A NOVEL INACTIVATING COMPOUND HETEROZYGOUS MUTATION IN KISS1R/GPR54: CASES OF THREE SIBLINGS

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Introduction

Idiopathic hypogonadotropic hypogonadism (IHH)

- A rare genetic disorder
- Caused by defect in the secretion of gonadotropin-releasing hormone (GnRH) the action of GnRH on the pituitary gonadotropins
- Incidence: 1–10/ 100 000 live births
- 50 genes have been reported; *KISS1R* is one of these genes

Kisspeptin

- A neuropeptide encoded by the KISS1 gene
- Acts upstream of gonadotropin-releasing hormone (GnRH) neurons
- Has a critical role for maturation and function of the reproductive axis

We present three siblings with NHH due to a compound heterozygous mutation including c.969C>A (p.Y323X) and novel c.170T>C (p.L57P) in *KISS1R* in a non-consanguineus family.

Case Report

▪Index case applied to our outpatient clinic with delayed puberty when he was 14 years old. On newborn period, he had bilateral cryptorchidism and micropenis and bilateral orchiopexy was done.

▪On his physical examination:

- ➢Height was 165.3 cm (0.14 SDS)
- ➢Weight was 62 kg (0.94 SDS)
- ➢Pubertal stage was Tanner stage 1
- ➢Stretched penis size was 4 cm
- ➢Bilateral testises were in skrotum and testis sizes were 3 ml.

▪His parents were nonconsanguineous.

▪Laboratory findings (shown in table 1) devealed IHH. The results of GnRH test confirmed IHH.

▪Karyotype of peripheral blood lymphocytes was 46 XY.

▪Genomic DNA was extracted from peripheral leukocytes and the promoter region, the three exons and exon-intron boundries of the *KISS1R* gene (NM_032551) were amplified by *polymerase chain reaction (*PCR) and sequenced.

▪In index case, we found a compound heterozygous mutation in the *KISS1R*, one of these was a nonsense variant (c.969C>A, p.Y323X) which was known as an inactivating mutation caused IHH and the other was a novel missense variant (c.170T>C, p.L57P).

▪Molecular analysis of the parents showed that both parents were heterozygous carriers. While the mutation c.969C>A (p.Y323X) was inherited from the father, c.170T>C (p.L57P) was inherited from the mother.

▪The moleculer analysis of his siblings were performed. Karyotype analysis of all three sisters were 46,XX. Genetic analysis of both sisters who were fourteen and twelve years old revealed the same compound heterozygous mutation in the proband whereas the genetic analysis of the youngest one was normal. Clinical and hormonal characteristics of all cases including the proband are shown in the table 1.

	Case 1 (Index)	Case 2	Case 3	Case 4
Age	14,08 yr	14 yr	12 yr	5 yr
Gender	Male	Female	Female	Female
Puberty	Tanner stage 1 SPL: 4 cm TV: 3cc/3cc	Tanner stage 3 Amenorrhea	Tanner stage 1	Tanner stage 1
Laboratory				
FSH (mIU/ml)	0,9	4,06	0,86	1,58
LH (mIU/ml)	0,13	1,21	0,07	<0,07
Total Testosteron (ng/dL)	15			
Estradiol (pg/ml)		14	<10	<10
AMH (ng/ml)	51,2 (2-30,7)			
Screening	Both testises were in scrotum. Right testis: 16 x 9 x 9 mm, Left testis: 15 x 8 x 8 mm	Uterus size: 47 x 18 x 11 mm Right ovary: 24 x 18x 14 mm Left ovary: 20 x 18 x 14 mm	Pelvic USG: Uterus and ovaries were not observed. Pelvic MRI: Uterus were not detected. Bilateral streak gonads (+).	Uterus: 33x 15 x 9 mm Right ovary: 19x 15 x 9.5 mm Right ovary: 22x 11x 9 mm
Karyotype	46XY	46XX	46XX	46XX
Genetic analysis	c.969C>A (p.Y323X) ve c.170T>C (p.L57P) compound heterozygous mutation in *KISS1R*	c.969C>A (p.Y323X) ve c.170T>C (p.L57P) compound heterozygous mutation in *KISS1R*	c.969C>A (p.Y323X) ve c.170T>C (p.L57P) compound heterozygous mutation in *KISS1R*	No mutation.

Discussion

▪In this study, while index case has IHH, two of his sister have uncompleted puberty and amenorrhea (Table 1) .

▪Thus, the inadequacies of controlling KISS1 protein can manifest itself in different clinical entities.

▪In this study, although three of the four siblings have the same inactivating compound heterozygous mutation, because of the phenotypic spectrum of GnRH deficiency resulting from disregulation of kisspeptin, two of them has uncompleted puberty and amenorrhea while one have IHH.

▪In conclusion, we found a compound heterozygous mutation of *KISS1R* gene causes normosmic idiopathic hypogonadotropic hypogonadism and also uncompleted puberty. In previous studies, the loss-of-functional mutations of *KISS1R/GPR54* which were inherited as autosomal recessive mutations are more likely reported in consanguineous families.

▪We identified these mutation in a non-consanguineous family which illustrates different phenotypic spectrum of *KISS1R/GPR54*. We recommend genetic counselling for *KISS1R* gene mutation in IHH patients, although the members are from a non-consanguineous family.

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