Personalized and predictive medicine for pediatric diabetes through a genetic test using next generation sequencing

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Introduction

Monogenic diabetes (MD) accounts for at least 3% of all pediatric diabetes cases. MD is often misdiagnosed as type 1 or type 2 diabetes, because of its wide phenotypic spectrum. While clinical and biochemical parameters can suggest MD, a definitive diagnosis requires genetic analysis. We conducted a broad study to diagnose MD cases. Then, we designed a new diagnostic tool to obtain a comprehensive analytical instrument for the diagnosis of MD. A correct diagnosis of MD is crucial to optimize treatment and thereby improve metabolic control.

Objective and Methods

Diagnostic tool: This custom assay, designed based on liquid phase capture (Haloplex HS, Agilent, Santa Clara, CA, USA), allows for the trapping of all coding regions of the selected 42 genes and the respective splicing regions. Known enhancer regions and introns associated with diabetes were also included in the panel. All variants were confirmed by PCR and Sanger sequencing.

Results

Diagnostic panel

Here, we developed a new diagnostic panel of 42 genes. Mutations in several genes of this panel may lead to diabetes and/or congenital hyperinsulinism.

Table 2: Genetic results obtained by the diagnostic panel

<table>
<thead>
<tr>
<th>Gene</th>
<th>Familial agreement</th>
<th>Pathogenicity</th>
</tr>
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<tbody>
<tr>
<td>GCK</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EIF2AK3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABCC8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAX4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EIF2AK3</td>
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</tbody>
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Analysis by diagnostic panel

We have now analyzed the first 19 consecutive patients with the diagnostic tool and identified a monogenic disease in 53% of the subjects (Tbl 2).

Conclusions

Our newly developed next generation diagnostic panel shows an actual pick-up rate of 53% in 19 consecutive patients, which is above the published rates of 21% to 37% in the UK and 25% to 30% in France. The panel detects missense variants, insertions, and deletions, even large deletions extending from one exon to the entire gene. These results indicate that the three patients with GCK diabetes didn’t need any treatment, the patients with HNF1A mutations could be switched to oral sulfonylurea or glinides. The child with congenital hyperinsulinism could successfully be treated by diazoxide. The child with neonatal diabetes due to the homoygous EIF2AK3 mutation (Wolcott Rallison syndrome) needed insulin injections and multidisciplinary care to avoid fever, infections possibly preventing liver failure associated with the syndrome. These cases illustrate how applied precision medicine can tailor treatment to the needs of the individual patient with the aim to reduce short and long-term complications.

References