부산대학교 어린이병원
Pusan National University Children's Hospital

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Identification of six novel mutations in monogenic diabetes and congenital hyperinsulinism detected by targeted-exome sequencing in Korea

Chong Kun Cheon, Ju Young Yoon
Department of Pediatrics, Pusan National University Children's Hospital, Pusan National University School of Medicine, Yangsan, Korea

Introduction

- Monogenic diabetes and congenital hyperinsulinism (CHI) and are common disorders of glucose-regulated insulin secretion in childhood, with 13 causative genes known for MODY and 10 causative genes identified for CHI.
- Genetic testing for monogenic diabetes and CHI is important for patient care.

Objectives

- The aim of this study was to delineate genetic and clinical manifestations of monogenic diabetes and CHI diagnosed by targeted-exome sequencing (TES).

Materials and Methods

- Nine probands and their family members (7 monogenic diabetes and 2 CHI) were included. We conducted TES in 7 clinical CHI and monogenic diabetes families to identify genetic variants in Korea.
- Variants in the dbSNP135 and TIARA databases for Koreans and the variants with minor allele frequencies >0.5% of the 1000 Genomes database were excluded.
- We selected only the functional variants and conducted a case-control comparison in the family members.
- The selected variants were scanned for the previously introduced gene set implicated in glucose metabolism

Results

Among the 5 patients with suspected maturity-onset diabetes of the young (MODY), 2 different MODY were identified in the three patients, and the diagnostic yield was 60%. We identified two novel mutations [C.1088C>T (Ala363Val) and c.1127T>C (Met376Thr)] in *HNF4A* gene causing MODY1. All the novel *HNF4A* mutation carriers were successfully transferred from insulin to sulfonylurea. A novel splicing mutation [c.538+8G>C] in *PAX4* gene was identified in a family with MODY9. A novel *PAX4* mutation carrier had a good clinical response when switched from insulin to diet. We also identified a novel variant in potentially candidate gene implicated in susceptibility to diabetes, albeit thus far not in an autosomal dominant mode of inheritance: *NOTCH2*. One of two families with neonatal diabetes showed a compound heterozygous mutation, c.2978C>A (Ala993Asp) and C.356C>T (Ala119Val), the latter of which is a novel mutation, in *INSR* gene who required metformin treatment. The other one showing persistent neonatal diabetes had a missense mutation, c.605G>A (Arg201His), which is a reported mutation, in *KCNJ11* gene, who required sulfonylurea such as glibenclamide. In two families with CHI two novel heterozygous mutations was identified: c.4237C>T (Pro1413Ser) and c.905C>T (Thr302Ile), the former of which is associated with diazoxide responsive CHI, the latter is related to diazoxide non-responsive CHI in terms of clinical courses among the patients (Table).

Table. Mutational and clinical characterization identified by TES and confirmed by Sanger sequencing in patients with monogenic diabetes/CHI

Disease category	Proband	Sex	Age at Dx	Gene	Nucleotide/Amino acid change	Treatment	Novelty	Initial Hb A1c	Initial c-pep tide (ng/ml)	Note
Neonatal DM	K1	M	8M	*KCNJ11*	c.[605G>A] (p.[Arg201His])	Glibenclamide	REPORTED	8.6%	0.37	Persistent DM
Neonatal DM	K2	F	7M	*INSR*	c.[356C>T] (p.[Ala119Val]; c[.2978C>A] (p.[Ala993Asp])	Metformin	NOVEL (A993D:SIFT=0.02, POLYPHEN2=0.978)	6.8%	28.60	RMS, MNC
CH	K3	F	48D	*ABCC8*	c.[4237C>T] (p.[Pro1413Ser])	Diazoxide	NOVEL (SIFT=0.0 POLYPHEN2=0.098)	5.0%	1.74	Diazoxide responsive→ discontinued the treatment after 6 months
CH	K4	F	33D	*KCNJ11*	c.[905C>T] (p.[Thr302Ile])	Diazoxide→ Sandostatin	NOVEL (SIFT=0.00 POLYPHEN2=1.00	4.8%	ND	Diazoxide nonresponsive
MODY1	K5	M	23y	*HNF4A*	c.[1088C>T] (p.[Ala363Val]); c.[1127T>C] (p.[Met376Thr])	Lantus+Metformin→ Amaryl	NOVEL (A363V:SIFT=0.02, PLYPHEN2=0.236) (M376V: SIFT=0.02, POLYPHEN2=0.236)	7.8%	7.00	Metabolic syndrome, steatohepatitis
MODY9	K6	M	15Y	*PAX4*	c.538+8G>C	Lantus+Humalog→ Diet	NOVEL	10.7%	0.95	DKA

DM, diabetes mellitus; Dx, diagnosis; M, male; F, female; D, days; M, months; CH, congenital hyperinsulinism; RMS, Rabson-Mendenhall syndrome; MNC, medullary nephrocalcinosis; MODY, Maturity onset diabetes of the young; DKA, diabetic ketoacidosis; ND, not done

Conclusions

- TES can be useful for screening for monogenic diabetes/CHI mutations. Given the extensive genetic and clinical heterogeneity of monogenic diabetes, TES might provide additional diagnostic potential.

References

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