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

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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 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 far from 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 INS 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

<table>
<thead>
<tr>
<th>Disease category</th>
<th>Proband</th>
<th>Sex</th>
<th>Age at Dx</th>
<th>Gene</th>
<th>Nucleotide/Amino acid change</th>
<th>Treatment</th>
<th>Novelty</th>
<th>Initial Hb A1c</th>
<th>Initial c-peptide (ng/ml)</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal DM</td>
<td>K1</td>
<td>M</td>
<td>8M</td>
<td>KCNJ11</td>
<td>c.[605G&gt;A] (p.[Arg201His])</td>
<td>Glibenclamide</td>
<td>REPORTED</td>
<td>8.6%</td>
<td>0.37</td>
<td>Persistent DM</td>
</tr>
<tr>
<td>Neonatal DM</td>
<td>K2</td>
<td>F</td>
<td>7M</td>
<td>INSR</td>
<td>c.[356C&gt;T] (p.[Ala119Val]; c.2978C&gt;A (p.[Ala993Asp])</td>
<td>Metformin</td>
<td>NOVEL</td>
<td>6.8%</td>
<td>28.60</td>
<td>RMS, MNC</td>
</tr>
<tr>
<td>CH</td>
<td>K3</td>
<td>F</td>
<td>48D</td>
<td>ABC8S</td>
<td>c.[4237C&gt;T] (p.[Pro1413Ser])</td>
<td>Diazoxide</td>
<td>NOVEL</td>
<td>5.0%</td>
<td>1.74</td>
<td>Diazoxide responsive</td>
</tr>
<tr>
<td>CH</td>
<td>K4</td>
<td>F</td>
<td>33D</td>
<td>KCNJ11</td>
<td>c.[905C&gt;T] (p.[Thr302Ile])</td>
<td>Diazoxide−Sandostatin</td>
<td>NOVEL</td>
<td>4.8%</td>
<td>ND</td>
<td>Diazoxide nonrespo</td>
</tr>
<tr>
<td>MODY1</td>
<td>K5</td>
<td>M</td>
<td>23y</td>
<td>HNF4A</td>
<td>c.[1088C&gt;T] (p.[Ala363Val]; c.1127T&gt;C (p.[Met376Thr])</td>
<td>Lantus+Metformin−Amaryl</td>
<td>NOVEL</td>
<td>7.8%</td>
<td>7.00</td>
<td>Metabolic syndrom</td>
</tr>
<tr>
<td>MODY9</td>
<td>K6</td>
<td>M</td>
<td>15Y</td>
<td>PAX4</td>
<td>c.[538+8G&gt;C]</td>
<td>Lantus+Humalog−Diet</td>
<td>NOVEL</td>
<td>10.7%</td>
<td>0.95</td>
<td>DKA</td>
</tr>
</tbody>
</table>

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