Prokinein receptors (PROKR1 and PROKR2) belong to the family of G protein-coupled receptors. Bi- or mono allelic mutations in PROKR1 gene (2p12.3, NM_001288933.2) have been identified in patients with combined hypergonadotropic hypogonadism (IHH) and anosmia-syphilis phenotype. Previously, PROKR2 mutations were reported in patients with multiple pituitary hormone (MPHD) and growth hormone deficiency (GHD), suggesting a potential role for the PROKR2 pathway in pituitary development, in addition to its role in GHRH neuron development (2). We present here clinical and molecular findings of one patient with MPHD and two patients with GHD.

**Patients and Methods**

Patient 1 and Patient 2 were presented with short stature (height SDS < -2) and Patient 3 was diagnosed with congenital hypothyroidism at age of 5 months and started on L-T4 replacement therapy and referred for further endocrinological evaluation.

Clinical findings of the patients are summarized in Table 1. All patients were born at term. There was no history of intrauterine growth restriction or hypospadias in the patients. All patients had normal vision and hearing. In the family history, there were short stature and delayed puberty.

Six months after presentation, Patient 1 and Patient 2 showed a low height velocity and growth hormone (GH) stimulation tests were performed. GHD was diagnosed and GH replacement therapy was started. Patient 1 and Patient 2 have completed pubertal development, menarche age of Patient 1 was 13.5 years and Patient 2 was 15 years. Patient 3 is still prepubertal. This patient was suspected to have hypogonadotropic hypogonadism without anosmia because of low gonadotropin levels, bilateral cryptorchidism and micropenis at presentation. Prolactin (PRL) level was also low (1.9 ng/ml). Dihydrotestosterone cream was applied for microgenital. GHD was diagnosed at presentation, but GH treatment was started at age of 2.2 years and orchirepexy was done at age of 2.7 years. GHRH stimulation test was performed at age of 10.5 years. LH and FSH responses were very low, these results have been supported by hypogonadotropic hypogonadism. Written informed consent was obtained from the patients and their parents for genetic analyses.

Chromosomal abnormalities using microarray and cytogenetic techniques were excluded before the admission of molecular genetic analysis. Screening of targeted regions for in-house designed short stature panel with 25 genes (BM44, FGFR2, FGFR3, GHR, GHRH, GHRHR, HESX1, HMIP, IGFI, IGFBP3, IGFBP5, IGF1, IGF2, LH/XO2, POU1F1, PROK1, PRKCI, SHXL, SOX5, SOX6, TWD1) and testing for certain rare Mendelian syndromes (XLH, hypothyroidism with anosmia, congenital stationary night blindness, bilateral deafness and renal anomalies) were performed before genetic analysis. It was revealed two different heterozygous clinical variants previously reported with Kallmann syndrome in each patient. In PROKR1 gene, Patient 1 and Patient 2 had heterozygous p.Arg85His mutation. Patient 3 had heterozygous p.Leu173Arg mutation. Family genetic analyses revealed that this mutation was transmitted from her father in the Patient 1, his mother in the Patient 2. The mother of Patient 3 was carrier for p.Leu173Arg mutation.

**Discussion**

It is reported that the phenotypes resulting from heterozygous PROKR2 mutations are remarkably variable with respect to age at diagnosis. If patients come to medical attention later in life without abnormalities of the olfactory and optic nerves. Oligogenic or digenic inheritance is recently to be the most plausible explanations for the phenotypes observed in patients with heterozygous mutations (1.2). The p.Arg85His and p.Leu173Arg mutations described previously have been associated with IHH. Functional analyses were performed for two mutations and shown to be deleterious to protein function, suggesting a causative role in the phenotype. It was reported that these mutations were inherited heterozygously from asymptomatic parents to several patients with IHH or hypothyroidism amenorrhea. A male patient with IHH who had PROKR2 mutation underwent spontaneous reversal of his GdR deficiency and suggests that gene-environment interaction may modify a phenotype later in life (3,4).

Patient 1 and Patient 2 had a slightly delayed puberty. Interestingly, Patient 1’s mother was not carrier for the mutation, but she had delayed puberty and mildly short stature. This condition may be related to other causes. Patient 2's mother who was carrier for the mutation had short stature and delayed puberty. Patient 3's mother who also carried the mutation did not have short stature, but her menarche age was slightly delayed. There were no phenotypic differences for two PROKR2 variants carriers in the intrasinus and interfamily members. It may be possible because of PROKR2 gene expression difference. It may cause oligogenic or digenic inheritance.

**Genetic analyses**

Table 1. Some clinical and laboratory findings of the patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yrs)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>SIIing height / Height</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>12</td>
<td>11</td>
<td>102.0/3</td>
<td>0.5</td>
</tr>
<tr>
<td>Patient 2</td>
<td>11</td>
<td>11.5</td>
<td>102.0/3</td>
<td>0.5</td>
</tr>
<tr>
<td>Patient 3</td>
<td>13.5</td>
<td>11.5</td>
<td>102.0/3</td>
<td>0.5</td>
</tr>
</tbody>
</table>

**Figure 1. Family pedigrees of the patients with PROKR2 allelic variants**

**Disclosure:** The authors have nothing to disclose.