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PROKR2 mutations and SPRY4 variants with uncertain significance in a Kallmann syndrome family: Incomplete penetrance

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ABSTRACT

Kallmann syndrome is a rare genetic disease characterized by the idiopathic hypogonadotropic hypogonadism with hyposmia or anosmia, which exhibits considerable heterogeneity in genotype and phenotype. Herein, we reported a 32-year-old male patient with Kallmann syndrome in a family associated with heterozygous mutations in PROKR2 and SPRY4 genes. The genotyping results indicated PROKR2 mutations and SPRY4 variants of uncertain significance, which might be incompletely penetrant in this family.

Introduction

Kallmann syndrome (KS) is a rare genetically heterogeneous disease characterized by isolated hypogonadotropic hypogonadism accompanied by anosmia or hyposmia, which is caused by impaired migration of olfactory and gonadotropin-releasing hormone (GnRH) neurons. KS results in the failure of the normal episodic GnRH secretion, and consequently delayed puberty and infertility in later life [1,2].

Recent studies indicated that mutations in quite a few genes, including *ANOS1* (Xp22.3), *FGF8* (10q24.3), *FGFR1* (8p11.2-p11.1), *PROK2* (3p13), *PROKR2* (20p12.3), *NELF* (9q34.3), *CHD7* (8q12.1-q12.2), *WDR11* (10q26.12), *HS6ST1*(2q14.3), *SEMA3A* (7q21.11), play an important role in the etiology of KS either independently or in an oligogenic manner [1,3], suggesting a genetic spectrum that lies between the extremes of rare monogenic and common polygenic diseases [4].

Here we reported a 32-year-old male patient with Kallmann syndrome in a family carrying heterozygous mutations in PROKR2 and SPRY4 genes, indicating incomplete penetrance of PROKR2 mutations and SPRY4 variants of uncertain significance in this family.

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Materials and methods

Case presentation

The proband, a 32-year-old male who was the first child of non-consanguineous parents of Chinese ancestry, was born at full term following a vaginal delivery. During childhood, he showed normal growth and cognitive development compared to his peers. Yet he had delayed puberty, characterized by the absence of laryngeal prominence, facial and pubic hair, enlargement of penis and scrotum, morning erections, spermatorrhea or ejaculation. He reported occasional penile erections monthly. A partial loss of the sense of smell was found though the patient was not able to confirm when it was initiated. He denied any pertinent family history, and no cognitive or behavioral concerns were observed. The sex hormones were tested at the age of 32 in the local hospital and the results showed that the luteinizing hormone (LH) level was 0.13 IU/L (0.57–12.07 IU/L), the testosterone was 0.69 nmol/L (4.94–32.01 nmo1/L) and the estradiol was < 37.0 pmol/L (40.4–161.5 pmol/1). Thus, he was referred to the tertiary hospital for further consult and management.

The patient was 172 cm in height and 61 kg in weight with a body mass index of 20.62 kg/m^2. Clinical examination revealed no dysmorphic features of the head, chest, abdomen and limbs, including no midline defects or digital anomalies. He was unable to correctly identify the odor on the smell test. Olfactory dysfunction was confirmed using brief smell identification test and no involuntary or mirror movements was noted. The testes were bilaterally descended with the volume of 0.5 ml on the left and 2 ml on the right and pubic hair was consistent with Tanner 1 stage. The stretched penile length was approximately 3.5 cm.

Gonadotropin-releasing hormone (GnRH) stimulation test

The GnRH stimulation test was performed in the morning between 08:00 and 10:00 following a minimum of 8 h of overnight fasting. Briefly, Gonadorelin® (BBCA Pharmaceutical, Anhui, China) was administered intravenous at a dosage of 100 μg. LH and FSH were measured at 0, + 15, + 30, + 60, and + 120 min after the injection. The antecubital venous blood samples in the other arm were obtained for the determination of LH and follicle-stimulating hormone (FSH) [5].

Human chorionic gonadotropin (hCG) stimulation test

The hCG stimulation test was performed in patient receiving intramuscular injection of hCG 2000 U on 5 consecutive days with blood samples collected before the first dose of hCG (0 min) and after 24, 48, 72, 96, 120 h [6].

Chromosome analysis

G-band Karyotyping Analysis was performed as described previously and Karyotype integrity and band resolution of metaphase chromosomes was determined according to the International System for Human Cytogenetic Nomenclature [7].

Clinical whole exome assay

Genetic testing was performed by BGI (Shenzhen, China) using high-throughput sequencing of whole exome sequencing and mitochondrial genome sequencing utilizing Roche KAPA HyperExome and MGISEQ-2000 Sequencing Platform, and the data were analyzed as described previously [8].

Results

Laboratory tests

The patient was found to be hypogonadotrophic with initial laboratory tests revealing a total testosterone of 0.40 nmol/L (8.6–29.0), LH 0.25 IU/L (1.7–8.6), FSH 1.40 IU/L (1.5–12.4), estradiol < 5.00 pg/ml (11.3–43.2), testosterone 0.40 nmol/L (8.6–29.0), progesterone 0.06 ng/ml (< 0.149), while prolactin was 13.96 ng/ml (3.86–22.8) and growth hormone was 2.09 ng/ml (0.02–2.47). Upon GnRH stimulation test, peak LH was 2.62 IU/L and peak FSH was 5.08 IU/L (Fig. 1 A). The stimulation test with hCG revealed that the peak testosterone was 0.89 nmol/L after 5 days of hCG injection (Fig. 1 B).

The patient's hematological data revealed the hemoglobin level of 127 g/L (130–175 g/L) and the hematocrit of 37.7% (40–50%). No significant abnormalities were observed in liver and kidney function including serum electrolytes urea, creatinine, alanine and aspartate aminotransferases, alkaline phosphatase, conjugated and total bilirubin, as well as routine testing of urine and feces.

Imaging

The left wrist and hand x-rays revealed a bone age of 16 years and 6 months according to TW3-RUS and 15 years according to TW3-Carpal (Fig. 2). Scrotal ultrasound showed small left testis (16.8 × 6.7 mm) and right testis (16.4 × 6.3 mm). Ultrasound examination showed both breasts have mammary gland-like echogenicity with diameters of 12.2 mm (left) and 12.9 mm (right) with normal representation of skin and subcutaneous tissue. Prostate ultrasound showed the volume of prostate was small (17 × 16 × 11 mm). No abnormalities were noticed on abdominal ultrasound examination including kidney, ureter and bladder.

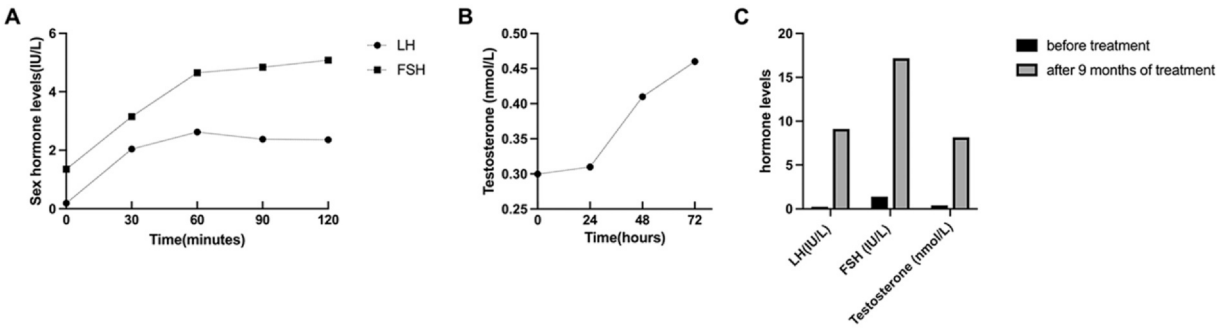

Fig. 1. Hormone levels. (A)GnRH stimulation test. (B)hCG stimulation test. (C)LH, FSH and testosterone levels before treatment and after 9 months of treatment. Abbreviations: LH, luteinizing hormone; FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin.

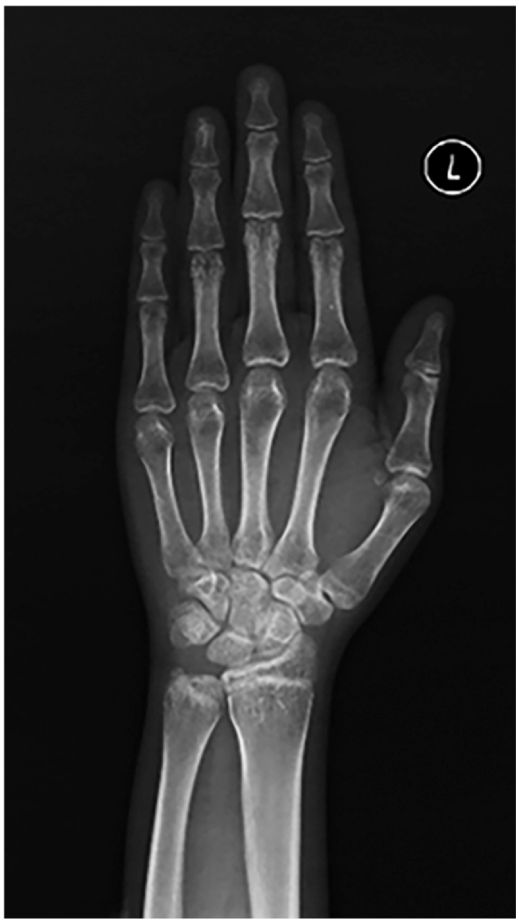

Fig. 2. Bone age. The left hand and wrist x-rays indicated that his bone age was 16 years 6 months for TW3- RUS and 15 years 0 months for TW3-Carpal.

Contrast-enhanced MRI of the pituitary demonstrated an abnormal signal in the middle part of the pituitary gland (Fig. 3). Dual-energy X-ray bone densitometry indicated his bone mineral density was below the expected value of the same age.

Genetic testing

Whole-exome sequencing showed that the NM_144773.2:c .533 G > C variant was detected in the PROKR2 gene of the patient (Fig. 4), and the nucleotide at position 533 of the coding DNA was changed from guanosine to cytosine, leading to a mutation changing a tryptophan residue at position 178 by serine (p.Trp178Ser).

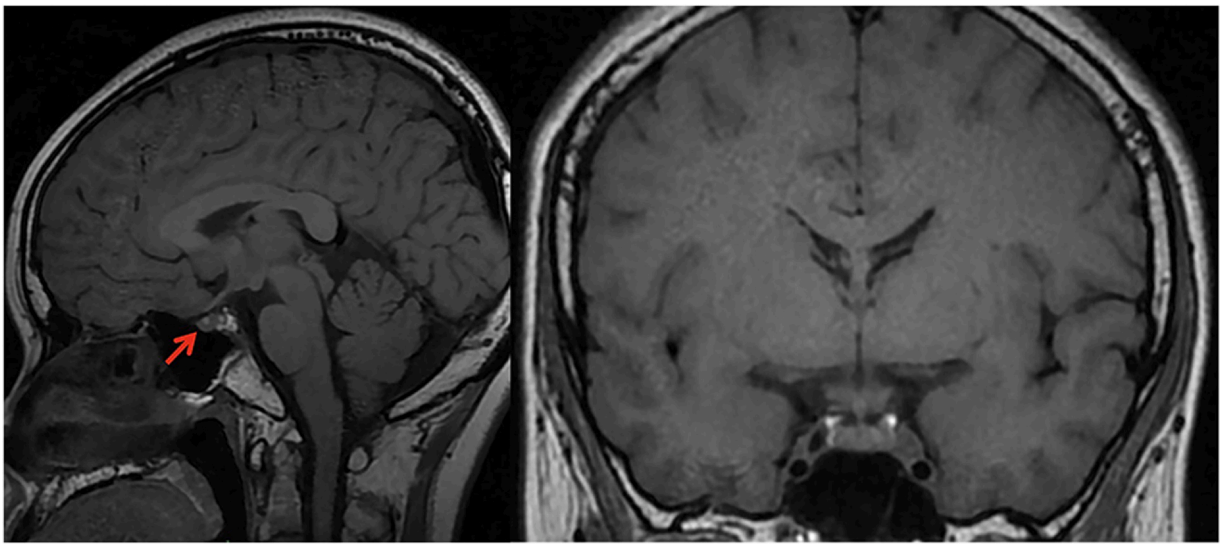

Fig. 3. MRI Imaging. Contrast-enhanced MRI of the pituitary demonstrated an abnormal signal in the middle part of the pituitary gland (marked with red arrow).

The NM_030964.3:c.423 A > C(p.Pro141 =) variant was detected in the SPRY4 gene of the patient (Fig. 4), the nucleotide at position 423 of the coding DNA was changed from adenosine to cytosine nucleotide, and the corresponding amino acid at position 141 was not changed (proline).

The results of genetic testing in the patient's family showed that NM_144773.2:c .533 G > C (p.Trp178Ser) variant was detected on the the PROKR2 gene of the patient's mother but not in his brother. Additionally, the NM_030964.3;c. 423 A > C;p.(Pro141 =) variant was detected on the SPRY4 gene of both the patient's mother and the patient's brother (Fig. 4). However, no clinical manifestations were observed in the patient's mother or brother.

Physiological and hormonal changes after treatment at follow-ups

The patient was clinically diagnosed with Kallmann syndrome and osteoporosis. Thus, Pulsatile GnRH Therapy was administered for Kallmann syndrome to maintain a physiologic pattern of the hypothalamus-pituitary-testis axis, while calcium and vitamin D supplementation followed by a single intravenous infusion of zoledronic acid were prescribed for osteoporosis based on the patient's wishes. The LH, FSH and testosterone levels were well elevated on follow-up in 1st, 3rd, 6th, and 9th month. The testes and penis gradually increased in size, pubic hair grew, and the breasts were slightly and transiently enlarged in the process. After 9 months of treatment, Tanner stage 3 genital development was observed in the patient with significant increases in LH (9.10 IU/L), FSH (17.17 IU/L) and testosterone (8.16 nmol/L) levels (Fig. 1 C). Ultrasonography showed that the left and right testes were about 25.7 × 19.1 × 9.4 mm and 25.0 × 18.4 × 9.9 mm, respectively. The patient had significantly increases in libido and ejaculation frequency with about 0.5–1 ml of semen in a single ejaculation. Further evaluations will be conducted in the coming regular follow-ups.

Discussion

Hypogonadotropic hypogonadism and anosmia/hyposmia are typical features of Kallmann syndrome [1]. The presented 32-year-old patient had delayed sexual development in adolescence and hypogonadotropic hypogonadism, accompanied by significant olfactory hyposmia. The GnRH stimulation test showed a good pituitary response to GnRH. Heterozygous variants in PROKR2 and SPRY4 genes were detected in both the patient and his mother, with a heterozygous variant in PROKR2also detected in his brother. However, no clinical manifestations of hypogonadotropic hypogonadism and anosmia/hyposmia was observed in the patient's mother or brother.

Kallmann syndrome is widely considered to be related to disruption of GnRH neuronal migration and/or defective GnRH synthesis and secretion [9]. In recent years, more and more studies imply the pathogenesis seems not fully understood [3]. The pathogenic genes implicated in Kallmann syndrome include KAL1, NSMF, FGFR1, FGF8, FGF17, IL17RD, SPRY4, FLRT3, PROK2, PROKR2, HS6ST1, CHD7, WDR11, SEMA3A and SOX10 [3,10]. The majority of Kallmann syndrome cases described are sporadic, some X-linked recessive, autosomal dominant, and autosomal recessive modes of inheritance [11]. In this case, the presented patient exhibited variants in PROKR2 and SPRY4 genes.

The pathogenicity of the NM_144773.2:c .533 G > C variant detected in the PROKR2 gene has been reported, according to the ACMG Classification Criteria and Guidelines for Genetic Variants published by the American College of Medical Genetics and Genomics (ACMG), the variant was judged to be a suspected pathogenic variant with the following evidence items [3,12–14] (PS3 + PP3 + PP4. PS3: Variants that have been clearly shown to cause impaired gene function in in vivo and in vitro functional experiments. PP3: Multiple statistical methods predicted that the variant would have deleterious effects on the gene or gene product,

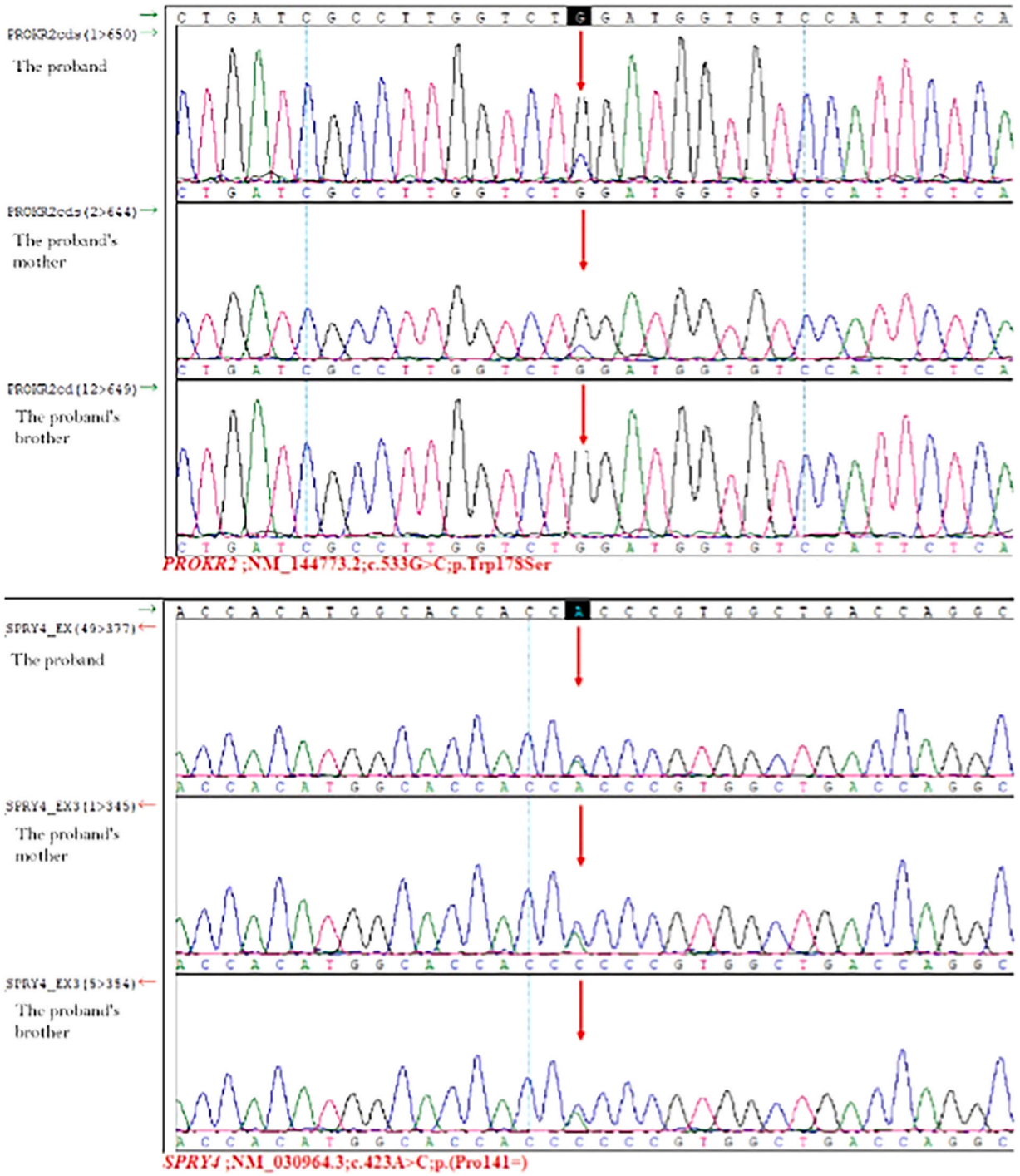

Fig. 4. Variants in the PROKR2 gene and SPRY4 gene. Whole-exome sequencing results showed that the NM_144773.2:c .533 G > C(p.Trp178Ser) variant in the PROKR2 gene was detected in the proband and his mother, but not in his brother, and the NM_030964.3:c.423 A > C(p.Pro141 =) variant in the SPRY4 gene in the proband, his mother and his brother.

including conserved prediction, evolutionary prediction, splice site effects, etc. PP4: The phenotype or family history of the variant carrier is highly consistent with a single gene genetic disorder). The PROKR2 gene c .533 G > C(p.Trp178Ser) variant, which is recurrent in probands from east Asia (China, Japan, and South Korea), is considered as a suspected pathogenic mutation [14].

The SPRY4 gene c.423 A > C (p. (Pro141 =)) variant has never been reported to be pathogenic, and the significance of this variant remains unclear. It is reported that the PROKR2 gene is inherited in an autosomal dominant manner [15]. The presented patient has heterozygous variants in the PROKR2 gene c .533 G > C(p.Trp178Ser) and clinical phenotype of hypogonadotropic

hypogonadism, which was consistent with the report described by Zhao, Y. et al. [13]. In view that no pathogenicity of the NM_030964.3:c.423 A > C(p.Pro141 =) variant detected on the SPRY4 gene was reported, according to the ACMG guidelines, the variant was judged as a variation of undetermined significance, according to the ACMG guidelines, with the following evidence items (PM2: Variants weren't found in normal control populations (or very low frequency loci in recessive genetic disorders) in the ESP database, Thousands database, and EXAC database.). Noteworthy, It was reported that the SPRY4 gene was located on chromosome 5 and its heterozygous allelic variant (c .158 G > A, p.R53Q) is associated with anosmia and adult-onset isolated hyypogonadotropic hypogonadism, which suggested that the variant could be inherited in an autosomal dominant manner [16].

Actually, a number of patients with Kallmann syndrome were sporadic, while many cases are clearly familial [17]. In this case, the patient's mother had a heterozygous variant at the same locus of the PROKR2 gene but was not associated clinical manifestations, suggesting that the mutated gene might be incompletely penetrant in his mother. Some studies indicate that incomplete penetrance is observed in FGFR1, PROK2, PROKR2, NDNF and PLXNA1 [12,18]. In addition, some studies show that variants in PROK2 or PROKR2 only could be asymptomatic, suggesting that these genetic variants might be incompletely penetrant [19]. In recent years, Kallmann syndrome is increasingly widely considered to be an oligogenic disease, involving variants in more than one gene [4]. The combined effects of oligogenic variants may be an important mechanism of incomplete penetrance of Kallmann syndrome [20]. Due to the high genetic heterogeneity of Kallmann syndrome, the genetic pattern and pathogenesis of the causative genes are still under continuous investigation [12,21]. Herein we tentatively put forward that the variants of PROKR2 and SPRY4 gene may contribute to the Kallmann syndrome in the patients in an oligogenic manner either with or without other related genes, and incomplete penetrance might be one of the important explanations of that no clinical manifestations were observed in the patient's mother or brother. Anyhow, further research is necessary to confirm the hypothesis and to explore the potential mechanism involved.

The genetic complexity of congenital hypogonadotropic hypogonadism is reflected in its genetic heterogenity with mutations in a number of genes, and different modes of inheritance involving X-linked, autosomal dominant and autosomal recessive. Incomplete penetrance, variable expressivity, and oligogenicity in addition to the Mendelian modes of inheritance, makes the assessment of a single variant's pathogenicity and the synergistic effects between variants more challenging [1,22]. In the presented family, the complexity and challenge is demonstrated, to which close attention should be paid in clinical management and genetic counseling. The advent of high-throughput sequencing dramatically enhances the ability to detect multiple rare variants in a patient, which is of great help in the precise genetic screening and subsequent management in families carry variants in genes associated with Kallmann syndrome [1,12,23].

It should be noted that although the patient had an abnormal signal shadow in the middle portion of the pituitary gland, which was considered to a possible pituitary micro adenoma, and no other hormonal abnormalities were observed in the pituitary gland, the diagnosis of Kallmann syndrome was considered, but follow-up was absolutely necessary. Additionally, based on the challenges of the display and identification of olfactory bulbs, olfactory tracts and olfactory grooves in conventional MRI, as well as the patient's willingness, we were not able to present the olfactory bulbs, olfactory tracts and olfactory grooves of the patient clearly in a great manner, which is considerably important and if possible more attention should be paid to, especially in clinical practice and academic research in the future [24,25].

Notwithstanding these limitations, we tentatively put forward that the heterozygous variants in PROKR2 and in SPRY4 genes might be crucial in the development of Kallmann syndrome in the present patient, and that no clinical manifestations were observed in the patient's mother or brother might be attributed to incomplete penetrance of PROKR2 mutations and SPRY4 variants. More attention should be paid and further research is necessary in further clinical practice and research.

Conclusions

The finding suggests incomplete penetrance of PROKR2 mutations and SPRY4 variants within the KS family studied, which demonstrates the necessity to consider oligogenic inheritance and variable expressivity in KS, and for further research to fully understand the genetic mechanisms involved.

Ethics statement

The study complies with the Declaration of Helsinki and was approved by the ethics committee of Huazhong University of Science and Technology in Wuhan, China. The patient consent for participation is waived by the ethics committee for retrospective analysis of the anonymized patient data to be published in this article.

Author contributions

YY, QH, JZ, QZ and XH analyzed and interpreted the data, wrote and revised the manuscript. QZ and XH conceived and performed genetic analysis. QW, LC, TZ and HL were involved in the care of patients. All authors contributed to the article and approved the submitted version.

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Data Availability

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

[1] J. Young, C. Xu, G.E. Papadakis, et al., Clinical management of congenital hypogonadotropic hypogonadism, Endocr. Rev. 40 (2) (Apr 1 2019) 669–710, https://doi.org/10.1210/er.2018-00116.
[2] S. Arora, O. Yeliosof, V.L. Chin, A case of novel mutation in ANOS1 (KAL1) gene and review of Kallmann syndrome, Endocrinol. Diabetes Metab. Case Rep. 2023 (2) (Jun 1 2023), https://doi.org/10.1530/EDM-22-0310.
[3] M.I. Stamou, N.A. Georgopoulos, Kallmann syndrome: phenotype and genotype of hypogonadotropic hypogonadism, Metabolism 86 (Sep 2018) 124–134, https://doi.org/10.1016/j.metabol.2017.10.012.
[4] G.P. Sykiotis, L. Plummer, V.A. Hughes, et al., Oligogenic basis of isolated gonadotropin-releasing hormone deficiency, Proc. Natl. Acad. Sci. USA 107 (34) (Aug 24 2010) 15140–15144, https://doi.org/10.1073/pnas.1009622107.
[5] H. Mosbah, C. Bouvattier, L. Maione, et al., GnRH stimulation testing and serum inhibin B in males: insufficient specificity for discriminating between congenital hypogonadotropic hypogonadism from constitutional delay of growth and puberty, Hum. Reprod. 35 (10) (Oct 1 2020) 2312–2322, https://doi.org/10.1093/humrep/deaa185.
[6] A.K. Lucas-Herald, A. Kyriakou, M. Alimussina, et al., Serum anti-mullerian hormone in the prediction of response to hCG stimulation in children With DSD, J. Clin. Endocrinol. Metab. 105 (5) (May 1 2020) 1608–1616, https://doi.org/10.1210/clinem/dgaa052.
[7] R.L. Binz, R. Pathak, Molecular cytogenetics reveals mosaicism in human umbilical vein endothelial cells, Genes (Basel) 13 (6) (Jun 3 2022), https://doi.org/10.3390/genes13061012.
[8] C. Cheng, X. Li, S. Zhao, Q. Feng, X. Ren, X. Chen, Compound heterozygous variants in DYNC2H1 in a foetus with type III short rib-polydactyly syndrome and situs inversus totalis, BMC Med Genom. 15 (1) (Mar 12 2022) 55, https://doi.org/10.1186/s12920-022-01205-z.
[9] S.A. Malone, G.E. Papadakis, A. Messina, et al., Defective AMH signaling disrupts GnRH neuron development and function and contributes to hypogonadotropic hypogonadism, Elife (8) (Jul 10 2019), https://doi.org/10.7554/eLife.47198.
[10] H. Miraoui, A.A. Dwyer, G.P. Sykiotis, et al., Mutations in FGF17, IL17RD, DUSP6, SPRY4, and FLRT3 are identified in individuals with congenital hypogonadotropic hypogonadism, Am. J. Hum. Genet 92 (5) (May 2 2013) 725–743, https://doi.org/10.1016/j.ajhg.2013.04.008.
[11] J. Choe, J.H. Kim, Y.A. Kim, J. Lee, Dizygotic twin sisters with normosmic idiopathic hypogonadotropic hypogonadism caused by an FGFR1 gene variant, Ann. Pedia Endocrinol. Metab. 25 (3) (Sep 2020) 192–197, https://doi.org/10.6065/apem.1938148.074.
[12] B. Cangiano, D.S. Swee, R. Quinton, M. Bonomi, Genetics of congenital hypogonadotropic hypogonadism: peculiarities and phenotype of an oligogenic disease, Hum. Genet 140 (1) (Jan 2021) 77–111, https://doi.org/10.1007/s00439-020-02147-1.
[13] Y. Zhao, J. Wu, H. Jia, et al., PROKR2 mutations in idiopathic hypogonadotropic hypogonadism: selective disruption of the binding to a Galpha-protein leads to biased signaling, FASEB J. 33 (3) (Mar 2019) 4538–4546, https://doi.org/10.1096/fj.201801575R.
[14] V.A. Patil, A.R. Lila, N. Shah, et al., Genetic spectrum of Kallmann syndrome: single-center experience and systematic review, Clin. Endocrinol. (Oxf.) 97 (6) (Dec 2022) 804–813, https://doi.org/10.1111/cen.14822.
[15] J. Tommiska, J. Toppari, K. Vaaralahti, et al., PROKR2 mutations in autosomal recessive Kallmann syndrome, Fertil. Steril. 99 (3) (Mar 1 2013) 815–818, https://doi.org/10.1016/j.fertnstert.2012.11.003.
[16] R. Indirli, B. Cangiano, E. Profka, et al., A rare SPRY4 gene mutation is associated with anosmia and adult-onset isolated hypogonadotropic hypogonadism, Front Endocrinol. (Lausanne) 10 (2019) 781, https://doi.org/10.3389/fendo.2019.00781.
[17] Y. Liu, X. Zhi, Advances in genetic diagnosis of kallmann syndrome and genetic interruption, Reprod. Sci. 29 (6) (Jun 2022) 1697–1709, https://doi.org/10.1007/s43032-021-00638-8.
[18] Hardelin J.P., Dode C. The complex genetics of Kallmann syndrome: KAL1, FGFR1, FGF8, PROKR2, PROK2, et al. Sex Dev. 2008;2(4–5):181–193. doi:10.1159/000152034.
[19] J. Sarfati, C. Dode, J. Young, Kallmann syndrome caused by mutations in the PROK2 and PROKR2 genes: pathophysiology and genotype-phenotype correlations, Front Horm. Res 39 (2010) 121–132, https://doi.org/10.1159/000312698.
[20] R. Mkaouar, L.C.B. Abdallah, C. Naouali, et al., Oligogenic inheritance underlying incomplete penetrance of PROKR2 mutations in hypogonadotropic hypogonadism, Front Genet 12 (2021) 665174, https://doi.org/10.3389/fgene.2021.665174.
[21] Y. Xia, H. Guo, H. Ge, et al., A novel noncanonical splicing mutation of ANOS1 gene in siblings with kallmann syndrome identified by whole-exome sequencing, Reprod. Sci. (Jul 6 2021), https://doi.org/10.1007/s43032-021-00672-6.
[22] J.T.C. Shieh, Genomic sequencing expansion and incomplete penetrance, Pediatrics 143 (1) (Jan 2019) S22–S26, https://doi.org/10.1542/peds.2018-1099E.
[23] U. Boehm, P.M. Bouloux, M.T. Dattani, et al., Expert consensus document: European Consensus Statement on congenital hypogonadotropic hypogonadism–pathogenesis, diagnosis and treatment, Nat. Rev. Endocrinol. 11 (9) (Sep 2015) 547–564, https://doi.org/10.1038/nrendo.2015.112.
[24] H.P. Burmeister, P.A. Baltzer, C. Moslein, et al., Reproducibility and repeatability of volumetric measurements for olfactory bulb volumetry: which method is appropriate? An update using 3 Tesla MRI, Acad. Radio. 18 (7) (Jul 2011) 842–849, https://doi.org/10.1016/j.acra.2011.02.018.
[25] J.J. Braun, V. Noblet, S. Kremer, et al., Value of MRI olfactory bulb evaluation in the assessment of olfactory dysfunction in Bardet-Biedl syndrome, Clin. Genet 90 (1) (Jul 2016) 79–83, https://doi.org/10.1111/cge.12697.