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Case Report

Adult-Onset Case of Female Idiopathic Hypogonadotropic Hypogonadism and Ataxia: Genetic Background

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Abstract: Adult-onset cases of idiopathic hypogonadotropic hypogonadism (IHH) are characterized by partial or normal puberty development until adolescence and by the impairment of the hypothalamic–pituitary–gonadal (HPG) axis in adulthood. *WDR11* and *DCC* genes are known to be involved in axonal development, particularly of hypothalamic GnRH neurons, and ciliogenesis. We report a female case of adult-onset hypogonadism and cerebellar ataxia, in which we identified two gene mutations. A panel of 48 genes was set up to search for variants in the causative genes of CHH. The variants found were analyzed following the American College of Medical Genetics and Genomics (ACMG) criteria to define their pathogenicity. We identified a missense heterozygous variant in the *WDR11* gene NM_018117.12:c.2306T>G (p.Met769Arg) and a mutation in a second gene *DCC* resulting in amino acid substitutions NM_005215.4:c.3533C>T (p.Ser1178Phe). These variants were classified as being of uncertain clinical significance. We assume that there is a link between the variants found and the impairment of the gonadotrophic and neurological phenotype of the patient. Therefore, we propose the genetic test to identify the best therapeutic approach to identify infertility in female patients with IHH; we believe it is necessary to test *WDR11* and *DCC* genes in larger populations with the same condition to introduce it in future protocols of assessment.

Keywords: hypogonadotropic hypogonadism; infertility; cerebellar ataxia; amenorrhea

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1. Introduction

Congenital hypogonadotropic hypogonadism (CHH) is a rare disorder with a genetic background characterized by the production, secretion or action deficit of gonadotropin-releasing hormone (GnRH), a key neuropeptide that regulates the reproductive competence of the hypothalamic–pituitary–gonadal axis. When it is associated with an impaired sense of smell, CHH is named Kallmann syndrome (KS) [1].

Over sixty genes have been implicated in the pathogenesis of the disease in approximately 50% of cases, as follows: *KAL1* (ANOS1) with X-linked transmission; *FGFR1* (encoding fibroblast growth factor receptor 1), *FGF8*, *CHD7*, *HS6ST1* (encoding heparan-sulphate 6-O-sulphotransferase 1), *SOX10*, *SEMA3A* (encoding semaphorin-3A), *IL17RD* (encoding interleukin-17 receptor D) with autosomal dominant inheritance; and *PROKR2* and/or *PROK2*, *FEZF139* with autosomal recessive inheritance. *GNRHR* (encoding gonadotropin-releasing hormone receptor), *GNRH1* (encoding gonadotropin-releasing hormone 1), *KISS1R*, *KISS1*, *TACR3* and *TAC3* were genes involved in CHH with a normal sense of smell (nCHH), while FGFR1 and PROKR2 can be implicated in both KS and nCHH patients [2]. The *WD Repeat Domain 11* (*WDR11*) is one of the most recent genes identified in subjects with IHH and KS. It encodes for a protein with repeated WD domains, each one interacting with

protein-binding partners that participate in a wide variety of cellular processes including the development of the central nervous system, particularly of hypothalamic GnRH neurons, and ciliogenesis in mice.

Kim et al., in 2010, focused their attention on a specific cell protein that interacts with *WDR11*, EMX1, a domain transcription factor involved in the development of olfactory neurons. Fifteen *WDR11* mutations have been reported in CHH patients; they are all missense heterozygous, whereby some have a mutation in a second-known gene, and one is associated with clinical reversibility [3–5].

Deleted in colorectal cancer (*DCC*) is a gene known to be involved in axonal development in the brain [3] and encoding proteins containing Fibronectin type-III (FN3) domains, which are considered biologically relevant in GnRH neuron development. Defects in this gene have been identified in congenital mirror movement [4] and agenesis of the corpus callosum [5] and CHH [6]. Hearing loss, congenital mirror movement and other malformations are often CHH-associated phenotypes [7].

Clinically, CHH is characterized by absent or incomplete puberty and infertility. In the neonatal age, in the male, it can reveal itself with cryptorchidism and micropenis. In adults, males present absent or minimal virilization, poor libido and erectile dysfunction; females have primary amenorrhea. In addition, other developmental anomalies may be associated with so-called "non-reproductive" phenotypes, such as labiopalatoschisis, dental and renal agenesis, bimanual synkinesis, sensorineural deafness and skeletal abnormalities [1,8].

Adult-onset cases of idiopathic hypogonadotropic hypogonadism (IHH) with partial or normal puberty development until adolescence have been reported. Generally, these cases suggest a milder impairment of the HPG axis and a better fertility with gonadotrophin treatment.

In CHH females, the ovulation induction therapy must be personalized to increase fertility and pregnancy rates, but current evidence regarding the fertility treatment management is limited [8].

We describe a case of secondary amenorrhea and ataxia occurring late in the adulthood of a woman carrying compound heterozygosity of *WDR11* and *DCC* missense mutations.

2. Case History

The patient, a 40-year-old female, was sent to our attention for consultation by neurologists because she was suffering from ataxia of recent onset and apparently secondary amenorrhea, which began immediately after menarche at 13 years old. She reported spontaneous pubertal development with no anosmia and acquired causes have been excluded. No family history of CHH has been reported; the patient has a sister and a brother who both had offspring [Figure 1].

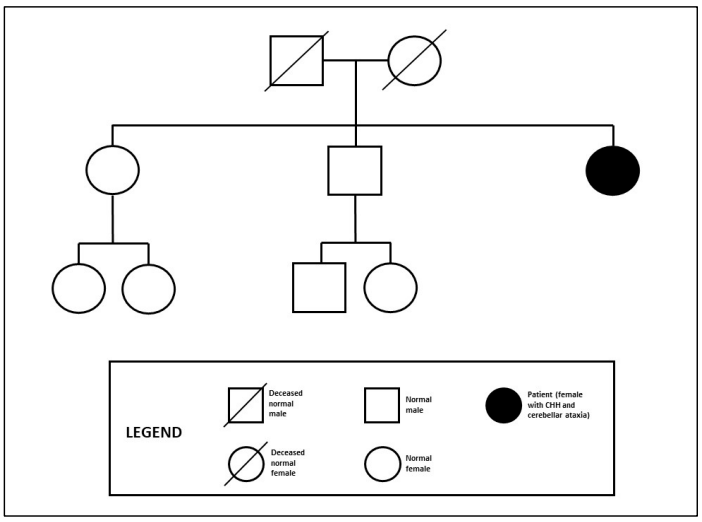

Figure 1. Genealogical tree of the patient.

From the age of 20, she started estrogen replacement therapy and at the age of 32 years, she underwent a cycle of ovulation induction therapy using human menopausal gonadotropin (HMG) and recombinant luteinizing hormone (LH) to promote fertility, but developed a severe ovarian hyperstimulation syndrome.

On physical examination, the patient showed bilateral breast enlargement and normal pubic hair distribution (Tanner stage B5 P5). She had a height of 167 cm and a weight of 67 kg with body mass index of 24 kg/m^2.

We performed a complete hormonal evaluation; the main results are illustrated in Table 1. Hormone measurements were conducted using chemiluminescence assays on the Advia Centaur XP ® platform (Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA).

Table 1. Hormone profiles of the patient (reference ranges in follicular phase of the menstrual cycle are reported). LH: luteinizing hormone; FSH: follicle-stimulating hormone; AMH: anti-mullerian hormone; TSH: thyroid-stimulating hormone; fT3: free triiodothyronine; fT4: free thyroxine; ACTH: adrenocorticotropic hormone.

Hormone	Value	Reference Range
LH	0.8 mUI/mL	1.9–12.5 mUI/mL
FSH	0.9 mUI/mL	2.5–10.2 mUI/mL
Oestradiol	10 pg/mL	19.5–144.2 pg/mL
Progesterone	0.05 ng/mL	0.30–1.20 ng/mL
AMH	1.02 ng/mL	1.22–15.8 ng/mL
TSH	1.10 µIU/mL	0.55–4.78 µIU/mL
fT3	3.78 pg/mL	2.3–4.2 pg/mL
fT4	1.42 ng/dL	0.70–1.76 ng/dL
ACTH	11.6 pg/mL	<47 pg/mL
Cortisol	12.38 µg/dL	4.3–22.4 µg/dL

The GnRH stimulation test (intravenous administration of 100 mcg of GnRH followed by blood samples at 15, 30, 60, 90 and 120 min) revealed a good LH and FSH response (respectively, 18 mIU/mL and 10 mIU/mL peaks).

On pelvic ultrasound, both ovaries appeared 5 mL in volume and the uterus showed a normal size and body/cervical ratio.

The brain Magnetic Resonance Imaging (MRI) showed wide-spread white matter changes with T2-weighted hyperintensities affecting deep and periventricular white matter and cerebellar atrophy; the pituitary gland appeared normal and free of focal alterations.

Chromosome karyotype analysis was normal.

Subject to informed consent, a peripheral venous blood sample (in EDTA) was performed. DNA was then extracted from lymphocytes (extraction KIT from Nuclear Laser Medicine S.r.l.) and it was quantified using Qubit. A panel of 48 genes was set up to search for variants in the causative genes of CHH (*GNRHR*, *GNRH1*, *KISS1R*, *KISS1*, *TAC3*, *TACR3*, *FSHB*, *LHB*, *KAL1*, *FGFR1*, *FGF8*, *PROK2*, *PROKR2*, *CHD7*, *SEMA3A*, *HS6ST1*, *SOX10*, *SEMA7A*, *SEMA3E*, *IL17RD*, *KLBSPRY4*, *DUSP6*, *ESX1*, *FGF17*, *POLR3A*, *POLR3B*, *PNPLA6*, *PLXNA1*, *FLRT3*, *WDR11*, *NELF*, *NTN1*, *DCC*, *FEZF1*, *NROB1*, *NR5A1*, *HESX1*, *LHX4*, *PROP1*, *STUB1*, *LEP*, *LEPR*, *PCSK1*, *IGSF10*, *FTO*, *EAP1*, *OTUD4* and *RNF216*), on the ION S5 (Thermofisher) platform. Sanger sequencing was used as the gold standard to confirm nucleotide changes identified using next-generation sequencing (NGS). The variants found were analyzed following the ACMG criteria to define their pathogenicity.

We identified a missense heterozygous variant in the *WDR11* gene NM_018117.12:c.2306T>G (p.Met769Arg) [Figure 2]. A mutation in a second gene *DCC* was found, resulting in amino acid substitutions NM_005215.4:c.3533C>T (p.Ser1178Phe) [Figure 3]. These mutations were classified as variants of uncertain significance (VUSs), following ACMG criteria.

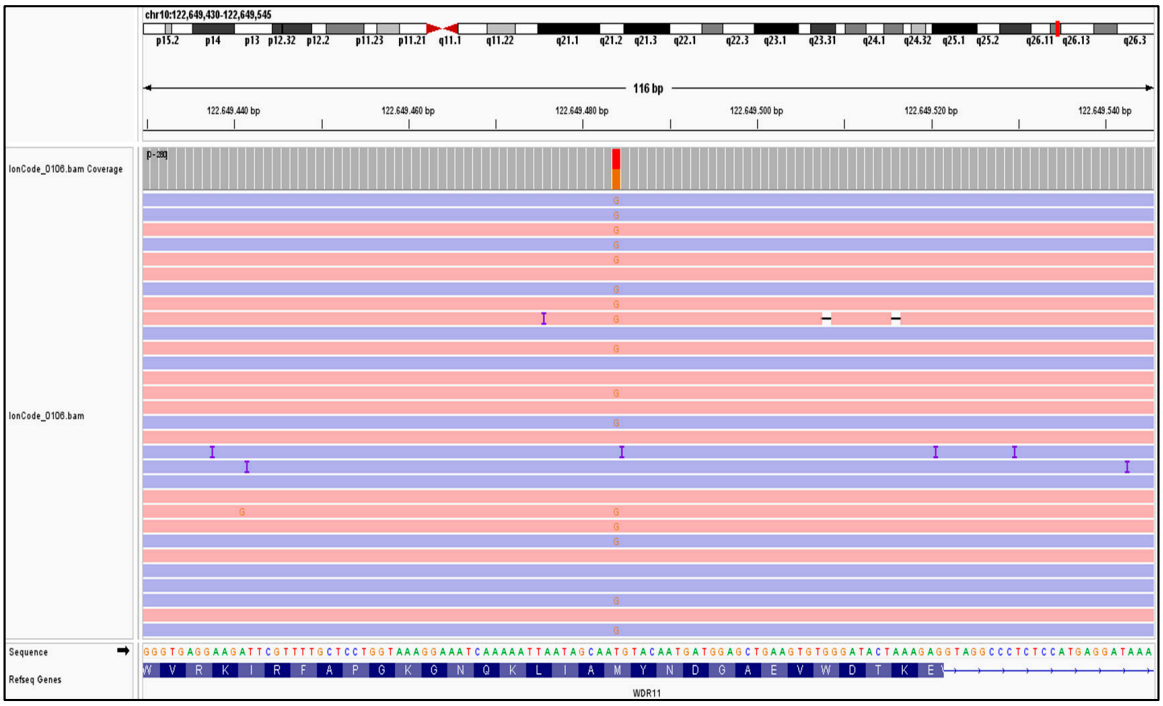

Figure 2. Snapshot of Binary Alignment Map (BAM) file for c.2306T>G(p.Met769Arg) heterozygous variant in the *WDR11* gene.

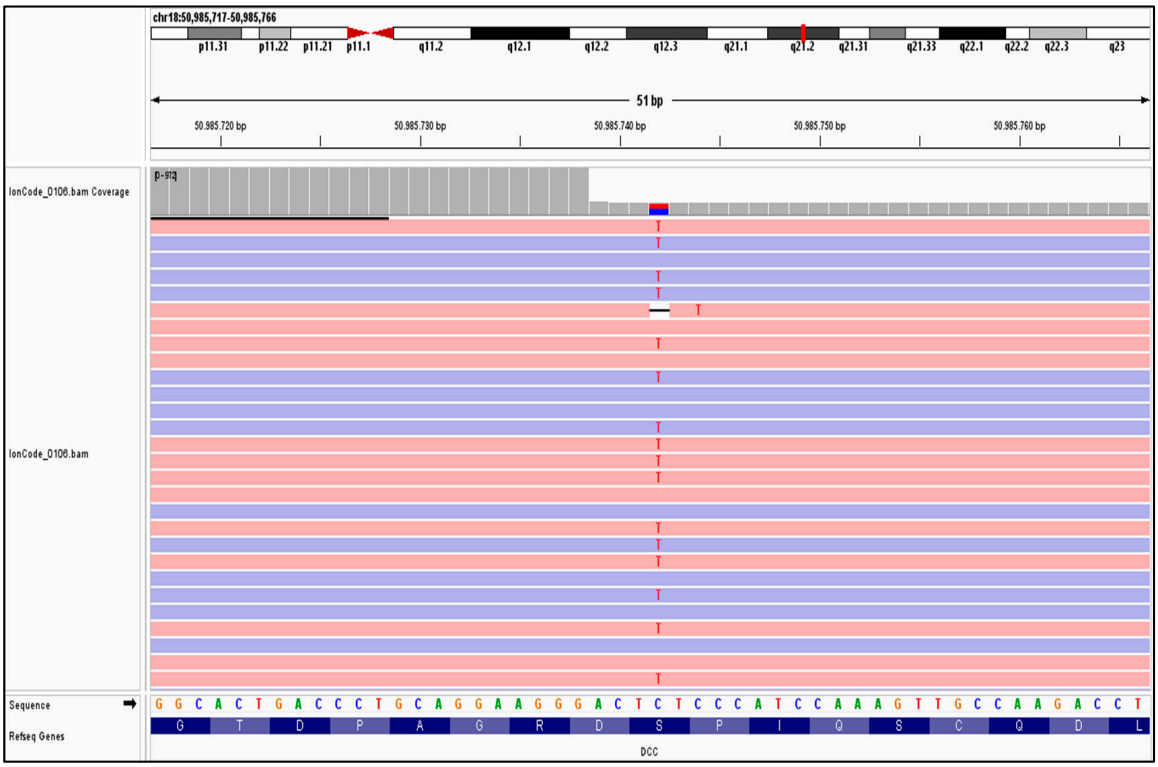

Figure 3. Snapshot of BAM file for c.3533C>T (p.Ser1178Phe) heterozygous variant in the *DCC* gene.

We have therefore placed a diagnosis of congenital hypogonadotropic hypogonadism, supported by the presence of the genetic variants found. At present, we have continued with the hormone replacement therapy, proposing to make an attempt of therapeutic withdrawal in order to evaluate a potential reversibility, as reported in the literature in similar cases [9]. This attempt was unsuccessful.

3. Discussion

We report a case of hypogonadism associated with spontaneous puberty and late onset ataxia probably due to a missense heterozygous variant in the *WDR11* gene NM_018117.12:c.2306T>G (p.Met769Arg) and a mutation in a second gene, *DCC*, resulting in amino acid substitutions NM_005215.4:c.3533C>T (p.Ser1178Phe). Kim et al., in 2010, focused their attention on a specific cell protein that interacts with *WDR11*, EMX1, a domain transcription factor involved in the development of olfactory neurons. Fifteen *WDR11* mutations have been reported in CHH patients; they are all missense heterozygous, some with a mutation in a second known gene and only one is associated with clinical reversibility [10–12]. Heterozygous *DCC* mutations have been identified in KS and CHH probands [6].

In the present case, we highlight the relevance of a *WDR11* gene mutation for its implication in the GnRH neuron migration and in the normal ciliogenesis, thus accounting for the failure in fertility restoration, leading to gonadotropin stimulation. In fact, it has been reported that *WDR11* knockout mice show profound infertility with significantly fewer germ cells present in the gonads; WDR11-deficient ovaries are smaller than wild type and present with disproportionally higher numbers of oogonia or primordial follicles and a reduced number of mature follicles [11,13].

Generally, adult-onset hypogonadism cases are characterized by normal gonad development until early adulthood with the complete activation of the HPG axis at puberty, suggesting a milder GnRH deficiency. As in this case, this initial gonadic activation allows pubertal development and the definition of secondary sexual characteristics.

CHH is rare in females; estrogen–progestin hormone replacement therapy is necessary for the maintenance of bone health and female appearance, to improve sexual life and to promote a general sense of well-being. Because reversibility occurs in both male and female CHH cases (10–15%) [9], we have decided to implement periodic treatment withdrawal with close monitoring and follow-up. To date, the evidence for the restoration of the reproductive potential is limited. The therapeutic approach to stimulate fertility is not standardized but is believed to be personalized in terms of gonadotrophin type and dosage, especially in these patients. In our case, the patient performed only one cycle of ovarian stimulation, with HMG and LH, before coming to our attention with unsuccessful results due to a hyperstimulation syndrome.

Furthermore, our patient developed neurological symptoms of progressive severity in adulthood, as a possible expression of a neurodegenerative disorder of unknown origin. Considering that both *WDR11* and *DCC* are involved in different brain development processes, we might hypothesize that there may be a link between the variants found and the neurological phenotype of the patient. Nowadays, *POLR3A* and *POLR3B*, *OTUD4*, *STUB1*, *PNPLA6* and *RNF216* are all genes associated with CHH syndromes and cerebellar ataxia with clinical manifestations that may vary and lead to an infant or adult onset [14–19]. The neurological management of these forms of ataxia is clearly not focused on correcting the causes, but on the symptoms, through neuromotor rehabilitation and speech therapy. Studies on large populations could also clarify if *WDR11* and *DCC* can be causative of this clinical association.

4. Conclusions

We believe that the present case may be useful in broadening the spectrum of knowledge about CHH. We propose to include *WDR11* and *DCC* genes among those associated with CHH and ataxia and to expand the genetic spectrum of patients affected with further studies on larger populations.

The management and therapeutic approach to female infertility of patients with IHH should be modified.

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Conflicts of Interest: The authors declare no conflicts of interest.

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