THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

# Next Generation Sequencing Panels for Neonatal Diabetes Mellitus (NDM) and Maturity-Onset Diabetes of the Young (MODY)

Monogenic diabetes mellitus includes a heterogeneous group of diabetes types that are caused by mutations in single genes. It is estimated that the monogenic forms of diabetes could represent as much as 1–2% of all cases of diabetes mellitus (1). The main phenotypes suggestive of an underlying monogenic cause include neonatal diabetes mellitus (NDM), maturity-onset diabetes of the young (MODY) and very rare diabetes-associated syndromes.

Neonatal Diabetes Mellitus (NDM) is diabetes diagnosed within the first 6 months of life and can be characterized as either permanent (PNDM), requiring lifelong treatment, or transient (TNDM), which typically resolves by 18 months of age. NDM is rare with an incidence of approximately 1:1,000,000-260,000 live births.

Maturity-onset diabetes of the young (MODY) is more common than NDM and usually occurs in children or adolescents but may be mild and not detected until adulthood. It is predicted that MODY accounts for approximately 1-2% of all Diabetes cases with an incidence of approximately 100 cases per million in the UK population.

Approximately thirty genes that are highly expressed in the pancreatic beta-cell have been identified in these monogenic subtypes of diabetes, and many other genes have been implicated in syndromes that often include diabetes. Several etiological mechanisms of beta-cell dysfunction are involved including reduced beta-cell number, failure of glucose sensing and increased destruction of the beta-cell, which result in inadequate insulin secretion despite chronic hyperglycemia (2-4).

*Our NDM/MODY Sequencing Panel is available, which includes sequence analysis of all the 41 genes listed below*.*

**The most common MODY genes - HNF1A, HNF4A and HNF1B - are not currently available for testing in this panel. The tests for these genes are exclusively licensed to Athena Diagnostics.*

| Gene | Inheritance | Disease Phenotype and Molecular Genetics |
|---|---|---|
| *GCK* [OMIM#138079] | AD or AR | Glucokinase (*GCK*) is a key regulatory enzyme in the pancreatic beta-cell. Heterozygous inactivating mutations in *GCK* cause a subtype of maturity-onset diabetes of the young (MODY2; OMIM# 125851), characterized by mild hyperglycemia, which is present at birth, but is often only detected later in life (5). Homozygous inactivating *GCK* mutations result in a more severe phenotype, presenting at birth as permanent neonatal diabetes mellitus (PNDM; OMIM# 606176) (5). Heterozygous activating *GCK* mutations have been reported that cause hypoglycemia (HI; OMIM# 601820). |
| *PDX1* [OMIM#600733] | AR | Mutation in the *PDX1* gene is a rare cause of MODY (6). In a consanguineous family in which an infant with pancreatic agenesis was homozygous for a 1-bp deletion in the *PDX1* gene, Stoffers et al. (1997) (7) found that members heterozygous for this mutation had early-onset type II diabetes mellitus, which they designated MODY4. |
| *NEUROD1* [OMIM#601724] | AR | Heterozygous loss-of-function mutations in *NEUROD1* are a very rare cause of MODY (8). Diabetes mellitus caused by heterozygous mutations in *NEUROD1* has been reported in three families (9, 10) and was subsequently designated as MODY6. More recently, two cases with neonatal diabetes by 2 months of age were described to exhibit cerebellar hypoplasia, developmental delay, sensorineural deafness, and visual impairment. They were found to carry two different homozygous frameshift mutations resulting in a truncated NEUROD1 protein (11). |
| *KLF11* [OMIM#603301] | AD | Heterozygous mutations in the *KLF11* gene cause MODY7 (12). |
| *CEL* [OMIM#609812] | AD | In 2 families with autosomal dominantly inherited diabetes and exocrine pancreas dysfunction, also referred to as MODY8, Raeder et. al (2006) identified frameshift deletions in the variable number of tandem repeats (VNTR) of the carboxyl-ester lipase gene, *CEL* (13). |
| *PAX4* [OMIM#167413] | AD | Heterozygous mutations in the *PAX4* gene cause MODY9 (14). |
| *INS* [OMIM#176730] | AD | Heterozygous mutations in *INS* are rare cause of MODY10 (15). In addition, heterozygous autosomal dominantly inherited mutations in the *INS* gene are the second most common cause of permanent neonatal diabetes (after mutations in *KCNJ11*), with diagnosis of diabetes sometimes occurring after 6 months of age (15-17). |
| *BLK* [OMIM#191305] | AD | Heterozygous mutations in the *BLK* gene cause MODY11 (18). |

| | | |
|---|---|---|
| *APPL1* [OMIM#616511] | AD | Heterozygous loss of function variants in the *APPL1* gene have been described in two families with MODY14 (19). |
| *ABCC8* [OMIM#600509] | AD | Spontaneous or autosomal dominant activating mutations in the *ABCC8* gene, encoding the SUR1 regulatory subunit of the ATP-sensitive potassium channels found in beta cells, cause both permanent (less often) and transient (more often) neonatal diabetes (20). |
| *KCNJ11* [OMIM#600937] | AD | Spontaneous or autosomal dominant activating mutations in the *KCNJ11* gene, encoding the inwardly rectifying potassium-channel subunit (Kir6.2) of the ATP-sensitive potassium channel expressed at the surface of the pancreatic beta cell cause both transient permanent (less often) and permanent (more often) neonatal diabetes (21, 22). |
| *GATA4* [OMIM# 600576] | AD | A heterozygous mutation in the *GATA4* gene has been identified in a patient with pancreatic agenesis (a rare cause of neonatal diabetes), white matter changes and multi-organ failure (23). Heterozygous mutations in *GATA4* have also been identified in individuals with a variety of heart defects, including atrial septal defects, ventricular septal defects, and tetralogy of Fallot (24). |
| *GATA6* [OMIM#601656] | AD | Heterozygous mutations in the *GATA6* gene have been found in patients with patients with pancreatic agenesis (a rare cause of neonatal diabetes) and congenital heart defects (25). Intrafamiliar variability has been reported with regard to both severity of diabetes (ranging from neonatally lethal diabetes to adult-onset diabetes associated with agenesis of the pancreas) and the types of congenital cardiac defects in affected individuals (26). |
| *MNX1* [OMIM#142994] | AR | Homozygous missense mutations in *MNX1* have been identified in individuals with permanent neonatal diabetes mellitus from three different consanguineous families (27, 28). All patients exhibited severe intrauterine growth retardation. One patient additionally exhibited sacral agenesis and imperforate anus, which are features of Currarino syndrome, a condition caused by heterozygous mutations in *MNX1* [OMIM#176450]. |
| *NKX2-2* [OMIM#604612] | AD | Homozygous nonsense or frameshift mutations have been identified in three individuals with severe defects in insulin secretion and presentation of diabetes at an early age without evidence of exocrine insufficiency. All three patients had intrauterine growth retardation and moderate-to-severe developmental delays (27). |
| *PTF1A* [OMIM#607194] | AR | Homozygous truncating mutations in *PTF1A* cause a syndrome of congenital diabetes involving flexion contractures of arms and legs, paucity of subcutaneous fat and optic nerve hypoplasia, in addition to complete agenesis of the cerebellum and complete absence of the pancreas (29, 30). |
| *RFX6* [OMIM#601346] | AR | Rare patients have been described with a syndrome characterized by diabetes within the first few days of life: pancreatic hypoplasia, intestinal atresia, gall bladder agenesis/ hypoplasia, and congenital diarrhea (31, 32). Five out of six such cases were subsequently reported to carry homozygous or compound heterozygous mutations in *RFX6*, highlighting the role of this transcription factor as a key regulator of beta-cell differentiation (33). |
| *ZFP57* [OMIM#612192] | AR | Transient neonatal diabetes characterized by severe intrauterine growth restriction and diagnosis of diabetes within days of life is most often related to overexpression of associated paternally imprinted genes at chromosome 6q24 (34). This is due to paternal uniparental disomy, a paternally inherited duplication, or a maternal methylation defect, such as from recessive mutations in *ZFP57* (35). These cases exhibit diabetes that resolves spontaneously within a few months, only to return later in life (usually adolescence). |
| *GLIS3* [OMIM#610192] | AR | Homozygous mutations in *GLIS3*, encoding a Krüppel-like zinc finger protein, have been reported in six individuals in three families with a syndrome of neonatal diabetes within the first few days of life, low birth weight, mild facial dysmorphism, and congenital primary hypothyroidism (36). |
| *DUT* [OMIM#601266] | AR | A homozygous mutation in *DUT* has been described in siblings with early-onset diabetes and bone marrow failure (37). In one sibling, diabetes was diagnosed at age 5 years, in the other it was diagnosed at age 28 years. |
| *EIF2AK3* [OMIM#604032] | AR | Mutations in *EIF2AK3* cause Wolcott-Rallison syndrome (WRS) an autosomal recessive disorder characterized by permanent neonatal or early infancy insulin-dependent diabetes. Epiphyseal dysplasia, osteoporosis, and growth retardation develop at a later age. *EIF2AK3* encodes a translation-regulating kinase present in many tissues that plays an important role in trafficking of proinsulin through the secretory pathway in beta cells (38). |
| *INSR* [OMIM#147670] | AD | Mutations in the *INSR* gene cause insulin-resistant diabetes mellitus and acanthosis nigricans (39). |
| *IER3IP1* [OMIM#609382] | AR | Homozygous missense mutations in *IER3IP1* have been identified in infants from two unrelated consanguineous families exhibiting a similar phenotype of neonatal diabetes with simplified gyral pattern microcephaly and severe infantile-onset epileptic encephalopathy (40). |
| *NEUROG3* [OMIM#610370] | AR | A total of five cases with diabetes and chronic intractable malabsorptive diarrhea that started soon after birth have been reported to have recessive mutations in *NEUROG3 (41, 42)*. NEUROG3 is a transcription factor involved in the determination of neural precursor cells in the neuroectoderm, it is expressed in endocrine progenitor cells and is required for endocrine cell development in the pancreas and intestine (43). |
| *SLC2A2* [OMIM#227810] | AR | Mutations in *SLC2A2*, encoding the facilitative glucose transporter GLUT2, cause Fanconi-Bickel syndrome (FBS) (44). FBS involves hepatomegaly related to hepatic and renal glycogen accumulation, renal proximal tubular dysfunction, delay of puberty and short stature, hypergalactosemia, and mild fasting hypoglycemia but postprandial hyperglycemia and diabetes or impaired glucose tolerance. Elevated glucose levels have in some cases been detected in patients under 1 year of age and FBS should thus be considered in the differential diagnosis of neonatal diabetes when any characteristic features are present (45). |

| | | |
|---|---|---|
| *WFS1* [OMIM#606201] | AR | Homozygous or compound heterozygous mutation in the *WFS1* gene cause Wolfram syndrome characterized by diabetes insipidus, diabetes mellitus, optic atrophy, and deafness (46). Several large case series have reported onset of diabetes as the earliest and most consistent feature of Wolfram syndrome, with subsequent development of other clinical features. In vitro studies and animal models suggest that WFS1 down regulates endoplasmic reticulum stress and that a reduction in its activity leads to increased apoptosis in beta cells and other tissues (47). Mutations in *WFS1* should be considered in patients with early-onset diabetes mellitus, particularly if they develop optic atrophy, diabetes insipidus, and/or deafness. |
| *CISD2* [OMIM#611507] | AR | Mutations in the *CISD2* gene cause Wolfram syndrome-2 (48). Onset of diabetes mellitus is typically before age 10 years (age range <1 – 17 years). |
| *HADH* [OMIM#601609] | AR | Mutations in *HADH* have been identified in patients with 3-hydroxyacyl-CoA dehydrogenase deficiency presenting as fulminant hepatic failure (49) and in patients with hyperinsulinemic hypoglycemia (HHF4) (50). The hypoglycemia is present at birth or in the neonatal period. |
| *GLUD1* [OMIM#138130] | AD | Heterozygous activating missense mutations in the *GLUD1* gene have been identified in patients with hyperinsulinism and hyperammonemia (51). |
| *CP* [OMIM#117700] | AR | Homozygous mutations in the *CP* gene cause aceruloplasminemia characterized by a triad of retinal degeneration, diabetes mellitus, and neurological symptoms (52). |
| *FOXP3* [OMIM#300292] | X-linked | Mutations in the X-linked gene *FOXP3* have been identified in patients with a rare form of neonatal monogenic autoimmune diabetes, enteropathy causing severe diarrhea and malnutrition, severe eczema, and autoimmune thyroid disease (IPEX syndrome) (53). Although patients with the classically described syndrome have a severe clinical course usually resulting in death within the first few years of life without stem cell transplant, other patients have a milder phenotype and a few have lived into childhood or beyond (54). |
| *AKT2* [OMIM#164731] | AD | Missense mutations in the *AKT2* gene have been identified in patients with hypoinsulinemic hypoglycemia with hemihypertrophy (55) and dyslipidemia and hepatic steatosis (56). |

## Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp. Deletion/duplication analysis of the panel genes is performed by oligonucleotide array-CGH. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by array-CGH. Array-CGH will not detect low-level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory.

Neonatal Diabetes/MODY Sequencing Panel (sequence analysis of 41 genes)

| | |
|---|---|
| Sample specifications: | 3 to10 cc of blood in a purple top (EDTA) tube |
| Cost: | $3000 |
| CPT codes: | 81407 |
| Turn-around time: | 8 weeks |

## Results:

Results, along with an interpretive report, are faxed to the referring physician as soon as they are completed. One report will be issued for the entire panel. All abnormal results are reported by telephone.

***For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.***

## References:


1. Eide SA, Raeder H, Johansson S et al. Prevalence of HNF1A (MODY3) mutations in a Norwegian population (the HUNT2 Study). Diabet Med 2008: 25: 775-781.
2. Philipson L, Ellard S, Hattersley A et al. Genetic Testing in Diabetes Mellitus: A clinical guide to monogenic diabetes. In: Weiss R, ed. Genetic Diagnosis of Endocrine Disorders. London: Elsevier, 2010.
3. Murphy R, Ellard S, Hattersley AT. Clinical implications of a molecular genetic classification of monogenic beta-cell diabetes. Nat Clin Pract Endocrinol Metab 2008: 4: 200-213.
4. Porter JR, Barrett TG. Monogenic syndromes of abnormal glucose homeostasis: clinical review and relevance to the understanding of the pathology of insulin resistance and beta cell failure. J Med Genet 2005: 42: 893-902.
5. Osbak KK, Colclough K, Saint-Martin C et al. Update on mutations in glucokinase (GCK), which cause maturity-onset diabetes of the young, permanent neonatal diabetes, and hyperinsulinemic hypoglycemia. Hum Mutat 2009: 30: 1512-1526.
6. Christesen HB, Jacobsen BB, Odili S et al. The second activating glucokinase mutation (A456V): implications for glucose homeostasis and diabetes therapy. Diabetes 2002: 51: 1240-1246.
7. Fajans SS, Bell GI, Paz VP et al. Obesity and hyperinsulinemia in a family with pancreatic agenesis and MODY caused by the IPF1 mutation Pro63fsX60. Transl Res 2010: 156: 7-14.
8. Wright NM, Metzger DL, Borowitz SM et al. Permanent neonatal diabetes mellitus and pancreatic exocrine insufficiency resulting from congenital pancreatic agenesis. Am J Dis Child 1993: 147: 607-609.
9. Stoffers DA, Zinkin NT, Stanojevic V et al. Pancreatic agenesis attributable to a single nucleotide deletion in the human IPF1 gene coding sequence. Nat Genet 1997: 15: 106-110.
10. Malecki MT, Jhala US, Antonellis A et al. Mutations in NEUROD1 are associated with the development of type 2 diabetes mellitus. Nat Genet 1999: 23: 323-328.
11. Rubio-Cabezas O, Minton JA, Kantor I et al. Homozygous mutations in NEUROD1 are responsible for a novel syndrome of permanent neonatal diabetes and neurological abnormalities. Diabetes 2010: 59: 2326-2331.

12. Neve B, Fernandez-Zapico ME, Ashkenazi-Katalan V et al. Role of transcription factor KLF11 and its diabetes-associated gene variants in pancreatic beta cell function. Proc Natl Acad Sci U S A 2005: 102: 4807-4812.
13. Raeder H, Johansson S, Holm PI et al. Mutations in the CEL VNTR cause a syndrome of diabetes and pancreatic exocrine dysfunction. Nat Genet 2006: 38: 54-62.
14. Plengvidhya N, Kooptiwut S, Songtawee N et al. PAX4 mutations in Thais with maturity onset diabetes of the young. J Clin Endocrinol Metab 2007: 92: 2821-2826.
15. Molven A, Ringdal M, Nordbø AM et al. Mutations in the insulin gene can cause MODY and autoantibody-negative type 1 diabetes. Diabetes 2008: 57: 1131-1135.
16. Støy J, Edghill EL, Flanagan SE et al. Insulin gene mutations as a cause of permanent neonatal diabetes. Proc Natl Acad Sci U S A 2007: 104: 15040-15044.
17. Edghill EL, Flanagan SE, Patch AM 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: 1034-1042.
18. Borowiec M, Liew CW, Thompson R et al. Mutations at the BLK locus linked to maturity onset diabetes of the young and beta-cell dysfunction. Proc Natl Acad Sci U S A 2009: 106: 14460-14465.
19. Prudente S, Jungtrakoon P, Marucci A et al. Loss-of-Function Mutations in APPL1 in Familial Diabetes Mellitus. Am J Hum Genet 2015: 97: 177-185.
20. Babenko AP, Polak M, Cavé H et al. Activating mutations in the ABCC8 gene in neonatal diabetes mellitus. N Engl J Med 2006: 355: 456-466.
21. Gloyn AL, Pearson ER, Antcliff JF et al. Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes. N Engl J Med 2004: 350: 1838-1849.
22. Vaxillaire M, Populaire C, Busiah K et al. Kir6.2 mutations are a common cause of permanent neonatal diabetes in a large cohort of French patients. Diabetes 2004: 53: 2719-2722.
23. Shaw-Smith C, De Franco E, Lango Allen H et al. GATA4 mutations are a cause of neonatal and childhood-onset diabetes. Diabetes 2014: 63: 2888-2894.
24. Garg V, Kathiriya IS, Barnes R et al. GATA4 mutations cause human congenital heart defects and reveal an interaction with TBX5. Nature 2003: 424: 443-447.
25. Balasubramanian M, Shield JP, Acerini CL et al. Pancreatic hypoplasia presenting with neonatal diabetes mellitus in association with congenital heart defect and developmental delay. Am J Med Genet A 2010: 152A: 340-346.
26. Yorifuji T, Kawakita R, Hosokawa Y et al. Dominantly inherited diabetes mellitus caused by GATA6 haploinsufficiency: variable intrafamilial presentation. J Med Genet 2012: 49: 642-643.
27. Flanagan SE, De Franco E, Lango Allen H et al. Analysis of transcription factors key for mouse pancreatic development establishes NKX2-2 and MNX1 mutations as causes of neonatal diabetes in man. Cell Metab 2014: 19: 146-154.
28. Bonnefond A, Vaillant E, Philippe J et al. Transcription factor gene MNX1 is a novel cause of permanent neonatal diabetes in a consanguineous family. Diabetes Metab 2013: 39: 276-280.
29. Sellick GS, Barker KT, Stolte-Dijkstra I et al. Mutations in PTF1A cause pancreatic and cerebellar agenesis. Nat Genet 2004: 36: 1301-1305.
30. Hoveyda N, Shield JP, Garrett C et al. Neonatal diabetes mellitus and cerebellar hypoplasia/agenesis: report of a new recessive syndrome. J Med Genet 1999: 36: 700-704.
31. Mitchell J, Punthakee Z, Lo B et al. Neonatal diabetes, with hypoplastic pancreas, intestinal atresia and gall bladder hypoplasia: search for the aetiology of a new autosomal recessive syndrome. Diabetologia 2004: 47: 2160-2167.
32. Chappell L, Gorman S, Campbell F et al. A further example of a distinctive autosomal recessive syndrome comprising neonatal diabetes mellitus, intestinal atresias and gall bladder agenesis. Am J Med Genet A 2008: 146A: 1713-1717.
33. Smith SB, Qu HQ, Taleb N et al. Rfx6 directs islet formation and insulin production in mice and humans. Nature 2010: 463: 775-780.
34. Mackay DJ, Temple IK. Transient neonatal diabetes mellitus type 1. Am J Med Genet C Semin Med Genet 2010: 154C: 335-342.
35. Mackay DJ, Callaway JL, Marks SM et al. Hypomethylation of multiple imprinted loci in individuals with transient neonatal diabetes is associated with mutations in ZFP57. Nat Genet 2008: 40: 949-951.
36. Senée V, Chelala C, Duchatelet S et al. Mutations in GLIS3 are responsible for a rare syndrome with neonatal diabetes mellitus and congenital hypothyroidism. Nat Genet 2006: 38: 682-687.
37. Dos Santos RS, Daures M, Philippi A et al. dUTPase (DUT) Is Mutated in a Novel Monogenic Syndrome With Diabetes and Bone Marrow Failure. Diabetes 2017: 66: 1086-1096.
38. Delépine M, Nicolino M, Barrett T et al. EIF2AK3, encoding translation initiation factor 2-alpha kinase 3, is mutated in patients with Wolcott-Rallison syndrome. Nat Genet 2000: 25: 406-409.
39. Moller DE, Cohen O, Yamaguchi Y et al. Prevalence of mutations in the insulin receptor gene in subjects with features of the type A syndrome of insulin resistance. Diabetes 1994: 43: 247-255.
40. Poulton CJ, Schot R, Kia SK et al. Microcephaly with simplified gyration, epilepsy, and infantile diabetes linked to inappropriate apoptosis of neural progenitors. Am J Hum Genet 2011: 89: 265-276.
41. Rubio-Cabezas O, Jensen JN, Hodgson MI et al. Permanent Neonatal Diabetes and Enteric Anendocrinosis Associated With Biallelic Mutations in NEUROG3. Diabetes 2011: 60: 1349-1353.
42. Pinney SE, Oliver-Krasinski J, Ernst L et al. Neonatal diabetes and congenital malabsorptive diarrhea attributable to a novel mutation in the human neurogenin-3 gene coding sequence. J Clin Endocrinol Metab 2011: 96: 1960-1965.
43. Wang J, Cortina G, Wu SV et al. Mutant neurogenin-3 in congenital malabsorptive diarrhea. N Engl J Med 2006: 355: 270-280.
44. Santer R, Schneppenheim R, Dombrowski A et al. Mutations in GLUT2, the gene for the liver-type glucose transporter, in patients with Fanconi-Bickel syndrome. Nat Genet 1997: 17: 324-326.
45. Yoo HW, Shin YL, Seo EJ et al. Identification of a novel mutation in the GLUT2 gene in a patient with Fanconi-Bickel syndrome presenting with neonatal diabetes mellitus and galactosaemia. Eur J Pediatr 2002: 161: 351-353.
46. Strom TM, Hörtnagel K, Hofmann S et al. Diabetes insipidus, diabetes mellitus, optic atrophy and deafness (DIDMOAD) caused by mutations in a novel gene (wolframin) coding for a predicted transmembrane protein. Hum Mol Genet 1998: 7: 2021-2028.
47. Amr S, Heisey C, Zhang M et al. A homozygous mutation in a novel zinc-finger protein, ERIS, is responsible for Wolfram syndrome 2. Am J Hum Genet 2007: 81: 673-683.
48. Riggs AC, Bernal-Mizrachi E, Ohsugi M et al. Mice conditionally lacking the Wolfram gene in pancreatic islet beta cells exhibit diabetes as a result of enhanced endoplasmic reticulum stress and apoptosis. Diabetologia 2005: 48: 2313-2321.
49. O'Brien L, Rinaldo P, Sims H et al. Fulminant hepatic failure associated with mutations in the medium and short chain L-3-hydroxyacyl-CoA dehydrogenase gene. J Inherit Metab Dis 2000: 127.
50. Molven A, Matre GE, Duran M et al. Familial hyperinsulinemic hypoglycemia caused by a defect in the SCHAD enzyme of mitochondrial fatty acid oxidation. Diabetes 2004: 53: 221-227.
51. Stanley CA, Lieu YK, Hsu BY et al. Hyperinsulinism and hyperammonemia in infants with regulatory mutations of the glutamate dehydrogenase gene. N Engl J Med 1998: 338: 1352-1357.
52. Miyajima H, Nishimura Y, Mizoguchi K et al. Familial apoceruloplasmin deficiency associated with blepharospasm and retinal degeneration. Neurology 1987: 37: 761-767.
53. Wildin RS, Ramsdell F, Peake J et al. X-linked neonatal diabetes mellitus, enteropathy and endocrinopathy syndrome is the human equivalent of mouse scurfy. Nat Genet 2001: 27: 18-20.
54. Rubio-Cabezas O, Minton JA, Caswell R et al. Clinical heterogeneity in patients with FOXP3 mutations presenting with permanent neonatal diabetes. Diabetes Care 2009: 32: 111-116.
55. Hussain K, Challis B, Rocha N et al. An activating mutation of AKT2 and human hypoglycemia. Science 2011: 334: 474.
56. Semple RK, Sleigh A, Murgatroyd PR et al. Postreceptor insulin resistance contributes to human dyslipidemia and hepatic steatosis. J Clin Invest 2009: 119: 315-322.