TITLE

Kallmann Syndrome due to a homozygous missense c.217C>T (p.R73C) mutation detected in the exon 2 of the PROK2 gene

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OBJECTIVES

Kallmann syndrome (KS), the prototype of anosmic idiopathic hypogonadotropic hypogonadism (IHH), is charecterized with HH acompanied by anosmia, absence or hypoplasia of olfactory bulbus due to defective morphogenesis. Mutations in 10 genes have been reported to cause KS while can clarify the underlying molecular defect in about 30-50% of cases. Beside, *PROK2* gene mutations are extremely rare cause of KS. Herein, we present KS due to a homozygous missense c.217C>T(p.R73C) mutation detected in exon-2 of the *PROK2* gene in a consanguineous Turkish family.

PATIENTS&METHODS

The index case was a 13 year-old male presented with delayed puberty and small penis. His past medical history was unremarkable. Parents were first cousin (Figure 1). In the physical examination his height was 143.1 cm (25th pc.), weight was 37.4 kg (25th pc.). His genitourinary system examination revealed a penis size of 4 cm, a 2 ml testis in the left scrotum with non-palpable right testis. He had anosmia. Hormonal work/up revealed prepubertal gonadotropin levels with undetectable testosterone (FSH:0.546mIU/ml, LH:0.13mIU/ml, total testosteron:<20 ng/dl). Ultrasonographic examination showed a 10x5x5 mm testis on right inguinal canal and left testis in the scrotum. A dagnosis of KS was considered and right orchiopexy had been performed. Molecular genetic analysis detected a previously reported homozygous missense c.217C>T(p.R73C) mutation in the exon-2 of *PROK2* gene (Figure 2). A prepubertal male sibling was also homozygous for the mutation. His clinical and laboratory investigations are still in process. Unaffected parents, three males and one female siblings were all heterozygous for the mutation.

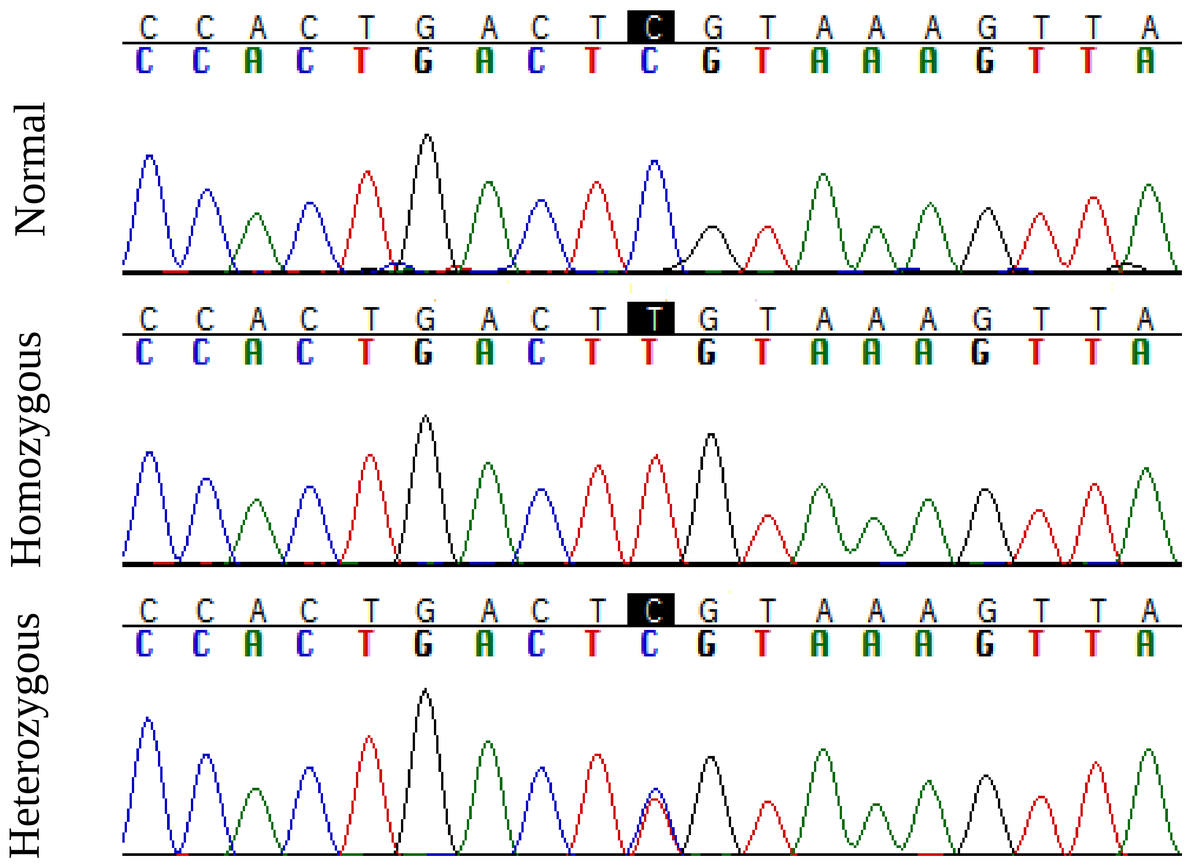

Figure 2: Sequencing chromatogram of the missense c.217C>T(p.R73C) mutation in the exon-2 of *PROK2* gene

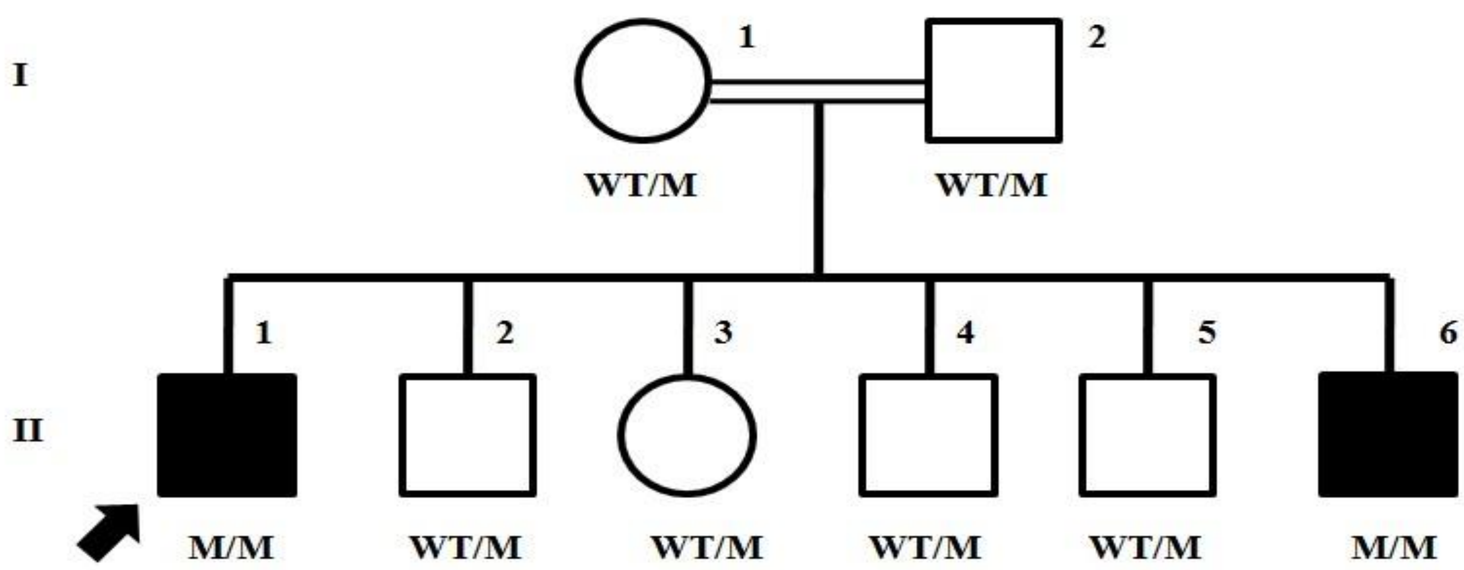

Figure 1: Pedigree of the family with PROK2 gene mutation. Index case and one prepubertal male sibling were carrying mutation homozygous while both parents and other apparently healthy siblings had heterozygous mutation (M: Mutated, WT: Wild type)

CONCLUSION

Since KS due to *PROK2* gene mutations is extremely rare, present family with cases with clinical characteristics of KS and homozygous missense c.217C>T(p.R73C) mutation detected in *PROK2* gene and those who were unaffected and heterozygous for the mutation would help to further understand the underlying molecular genetics etiology of KS.

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