**BMP4 mutations as a novel cause of normosmic hypogonadotropic hypogonadism**

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**Background:** BMP4, a member of the bone morphogenetic protein family which is part of the transforming growth factor-beta superfamily, is involved in the embryonic development of various organ and tissues including the cranio-facial structures, olfactory, pituitary, eyes, heart, and kidneys. Mutations in this gene are associated with orofacial cleft and microphthalmia in human patients. BMP4 plays an important role in the embryonic development of the GnRH neurons (Forni et al., 2013, Layman et al 2011) and anterior pituitary by regulating diverse cellular responses, such as cell differentiation, migration, adhesion, and proliferation (Massague et al 2000). BMP4 also has been described as inhibiting FSH production particularly (Nicol et al 2008). Recently, a heterozygous truncating mutation was described in a 6 years old prepubertal child with combined pituitary hormone deficiency (Rodriguez-Contreras et al 2019). Mutations in the BMP genetic network including BMP4 were reported to be found in patients with hypogonadotropic hypogonadism (HH) in a meeting abstract (Cassatella et al., ASHG 2013). However, no detailed description of BMP4 mutations in the etiology of HH has been found in the literature. Here we present three independent patients with isolated HH apparently due to deleterious sequence variants in BMP4.

**Methods:** We screened the whole exome sequencing data from 215 HH patients from Turkey.

**Results:** We identified apparently deleterious rare BMP4 sequence variants in three independent patients with HH. All patients were normosmic. The patients did not have deficiencies of other pituitary hormones. Variant p.N150K was found in homozygosity in a patient from a consanguineous family. Interestingly, this same variant has been reported to cause renal hypoplasia in heterozygosity as well as homozygosity in two independent patients (Weber et al 2008). Co-occurrence of HH with kidney anomalies are well known. In all three patients both FSH and LH were similarly deficient, i.e. there was not a particularly more pronounced deficiency of FSH over LH.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>DNA change</th>
<th>Protein change</th>
<th>Zygosity</th>
<th>Minor allele frequency in gnomAD</th>
<th>CADD score</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>NM_001202.3:c.450C&gt;G</td>
<td>NP_001193.2:p.As150Lys</td>
<td>Homozygous</td>
<td>0.00001</td>
<td>22.5</td>
</tr>
<tr>
<td>P2</td>
<td>NM_001202.3:c.41G&gt;A</td>
<td>NP_001193.2:p.Cys14Tyr</td>
<td>Heterozygous</td>
<td>0.00001</td>
<td>24.9</td>
</tr>
<tr>
<td>P3</td>
<td>NM_001202.3:c.751C&gt;T</td>
<td>NP_001193.2:p.His251Tyr</td>
<td>Heterozygous</td>
<td>0.00001</td>
<td>29.6</td>
</tr>
</tbody>
</table>

**Conclusion:** These results strongly suggest that inactivating variants in BMP4 are novel causes of normosmic hypogonadotropic hypogonadism. This phenotype is consistent with previously described role of BMP4 in the ontogeny of the GnRH neurons and the anterior pituitary.