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Case Report

Hypogonadotropic Hypogonadism as First Presentation of the Severe Neuroendocrine Disorder Caused by RNF216

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Abstract

Biallelic pathogenic variants in *RNF216* cause a syndrome characterized by hypogonadotropic hypogonadism, cerebellar ataxia, chorea, and cognitive impairment, a combination first described as Gordon Holmes syndrome (MIM 212840). We report 2 siblings who were referred due to absent or delayed puberty. The older sibling, a 17-year-old male, presented with absence of secondary sexual characteristics and a high-pitched voice. He had normal cognitive development and no anosmia. Clinical examination revealed Tanner stage P1/G1 and bilateral gynecomastia. Blood tests showed low gonadotropin and morning testosterone levels. His 15-year-old sister was referred due to primary amenorrhea. She had spontaneous thelarche and presented with Tanner stage P3/B3. Pituitary magnetic resonance imaging was performed on the brother due to suspicion of Kallmann syndrome, revealing a normal anterior pituitary, a hypoplastic posterior pituitary, and an extensive supratentorial leuko-encephalopathy. Whole-exome sequencing revealed a homozygous pathogenic variant in *RNF216* in both affected siblings. Both parents were heterozygous carriers. *RNF216* pathogenic variants cause a disorder characterized by combined neurodegeneration and reproductive dysfunction. Although neurological symptoms are typically recognized first, they often seem to follow the onset of hypogonadism. This highlights the need for awareness, as hypogonadotropic hypogonadism may be the initial manifestation of this severe neuroendocrine disorder, especially in males.

Key Words: hypogonadotropic hypogonadism, neuroendocrine disorder, RNF216

Introduction

Gordon Holmes syndrome (MIM 212840) is caused by homozygous or compound heterozygous pathogenic variants in the ring finger protein 216 (*RNF216*) gene on chromosome 7p22. *RNF216* encodes an E3 ubiquitin ligase of the "RING-between-RING" (RBR) class, which attaches ubiquitin to protein substrates, designating them for proteasome-mediated degradation or signal transduction. Failure in this process leads to the accumulation of toxic protein aggregates, resulting in neurotoxicity. Gordon Holmes syndrome is characterized by progressive cognitive decline; dementia; variable movement disorders, such as ataxia and chorea; and hypogonadotropic hypogonadism [1]. However, *RNF216*-related disorders can be heterogeneous, with some patients presenting with a Huntington-like disorder or 4H syndrome (hypodontia, hypomyelination, ataxia, and hypogonadotropic hypogonadism) [2]. Most pathogenic variants in *RNF216*-related disorders affect the RBR domain or the C-terminal extension. Additionally, pathogenic variants in other ubiquitination-related genes, such as *PNPLA6*, *STUB1*, and *OTUD4*, have also been found in patients with similar movement disorders and hypogonadotropic hypogonadism [3-5]. Recently, Wu et al reviewed the clinical and genetic spectrum of *RNF216*-related disorders [1]. While neurologic symptoms are typically recognized first and generally emerge in adolescence or young adulthood, there is significant variability in the onset. In many cases, the recognition of neurological disorders follows the onset of hypogonadotropic hypogonadism. Additionally, in some instances, hypogonadism appears to develop after pubertal maturation, indicating a progressive decline in neuroendocrine function. We report 2 siblings who first presented with hypogonadotropic hypogonadism. This highlights the need for awareness, as hypogonadotropic hypogonadism may be the initial manifestation of this severe and debilitating neuroendocrine disorder.

Case Presentation

Two siblings born to consanguineous parents were referred due to absent or delayed puberty progression. The elder sibling, a 17-year-old male adolescent, presented with absence of secondary sexual characteristics and a high-pitched voice. He had normal cognitive development and no anosmia. Clinical examination revealed Tanner stage P1/G1 and bilateral gynecomastia. His 15-year-old sister, with known Hashimoto thyroiditis, was referred due to primary amenorrhea. She had spontaneous thelarche and presented with Tanner stage P3/G3. She did not have hyposmia or anosmia.

Diagnostic Assessment

Clinical assessment was performed in both siblings (Table 1). Laboratory testing in the brother revealed hypogonadotropic

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Table 1. Characteristics of the 2 siblings with homozygous RNF216 mutations

	Brother—M, 17y	Sister—F, 15y	Normal range
Reason of referral	Absence of secondary sexual characteristics, high-pitched voice, normal cognitive development, no anosmia	Primary amenorrhea	
Clinical examination	W 97.2 kg, L 174 cm BMI 32.1 kg/m^2 (+2.4 SDS) Bilateral gynecomastia Hypotonia Tanner P1/G1	W 53.3 kg, L 160.9 cm BMI 21 kg/m^2 (0.0 SDS) Spontaneous thelarche Tanner P3/B3	
Lab tests	LH < 0.3 IU/L FSH < 0.3 IU/L T 0.40 nmol/L (11.4 ng/dL) NA TSH 1.57 mIU/L FT4 15.1 pmol/L FT3 5.7 pmol/L PRL 11.1 µg/L IGF-1 22 nmol/L (169 µg/L) (−2.3 SDS) C 342 nmol/L; 12.4 µg/dL	LH 1.1 IU/L FSH 4.6 IU/L NA E2 0.09 pmol/L (2.5 ng/L) TSH 2.33 mIU/L FT4 23.3 pmol/L FT3 4.6 pmol/L PRL 9.8 µg/L IGF-1 22 nmol/L (170 µg/L) (−2 SDS) C 149 nmol/L(5.4 µg/dL)	1.7-8.6 IU/L 1.2-7.7 IU/L 10-35 nmol/L (300-1000 ng/dL) 0.55-12.9 pmol/L (15-350 ng/L) 0.27-4.2 mIU/L 12.9-20.6 pmol/L 3.1-6.8 pmol/L 2-18 µg/L (M); 2-29 µg/L (F) 20-60 nmol/L (135-490 µg/L)
Brain MRI	Normal anterior pituitary, hypoplastic posterior pituitary, extensive supratentorial leuko-encephalopathy	Not yet performed	

Values are International System of Units and conventional units. Puberty staged according to Tanner.
Abbreviations: BMI, body mass index; C, cortisol; E2, estradiol; F, female; FT3, free T3; FT4, free T4; IGF-1, insulin-like growth factor 1; L, length; M, male; MRI, magnetic resonance imaging; NA, not applicable; PRL, prolactin; SDS, SD score; T, testosterone; W, weight; y, years.

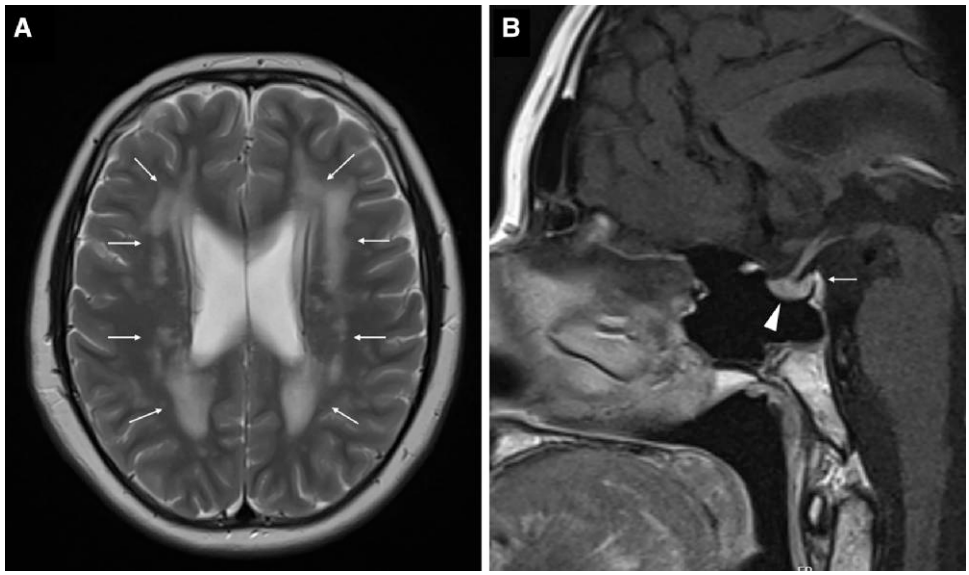

Figure 1. Brain and sellar magnetic resonance imaging of the brother. (A) Axial T2-weighted section shows extensive white matter lesions in both cerebral hemispheres (white arrows). (B) Midsagittal T2 fluid attenuated inversion recovery image shows a small and heterogeneous anterior pituitary (arrowhead) and hypoplastic posterior pituitary (white arrow).

hypogonadism, but examination of other pituitary hormones was normal. Due to suspicion of Kallmann syndrome, pituitary magnetic resonance imaging was performed, which revealed a rather small and heterogeneous anterior pituitary, a hypoplastic posterior pituitary, and an extensive supratentorial leuko-encephalopathy (Fig. 1). Laboratory testing in the sister revealed low but detectable levels of gonadotropins and low estradiol level. Whole-exome sequencing revealed a homozygous variant in *RNF216* (c.1705_1710del, p.(Leu569_Ile570del)) in both affected siblings (Fig. 2). Further segregation analysis revealed that both parents were heterozygous carriers.

Treatment

After the diagnosis of hypogonadotropic hypogonadism, the brother began intramuscular testosterone injections to induce puberty, starting with a dose of 80 mg monthly. The dose was gradually increased to the adult dose of 250 mg of testosterone every 3 weeks. We used an injectable combination of 4 testosterone esters, all of which are androgens/anabolic steroids: each ml dose of the solution contains 100 mg decanoate, 60 mg testosterone isocaproate, 60 mg testosterone phenylproprionate, and 30 mg testosterone proprionate. The sister was not started on any treatment other than levothyroxine for Hashimoto thyroiditis and vitamin D supplements for hypovitaminosis D.

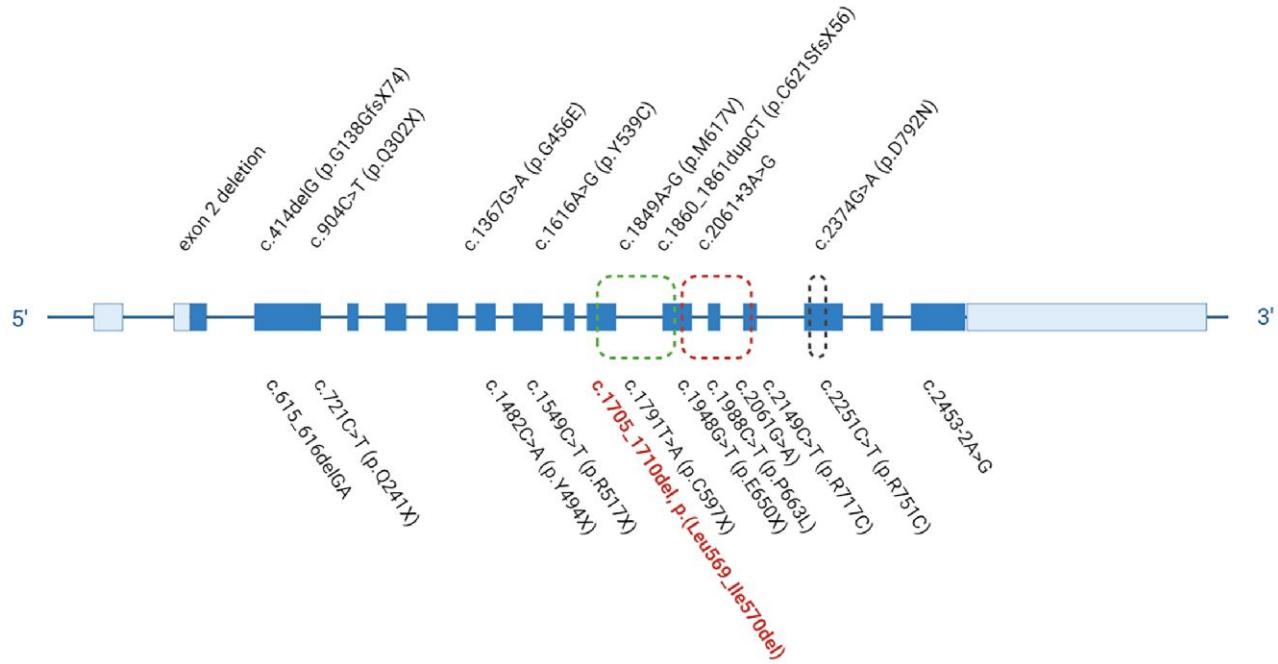

Figure 2. Position of disease-causing variants in the gene RNF216. The variant in red is identified in the patient from our institution. *RNF216* is located on chromosome 7p22 and contains 17 exons. The green box (left) represents the coding region of RING1 domain, the red box (middle) represents the coding region of IBR domain, and the black box (right) represents the RING2 domain.

Outcome and Follow-up

Both siblings are followed up in the endocrinology and neurology departments. The brother has responded well to puberty induction, with notable increases in male secondary characteristics such as a deeper voice and male-pattern hair growth. Neurologically, he has no issues, attends regular school, and shows no signs of movement disorders. The sister also attends regular school, and a brain magnetic resonance imaging is scheduled.

Discussion

RNF216, an E3 ubiquitin ligase, has a role in the ubiquitination system in disorders of combined neurodegeneration and reproductive dysfunction [3]. *RNF216* pathogenic variants cause a disorder characterized by variable combinations of cerebellar ataxia, chorea, cognitive decline, and hypogonadotropic hypogonadism. The majority of variants (85%) lead to amino-acid changes or truncation of the RBR domain or C-terminal extension, as observed in our family (Fig. 2). A recent review of all reported patients (n = 24) with causative *RNF216* variants revealed that most patients presented with ataxia or dysarthria (Table 2) [1]. The mean age of onset of neurological symptoms was 29.2 ± 8.4 years. Among individuals who developed neurological symptoms before age 30, the most common initial symptoms were ataxia (8/14) and dysarthria (7/14). In contrast, chorea was the most frequent initial symptom in those whose neurological symptoms began after age 30 (5/8). Throughout the disease course, almost all patients experienced cognitive impairment (92%) and ataxia (83%) (Table 2). White matter lesions and cerebellar atrophy were the most common imaging findings and were present in, respectively, 96% and 92% of patients.

Patients with *RNF216* variants also have pituitary dysfunction and in particular reduced GnRH responsiveness leading to hypogonadotropic hypogonadism and variable reproductive dysfunction [3]. Twenty-two patients from the recent review of all reported patients (n = 24) had varying degrees of hypogonadotropic hypogonadism, with the most common and typical symptom being the absence of spontaneous puberty or partial puberty (Table 3). Interestingly, male individuals seemed more vulnerable to hypogonadotropic hypogonadism than female individuals. No spontaneous or partial pubertal maturation occurred in 63% of the males but in only 13% of females. Males with normal or partial puberty later on presented with erectile dysfunction. Most females had normal puberty, although mostly followed by oligomenorrhea and amenorrhea, and some even had pregnancies with live-born children [1, 6]. This phenomenon has also been observed in animal studies, whereby targeted deletion *Rnf216* in mice resulted in disruption of spermatogenesis but was not required for female fertility [7, 8]. Hypogonadism in males therefore appears to be of both hypothalamic-pituitary and testicular origin and in females mainly of

Table 2. Neurological phenotype of patients with RNF216-disorder

Signs and symptoms	Initial presentation, %	Throughout disease course, %
Ataxia	43 (10/23)	83 (20/24)
Dysarthria	43 (10/23)	67 (16/24)
Chorea	26 (6/23)	46 (11/24)
Cognitive impairment	26 (6/23)	92 (22/24)
Psychological symptoms	22 (5/23)	29 (7/24)
Pyramidal signs	N/A	25 (6/24)

Abbreviation: NA, not applicable.
Source [1].

Table 3. Endocrinological phenotype of patients with RNF216-disorder

Signs and symptoms	%
Hypogonadotropic hypogonadism	92
No spontaneous or partial puberty	46 (11/24)
Males	63 (10/16)
Females	13 (1/8)

Source [1].

hypothalamic-pituitary origin. Extended GnRH treatment could restore LH secretion in few patients, although insufficiently and with diminishing response over time. Patients evaluated at a later stage of their disease showed an absent response, indicating progression of pituitary dysfunction [3].

Our 2 case reports highlight the importance of alertness when a patient presents with hypogonadism for signs of learning difficulties or neurological dysfunction. Hypogonadotropic hypogonadism can be the first manifestation of *RNF216* deficiency, especially in men. *RNF216*-related disorder is a very severe neuroendocrine and neurodegenerative disorder characterized by variable combinations of cerebellar ataxia, chorea, cognitive decline, and hypogonadotropic hypogonadism. The endocrinologist should be alert for neurological signs such as dysarthria, behavioral problems, learning difficulties, clumsy gait, choreatic, or ataxic movements and refer the patient in case of suspicion.

Learning Points

- RNF216, an E3 ubiquitin ligase, has a role in the ubiquitination system in disorders of combined neurodegeneration and reproductive dysfunction.
- RNF216-related disorder is characterized by variable combinations of cerebellar ataxia, chorea, cognitive decline, and hypogonadotropic hypogonadism.
- Hypogonadotropic hypogonadism may be the initial manifestation of RNF216 deficiency, especially in men.

Contributors

All authors made individual contributions to authorship. A.R. and L.A. were involved in the diagnosis and management of the patient and manuscript submission. W.A. and M.T. referred the patients and are involved in the follow-up of the patients. S.V. was involved in genetic diagnosis of the patients. All authors reviewed and approved the final draft.

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Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent was obtained directly from the patients' relatives or guardians.

Data Availability Statement

Original data generated and analyzed during this study are included in this published article.

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