Two Cases of Congenital Hypopituitarism Proven to Have Mutations of GLI2

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Objectives

GLI2 is a transcription factor in Sonic Hedgehog signaling and implicated in ventral forebrain and pituitary development. Phenotypes of GLI2 mutations are congenital hypopituitarism (CH), ectopic posterior lobe (EPP), midline facial defects and polydactyly. GLI2 mutations were first reported in patients with holoprosencephaly (HPE), but recently reported in patients with CH without HPE.

Case Presentation

Case 1: 7-year-old boy
He was born at full term by vaginal delivery without fetal distress. He had cleft lip and palate, micropenis, cryptorchidism. He did not have polydactyly. At 0 day of age, hypoglycemia and low levels of GH, TSH, ACTH, LH, FSH demonstrated CH. At 6 days of age, polyuria, low urine osmolality and low levels of ADH suggested central diabetes insipidus (CDI). Brain MRI showed a pituitary aplasia, EPP, and no signs of HPE.

Case 2: 16-year-old boy
He was born full term by vaginal delivery without fetal distress. He had micropenis and cryptorchidism. He did not have midline facial defects and polydactyly. At 6 months of age, diminished responses of GH, TSH, ACTH, cortisol, LH and FSH after insulin, TRH and LHRH stimulation demonstrated CH. CDI was not suggested.

Discussion

The clinical features of CH patients with GLI2 mutations
We evaluated the clinical features of 22 cases who had CH with pathogenic mutations in GLI2 and our cases. Table 1 shows the proportion of cases with each sign. Polydactyly and midline facial defect are frequent signs of GLI2 mutation compared with other transcriptional factor gene mutation. Because our cases lacked polydactyly or midline facial defect, it was difficult to suspect CH due to GLI2 mutation from clinical features. We could prove they had GLI2 mutations by next generation sequencer.

Table 1

<table>
<thead>
<tr>
<th>Published cases</th>
<th>Case1</th>
<th>Case2</th>
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<tbody>
<tr>
<td>Polydactyly</td>
<td>15/22</td>
<td>68.2%</td>
</tr>
<tr>
<td>Midline facial defect</td>
<td>10/22</td>
<td>45.5%</td>
</tr>
<tr>
<td>EPP</td>
<td>9/21</td>
<td>42.9%</td>
</tr>
<tr>
<td>CDI</td>
<td>1/22</td>
<td>4.5%</td>
</tr>
</tbody>
</table>

The features about posterior lobe of patients with GLI2 mutations
Table 2 shows the number of cases who had both EPP and CDI, EPP without CDI, CDI without EPP, and neither of them. 9 cases with EPP did not had CDI. In 1 case with CDI without EPP, the posterior lobe was not visible. Case 1 is the first case who has both CDI and EPP in patients with GLI2 mutations.

Table 2

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>EPP</td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>-</td>
<td>9</td>
</tr>
</tbody>
</table>

References

1) Roessler E et al 2003 Proc Natl Acad Sci USA
2) Fancour W et al 2012 J Clin Endocrinol Metab
3) Bertrandos CD et al 2012 Clin Genet
4) Bertrandos CD et al 2013 J Clin Endocrinol Metab
5) Bear KA et al 2014 J Mol Genet

Conclusion

Reporting two cases of CH proven to have novel mutations of GLI2.
Comparing the clinical features of our cases with published cases.