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NLM Citation: Temple IK, Mackay DJG. Diabetes Mellitus, 6q24-Related Transient Neonatal. 2005 Oct 10 [Updated 2018 Sep 13]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Diabetes Mellitus, 6q24-Related Transient Neonatal

Synonym: 6q24-TNDM

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Created: October 10, 2005; Updated: September 13, 2018.

Summary

Clinical characteristics

6q24-related transient neonatal diabetes mellitus (6q24-TNDM) is defined as transient neonatal diabetes mellitus caused by genetic aberrations of the imprinted locus at 6q24. 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-TNDM associated with a multilocus imprinting disturbance (MLID) can be associated with marked hypotonia, congenital heart disease, deafness, neurologic features including epilepsy, and renal malformations. Diabetes mellitus usually starts within the first week of life and lasts on average three months but can last longer 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-TNDM are at risk for relapse during pregnancy.

Diagnosis/testing

The diagnosis of 6q24-TNDM is established in a proband with transient neonatal diabetes mellitus and DNA methylation analysis demonstrating relative hypomethylation within the 6q24 differentially methylated region (DMR). 6q24-TNDM is caused by overexpression of the imprinted genes at 6q24 (*PLAGL1* and *HYMAI*). The DMR (i.e., *PLAGL1* TSS alt-DMR) is present within the shared promoter of these genes. Normally, expression of the maternal alleles of *PLAGL1* and *HYMAI* is silenced by DMR methylation and only the paternal alleles of *PLAGL1* and *HYMAI* are expressed. Additional molecular genetic testing can establish the underlying genetic mechanism, which is required for genetic counseling. Three different genetic mechanisms resulting in twice the normal dosage of *PLAGL1* and *HYMAI* (and thus causing 6q24-TNDM) are (1) paternal uniparental disomy of

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chromosome 6, (2) duplication of 6q24 on the paternal allele, and (3) hypomethylation of the maternal *PLAGL1* TSS alt-DMR, resulting in inappropriate expression of the maternal *PLAGL1* and *HYMAI* alleles. Maternal *PLAGL1* TSS alt-DMR hypomethylation may result from an isolated imprinting variant or as part of MLID. Biallelic *ZFP57* pathogenic variants account for almost half of TNDM-MLID.

Management

Treatment of manifestations: Rehydration and IV insulin are usually required at the time of diagnosis; subcutaneous insulin is introduced as soon as possible and used until blood glucose levels stabilize. Later recurrence of diabetes may require diet modifications alone, oral agents, or insulin.

Prevention of secondary complications: Prompt treatment of dehydration to avoid sequelae.

Surveillance: Periodic glucose tolerance tests (abnormalities suggest future recurrence); monitoring of growth and development.

Agents/circumstances to avoid: Factors that predispose to late-onset diabetes or risk factors for cardiovascular disease.

Evaluation of relatives at risk: Screening for diabetes mellitus in relatives who have inherited a paternal 6q24 duplication or who are at risk of having inherited two *ZFP57* pathogenic variants.

Genetic counseling

The risk to sibs and offspring of a proband of having 6q24-TNDM or of developing diabetes later in life depends on the genetic mechanism in the family. Recurrence risk counseling by a genetics professional is strongly recommended. 6q24-TNDM caused by paternal UPD6 is typically a *de novo*, non-recurrent event. 6q24-TNDM caused by paternal duplication of 6q24 can occur *de novo*, be inherited in an autosomal dominant manner, or be inherited as part of a complex chromosome rearrangement; TNDM caused by inherited duplication of 6q24 may recur in sibs and offspring of a proband if the duplication is inherited from the father. Prenatal diagnosis of paternal duplication of 6q24 is possible in pregnancies at risk for a structural chromosome abnormality. TNDM caused by hypomethylation of the *PLAGL1* TSS alt-DMR is a *de novo* non-recurrent event in the majority of individuals, particularly if hypomethylation is restricted to this DMR and does not affect other imprinted loci. However, TNDM as part of a multilocus imprinting disturbance (TNDM-MLID) has a significant genetic component. TNDM-MLID is inherited in an autosomal recessive manner when caused by pathogenic variants in *ZFP57*; however, the phenotype of homozygous or compound heterozygous sibs is variable and cannot be predicted by molecular genetic testing. Pathogenic variants in additional genes are suspected of causing TNDM-MLID but are currently unknown. Therefore, caution should be exercised when counseling the heritability of TNDM associated with imprinting disturbance at the *PLAGL1* TSS alt-DMR.

Diagnosis

Suggestive Findings

Diagnosis of 6q24-related transient neonatal diabetes mellitus (6q24-TNDM) **should be suspected** in individuals with the following clinical features:

- Severe intrauterine growth restriction
- Diabetes mellitus that commences in the first six weeks of life in a term infant and resolves by age 18 months. Presentation includes the following:
  - Hyperglycemia
  - Dehydration

- Plasma insulin concentrations that are low in the presence of high serum glucose concentrations
- Absence of ketoacidosis. Ketones are usually not present in the urine.
- Absence of islet cell antibodies
- Presence of a pancreas

Establishing the Diagnosis

The diagnosis of 6q24-TNDM **is established** in a proband with one of the following:

- Transient neonatal diabetes mellitus and DNA methylation analysis demonstrating relative hypomethylation within the *PLAGL1* TSS alt-DMR, through one of the following mechanisms:
  - Partial or complete paternal uniparental disomy of chromosome 6
  - Paternal duplication of 6q24
  - Hypomethylation of the maternal *PLAGL1* TSS alt-DMR
- Biallelic pathogenic (or likely pathogenic) variants in *ZFP57* identified on molecular genetic testing

  Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *ZFP57* variants of uncertain significance (or of one known *ZFP57* pathogenic variant and one *ZFP57* variant of uncertain significance) does not establish or rule out the diagnosis.

The maternal alleles of *PLAGL1* and *HYMAI* are silenced by methylation of the *PLAGL1* TSS alt-DMR, and only the paternal alleles of *PLAGL1* and *HYMAI* are expressed. In 6q24-TNDM, *PLAGL1* and *HYMAI* alleles are overexpressed through one of three genetic mechanisms (see Figure 1):

- **Hypomethylation of the *PLAGL1* TSS alt-DMR,** *either*:
  - As an isolated imprinting defect of the *PLAGL1* TSS alt-DMR; *or*
  - As part of a more generalized multilocus imprinting disturbance (MLID) caused by biallelic (homozygous or compound heterozygous) pathogenic variants in *ZFP57* or by as-yet-unknown mechanisms.
- **Partial or complete paternal uniparental disomy of chromosome 6 (UPD6)** that includes the *PLAGL1* and *HYMAI* loci
- **Paternal duplication of 6q24.** Usually a submicroscopic duplication results in the presence of two copies of *PLAGL1* and *HYMAI* on one paternal chromosome 6.

  Note: In individuals with 6q24 duplication of the paternal allele, the presence of two unmethylated alleles and one methylated allele of the *PLAGL1* TSS alt-DMR causes apparent partial hypomethylation of the *PLAGL1* TSS alt-DMR.

Table 1. Molecular Genetic Mechanisms for 6q24-Related Transient Neonatal Diabetes Mellitus

Locus	Genes of Interest	Imprint	Parental Origin of Imprint	Disease Mechanism
6q24	*PLAGL1*, *HYMA1*	Methylated [1]	Maternal	Hypomethylation, paternal UPD, or paternal duplication

1. In unaffected individuals, the maternally derived methylated copy is not expressed.

Molecular genetic testing approaches can include **DNA methylation studies**, **chromosomal microarray analysis (CMA)**, **uniparental disomy studies**, **targeted duplication analysis**, and **single-gene testing**.

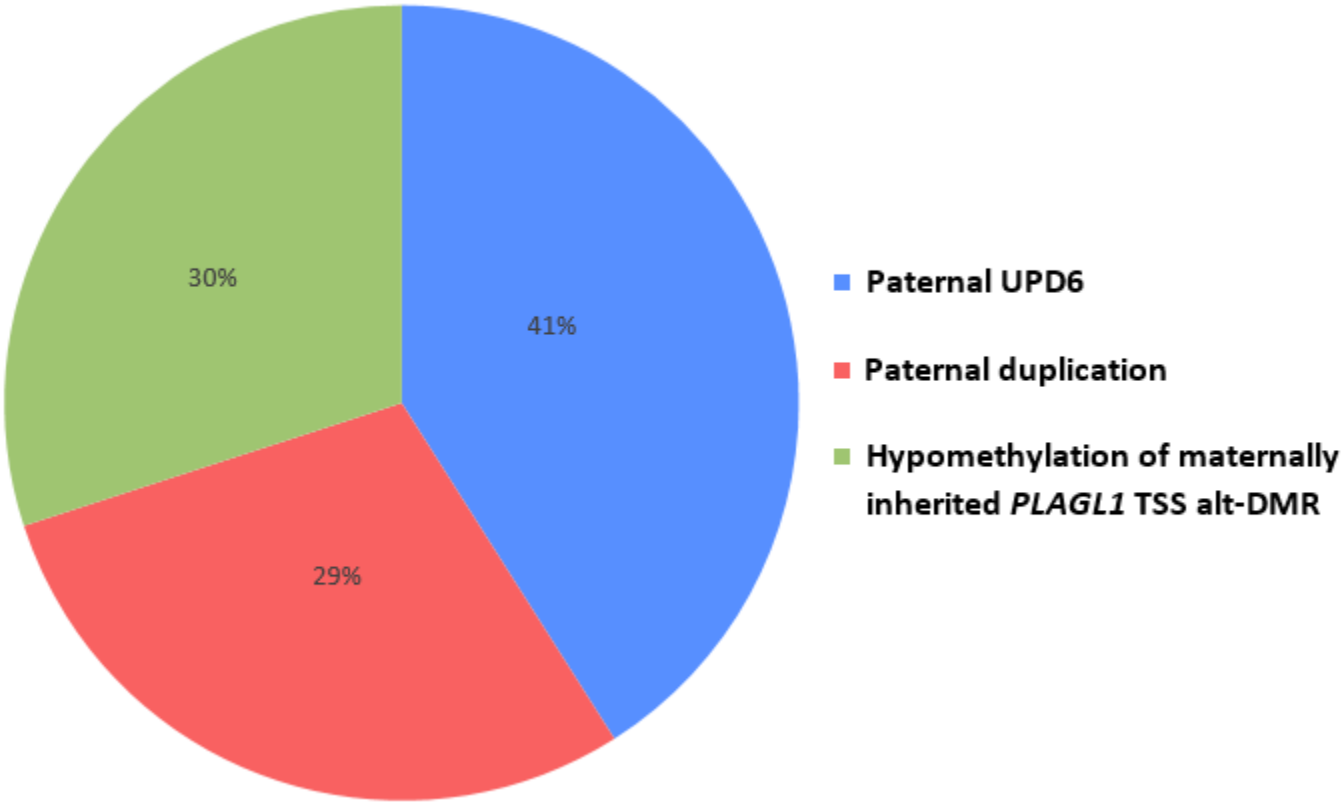

Figure 1. Three different genetic mechanisms cause 6q24-TNDM: paternal uniparental disomy of chromosome 6 (UPD6) (41%); duplication of 6q24 on the paternal allele (29%); and hypomethylation of the maternally inherited *PLAGL1* TSS alt-DMR (30%). Hypomethylation of the maternally inherited *PLAGL1* TSS alt-DMR may result from an isolated imprinting variant or as part of a more generalized defect termed multilocus imprinting disturbance (MLID). Biallelic *ZFP57* pathogenic variants account for almost half of TNDM-MLID; the other causes of MLID are not known.

Tier 1 Testing

DNA methylation studies can detect hypomethylation within the 6q24 DMR region regardless of the underlying genetic mechanism, thus establishing the diagnosis of 6q24-TNDM.

Note: DNA methylation analysis is the only technique that will diagnose 6q24-TNDM caused by any genetic mechanism, but it cannot establish the specific mechanism.

Tier 2 Testing

Tier 2 testing is necessary to differentiate the two different genetic mechanisms that cause expression of an extra copy of the paternal alleles of *PLAGL1* and *HYMAI* (see Table 1).

- **Chromosomal microarray analysis (CMA)** using oligonucleotide arrays or SNP genotyping arrays can detect a duplication of 6q24. Note that paternal disomy 6 commonly occurs by postzygotic somatic recombination resulting in isodisomy and can normally, therefore, be identified by proband-only SNP array analysis.
- **Uniparental disomy (UPD) studies** can detect partial or complete paternal UPD6.
- **Targeted duplication analysis of 6q24.** A variety of methods may be used for deletion/duplication analysis (copy number analysis) to identify an additional paternal copy of *PLAGL1* and *HYMAI* (see Table 2, footnote 4).

Tier 3 Testing

Tier 3 testing is necessary if tier 2 testing does not identify the genetic mechanism for 6q24 hypomethylation.

Single-gene testing. Sequence analysis of *ZFP57* is performed first and followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found.

Parallel or Additional Testing Options

A multigene panel that includes *ZFP57* and other genes of interest (see Differential Diagnosis) may also be considered. 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*; 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) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests (e.g., **methylation studies**).

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

Table 2. Molecular Genetic Testing Used in 6q24-Related Transient Neonatal Diabetes Mellitus (TNDM)

Method	Pathogenic Variants/Alterations Detected	Proportion of 6q24-TNDM Alterations Detected
Methylation analysis [1]	Hypomethylation within the 6q24 DMR region including imprinting center defects	100% [2]
Microarray (SNP based)	Duplication of 6q24, UPD6 [3]	~70%
UPD studies [4]	UPD6	~41%
Targeted duplication analysis [5]	Duplication of 6q24	~29% [6]

Table 2. continued from previous page.

Method		Pathogenic Variants/Alterations Detected	Proportion of 6q24-TNDM Alterations Detected
Single-gene testing	Sequence analysis [7]	*ZFP57* pathogenic variants [8]	9% [9]
	Gene-targeted deletion/ duplication analysis [5]	*ZFP57* intragenic deletion or duplication	None reported

DMR = differentially methylated region; UPD = uniparental disomy

1. Can establish diagnosis, but will not distinguish genetic mechanism; can be done by Southern blot, methylation-specific multiple ligation-mediated PCR analysis (MS-MLPA), or methylation-specific PCR.

2. Note: Only methylation analysis will detect an imprinting center defect, which is causative in ~30% of individuals.

3. Paternal disomy occurs by postzygotic somatic recombination resulting in isodisomy and can therefore be identified by proband-only SNP array analysis.

4. Use of genetic markers (usually short tandem repeats) to determine parental identity (maternal or paternal) of a chromosome or chromosomal segment in a proband. Note: This testing requires a DNA sample from the proband, mother, and father.

5. 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, methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

6. Reported duplications range in size from 200 kb to several megabases [Docherty et al 2010]. A small minority of individuals have a cytogenetically visible duplication of 6q24 [Temple et al 1996, Arthur et al 1997]. If conventional karyotype analysis identifies a visible chromosome translocation or duplication of 6q24, parental studies are required to determine if the abnormality is paternal in origin.

7. 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.

8. See Table A. Genes and Databases for chromosome locus and protein. See Molecular Genetics for information on allelic variants detected in this gene.

9. Docherty et al [2013]

Clinical Characteristics

Clinical Description

Intrauterine growth restriction may be noted in the third trimester. The mean birth weight in a study of 30 infants was 1,930 g at 39 weeks' gestation [Temple et al 2000]; this finding is in keeping with other studies [Metz et al 2002, Diatloff-Zito et al 2007]. Because the plasma concentration of insulin is low at the time of diagnosis, it is assumed that low birth weight is a result of low in utero levels of insulin, an important prenatal growth factor.

Diabetes mellitus tends to develop in the first week of life, although it may not be recognized until later. Hyperglycemia may be identified by chance during routine investigations in the newborn period for a sick dehydrated infant. Infants rapidly become dehydrated and usually require insulin. The diabetes may be resistant to treatment initially. Occasionally insulin is not required and neonates are treated with rehydration alone.

Diabetes mellitus lasts on average three months but has been reported to last longer than a year [Temple et al 2000]. The need for insulin gradually declines. This is often accompanied by a significant weight gain and catch-up growth, and some infants become overweight in the first year [Metz et al 2002].

Intermittent episodes of hyperglycemia may occur in childhood, particularly during intercurrent illnesses. Few studies have been performed during this period and so the extent of these episodes is not known. Shield et al [2004] studied seven children during this period and found low insulin secretion in four and normal insulin secretion in three.

Diabetes may recur in very early childhood. The average age of recurrence in the series of Temple et al [2000] was 14 years, coinciding with puberty. Some individuals require insulin; others are treated with oral drugs or diet

alone. In a series from France, five of seven individuals developed diabetes again after age eight years [Metz et al 2002].

Women are at risk for relapse during pregnancy and may present with gestational diabetes mellitus.

Permanent diabetes mellitus can occur in up to 50% in some series [Temple et al 2000], although this figure may overestimate the actual risk because of the bias of identifying affected individuals. There is usually some residual endogenous insulin production; however, insulin therapy may be needed.

Studies have not been performed to assess the level of diabetes-related complications that can occur in this disorder. One individual with poor compliance with treatment had persistent hyperglycemia from ages 14 to 28 years. He did not develop ketoacidosis but did develop evidence of microangiopathy [Valerio et al 2004].

Other. Macroglossia and umbilical hernia are sometimes observed. No other dysmorphic features are consistently associated with this condition. Screening for congenital hypothyroidism is prudent.

6q24-TNDM caused by generalized multilocus imprinting disturbance (MLID) can be associated with marked hypotonia, congenital heart disease, deafness, neurologic features including epilepsy, and renal malformations.

Intelligence and growth are usually normal in this condition except in individuals with loss of methylation at multiple loci, who may have developmental delay. However, the long-term outcomes for most individuals are still not known.

Genotype-Phenotype Correlations

Diabetes mellitus. No difference in the severity, duration, or relapse rate of diabetes has been detected between the 6q24-TNDM etiologic subgroups [Temple et al 2000].

Non-diabetes manifestations vary by causative genetic mechanism. Congenital anomalies were significantly more frequent in individuals with paternal uniparental disomy of chromosome 6 (UPD6) or MLID than in those with 6q24 duplication or isolated hypomethylation defects [Docherty et al 2013].

- **UPD6.** The majority of UPD6 is isodisomic; i.e., two copies of chromosome 6 are identical and therefore the affected individual is at increased risk for rare autosomal recessive disorders that may be unmasked by this unusual inheritance pattern. The most common is *HFE*-associated hereditary hemochromatosis, for which testing can be performed in adulthood. Methylmalonic acidemia and congenital adrenal hyperplasia caused by 21-hydroxylase deficiency have also been described as occurring through this mechanism.
- **6q duplication.** Cytogenetically visible duplication of 6q can also be associated with learning difficulties related to other genes within the duplicated region. Note: Individuals with a submicroscopic 6q24 duplication are usually of normal intelligence.
- **Hypomethylation of the maternal *PLAGL1* TSS alt-DMR.** An imprinted differentially methylated region overlaps an alternative transcriptional start-site of *PLAGL1*, and hypomethylation of this *PLAGL1* TSS-alt DMR is associated with TNDM. Non-diabetes manifestations are more likely in the subgroup with a more generalized hypomethylation at imprinted loci (i.e., MLID) and can include significant learning difficulties [Boonen et al 2008, Mackay et al 2008]. No correlation has been observed between clinical severity and either the degree of hypomethylation or the range of loci involved. For example, the features seen in individuals with 6q24-TNDM caused by homozygous or compound heterozygous *ZFP57* pathogenic variants can vary from severe intellectual disability and early infant death to a normal phenotype. It is therefore difficult to predict the phenotype in individuals with MLID, possibly because of the inability to interrogate all imprinted loci.

Penetrance

Reduced penetrance of the 6q24-TNDM has rarely been described, but has been noted in sibs of affected individuals. The sibs reported did not have a history of neonatal diabetes mellitus but were found to have either a paternal duplication of 6q24 or biallelic *ZFP57* pathogenic variants [Valerio et al 2004, Boonen et al 2013].

Prevalence

The incidence of neonatal diabetes is reported to be 1:215,000 to 1:400,000 [Polak & Shield 2004, Stanik et al 2007, Wiedemann et al 2010]; 50% of neonatal diabetes mellitus is transient rather than permanent (see Permanent Neonatal Diabetes Mellitus).

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with overexpression of *PLAGL1* (*ZAC*) and *HYMAI*.

Differential Diagnosis

Transient neonatal diabetes mellitus (TNDM) accounts for approximately 50% of diabetes mellitus presenting in the neonatal period [Cavé et al 2000, Metz et al 2002, Polak & Cavé 2007]. Flanagan et al [2007] showed that 70% of TNDM was caused by 6q24 aberrations. Other genetic causes of transient neonatal diabetes mellitus include pathogenic variants in *KCNJ11* and *ABCC8*, which usually cause permanent neonatal diabetes (see Permanent Neonatal Diabetes Mellitus).

Metz et al [2002] failed to demonstrate clear clinical indicators to differentiate 6q24-TNDM from other causes in a large cohort of 50 individuals presenting with neonatal diabetes.

Other genetic causes of neonatal diabetes mellitus (isolated and syndromic, transient and permanent):

- ***KCNJ11*- and *ABCC8*-related neonatal diabetes mellitus** (see Permanent Neonatal Diabetes Mellitus). Affected infants present with low birth weight and hyperglycemia. Compared to 6q24-TNDM, infants with *KCNJ11*- and *ABCC8*-related neonatal diabetes mellitus usually present slightly later, birth weight is higher, remission usually takes longer, and ketoacidosis is often present at diagnosis. Some of the children have epilepsy, hypotonia, and developmental delay in addition to diabetes mellitus (DEND syndrome). *KCNJ11*-related neonatal diabetes mellitus is inherited in an autosomal dominant manner, while *ABCC8*-related neonatal diabetes may be inherited in either an autosomal dominant or autosomal recessive manner.
- ***INS*-related neonatal diabetes mellitus** (see Permanent Neonatal Diabetes Mellitus). Although the median age of diagnosis is 11 weeks, the range of the age of onset overlaps with neonatal diabetes; therefore, pathogenic variants in *INS* should be considered in the differential diagnosis of 6q24-TNDM. Presentation includes ketoacidosis in half of infants. Clinical findings can vary among family members. In at least one family in the series neonatal diabetes was transient, becoming permanent diabetes at age two years. *INS*-related neonatal diabetes mellitus may be inherited in either an autosomal dominant or autosomal recessive manner.
- **Glucokinase-related neonatal diabetes mellitus.** Homozygous missense loss-of-function variants within *GCK*, the gene encoding glucokinase, have been reported as a rare cause of permanent neonatal diabetes mellitus. This condition should be considered, particularly in consanguineous families. Glucokinase-related neonatal diabetes mellitus is inherited in an autosomal recessive manner.
- ***PDX1*-related neonatal diabetes mellitus** is associated with pancreatic hypoplasia and results in a more severe insulin deficiency, lower birth weight, and younger age at diagnosis than is seen in infants with

other causes of permanent neonatal diabetes mellitus. Imaging of the pancreas may help identify infants with *PDX1*-related neonatal diabetes mellitus. *PDX1*-related neonatal diabetes mellitus is inherited in an autosomal recessive manner.

- **Renal cysts and diabetes syndrome** (OMIM 137920). The diabetes phenotype in individuals heterozygous for an *HNF1B* pathogenic variant manifests more frequently later in life. 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.
- **Wolcott-Rallison syndrome** (OMIM 226980), caused by biallelic pathogenic variants in *EIF2AK3*, is characterized by infantile-onset (often within the neonatal period) diabetes mellitus and spondyloepiphyseal dysplasia, which may develop after the neonatal period. Wolcott-Rallison syndrome is inherited in an autosomal recessive manner.
- **IPEX syndrome (*i*mmune dysregulation, *p*olyendocrinopathy, *e*nteropathy, *X*-linked)** can be caused by pathogenic variants in *FOXP3* and 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, most often insulin-dependent diabetes mellitus. Most infants have other autoimmune phenomena including Coombs-positive anemia, autoimmune thrombocytopenia, autoimmune neutropenia, and tubular nephropathy. Without aggressive immunosuppression or bone marrow transplantation, the majority of affected males die within the first year of life of either metabolic derangements or sepsis; a few with a milder phenotype have survived into the second and third decade. IPEX syndrome is inherited in an X-linked manner.
- **Neonatal diabetes mellitus and cerebellar agenesis** (OMIM 609069) is caused by biallelic pathogenic variants in *PTF1A*. The disorder is characterized by the combination of cerebellar agenesis and neonatal diabetes mellitus. Infants usually die within a few months of birth. Neonatal diabetes mellitus and cerebellar agenesis is inherited in an autosomal recessive manner.
- **Neonatal diabetes mellitus, annular pancreas, intestinal atresias, and gallbladder agenesis** (OMIM 615710) is caused by biallelic pathogenic variants in *RFX6.* A small number of affected individuals have been reported with various combinations of pancreatic hypoplasia, agenesis, and neonatal diabetes without clear evidence of abnormal pancreatic anatomy in association with gut atresias and gallbladder hypoplasia/atresia. The majority have died in the first year of life; however, some individuals are still living with normal development, although the follow up has not been long. This condition is inherited in an autosomal recessive manner.
- **Neonatal diabetes mellitus and congenital hypothyroidism caused by pathogenic variants in *GLIS3*** (OMIM 610199). This rare condition is characterized by the combination of neonatal diabetes mellitus, congenital hypothyroidism, glaucoma, polycystic kidneys, cholestasis, and hepatic fibrosis. However, the findings can be variable and not all the features are reported in all cases. Some individuals have survived infancy; mild intellectual disability has been reported. This condition is inherited in an autosomal recessive manner.
- **Neonatal diabetes mellitus and congenital heart disease caused by pathogenic variants in *GATA6*** (OMIM 600001). The combination of congenital heart disease (ventricular septal defect) and pancreatic hypoplasia was first reported by Gürson et al [1970]. Yorifuji et al [1994] reported a second Japanese family in which individuals in two generations had pancreatic hypoplasia, neonatal diabetes mellitus, and congenital heart disease. This condition is inherited in an autosomal dominant manner.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with 6q24-related transient neonatal diabetes mellitus (6q24-TNDM), the following evaluations are recommended if they have not already been completed:

- Birth weight, length, and head circumference and any subsequent growth parameters
- General dysmorphology examination, preferably by a clinical geneticist, including evaluation of tongue size and umbilicus
- Neurologic examination and developmental assessment
- Investigation of the anatomy of the pancreas by ultrasound examination or MRI
- Echocardiogram and ultrasound examination of the liver and kidneys to help identify those infants likely to have 6q24-TNDM caused by *ZFP57* pathogenic variants
- Brain MRI examination if evidence of developmental delay or hypotonia
- Serum glucose concentration
- C peptide measurement
- Pancreatic beta cell autoantibody measurements
- Liver function and thyroid function tests
- Consultation with a pediatric endocrinologist for follow up of diabetes
- Consultation with a clinical geneticist and/or genetic counselor

Individuals with multilocus imprinting disturbance (MLID) should be evaluated for hypotonia and other neurologic features including epilepsy, congenital heart disease, deafness, renal malformations, and pseudohypoparathyroidism with measurement of serum concentrations of calcium and phosphate and parathyroid hormone testing.

Treatment of Manifestations

Rehydration and IV insulin on a sliding scale are usually required. Some infants produce some insulin and can be treated by rehydration alone.

Subcutaneous injection of insulin is introduced as soon as possible, often within two weeks. Continuous insulin pump therapy (as opposed to intermittent insulin injections) has been used successfully in a number of cases in the UK and France [JP Shield, personal communication]. Successful treatment with subcutaneous insulin glargine has also been reported [Barone et al 2011].

Blood glucose concentration should be monitored and insulin doses changed accordingly as in the standard treatment for diabetes mellitus. Insulin can be discontinued when blood glucose concentrations stabilize.

Once diabetes mellitus is in remission, parents need to be alerted to the possibility of recurrence of the diabetes mellitus, particularly during periods of illness. Symptoms such as excessive thirst, polyuria, and repeated bacterial infections should prompt measurement of blood glucose concentration.

If diabetes mellitus recurs, treatment may require diet alone, oral agents, or insulin, although the doses of insulin needed tend to be less than those required in type 1 diabetes mellitus (i.e., some residual endogenous insulin remains). It should be noted that insulin is not always required even in the neonatal period. In several individuals, sulphonylureas or diet alone was adequate to treat relapses [Valerio et al 2004].

Note: Macroglossia could potentially cause airway obstruction; macroglossia severe enough to require treatment has not been reported.

Prevention of Secondary Complications

The main concerns are related to failure to make the diagnosis soon enough. Dehydration secondary to hyperglycemia can cause serious long-term sequelae if not treated promptly. Therefore, rehydration is most important in the early stages of the disease.

Surveillance

Periodic glucose tolerance tests can be used to assess insulin secretion. Most children with transient neonatal diabetes mellitus in remission have no evidence of beta cell dysfunction or insulin resistance in the fasting state. Insulin response to intravenous glucose loading is often normal but suggests future recurrence if abnormal [Shield et al 2004].

Measure growth (height, weight, head circumference) at regular intervals (i.e., at least every 6 months).

Developmental assessment to identify any special educational needs is appropriate.

Children with MLID need to be monitored for developmental delay and special educational needs.

Agents/Circumstances to Avoid

General factors that predispose to late-onset diabetes (e.g., excessive weight gain) or risk factors for cardiovascular disorders should be avoided.

Evaluation of Relatives at Risk

It is appropriate to test apparently asymptomatic at-risk relatives for the 6q24-TNDM genetic mechanism identified in the proband in order to identify family members who would benefit from follow up. (Hyperglycemia may be asymptomatic.)

Recommendations for follow up vary by underlying genetic mechanism:

- **6q24 duplication.** Individuals with a 6q24 duplication may not present with diabetes as neonates. However, such individuals are at risk of developing diabetes later in life. Knowing this risk may facilitate prompt evaluation and treatment if they develop symptoms of diabetes. These individuals can also be counseled regarding risks to their offspring. Screening for diabetes mellitus is appropriate for those infants who have inherited the paternal 6q24 duplication.
- **Biallelic *ZFP57* pathogenic variants.** Sibs who inherit biallelic variants are at risk for the same condition (although the clinical findings can be variable) and should undergo screening for diabetes mellitus.
- **Hypomethylation at *PLAGL1* TSS alt-DMR.** Although individuals with 6q24-TNDM as the result of hypomethylation at *PLAGL1* TSS alt-DMR generally represent simplex cases (i.e., a single occurrence in a family), it is not clear if all cases are *de novo*, and there have been relatively few families reported in the literature to determine recurrence risk (see also Genetic Counseling).Screening the mother and sibs of these individuals for hypomethylation may therefore be appropriate.

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

Pregnancy Management

There are no specific guidelines on pregnancy management for women with a history of 6q24-TNDM. However, it is important to inform health professionals during the pregnancy of a susceptibility to diabetes. Rarely, some affected women with classic 6q24-TNDM genetic aberrations (e.g., duplication of 6q24, paternal uniparental disomy of chromosome 6, methylation defects) will develop gestational diabetes; therefore, pregnancy is thought to be a risk factor for recurrence of diabetes.

If prenatal diagnosis identifies an affected fetus, fetal growth is anticipated to lag during the third trimester.

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for 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

6q24-related transient neonatal diabetes mellitus (6q24-TNDM) results from overexpression of imprinted genes at 6q24 (*PLAGL1* and *HYMAI*). Three different genetic mechanisms cause 6q24-TNDM:

- Paternal uniparental disomy of chromosome 6 (41%)

  Both complete and partial paternal uniparental disomy of chromosome 6 are typically *de novo* events.

- Duplication of 6q24 on the paternal allele (29%)

  Paternal duplication of 6q24 can occur *de novo* or be inherited. Occasionally, the duplication arises as part of a complex chromosomal rearrangement in a parent.

- Hypomethylation of the maternal *PLAGL1* TSS alt-DMR, resulting in loss of the imprinted marking that typically silences the maternal region (30%)

  Maternal *PLAGL1* TSS alt-DMR hypomethylation can result from an imprinting defect of the promoter *PLAGL1* TSS alt-DMR (isolated) or as part of a generalized multilocus imprinting disturbance (MLID); biallelic (homozygous or compound heterozygous) *ZFP57* pathogenic variants account for almost half of TNDM-MLID.

Paternal Uniparental Disomy of Chromosome 6 – Risk to Family Members

Parents, sibs, and offspring of a proband

- Karyotype testing of a proband with paternal uniparental disomy of chromosome 6 (UPD6) is recommended for more accurate determination of recurrence risk.
- The risk to parents, sibs, and offspring of a proband with 6q24-TNDM caused by paternal UPD6 and a normal karyotype is unlikely to be higher than the risk to the general population, as paternal UPD6 is a *de novo*, typically non-recurrent event.
- If the proband has a chromosome abnormality in addition to paternal UPD6, the risk to parents, sibs, and offspring is related to the specific abnormality identified in the proband.

Paternal Inherited/Derived Duplication of 6q24 (usually submicroscopic tandem duplication) – Risk to Family Members

Parents of a proband

- The father of a proband may have the (submicroscopic or visible) 6q24 duplication identified in the proband and may be at risk of developing diabetes mellitus later in life (or having had a history of early diabetes mellitus) **if** the 6q24 duplication was inherited from his father.
- Alternatively, the 6q24 duplication may be a *de novo* occurrence in the proband.
- Recommendations for the evaluation of the father of a proband with 6q24-TNDM include routine cytogenetic analysis and molecular genetic testing to identify a 6q24 duplication if present, and to exclude a balanced/unbalanced translocation involving the 6q24 critical region.

Sibs of a proband. The risk to the sibs of a proband depends on the genetic status of the father:

- If the father **does not** have a duplication of 6q24, the risk to the sibs depends on the possibility of germline mosaicism in the father (estimated risk: ~1%).
- If the father has the 6q24 duplication, the risk to each sib of inheriting the duplication is 50%. Because of reduced penetrance, sibs who inherit the paternal 6q24 duplication may not develop TNDM, but they are at increased risk of developing diabetes mellitus later in life.
- If the father has a complex chromosomal rearrangement involving 6q24, the risk to sibs is related to the specific rearrangement.

Offspring of a male proband. Each child of a male with 6q24-TNDM caused by duplication of 6q24 has a 50% chance of inheriting the duplication and is at high risk of developing 6q24-TNDM and/or diabetes mellitus later in life.

Offspring of a female proband. Each child of a female with 6q24-TNDM caused by duplication of 6q24 has a 50% chance of inheriting the duplication but is not at increased risk of developing 6q24-TNDM or diabetes mellitus later in life.

Other family members. The risk to more distant family members depends on the status of the proband's parents. Family members may be at risk if the proband has an inherited duplication of 6q24.

Hypomethylation of the Maternal *PLAGL1* TSS alt-DMR – Risk to Family Members

Risks depend on the underlying cause of the hypomethylation.

Proband with Isolated Hypomethylation at *PLAGL1* TSS alt-DMR

Parents of a proband. Parents of a proband with 6q24-TNDM caused by isolated maternal hypomethylation have not been reported as having a similar finding, as having neonatal diabetes mellitus, or as developing it later in life.

Sibs of a proband

- Sibs of a proband with 6q24-TNDM caused by isolated DMR hypomethylation are not reported to be at increased risk of having 6q24-TNDM or of developing diabetes mellitus.
- Because the cause of isolated DMR hypomethylation is not understood and it is possible that it is not *de novo* in all families, testing of sibs of a proband for hypomethylation of the *PLAGL1* TSS alt-DMR is appropriate.

Offspring of a proband. The risk to the offspring of individuals with 6q24-TNDM caused by isolated maternal hypomethylation of developing 6q24-TNDM or diabetes mellitus later in life is unknown.

Proband with Multilocus Imprinting Disturbance (MLID) as a Result of Biallelic Pathogenic Variants in *ZFP57*

Parents of a proband

- The parents of an affected child are likely obligate heterozygotes (i.e., carriers of one *ZFP57* pathogenic variant). In highly consanguineous families a parent may also be homozygous rather than heterozygous. This finding has been reported in at least one family [Mackay et al 2008].
- Parents heterozygous for *ZFP57* pathogenic variants are not known to be at risk of developing diabetes mellitus. No phenotype has yet been reported in heterozygotes.

Sibs of a proband

- At conception, assuming both parents of the proband are heterozygous for a *ZFP57* pathogenic variant, each sib of an affected individual has a 25% chance of inheriting two *ZFP57* pathogenic variants and being at risk of developing 6q24-TNDM (although clinical findings in sibs can be variable), a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.

  If one parent has biallelic *ZFP57* pathogenic variants and the other parent is heterozygous for a *ZFP57* pathogenic variant, each sib of an affected individual has a 50% chance of inheriting two *ZFP57* pathogenic variants and being at risk of developing 6q24-TNDM and a 50% chance of being an asymptomatic carrier.
- In sibs who have inherited two *ZFP57* pathogenic variants, the risk of developing 6q24-TNDM is not known but may be high. The non-diabetes manifestations are variable. Affected sibs, of whom one was severely developmentally delayed and the other only mildly delayed, have been reported [Boonen et al 2008]. At least one person homozygous for *ZFP57* pathogenic variants had a normal phenotype [Mackay et al 2008, Boonen et al 2013].

Offspring of a proband. The offspring of an individual with biallelic pathogenic variants in *ZFP57* are obligate heterozygotes (carriers) for a *ZFP57* pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *ZFP57* pathogenic variant.

Carrier detection. Carrier testing for at-risk relatives requires prior identification of the *ZFP57* pathogenic variants in the family.

Proband with Multilocus Imprinting Disturbance (MLID) with No Pathogenic Variants Identified in *ZFP57*

The risk to sibs, offspring, and parents is unknown as recurrence has not been reported in this subgroup.

Note: There is an increased incidence of assisted reproductive technology (ART) used by the parents of these probands; whether a causal relationship exists between ART and hypomethylation is not clear [Mackay et al 2008].

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, 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, are carriers, or are at risk of being carriers.

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

Consideration of prenatal testing for 6q24-TNDM depends on the genetic mechanism in the family: paternal UPD6 is typically a *de novo*, non-recurrent event; 6q24 duplication may recur when the duplication is inherited from the father; and hypomethylation at imprinted loci caused by biallelic *ZFP57* pathogenic variants is inherited in an autosomal recessive manner. Counseling by a genetics professional is strongly recommended.

Prenatal testing and preimplantation genetic testing for pregnancies at risk for:

- Paternal duplication of 6q24 requires prior identification of the structural chromosome abnormality in the family.
- Hypomethylation of the maternal *PLAGL1* TSS alt-DMR as a result of biallelic *ZFP57* pathogenic variants requires prior identification of the *ZFP57* pathogenic variants in the family. However, the phenotype associated with biallelic *ZFP57* pathogenic variants is variable and cannot be accurately predicted by the results of prenatal molecular genetic testing.

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.

- **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

- **Transient Neonatal Diabetes Registry**
  Wessex Clinical Genetics Service - Princess Anne Hospital
  Level G, Mailpoint 105

Coxford Road
Southampton Hampshire SO16 5YA
United Kingdom
Phone: +44 2380 796166
Transient Neonatal Diabetes Registry

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. Diabetes Mellitus, 6q24-Related Transient Neonatal: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
HYMAI	6q24.2	Not applicable		HYMAI	HYMAI
PLAGL1	6q24.2	Zinc finger protein PLAGL1	PLAGL1 database	PLAGL1	PLAGL1
ZFP57	6p22.1	Zinc finger protein 57 homolog	ZFP57 database	ZFP57	ZFP57

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 Diabetes Mellitus, 6q24-Related Transient Neonatal (View All in OMIM)

601410	DIABETES MELLITUS, TRANSIENT NEONATAL, 1; TNDM1
603044	PLAG1-LIKE ZINC FINGER 1; PLAGL1
606546	HYDATIDIFORM MOLE-ASSOCIATED AND IMPRINTED TRANSCRIPT; HYMAI
612192	ZFP57 ZINC FINGER PROTEIN; ZFP57

Molecular Pathogenesis

The molecular pathogenesis of 6q24-TNDM is not yet understood. The minimal disease-associated region has been refined [Docherty et al 2010] excluding all but *PLAGL1* and *HYMAI* as candidate genes for 6q24-TNDM. Maternal alleles are methylated within the differentially methylated region (DMR; imprinting center) of *PLAGL1* (*ZAC*) and *HYMAI*, thereby silencing their expression. Paternal alleles are not methylated and are expressed. Disease occurs through either loss of the methylation imprint that silences the maternal allele or a rearrangement that results in duplication and overexpression of the paternal allele. See Establishing the Diagnosis for genetic mechanisms.

All 6q24-TNDM mechanisms described result in overexpression of *PLAGL1*. In most human fetal tissues, *PLAGL1* is paternally expressed due to lack of paternal methylation within the DMR [Varrault et al 2001]. No enhancers or insulators of the region have been identified. In adult tissues, paternal expression is restricted to a minority of tissues such as skin fibroblasts. Biallelic expression results from an alternative non-imprinted promoter, 55 kb upstream of the imprinted promoter [Valleley et al 2007]. Many *PLAGL1* transcript variants differing in the 5' UTR and encoding two different isoforms are known for this gene.

The mechanism whereby *PLAGL1* overexpression causes transient early diabetes mellitus is not fully understood. *PLAGL1* codes for a zinc finger protein and overexpression causes cell cycle arrest and apoptosis in cell lines; *PLAGL1* regulates the pituitary adenylate cyclase-activating polypeptide receptor (PACAP1), which

stimulates insulin secretion. Downstream targets of *PLAGL1* are not fully characterized, although Arima et al [2005] showed that *PLAGL1* binds to the CpG island in *KCNQ1OT1*, which negatively regulates *CDKN1C*. Varrault et al [2006] showed that *PLAGL1* is an important member of a cellular network of imprinted genes involved in fetal growth.

A mouse model for TNDM [Ma et al 2004] demonstrated impaired glucose homeostasis in mice with overexpression of *plagl1* and showed a downregulation of pdx-1, a key transcription factor vital for normal pancreatic development. Although beta cell mass was reduced in fetal mice, it had recovered by the time of birth; nonetheless, insulin response to hyperglycemia was decreased. It is hypothesized that the beta cell mass is not sufficient to respond during times of excessive physiologic stress, resulting in "breakthrough" diabetes with intercurrent illnesses and sometimes with increasing age.

In keeping with this hypothesis, Valerio et al [2004] have demonstrated in 6q24-TNDM a specific defect of insulin secretion after glucose stimulation. Furthermore, insulin secretion is possible through the stimulatory G protein pathway.

At the molecular level, the picture is complicated by paternally expressed *HYMAI*, which overlaps *PLAGL1* and the 6q24-TNDM DMR. *HYMAI* lacks an open reading frame and is not translated. It may regulate *PLAGL1* expression; its relationship to *PLAGL1* and 6q24-TNDM is not yet known.

In fibroblasts from an individual with transient neonatal diabetes mellitus, the monoallelic expression of both *PLAGL1* and *HYMAI* was relaxed, providing strong supportive evidence that the presence of two unmethylated alleles of this locus is indeed associated with the inappropriate expression of neighboring genes [Mackay et al 2002]. The *PLAGL1* promoter is localized to the CpG island harboring the methylation imprint associated with 6q24-TNDM, and methylation of this promoter silences its activity [Varrault et al 2001].

ZFP57

Gene structure. The transcript NM_001109809.2 has four coding exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. *ZFP57* missense, nonsense, and frameshift pathogenic variants have been identified [Mackay et al 2008].

Normal gene product. The protein product (ZFP57; NP_001103279.2) of *ZFP57* has 53 amino acid residues. It is a Kruppel-associated box (KRAB)-containing protein with seven zinc fingers that functions as a transcriptional regulator.

Abnormal gene product. Biallelic pathogenic *ZFP57* variants result in inactivation of ZFP57, a protein important in maintaining genomic imprinting at the DMR of *PLAGL1* and *HYMAI*.

Chapter Notes

Acknowledgments

IKT and DJGM are supported by Diabetes UK and MRC for work on 6q24 transient neonatal diabetes.

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Revision History

- 13 September 2018 (sw) Comprehensive update posted live
- 15 January 2015 (me) Comprehensive update posted live
- 27 September 2012 (me) Comprehensive update posted live
- 23 December 2010 (cd) Revision: sequence analysis of *ZFP57* available clinically on a limited basis
- 4 February 2010 (me) Comprehensive update posted live
- 10 October 2005 (me) Review posted live
- 10 February 2005 (ikt) Original submission

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