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Molecular Case Studies

VARIANT DISCREPANCY RESOLUTION

Novel pathogenic *PDX1* gene variant in a Korean family with maturity-onset diabetes of the young

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Abstract The diagnosis of maturity-onset diabetes of the young (MODY), a monogenic form of diabetes mellitus caused by a mutation in a single gene, is often uncertain until genetic testing is performed. We report a 13-yr-old Korean boy who was initially diagnosed with type 2 diabetes (T2DM). MODY was suspected because of his nonobese body habitus and family history of multiple affected members. Targeted panel sequencing of all MODY-related genes was performed using the NextSeq 550Dx platform (Illumina). Sanger sequencing was performed using blood samples from the parents, siblings, and other relatives. A frameshift variant in the 3′ region of the last exon of *PDX1* was detected in the patient and his family members with diabetes. PP1_Moderate criterion was applied and this variant was confirmed to be the genetic cause of diabetes in the family and classified as likely pathogenic. The study highlights the importance of genetic testing for nonobese, early-onset diabetic patients with multiple affected family members. Increased awareness and aggressive genetic testing for MODY are needed.

[Supplemental material is available for this article.]

CASE PRESENTATION

Maturity-onset diabetes of the young (MODY) is a type of monogenic diabetes mellitus (DM) caused by a mutation in a single gene that affects the function of pancreatic β cells. The minimum prevalence of MODY in the United Kingdom is estimated to be as high as 68–108 cases per 1,000,000 population (Kleinberger and Pollin 2015; Shepherd et al. 2016). Several MODY genes have been identified, which are divided into different categories according to their molecular pathogenesis (Nkonge et al. 2020): transcriptional regulatory disorders (*HNF4A*, *HNF1A*, *PDX1*, and *HNF1B*) (Yamagata et al. 1996a, 1996b; Horikawa et al. 1997; Stoffers et al. 1997), enzyme disorders (*GCK*) (Froguel et al. 1992), protein misfolding disorders (*CEL* and *INS*) (Raeder et al. 2006; Stoy et al. 2007; Edghill et al. 2008), and ion channel disorders (*ABCC8* and *KCNJ11*) (Gloyn et al. 2004; Bowman et al. 2012). MODY differs from typical type 1 or type 2 DM (T1DM or T2DM) in its therapeutic approach. However, diagnosis of MODY is regarded with uncertainty by clinicians, until genetic testing is performed to confirm the diagnosis. Herein, we performed family screening for assessment of the pathogenicity of a rare pancreatic and duodenal homeobox 1 (*PDX1*) variant.

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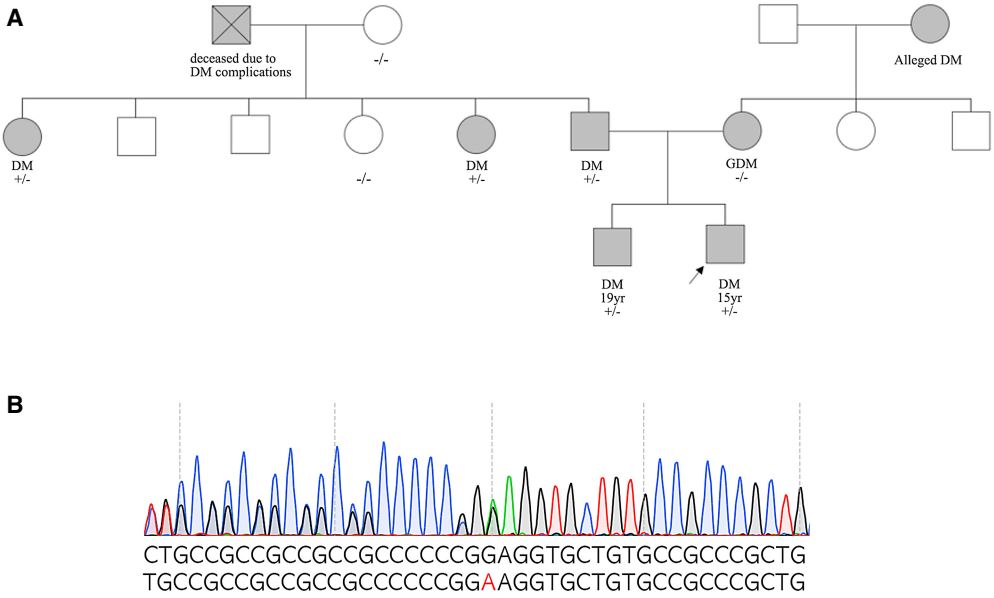

Figure 1. (*A*) Pedigree of the family. The proband is indicated using an arrow. Diabetic patients are indicated using filled symbols. (*B*) Electropherogram of c.735dup variant using a reverse primer. (GDM) Gestational DM, (–/–) wild type, (+/–) heterozygous for the pathogenic variant.

A 13-yr-old boy visited our outpatient clinic for investigation of DM. At the age of 10 yr and 4 mo, high blood glucose level was incidentally detected in a school checkup, and he was diagnosed to have T2DM at a hospital. The initial fasting plasma glucose, glycated hemoglobin (HbA1C), and fasting and 2-h-postprandial C-peptide levels were 188 mg/dL, 7.2%, 4.4 ng/mL, and 9.5 ng/mL, respectively. Islet-related autoantibodies, including anti-islet cell antibodies and insulin antibodies, were not detected in the blood. Despite 2 yr and 7 mo of metformin monotherapy, his HbA1c level was consistently >7.0%. At the time of the visit, his height was 169.7 cm (90–95th percentile), weight 68.7 kg (90–95th percentile), and body mass index (BMI) 23.9 kg/m^2 (75–90th percentile). He had a family history of multiple affected members across three generations, including an elder brother, father, grandfather, and two aunts (Fig. 1). His elder brother (BMI 24.3 kg/m^2) and his father (BMI 21.6 kg/m^2) were diagnosed with DM at the age of 14 and 35, respectively. His mother (BMI 22.2 kg/m^2) had developed gestational DM and diagnosed with DM at the age of 33. His elder brother and parents were being treated with oral antihyperglycemic agents. According to the Exeter MODY probability calculator, which was developed on a White European population (Shields et al. 2012), the probability of being MODY was 75.5% for both the proband and his elder brother, respectively. Genetic testing was performed as the patient was suspected to have MODY. Targeted panel sequencing of all MODY-related genes was performed using the NextSeq 550Dx platform (Illumina), sequenced to cover >97% of targets at >20× (Supplemental Table). Sanger sequencing was performed using blood samples from the parents, siblings, and other relatives.

VARIANT INTERPRETATION

The *PDX1* gene not only determines the fate of pancreatic cells during embryogenesis, but also plays a role in β-cell maintenance in adults (Colarusso and Zhou 2022). The PDX1 protein

Table 1. Details of pathogenic variant identified

Gene	Chromosome	HGVS DNA reference	HGVS protein reference	Variant type	Predicted effect	dbSNP/ dbVar ID	Genotype	ClinVar ID	Parent of origin
PDX1	13	c.735dup NM_000209.4	p.Gly246Argfs*21 NP_000200.1	Frameshift	Frameshift	N/A	Heterozygous	SCV00393234	Paternal

is composed of a transactivation domain and a homeodomain, and amino acid mutations in the vicinity of these domains lead to the development of MODY (Zubkova et al. 2019; Yoshiji et al. 2022). The frameshift variant (NM_000209.4:c.735dup[p.Gly246Argfs*21]) detected in this study was located at the 3′ end of the last exon of *PDX1* gene, because of which it was predicted that nonsense-mediated decay was hindered (Table 1). The variant was predicted to result in a <10% decrease in the total protein (PVS1_Moderate); however, this evidence was insufficient to prove its pathogenicity (Abou Tayoun et al. 2018). Recently, the same variant was reported from South Korea (Park et al. 2022), though enough evidence about its pathogenicity was not presented. Because null variants containing mutations downstream from the base position 735 that result in the occurrence of MODY have not been reported previously, we examined the allelic segregation pattern of this variant to validate its pathogenicity.

Sanger sequencing results revealed the same heterozygous frameshift variant of *PDX1* present in the symptomatic father and the elder brother, but not in the mother (Fig. 1A,B). It was also detected in two symptomatic paternal aunts with diabetes. The family members without diabetes, including the grandmother and the second aunt, were confirmed to be negative for this variant. For screening of the family members, the PP1_Moderate criterion was applied because the variant identified was observed to have segregated during more than four meioses in the family. Also, the variant was extremely rare in the general gnomAD population (PM2_Supporting), but interestingly, it was identified as a heterozygote in a male, 60- to 65-yr-old of Korean ancestry. In addition, PP4 was applied based on the calculated score of 75.5% on the Exeter MODY probability calculator. To conclude, the variant was classified as likely pathogenic. These data are now available in ClinVar (SCV003932341).

SUMMARY

The frameshift variant that resides in the 3′ region of the last exon of *PDX1* was confirmed to be the genetic cause of diabetes in this family, with a possibility of a dominant negative effect. For screening of the family members, the PP1_Moderate criterion was applied. Along with PVS1_Moderate, PM2_Supporting, and PP4, it was classified as likely pathogenic. Because all the reported alleles were detected in Koreans, this variant may be causing a disease-causing founder effect in the Korean population.

ADDITIONAL INFORMATION

Database Deposition and Access

The variant was submitted to ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) and can be found under accession number SCV003932341.

Ethics Statement

The Institutional Review Board of Seoul National University Bundang Hospital approved the study (IRB No.: B-2201-733-302). Written informed consent was obtained from all participants.

Competing Interest Statement

The authors have declared no competing interest.

Referees

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Author Contributions

H.K. and S.H.S. performed genetic testing and reclassified the variant. H.Y.K. and J.H.K. provided the clinical information. H.K. and H.Y.K. participated in manuscript preparation. S.H.S. and K.U.P. designed the study and reviewed the manuscript.

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