of the familial pathogenic variants.
- The heterozygous sibs of a proband with autosomal recessive PNDM may or may not have diabetes mellitus.
  - Heterozygotes for pathogenic variants in *ABCC8* may have normal glucose tolerance.
  - Heterozygotes for pathogenic variants in *GCK*, *INS*, or *PDX1* may have a milder form of diabetes mellitus (e.g., *GCK*- or *PDX1*-related MODY).

Offspring of a proband. The offspring of an individual with PNDM caused by biallelic pathogenic variants are obligate heterozygotes for a PNDM-related pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being heterozygous for a PNDM-related pathogenic variant.

Heterozygote detection. Heterozygote testing for at-risk relatives requires prior identification of the PNDM-related pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.
- Referral to a maternal-fetal medicine specialist should be considered for females with PNDM who are pregnant or considering pregnancy (see Pregnancy Management).

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from

probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the PNDM-related pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal and preimplantation genetic testing. While most health care professionals consider decisions regarding prenatal and preimplantation genetic testing to be the choice of the parents, discussion of these issues is appropriate.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Diabetes Genes**
  Providing information for patients and professionals on research and clinical care in genetic types of diabetes.
  United Kingdom
  diabetesgenes.org
- **International Society for Pediatric and Adolescent Diabetes (ISPAD)**
  Phone: +49 (0)30 24603-210
  Email: secretariat@ispad.org
  ispad.org
- **American Diabetes Association**
  Phone: 800-DIABETES (800-342-2383)
  Email: AskADA@diabetes.org
  diabetes.org
- **Diabetes UK**
  United Kingdom
  Phone: 0345 123 2399
  Email: helpline@diabetes.org.uk
  diabetes.org.uk
- **Monogenic Diabetes Registry**
  Monogenic Diabetes at the University of Chicago
  Phone: 773-702-0829
  Email: monogenicdiabetes@uchicago.edu
  Research

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Permanent Neonatal Diabetes Mellitus: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ABCC8	11p15.1	ATP-binding cassette sub-family C member 8	ABCC8 database	ABCC8	ABCC8
EIF2AK3	2p11.2	Eukaryotic translation initiation factor 2-alpha kinase 3	EIF2AK3 database	EIF2AK3	EIF2AK3
GATA6	18q11.2	Transcription factor GATA-6		GATA6	GATA6
GCK	7p13	Hexokinase-4	Glucokinase (hexokinase 4) (GCK) @ LOVD	GCK	GCK
GLIS3	9p24.2	Zinc finger protein GLIS3	GLIS3 database	GLIS3	GLIS3
HNF1B	17q12	Hepatocyte nuclear factor 1-beta	HNF1B database	HNF1B	HNF1B
INS	11p15.5	Insulin	INS database	INS	INS
KCNJ11	11p15.1	ATP-sensitive inward rectifier potassium channel 11	KCNJ11 database	KCNJ11	KCNJ11
MNX1	7q36.3	Motor neuron and pancreas homeobox protein 1		MNX1	MNX1
NEUROD1	2q31.3	Neurogenic differentiation factor 1	NEUROD1 database	NEUROD1	NEUROD1
NKX2-2	20p11.22	Homeobox protein Nkx-2.2		NKX2-2	NKX2-2
PDX1	13q12.2	Pancreas/duodenum homeobox protein 1	PDX1 database	PDX1	PDX1
PTF1A	10p12.2	Pancreas transcription factor 1 subunit alpha	PTF1A database	PTF1A	PTF1A
RFX6	6q22.1	DNA-binding protein RFX6		RFX6	RFX6
SLC2A2	3q26.2	Solute carrier family 2, facilitated glucose transporter member 2	SLC2A2 database	SLC2A2	SLC2A2
SLC19A2	1q24.2	Thiamine transporter 1	SLC19A2 database	SLC19A2	SLC19A2

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Permanent Neonatal Diabetes Mellitus (View All in OMIM)

138079	GLUCOKINASE; GCK
142994	MOTOR NEURON AND PANCREAS HOMEOBOX 1; MNX1
176730	INSULIN; INS
189907	HNF1 HOMEOBOX B; HNF1B

Table B. continued from previous page.

600509	ATP-BINDING CASSETTE, SUBFAMILY C, MEMBER 8; ABCC8
600733	PANCREAS/DUODENUM HOMEOBOX PROTEIN 1; PDX1
600937	POTASSIUM CHANNEL, INWARDLY RECTIFYING, SUBFAMILY J, MEMBER 11; KCNJ11
601656	GATA-BINDING PROTEIN 6; GATA6
601724	NEUROGENIC DIFFERENTIATION 1; NEUROD1
603941	SOLUTE CARRIER FAMILY 19 (THIAMINE TRANSPORTER), MEMBER 2; SLC19A2
604032	EUKARYOTIC TRANSLATION INITIATION FACTOR 2-ALPHA KINASE 3; EIF2AK3
604612	NK2 HOMEOBOX 2; NKX2-2
606176	DIABETES MELLITUS, PERMANENT NEONATAL, 1; PNDM1
607194	PANCREAS TRANSCRIPTION FACTOR 1, ALPHA SUBUNIT; PTF1A
610192	GLIS FAMILY ZINC FINGER PROTEIN 3; GLIS3
612659	REGULATORY FACTOR X, 6; RFX6
618856	DIABETES MELLITUS, PERMANENT NEONATAL, 2; PNDM2
618857	DIABETES MELLITUS, PERMANENT NEONATAL, 3; PNDM3
618858	DIABETES MELLITUS, PERMANENT NEONATAL, 4; PNDM4

Molecular Pathogenesis

KCNJ11* and *ABCC8 encode the proteins ATP-sensitive inward rectifier potassium channel 11 (Kir6.2) and ATP-binding cassette sub-family C member 8 (SUR1), respectively; both are components of the beta cell K_{ATP} channel. The K_{ATP} channel is a hetero-octameric complex with four Kir6.2 subunits forming the central pore, coupled to four SUR1 subunits. The K_{ATP} channels couple the energy state of the beta cell to membrane potential by sensing changes in intracellular phosphate potential (the ATP:ADP ratio). Following the uptake of glucose and its metabolism by hexokinase-4, the increase in the intracellular ATP:ADP ratio results in closure of the K_{ATP} channels, depolarization of the cell membrane, and subsequent opening of voltage-dependent Ca^{2+} channels. The resulting increase in cytosolic Ca^{2+} concentration triggers insulin release.

Pathogenic variants in either *ABCC8* or *KCNJ11* result in nonfunctional or dysfunctional K_{ATP} channels. In either case, channels do not close, and thus glucose-stimulated insulin secretion does not happen. All pathogenic variants in *KCNJ11* studied to date produce marked decrease in the ability of ATP to inhibit the K_{ATP} channel when expressed in heterologous systems. This reduction in ATP sensitivity means the channel opens more fully at physiologically relevant concentrations of ATP, leading to an increase in the K_{ATP} current and hyperpolarization of the beta cell plasma membrane with subsequent suppression of Ca^{2+} influx and insulin secretion [Hattersley & Ashcroft 2005].

GCK encodes hexokinase-4 (also called glucokinase), which serves as the glucose sensor in pancreatic beta cells and appears to have a similar role in enteroendocrine cells, hepatocytes, and hypothalamic neurons. In beta cells, hexokinase-4 controls the rate-limiting step of glucose metabolism and is responsible for glucose-stimulated insulin secretion [Matschinsky 2002]. *GCK* pathogenic missense variants alter the kinetics of the enzyme: the glucose $S_{0.5}$ is raised, and the ATP K_m is increased. The overall result for inactivating pathogenic variants is a decrease in the phosphorylating potential of the enzyme, which extrapolates to a marked reduction in beta cell glucose usage and hyperglycemia. Splice site pathogenic variants are predicted to lead to the synthesis of an inactive protein.

INS. Insulin is synthesized by the pancreatic beta cells and consists of two dissimilar polypeptide chains, A and B, which are linked by two disulfide bonds. Chains A and B are derived from a 1-chain precursor, proinsulin.

Proinsulin is converted to insulin by enzymatic removal of a segment that connects the amino end of the A chain to the carboxyl end of the B chain. This segment is called the C peptide. The diabetes-associated pathogenic variants lead to the synthesis of a structurally abnormal preproinsulin or proinsulin protein. *INS* pathogenic variants associated with PNDM disrupt proinsulin folding and/or disulfide bond formation. All of the pathogenic variants are likely to act in a dominant manner to disrupt insulin biosynthesis and induce endoplasmic reticulum (ER) stress.

PDX1 encodes pancreas/duodenum homeobox protein 1 (also known as transcription factor insulin promoter factor 1; PDX1), a master regulator of pancreatic development and of the differentiation of progenitor cells into the beta cell phenotype. In mature beta cells, PDX1 regulates the expression of critical genes including insulin, hexokinase-4, and the glucose transporter encoded by *SLC2A2* (solute carrier family 2, facilitated glucose transporter member 2) [Habener et al 2005].

Table 9. Permanent Neonatal Diabetes Mellitus: Mechanism of Disease Causation

Gene [1]	Mechanism of Disease Causation
ABCC8	Activating pathogenic variant; the K_{ATP} channels do not close, & glucose-stimulated insulin secretion does not happen.
EIF2AK3	Pathogenic variants disrupt the unfolded protein response in the ER.
GATA6	Heterozygous inactivating pathogenic variants can lead to pancreatic agenesis.
GCK	Inactivating pathogenic variants decrease the phosphorylating potential of the enzyme & resets/increases the glucose threshold by which insulin secretion is triggered in the beta cell.
GLIS3	Pancreatic transcription factor that is a member of the zinc finger protein family that can function as an activator or repressor of transcription
HNF1B	Heterozygous loss of function variants
INS	Dominant-negative; disrupts insulin biosynthesis & induces ER stress
KCNJ11	Activating pathogenic variant; the K_{ATP} channels do not close, & glucose-stimulated insulin secretion does not happen.
MNX1	Pancreatic transcription factor; loss-of-function variants
NEUROD1	Biallelic loss-of-function variants can lead to PNDM.
NKX2-2	Pancreatic transcription factor; loss of function
PDX1	Pancreatic transcription factor; loss-of-function variants
PTF1A	Pancreatic transcription factor important to pancreatic development; loss of function
RFX6	Pancreatic transcription factor essential for the development of the endocrine pancreas including the beta cell; loss-of-function variants
SLC2A2	Encodes for the glucose transporter GLUT2; homozygous or compound heterozygous inactivating mutations lead to PNDM or TNDM.
SLC19A2	Encodes for thiamin transporter 1; loss-of-function variants

ER = endoplasmic reticulum; GLUT2 = solute carrier family 2, facilitated glucose transporter member 2
1. Genes from Table 1 are in alphabetic order.

Gene-specific laboratory technical considerations

- ***PTF1A*.** Analysis of *PTF1A* should include sequencing of the downstream enhancer, which accounts for >60% of PNDM-related pathogenic variants in this gene [Demirbilek et al 2020].
- There are no gene-specific laboratory technical considerations for the other genes listed in Table 1.

Chapter Notes

Author Notes

Dr Sara Pinney (pinneys@chop.edu) is actively involved in clinical research regarding individuals with permanent neonatal diabetes mellitus (PNDM). Dr Pinney would be happy to communicate with persons who have any questions regarding diagnosis of PNDM or other considerations.

Dr Pinney is also interested in hearing from clinicians treating families affected by monogenic diabetes in whom no causative variant has been identified through molecular genetic testing of the genes known to be involved in this group of disorders.

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