

Etiologic spectrum and clinical characteristics of pediatric diabetes among 276 children and adolescents with diabetes in a single academic center

Ja Hye Kim

Asan Medical Center

Yena Lee

Asan Medical Center

Yunha Choi

Asan Medical Center

Gu-Hwan Kim

Asan Medical Center

Han-Wook Yoo

Asan Medical Center

Jin-Ho Choi (✉ jhc@amc.seoul.kr)

Asan Medical Center, University of Ulsan College of Medicine <https://orcid.org/0000-0003-1196-7826>

Research article

Keywords: Maturity-onset diabetes of the young, Monogenic diabetes, Type 1 diabetes mellitus, Type 2 diabetes mellitus

Posted Date: October 7th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-76758/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Version of Record: A version of this preprint was published on March 4th, 2021. See the published version at <https://doi.org/10.1186/s12887-021-02575-6>.

Abstract

Background

The prevalence of monogenic diabetes is estimated to be 1–5% of patients with diabetes mellitus (DM). The overlapping clinical features of various forms of diabetes make differential diagnosis challenging. Therefore, this study investigated the etiologic distribution and clinical characteristics of pediatric diabetes, including monogenic diabetes, in a single tertiary center over the last 20 years.

Methods

This study included 276 consecutive patients with DM diagnosed before 18 years of age from January 2000 to December 2019. Clinical features, biochemical findings, β -cell autoantibodies, and molecular characteristics were reviewed retrospectively.

Results

Of the 276 patients, 206 patients (74.6%), 49 patients (17.8%), and 21 patients (7.6%) were diagnosed with type 1 DM, type 2 DM, and clinically suspected monogenic diabetes, respectively. Among 21 patients with suspected monogenic diabetes, 8 patients had clinical maturity-onset diabetes of the young (MODY), and the remaining 13 patients had other types of monogenic diabetes. Among them, genetic etiologies were identified in 14 patients (5.1%) from 13 families, which included MODY 5, transient neonatal DM, developmental delay, epilepsy, and neonatal diabetes (DEND) syndrome, Wolfram syndrome, Donohue syndrome, IPEX syndrome, Fanconi-Bickel syndrome, Wolcott-Rallison syndrome, cystic fibrosis-related diabetes, and maternally inherited diabetes and deafness.

Conclusions

Genetically confirmed monogenic diabetes accounts for 5.1% of patients referred to pediatric endocrinology clinics. The frequency of mutations in the major genes of MODY is low among pediatric patients in Korea. Identification of the genetic cause of DM is critical to provide appropriate therapeutic options and genetic counseling.

Background

Among children and adolescents with diabetes mellitus (DM), type 1 DM is the most common, especially in North America and Europe [1]. However, the annual incidence of type 1 DM varies according to the ethnic background, and worldwide incidence has increased in the past two decades [1–3]. In Korea, the annual incidence of type 1 DM increased from 1.36/100,000 in 1995–2000 to 3.19/100,000 in 2012–2014 [4]. In addition, increasing worldwide rates of child obesity have been associated with a variable increase in the prevalence of type 2 DM depending on the ethnic background and region of residence [2].

Monogenic diabetes is a single gene disorder caused by mutations in one of more than 20 genes that control either the secretion or action of insulin [5]. The prevalence of monogenic diabetes is estimated to be 1–6% among children and adolescents with DM in Europe [6–11].

It is important to make an accurate etiologic diagnosis of DM considering that it can affect the therapeutic decisions, the prognosis of chronic complications, and genetic counseling [12]. However, the overlapping clinical features of various forms of DM make it difficult to perform differential etiologic diagnosis. Information on the distribution of the type of DM and the prevalence of monogenic diabetes has not been established in the Korean pediatric population. A few studies of MODY in Korea demonstrated that mutations in the major MODY gene were rare including some cases with *GCK* mutations [13–16]. Therefore, this study was performed to investigate the etiologic distribution and clinical characteristics of pediatric diabetes including monogenic diabetes in a single tertiary center over the last 20 years.

Methods/design

Subjects

This study included 276 consecutive pediatric patients under the age of 18 years at diagnosis of DM between January 2000 and December 2019 in the Department of Pediatrics, Asan Medical Center Children's Hospital, Seoul, Korea. Patients with secondary DM due to steroid or immunosuppressant use were excluded in this study.

Clinical and endocrine characteristics such as the patients' age at diagnosis, gender, C-peptide level, presence of β -cell autoantibodies [glutamic acid decarboxylase (GAD) antibody and insulin autoantibody], and presence of diabetic ketoacidosis (DKA) at diagnosis were retrospectively reviewed.

Type 1 DM was diagnosed in the presence of low C-peptide level, β -cell autoantibody positivity, and the absence of acanthosis nigricans or any extra-pancreatic features suggesting monogenic diabetes. The diagnosis of type 2 DM was based on clinical findings such as a family history of type 2 DM, obesity, and signs of insulin resistance (acanthosis nigricans). The patients were categorized as having monogenic diabetes when they showed clinical features such as a family history of DM, absence of β -cell autoantibodies, normal or high C-peptide levels, a low-dose insulin requirement, and signs of extra-pancreatic features [12].

Four patients with monogenic diabetes previously reported by our group [17–20] were included to delineate the clinical and molecular spectrum of monogenic diabetes in our cohort. This study was approved by the Institutional Review Board of Asan Medical Center, Seoul, Korea (IRB No. 2020 – 0667). The blood samples for DNA analysis were collected after obtaining written informed consent from the patients or their parents. In pediatric patients aged 7–17 years, the informed consent was obtained from both a parent and the patients.

Molecular analysis for patients with monogenic diabetes

Molecular analysis was performed by Sanger sequencing for patients with a clinical diagnosis of monogenic diabetes according to the patients' phenotype. Sanger sequencing of the major genes (*HNF1A*, *HNF4A*, and *GCK* genes) involved in maturity-onset diabetes of the young (MODY) was performed for cases with clinically suspected MODY: 1) a family history of diabetes in one parent and first-degree relatives of that affected parent; 2) negative autoantibodies; 3) lack of the characteristics of type 2 DM (obesity and acanthosis nigricans); and 4)

good metabolic control with diet, sulfonylurea, or low-dose insulin [12]. In a case with defects of the urogenital tract, *HNF1B* was analyzed. DNA sequencing of *INSR* was performed for a patient with severe insulin resistance.

For patients with MODY, whole exome sequencing was performed when there were no rare sequence variants in the major MODY genes. SureSelect Human All Exon V5 (Agilent Technologies, Santa Clara, CA, USA) was used for library preparation. Sequencing was performed using the NextSeq500 platform (Illumina Inc., San Diego, CA, USA), generating 2 × 150 bp paired-end reads. The sequence reads were aligned to the human reference genome (hg19) using the Burrow-Wheeler Alignment program (BWA version 0.7.12). SAMtools 0.1.19 and Genome Analysis Toolkits (GATK version 3.5) were used for single nucleotide polymorphism variant calling from aligned sequence reads. GATK version 3.5, FreeBayes 0.9.2.1, and Scalpel 0.5.3 were used for insertion-deletion variant calling. After removing duplicates with PICARD (version 1.96, <https://broadinstitute.github.io/picard/>), annotation was performed using Variant Effect Predictor [21] and dbNSFP [22]. The sequence variants of known genes previously associated with MODY were scanned [23]. All sequence variants were classified as pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign, or benign, in accordance with the guidelines of the American College of Medical Genetics Laboratory Practice Committee Working Group [24].

Results

Clinical and molecular characteristics of patients with type 1 and type 2 DM

Of the 276 patients, 206 patients (74.6%) were diagnosed with type 1 DM, 49 patients (17.8%) were diagnosed with type 2 DM, and 21 patients (7.6%) were diagnosed with clinically suspected monogenic diabetes. The clinical characteristics at diagnosis of type 1 DM, type 2 DM, and monogenic diabetes are shown in Table 1.

Table 1
Clinical features of patients with diabetes mellitus (DM) at diagnosis

	Type 1 DM	Type 2 DM	MODY	Neonatal DM	CFRD	Genetic syndromes	MIDD
Patients, n (%)	206 (74.6)	49 (17.8)	8 (2.9)	2 (0.7)	2 (0.7)	6 (2.2)	3 (1.1)
Age at diagnosis, years	9.9 ± 3.8	13.7 ± 2.1	13.5 ± 2.8	0.1	10.6	2.1 ± 2.7	4.1 ± 0.9
BMI Z-score	-0.83 ± 1.22	2.59 ± 1.47	-0.33 ± 1.00	NA	0.45 ± 4.01	NA	-3.29 ± 2.05
HbA1c, %	12.1 ± 2.5	10.0 ± 2.0	9.7 ± 3.0	NA	6.9	9.4 ± 2.9	8.2 ± 2.8
C-peptide, ng/mL	0.9 ± 1.0	4.7 ± 2.7	2.2 ± 1.9	0.45	3.1	22.9 ± 38.8	6.3 ± 4.9
Antibody positivity, n (%)	137/190 (72.1)	7/49 (14.3)	0	0	0	0	0
DKA at diagnosis, n (%)	40 (19.4)	1 (2.0)	0	0	0	0	0
BMI, body mass index; CFRD, cystic fibrosis-related diabetes; DKA, diabetic ketoacidosis; MIDD, maternally inherited diabetes and deafness; NA, not available							

Of these 206 patients with type 1 DM, the mean age at diagnosis was 9.9 ± 3.8 years (median, 10.4 years; range, 0.8–17.6 years). The frequency of DKA at diagnosis in the type 1 DM group was 19.4% (40 patients). The β-cell autoantibodies of 190 patients were analyzed. Among them, 137 patients (72.1%) had at least one β-cell autoantibody. The mean serum C-peptide level at diagnosis was 0.9 ± 1.0 ng/mL (reference range, 0.48–3.3 ng/mL).

Among 49 patients with type 2 DM (17.8%), the mean age at diagnosis was 13.7 ± 2.1 years (median, 13.5 years; range, 8.0–16.8 years). The mean fasting serum C-peptide level (available for 44 patients) was 4.7 ± 2.7 ng/mL. DKA and hyperosmolar hyperglycemic state were observed at diagnosis in 1 patient (2.0%) with type 2 DM. Antibody positivity was 14.3% (7 patients) in the type 2 DM group.

Clinical and molecular characteristics of patients with genetically confirmed monogenic diabetes

Of the 276 patients, 21 patients (7.6%) were suspected to have monogenic diabetes: 8 patients had clinical MODY, and the remaining 13 patients had other types of monogenic diabetes. Among them, genetic etiologies were identified in 14 patients (5.1%) from 13 families (Table 2, Supplementary Table 1).

Table 2
Mutations in genes associated with monogenic diabetes

Gene	Nucleotide change	Amino acid change	Exon/Intron	Segregation data	ACMG/AMP guidelines	Phenotype
<i>HNF1B</i>	c.443C > T	p.S148L	1	NA	Pathogenic	MODY 5
<i>KCNJ11</i>	c.602G > A	p.R201H	1	NA	Pathogenic	DEND syndrome
<i>WFS1</i>	c.2171C > T	p.P724L	8	Sibling	Pathogenic	Wolfram syndrome
<i>WFS1</i>	c.1725_1742del	p.G587_G592del	8	Sibling	Likely pathogenic	Wolfram syndrome
<i>INSR</i>	c.3196C > T	p.R1066*	17	Paternal	Pathogenic	Donohue syndrome
<i>INSR</i>	c.3614C > T	p.Q1232*	21	Maternal	Pathogenic	Donohue syndrome
<i>FOXP3</i>	c.201 + 1G > A	Splice site	1	Maternal	Pathogenic	IPEX syndrome
<i>SLC2A2</i>	c.13A > T	p.K5*	1	NA	Pathogenic	Fanconi-Bickel syndrome
<i>EIF2AK3</i>	c.1293G > A	p.W431*	6	NA	Likely pathogenic	Wolcott-Rallison syndrome
<i>CFTR</i>	c.4056G > C	p.Q1352H	25	NA	Uncertain significance	CFRD
<i>CFTR</i>	c.1322T > C	p.L441P	10	NA	Uncertain significance	CFRD
<i>MTTL1</i>	m.3243A > G	Mitochondrial gene	Mitochondrial gene	NA	Pathogenic	MIDD
Bold , novel mutation; ACMG/AMP, interpretation according to the guidelines of the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) [24]; NA, not available.						

MODY. Eight patients were suspected to have clinical MODY. Their mean age at diagnosis was 13.5 ± 2.8 years (range, 9.4–18.5 years). All patients were non-obese with body mass index of 19.3 ± 1.3 kg/m² and normal serum C-peptide level at diagnosis (2.2 ± 1.9 ng/mL). A 14.6-year-old girl was diagnosed with MODY 5 with heterozygous mutations in *HNF1B* [c.443C > T (p.S148L) in exon 2], which was previously reported to be pathogenic [25]. She underwent renal transplantation at the age of 16.1 years because of chronic renal failure. Whole exome sequencing for the remaining 7 patients did not identify any rare sequence variants in the genes associated with monogenic diabetes.

Neonatal diabetes mellitus. Two patients were diagnosed with neonatal DM: one with a transient form caused by paternal uniparental disomy of 6q24 and the other with a permanent form with a heterozygous mutation [c.602G > A (p.R201H)] in *KCNJ11*, leading to developmental delay, epilepsy, and neonatal diabetes (DEND) syndrome [18].

The patient was initially misdiagnosed as having type 1 DM; however, insulin therapy was successfully switched to oral sulfonylurea therapy.

Wolfram syndrome. Two male siblings were initially misdiagnosed as having type 1 DM at the age of 4.9 and 6.1 years, respectively, until urinary incontinence and bilateral optic nerve atrophy occurred. They were compound heterozygous for a known pathogenic c.2171C > T (p.P724L) mutation [26] and a novel c.1725_1742del (p.G587_G592del) mutation in *WFS1*.

Donohue syndrome. A male newborn with acanthosis nigricans, hirsutism, high insulin level, and intrauterine growth retardation was compound heterozygous for c.3196C > T (p.R1066*) and c.3614C > T (p.Q1232*) in the tyrosine kinase domain of the β -subunit in *INSR* [19].

IPEX syndrome. The patient was initially misdiagnosed as having type 1 DM at the age of 11 months. However, he showed unusual clinical features including pure red cell aplasia and membranous glomerulopathy at the age of 39 months, and posterior reversible encephalopathy syndrome after a vaccination against influenza A (H1N1) virus at the age of 11 years. DNA analysis of the *FOXP3* gene identified a splice site mutation of c.201 + 1G > A, which was inherited from his mother [17].

Fanconi-Bickel syndrome. A 3-day-old female presented with hyperglycemia, glycosuria, and galactosemia. She failed to grow during the follow-up period, and her liver function deteriorated with micronodular cirrhosis and marked fatty changes on liver biopsy. Homozygous mutation of c.13A > T (p.K5*) in exon 1 was identified by Sanger sequencing of *SLC2A2* [20].

Wolcott-Rallison syndrome. A 3-month-old Arab girl presented with neonatal DM, epiphyseal dysplasia, and liver failure and was diagnosed with Wolcott-Rallison syndrome caused by the pathogenic homozygous mutation of c.1293G > A (p.W431*) in *EIF2AK3*, which was previously reported to be pathogenic [27].

Cystic fibrosis-related diabetes. Cystic fibrosis-related diabetes was detected in two patients with *CFTR* mutations. They showed pancreatitis-related hyperglycemia at the age of 7.7 and 14.2 years, respectively, without β -cell autoantibodies.

Maternally inherited diabetes and deafness (MIDD). Three patients with m.3243A > G mutation in *MTTL1* were diagnosed as having MIDD with an HbA1c level of $8.2 \pm 2.8\%$ without β -cell autoantibodies. All patients have been treated with insulin injection.

Discussion

This study described the clinical characteristics of different types of DM based on the experience of a single tertiary center over the last 20 years. Type 1 DM accounted for most cases (74.6%) of DM in our cohort, followed by type 2 DM (17.8%). Genetic etiologies were confirmed in 14 patients (5.1%) from 13 families. Diverse genetic etiologies underlie in pediatric monogenic diabetes, and extra-pancreatic features are an important clue to the diagnosis of monogenic diabetes.

The frequencies of type 1 DM, type 2 DM, and MODY were 85.6%, 10.8%, and 1.2%, respectively, in the SEARCH study (USA); on the other hand, these ratios were 95.5%, 1.3%, and 1.5%, respectively, in the SWEET study (Europe) [28–30]. The diagnosis of type 2 DM (17.8%) and genetically confirmed monogenic diabetes (5.1%) was more

common in the present study compared with the previous studies. The variation in the frequencies could be explained by the availability of genetic testing and the prevalence of obesity in the region. Antibody positivity has been reported in up to 15% of patients with type 2 DM, and these autoantibody-positive patients are usually younger, less overweight/obese, and have higher hemoglobin A1c levels [31]. However, there were no significant differences in our study.

Monogenic diabetes comprises various phenotypes including neonatal DM, MODY, and rare syndromic diabetes with extra-pancreatic features including neurological, renal, intestinal, or skeletal abnormalities [5]. Therefore, monogenic diabetes might be initially misdiagnosed as type 1 or type 2 DM before the manifestation of extra-pancreatic features, as in the case of the patients with Wolfram syndrome, DEND syndrome, and IPEX syndrome in our study. Establishing the etiology of DM is important for therapeutic strategies, the prognosis of chronic complications [12], and appropriate genetic counseling for monogenic diabetes [5]. For example, the molecular diagnosis of monogenic diabetes can lead to changes in treatment often with improved glycemic control as some patients with monogenic diabetes carrying mutations in specific genes (e.g., *HNF1A*, *HNF4A*, *KCNJ11*, and *ABCC8*) can be treated with oral sulfonylureas instead of insulin [32].

MODY is defined as an autosomal dominantly inherited familial form of non-autoimmune diabetes due to a primary defect in pancreatic β -cell function with an age of onset before 25 years [33]. Mutations in 14 different genes are known to be associated with MODY [<https://www.omim.org/entry/606391>, accessed on August 2020]. Among them, mutations in *HNF4A*, *HNF1A*, and *GCK* are the most common causes of MODY [34]. The prevalence of MODY has been estimated to be 1–2% of cases of DM [35]. In an Italian study, MODY represented the second most prevalent cause (5.5%) of DM after type 1 DM; however, mutations in MODY-related genes were documented in approximately 1.85% of patients [7]. In Asian countries, sequence variants in MODY genes were identified in 15–19% of patients with clinically diagnosed MODY in India [36, 37]. Among them, *HNF1A* or *ABCC8* mutations were the most common [37]. The frequency of mutations in the major MODY genes (*HNF4A*, *GCK*, and *HNF1A*) has been shown to be extremely low among Korean patients with MODY [15]. However, with the advent of next-generation sequencing, genetic diagnostic rate of MODY has been increased. In 28 patients with early onset diabetes in Korea, four pathogenic or likely pathogenic variants were identified in three patients by whole exome sequencing [38]. In targeted panel sequencing, molecular genetic diagnosis was possible in 21.1% of patients among 109 patients with clinically suspected monogenic cause of diabetes [39].

The prevalence of MODY is dependent on the active referral of patients with highly probable MODY, indicating that some patients with MODY remain underdiagnosed [40]. Childhood type 2 DM can be confused with MODY due to a family history, presenting features, and a possible confounding factor of obesity/overweight [9]. Furthermore, MODY, especially in cases involving *HNF1A* mutations, can be misclassified as type 1 DM [7].

A limitation of this study is that it is not a national multicenter study, and it included data from a single tertiary center. Therefore, the frequency of specific types of DM may not reflect the actual frequency. As this study investigated etiologic distribution of DM in pediatric patients and included consecutive patients under 18 years of age at diagnosis who were referred to a pediatric endocrinology clinic in a single institute, the actual frequency of DM including MODY could not be estimated because of sampling bias.

Conclusions

This study showed that genetically confirmed monogenic diabetes accounts for 5.1% of patients referred to pediatric endocrinology clinics. The frequency of mutations in the major genes of MODY is low among pediatric patients in Korea. Healthcare providers should consider that diabetic patients with a family history or extra-pancreatic features without β -cell autoantibodies might have monogenic diabetes.

Abbreviations

DEND: developmental delay, epilepsy, and neonatal diabetes; DKA: diabetic ketoacidosis; DM: diabetes mellitus; GAD: glutamic acid decarboxylase; MIDD: maternally inherited diabetes and deafness; MODY: maturity-onset diabetes of the young; VUS: variant of uncertain significance

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Asan Medical Center, Seoul, Korea (IRB No. 2020-0667). Sanger sequencing and whole exome sequencing were performed after obtaining written informed consent from patients or their parents. In pediatric patients aged 7–17 years, the informed consent was obtained from both a parent and the patients. When the clinical data were obtained retrospectively without molecular analysis, informed consent was waived by the IRB.

Consent for publication

Not applicable

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

Whole exome sequencing in this study was supported by a grant (2018-481) from Asan Medical Center Children's Hospital, Seoul, Korea.

Author contributions

JHK and JHC designed the study and wrote the manuscript; YL, YC, GHK, and HWY collected the data and involved in data analysis. All the authors made final corrections and approved the manuscript.

Acknowledgements

Not applicable

References

1. Maahs DM, West NA, Lawrence JM, Mayer-Davis EJ. Epidemiology of type 1 diabetes. *Endocrinol Metab Clin North Am.* 2010;39(3):481–97.
2. Patterson C, Guariguata L, Dahlquist G, Soltesz G, Ogle G, Silink M. Diabetes in the young - a global view and worldwide estimates of numbers of children with type 1 diabetes. *Diabetes Res Clin Pract.* 2014;103(2):161–75.
3. Patterson CC, Dahlquist GG, Gyurus E, Green A, Soltesz G, Group ES. Incidence trends for childhood type 1 diabetes in Europe during 1989–2003 and predicted new cases 2005-20: a multicentre prospective registration study. *Lancet.* 2009;373(9680):2027–33.
4. Kim JH, Lee CG, Lee YA, Yang SW, Shin CH. Increasing incidence of type 1 diabetes among Korean children and adolescents: analysis of data from a nationwide registry in Korea. *Pediatr Diabetes.* 2016;17(7):519–24.
5. Vaxillaire M, Bonnefond A, Froguel P. The lessons of early-onset monogenic diabetes for the understanding of diabetes pathogenesis. *Best Pract Res Clin Endocrinol Metab.* 2012;26(2):171–87.
6. Haliloglu B, Abali S, Bugrul F, Celik E, Bas S, Atay Z, Guran T, Turan S, Bereket A. The Distribution of Different Types of Diabetes in Childhood: A Single Center Experience. *J Clin Res Pediatr Endocrinol.* 2018;10(2):125–30.
7. Delvecchio M, Mozzillo E, Salzano G, Iafusco D, Frontino G, Patera PI, Rabbone I, Cherubini V, Grasso V, Tinto N, et al. Monogenic Diabetes Accounts for 6.3% of Cases Referred to 15 Italian Pediatric Diabetes Centers During 2007 to 2012. *J Clin Endocrinol Metab.* 2017;102(6):1826–34.
8. Malachowska B, Borowiec M, Antosik K, Michalak A, Baranowska-Jazwiecka A, Deja G, Jarosz-Chobot P, Brandt A, Mysliwiec M, Stelmach M, et al. Monogenic diabetes prevalence among Polish children-Summary of 11 years-long nationwide genetic screening program. *Pediatr Diabetes.* 2018;19(1):53–8.
9. Mozzillo E, Salzano G, Barbetti F, Maffei C, Lombardo F, Franzese A, Delvecchio M, Marigliano M. Survey on etiological diagnosis of diabetes in 1244 Italian diabetic children and adolescents: impact of access to genetic testing. *Diabetes Res Clin Pract.* 2015;107(3):e15–8.
10. Fendler W, Borowiec M, Baranowska-Jazwiecka A, Szadkowska A, Skala-Zamorowska E, Deja G, Jarosz-Chobot P, Techmanska I, Bautembach-Minkowska J, Mysliwiec M, et al. Prevalence of monogenic diabetes amongst Polish children after a nationwide genetic screening campaign. *Diabetologia.* 2012;55(10):2631–5.
11. Irgens HU, Molnes J, Johansson BB, Ringdal M, Skrivarhaug T, Undlien DE, Sovik O, Joner G, Molven A, Njolstad PR. Prevalence of monogenic diabetes in the population-based Norwegian Childhood Diabetes Registry. *Diabetologia.* 2013;56(7):1512–9.
12. Hattersley AT, Greeley SAW, Polak M, Rubio-Cabezas O, Njolstad PR, Mlynarski W, Castano L, Carlsson A, Raile K, Chi DV, et al. ISPAD Clinical Practice Consensus Guidelines 2018: The diagnosis and management of monogenic diabetes in children and adolescents. *Pediatr Diabetes.* 2018;19(Suppl 27):47–63.
13. Cho YK, Cho EH, Choi HS, Kim SW. Novel deletion mutation in the glucokinase gene from a Korean man with GCK-MODY phenotype and situs inversus. *Diabetes Res Clin Pract.* 2018;143:263–6.
14. Cho EH, Min JW, Choi SS, Choi HS, Kim SW. Identification of Maturity-Onset Diabetes of the Young Caused by Glucokinase Mutations Detected Using Whole-Exome Sequencing. *Endocrinol Metab (Seoul).* 2017;32(2):296–301.
15. Hwang JS, Shin CH, Yang SW, Jung SY, Huh N. Genetic and clinical characteristics of Korean maturity-onset diabetes of the young (MODY) patients. *Diabetes Res Clin Pract.* 2006;74(1):75–81.

16. Lee HJ, Ahn CW, Kim SJ, Song YD, Lim SK, Kim KR, Lee HC, Huh KB. Mutation in hepatocyte nuclear factor-1alpha is not a common cause of MODY and early-onset type 2 diabetes in Korea. *Acta Diabetol.* 2001;38(3):123–7.
17. Bae KW, Kim BE, Choi JH, Lee JH, Park YS, Kim GH, Yoo HW, Seo JJ. A novel mutation and unusual clinical features in a patient with immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome. *Eur J Pediatr.* 2011;170(12):1611–5.
18. Cho JH, Kang E, Lee BH, Kim GH, Choi JH, Yoo HW. DEND Syndrome with Heterozygous KCNJ11 Mutation Successfully Treated with Sulfonylurea. *J Korean Med Sci.* 2017;32(6):1042–5.
19. Choi JH, Kang M, Kim JH, Cho J, Kim GH, Yoo HW. Identification and Functional Characterization of Two Novel Nonsense Mutations in the beta-Subunit of INSR That Cause Severe Insulin Resistance Syndrome. *Horm Res Paediatr.* 2015;84(2):73–8.
20. Yoo HW, Shin YL, Seo EJ, Kim GH. 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(6):351–3.
21. McLaren W, Gil L, Hunt SE, Riat HS, Ritchie GR, Thormann A, Flicek P, Cunningham F. The Ensembl Variant Effect Predictor. *Genome Biol.* 2016;17(1):122.
22. Liu X, Wu C, Li C, Boerwinkle E. dbNSFP v3.0: A One-Stop Database of Functional Predictions and Annotations for Human Nonsynonymous and Splice-Site SNVs. *Hum Mutat.* 2016;37(3):235–41.
23. Shim YJ, Kim JE, Hwang SK, Choi BS, Choi BH, Cho EM, Jang KM, Ko CW. Identification of Candidate Gene Variants in Korean MODY Families by Whole-Exome Sequencing. *Horm Res Paediatr.* 2015;83(4):242–51.
24. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med.* 2015;17(5):405–24.
25. Edghill EL, Bingham C, Ellard S, Hattersley AT. Mutations in hepatocyte nuclear factor-1beta and their related phenotypes. *J Med Genet.* 2006;43(1):84–90.
26. Inoue H, Tanizawa Y, Wasson J, Behn P, Kalidas K, Bernal-Mizrachi E, Mueckler M, Marshall H, Donis-Keller H, Crock P, et al. A gene encoding a transmembrane protein is mutated in patients with diabetes mellitus and optic atrophy (Wolfram syndrome). *Nat Genet.* 1998;20(2):143–8.
27. Rubio-Cabezas O, Patch AM, Minton JA, Flanagan SE, Edghill EL, Hussain K, Balafrej A, Deeb A, Buchanan CR, Jefferson IG, et al. Wolcott-Rallison syndrome is the most common genetic cause of permanent neonatal diabetes in consanguineous families. *J Clin Endocrinol Metab.* 2009;94(11):4162–70.
28. Pettitt DJ, Talton J, Dabelea D, Divers J, Imperatore G, Lawrence JM, Liese AD, Linder B, Mayer-Davis EJ, Pihoker C, et al. Prevalence of diabetes in U.S. youth in 2009: the SEARCH for diabetes in youth study. *Diabetes Care.* 2014;37(2):402–8.
29. Pacaud D, Schwandt A, de Beaufort C, Casteels K, Beltrand J, Birkebaek NH, Campagnoli M, Bratina N, Limbert C, Mp O'Riordan S, et al. A description of clinician reported diagnosis of type 2 diabetes and other non-type 1 diabetes included in a large international multicentered pediatric diabetes registry (SWEET). *Pediatr Diabetes.* 2016;17(Suppl 23):24–31.
30. Pihoker C, Gilliam LK, Ellard S, Dabelea D, Davis C, Dolan LM, Greenbaum CJ, Imperatore G, Lawrence JM, Marcovina SM, et al. Prevalence, characteristics and clinical diagnosis of maturity onset diabetes of the

- young due to mutations in HNF1A, HNF4A, and glucokinase: results from the SEARCH for Diabetes in Youth. *J Clin Endocrinol Metab*. 2013;98(10):4055–62.
31. Zeitler P. Approach to the obese adolescent with new-onset diabetes. *J Clin Endocrinol Metab*. 2010;95(12):5163–70.
 32. Pearson ER, Flechtner I, Njolstad PR, Malecki MT, Flanagan SE, Larkin B, Ashcroft FM, Klimes I, Codner E, Iotova V, et al. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. *N Engl J Med*. 2006;355(5):467–77.
 33. Molven A, Njolstad PR. Role of molecular genetics in transforming diagnosis of diabetes mellitus. *Expert Rev Mol Diagn*. 2011;11(3):313–20.
 34. Ellard S, Bellanne-Chantelot C, Hattersley AT, European Molecular Genetics Quality Network Mg. Best practice guidelines for the molecular genetic diagnosis of maturity-onset diabetes of the young. *Diabetologia*. 2008;51(4):546–53.
 35. Fajans SS, Bell GI. MODY: history, genetics, pathophysiology, and clinical decision making. *Diabetes Care*. 2011;34(8):1878–84.
 36. Chapla A, Mruthyunjaya MD, Asha HS, Varghese D, Varshney M, Vasani SK, Venkatesan P, Nair V, Mathai S, Paul TV, et al. Maturity onset diabetes of the young in India - a distinctive mutation pattern identified through targeted next-generation sequencing. *Clin Endocrinol (Oxf)*. 2015;82(4):533–42.
 37. Mohan V, Radha V, Nguyen TT, Stawiski EW, Pahuja KB, Goldstein LD, Tom J, Anjana RM, Kong-Beltran M, Bhangale T, et al. Comprehensive genomic analysis identifies pathogenic variants in maturity-onset diabetes of the young (MODY) patients in South India. *BMC Med Genet*. 2018;19(1):22.
 38. Kwak SH, Jung CH, Ahn CH, Park J, Chae J, Jung HS, Cho YM, Lee DH, Kim JI, Park KS. Clinical whole exome sequencing in early onset diabetes patients. *Diabetes Res Clin Pract*. 2016;122:71–7.
 39. Park SS, Jang SS, Ahn CH, Kim JH, Jung HS, Cho YM, Lee YA, Shin CH, Chae JH, Kim JH, et al: **Identifying Pathogenic Variants of Monogenic Diabetes Using Targeted Panel Sequencing in an East Asian Population.** *J Clin Endocrinol Metab* 2019.
 40. Shields BM, Hicks S, Shepherd MH, Colclough K, Hattersley AT, Ellard S. Maturity-onset diabetes of the young (MODY): how many cases are we missing? *Diabetologia*. 2010;53(12):2504–8.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementarytable.docx](#)