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Genetic Susceptibility to Transient and Permanent Neonatal Diabetes Mellitus

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Abstract

Neonatal diabetes mellitus (NDM) is a rare kind of diabetes characterized by hyperglycemia and low levels of insulin. Clinically, it is categorized into two main types: Transient NDM (TNDM) and Permanent NDM (PNDM). These types are diagnosed based on duration of insulin dependence early in the disease. In TNDM, diabetes begins in the first few weeks of life with remission in a few months. However, infant with PNDM have insulin secretion failure in the late fetal or early post-natal period with no remission. Mutation in the KCNJ11 and ABCC8 genes can cause both TNDM and PNDM, and infant with this mutation can respond to transition from insulin to sulfonylurea making identification of genes involved in the disease important for appropriate treatment.

Key Words: Mutations, Neonatal diabetes, PNDM, TNDM.

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1-Introduction

Neonatal diabetes mellitus (NDM) is a rare kind of diabetes (1:300,000–400,000 newborns) which diagnosed within the first 6 months of life. Clinically it is categorized based on the duration and progression in two subtypes: Transient neonatal diabetes mellitus (TNDM) and permanent neonatal diabetes mellitus (PNDM). These types of diabetes are monogenic diseases and caused by a singles gene mutation (1, 2). About 50% to 60% of cases of neonatal diabetes are TNDM.

NDM also can be existing as a part of a syndrome (syndromic NDM) (3). Clinical features cannot help the technician to identify which kind of NDM will improve in a neonate with diabetes. However, Molecular genetic tests can differentiate between these two types of NDM according to the identification of mutations in especial genes. The identification of underlying mutation is necessary for opting of appropriate therapy. For instance, sulfonylurea agents can be used instead of insulin in patient with mutations in KCNJ11 (4). Diabetes in infants usually are not related to classical type 1 diabetes (5) and studies show auto antibodies are rare and Human leukocyte antigen (HLA) haplotypes have a protective role in most cases of NDM (2).This article reviews susceptible genes inducing different kind of NDM.

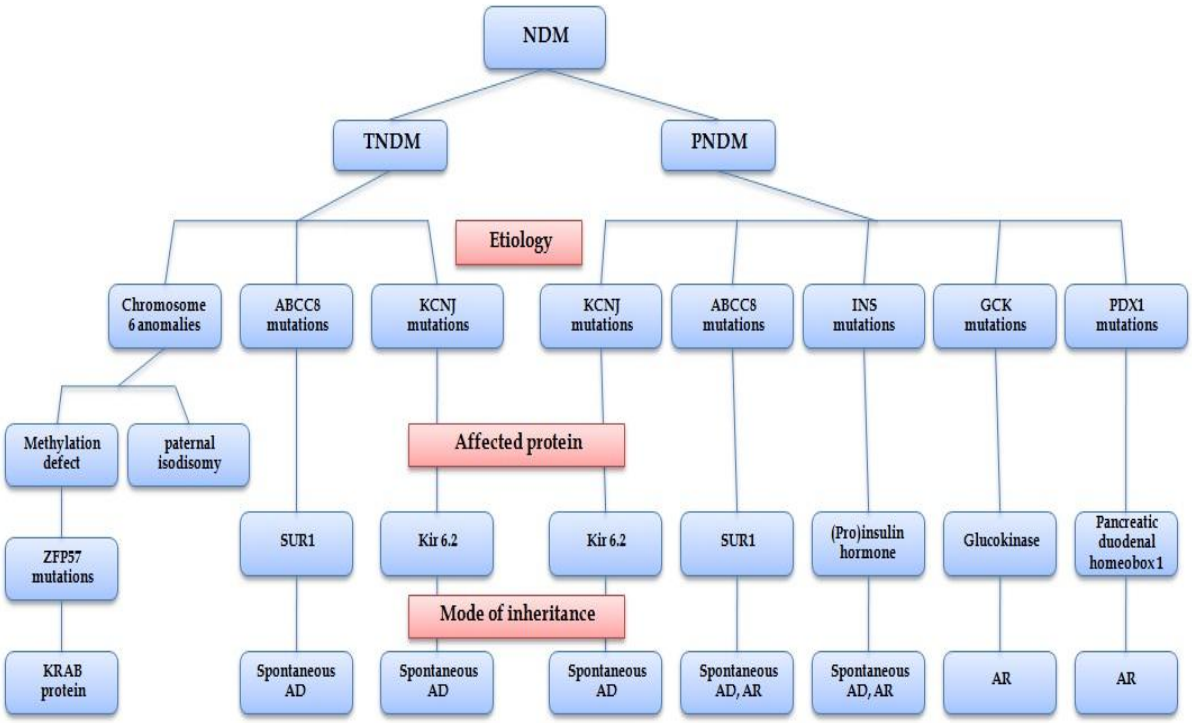

Fig. 1: Diagram of involved genes in NDM

Abbreviation; NDM: Neonatal Diabete Mellitus; TNDM: Transient Neonatal Diabete Mellitus; PNDM: Permanent Diabete Mellitus; AR: Autosomal recessice; AD: Autosomal Dominant.

2- Materials and Methods

This article as a review study focuses on the reported genes and their variations in susceptibility to different type of neonatal diabetes mellitus. We conducted a thorough literature search using Google and Google Scholar in Scopus and Pubmed databases by considering key words such as "NDM", "TNDM", "PNDM", "Mutations" and "Genetic variation". Here, after evaluating different kind of article including original, review and meta analysis, we summarized the last up-to-dated reported mutations, variations, their effects on protein structure, etiology and their mode of inheritance leading to different type of NDM.

3-Results

The mutations that cause NDM can be involved in beta-cell apoptosis, pancreas development and insulin processing, which provide useful tools for the identification of fundamental molecular etiology of the disease for researcher. Importantly, the identification of mutation in susceptibility to NDM can also lead to better prognosis, therapeutic approach and genetic counseling.

3.1-Transient Neonatal Diabetes Mellitus (TNDM)

TNDM is appeared within days of birth and resolves by age 18 months characterized by Intrauterine growth retardation (IUGR), hyperglycemia, failure to thrive and dehydration in some cases (6). TNDM is sporadic; however, paternal transmission can be seen in about one-third of reported patients. There are candidates genes contributing to neonatal diabetes mellitus type 1 (TNDM1) (OMIM: 601410) in the imprinted locus 6q24 region including: transcription factor ZAC1 (LOT1, PLAGL1) and HYMAI gene (7). ZAC1 (finger gene involved in apoptosis and cell-cycle control 1 genes) is the regular of Pituitary adenylate cyclase-activating polypeptide receptor (PACAP 1), a transcription factor, that has an important role in the regulation of insulin secretion. Hydatidiform Mole Associated And Imprinted (HYMAI) is a non-coding RNA with unknown function. Naturally, Differentially Methylated Region (DMR) methylation suppresses PLAGL1 and HYMAI maternal alleles; Consequently only paternal alleles can express. But paternal uniparental isodisomy of chromosome 6, maternal methylation defects and paternally inherited duplication of 6q24 make the PLAGL1 and HYMAI alleles to express more than usual (8). Studies indicate that maternal methylation defects include hypomethylation of the maternal PLAGL1 and HYMAI (hypomethylation at imprinted loci (HIL)) as a result of mutations in DMR (differentially methylated region) or ZFP57 gene. ZFP57 is on chromosome and 6p22.1 covering 8.6-kb genomic region. It has six exons coding the ZFP57 protein, Kruppel-associated box domain (KRAB) zinc finger protein, with 516 amino acids. Exons 4 and 5 encode KRAB A and KRAB B domain. Exon6 encodes seven C2H2 Zinc fingers. Studies show DNA methyltransferases (DNMTs) are recruited by ZFP57 and its cofactor (KRAB-associated protein 1), therefore intact ZFP57 protein is essential for the maintenance of DNA imprints (9, 10). Mackay et al. (2008) identified ZFP57 gene as a good candidate gene in susceptibility to TNDM in seven families (Table 1). Based on their study, all individuals identified with mutations in ZFP57 were hypomethylated at the Paternally expressed gene 3 (PEG3) and Growth factor receptor-bound protein 10 (GRB10) (11).

TNDM2 (OMIM: 610374) caused by mutations in the ABCC8 [ATP-binding cassette, sub-family C (CFTR/MRP),

member 8]. KCNJ11 mutations (potassium channel, inwardly rectifying subfamily J, member 11) gene also making neonate susceptible to TNDM3 (OMIM: 610582). The KCNJ11gene codes the Kir6.2 subunits and ABCC8 gene is responsible for the producing of sulfonylurea-receptor subunits (SUR1) of ATP-sensitive potassium K(ATP) channel (12, 13) . The K(ATP) channel of pancreatic β cell regulates glucose-stimulated insulin secretion. The more glucose metabolism increase, the more ATP/ADP produce and as a result the membrane become depolarized and the channel get closed. Consequently, Ca2+ level becomes increased and it induces insulin secretion from β cells (14, 15). Babenko et al. (2006) identified different mutations in ABCC8 gene causing TNDM2 (Table.1) (13). Yorifuji et al. (2005) identified a novel mutation in KCNJ11 in 4 individuals in 3-generation Japanese family with inherited diabetes mellitus among whom one had TNDM. Their study revealed that the mutation reduced ATP sensitivity by increasing spontaneous open probability (16). Based on Edghill et al. (2007) study, the majority of de novo KCNJ11 mutations happen during gametogenesis or embryogenesis increasing risk of susceptibility for subsequent sibs (17). Table.1 shows reported mutation regarding susceptibility to TNDM (11, 13, 16, 18-27).

Table 1: Reported mutations in susceptibility to TNDM

Gene	Variant	Cases	Ref.	Variant	Cases	Ref.
ZFP57	C241X	Family 1:proband 1 & 2	Mackay et al. 2008	H438D	Family 4: proband	Mackayet al. 2008
	E86VfsX28	Family 2: proband 1 & Case 2		R228H	Family 5: proband	
	G441GfsX17	Family 3: proband		H257N	Family 6: proband	
	R228H	Family 7: proband		T139S	A case	Boyraz et al. 2013
	S252F	A case	Boyraz et al. 2013	A325P	A case	
ABCC8	C435R	Family 13:Father and son	Babenko et al. 2006	R1379C	Family 19: proband	Babenko et al. 2007
	H1023Y	Family 28: proband		R1182Q	Family 28:Father and son	
	L582V	Family 36: proband/family 16 :I2,II3&II4,III1&III2		R1379C	Family 17:I2,II2,III3,III2,IV3,IV6	
	D209E	Proband with her mother	Flanagan et al. 2007	D212I	Proband and his mother and maternal aunt	Flanagan et al 2007
	D212N	Proband with his brother and mother		V324M	Proband	
	L451P	Proband and her sister		R826W	Proband	
	R1183W	Proband		R1183Q	Proband	
	R1380C	Proband		R1380H	Proband	
KCNJ	C42R	A case	Yorifuji et al. 2005	R201H	Proband	Colombo et al. 2005
	G53R	Study1:Proband/study 2:proband and his mother	Gloyn et al. 2005/Flanagan et al 2007	G53S	Study1:Proband/ study 2: proband, her brother and mother	Gloyn et al. 2005/Flanagan et al 2007
	I182 V	Proband		R50Q	Study1: a case/ study 2: a case	Suzuki et al. 2007/ Ioannou et al. 2011
	A174G	A case	Suzuki et al. 2007	R34G	Proband and paternal grand father	Flanagan et al 2007

	E179A	A case	Flanagan et al 2007	E227K	Study1:proband and his father and paternal grandmother/ Study2:proband	Flanagan et al 2007 / Martins et al.2015
	E229K	4 families:A proband, proband with his sister, proband with his mother, proband with his father		R365H	Proband	Flanagan et al 2007
	Q227K	Proband	Kocha et al. 2010	E322A	A case	Şıklar et al. 2011
	D352H	A case	Şıklar et al. 2011	G53V	Proband with her sister and brother	Khadilkar et al. 2010

3.2-Permanent Neonatal Diabetes Mellitus (PNDM)

PNDM describes as diabetes which onsets before the age of 6 months and persists through life. The five major genes involved in the disease are KCNJ11, ABCC8, INS, GCK, and PDX1. In the disease studies indicate mutations in KCNJ11 and ABCC8 genes account for approximately 40% of PNDM (28). PNDM can also be as a result of a number of syndromes including Wolfram syndrome, Immunodysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX syndrome), and Wolcott–Rallison syndrome (WRS)**.** Mutations in the Insulin gene (INS gene) also are the reasons of 12% of PNDM**.** The study done by Anna Gloyn and colleagues revealed that 10 out of 29 patients with PNDM were heterozygote for dominant inherited mutation in KCNJ1 gene (29). Based on previous studies, all mutations in KCJN11 gene are heterozygote and they can have effects on ATP mediated closure of the channel or combined with channel gaiting and channel conformation which can lead to keep it opened (30, 31). The mode of inheritance for KCNJ11 is an autosomal dominant, ABCC8 and INS is autosomal dominant or autosomal recessive GCK and PDX1 is autosomal recessive. Heterozygote mutations of GCK and PDX1 genes cause a milder form of diabetes mellitus such as GCK-familial monogenic diabetes [formerly known as Maturity-onset diabetes of the young type 2 (MODY 2)] and PDX1-familial monogenic diabetes (formerly known as MODY 4). However Gloyn et al. (2002) concluded that glucokinase deficiency is not the main reason of PNDM (32). Mutations in FOXP3, PTF1A, GLIS3, NEUROD1, RFX6, NEUROG3, EIF2AK3, GATA6, SLC19A2, HNF1B, PAX6 and WFS1 genes can cause syndromic form of neonatal diabetes. Proks et al. (2006) reported a de novo missense mutation in the ABCC8 gene in a male patient with PNDM who had severe developmental delay, and generalized epileptiform activity on Electroencephalogram (EEG). Studies indicated that the mutation can be increased the whole-cell K(ATP) current which can reduced sensitivity of the K(ATP) channel to inhibition by Mg-ATP (33). Based on the results of Stoy et al. (2007), heterozygous missense mutation in INS gene, which encodes pro insulin hormones, can be caused PNDM. In their study, PNDM patients identified with mutations in the INS gene have a median age of 9 weeks (34). Edghill et al. (2008) reported 16 different INS mutations in 35 patients with PNDM (35). Table 2 shows identified mutations in susceptible genes to PNDM (13, 23, 36-49). Gloyn et al. (2006) reported that phenotype can be variable between patients, even among individuals who have the same mutations (38).

Table 2: Reported mutations in susceptibility to PNDM

Gene	Variant	Cases	Ref	Gene	Variant	Cases	Ref
KCNJ1	F35V	Proband	Sagen et al. 2004	KCNJ1	V59M	3 proband in 3 families	Sagen et al. 2004
	R201H	Proband and her mother			F331I	Proband	
	Y330C	Proband , her sister, her mother and maternal grandmother			Gly334Val	Proband	Lau et al. 2015
	R201H	2 cases	Ioannou et al.2011		R201H	Proband	Gloyn et al. 2006
	C166F	Proband	Gloyn et al. 2006		V59M	Proband	
	R201 L	Proband	Ilkhanipoor et al. 2013	ABCC8	R168C	Proband	Jain et al .2012
ABCC8	V86A	A case	Ellard et al .2007		V86G	A case	Ellard et al. 2007
	F132L	A case			F132V	A case	
	D209E	A case			Q211K	A case	
	L225P	A case			E382K	A case	
	A1185E	A case			N72S	A case	
	P45L	A case			G1401R	A case	
	T229I	A case			V1523L	A case	
	P207S	A case			Y179X	A case	
	E1327K	A case			V1523A	A case	
	T1043QfsX74	A case			L213R	Proband	Babenko et al. 2006
	I1424V	A case	Babenko et al. 2006	INS	L13R	A case	Hussain et al. 2013
INS	C96Y	A case	Ahamed et al.2008		C109Y	A case	Talaat, et al.2014
	A24D	A case	Long et al.2015		L105P	A case	Kshirsagar et al. 2013
GCK	Q96X	Proband with her sister and brother	Bennett et al.2011	GCK	G261R	Proband	Bennett et al.2011
	M210K	Proband	Njølstad et al.2003		A378V	A case	Njølstad et al.2003
	IVS8+2	A case			G264S	A case	
	T168A	A case	Turkkahraman et al.2008	PDX1	E178G	A case	Nicolino et al.2010
PDX1	P87L	2 cases	Franco et al.2013		A152G	A case	Franco et al.2013
	R176Q	A case			C18X	A case	

4-Conclusion

Although main etiology of NDM is still unknown, studies indicate genetic factors can be seen in most cases. Recently, many progresses have been made through identification of genes involved in NDM. The molecular genetic testing is compulsory for infants with diagnosis of diabetes after 6 month especially when they have affected individuals in their family. Therefore, besides the importance of clinical and laboratory findings, significance of genetic analysis should be considered.

5-Conflict of Interest: None.

6-References

1. Brook CG, Clayton P, Brown R. Brook's clinical pediatric endocrinology. John Wiley & Sons; 2009.

2. Hattersley A, Bruining J, Shield J, Njolstad P, Donaghue K. ISPAD Clinical Practice Consensus Guidelines 2006-2007 The diagnosis and management of monogenic diabetes in children. Pediatr Diabetes 2006;7(6):352-60.

3. Edghill EL, Hattersley AT. Genetic disorders of the pancreatic beta cell and diabetes (permanent neonatal diabetes and maturity-onset diabetes of the young). Pancreatic beta cell in health and disease: Springer; 2008. p. 399-430.

4. Chan YM, Laffel LM. Transition from insulin to glyburide in a 4-month-old girl with neonatal diabetes mellitus caused by a mutation in KCNJ11. Pediatr Diabetes 2007;8(4):235-8.

5. Marquis E, Le Monnier de Gouville I, Bouvattier C, Robert JJ, Junien C, Charron D, et al. HLA-DRB1 and DQB1 genotypes in patients with insulin-dependent neonatal diabetes mellitus. A study of 13 cases. Tissue Antigens 2000;56(3):217-22.

6. Shield JP, Gardner RJ, Wadsworth EJ, Whiteford ML, James RS, Robinson DO, et al. Aetiopathology and genetic basis of neonatal diabetes. Arch Dis Child Fetal Neonatal Ed 1997;76(1):F39-42.

7. Arima T, Drewell RA, Arney KL, Inoue J, Makita Y, Hata A, et al. A conserved imprinting control region at the HYMAI/ZAC domain is implicated in transient neonatal diabetes mellitus. Human molecular genetics 2001;10(14):1475-83.

8. Temple IK, Gardner RJ, Mackay D, Barber J, Robinson DO, Shield J. Transient neonatal diabetes: widening the understanding of the etiopathogenesis of diabetes. Diabetes 2000;49(8):1359-66.

9. Quenneville S, Verde G, Corsinotti A, Kapopoulou A, Jakobsson J, Offner S, et al. In embryonic stem cells, ZFP57/KAP1 recognize a methylated hexanucleotide to affect chromatin and DNA methylation of imprinting control regions. Molecular cell 2011;44(3):361-72.

10. Zuo X, Sheng J, Lau H-T, McDonald CM, Andrade M, Cullen DE, et al. Zinc finger protein ZFP57 requires its co-factor to recruit DNA methyltransferases and maintains DNA methylation imprint in embryonic stem cells via its transcriptional repression domain. Journal of Biological Chemistry 2012;287(3):2107-18.

11. Mackay DJ, Callaway JL, Marks SM, White HE, Acerini CL, Boonen SE, et al. Hypomethylation of multiple imprinted loci in individuals with transient neonatal diabetes is associated with mutations in ZFP57. Nature genetics 2008;40(8):949-51.

12. Ellard S, Flanagan SE, Girard CA, Patch A-M, Harries LW, Parrish A, et al. Permanent neonatal diabetes caused by dominant, recessive, or compound heterozygous SUR1 mutations with opposite functional effects. The American Journal of Human Genetics 2007;81(2):375-82.

13. Babenko AP, Polak M, Cavé H, Busiah K, Czernichow P, Scharfmann R, et al. Activating mutations in the ABCC8 gene in neonatal diabetes mellitus. New England Journal of Medicine 2006;355(5):456-66.

14. Koster JC, Permutt MA, Nichols CG. Diabetes and insulin secretion the ATP-sensitive K+ Channel (KATP) connection. Diabetes 2005;54(11):3065-72.

15. Seino S, Miki T. Physiological and pathophysiological roles of ATP-sensitive K+ channels. Progress in biophysics and molecular biology 2003;81(2):133-76.

16. Yorifuji T, Nagashima K, Kurokawa K, Kawai M, Oishi M, Akazawa Y, et al. The C42R mutation in the Kir6. 2 (KCNJ11) gene as a cause of transient neonatal diabetes, childhood diabetes, or later-onset, apparently type 2 diabetes mellitus. The Journal of Clinical Endocrinology & Metabolism 2005;90(6):3174-78.

17. Edghill EL, Gloyn AL, Goriely A, Harries LW, Flanagan SE, Rankin J, et al. Origin of de novo KCNJ11 mutations and risk of neonatal diabetes for subsequent siblings.

The Journal of Clinical Endocrinology & Metabolism 2007;92(5):1773-7.

18. Boyraz M, Ulucan K, Taşkın N, Akçay T, Flanagan SE, Mackay DJ. Transient Neonatal Diabetes Mellitus in a Turkish Patient with Three Novel Homozygous Variants in the ZFP57 Gene. Journal of clinical research in pediatric endocrinology 2013;5(2):125.

19. Flanagan SE, Patch A-M, Mackay DJ, Edghill EL, Gloyn AL, Robinson D, et al. Mutations in ATP-sensitive K+ channel genes cause transient neonatal diabetes and permanent diabetes in childhood or adulthood. Diabetes 2007;56(7):1930-7.

20. Colombo C, Delvecchio M, Zecchino C, Faienza M, Cavallo L, Barbetti F. Transient neonatal diabetes mellitus is associated with a recurrent (R201H) KCNJ11 (KIR6. 2) mutation. Diabetologia 2005;48(11):2439-41.

21. Gloyn AL, Reimann F, Girard C, Edghill EL, Proks P, Pearson ER, et al. Relapsing diabetes can result from moderately activating mutations in KCNJ11. Human molecular genetics 2005;14(7):925-34.

22. Suzuki S, Makita Y, Mukai T, Matsuo K, Ueda O, Fujieda K. Molecular basis of neonatal diabetes in Japanese patients. The Journal of Clinical Endocrinology & Metabolism 2007;92(10):3979-85.

23. Ioannou YS, Ellard S, Hattersley A, Skordis N. KCNJ11 activating mutations cause both transient and permanent neonatal diabetes mellitus in Cypriot patients. Pediatric diabetes 2011;12(2):133-7.

24. Kochar I, Kulkarni K. Transient Neonatal Diabetes due to Kcnj11 Mutation. Indian pediatrics 2010;47(4):359-60.

25. Martins L, Lourenço R, Maia AL, Maciel P, Monteiro MI, Pacheco L, et al. Transient neonatal diabetes due to a missense mutation (E227K) in the gene encoding the ATP-sensitive potassium channel (KCNJ11). Clinical case reports 2015;3(10):781-5.

26. Şıklar Z, Ellard S, Okulu E, Berberoğlu M, Young E, Savaş Erdeve Ş, et al. Transient neonatal diabetes with two novel mutations in the KCNJ11 gene and response to sulfonylurea treatment in a preterm infant. Journal of Pediatric Endocrinology and Metabolism 2011;24(11-12):1077-80.

27. Khadilkar V, Khadilkar A, Kapoor R, Hussain K, Hattersley A, Ellard S. KCNJ11 activating mutation in an Indian family with remitting and relapsing diabetes. The Indian Journal of Pediatrics 2010;77(5):551-4.

28. Edghill EL, Flanagan SE, Ellard S. Permanent neonatal diabetes due to activating mutations in ABCC8 and KCNJ11. Reviews in endocrine and metabolic disorders 2010;11(3):193-8.

29. Gloyn AL, Pearson ER, Antcliff JF, Proks P, Bruining GJ, Slingerland AS, et al. Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6. 2 and permanent neonatal diabetes. New England Journal of Medicine 2004;350(18):1838-49.

30. Shimomura K. The KATP channel and neonatal diabetes. Endocrine journal 2009;56(2):165-75.

31. Proks P, Antcliff JF, Lippiat J, Gloyn AL, Hattersley AT, Ashcroft FM. Molecular basis of Kir6. 2 mutations associated with neonatal diabetes or neonatal diabetes plus neurological features. Proceedings of the National Academy of Sciences of the United States of America 2004;101(50):17539-44.

32. Gloyn A, Ellard S, Shield J, Temple I, Mackay D, Barrett T, et al. Complete glucokinase deficiency is not a common cause of permanent neonatal diabetes in European cases of neonatal diabetes. American Journal of Human Genetics 2001;69(4):607.

33. Proks P, Arnold AL, Bruining J, Girard C, Flanagan SE, Larkin B, et al. A heterozygous activating mutation in the sulphonylurea receptor SUR1 (ABCC8) causes neonatal diabetes. Human molecular genetics 2006;15(11):1793-800.

34. Støy J, Edghill EL, Flanagan SE, Ye H, Paz VP, Pluzhnikov A, et al. Insulin gene mutations as a cause of permanent neonatal diabetes. Proceedings of the National Academy of Sciences 2007;104(38):15040-4.

35. Edghill EL, Flanagan SE, Patch A-M, Boustred C, Parrish A, Shields B, et al. Insulin mutation screening in 1,044 patients with diabetes mutations in the INS gene are a common cause of neonatal diabetes but a rare cause of diabetes diagnosed in childhood or adulthood. Diabetes 2008;57(4):1034-42.

36. Sagen JV, Ræder H, Hathout E, Shehadeh N, Gudmundsson K, Bævre H, et al. Permanent Neonatal Diabetes due to Mutations in KCNJ11 Encoding Kir6. 2 Patient Characteristics and Initial Response to Sulfonylurea Therapy. Diabetes 2004;53(10):2713-8.

37. Lau E, Correia C, Freitas P, Nogueira C, Costa M, Saavedra A, et al. Permanent neonatal diabetes by a new mutation in KCNJ11: unsuccessful switch to sulfonylurea. Archives of endocrinology and metabolism 2015(AHEAD):0-.

38. Gloyn AL, Diatloff-Zito C, Edghill EL, Bellanné-Chantelot C, Nivot S, Coutant R, et al. KCNJ11 activating mutations are associated with developmental delay, epilepsy and neonatal diabetes syndrome and other neurological features. European journal of human genetics 2006;14(7):824-30.

39. Ilkhanipoor H, Karamizadeh Z. Changing the Treatment of Permanent Neonatal Diabetes Mellitus from Insulin to Glibenclamide in a 4-Month-Old Infant with KCNJ11 Activating Mutation. International journal of preventive medicine 2013;4(9):1078.

40. Jain V, Kumar S, Flanagan SE, Ellard S. Permanent neonatal diabetes caused by a novel mutation. Indian pediatrics 2012;49(6):486-8.

41. Hussain S, Mohd Ali J, Jalaludin MY, Harun F. Permanent neonatal diabetes due to a novel insulin signal peptide mutation. Pediatric diabetes 2013;14(4):299-303.

42. Ahamed A, Unnikrishnan AG, Pendsey SS, Nampoothiri S, Bhavani N, Praveen VP, et al. Permanent neonatal diabetes mellitus due to a C96Y heterozygous mutation in the insulin gene. A case report. J Pancreas 2008;9(6):715-8.

43. Talaat IM, Kamal NM. Permanent Neonatal DM in Monozygotic Twins with p. C109Y Mutation in INS Gene: First Report from Saudi Arabia. Journal of Diabetes & Metabolism 2014;2014.

44. Long KC, Ali JM, Jalaludin MY, Harun F. Permanent neonatal diabetes due to a heterozygous INS mutation. International journal of pediatric endocrinology 2015;2015(Suppl 1):P29.

45. Kshirsagar VY, Ahmed M, Colaco S, Houghton JA, Ellard S. Permanent neonatal diabetes due to a novel L105P (c. 314T> C; p. Leu105Pro) heterozygous mutation in insulin gene. International Journal of Diabetes in Developing Countries 2013;33(4):226-8.

46. Bennett K, James C, Mutair A, Al-Shaikh H, Sinani A, Hussain K. Four novel cases of permanent neonatal diabetes mellitus caused by homozygous mutations in the glucokinase gene. Pediatric diabetes 2011;12(3pt1):192-6.

47. Njølstad PR, Sagen JV, Bjørkhaug L, Odili S, Shehadeh N, Bakry D, et al. Permanent neonatal diabetes caused by glucokinase deficiency inborn error of the glucose-insulin signaling pathway. Diabetes 2003;52(11):2854-60.

48. Turkkahraman D, Bircan I, Tribble ND, Akçurin S, Ellard S, Gloyn AL. Permanent neonatal diabetes mellitus caused by a novel homozygous (T168A) glucokinase (GCK) mutation: initial response to oral sulphonylurea therapy. The Journal of pediatrics 2008;153(1):122-6.

49. Nicolino M, Claiborn KC, Senée V, Boland A, Stoffers DA, Julier C. A novel hypomorphic PDX1 mutation responsible for permanent neonatal diabetes with subclinical exocrine deficiency. Diabetes 2010;59(3):733-40.