CASE REPORT

Reversible Kallmann syndrome: report of the first case with a KAL1 mutation and literature review

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Abstract

Kallmann syndrome (KS) describes the association of isolated hypogonadotropic hypogonadism with hypo/anosmia. A few KS patients may reverse hypogonadism after testosterone withdrawal, a variant known as reversible KS. Herein, we describe the first mutation in KAL1 in a patient with reversible KS and review the literature. The proband was first seen at 22 years complaining of anosmia and lack of puberty. His brother had puberty at 30 years and a maternal granduncle had anosmia and delayed puberty. On physical examination, he was P₂G₁, testes were 3 ml and bone age was 14 years. During 20 years of irregular testosterone replacement, he developed secondary sexual characteristics and testicular enlargement. At the age of 41 years, after stopping testosterone replacement for 5 months, his testes were 15 ml, serum testosterone, LH, and FSH responses to GnRH were normal, and his wife was pregnant. The molecular study revealed a cytosine insertion in exon 2 of KAL1, generating a frameshift at codon 75 and a premature stop at codon 85. The expected gene product is a truncated peptide with 85 of the 610 amino acids present in the wild-type protein. Fourteen cases of reversible KS have been described but the genotype was only studied in a single case showing a heterozygous fibroblast growth factor receptor type 1 (FGFR1) mutation. Considering the low prevalence of mutations in KAL1 or FGFR1 in KS, it is possible that these genotypes are more prevalent in reversible KS than in other KS patients, but additional studies are necessary to confirm this hypothesis.

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Introduction

Kallmann syndrome (KS) describes the association of isolated hypogonadotropic hypogonadism (HH) with hypo/anosmia. The association of hypogonadism and anosmia was first described in 1856 by Maestre de San Juan in an autopsy report of a man with small penis, infantile testes, no pubic hair, and absence of olfactory bulbs, who was known to lack the sense of smell (1). In 1944, Kallmann recognized the genetic basis of this condition in three families, and thereafter this association has been known as Kallmann syndrome (2). Hypogonadism in one form of KS was later shown to be due to deficient gonadotropin-releasing hormone (GnRH) secretion caused by defective migration of GnRH neurons which depend on the guidance of olfactoterminal nerve axons to reach the hypothalamus (3–5).

Kallmann syndrome can be sporadic or familial and affects more males than females (6). Familial cases display different modes of inheritance: X-linked, autosomal dominant and, more rarely, autosomal recessive inheritance (7). So far, inactivating mutations in two distinct genes have been implicated in this condition, KAL1 (Xp22.3) and FGFR1 (8p11p12) (8–11). KAL1

mutations are responsible for X-linked KS (XKS) and fibroblast growth factor receptor type 1 (FGFR1) mutations underlie one form of autosomal dominant KS (AKS), but mutations in these two genes account for only 20–25% of KS cases (10, 12–14).

KAL1 encodes anosmin1, a secreted glycoprotein expressed in various extracellular matrices, and FGFR1 encodes FGFR1, a member of the receptor tyrosine kinase superfamily that binds fibroblast growth factor 2 (FGF2) and other FGF ligands. Anosmin1 and FGFR1 are both expressed during organogenesis of the olfactory-GnRH system where they regulate neuronal migration and axon elongation and branching (15–17). Mutations in these genes lead to defective olfactory tract formation and are likely to account for associated defects in other developing tissues observed in KS patients, such as renal agenesis, synkinesia and cleft lip, palate, and dental agenesis (8, 13, 14, 18, 19). A defective migration of GnRH neurons to their final destination in the hypothalamic anterior septo-preoptic area has been documented in a 19-week human fetus with a KAL1 deletion, but a similar defect has not been investigated in KS patients with FGFR1 mutations (5).

In addition to the classical phenotypes, other variants of KS have been frequently observed among individuals with the same mutation within a family, including normal and mild phenotypes (e.g. isolated anosmia, delayed puberty without anosmia). Both *KAL1* and *FGFR1* genotypes have been shown to underlie this same phenotypic variability (13, 14, 20–23). Interestingly, a few KS patients have been reported to sustain improved gonadal function, including fertility, after testosterone withdrawal, a variant known as reversible KS (24–31). The only previous molecular study of a patient with reversible KS has shown a heterozygous *FGFR1* mutation (32). In the present study, we describe a male patient with reversible KS showing a mutation in *KAL1* and review all reversible KS found in the literature.

Case report

A 22-year-old male presented at our outpatient pituitary clinic due to absent pubertal development. He also had anosmia and neurosensorial hearing impairment but no mirror movements or midline defects. His family history included a mentally retarded brother who entered puberty at the age of 30 years and one maternal granduncle with delayed puberty and anosmia. On physical examination, his weight was 55 kg, height was 163 cm, and arm span was 163 cm. Tanner pubertal stage was P₂G₁, testes were 3 ml each, and axillary hair was scarce (33). Bone age was 14 years. Serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were low and total testosterone was in the peripubertal range. Sexual chromatin in the cells of the oral mucosa was negative. He was diagnosed with KS, a luteinizing hormone-releasing hormone (LHRH) stimulation test was indicated, but he refused the test.

Testosterone replacement (Durateston, Organon do Brasil, São Paulo, Brazil; 250 mg i.m. each 4 weeks) was soon started, but his adherence to treatment and follow-up visits were irregular. He was seen again at the ages of 26 and 28 years, with increased pubic, facial and body

hair, and penis and testicular enlargement. At the age of 37 years, he complained of decreased libido in the week preceding each testosterone injection, and his total testosterone, measured 4 weeks after the injection, was low (54 ng/dl), and a shorter interval between injections was suggested. He was seen again 4 years later, complaining of reduced libido after discontinuing testosterone for the last 5 months. He also reported that his wife was pregnant (first trimester). He was fully virilized, his testicular volume was 15 ml each, total testosterone was normal (453 ng/dl) and serum LH and FSH were both normal before and after i.v. administration of 100 g LHRH (LH peak, 16.8 mIU/ml; FSH peak, 13.1 mIU/ml).

The patient was kept off testosterone replacement. Eight months after the last testosterone injection, he complained of decreased libido, lack of energy, weight loss (3.5 kg), and his total testosterone was in the low normal range (288 ng/dl). Bone densitometry revealed osteopenia at the lumbar spine (*T*-score 1.8). Prolactin, thyroid-stimulating hormone, FT₄, and cortisol serum levels were normal. A summary of clinical and hormonal features of the patient is shown in Table 1.

Mutational analysis of *KAL1* and *FGFR1*

After the patient consent, DNA was extracted from peripheral lymphocytes of the patient using a Qiagen Midi Kit (Qiagen), following manufacturer's protocol. Exons 1–14 of *KAL1* and exons 1–18 of *FGFR1* were amplified by PCR. One hundred nanograms of human genomic DNA were used as template in a 100 l PCR mixture containing 20 mM Tris–HCl (pH 8.4), 50 mM KCl, 1.5 mM MgCl₂, 0.2 mM deoxy-NTPs, 2.5 U Taq polymerase (PCR Reagent System, Life Technologies), and 0.1 M upstream and downstream specific primers. The sequence of the PCR primers and the PCR thermal cycling program used were based on previous publications (8, 12, 19). PCR products were analyzed in 1.8% agarose gels and purified using a PCR Product Purification Kit (Life Technologies). Direct sequencing of the

Table 1 Clinical and hormonal features at presentation and during follow-up of the patient.

Age (years)	22	26	28	37	41	41.8
Height (cm)	164	169	170	174	174	174
Weight (kg)	49	50	55.4	63.5	65.9	62.4
Testicular volume (ml)	3	5	10	12	12	15
Pubic hair (Tanner)	II	III	IV	V	V	V
Testosterone (ng/dl) ^a	Low	NA	NA	54	454	288
LH (mIU/ml) ^a	Low	NA	NA	NA	2.8	2.6
FSH (mIU/ml) ^a	Low	NA	NA	NA	3.4	1.8

^aAt diagnosis, serum testosterone, LH, and FSH concentrations, as determined by in-house RIAs, were 212 ng/dl, 2.0, and 3.0 mIU/ml respectively, and normal reference ranges were 400–1200 ng/dl, 5–15 mIU/ml, and 5–15 respectively. During follow-up, automated chemiluminescence assays were used for serum testosterone, LH, and FSH measurements (Advia Centaur, Bayer). Total testosterone: assay sensitivity 10 ng/dl, intraassay coefficient of variation (CV) 4.4%, and interassay CV 6.2%. LH: assay sensitivity 0.07 mIU/ml, intraassay CV 1.5%, and interassay CV 2.3%. FSH: assay sensitivity 0.3 mIU/ml, intraassay CV 2.9%, and interassay CV 2.7%. Adult reference values: LH 1.5–9.3 mIU/ml; FSH 1.4–18.1 mIU/ml; and total testosterone 240–830 ng/dl.

Figure 1 KAL1 mutation in the reversible KS patient. A, Identification of the KAL1 mutation. Electropherogram of DNA sequence, sense orientation. Arrow indicates insertion of an extra nucleotide (C) in codon 75 (75insC). Insertion was confirmed by sequencing products of two different PCRs (exon 2, *KAL1* gene). B, Normal anosmin1 structure. C, Expected truncated protein due to premature stop codon at codon 85.

PCR products was carried out in both directions, using the ABI Prism Big Dye terminator cycle sequencing ready reaction version 2.0 (Applied Biosystems, Foster City, CA, USA) in an ABI Prism 3100 DNA Sequencer (Perkin-Elmer Applied Biosystems).

As shown in Fig. 1, direct sequencing of the PCR products revealed a cytosine insertion in exon 2 of *KAL1*, causing a frameshift at codon 75 and a premature stop at codon 85. The expected gene product is a truncated peptide with only 85 of the 610 amino acids present in the wild-type protein. This insertion was confirmed by sequencing the products of two different PCRs. Sequencing of the exon 2 of *KAL1* under the same conditions using DNA from a normal male as template revealed no abnormalities. No mutation was found in *FGFR1*.

Review of the literature

Cases of reversible Kallmann syndrome were searched in Pubmed (US National Library of Medicine) using the search terms ‘Kallmann’, ‘reversible Kallmann’, ‘delayed puberty’, and ‘variant Kallmann syndrome’. The diagnosis of reversible KS included all patients, who became fertile without gonadotropin or GnRH therapy and/or who showed improved testosterone secretion after discontinuing gonadotropin, GnRH, or testosterone replacement.

As shown in Table 2, 14 unrelated patients with reversible KS, including our patient, have been described in the medical literature. All patients presented delayed puberty associated with anosmia. In four, additional features of KS were described: neuro-sensorial hearing loss ($n=2$), facial asymmetry ($n=2$), thoracic asymmetry ($n=1$), and palatine cleft ($n=1$). Five patients had other family members with KS and one family presented a high rate of consanguinity (26). The diagnosis of KS in these patients was established between 15 and 31 years of age. Ten patients were treated exclusively with testosterone replacement, three were also given human chorionic gonadotropin to induce fertility, and a single one received FSH additionally. Testosterone replacement was discontinued in seven patients by their own judgment and in three patients for inclusion in studies of gonadotropin secretion in KS.

Reversal of hypogonadism was diagnosed after 1.25–15 years (mean 7.2 years) of starting testosterone replacement. Reversal of hypogonadism was suspected because of wife’s pregnancy in seven patients (five on testosterone and two off testosterone replacement), and paternity was tested and confirmed by HLA haplotype analysis in three families. Other signs indicating reversal of hypogonadism were testicular enlargement

Table 2 Clinical, hormonal, and molecular characteristics of 14 patients with reversible Kallmann syndrome reported in the literature.

Age (years)		Testicular size		Testosterone (ng/dl)		Sign of reversal	Molecular diagnosis	Reference
At diagnosis	At reversal	At diagnosis	At reversal	At diagnosis	At reversal			
17.5	19.25	N/A	4.5×2.5 cm	N/A	535	Testicular growth	ND	(27)
27	40	3.5×2 cm	N/A	N/A	31	Pregnancy ^a	ND	(26)
31	31.8	3×2 cm	N/A	18	54	Pregnancy ^a	ND	(29)
25	27.1	2.5 cm	4.5×2.5 cm	50	741	Testicular growth	ND	(25)
23	33	2.2×1.2 cm	16 ml	14	102	Pregnancy ^a	ND	(30)
16	20	1.0 cm	2.5×2.0 cm	14	183	Pregnancy	ND	(24)
21	37	3–6 ml	NA	28	428	Reassessment	ND	(31)
22	28	6 ml	16 ml	57	714	Testicular growth	ND	(28)
23	32	2 ml	20 ml	28	485	Well off testosterone	ND	(28)
16.5	20	2 ml	15 ml	28	428	Pregnancy	ND	(28)
17.7	18.9	4 ml	25 ml	57	314	Testicular growth	ND	(28)
19.4	29.4	1 ml	12 ml	28	286	Pregnancy	ND	(28)
25	30	7 ml	10–12 ml	15	318	Reassessment	<i>FGFR1</i>	(32)
22	42	3 ml	15–18 ml	212	485	Pregnancy	<i>KAL1</i>	Present study

ND, not determined.
^aPaternity tested and confirmed by HLA haplotype analysis.

during testosterone replacement and maintenance of sexual function after discontinuation of testosterone. Hormonal evaluation confirming reversal of hypogonadism was performed after 6 weeks to 4 years off testosterone replacement. In spite of fertility restoration, six patients with reversible KS were kept on testosterone replacement due to complaints of erectile dysfunction and/or subnormal serum testosterone levels.

Discussion

In addition to the two classical diagnostic criteria for KS (hypogonadotropic hypogonadism and anosmia), our patient had neurosensorial hearing loss, which may also be present in KS, and a positive family history of delayed puberty in a brother and a maternal grand-uncle. Although his compliance with testosterone replacement therapy was variable, he achieved full virilization. The possibility that his hypogonadism had reversed was raised by his account of his wife's pregnancy, but a DNA paternity test was not performed. Reversal of his hypogonadal state was confirmed by testicular enlargement, from 3 to 15 ml, over nearly 20 years of irregular testosterone without gonadotropin replacement, and by a normal serum testosterone level long after testosterone replacement had been discontinued.

The real prevalence of reversible KS is unknown, but it is probably higher than the 5% found in a series of 76 KS patients without performing routine reassessment of gonadal function whilst off testosterone replacement therapy (28). In practice, special attention should be paid to testicular volume, both at diagnosis and during follow-up of KS patients, since testicular enlargement indicates increased gonadotropin secretion. In addition, periodical interruption of testosterone replacement and reassessment of gonadal function in KS patients may be desirable in order to avoid unnecessary hormone replacement and inappropriate reproductive prognosis.

The molecular study of our patient showed a novel mutation in *KAL1*, the gene responsible for XKS, and no mutations in *FGFR1*, the gene responsible for an AKS. This *KAL1* mutation predicts a prematurely truncated protein that lacks all functional domains of anosmin1: the N-terminal cysteine-rich region, the whey acidic protein (WAP)-like four disulfide core motifs, the four tandem fibronectin type III (FnIII)-like repeats homologous to neural cell adhesion molecules with heparan sulfate (HS)-binding activity, and the histidine-rich C-terminus. *In vitro* studies have shown that the WAP domain influences axon targeting and that the FnIII domains are essential for this function and also for axon branching (15, 17). *In vitro*, both *FGFR1* and anosmin1 require HS for their cooperation within a multimeric *FGFR1*–*FGF2*–HS–anosmin1 complex leading to functional and specific activation of *FGFR1* signaling through the MAPK pathway. Accordingly, anosmin1

can be viewed as an *FGFR1*-specific modulatory coligand that interacts with the *FGFR1*–*FGF2* complex to amplify intracellular downstream signaling (16).

In our patient, a severely dysfunctional protein was predicted from his *KAL1* mutation. However, in the absence of anosmin1, *FGF2* activation of the *FGFR1* receptor is more likely to be decreased than abolished (16). In the patient with reversible KS with a heterozygous *FGFR1* mutation previously described, intracellular signaling was also likely decreased, but not abolished, which can be explained by his *FGFR1* haploinsufficiency (32). The reversal of the hypogonadism in KS indicates that at least a population of GnRH neurons have successfully migrated to the hypothalamus and established functional connections with other neurons as well as with the vessels in the median eminence. Theoretically, variations in the amount of neurons effectively reaching the hypothalamus and establishing adequate connections could explain the broad spectrum of gonadal function in KS, including severe hypogonadism, delayed puberty, and reversible hypogonadism.

The possibility that patients with reversible KS represent an extreme degree of pubertal delay that would eventually enter puberty if left untreated cannot be ruled out. Delayed puberty with or without anosmia is known to occur in other family members of KS patients sharing the same mutation (6, 23, 32). On the other hand, testosterone replacement therapy could play a role in reversible KS. Precocious puberty can be triggered by increased androgen levels as observed in patients with congenital adrenal hyperplasia, androgen-secreting tumors, and testotoxicosis.

In conclusion, the present mutation represents the first mutation in *KAL1*, the gene responsible for X-linked KS, in a patient presenting reversible KS. This finding, together with the previous report of a heterozygous *FGFR1* mutation, indicates that the reversible KS phenotype is not restricted to mutations in a single gene. Considering the low prevalence (~10%) of mutations in each of these two genes in familial KS, it is rather intriguing that they have already been found in the only patients with reversible KS with molecular studies reported so far. It is tempting to speculate that mutations in *KAL1* and *FGFR1* may be more prevalent among patients with reversible KS than in other KS patients, but molecular studies in a larger number of patients are necessary to confirm this hypothesis.

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