A novel mutation within the AVP gene in an 18-year-old male patient with Kallmann syndrome and combined pituitary hormone deficiency

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Introduction

Kallmann syndrome is the most common form of hypogonadotropic hypogonadism and is associated with genes such as KAL1, KAL2, PROK2, and PROKR2. Hypopituitarism is involved with gene mutation of PROP1, POU1F1, HESX1, and PTX2. We report a c.127C>G (p.Pro43Ala) variation of the AVP gene, in a Kallmann syndrome patient with combined pituitary hormone deficiency through whole exome sequencing.

Case presentation

Chief complaint: general weakness, short stature, and no puberty signs

Present illness and past history: An 18-year-old boy was admitted to our hospital for general weakness, short stature, and no puberty signs on August 15th, 2013. He was born at gestational age 40 weeks with weighing 3,800 g by cesarean section delivery due to cephalopelvic disproportion. At 7 years old, he has been taken antiepileptic drug because of epilepsy. In addition when he was 15 years old, he was diagnosed with primary hypothyroidism in medical check up and has been taken thyroxin.

Physical examination: His height and weight were 156 cm (<1st percentile) and 47 kg (<1st percentile) respectively. His testicular sizes were each 4 cc.

Laboratory findings: In cocktail test, he was diagnosed with growth hormone deficiency, secondary adrenal insufficiency, and hypogonadotropic hypogonadism. He also had anosmia. Thus, he was diagnosed with Kallmann syndrome. Additionally, water deprivation test was done due to polyuria (4 L/day) during hospitalization period. And central diabetes insipidus was confirmed in water deprivation test.

Table 1. Cocktail test

<table>
<thead>
<tr>
<th>Glucose (mg/dL)</th>
<th>0 min</th>
<th>20 min</th>
<th>30 min</th>
<th>45 min</th>
<th>60 min</th>
<th>90 min</th>
<th>120 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>83</td>
<td>23</td>
<td>26</td>
<td>36</td>
<td>45</td>
<td>38</td>
<td>57</td>
<td></td>
</tr>
</tbody>
</table>

GH (ng/mL): 0.03 0.03 0.02 0.03 0.02 0.04 0.02
Cortisol (ug/dL): 0.06 0.23 0.2 0.19 0.38 0.31
LH (mIU/mL): 1.31 1.19 0.8 1.16 0.91
FSH (mIU/mL): 0.25 0.35 0.51 0.87 0.46

Abbreviations: GH, growth hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; min, minute.

Table 2. Water deprivation test

<table>
<thead>
<tr>
<th>Urine osm. (mOsm/Kg)</th>
<th>0 min</th>
<th>120 min after administration</th>
<th>120 min after administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>427</td>
<td>562</td>
<td>690</td>
<td></td>
</tr>
</tbody>
</table>

Blood osm. (mOsm/Kg): 293 290 293 292

ADH (pg/mL): 3.54 3.29

Abbreviations: ADH, antidiuretic hormone; min, minute; osm, osmolality

The sella MRI showed an absent olfactory bulb and pituitary stalk, a small anterior pituitary gland, and an ectopic posterior pituitary bright spot at the base of the hypothalamus.

Fig 1. Magnetic resonance imaging finding. (A) T2-weighted coronal image shows absent olfactory bulbs. (B) T1-weighted sagittal image shows ectopic posterior pituitary gland (arrow), atrophic anterior pituitary gland and absent infundibular stalk (arrow head).

Genetic analysis: He was diagnosed with Kallmann syndrome and combined pituitary hormone deficiency. To find out genetic cause related to Kallmann syndrome with combined pituitary hormone deficiency, we performed whole exome sequencing and found a c.127C>G (p.Pro43Ala) variation of the AVP gene. This variation also confirmed by Sanger Sequencing. And this mutation was not observed in an in-house exome database (n=192 individuals). His father did not have this variation. However, the AVP gene mutation analysis was not performed in his mother because she was not contacted.

Patient

Fig 2. Sanger sequencing analysis representing c.127C>G (p.Pro43Ala) variation of the AVP gene in this patient.

Conclusion

Kallmann syndrome with combined hypopituitarism was associated with many genetic defects and it is difficult to find out genetic cause with only clinical aspects. Direct sequencing of all related genes is not cost-effective. So, after we performed whole exome sequencing, we confirmed the detected variation through Sanger sequencing. That would be more cost-effective and less time consuming method.

References