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 40weeks 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 synthyroid.

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

	0min	20min	30min	45min	60min	90min	120min
Glucose (mg/dL)	83	23	26	36	45	38	57
GH (ng/dL)	0.03	0.03	0.02	0.03	0.02	0.04	0.02
Cortisol (ug/dL)	0	0.06	0.23	0.2	0.19	0.38	0.31
LH (mIU/mL)	0		1.31	1.19	0.8	1.16	0.91
FSH (mIU/mL)	0		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

	0min	After 120 min	At 60min after administration of vasopressin	At 120min after administration of vasopressin
Urine osm. (mOsm/Kg)	427	270	562	590
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.

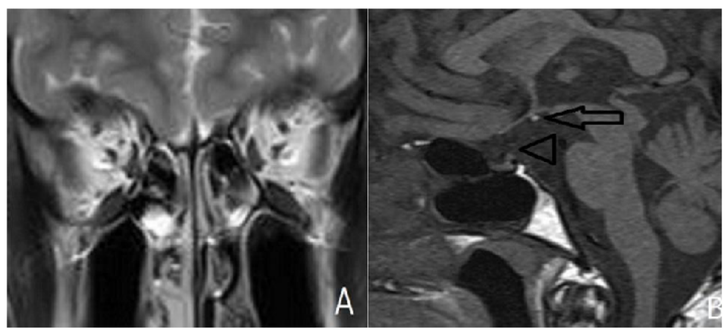

Fig 1. Magnetic resonance imaging finding. (A) T2-weighted coronal image shows absent olfactory bulbs. (B) T1-weighted sagittal image shows ectopic posterior pituitary gland (arrow), atropic anterior pituitary gland and absent infundibular stalk (arrow head).

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 indivisuals). His father did not have this variation. However, the *AVP* gene mutation analysis was not perfomed in his mother because she was not contacted.

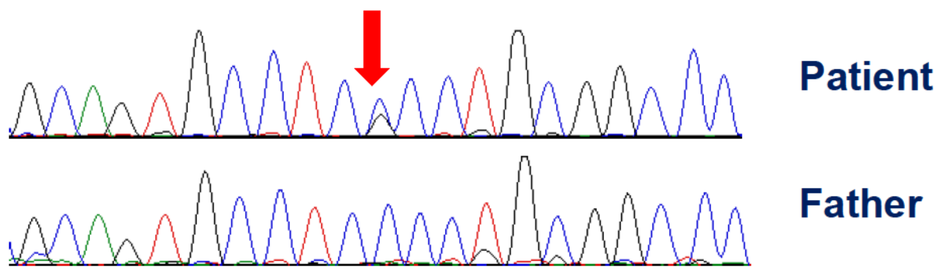

Fig 2. Sanger sequencing analysis representing c.127C>G (p.Pro43Ala) variation of the *AVP* gene in this patient.

Conclusion

Kallmann syndrome with combined hypopituitarism was associated with many genetic defects and it is difficult to find out genentic 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 sequncing. That would be more cost-effective and less time consuming method.

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