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Rare FGFR1 c.1977+1G>A splice-site variant in hypogonadotropic hypogonadism-2 with anosmia

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Abstract

Congenital idiopathic hypogonadotropic hypogonadism (IHH) is a rare disorder caused by deficient gonadotropin-releasing hormone secretion or action and may present with anosmia when the olfactory system is affected. FGFR1 is one of the most frequently implicated genes and is associated with considerable phenotypic variability. Here, we report a 14-year-old female with anosmia, delayed pubertal development, low luteinizing hormone and follicle-stimulating hormone levels, myopia, scoliosis, pectus deformity, disproportionately long limbs and fingers, and absent ovaries. Family history revealed delayed puberty in her father and elder brother, suggesting variable intrafamilial expression. Genomic DNA isolated from peripheral blood was analyzed by whole-exome sequencing, and a heterozygous FGFR1 splice-site variant, NM_023110.3:c.1977+1G>A, was identified. This variant affects a canonical donor splice site and supports the molecular diagnosis of FGFR1-associated hypogonadotropic hypogonadism-2 with anosmia. The case expands the recognized clinical spectrum of FGFR1-related disease and underlines the value of genetic testing for diagnosis, counselling, and follow-up in patients with suspected congenital hypogonadotropic hypogonadism.

Introduction

Congenital idiopathic hypogonadotropic hypogonadism (IHH) is characterized by absent or incomplete pubertal development caused by deficient secretion or action of gonadotropin-releasing hormone, resulting in low circulating gonadotropins and sex steroids in the absence of structural hypothalamic-pituitary abnormalities. When associated with anosmia or hyposmia, the condition is classically referred to as Kallmann syndrome. Pathogenic variation in FGFR1 is a well-established cause of both anosmic and normosmic forms of congenital hypogonadotropic hypogonadism and may be inherited in an autosomal dominant manner with variable expressivity (Cariboni and Maggi, 2006; Akkuş et al., 2017; Xu et al., 2023).

FGFR1 signaling plays an important role in olfactory bulb development and in the embryonic migration of gonadotropin-releasing hormone neurons. In addition to reproductive manifestations, affected individuals may display non-reproductive anomalies such as cleft palate, dental defects, or skeletal findings, and some cases occur within an oligogenic background involving other components of the fibroblast growth factor pathway (Tornberg et al., 2011; Miraoui et al., 2013; Men et al., 2020). Therefore, careful phenotyping together with molecular analysis is important for appropriate clinical interpretation and genetic counselling.

We report a 14-year-old female who presented with anosmia, myopia, scoliosis, pectus deformity, disproportionately long limbs and fingers, absent ovaries, and low luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels. Her father and elder brother both had a history of delayed puberty and tall, slender habitus with disproportionately long limbs and fingers; the brother also had a pituitary tumor. Because the combination of reproductive and extra-reproductive findings suggested a syndromic form of congenital hypogonadotropic hypogonadism, molecular analysis was performed to clarify the underlying genetic cause.

Material and methods

After written informed consent for publication had been obtained from the patient's parents, peripheral blood was collected for molecular analysis. No ethics committee approval was required because the genetic test was performed for diagnostic purposes. Genomic DNA was isolated from peripheral blood. Whole-exome sequencing was then performed after enzymatic fragmentation, enrichment of coding regions with capture probes, library preparation with Illumina-compatible adaptors, and sequencing on an Illumina platform. Variants were filtered against public and clinical databases, including gnomAD, HGMD, and ClinVar, with priority given to rare coding and splice-site variants relevant to the phenotype. Variant nomenclature is reported according to HGVS recommendations.

Results and discussion

Whole-exome sequencing identified a heterozygous FGFR1 variant, NM_023110.3:c.1977+1G>A. This change affects the canonical +1 donor splice position and is therefore expected to interfere with normal pre-mRNA splicing. The finding is consistent with the established loss-of-function mechanism described for many FGFR1-related cases of congenital hypogonadotropic hypogonadism and supports the molecular diagnosis in the present patient. The clinical presentation in our patient is compatible with the

broad phenotypic spectrum reported for FGFR1-associated disease. Along with anosmia and hypogonadotropic hypogonadism, she showed skeletal features including pectus deformity, scoliosis, and long slender extremities. Similar extra-reproductive manifestations and marked clinical variability have been described in FGFR1-mutated patients, even within the same family, which is in line with the family history observed here (Akkuş et al., 2017; Men et al., 2020; Sheng et al., 2025).

FGFR1-related hypogonadotropic hypogonadism may also occur in an oligogenic context, and genes within the fibroblast growth factor signaling pathway have previously been implicated as contributors to disease severity and phenotypic diversity (Tornberg et al., 2011; Miraoui et al., 2013). Moreover, recent work on FGFR1 variant interpretation has emphasized the value of combining variant type, gene context, and phenotype for pathogenicity assessment (Xu et al., 2023). In our case, the splice-site location, the compatible phenotype, and the family history together support clinical relevance of the identified variant.

This report has important limitations. It describes a single patient, segregation analysis in additional family members was not available, and no RNA-based or functional assay was performed to directly demonstrate the splicing consequence of c.1977+1G>A. Future studies integrating family segregation and transcript-level analyses would strengthen genotype-phenotype interpretation and help clarify whether additional genetic factors contribute to the intrafamilial variability observed in this family.

Conclusions

The present case highlights a rare FGFR1 splice-site variant in a patient with hypogonadotropic hypogonadism-2 with anosmia and emphasizes the clinical utility of molecular testing in diagnostically challenging presentations. Early recognition of FGFR1-associated disease may improve counselling, longitudinal follow-up, and individualized management.

Authors' contributions

V. S. Hançer:
Conceptualization; Methodology; Investigation; Supervision; Validation; Project administration; Writing – review & editing.

A. Babameto-Laku:
Investigation; Data curation; Resources; Validation; Writing – review & editing.

P. Hoxha:
Investigation; Data curation; Resources; Validation; Writing – review & editing.

Ö. G. Geyik:
Data curation; Formal analysis; Visualization; Roles/Writing – original draft; Writing – review & editing.

S. Bozkurt:
Validation; Writing – review & editing.

Conflict of interest

Authors declare no conflict of interest.

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