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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 26 weeks). The diabetes mellitus is associated with partial or complete insulin deficiency. Clinical manifestations at the time of diagnosis include intrauterine growth restriction, hyperglycemia, glycosuria, osmotic polyuria, severe dehydration, and failure to thrive. Therapy with insulin corrects the hyperglycemia and results in dramatic catch-up growth. The course of PNDM varies by genotype.

Diagnosis/testing

Persistent hyperglycemia (plasma glucose concentration >150-200 mg/dL) in infants younger than age six months establishes the diagnosis of PNDM. Molecular testing is recommended: identification of pathogenic variant(s) in *ABCC8* or *KCNJ11* can guide treatment.

Management

Treatment of manifestations: Start rehydration and intravenous insulin infusion promptly after diagnosis. When the infant is stable and tolerating oral feedings begin subcutaneous insulin therapy. Children with pathogenic variants in *ABCC8* or *KCNJ11* can be treated with oral sulfonylureas; all others require long-term insulin therapy. High caloric intake is necessary for appropriate weight gain. Pancreatic enzyme replacement therapy is required for those with exocrine pancreatic insufficiency.

Prevention of secondary complications: Aggressive treatment and frequent monitoring of blood glucose concentrations to avoid acute complications such as diabetic ketoacidosis and hypoglycemia and reduce the long-term complications of diabetes mellitus.

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Surveillance: Lifelong monitoring of blood glucose concentrations at least four times a day; periodic developmental evaluations. After age ten years, annual screening for chronic complications of diabetes mellitus including urinalysis for microalbuminuria and ophthalmologic examination for retinopathy.

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.

Genetic counseling

The mode of inheritance of PNDM is autosomal dominant for mutation of *KCNJ11*, autosomal dominant or autosomal recessive for mutation of *ABCC8* and *INS*, and autosomal recessive for mutation of *GCK* and *PDX1*.

Individuals with autosomal dominant PNDM may have an affected parent or may have a *de novo* pathogenic variant. Each child of an individual with autosomal dominant PNDM has a 50% chance of inheriting the pathogenic variant.

The parents of a child with autosomal recessive PNDM are obligate heterozygotes and therefore carry one pathogenic variant. Heterozygotes for pathogenic variants in *GCK* and *PDX1* have a mild form of diabetes mellitus known as *GCK*-familial monogenic diabetes (formerly known as MODY2) and *PDX1*-familial monogenic diabetes (formerly known as MODY4). At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier (or of having familial monogenic diabetes), and a 25% chance of being unaffected and not a carrier.

Prenatal diagnosis for pregnancies at increased risk is possible if the pathogenic variant(s) in the family are known.

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 >150-200 mg/dL) in infants younger than age six months
- 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

Note: Measurement of hemoglobin A1c 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; biochemical evidence of pancreatic insufficiency (e.g., low fecal elastase, high stool fat) may help with the diagnosis in these infants.

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 variant(s) in one of the genes listed in Table 1 can guide treatment (see Management).

Molecular genetic testing approaches can include **serial single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**.

Serial single-gene testing

- Individuals with one parent with diabetes mellitus:
  - Sequence analysis of *KCNJ11* first.
  - If no *KCNJ11* pathogenic variant is found, sequence analysis of *ABCC8* and *INS*
- Individuals whose parents both have diabetes mellitus: sequence analysis of *GCK* and *PDX1*
- Individuals without a family history of diabetes mellitus:
  - Sequence analysis of *ABCC8* and *KCNJ11* first (as identification of pathogenic variants changes management)
  - If no pathogenic variants are identified, sequence analysis of *GCK* and *INS*
- Individuals with pancreatic insufficiency or agenesis without extra-pancreatic abnormalities:
  - Sequence analysis of *PDX1* first.
  - If no pathogenic variants are identified, consider sequence analysis of *PTF1A* [Houghton et al 2016].
- Individuals with syndromic PNDM: the extrapancreatic characteristics should guide genetic testing (see Genetically Related Disorders and Differential Diagnosis).

Note: Deletion/duplication analysis of *GCK*, *INS, PDX1,* and *PTF1A* (and for genes associated with syndromic PNDM) should be considered when sequencing is negative, as homozygous deletions in these genes can be associated with permanent neonatal diabetes mellitus.

A multigene panel that includes *ABCC8*, *GCK*, *INS*, *KCNJ11*, and *PDX1* and other genes of interest (see Differential Diagnosis) may also be considered. Notes: (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*; thus, clinicians need to determine which multigene panel 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. (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.

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

More comprehensive genomic testing (when available) including exome sequencing and genome sequencing may be considered if serial single-gene testing (and/or use of a multigene panel that includes *ABCC8*, *GCK*, *INS*, *KCNJ11*, and *PDX1*) fails to confirm a diagnosis in an individual with features of PNDM. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

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]	Proportion of Permanent Neonatal Diabetes Mellitus Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [2] Detectable by Method	
		Sequence analysis [3]	Gene-targeted deletion/ duplication analysis [4]
ABCC8	19% [5]	100%	None reported [7]
GCK	4% [8]	100%	None reported [7]
INS	20% [9]	>99%	1 family [10]
KCNJ11	30% [11]	100%	None reported [7]
PDX1	<1% [12]	100%	None reported [7]
Unknown [13]		NA	

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. 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.
5. Attributed to activating pathogenic variants of *ABCC8* [Babenko et al 2006]
6. No data on detection rate of gene-targeted deletion/duplication analysis are available.
7. No deletions or duplications involving *ABCC8*, *GCK*, *KCNJ11*, or *PDX1* have been reported to cause permanent neonatal diabetes mellitus. Note that the *KCNJ11* and *ABCC8* defects are activating pathogenic variants and therefore must be missense. Duplication/ deletion analysis would not identify *ABCC8* and *KCNJ11* defects.
8. Njølstad et al [2001], Njølstad et al [2003]. Note: Carrier parents have mild diabetes mellitus or glucose intolerance (*GCK*-familial monogenic diabetes, previously known as MODY2).
9. Støy et al [2007], Polak et al [2008]
10. A 646-bp deletion in *INS* was reported in individuals with neonatal diabetes [Raile et al 2011, Garin et al 2010, Støy et al 2010]; see Table 5.
11. Attributed to activating pathogenic variants in *KCNJ11* [Ellard et al 2007]
12. Attributed to inactivating pathogenic variants [Stoffers et al 1997a]. Note: Carrier parents have mild, adult-onset diabetes mellitus (*PDX1*-familial monogenic diabetes, previously known as MODY4).
13. The genetic causes of approximately 30% of PNDM remain unknown [Rubio-Cabezas et al 2014].

Clinical Characteristics

Clinical Description

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 26 weeks) [Gloyn et al 2004b].

The diabetes mellitus is associated with partial or complete insulin deficiency.

Clinical manifestations at diagnosis include intrauterine growth restriction (IUGR; a reflection of insulin deficiency in utero), hyperglycemia, glycosuria, osmotic polyuria, severe dehydration, and failure to thrive.

Therapy with insulin corrects the hyperglycemia and results in dramatic catch-up growth.

Phenotype Correlations by Gene

The course of PNDM is highly variable depending on the genotype.

***ABCC8* and *KCNJ11*.** Most individuals with PNDM caused by pathogenic variants in *ABCC8* and *KCNJ11* are diagnosed before age three months, but a few present in childhood or early adult life. The majority of affected infants have low birth weight resulting from lower fetal insulin production. The typical presentation is symptomatic hyperglycemia, and in many individuals, ketoacidosis.

Although most individuals with pathogenic variants in *KCNJ11* have isolated diabetes, 20% have associated neurologic features, called DEND syndrome (*d*evelopmental delay, *e*pilepsy, and *n*eonatal *d*iabetes mellitus) [Hattersley et al 2006]. A milder form, called intermediate DEND syndrome, presents with less severe developmental delay and without epilepsy. In individuals with *KCNJ11* pathogenic variants, treatment with sulfonylureas corrects the hyperglycemia [Pearson et al 2006] and may reverse some of the neurologic manifestations [Hattersley & Ashcroft 2005, Slingerland et al 2006]. Neurologic manifestations might be prevented by early treatment with these agents [Greeley et al 2010] (see Management).

***GCK*.** PNDM caused by biallelic *GCK* pathogenic variants is characterized by IUGR, insulin-requiring diabetes from the first day of life, and hyperglycemia in both parents.

***INS*.** Individuals with PNDM caused by heterozygous *INS* pathogenic variants or biallelic deletions of *INS* present with diabetic ketoacidosis or marked hyperglycemia. Most newborns are small for gestational age [Støy et al 2007, Polak et al 2008]. The median age at diagnosis is nine weeks, but some children present after age six months [Edghill et al 2008].

***PDX1*.** Pancreatic hypoplasia caused by biallelic *PDX1* pathogenic variants results in a more severe insulin deficiency than in *ABCC8, GCK, or KCNJ11*-related neonatal diabetes as shown by a lower birth weight and a younger age at diagnosis. These individuals also have exocrine pancreatic insufficiency.

Genotype-Phenotype Correlations

***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 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 NDM 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 type 1b diabetes mellitus [Støy et al 2010].

***KCNJ11*.** Clear genotype-phenotype correlations exist for those forms of PNDM associated with *KCNJ11* pathogenic variants.

Genotype-phenotype studies correlate *KCNJ11* pathogenic variants and phenotype with the extent of reduction in K_{ATP} channel ATP sensitivity.

Some *KCNJ11* pathogenic variants are associated with transient neonatal diabetes mellitus (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].

The location of the *KCNJ11* pathogenic variant appears to predict the severity of the disease (isolated diabetes mellitus, intermediate DEND syndrome, DEND syndrome), however, there are some exceptions. 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, ***KCNJ11***, **Normal gene product** for a discussion of Kir6.2 and ***ABCC8,* Normal gene product for Sur1.**

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].

- 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.Ile296Val, p.Cys166Phe [Gloyn et al 2006], p.Gly334Asp [Masia et al 2007b], 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.

Penetrance

Reduced penetrance has been seen in PNDM caused by pathogenic variants in *KCNJ11* and *ABCC8* [Flanagan et al 2007].

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 permanent neonatal diabetes ranges from 1:215,000 to 1:260,000 live births [Stanik et al 2007, Slingerland et al 2009, Wiedemann et al 2010].

Genetically Related (Allelic) Disorders

***ABCC8, GCK,* and *KCNJ11*.** Pathogenic variants in *ABCC8*, *GCK* and *KCNJ11* are known to be associated with familial hyperinsulinism (FHI). FHI is characterized by hypoglycemia that ranges from severe, difficult-to-manage neonatal-onset disease to childhood-onset disease with mild symptoms and difficult-to-diagnose hypoglycemia. Neonatal-onset disease manifests within hours to one to two days after birth; childhood-onset disease manifests during the first months or years of life. FHI caused by pathogenic variants in either *ABCC8* or *KCNJ11* (FHI-K_{ATP}) is most commonly inherited in an autosomal recessive manner and less commonly in an autosomal dominant manner. FHI caused by pathogenic variants in *GCK* is inherited in an autosomal dominant manner. Infants with GCK-related FHI tend to be large for gestational age at birth and may present in early infancy (range: 2 days to 30 years).

ABCC8* and *KCNJ11

- **Common variants** in *ABCC8* and *KCNJ11*, particularly p.Glu23Lys in *KCNJ11*, have been associated with type 2 diabetes mellitus [Hani et al 1998, Gloyn et al 2001, Hansen et al 2001, Hart et al 2002, Gloyn et al 2003, Nielsen et al 2003, Florez et al 2004].
- **Activating pathogenic variants** in *ABCC8* and *KCNJ11* with less severe effects on channel function have been found to cause TNDM that is similar to the biphasic course seen in the 6q24-related TNDM phenotype. Typically, infants with TNDM caused by K_{ATP} channel pathogenic variants present before age six months, then 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].

ABCC8. A dominant *ABCC8* pathogenic variant is associated with hyperinsulinemic hypoglycemia in the neonatal period and may lead to diabetes mellitus later in life [Huopio et al 2003]. See Maturity-Onset Diabetes of the Young Overview.

GCK. Dominant inactivating pathogenic variants in *GCK* are associated with *GCK*-familial monogenic diabetes, a mild form of diabetes mellitus presenting later in life.

INS. Heterozygous pathogenic variants in *INS* have been reported in individuals with infancy-onset diabetes, type 1b (antibody negative) diabetes, familial monogenic diabetes and early-onset type 2 diabetes [Støy et al 2010].

KCNJ11. A subset of individuals with biallelic pathogenic variants in *KCNJ11* will present with transient instead of permanent neonatal diabetes mellitus (see Differential Diagnosis).

PDX1. Dominant inactivating pathogenic variants of *PDX1* are associated with *PDX1*-familial monogenic diabetes, a mild form of diabetes mellitus.

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.

6q24-related TNDM is defined as transient neonatal diabetes mellitus caused by overexpression of the imprinted genes at 6q24 (*PLAGL1* and *HYMAI*). The cardinal features are: severe intrauterine growth restriction (IUGR), 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 are often present. In the subset of children with *ZFP57* pathogenic variants, other manifestations can include structural brain abnormalities, developmental delay, and congenital heart disease. Diabetes mellitus usually starts within the first week of life and 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. Recurrence in adolescence is more akin to type 2 diabetes mellitus. Relapse in women during pregnancy is associated with gestational diabetes mellitus.

The two most common causes of transient neonatal diabetes are 6q24-related TNDM and pathogenic variants in *ABCC8* or *KCNJ11*. In 50 children presenting with neonatal diabetes, Metz et al [2002] failed to demonstrate clear clinical indicators to differentiate 6q24-related TNDM from other causes. However, the clinical presentation may be slightly different: neonates with 6q24-related TNDM have more severe IUGR, present earlier, remit earlier, and relapse later than K_{ATP}-related TNMD. The presence of other distinguishing features of 6q24-related TNDM may guide the approach to genetic testing, such macroglossia (seen in 1/3 of individuals) and umbilical hernia [Rubio-Cabezas et al 2014].

- For infants presenting in the first two weeks of life, it is reasonable to test for 6q24-related aberrations first, followed by testing for *KCNJ11* and *ABCC8* pathogenic variants.

- For infants presenting from the third week of life onward, it may be more appropriate to test for *KCNJ11* and *ABCC8* pathogenic variants first, followed by testing for 6q24-related aberrations.
- In infants presenting between age six and 12 months or later who are antibody negative or have a family history consistent with autosomal dominant inheritance, evaluation for pathogenic variants in *INS* should be considered first.

For infants with associated extra-pancreatic features or consanguineous parents, other genetic analysis may be appropriate.

Syndromic causes of permanent neonatal diabetes mellitus

- ***GATA4*-related PNDM.** Heterozygous inactivating pathogenic variants in *GATA4* are associated with pancreatic agenesis or pancreatic hypoplasia leading to PNDM and congenital heart defects [D'Amato et al 2010, Shaw-Smith et al 2014]. GATA4 is a zinc finger transcription factor closely related to GATA6. The diabetes phenotype in individual carrying pathogenic variants is quite variable, ranging from TNDM, PNDM and diabetes presenting later in life. The severity of the exocrine insufficiency is also variable. Extrapancreatic manifestations include cardiac abnormalities and neurodevelopmental delays. Inheritance is autosomal dominant, but in most reported individuals the pathogenic variants have arisen *de novo*.
- ***GATA6*-related PNDM** (OMIM 600001). Heterozygous inactivating pathogenic variants in *GATA6* are the most common cause of pancreatic agenesis [Lango Allen et al 2011]. Extrapancreatic features are common and include structural heart defects, biliary tract and gut anomalies, and other endocrine abnormalities. The diabetic phenotype in those with pathogenic variants in *GATA6* is broad, ranging from PNDM with exocrine insufficiency to transient episodes of hyperglycemia. In the largest published series of *GATA6*-PNDM, the median age at diagnosis of diabetes was two days and the median birth weight was 1588 grams. Individuals with heterozygous pathogenic variants in *GATA6* have also been diagnosed with diabetes at an older age [Lango Allen et al 2011, De Franco et al 2013]. Inheritance is autosomal dominant, but in most reported individuals the pathogenic variants have arisen *de novo*.
- ***PTF1A*-related PNDM** (OMIM 609069). Homozygous inactivating pathogenic variants in *PTF1A* cause pancreatic agenesis leading to PNDM associated with cerebellar agenesis and severe neurologic dysfunction [Sellick et al 2004]. *PTF1A* encodes a basic helix-loop-helix protein of 48 kd. The protein plays a role in determining whether cells allocated to the pancreatic buds continue toward pancreatic organogenesis or revert back to duodenal fates [Kawaguchi et al 2002]. Infants with *PTF1A*-related PNDM present with severe IUGR, and very low circulating insulin and C-peptide in the presence of severe hyperglycemia. Neurologic features include flexion contractures of extremities and absence of the cerebellum demonstrated on brain imaging [Sellick et al 2004]. A recent report described an individual with *PTF1A*-related PNDM without neurologic manifestations [Houghton et al 2016]. Exocrine pancreatic dysfunction may be present as well. Inheritance is autosomal recessive.
- **Immune dysregulation, polyendocrinopathy, and enteropathy, X-linked (IPEX) syndrome** is characterized by the development of overwhelming systemic autoimmunity in the first year of life resulting in the commonly observed triad of watery diarrhea, eczematous dermatitis, and endocrinopathy seen most commonly as insulin-dependent diabetes mellitus. The majority of affected males have other autoimmune phenomena including Coombs-positive anemia, autoimmune thrombocytopenia, autoimmune neutropenia, and tubular nephropathy. Typically, serum concentration of immunoglobulin E (IgE) is elevated. The majority of affected males die within the first year of life of either metabolic derangements or sepsis. *FOXP3* is currently the only gene in which mutation is known to cause IPEX syndrome. Inheritance is X-linked.
- **Wolcott-Rallison syndrome** (OMIM 226980) is characterized by infantile-onset diabetes mellitus and exocrine pancreatic dysfunction (25%) as well as the extra-pancreatic manifestations of epiphyseal dysplasia (90%), developmental delay (80%), acute liver failure (75%), osteopenia (50%), and hypothyroidism (25%). In addition, older individuals with Wolcott-Rallison syndrome may develop

chronic kidney dysfunction [Senée et al 2004]. The prognosis is poor. *EIF2AK3*, the gene encoding eukaryotic translation initiation factor 2-alpha kinase 3, is the only gene in which pathogenic variants are known to cause Wolcott-Rallison syndrome. Durocher et al [2006] observed that the severity of the manifestations and age of presentation in individuals with the same pathogenic variant may vary and concluded that no simple relationship exists between the clinical manifestation and *EIF2AK3* pathogenic variants in Wolcott-Rallison syndrome. This is the most common cause of PNDM in consanguineous families [Rubio-Cabezas et al 2009]. Inheritance is autosomal recessive.

- **A syndrome of neonatal diabetes mellitus with congenital hypothyroidism** (OMIM 610199) has been associated with mutation of *GLIS3*. *GLIS3* encodes zinc finger protein GLIS3 (also known as GLI similar protein 3), a transcription factor expressed in the pancreas from early developmental stages. GLIS3 plays a role in the transcriptional regulation of neurogenin-3 and insulin [Kim et al 2012, ZeRuth et al 2013]. In addition to neonatal diabetes and congenital hypothyroidism, the syndrome can present with congenital glaucoma, hepatic fibrosis, polycystic kidneys, and dysmorphic facial features [Senée et al 2006]. Inheritance is autosomal recessive and partial gene deletions are the most common type of pathogenic variant [Dimitri et al 2011].
- **A syndrome of neonatal diabetes mellitus with pancreatic hypoplasia, intestinal atresia, and gall bladder hypoplasia** (OMIM 615710) has been associated with pathogenic variants in *RFX6*. RFX6 is a transcription factor required for the differentiation of four of the five islet cell types and for the production of insulin. RFX6 acts downstream of the pro-endocrine factor neurogenin-3. Pancreatic exocrine function is normal [Smith et al 2010]. Inheritance is autosomal recessive.
- **A syndrome of neonatal diabetes mellitus, cerebellar hypoplasia, sensorineural deafness, and visual impairment** has been associated with pathogenic variants in *NEUROD1* (OMIM 601724), encoding neurogenic differentiation factor 1, a transcription factor that plays an important role in the development of the endocrine pancreas. Pancreatic exocrine function is normal [Rubio-Cabezas et al 2010]. Inheritance is autosomal recessive.
- **A syndrome of congenital malabsorptive diarrhea and neonatal diabetes mellitus** (OMIM 610370) has been associated with pathogenic variants in *NEUROG3*, encoding neurogenin-3, a basic helix loop helix transcription factor essential in the development of enteroendocrine, Paneth, goblet, and enterocyte cells in the intestine and pancreatic endocrine cells [Pinney et al 2011]. Diabetes may also present later in childhood [Wang et al 2006]. Pancreatic exocrine function may also be affected. Inheritance is autosomal recessive.
- **A syndrome of neonatal diabetes mellitus and renal abnormalities** (OMIM 137920) has been associated with pathogenic variants in *HNF1B*. HNF1 beta is a key regulator of a transcriptional network that controls the specification, growth and differentiation of the embryonic pancreas. The diabetes phenotype in individuals heterozygous for a single pathogenic variant in *HNF1B* manifests more frequently later in life (renal cysts and diabetes syndrome – RCAD, or MODY5). The neonatal presentation due to biallelic pathogenic variants in *HNF1B* is characterized by evidence of severe insulin deficiency (low birth weight, diabetes ketoacidosis) and pancreatic exocrine insufficiency due to hypoplastic pancreas. Other manifestations include genital tract malformations, hyperuricemia and gout, as well as abnormal liver function. The inheritance is autosomal recessive but penetrance is incomplete [Yorifuji et al 2004, Edghill et al 2006, Haldorsen et al 2008, Tjora et al 2013].
- **A syndrome of neonatal diabetes with brain malformations, microcephaly, and microphthalmia** has been associated with pathogenic variants in *PAX6* (OMIM 607108). PAX6 is a transcription factor involved in eye and brain development that also plays a role in pituitary development and in ß-cell differentiation and function. In heterozygous individuals, diabetes presents later in life, however in individuals with biallelic pathogenic variants, the diabetes manifests in the neonatal period. The central nervous system (CNS) phenotype includes microcephaly and panhypopituitarism. The ocular phenotype includes aniridia, keratopathy, optic nerve defects, cataracts, microphthalmia and anophthalmia [Yasuda et al 2002, Solomon et al 2009].

- **Wolfram syndrome – diabetes mellitus with optic atrophy, diabetes insipidus, and/or deafness.** The associated gene, *WFS1*, encodes an endoplasmic reticulum (ER) membrane-embedded protein involved in regulating ER stress. The earliest and most consistent phenotypic characteristic in individuals with Wolfram syndrome is diabetes, which is usually diagnosed during childhood, but it can also present in the first year of life. The inheritance is autosomal recessive [Rigoli et al 2011, Rohayem et al 2011]. See *WFS1* Spectrum Disorder.
- **A syndrome of neonatal diabetes mellitus, deafness, and thiamine-responsive megaloblastic anemia** caused by pathogenic variants in *SLC19A2*. *SLC19A2* encodes a thiamine transporter. Also known as Rogers syndrome, this syndrome can also be associated with neurologic deficits, visual disturbances, and cardiac abnormalities. The diabetes phenotype can manifests in the first six months of life or later. The inheritance is autosomal recessive [Shaw-Smith et al 2012]. See Thiamine-Responsive Megaloblastic Anemia Syndrome.
- **A syndrome of neonatal diabetes mellitus, developmental delays, sacral agenesis and imperforated anus** caused by pathogenic variants in *MNX1*. Other manifestations include IUGR, hypoplastic lungs. Inheritance is autosomal recessive [Flanagan et al 2014].
- **A syndrome of neonatal diabetes mellitus, developmental delays, hypotonia, short stature and deafness** caused by pathogenic variants in *NKX2-2*. Other manifestations include IUGR, cortical blindness, and impaired visual tracking. Inheritance is autosomal recessive [Flanagan et al 2014].
- **A syndrome of neonatal diabetes, microcephaly, lissencephaly, and epileptic encephalopathy** caused by pathogenic variants in *IER3IP1*. *IERI31P1* encodes a highly conserved protein with marked expression in beta cells in cerebral cortex but which function is not well known. Inheritance is autosomal recessive [Shalev et al 2014].

Testing strategy for syndromic permanent neonatal diabetes mellitus. Individuals with PNDM **and**:

- Pancreatic exocrine insufficiency or agenesis and cardiac abnormalities should be tested for pathogenic variants in *GATA4* and *GATA6*;
- Enteropathy and dermatitis should be tested for pathogenic variants in *FOXP3* (IPEX syndrome);
- Cerebellar involvement should be tested for pathogenic variants in *PTF1A*;
- Congenital hypothyroidism should be tested for pathogenic variants in *GLIS3*;
- Cerebellar hypoplasia, sensorineural deafness, and visual impairment should be tested for pathogenic variants in *NEUROD1*;
- Pancreatic hypoplasia, intestinal atresia, and gall bladder hypoplasia should be tested for pathogenic variants in *RFX6*;
- Congenital malabsorptive diarrhea should be tested for pathogenic variants in *NEUROG3*;
- Skeletal abnormalities and liver dysfunction should be tested for pathogenic variants in *EIF2AK3* (WRS - Wolcott-Rallison syndrome);
- Megaloblastic anemia and deafness should be tested for pathogenic variants in *SLC19A2* (TRMA; thiamine-responsive megaloblastic anemia);
- Renal and genital abnormalities should be tested for pathogenic variants in *HNF1B;*
- Brain malformations, microcephaly and microphthalmia should be tested for pathogenic variants in *PAX6*;
- Optic atrophy, diabetes insipidus and deafness should be tested for pathogenic variants in *WFS1* (Wolfram syndrome).

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with neonatal diabetes mellitus as a result of pathogenic variants in *ABCC8* or *KCNJ11*, a complete neurologic evaluation should be performed.

To establish the extent of disease in an individual with suspected or confirmed pathogenic variants in *PDX1*, imaging of the pancreas and evaluation of pancreatic exocrine function (stool elastase, serum concentrations of fat-soluble vitamins) should be performed.

Consultation with a clinical geneticist and/or genetic counselor should be obtained early in the evaluation of PNDM.

Treatment of Manifestations

Initial treatment. Rehydration and intravenous insulin infusion should be started promptly after diagnosis, particularly in infants with ketoacidosis.

Long-term medical management. An appropriate regimen of subcutaneous insulin administration should be established when the infant is stable and tolerating oral feedings. Few data on the most appropriate insulin preparations for young infants are available.

- Intermediate-acting insulin preparations (neutral protamine Hagedorn [NPH]) tend to have a shorter duration of action in infants, possibly because of smaller dose size or higher subcutaneous blood flow.
- The longer-acting preparations with no significant peak-of-action effect such as Lantus® (glargine) or Levemir® (detemir) may work better in small infants.
- In individuals with very low insulin requirements, diluted insulin (5 or 10 U/mL) may be more appropriate if used with caution.
- Some centers recommend the use of continuous subcutaneous insulin infusion for young infants [Polak & Cave 2007] as a safer, more physiologic, and more accurate way of administering insulin.
- Caution:
  - In general, rapid-acting (lispro and aspart) and short-acting (regular) preparations (except when used as a continuous intravenous or subcutaneous infusion) should be avoided as they may cause severe hypoglycemic events.
  - Extreme caution should be observed when using a diluted insulin preparation in order to avoid dose errors.

Identification of a *KCNJ11* or *ABCC8* pathogenic variant is important for clinical management since most individuals with these pathogenic variants can be treated with oral sulfonylureas. Children with pathogenic variants in *KCNJ11* or *ABCC8* can be transitioned to therapy with oral sulfonylureas; high doses are usually required (0.4-1.0 mg/kg/day of glibenclamide). Transfer protocols are available at www.diabetesgenes.org. Treatment with sulfonylureas is associated with improved glycemic control [Hattersley & Ashcroft 2005, Pearson et al 2006, Thurber et al 2015, Babiker et al 2016].

Long-term insulin therapy is required for all other causes of PNDM, although mild beneficial effect of oral sulfonylureas in persons with *GCK* pathogenic variants has been reported [Turkkahraman et al 2008, Hussain 2010].

High caloric intake should be maintained to achieve weight gain.

Pancreatic enzyme replacement therapy is required in persons with exocrine pancreatic insufficiency.

Prevention of Secondary Complications

Aggressive treatment and frequent monitoring of blood glucose concentrations is essential to avoid acute complications such as diabetic ketoacidosis and hypoglycemia.

Long-term complications of diabetes mellitus can be significantly reduced by maintaining blood glucose concentrations in the appropriate range. The American Diabetes Association recommends the following glycemic goals across all pediatric age-groups [American Diabetes Association 2016a]:

- Glycemic targets for children younger than age six years:
  - 90-130 mg/dL before meals
  - 90-150 mg/dL at bedtime/overnight
- Hemoglobin A1c value < 7.5%

Surveillance

Lifelong monitoring (≥4x/day) of blood glucose concentrations is indicated to achieve the goals of therapy.

Children with PNDM, particularly those with a pathogenic variant in *KCNJ11* or *ABCC8*, should undergo periodic developmental evaluations.

Yearly screening for chronic complications associated with diabetes mellitus should be started after age ten years and should include the following:

- Urinalysis for microalbuminuria
- Ophthalmologic examination to screen for retinopathy

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

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

Pregnancy Management

The management of pregnant women with PNDM should conform to the guidelines for treatment of other forms of diabetes during gestation [American Diabetes Association 2016b]. Glycemic control during gestation is not only important to prevent complications in the mother, but also to prevent fetal overgrowth (due to fetal hyperinsulinemia triggered by the excess of maternal glucose crossing the placenta) and associated complications. Referral to a maternal-fetal medicine specialist should be considered. In addition, 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 of diabetes during pregnancy; however, emerging data support the safety and efficacy of glyburide in the treatment of diabetes during pregnancy [Moretti et al 2008]. Thus, in women with PNDM treated with glyburide before pregnancy, it is reasonable to continue this treatment if appropriate glycemic control can be achieved.

Therapies Under Investigation

Search ClinicalTrials.gov in the US 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:

- ***ABCC8*** and ***INS.*** Autosomal dominant or autosomal recessive
- ***GCK*** and ***PDX1.*** Autosomal recessive
- ***KCNJ11.*** Autosomal dominant

Autosomal Dominant Inheritance – Risk to Family Members

Table 2. Autosomal Dominant PNDM – Risk to Parents of a Proband by Gene

Gene	% of Probands with an Affected Parent	% of Probands with a *De Novo* Pathogenic Variant
ABCC8	~10% [1]	Most reported cases [2]
INS	27%	73%
KCNJ11	~10%	90%

1. A parent may have type 2 diabetes despite having the same *ABCC8* pathogenic variant as their child with neonatal diabetes mellitus [Babenko et al 2006].
2. Patch et al [2007]

Parents of a proband (see Table 2)

- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant in *ABCC8*, *INS*, or *KCNJ11* include molecular genetic testing and clinical testing for diabetes mellitus (oral glucose tolerance testing).
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Germline mosaicism for a pathogenic variant in *KCNJ11* has been reported [Gloyn et al 2004a, Edghill et al 2007]; the overall incidence of germline mosaicism is unknown.
- Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of failure by health care professionals to recognize the syndrome and/or a milder phenotypic presentation. Therefore, an apparently negative family history cannot be confirmed until appropriate 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, the risk to the sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.

- If the *ABCC8*, *INS*, or *KCNJ11* 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 (though still <1%) because of the possibility of parental germline 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 *ABCC8*, *INS*, or *KCNJ11* 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, 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 autosomal recessive PNDM are obligate heterozygotes and therefore have one PNDM-related pathogenic variant.
- The parents of a child with autosomal recessive PNDM may or may not be affected (see Genotype-Phenotype Correlations).
  - ***ABCC8*.** In 43% of affected individuals, *ABCC8*-related PNDM 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]. Heterozygotes for pathogenic variants in *INS* associated with recessively inherited NDM may have adult onset diabetes [Raile et al 2011].
  - ***GCK* and *PDX1*.** Heterozygotes for pathogenic variants in *GCK* and *PDX1* have milder forms of diabetes mellitus (*GCK*-familial monogenic diabetes and *PDX1*-familial monogenic diabetes, respectively).

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being heterozygous, and a 25% chance of being unaffected and not heterozygous.
- Heterozygotes for pathogenic variants in *GCK*, *INS*, or *PDX1* have a milder form of diabetes mellitus (e.g., *GCK*-familial monogenic diabetes, previously known as MODY2, or *PDX1*-familial monogenic diabetes, previously known as MODY4). Heterozygotes for pathogenic variants in *ABCC8* have normal glucose tolerance. See MODY Overview.

Offspring of a proband. The offspring of an individual with autosomal recessive neonatal diabetes mellitus are obligate heterozygotes for a 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. Carrier testing for at-risk relatives requires prior identification of the PNDM-related pathogenic variants in the family.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant or clinical evidence of the disorder, it is likely that the proband has a *de novo* pathogenic variant. However, possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, 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.

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 for PNDM are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

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

  www.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
GCK	7p13	Hexokinase-4	Glucokinase (hexokinase 4) (GCK) @ LOVD	GCK	GCK
INS	11p15.5	Insulin	INS database	INS	INS
KCNJ11	11p15.1	ATP-sensitive inward rectifier potassium channel 11	KCNJ11 database	KCNJ11	KCNJ11
PDX1	13q12.2	Pancreas/duodenum homeobox protein 1	PDX1 database	PDX1	PDX1

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
176730	INSULIN; INS
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
606176	DIABETES MELLITUS, PERMANENT NEONATAL, 1; PNDM1

ABCC8

Gene structure. *ABCC8* is located 4.5 kb centromeric to *KCNJ11* on chromosome 11p15.1. The gene spans approximately 84 kb of genomic DNA and is made up of 39 exons. The shorter transcript variant NM_000352.4 is 4935 bp. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. More than 25 different *ABCC8* variants have been associated with permanent neonatal diabetes (see Table 3). In addition, several other variants in compound heterozygotes have been associated with PNDM. (See Flanagan et al [2009] for variants in *ABCC8* that cause both neonatal diabetes mellitus and persistent hyperinsulinemic hypoglycemia of infancy.)

Table 3. Selected *ABCC8* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	References	Reference Sequences
c.215A>G	p.Asn72Ser	Ellard et al [2007]	NM_000352.3 NP_000343.2

Table 3. continued from previous page.

DNA Nucleotide Change	Predicted Protein Change	References	Reference Sequences
c.257T>C	p.Val86Ala	Ellard et al [2007]	
c.257T>G	p.Val86Gly	Ellard et al [2007]	
c.394T>G	p.Phe132Val	Ellard et al [2007]	
c.394T>C	p.Phe132Leu	Proks et al [2006]	
c.404T>C	p.Leu135Pro	Ellard et al [2007]	
c.627C>A	p.Asp209Glu	Ellard et al [2007], Flanagan et al [2007]	
c.631C>A	p.Gln211Lys	Ellard et al [2007]	
c.638T>G	p.Leu213Arg	Babenko et al [2006]	
c.674T>C	p.Leu225Phe		
c.1144G>A	p.Glu382Lys	Ellard et al [2007]	
c.3554C>A	p.Ala1185Glu	Ellard et al [2007]	
c.4270A>G	p.Ile1424Val	Babenko et al [2006], Masia et al [2007a]	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

For more information see Patch et al [2007], Figure 2 (full text) and Edghill et al [2010], Figures 2 and 3.

Normal gene product. The transcript variant NM_000352.4 encodes ATP-binding cassette sub-family C member 8 protein (SUR1) (NP_000343.2), which has 1581 amino acids. See ***KCNJ11***, **Normal gene product**.

Abnormal gene product. Pathogenic variants in *ABCC8* result in nonfunctional or dysfunctional K_{ATP} channels. The increased activity of K_{ATP} channels resulting from pathogenic variants in *ABCC8* is caused by an increase in the magnesium-dependent stimulatory action of SUR1 on the pore [Babenko et al 2006, Masia et al 2007a], or by alteration in the inhibitory action of ATP on a mutated SUR1 channel [Proks et al 2006].

GCK

Gene structure. *GCK* spans more than 45 kb of genomic DNA; the transcript variant NM_000162.3, which encodes the isoform expressed specifically in pancreatic islet beta cells, has ten exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. At least ten variants of *GCK* have been reported in association with PNDM (see Table 4). These are nonsense, missense, or frameshift variants.

Table 4. Selected *GCK* Pathogenic Variants

DNA Nucleotide Change (Alias [1])	Predicted Protein Change	References	Reference Sequences
c.629T>A	p.Met210Leu	Njølstad et al [2001]	NM_000162.3 NP_000153.1
c.683C>T	p.Thr228Met		
c.790G>A	p.Gly264Ser	Njølstad et al [2003]	
1133C>T	p.Ala378Val		
c.1190G>T	p.Arg397Leu	Porter et al [2005]	
c.1505+2T>G (IVS8+2T>G)	NA	Njølstad et al [2003]	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
NA= not applicable
1. Variant designation that does not conform to current naming conventions

Normal gene product. The isoform NP_000153.1, expressed specifically in pancreatic islet beta cells, has 465 amino acid residues. Glucokinase is a hexokinase that 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, glucokinase controls the rate-limiting step of glucose metabolism and is responsible for glucose-stimulated insulin secretion [Matschinsky 2002].

Abnormal gene product. The reported 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

Gene structure. The *INS* transcript variant NM_000207.2 has three exons. Exon 2 encodes the signal peptide, the B chain, and part of the C peptide; exon 3 encodes the reminder of the C peptide and the A chain. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. More than 25 variants have been described in association with PNDM [Støy et al 2007, Polak et al 2008, Støy et al 2010]. See Table 5 and Genotype-Phenotype Correlations.

See Støy et al [2010] for variants in *INS* that cause diabetes mellitus.

Table 5. Selected *INS* Pathogenic Variants

DNA Nucleotide Change [1]	Predicted Protein Change	References	Reference Sequences
c.-366_343del [2, 3]	NA	Støy et al [2007], Polak et al [2008], Støy et al [2010]	NM_000207.2 [4] NP_000198.1
c.-370-?186+?del [2, 3, 5, 6]			
c.-331C>A [2, 3, 7, 8]			
c.-331C>G [2, 3, 4, 9]			
c.-218A>C [2, 3, 7, 10]			
c.3G>A [2]	p.0? [11]		
c.3G>T [2]	p.0? [11]		

Table 5. continued from previous page.

DNA Nucleotide Change [1]	Predicted Protein Change	References	Reference Sequences
c.71C>A	p.Ala24Asp		
c.94G>A	p.Gly32Ser		
c.94G>C	p.Gly32Arg		
c.127T>G	p.Cys43Gly		
c.140G>T	p.Gly47Val		
c.143T>G	p.Phe48Cys		
c.184C>T [2]	p.Gln62Ter		
c.265C>T	p.Arg89Cys		
c.268G>T	p.Gly90Cys		
c.287G>A	p.Cys96Tyr		
c.323A>G	p.Tyr108Cys		
c.*59A>G [2, 12]	NA		

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
NA = not applicable
1. Negative number indicates the number of base pairs preceding the A of the ATG start codon. An asterisk indicates a position in the 3'UTR; the number is the position relative to the first base past the stop codon.
2. A 646-bp deletion. See Table 1 (footnote 10) and Genotype-Phenotype Correlations.
3. Garin et al [2010]
4. Reference sequences of the insulin preproprotein (or preproinsulin)
5. Denotes an exon deletion starting at an unknown position in the promoter of coding DNA nucleotide -370 and ending at an unknown position in the intron 3' of the coding DNA nucleotide 186 [Støy et al 2010]
6. Raile et al [2011]
7. Bonnefond et al [2011]
8. -94 relative to transcription initiation site
9. -93 relative to transcription initiation site
10. A+20 relative to transcription initiation site
11. p.0? = effect unknown; probably no protein is produced
12. 59 nucleotides 3' of the termination codon (in the 3'UTR)

Normal gene product. The insulin preproprotein NP_000198.1 encoded by transcript NM_000207.2 has 110 amino acids. 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.

Abnormal gene product. The diabetes-associated pathogenic variants lead to the synthesis of a structurally abnormal preproinsulin or proinsulin protein. The variants associated with PNDM disrupt proinsulin folding and/or disulfide bond formation. Some reported variants disrupt normal disulfide bonds (p.Cys43Gly and p.Cys96Tyr) or add an additional unpaired cysteine residue (p.Arg89Cys and p.Gly90Cys) at the A-chain C-peptide cleavage site. The variant p.Tyr108Cys may cause mispairing of cysteines in a critical region close to a disulfide bond [Støy et al 2007]. All of the pathogenic variants are likely to act in a dominant manner to disrupt insulin biosynthesis and induce endoplasmic reticulum (ER) stress. The exact mechanism by which these unpaired cysteines disrupt ER function remains unclear [Izumi et al 2003]. Three other pathogenic variants (p.Gly32Ser, p.Gly32Arg, and p.Gly47Val) are located in a residue that is invariant in both insulin and the

insulin-like growth factors and must play an important structural role. It is believed that these glycine variants also act similarly to impair proinsulin folding and thereby induce ER stress via the unfolded protein response.

KCNJ11

Gene structure. *KCNJ11* is located 4.5 kb telomeric to *ABCC8* on chromosome 11p15.1. The gene spans approximately 3.4 kb of genomic DNA and has a single exon. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. More than 20 different pathogenic variants in *KCNJ11* have been reported in association with neonatal diabetes mellitus (see Table 6). The two common hot spots for recurrent mutation are at amino acid residues Val59 and Arg201 [Hattersley & Ashcroft 2005]. (See Flanagan et al [2009] for variants in *KCNJ11* that cause both neonatal diabetes mellitus and persistent hyperinsulinemic hypoglycemia of infancy.)

Table 6. Selected *KCNJ11* Variants

Variant Classification	DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
Benign	c.67G>A	p.Glu23Lys [1]	NM_000525.3 NP_000516.3
Pathogenic	c.103T>G	p.Phe35Val	
	c.103T>C	p.Phe35Leu	
	c.124T>C	p.Cys42Arg	
	c.149G>C	p.Arg50Pro	
	c.155A>G	p.Gln52Arg	
	c.157G>C	p.Gly53Arg	
	c.157G>A	p.Gly53Ser	
	c.158G>A	p.Gly53Asp	
	c.175G>A	p.Val59Met	
	c.176T>G	p.Val59Gly	
	c.497G>T	p.Cys166Phe	
	c.497G>A	p.Cys166Tyr	
	c.499A>C	p.Ile167Leu	
	c.509A>G	p.Lys170Arg	
	c.510G>C	p.Lys170Asn	
	c.544A>G	p.Ile182Val	
	c.602G>A	p.Arg201His	
	c.601C>T	p.Arg201Cys	
	c.602G>T	p.Arg201Leu	
	c.755T>C	p.Val252Ala	
	c.886A>C	p.Ile296Leu	
	c.886A>G	p.Ile296Val	
	c.964G>A	p.Glu322Lys	
	c.989A>G	p.Tyr330Cys	
	c.997T>A	p.Phe333Ile	

Table 6. continued from previous page.

Variant Classification	DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
	c.1001G>A	p.Gly334Asp	

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GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Associated with type 2 diabetes mellitus; see Genetically Related Disorders.

Normal gene product. The transcript variant NM_000525.3 encodes the 390-amino acid isoform known as Kir6.2 (NP_000516.3). *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 glucokinase, there is an 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.

Abnormal gene product. 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].

PDX1

Gene structure. The *PDX1* transcript NM_000209.3 has 2573 bp and comprises two exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. At least four *PDX1* variants have been described in association with pancreatic agenesis and PNDM:

- A homozygous single-nucleotide deletion c.188_189delC in one person [Stoffers et al 1997b]
- A homozygous pathogenic missense variant p.Glu178Gly in the *PDX1* homeodomain associated with neonatal diabetes without exocrine insufficiency in two individuals [Nicolino et al 2010]
- Compound heterozygosity for p.Glu164Asp and p.Glu178Lys pathogenic variants within exon 2 of *PDX1* [Schwitzgebel et al 2003]. See Table 7.

Table 7. Selected *PDX1* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.188_189delC	p.Pro63ArgfsTer60	NM_000209.3 NP_000200.1
c.492G>T	p.Glu164Asp	
c.532G>A	p.Glu178Lys	
c.533A>G	p.Glu178Gly	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. The pancreas/duodenum homeobox protein 1 or transcription factor insulin promoter factor 1 (PDX1) is a master regulator of pancreatic development and of the differentiation of progenitor cells into the beta-cell phenotype.

During embryogenesis in the mouse, pdx1 expression initiates on commitment of the foregut endoderm to a pancreatic fate. In the adult organism, pdx1 expression is limited to the beta cell and its importance in maintaining beta-cell phenotype is illustrated by multiple animal models. In mature beta cells, pdx1 regulates the expression of critical genes including insulin, glucokinase, and the glucose transporter *Glut2* [Habener et al 2005].

Abnormal gene product. The single-nucleotide deletion c.188_189delC predicts the formation of a truncated, inactive protein (p.Pro63ArgfsTer60), whereas the mutated proteins p.Glu164Asp or p.Glu178Lys undergo increased degradation leading to a reduction in protein levels and ultimately to decreased transcriptional activity. The p.Glu178Gly variant reduces PDX1 transactivation.

Chapter Notes

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Revision History

- 29 July 2016 (sw) Comprehensive update posted live
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- 4 March 2008 (cd) Revision: sequence analysis and prenatal diagnosis available for INS mutations
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