Movement Disorders
CLINICAL PRACTICE
CASE REPORT

Gordon Holmes Syndrome Caused by RNF216 Novel Mutation in 2 Argentinean Siblings

Cristian R. Calandra, MD,[1,*] Yamile Mocarbel, MD,[2] Sebastian A. Vishnopolska, MSc,[3,4] Vanessa Toneguzzo, MD,[5] Jaen Oliveri, MD,[6] Enrique Carlos Cazado, MD,[2] German Biagioli, BCs,[3,7] Adrián G. Turjanksi, PhD,[3,4,7] and Marcelo Marti, PhD[3,4,7]

Gordon Holmes syndrome (GHS) is the clinical association of ataxia and hypogonadism[1] frequently encountered in patients with autosomal-recessive cerebellar ataxias. Mutations in genes, such as *RNF216*, *OTUD4*, *STUB1*, *PNPLA6*, and *POLR3A/3B/1C*, are associated with ataxia and hypogonadism,[2–6] but the patient's observed phenotypes are generally wider than expected. Here, we report the case of 2 Argentinean siblings with GHS caused by a novel homozygous mutation in the *RNF216* gene.

Case Report

Two male siblings, born from nonconsanguineous parents (Fig. S1), were referred to our hospital. Patient 1 was examined at age 28 showing clinical signs of hypogonadism, pes cavus, slight gait disturbance, and dysarthria (Fig. S2). Bone densitometry showed low mineral bone density. He was diagnosed with hypogonadotropic hypogonadism (Table S1) and began treatment with testosterone. At age 29, he experienced profound progression of gait and speech disturbances. Further examination revealed appendicular and truncal cerebellar ataxia (Video S1), dysarthria, and brisk tendon reflexes. Montreal Cognitive Assessment (MOCA) score was 12/30. At age 31, he was severely ataxic (Video S1) and demented (MOCA 10/30).

Patient 2 was also diagnosed with hypogonadotropic hypogonadism at age 18 years attributed to poor development of secondary sexual characteristics and low stature (Table S1). He was referred to our hospital 9 years later. Physical examination revealed eunuchoid appearance, gynoid fat distribution, dysarthria, appendicular and truncal cerebellar ataxia, brisk tendon reflexes, and a MOCA score of 17/30. Cerebellar signs were milder than those observed in patient 1. Two years later, the cerebellar ataxia slightly progressed (Video S1) and the MOCA score was 14/30.

Both siblings dropped out of high school because of learning difficulties. Their brain MRI revealed cerebral white matter changes, diffuse brain cortex, and cerebellar atrophy (Fig. 1; Table S1).

We performed whole-exome sequencing (WES) in patient 1. We found a novel homozygous variant in gene *RNF216* (NM_207116:c.2042C>T; NM_207111:c.1988C>T), which encodes an E3 ubiquitin ligase, not previously reported and predicted to produce a missense change (NM_207116:P606L), disrupting a highly conserved position in a zinc-finger IBR domain (Fig. 2). A structural model shows that the proline is adjacent to the zinc coordinating cysteine, in the elbow of a ß-turn motif. Prolines, because of their imino acid nature, are predominantly found in turns, and mutations to helix prone residues, such as leucine, are thus expected to destabilize the key zinc coordination motif, resulting in a nonfunctional protein. Consistently, numerous pathogenicity prediction softwares classify this variant as likely damaging (Table S2). We define the variant as likely pathogenic according to the American College of Medical Genetics and Genomics Guidelines (PM1, PM2, PM3, PP1, PP3, and PP4).[7]

Sanger sequencing confirmed the variant and showed that the affected brother (patient 2) is also homozygous, whereas both parents are heterozygous (Fig. 2).

[1]Department of Neurology, Hospital El Cruce, Florencio Varela, Buenos Aires, Argentina; [2]Department of Endocrinology, Hospital de Clínicas José de San Martín, Buenos Aires, Argentina; [3]Departamento de Química Biológica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires. Ciudad Universitaria, Intendente Guiraldes 2160, C1428EGA, Ciudad Autónoma de Buenos Aires, Argentina; [4]Instituto de Química Biológica de la Facultad de Ciencias Exactas y Naturales (IQUIBICEN) CONICET, Ciudad Universitaria, Intendente Guiraldes 2160, C1428EGA, Ciudad Autónoma de Buenos Aires, Argentina; [5]Department of Neurology, Hospital de Clínicas José de San Martín, Buenos Aires, Argentina; [6]Department of Clinical Genetics, Hospital El Cruce, Florencio Varela, Buenos Aires, Argentina; [7]Bitgenia, Alicia Moreau de Justo, 1750, Buenos Aires, Argentina

***Correspondence to:** Dr. Cristian R. Calandra, Hospital El Cruce, Avenida Calchaquí 5401, Florencio Varela, Buenos Aires (CP 1888), Argentina; E-mail: cristianrcalandra@gmail.com
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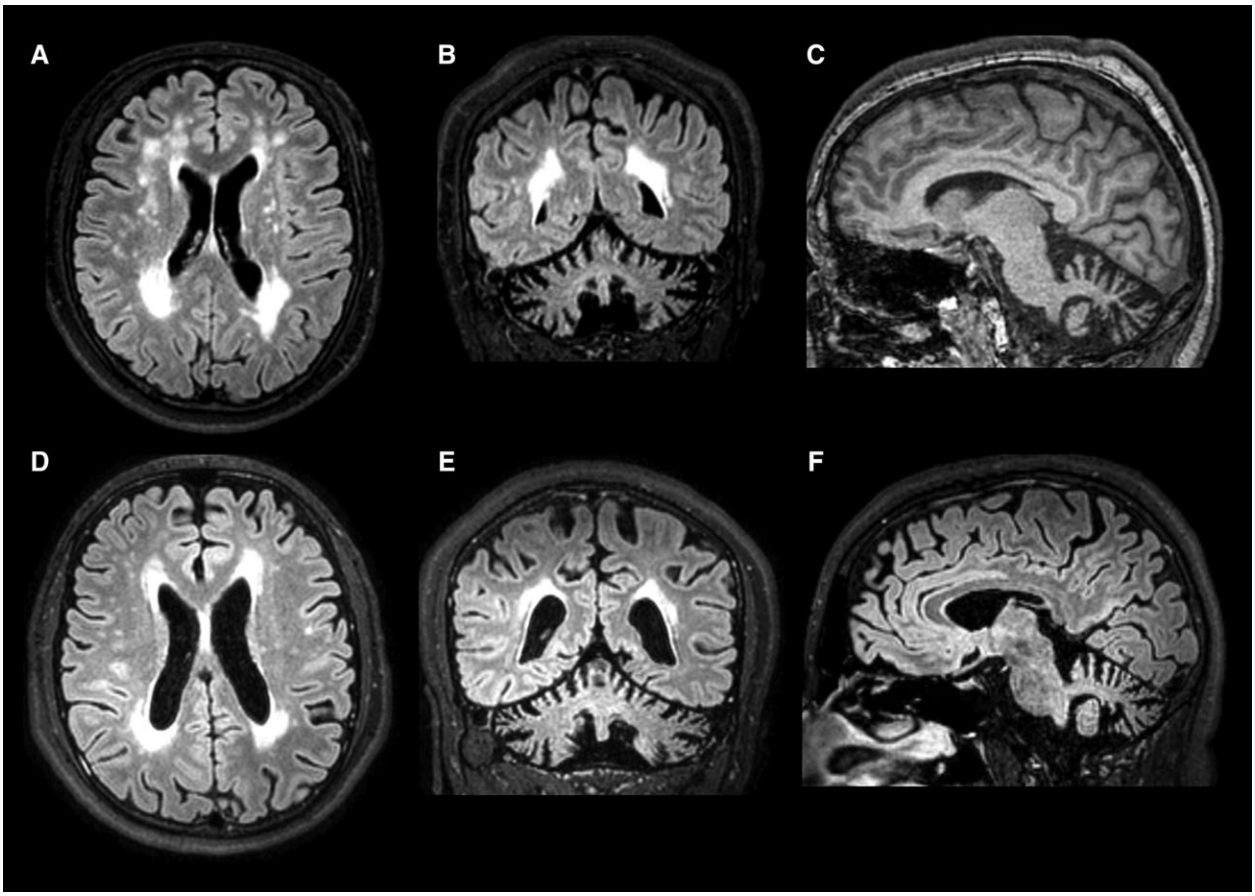

FIG. 1. Neuroimaging findings. Multiple cerebral white matter changes, cortical brain, and cerebellar atrophy in axial and coronal FLAIR-weighted images (A,B, patient 1; D,E, patient 2). Thin posterior segment of corpus callosum and cerebellar atrophy in sagittal T1-weighted image (C, patient 1) and sagittal FLAIR-weighted image (F, patient 2).

Discussion

The gene *RNF216* encodes an E3 ubiquitin ligase which marks different proteins for proteasome-mediated degradation. Previously, Margolin et al. reported on a consanguineous family with ataxia, dementia, and hypogonadotropism caused by a combination of mutations in *RNF216* and *OTUD4 genes*.[2] In the present case, the three variants found in *OTUD4* were considered probably benign (Table S3). RNF216-mediated neurodegeneration has been discovered very recently, with a total of 17 patients, 10 families, and 12 different mutations published to date (including ours; Table S4). Patients with these mutations not only show GHS characteristics, but also other clinical features such as chorea, psychiatric disorders, dementia, dysarthria, and corticospinal signs. Age of onset of the endocrine manifestations might differ among patients. Hormone replacement therapy is of utmost importance. Neuroimaging studies demonstrate cerebral and cerebellar atrophy and focal hyperintense signal changes on T2- and fluid-attenuated inversion recovery (FLAIR)-weighted images involving the periventricular and subcortical brain white matter, globus pallidus, putamen, thalamus, and pons.[2,8–10] Patients 1 and 2 showed a thin posterior segment of the corpus callosum, not previously reported. It is important to emphasize that the phenotype of RNF216-mediated neurodegeneration might have not been yet fully described because of the small number of cases reported on so far.

All previous reported cases with homozygous mutations in *RNF216* were from consanguineous families.[2,8–10] Interestingly, although consanguinity was not reported in the present case, the sibling's parents came from two small nearby towns (only 11 km apart) in the Argentinean countryside. We hypothesize that our findings could be explained by a common ancestor to both families, thus involving some degree of consanguinity unknown by the parents. Supporting this idea, we found a decreased heterozygous to homozygous single-nucleotide polymorphism ratio in patient 1 after WES (1.31 compared to the observed average of 1.50 in other exomes sequenced by our group).

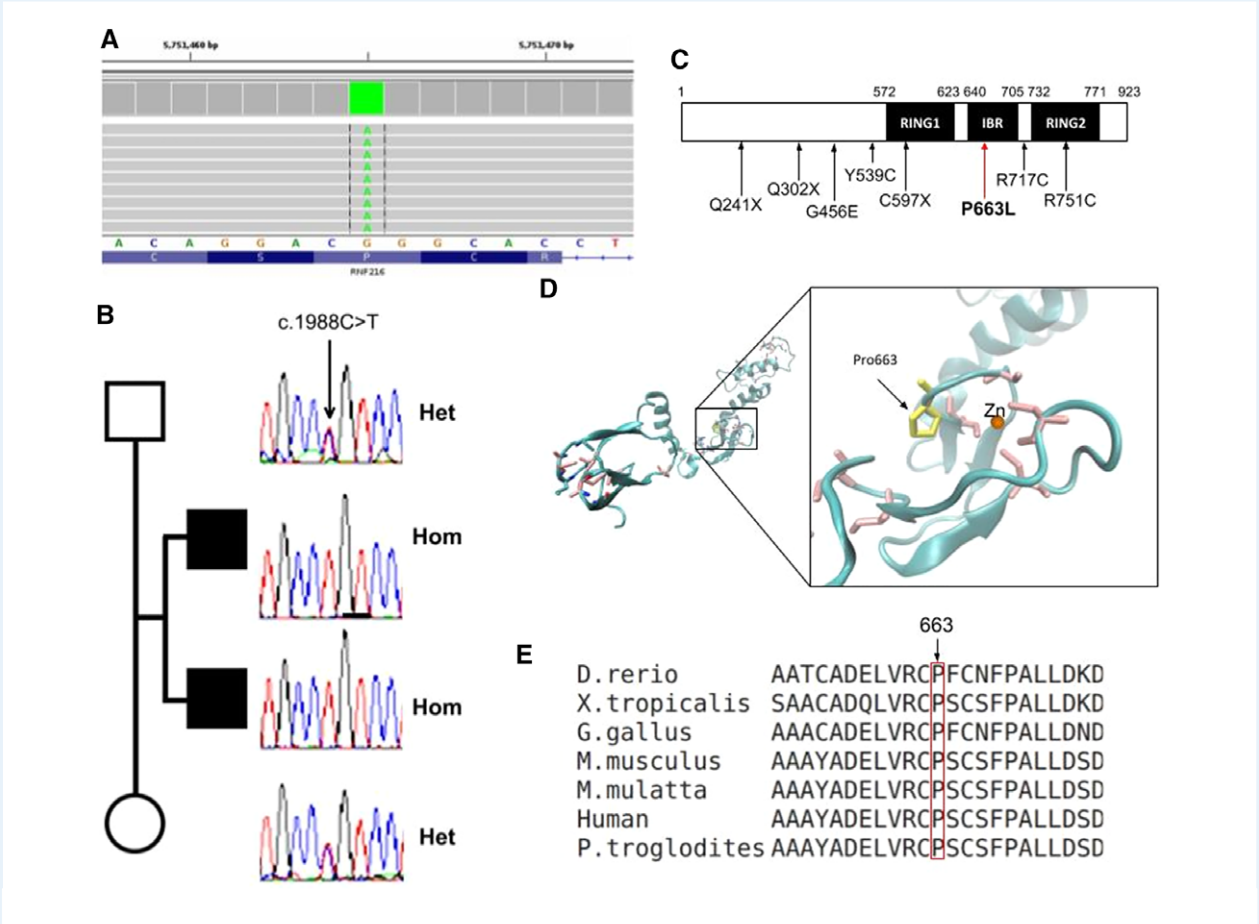

FIG. 2. Molecular and bioinformatic results. (A) Exome result of patient 1 in BAM format, the variant is found in the homozygous state. (B) Sanger results of gene RNF216 for the core family. (C) Relative location of the presently found variant together with other reported missense and nonsense pathogenic variants in the RNF216 gene isoform-2. (D) Model of zinc rings and IBR domain (modeled using 4KBL structure as template). Cystein residues coordinating the zinc ion are shown in pink; mutated proline in yellow. (E) Multiple alignment of proteins homologous to RNF216 isoform-2 in different species.

In summary, we present 2 Argentinean siblings with a GHS as part of the clinical spectrum of the RNF216-mediated neurodegeneration caused by a novel homozygous mutation.

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Author Roles

1. Research Project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing the First Draft, B. Review and Critique.

C.R.C.: 1A, 1B, 1C, 3A, 3B
Y.M.: 1A, 1B, 1C, 3A, 3B
S.A.V.: 1B, 1C, 3A, 3B
V.T.: 1C, 3A, 3B
J.O.: 1A, 1C, 3A,3B
E.C.C.: 1C, 3A, 3B
G.B.: 1C, 3A, 3B
A.G.T.: 1C, 3A, 3B
M.M.: 1A, 1B, 1C, 3A, 3B

Disclosures

Ethical Compliance Statement: The authors confirm that the approval of an institutional review board was not required for this work. Written informed consent to publish all shown material was obtained from the patients. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Supporting Information

Supporting information may be found in the online version of this article.

Figure S1. Family pedigree. HH, hypogonadotropic hypogonadism; A, ataxia; D, dementia.

Figure S2. Patient 1. (A) Arm span >5 cm. (B,C) Eunuchoid appearance, gynoid fat distribution, and bilateral lipomastia. (D) Pes cavus.

Video S1. Patient 1, Segment 1: first physical exam. Ataxic gait without assistance. Patient 1, Segment 2: first physical exam. Bilateral upper limb ataxia. Patient 1, Segment 3: last physical exam. Ataxic gait with assistance. Patient 1, Segment 4: last physical exam. Severe cerebellar dysarthria. Patient 2, Segment 5: ataxic gait without assistance. Patient 2, Segment 6: alteration of tandem gait.

Table S1. Clinical manifestations, laboratory, and MRI findings

Table S2. Variant genomic data referred to human genome GRCh37 and pathogenicity prediction analysis

Table S3. Variants in OTUD4 gene

Table S4. RNF216-mediated neurodegeneration