Identification of Novel Candidate Gene Variants in Korean MODY Families by Whole Exome Sequencing

Eun Mi Cho, Ye Jee Shim and Cheol Woo Ko
Pediatrics, Kyungpook National University School of Medicine, Daegu, Republic of Korea.

Background & Aims

Maturity-onset diabetes of the young (MODY) is one of monogenic diabetes mellitus caused by a single gene defect. To date, thirteen MODY genes have been identified worldwide. However, there is a big discrepancy in the genetic locus between Asian and Caucasian patients with MODY. Thus we conducted whole exome sequencing in Korean MODY families to identify novel candidate gene variants.

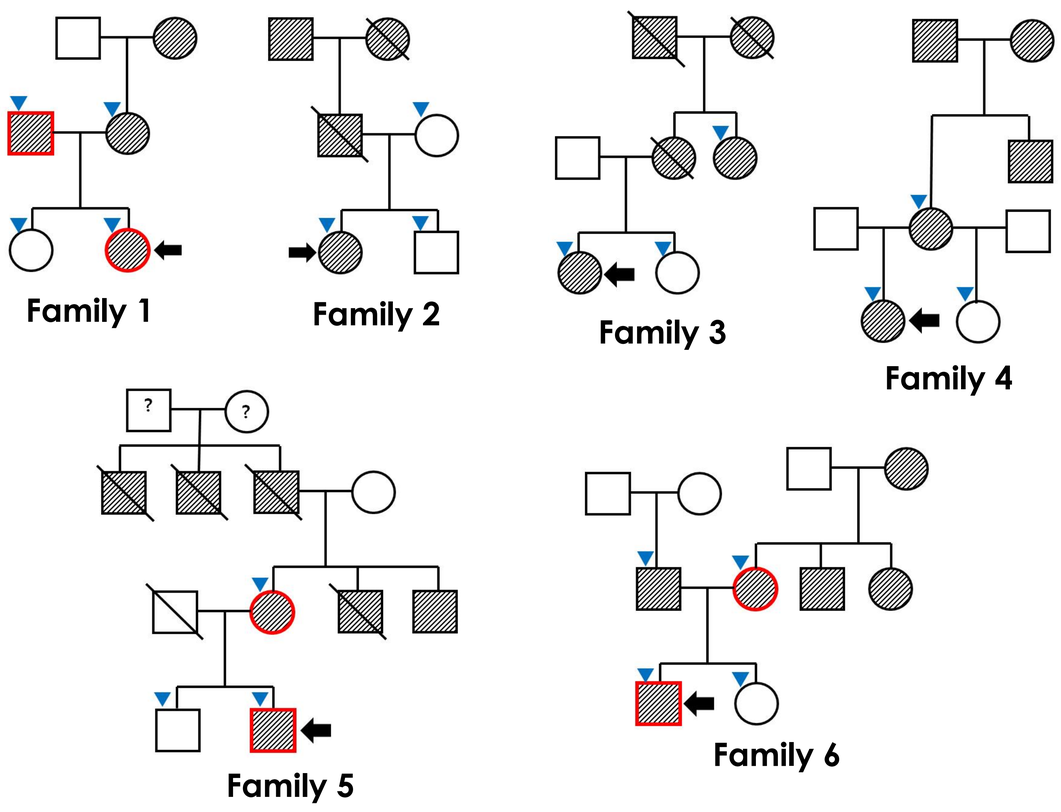

Figure 1. Partial pedigrees of the six MODY families involved in this study. Black arrows indicate respective probands in each family. Blue inverted triangles denote the family members whose blood sampling was available. Red bordered individuals means the subjects who shared common variant among the candidate genes of MODY and not in other family members.

Methods

Six MODY probands and their family members were included for whole exome sequencing. Variants in dbSNP135 and TIARA database for Korean and the variants with minor allele frequencies > 0.5% of 1000g were excluded. We selected only the functional variants (gain of stop codon, frameshifts and nonsynonymous SNVs) and conducted a case-control comparison in the family members. Finally, the selected variants were scanned for the previously introduced gene set implicated in glucose metabolism. This are the genes with an essential role in pancreatic beta cells, genes previously known to cause monogenic diabetes or associated syndromes and genes from the genome wide association data of type 2 diabetes. The corresponding genomic regions were validated by Sanger sequencing. The finally selected candidate variants were verified by the *in silico* analysis database, PROVEAN, SIFT, and Polyphen-2.

Results

Three variants c.620C>T; p.Thr207Ile in *PTPRD*, c.559C>G; p.Gln187Glu in *SYT9* and c.1526T>G; p.Val509Gly in *WFS1* were respectively identified in three families. We could not find any disease causative alleles of known MODY 1-13 genes. A summary of the results of exome sequencing and the process of variants reduction are described in Table 1 for all MODY probands.

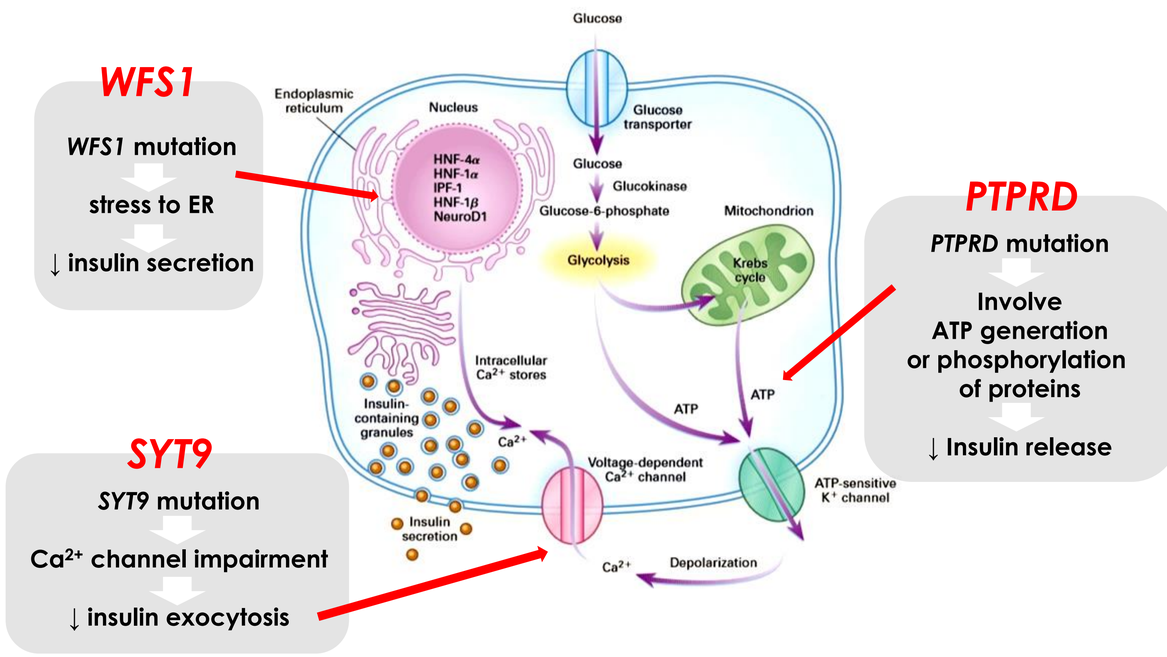

Table 1. Results of whole exome sequencing of six MODY probands and the process of variants reduction.

Family	1	2	3	4	5	6
Subject	Proband	Proband	Proband	Proband	Proband	Proband
Exonic regions	20,178	19,891	20,044	18,981	19,859	19,971
After filtering*	468	470	428	481	476	463
Functional variants†	250	224	224	235	238	243
Case-control comparison	98 43 paternal 55 maternal	51	31	52	63	120 60 paternal 60 maternal
In interested genes‡	Val509Gly *In WFS1* (paternal side)	.	.	.	Gln187Glu *In SYT9*	Thr207Ile *In PTPRD* (maternal side)
PROVEN	Deleterious				Neutral	Deleterious
SIFT	Tolerated				Tolerated	Damaging
Polyohen-2	Benign				Benign	Possibly damaging

***The variants with the frequency ≤ 0.5% in 1000g and not in dbSNP135 and TIARA database.**
† gain of stop codon, frameshifts, and nonsynonymous SNVs.
‡The previously introduced gene set implicated in glucose metabolism. This are the genes with an essential role in pancreatic beta cells, genes previously known to cause monogenic diabetes or associated syndromes and genes from the genome wide association data of type 2 diabetes.

Conclusion

We concluded that Thr207Ile in *PTPRD* is pathogenic for causing MODY in family 6. Because family 1 shows a strong maternal history of diabetes, an offspring study will be necessary for Val509Gly in *WFS1* in the future. Further evaluation is necessary about the role of *PTPRD, SYT9* and *WFS1* in normal insulin release from pancreatic beta cells.