Identification of a novel *KISS1R* (*GPR54*) gene variant (c.505+2T>G) in a patient with congenital hypogonadotropic hypogonadism: A case report and literature review

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Abstract. Congenital hypogonadotropic hypogonadism (CHH) is a rare disorder (incidence, 1/15.000-1/50.000) characterized by delayed or absent puberty due to a deficient secretion of gonadotropin-releasing hormone (GnRH). A *KAL1* mutation is the most common genetic cause of CHH, which is typically associated with anosmia. By contrast, the less common kisspeptin-1 receptor (*KISS1R*) mutation is more frequently observed in normosmic patients. This study aimed to investigate a 21-year-old male with normosmic CHH caused by a novel homozygous splice-site mutation in the *KISS1R* gene (c.505+2T>G). The location of the identified variant (c.505+2T>G) near the exon-intron junction suggests the possibility of receptor dysfunction. 2The clinical features included micropenis, reduced body hair, erectile dysfunction and small testes. The hormonal analysis confirmed low testosterone levels with inappropriately normal gonadotropin levels. The pituitary magnetic resonance imaging indicated normal results, and a GnRH stimulation test confirmed a hypothalamic origin of the deficiency. The patient responded well to human chorionic gonadotropin alpha monotherapy, indicating increased testosterone levels, spermatogenesis and testicular volume. During a 24-week follow-up, the patient maintained hormonal and clinical improvements, including the normalization of erectile function and increased body hair growth. To our knowledge, this *KISS1R* variant has not been previously investigated. Thus, the findings of the present study contribute novel insights into the genetic spectrum of CHH. Given the consanguinity in the family, this case also emphasizes the value of genetic counseling in familial forms of CHH.

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Introduction

Hypogonadotropic hypogonadism (HH) is a rare disorder caused by the decreased secretion or dysfunction of gonadotropin-releasing hormone (GnRH). In addition to the acquired causes of HH, congenital etiologies have also been established, which are less frequently observed (1). Congenital HH (CHH) has an estimated prevalence of 1 in 15,000 to 50,000 and shows a significant male predominance with a male-to-female ratio of ~3.6:1. Although the majority of the cases are associated with anosmia, about one-third of the patients have a normosmic presentation. Among the >40 mutations identified in CHH, the most common is the *KAL1* mutation, which typically presents with symptoms of anosmia (2,3). Among the rarer causes, mutations in the kisspeptin-1 receptor gene (*KISS1R*/*GPR54*), which follow an autosomal recessive inheritance pattern, have been identified. The *KISS1R* gene encodes a G protein-coupled receptor expressed in the hypothalamus that plays a critical role in kisspeptin signaling. Mutations of the *KISS1R* gene impair kisspeptin-mediated signaling, resulting in a reduction in GnRH secretion. Thus, the pituitary gland receives insufficient GnRH stimulation, resulting in inadequate secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Unlike many other mutations associated with CHH, *KISS1R* mutations may not be accompanied by symptoms of anosmia (4,5). CHH is characterized by low or inappropriately normal levels of FSH and LH, accompanied by decreased serum testosterone concentrations. In patients who are diagnosed during adulthood, the clinical findings may include reduced testicular volume (<4 ml), underdeveloped secondary sexual characteristics, micropenis, erectile dysfunction, decreased libido, impaired sperm quality, gynecomastia and various psychiatric symptoms (6). One treatment option for CHH is pulsatile GnRH therapy. Furthermore, human chorionic gonadotropin (hCG) alpha, which is purified from the urine of pregnant women, can be used as a substitute for LH. This treatment has a success rate of ~75%. The combination

therapy of hCG alpha and FSH represents another therapeutic approach (7). This study aimed to investigate a 21-year-old male diagnosed with CHH due to a rare mutation in the *KISS1R* gene.

Case report

This study included a 21-year-old, single male patient who presented to the Endocrinology and Metabolic Diseases Clinic of Ankara Etlik City Hospital (Ankara, Turkey) in July 2024 with complaints of micropenis, decreased muscle strength, sparse body hair and erectile dysfunction. The patient had no history of chronic illness, trauma or previous surgery. The patient's parents were first-degree cousins. The patient had a 14-year-old sister who presented with delayed puberty, in whom a genetic analysis revealed a homozygous *KISS1R* mutation (c.505+2T>G variant). The patient's sister is currently under follow-up and treatment at Ankara Etlik City Hospital Pediatric Endocrinology Clinic (Ankara, Turkey). The patient's other sibling, an 18-year-old sister, is healthy and 20 weeks pregnant at the time of writing the manuscript. Physical examination of the patient revealed sparse facial and pubic hair, increased subcutaneous adiposity, gynecomastia, micropenis and small testes. The patient's body mass index was 27.3 kg/m^2 (Normal range: 18.5-24.9 kg/m^2) (height, 176 cm; weight, 84.6 kg). Olfactory and auditory functions were intact.

The laboratory examination revealed a FSH level of 5.58 IU/l (reference: 1.5-12.4 IU/l), LH of 4.19 IU/l (reference: 1.7-8.6 IU/l) and total testosterone of 54.9 ng/dl (reference: 249-836 ng/dl), which is consistent with HH (8). Other anterior pituitary hormone levels and routine biochemical parameters were within normal limits. A 0.1 mg GnRH stimulation test was performed (9). The response shown by the LH and FSH levels confirmed the hypothalamic origin of HH (Table I).

The pituitary magnetic resonance imaging (MRI) with intravenous contrast revealed a normal pituitary gland measuring 6 mm in height, with no evidence of mass lesions (Fig. 1). Although semen analysis was planned, the patient was unable to complete the procedure. The bone mineral density assessment by dual-energy X-ray absorptiometry showed a Z-score of -2.0 at the femoral neck and -2.5 at the lumbar spine (L1-L4) (data not shown; expected normal Z score for age, >-2.0), indicating decreased bone density (10). Genomic DNA was isolated from peripheral blood samples using the QIAamp DNA Blood Kit (Qiagen GmbH) on an automated extraction system. Library preparation was performed using the SOPHiA DDM™ Clinical Exome Solution v3 (SOPHiA Genetics) and sequencing was carried out on the NextSeq 2000 platform (Illumina, Inc.) in accordance with the manufacturer's standard protocols. Raw sequencing data were analyzed using the SOPHiA DDM™ platform (SOPHiA Genetics) and sequence reads were aligned to the human reference genome GRCh37. A clinical gene panel associated with hypogonadism was analyzed. Variants were filtered based on a minimum read depth of 30x and a minor allele frequency of <1%. Splice-site variants were evaluated within ±20 base pairs of exon-intron boundaries. Genetic analysis identified a homozygous c.505+2T>G variant, which was classified as likely pathogenic according to the American College of Medical Genetics and Genomics guidelines (Fig. 2). The variant was subsequently confirmed by Sanger sequencing using the BigDye™ Terminator v3.1 Cycle Sequencing Kit (Thermo Fisher Scientific, Inc.) on an Applied Biosystems 3130 Genetic Analyzer (Thermo Fisher Scientific, Inc.) (11). Based on this result, a definitive diagnosis of CHH due to *KISS1R* mutation was established.

Table I. Gonadotropin-releasing hormone stimulation test results.

Time-point, min	FSH, IU/l	LH, IU/l
0	5.81	4.2
30	8.8	17.6
60	9.91	17.1

FSH, follicle-stimulating hormone; LH, luteinizing hormone.

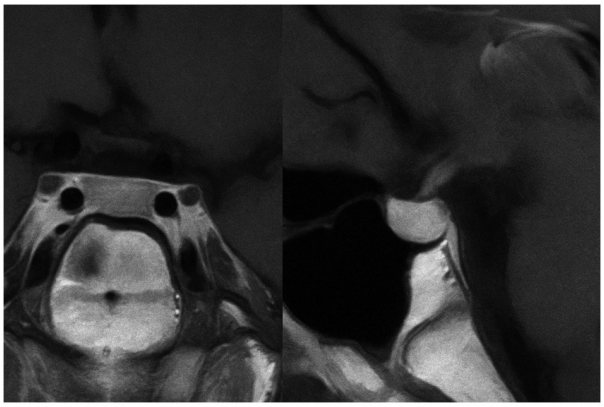

Figure 1. Pituitary gland in the coronal (left) and sagittal (right) sections on the T1 sequence on magnetic resonance imaging.

The patient was started on subcutaneous hCG alpha treatment at a dose of 6,500 IU once a week. By the 12th week of treatment, a significant increase in the total testosterone levels was observed, along with significant improvements in muscle strength, body hair growth and erectile function. Furthermore, the semen analysis performed during this period revealed an adequate sperm reserve and function (12). Clinical and laboratory improvements were maintained through to the 24th week of treatment (Table II). At that time, hCG alpha therapy was continued at the same dose, and the patient was scheduled for regular endocrinological follow-up every 3-6 months. As hCG alpha provides an exogenous LH-like stimulus; its beneficial effects on testosterone production and spermatogenesis are expected to be dependent on ongoing treatment and to diminish if therapy is discontinued (13). At the time of writing, the patient remains on hCG alpha with sustained clinical and biochemical response.

Discussion

This study assessed a 21-year-old male presenting with decreased body hair, micropenis and erectile dysfunction for HH. After a thorough evaluation to exclude acquired causes of HH (including chronic systemic disease, hyperprolactinemia, previous cranial irradiation or trauma, and pituitary

Table II. Biochemical, semen analysis and scrotal USG results before and after treatment.

Parameters	Normal values	Week 0	Week 12	Week 24
FSH, IU/l	1.5-12.4	5.58	0.39	1.24
LH, IU/l	1.7-8.6	4.19	0.45	1.41
Total testosterone, ng/dl	249-836	54.9	628	474
TSH, mIU/l	0.4-4.2	2.12	1.82	1.08
Free T4, ng/dl	0.9-1.7	1.28	0.91	1.15
Free T3, ng/l	2-4.4	3.38	3.98	3.98
Spermiogram				
Sperm concentration, million/ml	≥15	-	15.6	74.6
Total mobility, %	≥40	-	12	19
Motile sperm concentration, million/ml	≥5	-	1.2	14.2
Concentration of progressively motile sperm, million/ml	≥5	-	0	11.2
Total sperm count, million	≥39	-	25	37.3
Testicular volumes on USG, right/left, ml	≥10	7/6	11/6	11/6

FSH, follicle-stimulating hormone; LH, luteinizing hormone; TSH, thyroid stimulating hormone; USG, ultrasonography.

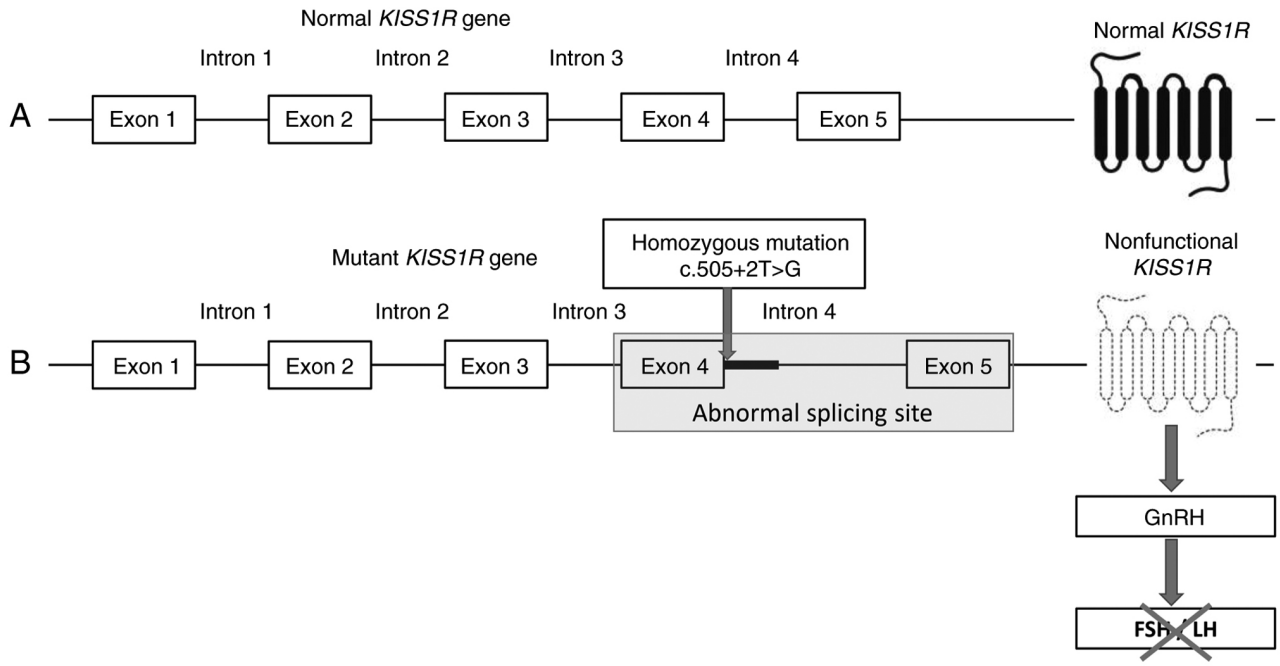

Figure 2. Schematic representation of the *KISS1R* gene and receptor. (A) Normal gene splicing and functional *KISS1R* leading to normal GnRH signaling. (B) Mutant *KISS1R* gene carrying the c.505+2T>G variant disrupts the splice donor site between exons 4 and 5, resulting in aberrant mRNA splicing and a truncated, nonfunctional receptor, ultimately reducing GnRH and gonadotropin secretion. *KISS1R*, kisspeptin-1 receptor; GnRH, gonadotropin-releasing hormone.

or hypothalamic lesions on MRI), a congenital etiology was suspected. The genetic testing results revealed a homozygous mutation in the *KISS1R* gene. To our knowledge, this specific variant, c.505+2T>G, has not been previously reported in the literature. Thus, this case represents the first documented instance of this novel *KISS1R* mutation in a patient with CHH, expanding the known genetic spectrum of the disorder.

CHH is a rare hypothalamic-pituitary disorder characterized by absent or delayed pubertal development. This case shows a typical clinical presentation of CHH in a young male with absent pubertal progression, low serum gonadotropin levels and a normal pituitary gland on contrast-enhanced MRI. CHH results from defects in the migration or secretion of GnRH neurons. Both the sporadic and familial forms of CHH have been described (2). The absence of anosmia in this patient helped distinguish the condition from Kallmann syndrome (14). The genetic analysis results revealed a *KISS1R* mutation, consistent with normosmic CHH (15). The *KISS1R* gene encodes a G protein-coupled receptor for the *KISS1* peptide. It comprises five exons and four introns (Fig. 2).

c.505+2T>G is an intronic mutation located in intron 4, and intronic mutations are often polymorphic rather than structural/functional mutations. However, of note, the c.505+2T>G mutation reported in the present study was located close to the splicing junctional site (the junction of exon 4 and intron 4), suggesting the possibility of certain abnormalities in the receptor. However, further confirmatory molecular experiments are needed to prove its pathological role (16,17).

A study by Francou *et al* (18) assessed 603 patients with normosmic CHH and identified *KISS1R* mutations in ~2% of all cases, emphasizing the rarity of this genetic variant. During the diagnostic evaluation, significantly low serum levels of LH and FSH in conjunction with testosterone deficiency were found. This classic hormonal profile was also observed in the patient of the present study. The primary differential diagnosis for CHH is a constitutional delay of puberty; however, unlike CHH, individuals with constitutional delay typically experience spontaneous pubertal progression over time, which is not expected in CHH (19).

The primary goals of treatment in CHH include achieving an age-appropriate virilization, preserving or restoring fertility, optimizing sexual function, attaining normal adult height and supporting psychosocial well-being (20). While exogenous testosterone is effective in promoting the development of secondary sexual characteristics, it suppresses intratesticular testosterone production and inhibits spermatogenesis and testicular volume increase (21). In patients such as the case of the present study, where both virilization and fertility are desired, the treatment options include pulsatile GnRH therapy, hCG alpha monotherapy or combined treatment of hCG alpha and FSH (22). However, several studies have shown that in patients with a history of cryptorchidism and baseline testicular volumes <4 ml, the likelihood of achieving fertility through such treatments remains low (23-25). A 19-year-old male patient with CHH, as reported by Brioude *et al* (26), remained azoospermic after 1 year of testosterone therapy. Given the patient's desire for fertility, combined gonadotropin therapy was initiated, which comprised subcutaneous hCG alpha at 1,500 IU three times per week and FSH at 150 IU three times per week. After 22 months of treatment, the patient showed a significant increase in testicular volume and normalization of the sperm count, resulting in a successful pregnancy in the patient's partner. In this case of CHH, the treatment objective was to achieve both virilization and fertility. Thus, subcutaneous hCG alpha therapy was initiated at a total weekly dose of 6,500 IU. The follow-up assessments at weeks 12 and 24 showed significant improvements in secondary sexual characteristics and adequate progression of spermatogenesis, as demonstrated by semen analysis.

In conclusion, the present study reported a novel *KISS1R* gene variant (c.505+2T>G) associated with CHH in a young male patient. The clinical presentation was consistent with the classical features of CHH and the patient responded favorably to hCG alpha therapy, which was aimed at achieving both virilization and fertility. This case emphasizes the importance of considering CHH in the differential diagnosis of delayed puberty, as early identification and treatment are essential to prevent long-term physical and psychosocial consequences. Furthermore, genetic analysis and counseling play a critical role in confirming its diagnosis and guiding its management. The present findings contribute to the expanding body of literature on *KISS1R*-related CHH and introduce a previously unreported mutation, providing valuable insights into the genetic spectrum of this rare condition.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

BM and EU identified and managed the case, curated the clinical data, performed the literature review and drafted the manuscript. AB conducted and interpreted the genetic testing confirming the novel variant and authored the genetics section. SH and IOU contributed to data acquisition (laboratory, imaging and follow-up) and assisted in manuscript preparation. MK contributed to the endocrine assessment and interpretation of biochemical findings. TA and EC collected the data, performed the statistical analyses, critically reviewed the article for significant intellectual content and provided overall supervision. BM and EU confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study was conducted in accordance with the ethical standards of institutional and national research committees, the Declaration of Helsinki and its later amendments, or comparable ethical standards. This case report does not require ethics committee approval from our affiliated institution.

Patient consent for publication

The patient was informed of the purpose of the publication. The patient provided written consent to the publication of his clinical findings and imaging results in the journal.

Competing interests

The authors have no competing interests to declare that are relevant to the content of this article.

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