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A novel gene mutation and atypical clinical phenotype of Kallmann syndrome

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※No potential COI to disclose

Background

The Kallmann syndrome is diagnosed by hypogonadotropic hypogonadism and hyposmia/anosmia. More than 19 genes implicated in these conditions, and it is considered that mutations in fibroblast growth factor (FGF) 8 and FGFR1 account for more than 10% of these cases. FGF activity include secrete proteins involved in cellular proliferation, migration, differentiation, and survival. Mutation of IL17RD involves in the regulation of FGF activity and is thought to be one of the genes causing Kallmann syndrome.

Case

A 19-year-old woman

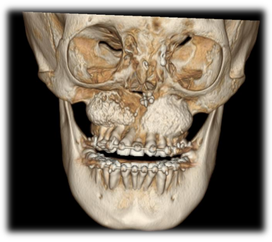
【Chief somplaint】primary amenorrhea.

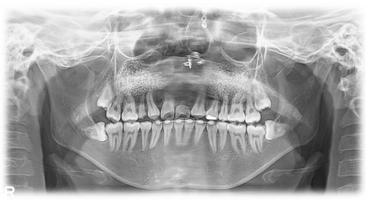
【Development】Motor developmental delay
Standing at 3 years old, Walking at 5 years old

【Family history】
No siblings
Father(39 y.o.)　170cm 80kg, Kidney stone(+)
Mother(39 y.o.) 163cm 50kg
Parents non consanguineous
No relatives with remarkable past history

【Perinatal period】Spontanious pregnancy
40 weeks of gestational age.
Birth weight: 2456 g(-1.72SD), Height 47 cm(-1.33SD)

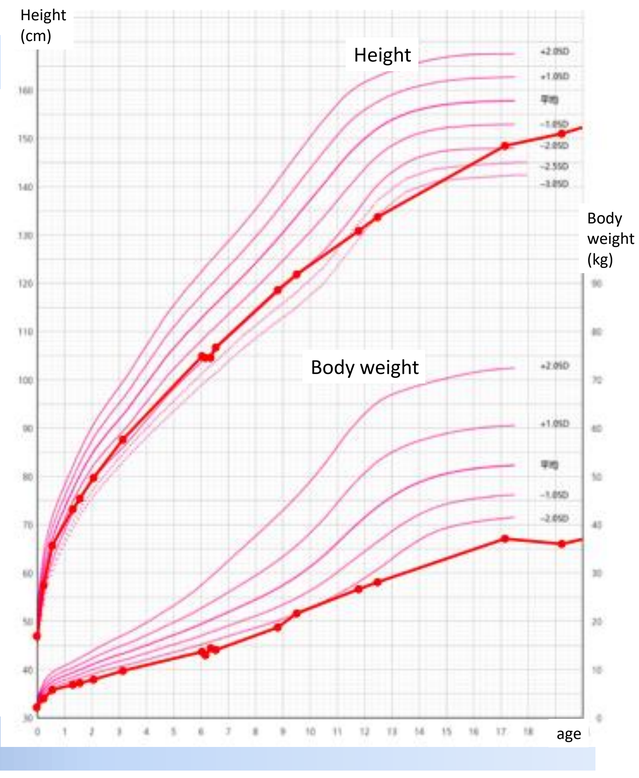
【Past history】
She had multiple facial plastic surgery.
(Rhinoplasty, Surgery for facial cleft, Palate osteoectomy, Expander insersion surgery, Extraction of maxillary impacted tooth, Surgery for medial wall of orbit)





▶3D computed tomography image and Panoramic tomography X-ray at 18 year-old (after multiple plastic surgery)

▶Growth chart



Physical findings

at 19 years old
Height:151.6 cm (-1.2 SD), Body weight:36.9 kg
Body Mass Index (BMI):16.1
No sense of smell, Asymmetric facial appearance
mild hirsutism, mild valgus elbow, high arched palate
Tanner stage :Breast 1, Pubic hair 1, no axillary hair

Laboratory findings and Images

		reference
FT3 （pg/ml）	3.73	1.8-4.7
FT4 （ng/dl）	1.11	0.89-1.53
IGF-1 （ng/ml）	222	182-539
E2 （pg/ml）	<10	adult 14.2-200.1

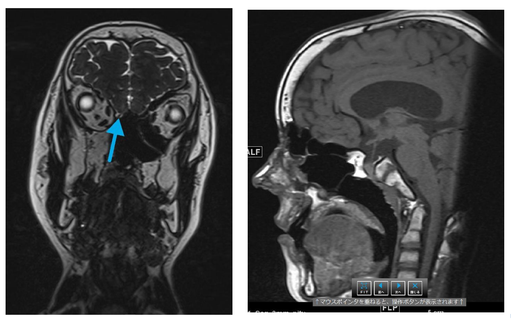
	0 min.	peak
GH (ng/ml)	13.2	47.3 (30 min.)
TSH (μIU/ml)	0.906	7.391 (30 min.)
PRL（ng/ml）	8.06	32.90 (30 min.)
LH（mIU/ml）	0.30	2.15 (90 min.)
FSH（mIU/ml）	0.97	5.49 (90 min.)
ACTH（pg/ml）	17.0	28.0 (30 min.)
Cortisol (μg/dl)	15.2	19.6 (30 min.)

We performed stimulation tests with GRF, CRH, TRH and LHRH to distinguish central delayed puberty.

Laboratory findings and Images

【Abdominal ultrasonography】
A renal cyst(20 mm) in the left lower kidney was detected. Small uterus but no ovaries were detected.

▶ Head MRI
Pituitary gland hypoplasia and the bone defect of the Turkish saddle. Hypoplasia of hard palate and nasal septum.



【Olfaction test】No sense of smell

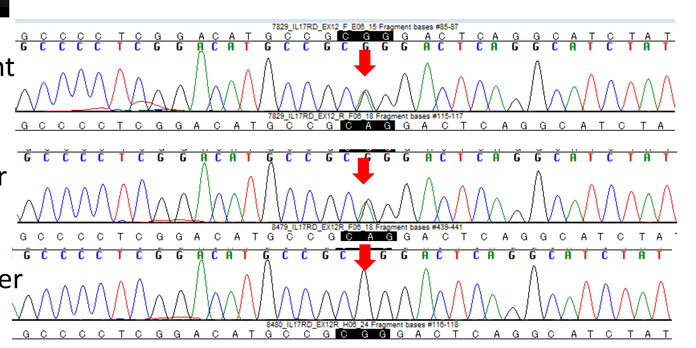
【Auditory test】normal hearing

【Bone age】11 years old
（Chronological age 19 y.o.）

【Bone mineral density】(L2-L4)
0.488 g/cm^2 (T-score -5.9SD)

【Karyotype】46,XX

【Genetic testing】
Heterozygous missense mutation in exon 12 of IL17RD,
c.1979 G> A, p.Arg 660 Gln
(chr 3: 57131752 C> T)



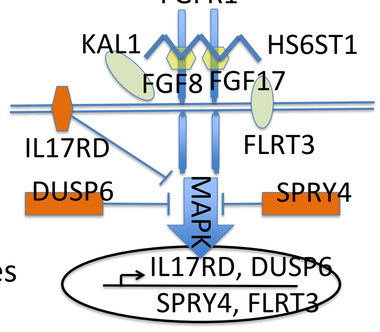
The analyzed gene　(with Next Generation Sequencers（MiSeq）)
CHD7, FGF8, FGFR1, FSHB, GNRH1, GNRHR, HESX1, HS6ST1, ANOS1/KAL1, KISS1, KISS1R, LEP, LEPR, LHB, LHX3, LHX4, NELF, NR0B1, OTX2, POU1F1, PROK2, PROKR2, PROP1, SEMA3A, SOX2, SOX3, TAC3, TACR3, WDR11

Discussion

LH, FSH and LHRH stimulation tests showed Hypogonadotropic Hypogonadism.
We diagnosed from the result above as Kallmann syndrome. The patient started estrogen replacement therapy and will eventually move on to Kaufmann's treatment.

IL17RD genes encode components of the FGF pathway and act primarily as a contributing factor to the underlying oligogenic structure of CHH, and it's mutation affects FGF signaling, inhibiting or stimulating growth through MAPK/ERK signaling.
The gene mutation in this case is considered to be a novel mutation. The mutation was not registered in the 1000 Genome Project/ ExAC/ HGVD. In silico analysis was Disease causing (PolyPhen2 scored 1.0). According to the previous reports IL17RD mutation is a autosomal dominant mutation with low or no sense of smell, tooth abnormality and decreased bone mineral density, renal abnormality, and strongly linked to hearing loss. Many of the patients first aware the delay of puberty with hypogonadotropic hypogonadism. In this case, not only the teeth but also the facial dysplasia and the bone defect of the Turkish saddle was recognized, as well as renal cysts and hypoplasia of the pituitary but not the hearing loss.

Although the patient's father had the same mutation, his appearance is normal and has no symptoms so far except for the kidney stone.
He has not undergone blood test yet. This difference in phenotype could be explained by phenotypic variation or existence of other mutation in another gene.



▶ FGF-Network-Associated Genes
(Hichem Miraoui et al. The American Journ. of Human Genetics 92, May 2, 2013)

▼Comparison to phenotype of previous report

case	exon	CHH	anosmia	pubertal delay	dental defect	hearing disability	low BMD
1	6	+	+	+	+	-	n/a
6	6	+	+	+	+	-	n/a
2	13	+	+	+	+	+	+
7	13	+	+	+	+	-	n/a
4	14	+	+	+	n/a	+	+
5	14	+	+	n/a	+	+	n/a
9	14	+	+	+	n/a	+	+
10	14	+	+	n/a	n/a	+	n/a
3	15	+	+	n/a	n/a	+	n/a
8	15	+	+	n/a	n/a	+	n/a
Pt.	**12**	+	+	+	+	-	+

Conclusion

We experienced a case of Kallmann syndrome with novel heterozygous missense mutation in Exon 12 of IL17RD, c.1979 G> A, p.Arg 660 Gln (chr 3: 57131752 C> T).

References

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