

Review

The Molecular Basis of Neonatal Diabetes Mellitus and Transient Hyperglycemia in the Neonate

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Abstract

Neonatal diabetes mellitus (NDM) is a rare monogenic disorder characterized by persistent hyperglycemia requiring insulin therapy, typically diagnosed within the first six months of life, and may be transient or permanent. However, hyperglycemia in the neonatal population may be observed outside the NDM range. This narrative review aims to provide an overview of the genetic and molecular mechanisms underlying NDM, including both transient and permanent forms on the one hand and the developmental and regulatory pathways contributing to transient hyperglycemic states in neonates on the other. A comprehensive literature search of PubMed, Scopus, and Google Scholar was conducted, focusing on genetic and molecular mechanisms associated with NDM and transient neonatal hyperglycemia. Mutations in more than 40 genes or chromosomal loci have been implicated in the pathogenesis of NDM, affecting the development and function of pancreatic beta-cells, as well as insulin synthesis and secretion. Abnormalities of the 6q24 locus have been recognized as the most common cause of transient NDM, whereas mutations in genes encoding ATP-sensitive potassium (K_{ATP}) channels, particularly *KCNJ11*, are more commonly identified in permanent NDM cases. Transient hyperglycemia may occur in preterm and/or critically ill neonates due to immaturity and transient beta-cell dysregulation, insulin resistance, epigenetic modifications, or drug administration. In NDM cases, the clinical course, the presence of extra-pancreatic manifestations, and the optimal treatment depend on the causative gene. Therefore, genetic diagnosis is imperative, as it can facilitate individualized management strategies, long-term follow-up, and genetic counselling.

Keywords: neonatal hyperglycemia; neonatal diabetes mellitus; transient neonatal diabetes mellitus; permanent neonatal diabetes mellitus; genetic etiology; molecular mechanisms



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1. Introduction

Hyperglycemia is one of the most common metabolic disturbances in the neonatal intensive care unit (NICU) and is generally transient, reflecting a disturbance in the balance between glucose delivery and insulin activity, rather than a disorder of glucose metabolism [1]. Preterm and low-birth-weight neonates are more commonly affected, with a prevalence that is inversely related to gestational age and birth weight [2,3]. Furthermore, neonates who are critically ill, those with hypoxic–ischemic injury or sepsis, or those

receiving medications such as steroids and inotropes are at increased risk of developing hyperglycemia [2].

Neonatal diabetes mellitus (NDM) is a genetic disease presenting during infancy, characterised by severe hyperglycemia requiring treatment [4,5]. It is a rare disease, with a reported prevalence of 1:90,000 to 1:160,000 live births, although significant variation is observed across geographic regions [6]. In countries with a high rate of consanguinity, a prevalence of 1:21,000 has been reported [7,8].

NDM typically presents during the first six months of life, although it may also appear between six and 12 months of age [4,5]. However, occurrence beyond the sixth month is more commonly associated with autoimmune diabetes rather than monogenic forms [9]. Intrauterine growth restriction and low birth weight are frequently observed among neonates with NDM, as insulin, an anabolic hormone, is imperative for normal embryonic growth [10]. The clinical presentation may be insidious, with failure to thrive and classic diabetes symptoms, including polyuria and polydipsia, which are often difficult to recognize in young infants [5,11,12]. In this age group, diabetes may initially present as a sepsis-like illness or acutely as diabetic ketoacidosis [12–14]. The diagnosis of NDM should be considered in cases of severe hyperglycemia that persists beyond a week or in cases of extremely high glucose levels (>1000 mg/dL, >55.5 mmol/L). The diagnosis is further supported by the presence of low or undetectable insulin and C-peptide levels during hyperglycemia [10,12].

Based on the duration of the required treatment, NDM can be distinguished as either transient or permanent and may be isolated or part of a syndrome accompanied by extra-pancreatic manifestations [13]. In permanent NDM (PNDM), lifelong therapy is necessary [5]. In cases of transient NDM (TNDM), remission occurs at various points during the initial postnatal period [6,13]. However, relapse during adolescence or adulthood is common [15]. The diagnosis of TNDM can be challenging due to its similarity to other causes of transient neonatal hyperglycemia, and the high rate of relapse in TNDM cases necessitates a definitive diagnosis in order to establish a follow-up plan.

NDM is a monogenic disease caused by pathogenic variants in genes or chromosomal loci implicated in the development and function of pancreatic beta-cells and in insulin synthesis and secretion. The diagnosis is confirmed through genetic testing [4,11,16,17]. Advances in genetic testing have substantially improved our understanding of the molecular basis of NDM, and pathogenic variants in more than 40 genes have been implicated in its development [17,18]. Gene mutations may occur sporadically or may be inherited in an autosomal or recessive manner [5].

In both TNDM and PNDM, a definitive diagnosis is imperative for predicting clinical progression, detecting extra-pancreatic manifestations, implementing individualized management strategies and long-term follow-up, and providing genetic counselling [13,16]. The current guidelines of the International Society for Pediatric and Adolescent Diabetes (ISPAD) recommend immediate genetic testing for all infants diagnosed with diabetes before the sixth month of age and for those diagnosed between the sixth and the 12th month with negative autoantibodies, extra-pancreatic manifestations, and/or a family history [16].

The aim of this narrative review is to provide a comprehensive overview of the genetic and molecular mechanisms underlying NDM, including both transient and permanent forms, and the developmental and regulatory pathways contributing to transient hyperglycemic states in neonates.

2. Methods

A comprehensive search was conducted to identify relevant articles using the online databases PubMed, Scopus, and Google Scholar from database inception up to November 2025. The search strategy included combinations of the following keywords: “neonatal hyperglycemia”, “neonatal diabetes mellitus”, “transient neonatal diabetes mellitus”, “permanent neonatal diabetes mellitus”, “genetic etiology”, “molecular mechanisms”. Eligible studies included systematic and narrative reviews, original research articles (prospective and retrospective cohort studies), case series, and case reports. Only full-text, peer-reviewed studies published in English and addressing the genetic causes of NDM and molecular mechanisms of transient hyperglycemic states in the neonatal period were included. Studies focusing on forms of diabetes other than neonatal diabetes mellitus were excluded. The reference lists of the retrieved articles were manually screened for relevant articles that may have been missed in the initial research. Article screening and data extraction were performed independently by two authors. The process involved screening the titles and abstracts of articles, followed by a full-text evaluation. Any discrepancies were resolved by consensus through discussion with all co-authors. Given the narrative nature of the review, a formal tool for risk-of-bias assessment was not used, which represents a limitation of the study. However, the potential biases and methodological limitations of the included studies were evaluated.

3. Genetic Causes of NDM

NDM, a rare monogenic disorder, is the clinical manifestation of diverse molecular mechanisms arising from genetically heterogeneous causes. To date, more than 40 genes and genomic loci have been implicated in the pathogenesis of NDM through various molecular pathways. These genetic defects are associated with specific inheritance patterns, variable clinical phenotypes, and extra-pancreatic features.

Although NDM is clinically classified as transient or permanent, based on disease course, research has demonstrated that individual genes may cause either presentation (Figure 1). For the purpose of this narrative review, the genetic causes of NDM have been classified into four categories based on underlying pathogenic mechanisms.

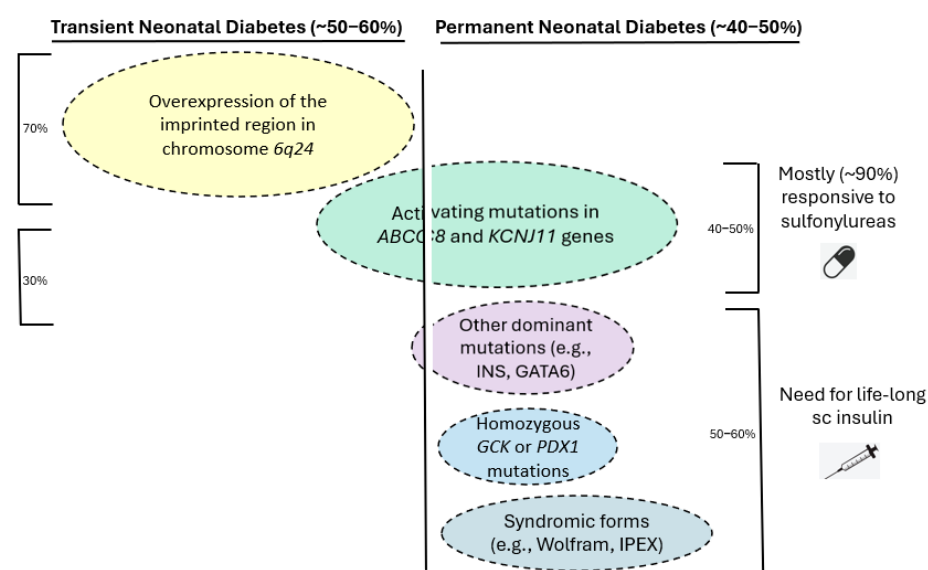


Figure 1. Schematic representation of the association between specific genetic causes and transient or permanent neonatal diabetes mellitus (NDM), as well as treatment implications for selected genetic forms of permanent NDM (e.g., K_{ATP} -related NDM). The oval sizes reflect approximate frequencies among genetically confirmed NDM cases.

3.1. Imprinting Defects of the 6q24 Locus

It is documented that approximately 70% of TNDM cases are attributable to genetic or epigenetic alterations in an imprinted region of chromosome 6q24 [19]. The 6q24 locus consists of a CpG island whose methylation status depends on parental origin. Normally, it is unmethylated on the paternal and methylated on the maternal allele, leading to expression of the paternal allele, whereas the maternal allele is inactive [4,12]. It has been demonstrated that three distinct mechanisms are implicated in the NDM due to 6q24 alterations: paternal uniparental disomy, unbalanced paternal duplication of 6q24, and hypomethylation of the maternal allele [11].

In paternal uniparental disomy, which accounts for approximately 40% of cases, both alleles are inherited from the father [11,20]. While in most cases it occurs as uniparental isodisomy, it may also be partial [16,19]. Its occurrence is regarded as sporadic, arising from stochastic events during the earliest stages of embryonic development [19,21]. Approximately 30–40% of TNDM cases involving 6q24 alterations are attributable to an unbalanced partial duplication of the long arm of the paternal chromosome 6, resulting in three copies of 6q24, two of which are inherited from the father [5,11,21,22]. Although duplications may occur *de novo*, they account for the majority of familial cases [16]. Duplications are inherited in an autosomal dominant manner [11]. Affected males have a 50% chance of transmitting the duplication and the disease to their offspring. Affected females have a 50% probability of transmitting the duplication, but their offspring will not be affected by the disease. However, in cases of male offspring who carry the duplication, the next generation may develop diabetes [16,19]. The remaining 20–30% of 6q24-related TNDM is caused by hypomethylation of the maternal allele, and subsequent activation [5,21]. Hypomethylation may result from epigenetic events without an underlying genetic cause or may be part of a generalized hypomethylation involving multiple imprinted loci, such as the recessively inherited mutations of the *ZFP57* [16,23]. The *ZFP57* gene, located on chromosome 6p22.3, is a transcription factor essential for maintaining methylation of imprinted loci during development [24].

Irrespective of the underlying genetic or epigenetic pathway, the result is the overexpression of the imprinted genes polyadenoma gene-like 1 (*PLAGL1*) and the hydatidiform mole-associated imprinted transcript (*HYMAI*) [4]. The *PLAGL1* gene encodes a zinc-finger transcription factor that regulates the cell cycle and apoptosis through various molecular mechanisms [25]. It has been demonstrated that the overexpression of *PLAGL1* in pancreatic beta-cells results in increased p21 expression and an interaction with the tumor suppressor p53, leading to reduced cell proliferation and enhanced apoptosis [26,27]. Studies in experimental animals have shown that overexpression of *PLAGL1* and *HYMAI* impair insulin excretion and endocrine pancreatic development, leading to a disease resembling TNDM in humans [28,29]. The *HYMAI* gene encodes a non-coding RNA whose function remains incompletely characterized [13,24,28].

Alterations in the 6q24 locus are exclusively associated with TNDM (Table 1) [30]. A common feature is the early presentation of hyperglycemia, with a median chronological age of onset of less than a week in most cohorts [23,30–33]. Initial presentation with DKA is rarely reported [34]. The age at which remission most commonly occurs is between three and four months [31–33]. Busiah et al. reported that 97% of patients with 6q24 alterations entered remission before the age of one year [30]. However, in a large proportion of patients, diabetes relapses occur most commonly during adolescence [4,31,32].

Table 1. Clinical and genetic characteristics of patients with 6q24 neonatal diabetes mellitus.

Author	Population	Genetic Etiology	Median Age of Diagnosis, Days	Median Age of Remission, Weeks	SGA	Congenital Anomalies/Disorders
Busiah, 2013 [30]	40	45% UPD6pat 33% 6q24 duplication 23% maternal hypomethylation	5.0 (1.0–14.5)	14.4 (7.8–28.3)	92%	Macroglossia 32% Cardiac 8% Urinary tract 17% Neurological disorders 18% Umbilical hernia 8%
Docherty, 2013 [23]	163	41% UPD6pat 33% paternal 6q24 duplication 26% maternal hypomethylation	4.0	12.0	ND	Macroglossia 44% Umbilical hernia 21% Dysmorphic facial features 18% Urinary tract 9% Cardiac 9% Hypothyroidism 4%
Bonfanti, 2021 [32]	12	50% UPD6pat 17% paternal 6q24 duplication 33% maternal hypomethylation	7.0	12.0	ND	Macroglossia/Umbilical hernia 33%
McCullough, 2024 [31]	33	52% UPD6pat 21% paternal 6q24 duplication 24% maternal hypomethylation	2.0 (1.0–7.0)	12.0 (8.0–24.0)	71%	Macroglossia 56% Umbilical hernia 22% Speech pathologies 36%
Pietrusinski, 2025 [33]	5	60% UPD6pat/maternal hypomethylation	4.4	16.0	80%	Macroglossia 0% Umbilical hernia 40% Neurodevelopmental disorders 40%

UPD6pat: paternal uniparental disomy of chromosome 6; ND: No data.

Intrauterine growth restriction is frequently observed in these patients due to insulin's pivotal role as a growth factor during intrauterine development [4]. It has been reported that approximately 80–90% of neonates are born small for gestational age (SGA) [4,30,33]. It is noteworthy that higher birthweight for the gestational age has been associated with earlier remission [23]. Congenital malformations may accompany 6q24 TNDM. Macroglossia and umbilical hernias are the most frequently reported, and less commonly, renal and heart defects, hypothyroidism, and neurological disorders [30]. In the largest cohort to date of 163 patients with 6q24 TNDM, Docherty et al. observed that congenital anomalies were significantly more prevalent in patients with paternal uniparental disomy or hypomethylation at multiple loci, compared with those with paternal duplication of 6q24 or isolated maternal hypomethylation [23]. However, McCullough et al. reported no difference in clinical features, regardless of the genetic etiology [31].

During the early phase, insulin is typically used to achieve euglycemia. However, successful management with oral sulfonylureas has occasionally been reported [11,35]. The management of patients following relapse should be individualized and may include insulin and noninsulin agents [11,36].

As imprinting changes and copy number variations are involved in the 6q24 TNDM, standard sequencing panels are not capable of detection, and methylation-specific assays are required [33]. Alkorta-Aranburu et al. reported that a combination of methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) and next-generation sequencing (NGS) led to genetic diagnosis in 67% of NDM cases, including 6q24 abnormalities [20].

3.2. Defects in Beta-Cell Function and Insulin Secretion

3.2.1. ATP-Sensitive Potassium (K_{ATP}) Channels Mutations

Insulin secretion by pancreatic beta-cells in response to glucose is dependent on the function of the ATP-sensitive potassium (K_{ATP}) channels [4]. K_{ATP} channels are hetero-octameric structures comprising two subunits. The Kir6.2 subunit, encoded by the *KCNJ11* gene, forms a central pore and is surrounded by the regulatory SUR1 subunit, encoded by the *ABCC8* gene (Table 2) [5]. The regulation of insulin secretion is achieved through alterations in beta-cell membrane electric activity that are associated with the intracellular metabolic state [37].

Table 2. Overview of the main genetic causes of neonatal diabetes mellitus associated with beta-cell dysfunction and impaired insulin secretion.

Gene	Location	Mode of Inheritance	Gene Product	Type of NDM	Associated Malformations
<i>KCNJ11</i>	11p15.1	de novo/AD	Kir6.2	PNDM (more often)/TNDM	Neurodevelopmental impairment, DEND syndrome
<i>ABCC8</i>	11p15.1	de novo/AD	SUR1	PNDM/TNDM (more often)	Neurodevelopmental impairment, DEND syndrome (very rare)
<i>GCK</i>	7p15.3–p15.1	AR	GCK	PNDM	Not present
<i>SLC2A2</i>	3q26.1–26.3	AR	GLUT2	PNDM/TNDM	Fanconi-Bickel syndrome (renal Fanconi syndrome, rickets, growth retardation, hepatomegaly, impaired galactose metabolism, diabetes)
<i>SLC19A</i>	1q23.3	AR	THTR1	PNDM	Rogers syndrome (Thiamine-responsive megaloblastic anemia, sensorineural deafness, diabetes)

AD: autosomal dominant; AR: autosomal recessive; NDM: Neonatal diabetes mellitus; PNDM: Permanent neonatal diabetes mellitus; TNDM: Transient neonatal diabetes mellitus; DEND: Developmental delay, epilepsy, and neonatal diabetes.

In the presence of low glucose concentrations, K_{ATP} channels remain open, maintaining hyperpolarization of the cell membrane. As glucose concentrations rise, glucose uptake into pancreatic beta-cells is mediated primarily by facilitative glucose transporters (predominantly GLUT1 in humans, with contributions from GLUT2). An increased intracellular ATP/ADP ratio leads to closure of K_{ATP} channels, reducing potassium efflux and causing membrane depolarization. Depolarization subsequently opens voltage-dependent calcium channels, resulting in calcium influx and triggering insulin secretion via exocytosis of insulin secretory granules [4,11,16,38].

Gain-of-function mutations in either *KCNJ11* or *ABCC8* permanently activate K_{ATP} channels, rendering them unable to regulate membrane potential. Consequently, beta-cells are incapable to secrete insulin [4,18]. These mutations are the most prevalent genetic cause of NDM, accounting for approximately 50% of cases. They represent the most common genetic cause of PNDM and the second most common in TNDM [11]. *KCNJ11* mutations have been demonstrated to be associated with PNDM in 90% of cases, whereas *ABCC8* mutations are associated with TNDM in approximately two-thirds of cases [16,39].

Activating heterozygous mutations cause *KCNJ11* NDM. In approximately 90% of cases, mutations occur de novo; in the remaining cases, there is autosomal dominant inheritance [16,40]. To date, more than 70 *KCNJ11* variants have been reported to be implicated in NDM pathogenesis [38]. The common pathogenic pathway is reduced ATP

inhibition of K_{ATP} channels. NDM-causing mutations involve both N- and C- terminal domains of *KCNJ11* (Kir6.2) and include residues directly involved in ATP binding and residues in close proximity that indirectly affect ATP binding and activity [18,38,41].

Activating *ABCC8* mutations causing NDM may be homozygous or heterozygous [4,6]. Moreover, NDM cases caused by compound heterozygosity for both activating and inactivating mutations have been described [42,43]. The SUR1 protein consists of three transmembrane domains and two nucleotide-binding domains (NBD1, NBD2). It has been demonstrated that Mg-nucleotide binding to the NBDs induces structural changes in the NBD dimer, leading to the opening of the Kir6.2 pore, membrane hyperpolarization, and inhibition of insulin secretion [38,44]. NDM is associated with mutations that either enhance Mg-nucleotide binding, stabilize Mg-nucleotide-induced structural alterations, or increase the intrinsic channel open probability [38,41].

The distinction between TNDM and PNDM is not feasible at presentation, and the diagnosis is based on the duration of hyperglycemia [4]. Intrauterine growth restriction is a common feature, affecting approximately half of the patients [30,45,46]. In most cases, the diagnosis is made before six months of age. Busiah et al. reported a median time to diagnosis of 45.5 days, which is significantly longer than in patients with TNDM due to 6q25 (45.5 days vs. 5 days, $p < 0.0001$) [30]. Presentation with DKA is not uncommon and has been reported in up to 85% of patients [46,47]. In a prospective study involving 71 patients with K_{ATP} NDM, 44% were diagnosed with TNDM, with a median time to remission of 39.4 weeks [30].

K_{ATP} channels are expressed in neurons across various brain regions, particularly in the hypothalamus, the basal ganglia, and the cortex, providing a rationale for neurological symptoms in approximately 20–30% of patients with K_{ATP} NDM [5,30,38,41,48]. A broad spectrum of neurological disorders may be present, ranging from mild psychomotor disorders to severe developmental delay and epilepsy (DEND syndrome), which affects less than 5% of patients [4]. The clinical phenotype has been shown to correlate with the degree to which each mutation reduces ATP sensitivity of the K_{ATP} channel [38,49]. DEND phenotype is rare among patients with *ABCC8* NDM. However, neurological symptoms may be present, including developmental delay, attention deficit hyperactivity disorder, visual impairments, and spatial dyspraxia [5,6,30]. Malformations of other organ systems are uncommon in patients with K_{ATP} [30].

3.2.2. Glucokinase (GCK) Gene Mutations

Glucokinase (GCK), an enzyme considered to be the glucose sensor of beta-cells, catalyzes the first step of glucose metabolism and is essential for maintaining normoglycemia [16]. GCK, a 465-amino-acid protein expressed mainly in the liver, pancreas, and brain, is encoded by the GCK gene, which is located on chromosome 7 (7p15.3–p15.1) [50–52]. The GCK gene employs tissue-specific promoters to initiate transcription at distinct first exons (1a, 1b, 1c), allowing pancreatic, brain, and liver cells to produce distinct GCK transcripts under distinct regulatory controls [50,51].

GCK catalyzes the first step of glycolysis, the ATP-dependent phosphorylation of glucose to glucose-6-phosphate (G6P). In pancreatic beta-cells, this process promotes insulin secretion, while in the liver, it facilitates glucose metabolism, including glycogen synthesis [51,52]. Through GCK activity, pancreatic beta-cells can regulate glucose phosphorylation and, consequently, glucose metabolism in response to glucose concentration [50]. The low affinity for glucose, the sigmoidal saturation curve, and the lack of GCK inhibition by its product, G6P, enable GCK to function as an effective glucose sensor [50,51].

As GCK plays a pivotal role in regulating insulin secretion, mutations in the GCK gene have been associated with both hyperglycemia and hypoglycemia, and more than

700 mutations have been identified [52]. Heterozygous loss-of-function mutations are associated with a subtype of maturity-onset diabetes of the young (GCK-MODY), which is characterized by mild hyperglycemia [53–55]. Homozygous or compound heterozygous loss-of-function mutations are associated with complete loss of GCK activity and PNDM [50,52,55]. Although rare, accounting for 2–3% of PNDM cases, an increased prevalence has been reported in populations with a high rate of consanguinity [56].

Intrauterine growth restriction is a common feature among CKG PNDM patients, with hyperglycemia usually presenting during the first days of life [16,54]. Typically, no associated extra-pancreatic malformations are present [16]. Patients with GCK PNDM require lifelong therapy with insulin. The combination with sulfonylureas has been demonstrated to enhance insulin secretion, thereby improving glycemic control [6,50,55].

3.2.3. SLC2A2 Gene Mutations

The solute carrier family 2 transporter 2 (*SLC2A2*) gene is located on chromosome 3q26.1–26.3 and encodes GLUT2. GLUT2 is a glucose transporter that contributes to the insulin secretion pathway in pancreatic beta-cells [57]. *Slca2* knock-out mice have been demonstrated to present with severe diabetes from birth and early mortality [58]. However, it has been suggested that GLUT1 and GLUT3 can compensate for the absence of GLUT2 in human pancreatic beta-cells, thereby preserving insulin secretion and maintaining normoglycemia [59].

Homozygous or compound heterozygous mutations in the *SLC2A2* gene cause Fanconi-Bickel syndrome, which typically presents in late infancy with hepatomegaly, renal Fanconi syndrome, growth retardation, and rickets [59,60]. Neonatal diabetes is rarely reported [61]. However, Sansbury et al., in a cohort of 104 patients with NDM in which common genetic NDM causes had been excluded, identified five patients with homozygous *SLC2A2* mutations, four of whom were eventually diagnosed with TNDM. It is noteworthy that only one patient exhibited features of Fanconi-Bickel syndrome at the time of diagnosis, while the remaining four developed them later [60].

3.3. Defects in Insulin Biosynthesis and Beta-Cell Destruction

3.3.1. Insulin (INS) Gene Mutations

Mutations in the insulin gene (*INS*) represent the second most common cause of PNDM. In the United States and Western Europe, approximately 70% of PNDM cases are attributable to K_{ATP} channel and *INS* mutations [4,42]. *INS* mutations are a rare cause of TNDM [4].

The insulin biosynthesis is a complex process that occurs in several stages in the endoplasmic reticulum (ER) and the Golgi apparatus [18]. Preproinsulin, the insulin precursor, following its synthesis in ribosomes, is translocated to the ER where it is proteolytically cleaved by a signal peptidase to form proinsulin [18,62]. In the ER, proinsulin undergoes rapid oxidative folding and forms three specific disulfide bonds involving six cysteine residues, which are crucial for its structure and transport. Intracellular trafficking of proinsulin via the Golgi apparatus and packaging into immature secretory granules is followed by proteolytic processing by prohormone convertases to form mature insulin and C-peptide, which are subsequently packaged into secretory granules [18,62–64]. The pathway of insulin secretion can be disrupted, leading to NDM through two distinct mechanisms, involving heterozygous gain-of-function mutations and homozygous loss-of-function mutations of the *INS* gene (Table 3) [17].

Table 3. Overview of the main genetic causes of neonatal diabetes mellitus associated with defects in insulin biosynthesis and beta-cell survival.

Gene	Location	Mode of Inheritance	Gene Product	Type of NDM	Associated Malformations
<i>INS</i>	11p15.5	de novo, AD (more often)/AR	Insulin	PNDM (more often)/TNDM	Not present
<i>EIF2AK3</i>	2p11.2	AR	PERK	PNDM	Wolcott-Rallison syndrome (neurodevelopmental disorders, skeletal dysplasias, renal disorders, liver impairment, diabetes)
<i>EIF2B1</i>	12q24.31	de novo, AD	eEIF2Ba	PNDM	Liver impairment
<i>IER3IP1</i>	18q12	AR	IER3IP1	PNDM	MEDS syndrome (diabetes, microcephaly, epilepsy)
<i>WFS1</i>	4p16.1	AR/de novo, AD	wolframin	PNDM	Homozygous: Wolfram syndrome (diabetes mellitus, diabetes insipidus, optic atrophy, deafness) Heterozygous: diabetes, congenital sensorineural deafness, congenital cataract

AD: autosomal dominant; AR: autosomal recessive; NDM: Neonatal diabetes mellitus; PNDM: Permanent neonatal diabetes mellitus; TNDM: Transient neonatal diabetes mellitus.

Dominant pathogenic variants cause proinsulin misfolding and accumulation within the ER in more than 80% of cases [4,64]. More than 70 dominant *INS* mutations have been recognized. Proinsulin misfolding may be due to mutations that directly impede disulfide bond formation, such as cysteine mutations, or to non-cysteine mutations that interfere with proper cysteine alignment [63,65,66]. Misfolded proinsulin is trapped and accumulated in the ER, disrupting ER homeostasis and inducing ER stress. This may activate the apoptotic pathway, leading to beta-cell death [17,18,67]. However, mechanisms other than apoptosis have recently been suggested, including impaired beta-cell development due to defects in proliferation or dedifferentiation and loss of beta-cell identity [63,68]. More than 80% of heterozygous *INS* mutations occur de novo, the remaining are inherited in an autosomal dominant manner [69].

Recessive loss-of-function mutations, homozygous or compound heterozygous, result in markedly reduced or absent insulin biosynthesis. Reduced preproinsulin synthesis may be caused by several mechanisms on the transcriptional or translational level. These include failure of *INS* transcription due to gene deletion or truncation, mRNA instability, or lack of translation initiation due to loss of the start codon [62,67,70].

Consistent with the presentation of NDM due to other genetic factors, *INS* NDM patients frequently exhibit IUGR. Most patients are diagnosed during the first six postnatal months, although later presentation is possible [16]. Recessive mutations that result in a lack of insulin biosynthesis from embryonic life are characterised by more severe growth restriction and typically occur earlier, within the first postnatal days [16,18,71]. Typically, no extra-pancreatic features are present (9). Lifelong insulin replacement is necessary [11].

3.3.2. Gene Mutations Associated with ER Stress Response

The most prevalent cause of PNDM in highly consanguineous populations is homozygous mutations in the eukaryotic translation initiation factor 2 α kinase 3 (*EIF2AK3*) gene, which cause Wolcott-Rallison syndrome [72,73]. *EIF2AK3*, located on chromosome 2p11.2, encodes the PKR-like ER kinase (PERK) [74]. PERK is a transmembrane enzyme that functions as a sensor of misfolded proteins within the ER lumen. It is activated by

autophosphorylation and regulates the unfolded protein response [75]. In the absence of functional protein, accumulation of unfolded proteins in the ER leads to apoptosis [72].

Multisystem involvement is characteristic of Wolcott-Rallison syndrome. PNDM is uniformly present, with a median age of presentation of 2.5 months [74]. A recent systematic review, involving 159 patients with Wolcott-Rallison syndrome, reported that the most common manifestations include liver impairment, impaired growth, skeletal abnormalities, neurodevelopmental disorders, renal disorders, and hematopoietic disorders [76]. To date, no genotype–phenotype correlation has been documented [76,77].

The eukaryotic translation initiation factor 2B subunit alpha (*EIF2B1*) encodes eEIF2Ba, which is part of the eIF2B complex that regulates translation initiation and protein synthesis. Impaired regulation of protein translation leads to severe ER stress in pancreatic beta-cells and apoptosis. De novo heterozygous *EIF2B1* variants have been associated with PNDM and transient liver dysfunction. Homozygous *EIF2B1* mutations have been associated with a completely distinct phenotype of leukoencephalopathy with vanishing white matter [78].

Mutations in the immediate early response 3 interacting protein 1 (*IER3IP1*) gene impair ER-to-Golgi proinsulin transport and cause ER accumulation of unfolded proteins, leading to alterations in ER microstructure and ER stress. To date, 10 patients have been described with homozygous *IER3IP1* mutations, all presenting with a similar phenotype of microcephaly, epilepsy, and PNDM (MEDS syndrome) [79,80].

Homozygous mutations in the *WFS1* gene, which encodes the ER protein wolframin, which plays a pivotal role in maintaining Ca^{2+} homeostasis and regulating ER stress, have been associated with Wolfram syndrome. This syndrome is characterized by diabetes mellitus, diabetes insipidus, optic atrophy and hearing loss and typically presents during childhood or adolescence [81]. However, De Franco et al. reported five cases of de novo heterozygous missense mutations in *WFS1* that presented with a distinct, more severe phenotype. These patients presented with PNDM, congenital sensorineural deafness, and congenital cataract. Functional studies showed that these dominant mutations induced marked ER stress and reduced beta-cell survival, leading to early cell death. The authors suggested that this process may begin during embryonic development [82].

3.4. Defects in Pancreatic Morphogenesis

3.4.1. PDX1 Gene Mutations

The pancreatic and duodenal homeobox 1 (*PDX1*) gene plays a key role in pancreatic organogenesis and in the maturation of beta-cells and their ability to secrete insulin [83]. Recessive loss-of-function mutations are a known cause of pancreatic agenesis or hypoplasia and PNDM [84–86]. However, more recently, cases of biallelic *PDX1* variants presenting with PNDM and no clinical manifestations of exocrine pancreatic deficiency or pancreatic agenesis have been documented [87–90]. It has been suggested that a correlation between the mutation type and phenotype exists. Pancreatic agenesis has been observed to result from null mutations that disrupt protein function, whereas hypomorphic mutations, which partially diminish protein function, have been associated with PNDM and occasionally exocrine insufficiency [88,89].

3.4.2. PTF1A Gene Mutations

The pancreas transcription factor 1 alpha (*PTF1A*) gene encodes PTF1A, a basic helix-loop-helix protein crucial for pancreas and cerebellum development [91]. Homozygous loss-of-function truncation mutations have been associated with a severe phenotype characterized by NDM, pancreatic agenesis, and cerebellar hypoplasia or agenesis, with early mortality [92–94]. A distinct, milder phenotype has been documented in patients with recessive inactivating mutations in an enhancer located 25kb downstream of *PTF1A*. This

enhancer is pancreatic-specific and critical for pancreatic progenitor differentiation [95]. The phenotype comprises pancreatic agenesis, leading to PNDM and exocrine pancreatic insufficiency, with no cerebral involvement [96–99]. In a recent multicenter study of 30 patients with NDM caused by *PTF1A* enhancer mutations, Demirbilek et al. reported a median age of diabetes presentation of five days and exocrine pancreatic insufficiency in all patients. Growth retardation, anemia, and cholestasis were the most commonly reported additional features [91].

3.4.3. GATA6 Gene Mutations

The transcription factor GATA6, encoded by the *GATA6* gene, contains two zinc-finger domains and is critical for pancreatic organogenesis and for the generation and function of both endocrine and exocrine cells [100]. De novo heterozygous inactivating *GATA6* mutations have been recognized as the most common cause of pancreatic agenesis [101]. Other commonly reported features include cardiac, hepatobiliary, and intestinal malformations [100–102]. However, considerable heterogeneity in phenotype is evident [100]. A wide spectrum of diabetes presentation in patients with *GATA6* mutations has been documented, including mainly NDM, as well as childhood-onset and adult-onset diabetes [100]. A genotype–phenotype correlation cannot be established due to the observed variability of phenotype in patients carrying the same mutation. It has been suggested that genetic, environmental and stochastic factors may contribute to the clinical heterogeneity [103,104]. However, pancreatic involvement has been documented to be more common in the presence of inactivating mutations within the second zinc-finger domain of *GATA6* [104,105].

3.4.4. HNF1B Gene Mutations

The hepatocyte nuclear factor 1b (*HNF1B*) gene is located on chromosome 17q12 and encodes the hepatocyte nuclear factor 1 beta (HNF1b), a transcription factor crucial for the development of many organs, including the kidneys, pancreas, liver, and intestines [106,107]. Heterozygous loss-of-function mutations in the *HNF1B* gene are associated with a multisystem disorder, most commonly presenting as diabetes (maturity-onset diabetes of the young 5 [MODY5]) and renal cysts (RCAD syndrome) [108]. The role of *HNF1B* in early kidney and pancreatic development has been demonstrated in studies with experimental animals [109,110]. However, heterozygous *HNF1B* mutations have been rarely reported as a cause of NDM. A few cases of both TNDM and PNDM have been described, typically accompanied by pancreatic hypoplasia and renal malformations [106,107,111,112].

3.5. Defects in Beta-Cell Development

3.5.1. NEUROG3 Gene Mutations

Neurogenin-3 (NEUROG3) is a basic helix-loop-helix transcription factor essential for endocrine cell development in the pancreas, intestine, and hypothalamus. *Neurog3*-null mice are characterized by the absence of endocrine cells in the pancreas and intestine and by lethality during the early postnatal period [113].

In humans, autosomal recessive *NEUROG3* mutations have been associated with variable phenotypes, including enteric anendocrinosis, which presents as severe malabsorptive congenital diarrhea; diabetes; and, less frequently, hypothyroidism, hypogonadotrophic hypogonadism, and short stature (Table 4) [114–117]. Diabetes is present in more than half of the cases either as NDM or childhood-onset diabetes [114]. It has been suggested that null mutations lead to NDM, whereas hypomorphic mutations lead to childhood-onset diabetes [118]. However, the occurrence during adolescence has been reported among patients carrying null mutations, suggesting a potential role of epigenetic modifications or environmental factors in the occurrence of different phenotypes [119,120].

Table 4. Overview of the main genetic causes of neonatal diabetes mellitus associated with defects in beta-cell development and pancreatic morphogenesis.

Gene	Location	Mode of Inheritance	Gene Product	Type of NDM	Associated Malformations
<i>PDX1</i>	13q12.1	AD	PDX1	PNDM	Nonsense mutations: pancreatic agenesis/hypoplasia Hypomorphic mutations: $\pm$ exocrine pancreatic insufficiency
<i>PTF1A</i>	10p12.2	AR/AD	PTF1A	PNDM	Homozygous: pancreatic agenesis, cerebellar hypoplasia/agenesis Heterozygous: pancreatic agenesis Growth retardation, anemia, cholestasis
<i>HNF1B</i>	17q12	AD	HNF1B	PNDM/TNDM	Pancreatic hypoplasia, renal cysts
<i>GATA6</i>	18q11.2	AD	GATA6	PNDM	Pancreatic agenesis, cardiac, hepatobiliary, intestinal malformations
<i>GATA4</i>	8p23.1	AD	GATA4	PNDM	Pancreatic agenesis, congenital heart defects
<i>CNOT1</i>	16q21	de novo, AD	CNOT1	PNDM	Pancreatic agenesis, holoprosencephaly
<i>RFX6</i>	6q22.1	AR	RFX6	PNDM	Mitchell–Riley syndrome (diabetes, bowel atresia, gallbladder agenesis/hypoplasia)
<i>NEUROG3</i>	10q21.3	AR	NEUROG3	PNDM	Malabsorptive congenital diarrhea (enteric anendocrinosis), hypogonadotrophic hypogonadism, short stature
<i>NEUROD1</i>	2q31.3	AR	NEUROD1	PNDM	Cerebellar hypoplasia, sensorineural deafness, visual impairments
<i>NKX2-2</i>	20p11.22	AR	NKX2-2	PNDM	Neurodevelopmental impairment, corpus callosum hypoplasia
<i>GLIS3</i>	9p24.2	AR	GLIS3	PNDM	congenital hypothyroidism, polycystic kidneys, hepatomegaly, cholestasis, characteristic facial features

AD: autosomal dominant; AR: autosomal recessive; NDM: Neonatal diabetes mellitus; PNDM: Permanent neonatal diabetes mellitus; TNDM: Transient neonatal diabetes mellitus.

3.5.2. *NEUROD1* Gene Mutations

NEUROD1, encoded by the *NEUROD1* gene, is a basic helix-loop-helix transcription factor with an important role in the development and functional maturation of the endocrine pancreas [121]. Experimental studies have demonstrated that *Neurod1* is essential for beta-cell maturation and that *Neurod1* deficiency compromises the proliferation, differentiation, and functional properties of endocrine cells, resulting in impaired insulin production. *Neurod1*-knockout mice exhibit profound beta-cell dysfunction, resulting in severe diabetes and death in the perinatal or early postnatal period [121,122].

In humans, heterozygous loss-of-function mutations have been associated with MODY, particularly MODY6 and adult-onset diabetes [121]. However, homozygous inactivating *NEUROD1* mutations have been reported as a rare cause of PNDM [123]. Rubio-Cabezas et al. identified two patients with homozygous *NEUROD1* mutations who presented with PNDM, including a morphologically normal pancreas, cerebellar hypoplasia, sensorineural deafness, and visual impairments. Moreover, Demirbilek et al. reported another

case of a homozygous *NEUROD1* mutation presenting with a similar phenotype [123]. Therefore, biallelic loss-of-function *NEUROD1* mutations are regarded as a rare cause of syndromic PNDM.

4. Transient Hyperglycemic States in Neonates

Transient hyperglycemia is a common metabolic disturbance, particularly among preterm and critically ill neonates. It reflects reversible disturbances in glucose homeostasis, rather than the genetic susceptibility underlying NDM. In contrast to NDM, which is characterized by persistent defects in beta-cell development and survival, insulin biosynthesis or secretion due to monogenic mutations, transient hyperglycemia is attributable to developmental immaturity and stress responses that impair glucose regulation during early postnatal life [1].

Hyperglycemia is very common in preterm neonates, with a reported prevalence varying from 20–80% [3]. The risk of hyperglycemia is inversely correlated with gestational age and birthweight [3]. It has been demonstrated that neonates with a birthweight of less than 1000 g have 18 times higher risk of hyperglycemia compared to neonates with a birthweight of 1000–2000 g [124]. Predisposition to hyperglycemia in preterm neonates is multifactorial, reflecting beta-cell functional immaturity, decreased insulin sensitivity, increased counter-regulatory hormone activity, and exogenous factors such as high glucose infusion rates and administration of vasoactive drugs or glucocorticoids [1].

Reduced beta-cell mass and functional immaturity of beta-cells in preterm neonates may result in insufficient insulin secretion and poor insulin secretory response to glucose [2,125–127]. Impaired insulin secretion in neonates, and particularly in very preterm neonates, may reflect delayed maturation of glucose-sensing mechanisms. Key elements of glucose-sensing, such as GLUT2 and GCK, have been shown to have reduced expression and functional activity in the immature beta-cell [126]. The response of beta-cells in preterm neonates to hyperglycemia is characterized by increased secretion of proinsulin, a non-processed precursor with approximately one-tenth the biological activity of mature insulin [128–130]. Proinsulin is normally processed by proconvertases in the immature secretory granules of the beta-cell to form mature insulin; however, in preterm beta-cells, this processing is inefficient. Consequently, an increased proinsulin/insulin ratio is observed in preterm neonates, which underlies a defective processing system in the immature beta-cell [3,131].

It has been demonstrated that gluconeogenesis continues in the preterm neonate, despite glucose infusion or total parenteral nutrition, and that this may persist up to the chronological age of five weeks [132,133]. This has been at least partly attributed to the immaturity of hepatic glucose sensing and regulation. Low levels of the glucose transporters GLUT2 and GLUT4, which are associated with immaturity, may contribute to this phenomenon [2]. GLUT2 facilitates the bidirectional transportation of glucose within the liver, in accordance with alterations in plasma glucose levels. Consequently, low levels of GLUT2 are associated with impaired glucose sensing and incomplete suppression of endogenous glucose production [3,131]. Lower pancreatic GLUT2 expression is associated with impaired insulin secretion in response to glucose [3]. In addition to functional beta-cell immaturity, delayed introduction of enteral feeding, which is common in very preterm neonates, is associated with reduced incretin levels, which are known to promote insulin secretion [2].

However, persistent glucose production despite high glucose levels may not be solely attributed to sustained gluconeogenesis. Alternative mechanisms, including impaired hepatic glucose sensing and altered intracellular glucose metabolism, may contribute [128]. Reduced GCK activity in preterm neonates may result in reduced phosphorylation of

glucose to G6P, and ineffective glucose metabolism may lead to failure of hepatic glucose output suppression [128,131]. Moreover, the less abundant insulin-sensitive tissues in preterm neonates, such as skeletal muscle and adipose tissue, and reduced GLUT4 levels may contribute to reduced insulin-stimulated glucose uptake, thereby contributing to peripheral insulin resistance [2,3]. An additional potential contributor to reduced peripheral glucose uptake and decreased glycogen synthesis may be zinc deficiency, which is common in very preterm neonates. Zinc increases intracellular signaling by promoting PI3K/Akt pathway activation, thereby promoting GLUT4 translocation to the plasma membrane, enhancing peripheral glucose uptake. Zinc also inhibits glycogen synthase kinase 3-beta, thereby promoting glycogen synthesis. Therefore, zinc deficiency may impair glucose uptake and glycogen storage, contributing to insulin resistance and hyperglycemia [3].

Additional factors contributing to insulin resistance are increased levels of pro-inflammatory cytokines, such as interleukin-1, interleukin-6, and tumor necrosis factor-alpha, which are elevated in sepsis, necrotizing enterocolitis, and other morbidities associated with prematurity. Moreover, exposure to vasoactive agents and corticosteroids exacerbates insulin resistance by increasing counter-regulatory hormones and impairing insulin receptor signaling [3].

Impaired beta-cell development has also been documented in neonates with intrauterine growth-restriction (IUGR) [134]. Pancreatic islets of severely affected fetuses have been demonstrated to be smaller, less vascularized, with fewer beta-cells, resulting in lower insulin secretion [134,135]. The severity of these alterations correlates with the degree of placental insufficiency [134,136,137]. Intrauterine hypoxemia and the increased catecholamine secretion secondary to placental insufficiency induce adaptive metabolic responses that impact pancreatic islets development and inhibit insulin secretion [138,139]. In addition, increased hepatic glucose production in utero due to increased hepatic phosphoenolpyruvate carboxykinase (PEPCK) and G6P expression may persist postnatally and contribute to the development of insulin resistance [138]. Moreover, it has been suggested that epigenetic modifications in key developmental genes may contribute to the association of IUGR and long-term disturbances of glucose homeostasis [140]. Experimental studies in mice have shown that *Pdx1* expression, a key regulator of pancreatic organogenesis and beta-cell maturation, is persistently reduced in beta-cells from growth restricted (IUGR) offspring, supporting an epigenetic mechanism of developmental programming [140,141].

Alterations in glucose homeostasis are commonly observed in neonates following hypoxic-ischemic injury, and hyperglycemia has been reported in up to 50% of affected neonates. It has been suggested that early hyperglycemia probably reflects reduced cerebral glucose uptake and severe cellular energy failure, characterized by increased adenosine triphosphate consumption and enhanced anaerobic glycolysis with hydrogen ion accumulation [142]. Inflammation, mitochondrial dysfunction, and oxidative stress are the main molecular cascades underlying brain injury in hypoxic-ischemic encephalopathy and are associated with increased insulin resistance [143]. Neonates with hypoxic-ischemic injury have elevated circulating proinflammatory cytokines, including interleukin-1, interleukin-6, and tumor necrosis factor-alpha, which have been shown to impair insulin receptor signaling and promote insulin resistance [2,144]. Moreover, activation of the hypothalamic-pituitary-adrenal axis leads to increased levels of corticosteroids and counter-regulating hormones, which enhance gluconeogenesis and glycogenolysis, and increase insulin resistance, thereby contributing to hyperglycemia [142,145].

In conclusion, in addition to preterm and low-birth-weight neonates, who are at risk of hyperglycemia due to functional immaturity-related mechanisms, critically ill neonates are also at increased risk of hyperglycemia through distinct pathophysiological mechanisms. The stress response associated with critical illness, such as sepsis and hypoxic-

ischemic injury, is characterized by elevated levels of circulating proinflammatory cytokines, which contribute to insulin resistance. In addition, stress of any etiology activates the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system, resulting in increased secretion of counter-regulatory hormones, including catecholamines, cortisol, and growth hormone, which promote insulin resistance and stimulate hepatic glucose production. Moreover, medications commonly used in critically ill neonates, such as inotropes and corticosteroids, suppress insulin secretion and increase insulin resistance.

5. Conclusions

Monogenic NDM is a rare genetic disorder caused by diverse single-gene mutations that impair pancreatic beta-cell development or survival, insulin biosynthesis and secretion, or pancreatic morphogenesis. Rapid advances in molecular techniques have led to a continuously expanding understanding of the genetic basis of NDM. More than 40 genes and chromosomal loci have been identified to be implicated in the pathogenesis of NDM. A precise genetic diagnosis can be established in more than 80% of affected individuals. The clinical course of diabetes, the presence of extra-pancreatic malformations, and long-term prognosis vary according to the underlying genetic defect. However, the phenotype cannot always be accurately predicted, and further studies are needed to refine genotype–phenotype correlations.

TNDM is characterized by early remission, although relapse occurs in more than half of the patients. TNDM is most commonly associated with abnormalities at the imprinted 6q24 locus. However, other genes, such as *ABCC8* and, less frequently, *KCNJ11* and *INS*, may be implicated. In contrast, PNDM requires lifelong antidiabetic treatment and most commonly results from activating variants in genes encoding K_{ATP} channel subunits, particularly *KCNJ11*. However, a wide variety of other genes may also be implicated, including mutations in *INS*, *GCK*, and in genes encoding transcription factors essential for pancreatic development, such as *PDX1* and *PTF1A*.

In contrast to NDM, transient hyperglycemic states frequently observed in preterm and critically ill neonates, such as those with sepsis or HIE, are not driven by monogenic defects but reflect developmental immaturity of glucose homeostasis or stress-related responses. These conditions typically resolve with maturation or recovery from critical illness and do not confer long-term implications as monogenic NDM. Distinguishing NDM from transient hyperglycemic states is essential to guide appropriate genetic testing, management, and long-term follow-up. Differentiating TNDM and transient hyperglycemia is particularly challenging, as both conditions remit. Therefore, clinical judgement and molecular testing are required for accurate diagnosis, which is crucial to ensure long-term follow-up in TNDM, given the high rate of relapse.

Molecular diagnosis is therefore central to NDM diagnosis, enabling accurate classification and optimization of care. As molecular diagnostic technologies continue to advance, additional genes involved in NDM pathogenesis are expected to be identified, further expanding current knowledge. Moreover, further genetic and functional studies are essential to more accurately define genotype–phenotype correlations, improve prognosis prediction, ensure optimal follow-up and management, and thus improve outcomes for patients with NDM.

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