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Adult-onset reversible idiopathic hypogonadotropic hypogonadism in male adult carrying a *WDR11* missense mutation

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SUMMARY

Idiopathic hypogonadotropic hypogonadism (IHH) occurs mostly in childhood or adolescence and very rarely in adulthood. It is characterised by delayed onset of secondary sexual characteristics. Many genetic abnormalities have been reported in congenital IHH cases, but rarely in adult-onset IHH cases. IHH requires lifelong hormone replacement therapy; however, a few reports suggest the reversibility of this condition.

In this case, after having his first child, a man in his 20s was diagnosed with gynecomastia followed by IHH. He improved with gonadotropin-releasing hormone replacement therapy and had two more children. The treatment was discontinued after 4 years, but the improvement was sustained. He had a heterozygous missense variant in *WDR11* (c.2390G>A; p.Arg797His), which may play a role in adult-onset IHH reversal. Accumulation of such cases can contribute to our understanding of the pathogenesis and genetic component of IHH.

BACKGROUND

Idiopathic hypogonadotropic hypogonadism (IHH) is caused by impaired gonadotropin-releasing hormone (GnRH) synthesis in the hypothalamus without any preceding trauma or inflammation. Common symptoms of IHH include anosmia and delayed growth and puberty which can be diagnosed in childhood or adolescence. However, adult-onset cases have normal gonad function and sexual development until adolescence or early adulthood. Congenital IHH can be inherited as X linked recessive, autosomal dominant or recessive forms in addition to apparently sporadic forms. Mutations in genes associated with congenital IHH account for 10%–20% of IHH cases. Many of these genes are implicated in the underlying molecular mechanisms (for reviews, see [1] and [2]).

Although the majority of patients with IHH need lifelong hormone replacement therapy, some patients may retain the improvements in hormone levels even after discontinuation of treatment. Hence, we describe an interesting case of a man with a *WDR11* mutation that helped reverse his IHH. We also reviewed the National Center Biotechnology Information database (see https://www.ncbi.nlm.nih.gov/nuccore/NM_018117.12).

CASE PRESENTATION

A man in his 20s visited the endocrinology and breast surgery clinic of our affiliated hospital with a 2-month history of decreased libido, erectile dysfunction, lack of energy, bilateral breast enlargement, and reduced pubic, facial and body hair. Serum luteinising hormone (LH) and follicle-stimulating hormone (FSH) were low and total testosterone was within the peripubertal range. He was referred to our medical centre for further management.

On further questioning, he reported spontaneous pubertal development with no obvious anosmia. His medical history was unremarkable. Further questioning revealed no obvious mental or physical cause of the symptoms.

On physical examination, the patient appeared young for his age, with minimal facial hair and scarce axillary hair. He had a body mass index of 21.6 kg/m^2 (weight 64 kg, height 172 cm). The blood pressure was 105/61 mm Hg, and other vital signs were normal. Both breasts were enlarged, with no nipple retraction, masses or discharge. Both testicles were 10 mL in volume as measured by an orchidometer. Pubic hair distribution was in the form of an inverted triangle (female type). Blood parameters (blood cell counts, metabolites) were in the normal range, including ferritin. He was not tested for autoimmunity. The endocrinological data are shown in table 1. His semen test showed oligozoospermia and asthenospermia. LH-releasing hormone (LHRH) stimulation test (intravenous administration of 100 mg LHRH; Tanabe, Osaka, Japan) revealed an attenuated and delayed LH response (peak: 2.52 mIU/mL at 120 min) and poor FSH response (peak: 0.10 mIU/mL at 120 min) (table 2). An LHRH repeated stimulation test (LHRH stimulation test repeated 5 days after intravenous administration of 100 mg of LHRH) showed recovery of the LH response (table 3). The stimulation tests of corticotropin-releasing hormone, thyrotropin-releasing hormone and growth hormone-releasing hormone revealed normal responses. MRI did not detect any abnormalities in the pituitary. These data supported the diagnosis of adult-onset IHH.

INVESTIGATIONS

Genomic DNA isolated from the patient's blood was subjected to IHH-related gene mutation analysis for *CHD7, FGF8, FGFR1, GNRH1, GNRHR, ANOS1, KISS1R, PROKR2, TACR3, IGSF1, KISS1, PROK2, SOX10, TAC3* and *WDR11* (performed at Kazusa DNA Research Institute; Chiba, Japan). The subject gave informed consent to the investigator. The exons of the protein-coding region of the target genes and their intron boundaries were amplified by hybridisation or PCR. Next-generation sequencing was performed to detect the presence or absence

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Table 1 Initial laboratory data of the patient

Parameters	Value	Reference range
Luteinising hormone (mIU/mL)	0.23	0.79–5.72
Follicle-stimulating hormone (mIU/mL)	<0.05	2.00–8.30
Testosterone (ng/mL)	0.1	1.31–8.71
Free testosterone (pg/mL)	<0.6	7.6–23.8
Adrenocorticotropic hormone (pg/mL)	29.5	7.2–63.3
Cortisol (µg/dL)	34.9	7.07–19.6
Thyroid-stimulating hormone (µIU/mL)	0.98	0.61–4.23
Prolactin (ng/mL)	7.93	4.29–13.69

of low-frequency sequence alterations in the protein-coding regions of the target genes.

The patient was found to be heterozygous for a *WDR11* missense variant (c.2390G>A; p.Arg797His). No genetic mutations in *CHD7, FGF8, FGFR1, GNRH1, GNRHR, ANOS1, KISS1R, PROKR2, TACR3, IGSF1, KISS1, PROK2, SOX10, TAC3* or *MKRN3* were found.

TREATMENT

The treatment strategy consisted of intermittent subcutaneous GnRH injections. Administration of 20 µg gonadorelin acetate (Hypocrine Injection, Nipro ES Pharma Co, Tokyo, Japan) every 2 hours over 6 months led to improvement in serum testosterone level and sperm count and quality.

OUTCOME AND FOLLOW-UP

During 4 years of disease management, he fathered two children.

The patient also reported a reduced sense of smell. The prosultiamine tolerance test showed a slight delay in the latent period.

The patient accidentally discontinued the treatment for more than 1 month, and he felt no change during this period. Therefore, the patient was kept off GnRH subcutaneous injections for 5 months to record further observations. After 5 months of discontinued gonadorelin acetate replacement therapy, LH, FSH and testosterone levels remained in the normal range. Additionally, there were normal LH and FSH responses in LHRH stimulation tests (table 4).

DISCUSSION

This report describes an interesting case of a man with reversible IHH due to a *WDR11* mutation.

IHH is traditionally divided into Kallmann syndrome with olfactory impairment and normosmic IHH. IHH is caused by impaired GnRH synthesis in the hypothalamus. Most cases of IHH emerge between the fetal stage and puberty; however, some adult-onset cases show normal pre-puberty development. Adult-onset IHH was first reported in 1997.[3] To date, there are only two published reports of genetic mutations in adult-onset IHH (in *GNRHR* and *FGF8*).[4 5]

A large degree of variability in inheritance and penetrance has been noted in IHH, and an increasing body of evidence suggests that this is a multigenic disorder. No acquired causes, such as anatomical disorders, inflammation or infiltration, have been reported. Variants in known IHH genes currently account for only 50% of IHH cases with family history; therefore, more genes are yet to be identified. The chromosome 10q26 region has been previously associated with genital development in men. *WDR11*, on chromosome 10, encodes a protein that is a member of the WD-repeat protein family and participates in a wide variety of cellular processes. The first *WDR11* mutation in an IHH case was reported in 2010[6] and recent large analyses have identified *WDR11* mutation as a potential cause of IHH. To date, the *WDR11* c.2390G>A mutation identified in our patient has not been previously associated with adult-onset IHH.

Our adult-onset case showed hormone reversal 5 months after the discontinuation of GnRH therapy. It was earlier believed that patients with IHH needed lifelong hormonal treatment; however, 10%–22% of IHH cases show a reversal in hormone levels even after the discontinuation of treatment,[7] although approximately 10% of such cases did not sustain the reversal. They experienced psychiatric and/or metabolic stress before relapse.[8] The exact mechanism of this reversibility remains unclear; one explanation includes plasticity in the network of GnRH-producing neurons, even in adulthood.[7]

There have been no previous reports of *WDR11* mutations in patients with a reversal; however, some reversal patients with genetic mutations in other genes have been reported.[9] To date, 14 *WDR11* mutations have been identified in patients with IHH.[6] Four of the 14 had a mutation in a second gene, and all of them had a single-point mutation resulting in amino acid substitutions or premature stop codons. The c.2390G>A mutation in our patient results in an Arg to His substitution at amino acid 797 which significantly alters the *WDR11* protein structure and could impact its function. These mutations could potentially alter the structure of the *WDR11* protein-signalling complex that interacts directly with molecules during the development and functioning of the reproductive system. We postulate that impaired pubertal development in patients with IHH results from impaired interaction of *WDR11* with additional undetected or known mutant proteins.

The *WDR11* c.2390G>A mutation could be a de novo mutation because the patient's parents had normal sexual differentiation and reproductive history. However, we could not confirm this since we were unable to sequence the parents' *WDR11*

Table 2 LHRH stimulation test

Time (min)	0	15	30	60	90	120
LH (mIU/mL)	0.41	1.31	1.87	2.02	2.29	2.52
FSH (mIU/mL)	<0.05	0.06	0.06	0.08	0.09	0.10

LHRH stimulation test revealed low and delayed LH response (peak: 2.52 mIU/mL at 120 min) and poor response of FSH (peak: 0.10 mIU/mL at 120 min).
FSH, follicle-stimulating hormone; LH, luteinising hormone; LHRH, luteinising hormone-releasing hormone.

Table 3 LHRH repeated stimulation test

Time (min)	0	15	30	60	90	120
LH (mIU/mL)	2.38	8.38	12.39	11.25	9.75	8.91
FSH (mIU/mL)	0.53	0.61	0.78	0.82	0.87	0.85

LHRH repeated stimulation test caused recovered LH reaction.
FSH, follicle-stimulating hormone; LH, luteinising hormone; LHRH, luteinising hormone-releasing hormone.

Table 4 Laboratory data 5 months after discontinuing GnRH treatment

Testosterone (ng/mL)	5.75		(Reference range 1.31–8.71)			
LHRH stimulation test						
Time (min)	0	15	30	60	90	120
LH (mIU/mL)	3.81	29.74	42.77	34.32	29.03	23.32
FSH (mIU/mL)	3.37	6.43	8.62	9.05	9.10	8.17

Testosterone, LH, FSH basal levels and LHRH stimulation test became all within normal limits 5 months after discontinuing GnRH treatment.
FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinising hormone; LHRH, luteinising hormone-releasing hormone.

genes. This mutation acts as a 'likely benign' variant and does not always occur in association with IHH pathogenesis. Oligogenic inheritance involving more than one gene has recently been reported in IHH[10]; however, this patient did not have a mutation in the other IHH-associated genes that were tested.

Metabolic or psychological stress has been reported in cases in which reversibility was not maintained and hypogonadotropic hypogonadism recurs. In light of this, it could be that people who originally had a predisposition to IHH due to genetic mutations developed the disease in adulthood because of environmental factors. However, no physical or psychological stress was observed in this patient. It is also unclear whether the reversal will be maintained in the future because the observation period after discontinuation was short. Since changes in testicular appearance and volume may indicate increased GnRH secretion and subsequently increased testosterone levels (as in the case of our patient), critical attention should be paid to these indicators, both at diagnosis and during follow-up of the patient with IHH.

In summary, we describe a male patient with adult-onset IHH who had a pathogenic candidate variant in the *WDR11* gene and spontaneously recovered and was able to have children again.

Patient's perspective

I am grateful that I was able to have two children as a result of the diagnosis and treatment.

After starting treatment, all of my subjective symptoms improved except for gynecomastia.

I am still on treatment suspension, but there has been no change in subjective symptoms.

Learning points

- Patients with normal puberty may also develop idiopathic hypogonadotropic hypogonadism as adults and can have children, after undergoing hormone replacement therapy.
- Reversibility of symptoms may occur after treatment interruption.
- Even in the cases who may retain the improvements in hormone levels even after discontinuation of treatment, genetic abnormalities may have been present.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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