CASE REPORT

DOI: 10.4274/jcrpe.galenos.2022.2022-3-18

J Clin Res Pediatr Endocrinol 2024;16(1):91-94

A Novel *KISS1R* Loss-of-function Variant in a Chinese Child with Congenital Hypogonadotropic Hypogonadism

Peng Zhou, Jin Wu

Sichuan University, West China Second University Hospital, Department of Pediatrics; Sichuan University, West China Second University Hospital, Ministry of Education, Key Laboratory of Birth Defects and Related Diseases of Women and Children, Chengdu, China

What is already known on this topic?

Congenital hypogonadotropic hypogonadism (CHH) is a rare genetic disorder, resulting from impaired production, secretion, or action of gonadotropin-releasing hormone (GnRH). Mutations of the *KISS1R (GPR54)* gene can result in CHH. Minipuberty is a critical period for genital development due to the activation of the GnRH axis in the initial postnatal months.

What this study adds?

A novel compound heterozygous mutation of *KISS1R* causing CHH in a Chinese boy was reported. The report adds to the spectrum of mutations in the KISS1R gene seen in children with CHH. Evaluation of minipuberty in male newborns and infants who present with micropenis, with or without undescended testes, can help in the early diagnosis and possible early treatment of nCHH.

Abstract

Congenital hypogonadotropic hypogonadism (CHH) is a rare genetic disorder, resulting from impaired production, secretion, or action of gonadotropin-releasing hormone (GnRH). Variants of the *KISS1R* gene can result in CHH. Herein we describe a Chinese boy with CHH, caused by a novel, compound heterozygous variant in *KISS1R*. A male infant presented to the pediatric urological surgeon at three months of age for micropenis. Laboratory investigations done at this time revealed low levels of serum gonadotropins and testosterone, suggesting a lack of minipuberty. Topical application of dihydrotestosterone gel was recommended, but the parents refused treatment. The child was brought to our hospital at 3.3 years of age for the same complaint. A diagnosis of CHH was considered, and next generation sequencing revealed a compound heterozygous variant including a novel c.182C > A (p.S61*) and a c.418C > T (p.R140C) in *KISS1R*. We describe a novel compound heterozygous variant in the *KISS1R* in a boy with CHH, born to non-consanguineous Chinese parents. This report adds to the spectrum of variants in *KISS1R* seen in children with CHH.

Keywords: Hypogonadotropic hypogonadism, *KISS1R*, minipuberty

Introduction

Congenital hypogonadotropic hypogonadism (CHH) is a rare genetic disorder caused by a defect in the production, secretion, or action of gonadotropin-releasing hormone (GnRH), which regulates the reproductive axis. CHH may present with reproductive symptoms, such as cryptorchidism, micropenis, absent or incomplete puberty, infertility, amenorrhea, and a lack of breast development, and with non-reproductive features, such as bimanual synkinesis, abnormal eye movements, agenesis of the corpus callosum, unilateral or bilateral renal agenesis, cleft lip or palate, alteration of digital bones, and daltonism (1). CHH can be broadly divided into two categories; cases resulting from the abnormal embryonic migration of GnRH neurons from the olfactory placode to the forebrain and associated with anosmia/hyposmia [Kallmann syndrome (KS)], and cases characterized by pure neuro-endocrine impairment of GnRH secretion or action, namely normosmic CHH (nCHH). The incidence of CHH is uncertain. KS has an incidence of 1:125,000 in females and 1:30,000 in males, as reported in a recent epidemiological study (2).

Address for Correspondence: Jin Wu MD, Sichuan University, West China Second University Hospital, Department of Pediatrics, Chengdu, China
E-mail: wangdo620@163.com **ORCID:** orcid.org/0000-0002-6721-5431

Conflict of interest: None declared
Received: 23.03.2022
Accepted: 26.04.2022

CHH is seldom diagnosed during childhood, a physiologically hypogonadal period. However, minipuberty is a window for early diagnosis of CHH. Minipuberty is a critical period for genital development due to the activation of the GnRH axis in the initial postnatal months. In boys, there is a rise in the serum testosterone (T) and gonadotropin levels, which peak at three months of age and almost approach adult male levels. This is followed by a decline to low prepubertal levels by about six months. Due to impaired activation of the GnRH axis in minipuberty, low serum T and gonadotropin levels can be observed in infants affected by CHH (3).

Variants of *KISS1R* are found in approximately 5 % of patients with nCHH (4). More than 30 different *KISS1R* variants have been reported to date (5). With the widespread use of genetic testing, genetic causes of CHH are increasingly being identified (1). We present a boy with nCHH born to non-consanguineous, Chinese parents, where a compound heterozygous variant was identified on genetic testing. This included a novel c.182C > A (p.S61*) variant, which was predicted to be pathogenic and the variant c.418C > T (p.R140C), a variant of uncertain significance (VUS) in *KISS1R*.

Case Report

The proband, born to non-consanguineous Chinese parents, was noticed to have a small penis since birth. A pediatric urologist was consulted for the same complaint when the infant was three months old. Investigations showed low levels of serum T and gonadotropins-follicle stimulating hormone (FSH) and luteinizing hormone (LH) (T < 0.03 ng/mL, FSH < 1.1 mIU/mL, and LH < 0.11 U/L). The karyotype was 46, XY. An absence of minipuberty was diagnosed and dihydrotestosterone topical gel was recommended for treatment of micropenis. However, the parents refused treatment at this time.

At 3.3 years of age, the boy was referred to our hospital for investigation of micropenis. There was no family history of any reproductive problems or non-reproductive features associated with CHH. The child could perceive smell. On physical examination, he had a micropenis with stretched length of 1.5 cm (< -4 standard deviation) (6). Neither hypospadias nor cryptorchidism was present. The right testicular volume was 1 mL and the left 0.5 mL. There were no dysmorphic features on general examination and neurological examination was normal.

Investigations showed a basal serum T level of < 0.07 ng/mL, LH < 0.1 IU/L and FSH 1.9 IU/L. The GnRH stimulation test showed a peak LH of 3.9 IU/L at 30 mins and an FSH peak of 26.7 IU/L at 60 mins (Table 1). The results of the 3-day human chorionic gonadotropin (hCG) stimulation test are also shown in Table 1. Serum T increased by 5-10 times on stimulation, which is considered a good response. Serum thyroid stimulating hormone (TSH), free thyroxine (FT4), prolactin, adrenocorticotropic hormone (ACTH), morning cortisol, and insulin-like growth factor-1 (IGF-1) levels were all within the normal range.

An ultrasound scan of the scrotum revealed a right testis of 12 x 6 x 8 mm and a left testes of 11 x 5 x 10 mm. Bone age was 2.2 years (10^{th}-25^{th} percentile) assessed by the Tanner-Whitehouse 2 (TW2) method. Magnetic resonance imaging (MRI) of the brain detected multiple abnormal signals, presenting with slightly longer signals on T1 and T2 weighted images, and slightly higher signal on the flair sequence, in the centrum semiovale and lateral ventricles. The upper edge of the pituitary was sunken. The olfactory bulb and olfactory tract were normal.

Whole exome sequencing and Sanger sequencing revealed a compound heterozygous variant in *KISS1R*. Variant c.182C > A (p.S61*) was inherited from the mother while c.418C > T (p.R140C) was inherited from the father (Figure 1). After annotation via InterVar and classification according to the American College of Medical Genetics and Genomics (ACMG) guidelines, the c.182C > A (NM_032551.5) was classified as pathogenic with evidence levels PVS1 + PM2 + PP3, while c.418C > T was classified as VUS with evidence levels PM1 + PM2 + PP3.

A final diagnosis of nCHH was made and treatment with hCG was recommended to induce penile growth. However, the parents again refused treatment. At 4.6 years of age, the boy was again referred to our hospital for the same complaint. At this visit, the parents opted to use dihydrotestosterone topical gel to treat micropenis rather than hCG or intramuscular T. The child started local application of 2.5% dihydrotestosterone topical gel (0.2-0.3 mg/kg/day) and is due for follow-up after three months.

Table 1. GnRH test and hCG stimulation test

	0 min	30 min	60 min	90 min	120 min		Pre-hCG	Day 3 post-hCG
LH (IU/L)	< 0.1	3.9	3.5	2.5	1.9	Testosterone (ng/mL)	< 0.07	2.19
FSH (IU/L)	2.0	21.7	26.7	25.1	23.6	Dihydrotestosterone (pg/mL)	< 50	69.61

GnRH: gonadotropin-releasing hormone, LH: luteinizing hormone, FSH: follicle-stimulating hormone, hCG: human chorionic gonadotropin

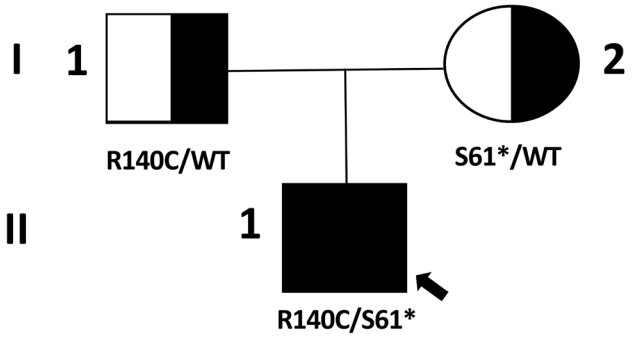

Figure 1. Circles represent females and squares males. Half-shaded symbols indicate unaffected heterozygous and solid symbols affected subjects. The proband, subject II-1 (arrow), was compound heterozygous for the *KISS1R* variants R140C/S61*. The unaffected father (I-1) was heterozygous for the R140C variant and the unaffected mother (I-2) was heterozygous for the S61* variant

Discussion

Interaction of the KISS1R protein and its natural ligand Kisspeptin-1 plays a critical role in initiation and development of puberty. Loss-of-function variants of *KISS1R* responsible for nCHH in humans were first reported in 2003 (7). Most of the previous cases of nCHH associated with *KISS1R* were homozygous variants described in adults and teenagers born of consanguineous parents (5).

In this case report, we describe a prepubertal boy with micropenis, a lack of minipuberty and delayed bone age, suggestive of CHH. CHH remains a diagnosis of exclusion (8) and so malnutrition, any chronic disease, or excessive exercise, the functional causes were exluded. Structural causes, such as tumors, apoplexy, surgery, or infiltrative diseases were also ruled out by brain MRI. Combined pituitary hormone deficiency was also excluded by normal levels of TSH, FT4, prolactin, ACTH, morning cortisol and IGF-1. So the diagnosis of CHH was considered. Whole exome sequencing revealed a compound heterozygous variant in the *KISS1R*, including a novel c.182C > A (p.S61*) (pathogenic) variant and a c.418C > T (p.R140C) (VUS) variant. Loss-of-function variants of *KISS1R* are responsible for nCHH in humans. The boy could perceive smell. The MRI also showed normal olfactory bulb and olfactory tract, presumably since *KISS1R* is involved in GnRH neuron activation and not migration. When clinical data and genetic results were considered together, these variants are most likely to explain the nCHH found in the proband.

The proband was the only child of his parents. He presented with micropenis. Patients with kisspeptin receptor insufficiency may manifest with either complete or partial gonadotropic deficiency. Micropenis in these patients is due to fetal T deficiency resulting from absence of testicular stimulation by gonadotropins during the second and third trimesters of pregnancy (9). Hormonal evaluation revealed low gonadotropins and T concentrations at three months of age, supporting a diagnosis of a lack of minipuberty. Minipuberty is the transient, sex-specific activation of the hypothalamic-pituitary-gonadal axis during the first six months of life in boys (10). A lack of minipuberty in infancy provides a valuable opportunity for the diagnosis of CHH, since childhood is generally a period of physiological hypogonadism (8).

A compound heterozygous variant was found in *KISS1R* in the presented case. The first variant was a nonsense variant, which cause an early termination for translation and was classified as pathogenic according to the ACMG guideline. The second variant was a missense variant, its frequency was extremely low in gnomAD database (0.000006571 for whole database and 0.0001924 for East Asian subgroup of gnomAD database), and relative higher (0.1445%) in the South Asia subgroup of the GenomAsia database (1 allele count in a total of 692). The frequency difference between GenomAsia and gnomAD maybe due to the total cohort number: gnomAD (n = 5198) compared to GenomAsia (n = 692). Other evaluation results included: in cohort > 1000 a pathogenic variant was detected at the trans position in autosomal recessive disease; multiple protein prediction software predicted that the variation was deleterious; and genotype was correlated with phenotype so the variant was classified as VUS.

However, no functional studies were performed to demonstrate the pathogenicity of these variants. Our patient will need long-term follow-up to observe the efficacy of dihydrotestosterone topical gel. Multiple abnormal signals in the centrum semiovale and lateral ventricles, and a sunken upper edge of the pituitary were observed in MRI of the brain, which are not explained at present.

Conclusion

In conclusion, we report a novel compound heterozygous variant of *KISS1R* causing nCHH in a Chinese boy. Evaluation of minipuberty in male newborns and infants who present with micropenis, with or without undescended testes, can help in the early diagnosis and possible early treatment of nCHH. Genetic testing is also recommended to assist the diagnosis of CHH and to provide genetic counseling to the family. Our case adds to the increasing evidence concerning the spectrum of CHH caused by variants in *KISS1R*.

Acknowledgements

We would like to thank the family who participated in the study. We also thank Zuozhen Yang of CpherGene LLC for his assistance in genetic analysis.

Ethics

Informed Consent: Consent form was filled out by all participants.

Authorship Contributions

Surgical and Medical Practices – Concept – Design - Data Collection or Processing - Analysis or Interpretation - Literature Search - Writing: Peng Zhou, Jin Wu.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Oleari R, Massa V, Cariboni A, Lettieri A. The Differential Roles for Neurodevelopmental and Neuroendocrine Genes in Shaping GnRH Neuron Physiology and Deficiency. Int J Mol Sci 2021;22:9425.
2. Laitinen EM, Vaaralahti K, Tommiska J, Eklund E, Tervaniemi M, Valanne L, Raivio T. Incidence, phenotypic features and molecular genetics of Kallmann syndrome in Finland. Orphanet J Rare Dis 2011;6:41.
3. Swee DS, Quinton R. Congenital Hypogonadotrophic Hypogonadism: Minipuberty and the Case for Neonatal Diagnosis. Front Endocrinol (Lausanne) 2019;10:97.
4. Bianco SD, Kaiser UB. The genetic and molecular basis of idiopathic hypogonadotropic hypogonadism. Nat Rev Endocrinol 2009;5:569-576. Epub 2009 Aug 25
5. Alzahrani AJ, Ahmad A, Alhazmi T, Ahmad L. An Isolated Hypogonadotropic Hypogonadism due to a L102P Inactivating Mutation of KISS1R/GPR54 in a Large Family. Case Rep Pediatr 2019;2019:3814525.
6. Schonfeld WA, Beebe GW. Normal growth and variation in the male genitalia from birth to maturity. J Urology 1942;48:759-777.
7. de Roux N, Genin E, Carel JC, Matsuda F, Chaussain JL, Milgrom E. Hypogonadotropic hypogonadism due to loss of function of the KiSS1-derived peptide receptor GPR54. Proc Natl Acad Sci U S A 2003;100:10972-10976. Epub 2003 Aug 27
8. Grinspon RP, Freire AV, Rey RA. Hypogonadism in Pediatric Health: Adult Medicine Concepts Fail. Trends Endocrinol Metab 2019;30:879-890. Epub 2019 Aug 27
9. Kohva E, Huopio H, Hietamäki J, Hero M, Miettinen PJ, Raivio T. Treatment of gonadotropin deficiency during the first year of life: long-term observation and outcome in five boys. Hum Reprod 2019;34:863-871.
10. Young J, Xu C, Papadakis GE, Acierno JS, Maione L, Hietamäki J, Raivio T, Pitteloud N. Clinical Management of Congenital Hypogonadotropic Hypogonadism. Endocr Rev 2019;40:669-710.