Two Cases of Congenital Hypopituitarism Proven to Have Mutations of *GLI2*

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Background

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.

Objectives

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

Case Presentation

Case1: 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.
11 genes related to congenital hypopituitarism were screened on Miseq next generation sequencer. The heterozygous substitution c.3544 C>T results in a stop codon at position 1182 (p.Gln1182*) within *GLI2*.

【0 day of age labo data】
BS 5 mg/dl
GH < 0.07 ng/ml
TSH < 0.03μIU/ml
FT3 0.8 pg/ml
FT4 < 0.4 ng/dl
LH < 0.5 mIU/ml
FSH < 0.37 mIU/ml
ACTH < 0.5 pg/ml
cortisol < 1.16μg/dl

【6 days of age labo data】
Na 148 mEq/L
BUN/Cr 34/1.2 mg/dL
AVP < 0.3 pg/mL
plasma osmolality 296 mOsm/kg
urine osmolality 232 mOsm/kg

Case2: 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.
Brain MRI showed a pituitary hypoplasia, EPP, and no signs of HPE.
11 genes related to congenital hypopituitalism were screened on Miseq next generation sequencer.
The heterozygous duplication of nucleotide 3076 (c.3076dupC) leads to a frameshift mutation and stop codon at position 1025 (p.Ser1025fs) within *GLI2*.

【6 months of age】

	Base	Peak
GH [ng/mL]	0.43	0.56
ACTH [pg/mL]	28	28
Cortisol [μg/dL]	6.7	6.9
TSH [μU/mL]	<0.1	1.4
LH [mIU/mL]	<0.2	0.3
FSH [mIU/mL]	<0.2	<0.2

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

	Published cases	Case1	Case2
Polydactyly	15/22 (68.2%)	−	−
Midline facial defect	10/22 (45.5%)	+	−
EPP	9/21 (42.9%)	+	+
CDI	1/22 (4.5%)	+	−

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

		CDI	
		+	−
EPP	+	0	9
	−	1	0

Conclusion

1) Polydactyly and midline facial defect are frequent signs of *GLI2* mutation.In CH patients who has them, we can suspect they have *GLI2* mutation.
2) Case 1 is the first case who has CDI with EPP in patients with *GLI2* mutations.

References

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