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Reversible Kallmann Syndrome, Delayed Puberty, and Isolated Anosmia Occurring in a Single Family with a Mutation in the Fibroblast Growth Factor Receptor 1 Gene

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Kallmann syndrome (KS) is a clinically and genetically heterogeneous disorder. Recently, loss-of-function mutations in the fibroblast growth factor receptor 1 (*FGFR1*) gene have been shown to cause autosomal dominant KS. To date, the detailed reproductive phenotype of KS associated with mutations in the *FGFR1* has yet to be described. We report a kindred comprising a male proband with KS and spontaneous reversibility, whose mother had delayed puberty and whose maternal grandfather isolated anosmia. The proband presented at age 18 yr with KS and was subsequently treated with testosterone (T) therapy. Upon discontinuation of T therapy, he recovered from his hypogonadotropic hypogonadism, as evidenced by a normal LH secretion pattern, sustained normal serum T levels, and active spermatogenesis. The three members of this single family harbor the same *FGFR1* mutation ($Arg^{622}X$) in the tyrosine kinase domain. This report demonstrates 1) the first genetic cause of the rare variant of reversible KS, 2) the reversal of hypogonadotropic hypogonadism in a proband carrying an *FGFR1* mutation suggests a role of *FGFR1* beyond embryonic GnRH neuron migration, and 3) a loss of function mutation in the *FGFR1* gene causing delayed puberty. (*J Clin Endocrinol Metab* 90: 1317–1322, 2005)

KALLMANN SYNDROME (KS) is defined as a congenital and irreversible form of hypogonadotropic hypogonadism (HH) in association with anosmia (1). Anosmia is secondary to underdeveloped or absent olfactory bulbs or tracts (2), whereas HH is thought to result from impaired secretion of GnRH (3). Additional frequently observed features of KS include both neurological (*i.e.* synkinesia and hearing loss) and nonneurological (*i.e.* renal aplasia and midline craniofacial abnormalities) phenotypes (4–8). Although microphallus and cryptorchidism may represent the earliest clinical manifestation of the reproductive phenotype of this disorder, most KS patients present in adolescence with a failure to go through puberty or, less frequently, with partial pubertal development (25%) (9, 10). KS probands typically cannot complete puberty unless exposed to physiological doses of gonadotropins or pulsatile GnRH and require lifelong replacement therapy to achieve and maintain sexual maturation as well as adequate bone mineral density (9, 11). In contrast to this classical presentation of KS, a few subjects have been described who present with a rare variant of KS in which gonadotropin and testosterone (T) secretion recover spontaneously (12, 13).

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Abbreviations: AD, Autosomal dominant; CV, coefficient of variation; FGFR1, fibroblast growth factor receptor 1; HH, hypogonadotropic hypogonadism; I_B, inhibin B; IHH, idiopathic HH; KS, Kallmann syndrome; MRI, magnetic resonance imaging; T, testosterone; X-KS, X-linked form of Kallmann syndrome.

KS is a genetically heterogeneous disorder. Although most cases are sporadic, three different patterns of inheritance have been described [X-linked (OMIM 308700), autosomal dominant (AD; OMIM 147950), and autosomal recessive (AR) (OMIM 244200) forms). Mutations in the *KAL1* gene cause the X-linked form of KS (X-KS) (14–16). *KAL1* encodes for anosmin-1, an embryonic component of the extracellular matrices. Studies of a 19-wk-old human fetus with a *KAL1* deletion have provided important insights into the pathology of X-KS, revealing both an absence of olfactory bulbs and abnormal migration of GnRH neurons that had accumulated outside the brain in the upper nasal area (17). These findings are consistent with the severe reproductive phenotype seen in subjects with the X-KS form (10, 18).

Recently, mutations in the fibroblast growth factor receptor 1 (*FGFR1*) gene on 8p12 have been shown to underlie one AD form of KS. Although associated nonreproductive features included cleft palate, mirror movements, and dental agenesis, the reproductive phenotype was not described in detail (19, 20). Interestingly, familial cases of *FGFR1* mutations have been described and demonstrate both male and female asymptomatic carriers (19). We therefore hypothesized that *FGFR1* mutations could cause the rare variant of KS with a spontaneous recovery of HH.

In this report we describe a family with this rare variant of KS displaying a heterozygous mutation ($Arg^{622}X$) in the tyrosine kinase domain of the FGFR1 gene. The proband demonstrated reversibility of his condition after several years of T treatment. Furthermore, the proband's mother and maternal grandfather were found to harbor the same muta-

tion and were noted to have delayed puberty and isolated anosmia, respectively. This family advances our understanding of the spectrum of KS and raises important questions about the role of *FGFR1* in GnRH neuronal function in the adult human.

Subjects and Methods

Case presentation

The proband (subject III-1 in Fig. 1), a 25-yr-old male of Portuguese descent (Azore Islands), presented to an endocrinologist at age 18 yr with arrested puberty. He had no history of cryptorchidism or microphallus and reported some spontaneous testicular growth by age 14 yr, but no additional sexual development thereafter. He also reported occasional morning erections, a low libido, and no ejaculations. He had always been smaller than his peers during childhood and experienced no typical growth spurt, but continued steady, slow growth until the time of presentation. He reported a normal diet, no gastrointestinal symptoms, and no history of excessive exercise and denied use of anabolic steroids or nutritional supplements. He had a transient history of depression as a teenager, apparently related to the psychosocial implications of delayed puberty. His initial physical exam revealed an unvirilized young man (no facial hair and Tanner stage II axillary and pubic hair), no gynecomastia, and a testicular size of 7 cc bilaterally. Additionally, he had no sense of smell and was color blind. He had no hearing loss, dental agenesis, or cleft lip/palate. His serum T level was extremely low at 15 ng/dl (0.5 nmol/liter) with undetectable gonadotropin levels. He had an XY karyotype, a bone age of 13 yr for a chronological age of 18 yr, and a normal magnetic resonance imaging (MRI) of the hypothalamic-pituitary area. On the basis of these findings, he was diagnosed with KS, and T replacement therapy (300 mg every 3 wk) was instituted, which induced a growth spurt, full virilization, and normal sexual function.

At age 23 yr, he presented to the Reproductive Endocrine Unit of Massachusetts General Hospital for evaluation of pulsatile GnRH therapy for KS. He had discontinued T therapy 6 months before his visit as required by our protocol. His physical examination at this time revealed eunuchoidal body proportions with a height of 178 cm, an arm span of 196 cm, an upper to lower segment ratio of 0.7 (normal, >0.9), and a weight of 67 kg (body mass index, 21 kg/m^2). He had a light beard, Tanner stage V axillary and pubic hair, and no gynecomastia. He had a stretched phallus length of 7 cm and scrotal testes of 10–12 ml bilaterally (normal, >15 ml). He had pes cavus, with thoracic asymmetry with his right side more prominent than the left, and abnormalities of the digits, with hyperlaxity of the distal phalanges. He also had asymmetry of the eyes, with the right palpebral fissure greater than the left. His occulomotor function was normal, and his visual fields were full to confrontation. There was no evidence of synkinesia.

A detailed family history revealed two additional family members of interest: the proband's mother (subject II-1) and maternal grandfather (I-1). The 55-yr-old mother had menarche at age 16.5 yr, followed by regular menstrual cycles. As a teenager, she was healthy with a normal weight and no history of anorexia or excessive exercise. She is currently menopausal and has always had a normal sense of smell. The 77-yr-old maternal grandfather has congenital anosmia with an unremarkable puberty and reproductive history. He denies any comorbidities affecting the sense of smell, including history of head injury or chronic rhinitis. Both denied color blindness or other associated phenotypes, and there was no indication of parental consanguinity. Although detailed medical histories were obtained from the family members, they were not available for clinical examination.

Both the proband's 58-yr-old father (subject II-2) and the proband's 29-yr-old brother (subject III-2) were normally virilized, underwent normal puberty, and had a normal sense of smell.

Clinical studies

Characterization of baseline gonadotropin secretion 6 months after discontinuation of T therapy. The proband was admitted to the Massachusetts General Hospital's General Clinical Research Center for a full neuroendocrine evaluation consisting of a 12-h overnight frequent sampling study, with blood samples drawn every 10 min for measurements of LH levels to assess endogenous GnRH secretion. To assess other functions of the pituitary, a standard insulin tolerance test, thyroid function tests, and serum prolactin measurement were performed. Pulsatile hormone secretion was analyzed using a modification of the Santen and Bardin method (21), and mean LH, FSH, T, and inhibin B (I_B) levels were measured in serum pools comprising equal aliquots of each individual sample.

A

	TV (mL)	Sperm Count (10^6/mL)	T (ng/dL)[a]	LH (IU/L)	FSH (IU/L)	I_B (pg/mL)
At Presentation	7	0	15	<1.6	<1.6	
6 M off T	11	1.7	318	11	11.6	99
2 Yrs off T	11		460			

[a]Conversion factor, nmol/liter = ng/dL X 0.0346

B

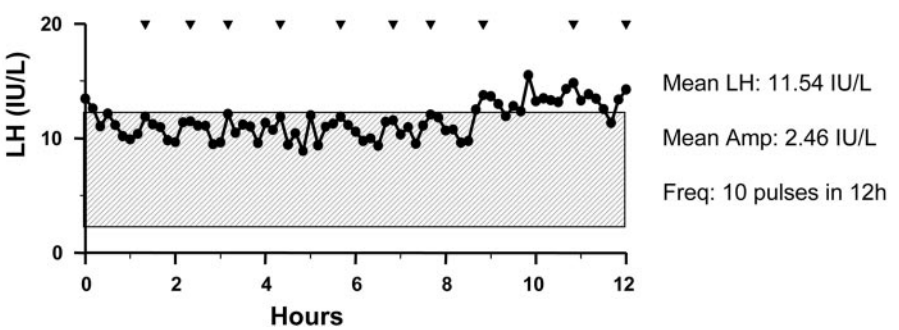

FIG. 1. A, Clinical and biochemical parameters of the proband at different time points during his care. B, Neuroendocrine assessment of the proband 6 months after discontinuing T therapy. An overnight 10-min sampling study for LH depicts endogenous LH secretion. ▼, LH pulses, and the normal range of serum LH is *shaded*.

Hormonal and radiological studies performed 2 yr after discontinuing T therapy. Two years after discontinuing T therapy, the patient agreed to have serial blood tests for T. The clinical evaluation also included assessment of renal structure by iv pyelogram, formal smell testing using the University of Pennsylvania Smell Identification Test (UPSIT, Sensonics, Inc., Haddon Heights, NJ), dual energy x-ray absorptiometry to assess bone mineral density, a cranial MRI with thin coronal slides to visualize the olfactory bulbs, olfactory tracts, and the fronto-olfactory gyri, and bilateral hand x-rays to examine the abnormalities of the digits.

Molecular studies of the FGFR1 gene

After obtaining additional written informed consent for genetic studies, whole blood samples were obtained from the proband and his family members, and DNA was extracted. Coding sequences for exons 2–13 of the *FGFR1* gene and their exon-intron boundaries were determined using previously described primers and methods (19), and those for exons 14–18 of the FGFR1 gene were determined using methods more recently described (20). Exon 1 was not screened, because the start methionine is located in exon 2. Amplified products were sequenced in both directions using the AmpliTaq Dye Terminator Cycle Sequencing Kit and an ABI PRISM 377 DNA sequencer (PerkinElmer, Foster City, CA). Fifty healthy volunteers who were consecutive donors to the Massachusetts General Hospital blood bank (n = 100 chromosomes) were also screened for mutations in the *FGFR1* gene. All genes and proteins are described using standard nomenclature (22).

Hormone assays

Serum LH and FSH concentrations were determined by microparticle enzyme immunoassay using the automated AxSYM system (Abbott Laboratories, Chicago, IL). The Second International Reference Preparation was used as the reference standard. The assay sensitivity for both LH and FSH was 1.6 IU/liter, the intraassay coefficients of variation (CVs) for LH and FSH were less than 7% and less than 6%, respectively. The interassay CVs were less than 7.4% for both hormones. Serum T concentrations were measured using the Coat-A-Count RIA Kit (Diagnostic Products Corp., Los Angeles, CA), which had intra- and interassay CVs of less than 10%. I_B was measured using a commercially available (Serotec, Oxford, UK) double-antibody, enzyme-linked immunosorbent assay. In our use, the clinical detection limit of this assay is 50 pg/ml, with a CV of 4–6% within plate and 15–18% between plates.

Results

Clinical studies

Assessment of the hypothalamic-pituitary-gonadal axis 6 months after discontinuing T therapy. Data from the 12-h frequent sampling revealed a recovery of normal pulsatile adult male endogenous LH secretion with mean LH of 11 IU/liter, an LH frequency of 10 pulses in 12 h, and an LH amplitude of 2.8 IU/liter (Fig. 1B). The patient recovered from hypogonadism with a normal serum T level of 318 ng/dl (11 nmol/liter). He had a pooled serum FSH of 11 IU/liter, an estradiol of less than 25 ng/dl, and an I_B level of 99 pg/ml (normal, 100–350; Fig. 1A). Similarly, the semen specimen revealed active spermatogenesis, but with a low sperm count (volume, 0.5 ml; 1.7 million sperm/ml). All other pituitary functions were within normal limits.

Hormonal and radiological results 2 yr after discontinuing T therapy. After discontinuation of androgen therapy for more than 2 yr, the patient presented with a normal energy level, normal libido, normal potency with ejaculation, and repeated morning serum T levels well within the normal range [400–460 ng/dl (14–16 nmol/liter); Fig. 1A]. Smell testing revealed complete anosmia. The renal exam did not show any evidence of renal malformations, and an MRI of the olfactory system revealed the absence of olfactory bulb and nerves as well as hypoplastic olfactory sulci. The dual energy x-ray absorptiometry indicated severe osteopenia at the spine (T-score, −1.8), femoral neck (T-score, −2.2), and total hip (T-score, −1.6). The x-ray of the hands showed no malformation.

Molecular analysis of the FGFR1 gene

Direct sequencing of the PCR products amplified from the DNA of the proband revealed a heterozygous single nucleotide substitution in exon 14 (c.1864 C>T) resulting in a nonsense mutation in the protein kinase domain of the FGFR1 gene (p.Arg^{622}X). This mutation was confirmed on both strands and in repeated samples. The proband's mother and grandfather were also confirmed to be heterozygous for the mutation, whereas the proband's father did not carry the mutation (Fig. 2). Arg^{622} is highly conserved across species and within the FGFR family (Fig. 3). This mutation (Arg^{622}X) was not found in the genomic DNA of the healthy volunteer comparison group.

Discussion

This report describes a unique family with a proband, his mother, and his maternal grandfather, all harboring a nonsense mutation in the tyrosine kinase domain of the *FGFR1* gene, yet differing markedly in their expression of KS. Indeed, the proband presents with a rare variant of KS and underwent spontaneous recovery of HH after 4 yr of andro-

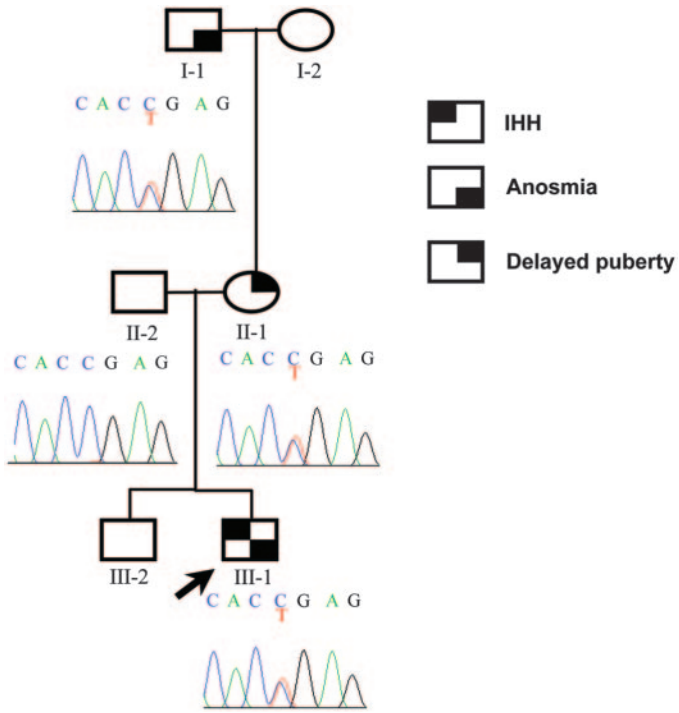

FIG. 2. Pedigree of the proband consistent with an autosomal dominant mode of inheritance and variable penetrance of the FGFR1 mutation (Arg^{622}X). The proband is identified by the *arrow*. *Circles* denote females; *squares* denote males. Phenotypes are as described. The sequence results for the Arg^{622}X (c.1864C>T) mutation in exon 14 are noted *below* the corresponding individual.

FIG. 3. Comparison of the amino acid sequences including Arg^{622} marked with an *asterisk* across different species and within the FGFR family. This alignment reveals conservation of residues flanking Arg^{622}.

gen replacement therapy. His mother had delayed puberty and a normal sense of smell, whereas his grandfather exhibited a normal reproductive phenotype and only isolated anosmia. This family illustrates how mutations in *FGFR1* can manifest a spectrum of reproductive phenotypes ranging from idiopathic HH (IHH) to delayed puberty to asymptomatic carriers.

We have previously reported the first genetic cause of reversal of IHH, but in an individual with a normal sense of smell harboring a mutation in the *GNRHR* gene (13). This previous patient had the fertile eunuch variant of the normosomic form of IHH and underwent a reversal of his IHH after prolonged hCG therapy. He was homozygous for a mutation in the first extracellular loop of the GnRH receptor ($Gln^{106}Arg$), which markedly reduced GnRH binding. We hypothesized that human chorionic gonadotropin-induced T secretion slowed the GnRH pulse generator and, in turn, allowed more effective signaling through the mutant receptor or other alterations in the pathway of GnRH signaling.

In contrast, this case documents the first genetic basis for a rare variant of KS with spontaneous reversal of HH. Indeed, the proband presented in this study had partial KS and was found to carry a heterozygous substitution in exon 14 (c1864 C>T) resulting in a stop codon at amino acid 622 in the tyrosine kinase domain of the *FGFR1* gene. The amino acid Arg^{622} in the tyrosine kinase domain of the receptor is highly conserved across species and within the FGFR family, suggesting a critical role for this residue in the intracellular signaling of the receptor. The mutation $Arg^{622}X$ is located more than 55 bp upstream of the end of exon 14. Therefore, this mutated allele is likely to undergo a nonsense-mediated decay resulting in haplo-insufficiency (23).

FGF signaling is involved in a variety of developmental processes, including maturation of GnRH neurons (24). It is thought that loss of function mutations in *FGFR1* could cause a defect in GnRH neuron migration via a disruption of olfactory bulb formation (through a possible interaction with anosmin-1) (19). Indeed, conditional knockout of the *FGFR1* gene resulted in the complete absence of olfactory bulbs in the telencephalon of the mouse (25). Two KS patients harboring heterozygous mutations of the *FGFR1* gene ($Ser^{107}X$; $Pro^{745}Ser$) were described with aplasia and hypoplasia of the olfactory bulbs, respectively, confirming that heterozygote mutations in *FGFR1* result in abnormal olfactory bulb development (20). Our family indicates that *FGFR1* mutations can cause milder cases of KS despite a disruption of the anatomy of the olfactory bulb. These findings suggest that GnRH neuronal migratory defects in *FGFR1* mutations are not always complete, and variable degrees of endogenous GnRH secretion may occur.

Although the etiology of the patient's reversal of HH is unclear, this well documented case raises several interesting hypotheses regarding GnRH neuronal migration. It is known that olfactory stem cells are present and divide in the olfactory epithelium during adulthood (26). When these cells are placed in culture (*e.g.* the FNC-B4 cell line) and stimulated with FGF2 or sex steroids, they differentiate into mature GnRH neurons (27–29). The recent discovery of neural progenitors in the subcortical white matter of the adult human brain indicates that postnatal neurogenesis is a potential mechanism by which the nervous system replaces certain neuronal lineages (30). Therefore, the migration of GnRH neurons, previously thought to be completed during the embryonic period, might still be occurring in adulthood, given the proper stimuli (*i.e.* exposure to sex steroids).

In addition, disruption of the *FGFR1* signaling pathway could result in an abnormally small number of GnRH neurons completing their migration to the hypothalamus, resulting in an incomplete GnRH pulse generator maturation and partial IHH. Support for this hypothesis comes from studies in the mouse. Although the homozygous *FGFR1* K/O is lethal due to a defect in gastrulation (31), targeted expression of a dominant-negative $FGFR_1$ in GnRH neurons exhibit a 30% decrease in GnRH neuronal population in the hypothalamus (32). Perhaps, the final maturation of the GnRH neuronal network is triggered by exogenous sex steroids.

Finally, FGFR1 signaling in the hypothalamus (24–35) may cause maturation/plasticity of the GnRH neuronal network. GnRH axons have been shown to dynamically extend or retract beyond their glial sheaths during the rat estrous cycle, enabling direct contact between the GnRH axon terminals and the external zone of the median eminence (36). Similar changes may occur in the adult male and could be triggered by the FGF-FGFR pathways. Therefore, a defect in *FGFR1* signaling could be overcome by a relative increase in the ligand (*i.e.* FGF2) stimulated by androgen therapy (37).

Regardless of the mechanism of reversal in the case described, our proband highlights the role of androgen exposure as a potential modifier of the *FGFR1* reproductive phenotype. This case also contradicts the dogmatic belief that IHH is always a permanent condition. Approximately 25% of IHH subjects have partial IHH, as evidenced by some degree of spontaneous sexual development, and are treated with long-term therapy for hypogonadism (10). For these partial cases, additional evaluation of the hypothalamic-pituitary-gonadal axis after discontinuing therapy will be critical given the potential for reversibility. Indeed, this subset may provide a new model for the cure of some forms of infertility.

This case demonstrates an unexpectedly variable reproductive phenotype among family members harboring the same mutation, including not only partial KS with the rare reversal of HH in the proband, but also delayed puberty in the proband's mother and a normal reproductive phenotype in the maternal grandfather. Interestingly, the same mutation has been described in a familial case of KS (19). Among the affected, two subjects also presented with cleft lip/palate. A female family member was an asymptomatic carrier. How-

ever, no information was provided on the spectrum of reproductive phenotype in the three affected patients with KS (19). The variable reproductive and nonreproductive phenotypes within and across families harboring the same mutation suggest the presence of modifier genes and/or epigenetic influences.

Existing literature supports the roles of genetic factors in modulating the timing of puberty (38, 39). The plausible role of *FGFR1* mutations in the phenotype of delayed puberty is reinforced by three key findings: 1) the proband reversed his HH after T therapy, a clinical situation resembling delayed puberty; 2) in our experience, 12% of probands with KS have relatives with delayed puberty compared with 2% in the general population (11); and 3) a Japanese KS patient with a nonsense (p.Ser107X) mutation in the FGFR1 gene, whose mother refused genetic testing but reported a history of delayed puberty (20). Therefore, delayed puberty might be at the mildest end of the reproductive spectrum of IHH. Conversely, mutations in *FGFR1* may cause delayed puberty in pedigrees without the context of IHH. Screening of such populations is needed to provide additional insight into the role of the *FGFR1* gene in the pathophysiology of delayed puberty.

In conclusion, this family is unique for several reasons. It provides a novel molecular defect in a rare variant of KS. This case demonstrates that a patient with an *FGFR1* mutation can undergo spontaneous recovery of reproductive function, an observation that challenges our assumption that IHH is lifelong. This finding has clinical implications, because patients with partial IHH should be reexamined after discontinuing therapy to evaluate the potential for a reversal of HH. This report indicates that FGFR1 mutations also cause delayed puberty. Finally, we observed unexpectedly variable reproductive and nonreproductive phenotypes among individuals carrying the same *FGFR1* mutation, thereby highlighting possible roles of modifier genes or epigenetic factors.

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