




SHORT COMMUNICATION

RNF170 mutation causes autosomal dominant sensory ataxia with variable pyramidal involvement

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Funding information

S.H.V.D. is funded by a PhD fellowship of the Research Foundation - Flanders (FWO) (1164018N, file number 40900). Research is furthermore funded by the Fund for Clinical Academic studies of the University Hospitals of Leuven, Belgium (S61184). P.V.D. and H.V.E. are Senior Clinical investigators of FWO. P.V.D. is supported by the ALS Liga België and the KU Leuven funds "Een Hart voor ALS", "Laeversfonds voor ALS Onderzoek" and the "Valéry Perrier Race against ALS Fund". K.G.C. and P.V.D. hold the Emil von Behring Chair in Neuromuscular and Neurodegenerative Disorders by CSL Behring.

Abstract

Background: Although hereditary ataxias are a group of clinically and genetically heterogeneous disorders, specific clinical clues can sometimes incriminate certain genes. This can trigger genetic testing in sporadic patients or prompt dissecting certain genes more thoroughly when initial genetic testing is negative. Also for the assembly of gene panels and interpretation of the results, genotype–phenotype correlations remain important to establish.

Methods: We clinically evaluated a Belgian family with autosomal dominant inherited sensory ataxia and variable pyramidal involvement and performed targeted clinical exome sequencing. Secondly, we retrospectively screened sequencing data of an in-house cohort of 404 patients with neuromuscular disorders for variants in the identified gene *RNF170*.

Results: All affected family members showed sensory ataxia on examination. Pyramidal involvement, and sometimes slow-pursuit abnormalities and/or a sensory neuropathy, were more variable findings. We identified the heterozygous variant p.Arg199Cys in *RNF170* in all three affected siblings of our family. We did not find additional pathogenic variants in *RNF170* in our in-house neuromuscular cohort.

Conclusions: We confirm the heterozygous variant p.Arg199Cys in *RNF170* in a Belgian family with autosomal dominant sensory ataxia and variable pyramidal involvement. This constitutes a rare but clinically recognizable phenotype that warrants testing of *RNF170*. Unlike the distinctive bi-allelic loss of function variants in *RNF170* associated with hereditary spastic paraplegia (HSP), the p.Arg199Cys variant is the only one reported in sensory

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ataxia. It is important for neurologists to be aware of this characteristic phenotype and to include this gene in gene panels for ataxia and HSP.

KEYWORDS

case study, genotype–phenotype correlation, medical genetics, sensory ataxia, spastic paraparesis

INTRODUCTION

Hereditary ataxias (HA) are a group of clinically and genetically heterogeneous disorders, with which >100 genes have been associated [1]. Clinical presentation is often non-specific, making it nearly impossible to deduce the underlying molecular deficit from the patient's phenotype. Therefore, next-generation sequencing is an invaluable diagnostic tool. In some cases, however, clinical clues can point in the direction of certain genes, as is the case for *SPG7* and *SACS*. This can trigger genetic testing in sporadic patients or prompt dissecting certain genes more thoroughly when initial genetic testing is negative. Also for the assembly of gene panels and their analysis, awareness of genotype–phenotype correlations remains of great importance. We describe the clinically recognizable phenotype of patients with a specific heterozygous *ring finger protein 170* (*RNF170*) mutation and evaluate the presence of variants in this gene in a local cohort of 404 patients with neuromuscular disorders.

METHODS

Clinical case

We clinically evaluated the affected members of a family with an autosomal dominant (AD) history of sensory ataxia. We performed targeted clinical exome sequencing on the proband using DNA extracted from blood lymphocytes after obtaining written informed consent. We analyzed a gene panel containing 187 genes known to be associated with HA and/or hereditary spastic paraplegia (HSP). Variants were classified according to the American College of Medical Genetics and Genomics (ACMG) criteria [2]. We used Sanger sequencing to confirm the identified *RNF170* variant in the proband and for segregation analysis in the affected siblings.

Retrospective analysis of in-house cohort

To establish the frequency of (other) pathogenic *RNF170* variants, we retrospectively screened *RNF170* in an in-house cohort of 404 non-related patients with neuromuscular disorders (onset age 31 ± 18 years [mean \pm standard deviation]; 167 female) for whom the same gene panel had been performed. This study was approved by the Medical Ethics Committee UZ KU Leuven (S64335).

RESULTS

Case description

A 66-year-old Belgian woman (III.2) had experienced a sense of fatigue in the legs since the age of 35 years, evolving to an uncoordinated gait pattern and reduced sensation in the feet at the age of 60 years (Figure 1). Neurological examination showed manifest sensory loss, ataxia, diminished reflexes and hypertonia with Babinski signs in the lower limbs and discrete ataxia in the upper limbs. Gait was spastic-ataxic, Romberg sign was present and smooth eye pursuit mildly jerky. No nystagmus nor dysarthria was noted. Somatosensory evoked potentials (SSEPs) were absent in the lower extremities. Nerve conduction studies (NCS) and Electromyography (EMG) revealed no signs of neuropathy. Magnetic resonance imaging (MRI) full spine was normal (Figure S1), brain MRI showed limited corticosubcortical frontal atrophy. Metabolic work-up was normal. Friedreich's ataxia, spinocerebellar ataxia 1, 2, 3, 6, 7, 8, 10, 12, 17 and dentatorubral-pallidoluysian atrophy were excluded by targeted gene testing.

The patient's father (II.4), her older brother (III.1) and younger sister (III.3) had experienced similar symptoms of progressive gait instability and sensory loss in the lower limbs since the age of 64, 68 and 55 years, respectively (Figure 1). The siblings displayed ataxia, reduced reflexes and sensory disturbances in the legs on examination. Past examination of the father, who died at the age of 84 years, had shown similar findings along with Babinski signs and progressive hypertonia in the lower limbs and mild ataxia in the upper limbs. SSEPs were abnormal for both siblings. NCS/EMGs were normal for the father and sister but showed reduced sensory nerve action potentials (SNAPs) for the brother, compatible with axonal sensory neuropathy. The MRI of the spine of the father was normal, but it was not performed in the siblings.

Analysis of the gene panel for the proband showed a likely pathogenic missense variant in *RNF170* (ENST00000534961.1:c.595C>T; p. Arg199Cys; g.42711484G>A), confirmed by Sanger sequencing. No second variant in *RNF170* was detected (Table S1). The proband's affected siblings both harbored the same variant. Blood samples of the parents were not available.

Retrospective analysis of in-house cohort

In our local cohort of 404 patients with neuromuscular disease, we identified seven variants in 13 patients (Table S2); however, none was considered disease-causing. No patient carried two variants in *RNF170* (Table S1).

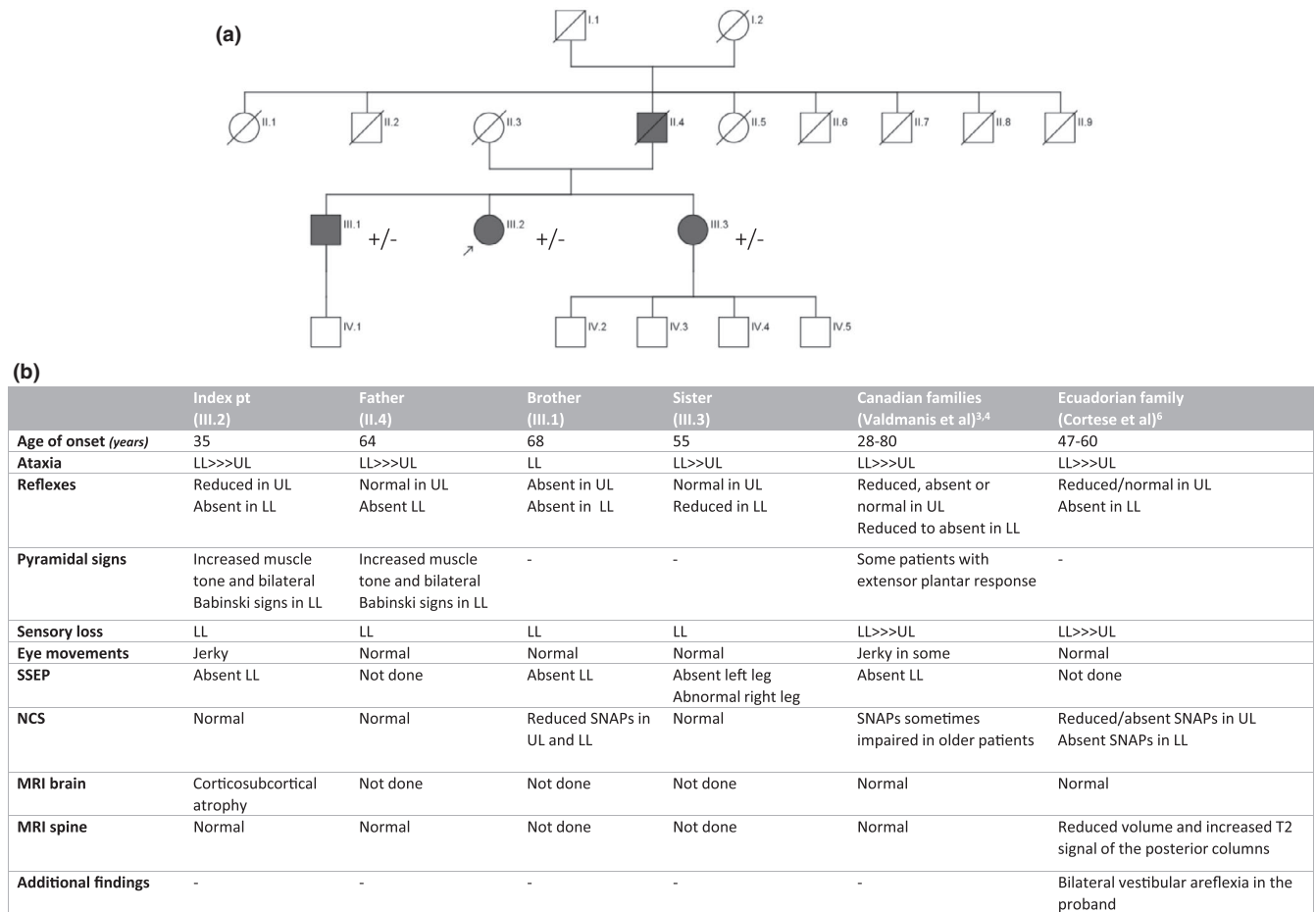


FIGURE 1 Pedigree and clinical characteristics of patients with the *RNF170* p. Arg199Cys mutation. (a) Pedigree of the family with sensory ataxia described in this article. The proband is indicated with an arrow. A '+/-' sign indicates patients that are tested and found heterozygous for the p. Arg199Cys variant. (b) Clinical findings in this family as well as core features of the two Canadian families and the Ecuadorian family with the *RNF170* p. Arg199Cys mutation [3–6]. Abbreviations: LL, lower limbs; MRI, magnetic resonance imaging; NCS, nerve conduction studies; SNAP, sensory nerve action potential; SSEP, somatosensory evoked potential; UL, upper limbs

DISCUSSION

In a European family with AD late-onset sensory ataxia, we identified the heterozygous p. Arg199Cys variant in *RNF170*. This variant has been described previously in two Canadian families and an Ecuadorian family, in which the affected members showed a very similar phenotype of sensory ataxia, variable pyramidal involvement and sometimes slow-pursuit abnormalities and/or sensory neuropathy (Figure 1) [3–6]. Interestingly, the heterozygous p. Arg199Cys mutation is the only variant reported in *RNF170* for patients with this phenotype and no other heterozygous variants have yet been classified as pathogenic in this gene. In our in-house cohort, we did find a patient who carried a different heterozygous variant at the same position (ENST00000534961.1:c.596G>A; p. Arg199His; g.42711483C>T) but the frequency in population databases was too high to fit with the AD inheritance pattern in the family and the phenotype was different from that of our proband [7]. This indicated that p. Arg199His is not pathogenic. A possible explanation for the different effect of these two identically located amino acid substitutions is the different physiochemical properties of the substituting

residues. Studies in mice have suggested that the positive charge of the residue at position 199 is crucial for the stability of the protein because of ionic interactions with amino acids located in transmembrane domains [8]. The other six *RNF170* variants in our cohort were also not considered pathogenic.

The reason why only the heterozygous p. Arg199Cys variant has been linked to the phenotype, and this in several apparently unrelated families, remains unclear. The two Canadian families shared the disease haplotype, indicating a founder mutation [4]. However, a common ancestry seems less likely for the other, geographically scattered families although a shared genetic background cannot be excluded since haplotype analysis was not performed. Given the lack of genetic variation in the immediate vicinity in population databases, except for the presumably benign p. Arg199His variant discussed earlier, the region does not seem to be a mutational hotspot [7]. Interestingly, amino acid residues important for the ionic interactions between transmembrane domains in *RNF170* mentioned above (Arg199, Arg201, Asp232, Asp233) are well conserved across species and their positions show lack of non-synonymous variants in population databases (Figure S2) [7,8]. We

RNF170

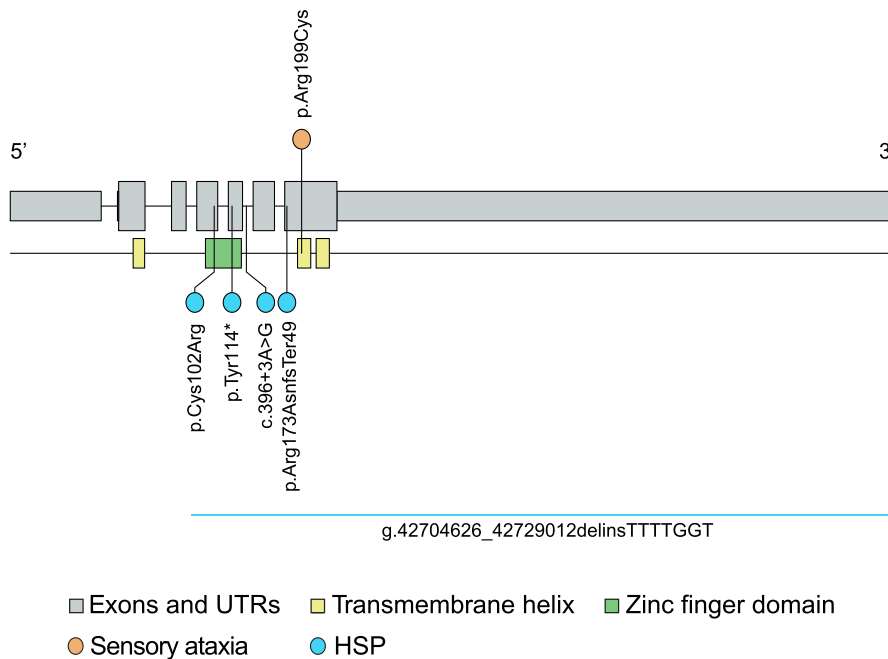


FIGURE 2 Mutational landscape of phenotypes related to RNF170. The figure shows a lollipop of gene RNF170 locating the heterozygous variant described in sensory ataxia (orange) and the homozygous variants in HSP (blue) (including the large deletion in HSP shown as a blue line) in relation to gene structure and protein domains [9,10]. Introns are scaled with a factor 1/100. Abbreviations: HSP, hereditary spastic paraplegia; UTR, untranslated region.

hypothesize that (charge-changing) mutations of these residues may produce a similar phenotype as the one associated with the p. Arg199Cys mutation. In our family, the absence of symptoms in the paternal grandparents (I.1 and I.2) (both died at age > 70 years), aunts and uncles (as far as known by our proband), suggests the possibility of a de novo mutation in the father although reduced penetrance cannot be excluded.

Bi-allelic mutations in RNF170 cause early-onset HSP [9,10]. In contrast to the unique heterozygous p. Arg199Cys mutation in patients with sensory ataxia, distinct bi-allelic mutations have been described in HSP families. Although there is some minor overlap between the two phenotypes (sometimes subclinical impaired SSEPs in HSP patients, pyramidal involvement in sensory ataxia patients and [mild] cerebellar signs in both), it appears that RNF170 mutations cause two distinct phenotypes with different inheritance through different mechanisms. For the heterozygous p. Arg199Cys variant, located in the transmembrane region of the protein, a gain of function mechanism is suspected [5,8]. For the bi-allelic variants in HSP, the mechanism is presumably loss of function [9]. Heterozygous carriers in these families have been found to be unaffected [9]. The different reported mutations in RNF170 and their relation to phenotype, gene structure and protein domains are shown in Figure 2.

Given the characteristic clinical picture of sensory ataxia and variable pyramidal involvement in patients with a heterozygous RNF170 mutation, clinicians can recognize this phenotype and ensure testing for RNF170. Especially for patients with ataxia and AD inheritance pattern, careful clinical characterization is important since sensory ataxia is often mistaken for cerebellar ataxia [11]. This confusion would cause clinicians to prioritize screening for repeat expansion disorders and even lead to failure of obtaining the correct

genetic diagnosis in the end. Gene panels for ataxia can therefore best include genes associated with sensory ataxia such as RNF170 and should also be performed in patients with an AD family history, after exclusion of repeat expansions when ataxia is mainly cerebellar. Also in gene panels for HSP, RNF170 should evidently be included.

Other possible genetic causes of sensory ataxia include Friedreich's ataxia, ataxia with vitamin E deficiency, abetalipoproteinemia, spinocerebellar ataxia with neuropathy, Charcot-Marie-Tooth disease 4C, "Cerebellar ataxia, neuropathy, vestibular areflexia syndrome" (CANVAS) and mitochondrial neuropathies, but often other features (and/or cerebellar ataxia) dominate the clinical picture in these patients [6,11,12].

In summary, although patients with HA often show non-specific and highly variable phenotypes due to genetic and phenotypic heterogeneity, patients with a heterozygous RNF170 mutation exhibit a clinically recognizable phenotype of sensory ataxia, variable pyramidal involvement and sometimes slow-pursuit abnormalities and/or sensory neuropathy. SSEPs are typically impaired and SNAPs often well preserved, compatible with preganglionic pathology. We confirm the relation between the specific heterozygous p. Arg199Cys mutation and sensory ataxia for the first time in a Belgian family. Neurologists should be vigilant for this phenotype and thus enable testing for RNF170, nowadays most commonly as part of a gene panel for ataxia/HSP.

ACKNOWLEDGMENTS

We are grateful to the patients and family members who agreed to participate in this study.

CONFLICT OF INTERESTS

None.

AUTHOR CONTRIBUTIONS

Sien Hilde Van Daele: Conceptualization (lead); Formal analysis (equal); Investigation (lead); Methodology (equal); Visualization (lead); Writing-original draft (lead); Writing-review & editing (equal).

Matthieu Moisse: Formal analysis (equal); Writing-review & editing (supporting). **Valérie Race:** Formal analysis (equal); Writing-review & editing (equal). **Amélie Van Eesbeeck:** Formal analysis (equal); Writing-review & editing (supporting). **Liesbeth Keldermans:** Formal analysis (equal); Writing-review & editing (supporting). **Sascha Vermeer:** Formal analysis (equal); Supervision (equal); Writing-review & editing (equal). **Hilde Van Esch:** Formal analysis (equal); Supervision (equal); Writing-review & editing (equal). **Kristl G. Claeys:** Formal analysis (equal); Supervision (equal); Writing-review & editing (equal). **Philip Van Damme:** Formal analysis (equal); Methodology (equal); Supervision (lead); Writing-review & editing (equal).

ETHICS APPROVAL

This study was approved by the Medical Ethics Committee UZ KU Leuven (S64335). The subjects gave written consent to disclose for publication.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

Supplementary Material

How to cite this article: Van Daele SH, Moisse M, Race V, et al. *RNF170* mutation causes autosomal dominant sensory ataxia with variable pyramidal involvement. *Eur J Neurol*. 2022;29:345-349. <https://doi.org/10.1111/ene.15091>