INTRODUCTION

- Family history is observed in approximately 10% of the cases with type 1 diabetes mellitus (T1DM).
- The most important gene that determines susceptibility is the human leukocyte antigen complex (HLA) on chromosome 6.
- In HLA genes, specific combinations of alleles at DQ3, DQ4, DQ8, DQ1, DQA1 and DQB1 locus either predispose or protective for T1DM.

AIM

- to investigate the molecular genetic etiology by whole exome sequence (WES) analysis in cases with familial T1DM who had no HLA haplotype predisposition or incomplete predisposition.

METHOD

- Patients had at least one first degree relatives with T1DM were included.
- In the first step, HLA DRB1, DQA1 and DQB1 loci were investigated with polymerase chain reaction-sequence specific oligonucleotide (PCR-SSO) method.
- In the second step, the presence of variants that could explain the clinic in cases where both tissue types were negative in HLA typing (DQ2 (-) / DQ8 (-)) and only one of the HLA types was found positive (DQ2 (+) / DQ8 (-), and DQ2 (-) / DQ8 (+)) was investigated by WES analysis.

RESULTS

- Four cases (13.3%) had consanguineous marriage between their parents out of 30 patients (female / male: 17:13).
- Mean age: 14.96 years.
- Diabetes duration: 7.56±3.84 years.
- As a result of filtering all exome sequence analysis data of 2 cases with DQ2 (-) and DQ8 (-), 7 cases with DQ2 (+) and DQ8 (-), and 1 case with DQ2 (-) and DQ8 (+), 7 different variants in 7 different genes were detected in 5 cases.
- The probability of the detected variants were determined according to the “American College of Medical Genetics and Genomics (ACMG)” criteria.
- These 7 variants detected were evaluated as high-score VUS (Variants of unknown/uncertain significance).

<table>
<thead>
<tr>
<th>Cases</th>
<th>Gene</th>
<th>HGVS-Code</th>
<th>HGVS-Protein (amino acid exchange)</th>
<th>Zygosity</th>
<th>Mutation type</th>
<th>Classification</th>
<th>Pathology associated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>GATA</td>
<td>c.278G&gt;A</td>
<td>p.Asn93Thr</td>
<td>Heterozygous</td>
<td>Missense</td>
<td>VUS</td>
<td>Autoimmune diseases</td>
</tr>
<tr>
<td>Case 2</td>
<td>KCNK11</td>
<td>c.1720G&gt;A</td>
<td>p.Glu574Asp</td>
<td>Heterozygous</td>
<td>Synonymous</td>
<td>VUS</td>
<td>IDDM, monogenic diabetes</td>
</tr>
<tr>
<td>Case 3</td>
<td>CASP10</td>
<td>c.9292+290MT</td>
<td>Heterozygous</td>
<td>Intronic</td>
<td>VUS</td>
<td>T2DM, monogenic diabetes</td>
<td></td>
</tr>
<tr>
<td>Case 4</td>
<td>BLVRA</td>
<td>c.1660±1T</td>
<td>p.Glu55*</td>
<td>Heterozygous</td>
<td>Nonsense</td>
<td>VUS</td>
<td>Hypothyroidism, T2DM</td>
</tr>
<tr>
<td>Case 5</td>
<td>POLG</td>
<td>c.3151G&gt;C</td>
<td>p.Glu1051R</td>
<td>Heterozygous</td>
<td>Missense</td>
<td>VUS</td>
<td>Progressed external ophthalmoplegia, mitochondrial DNA depletion syndrome (MERRF, ALPERS), mitochondrial recessive ataxia syndrome, Alpers-Huttenlocher Syndrome, Ataxia Syllomysitis, myocytic epilepsy, myopathy sensory ataxia (MMSA), Childhood myocerebrohepatopathy syndrome (MCHS), T2DM</td>
</tr>
<tr>
<td>Case 5</td>
<td>AKT2</td>
<td>c.709-3C&gt;G</td>
<td>Splice area</td>
<td>Heterozygous</td>
<td>VUS (Learning Pathogenic)</td>
<td>NHSP/PLACE, Mitochondriopathy, Mitochondrial</td>
<td>T2DM</td>
</tr>
<tr>
<td>Case 5</td>
<td>FBNI</td>
<td>c.37C&gt;G</td>
<td>L11Q, L11R</td>
<td>Heterozygous</td>
<td>Missense</td>
<td>VUS</td>
<td>Marfan Syndrome, Stiff Skin Syndrome, Marfan Lymphoproliferative Syndrome, Polysyndactyly Type 2, Arthrogryposis Well-Marchesani Syndrome, T1DM, T2DM</td>
</tr>
</tbody>
</table>

CONCLUSIONS

- In a previously studied T1DM has been reported in monozygotic twins with POLG mutation.
- In another study, POLG mutation was shown to be responsible for diabetic nephropathy in patients with T1DM.
- In this study, 7 different variants in 7 different genes were detected in 5 patients by whole-exome sequence analysis in familial T1DM patients with no or weak HLA tissue type susceptibility.
- We thought that the heterozygous c.3151G>C mutation detected in the POLG gene in our case was associated with the current T1DM phenotype.

REFERENCES


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CONTACT INFORMATION

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