Prevalence of melanocortin 4 receptor (MC4R) mutations in Turkish obese children

Ayça Aykut1, Samim Özen2, Damla Gökşen2, Hüseyin Onay1, Tahir Atik3, Şükran Darcan2, Ferda Özkınay1.3

Ege University School of Medicine Department of 1: Medical Genetics, 2: Pediatric Endocrinology, 3: Pediatric Genetics, İzmir, Turkey

Background:
- Melanocortin-4-receptor gene (MC4R) is a key regulator of energy homeostasis, food intake and body weight which has intensively been analyzed in molecular genetic obesity research.
- MC4R dysfunction in humans causes hyperphagia, impaired satiety and obesity.

Objective and hypotheses:
- To identify MC4R mutations prevalence in familial obese Turkish children and adolescents

Method:
- Ninety three (45 female/48 male) pediatric and adolescent patients aged between 1.3–15 years old with early onset obesity (before 6 years) were enrolled.
- Obesity was defined as a body mass index (BMI) standard deviation score (SDS) of + 2.0 according to the Turkish Population.
- Children with genetic syndromes associated with obesity or mental retardation, or taking drugs that promote changes in eating behavior were excluded.
- Coding region of the MC4R gene was sequenced by Illumina MiSeq Next Generation Sequencing System.

Results:
- Mean age of the patients was 7.3 ± 3.7 years and mean BMI was SDS 3.7 ± 0.75D.
- Seventy nine patients (85%) were pre-pubertal and 14 (15%) were pubertal.
- We identified four different mutations in eight patients, giving a mutation detection rate of 8.6 %.
- Three were previously identified missense heterozygous mutations (p.N274S, p.S136F and p.V166I).
- One was a novel homozygous mutation (p.I291Sfs*10) detected in a severely obese 2-year-old boy.

- By in-silico analysis softwares this novel mutation predicted to be disease causing and it is expected to have a-32 amino acids shorter MC4R protein.

Table 1 shows clinical and molecular features in MC4R mutation (+) patients.

Table 1. Clinical and molecular features of MC4R mutation (+) patients.

<table>
<thead>
<tr>
<th>Family/Patient</th>
<th>Sex/Age</th>
<th>Height BMI SDS</th>
<th>Clinical features</th>
<th>HOMA-IR</th>
<th>DNA</th>
<th>Protein</th>
<th>MT</th>
<th>Polyphen2 score</th>
<th>SIFT</th>
<th>ExAC* Frequency</th>
<th>Allele</th>
<th>Novel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family 1/ P1</td>
<td>M/10</td>
<td>1.9/3.7</td>
<td>IR</td>
<td>6.3</td>
<td>c.821 A&gt;G/wt</td>
<td>p.N274S/wt</td>
<td>DC</td>
<td>PD</td>
<td>D</td>
<td>0.00001647</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Family 2/ P2</td>
<td>F/8.6</td>
<td>1.9/2.7</td>
<td>IR, HT, NASH</td>
<td>4.4</td>
<td>c.496 G&gt;A/wt</td>
<td>p.V166I/wt</td>
<td>DC</td>
<td>PD</td>
<td>D</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Family 3/ P3</td>
<td>M/8.5</td>
<td>3.2/4.6</td>
<td>IR, depression,</td>
<td>8.1</td>
<td>c.496 G&gt;A/wt</td>
<td>p.V166I/wt</td>
<td>DC</td>
<td>PD</td>
<td>D</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Family 4/ P4</td>
<td>M/14</td>
<td>0.8/3.6</td>
<td>IR, HT, NASH,</td>
<td>7.3</td>
<td>c.407 C&gt;T/wt</td>
<td>p.S136F/wt</td>
<td>DC</td>
<td>PD</td>
<td>D</td>
<td></td>
<td></td>
<td>-</td>
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<td>Family 5/ P5</td>
<td>M/2</td>
<td>1.8/7.3</td>
<td>IR</td>
<td>3.2</td>
<td>c.870 delG/</td>
<td>p.I291Sfs*10/</td>
<td>DC</td>
<td>NA</td>
<td>D</td>
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<tr>
<td>Family 1/ P6</td>
<td>F/8</td>
<td>1.2/2.9</td>
<td>IR</td>
<td>3.4</td>
<td>c.821 A&gt;G/wt</td>
<td>p.N274S/wt</td>
<td>DC</td>
<td>PD</td>
<td>D</td>
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<td>-</td>
</tr>
<tr>
<td>Family 3/ P7</td>
<td>F/14</td>
<td>1.0/3.1</td>
<td>IR, HT, NASH,</td>
<td>4.6</td>
<td>c.407 C&gt;T/wt</td>
<td>p.S136F/wt</td>
<td>DC</td>
<td>PD</td>
<td>D</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Family 6/ P8</td>
<td>M/14.5</td>
<td>1.3/3.0</td>
<td>IR</td>
<td>6.2</td>
<td>c.821 A&gt;G/wt</td>
<td>p.N274S/wt</td>
<td>DC</td>
<td>PD</td>
<td>D</td>
<td>0.00001647</td>
<td></td>
<td>-</td>
</tr>
</tbody>
</table>

D: Damaging, DC: Disease causing; F: Female; IR: Insulin resistance, NA: Not available, NAH: Non alcoholicsteatohepatitis, M: male, MT: MutationTaster, P: Patient, PD: Probably Damaging, T: Tolerated, wt: Wild Type,
*Exome Aggregation Consortium (http://exac.broadinstitute.org), ** The allele frequency in the ExAC database does not contain representative controls for all ethnic groups.

Conclusion: MC4R gene mutations is quite common in childhood obesity in Turkish population. Investigating the mutations in MC4R gene in patients with severe childhood-onset obesity is necessary.