

Mutation in *RNF170* causes sensory ataxic neuropathy with vestibular areflexia: a CANVAS mimic

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Introduction

Sensory neuronopathy or ganglionopathy is a type of peripheral neuropathy characterized by primary and selective destruction of the dorsal root ganglia leading to degeneration of both central and peripheral neurites of sensory neurons(1).

There is a narrow differential diagnosis for a sensory ganglionopathy which includes paraneoplastic (anti-Hu antibodies), autoimmune (Sjogren Syndrome,), toxic (cisplatin, pyridoxine) and genetic causes (Friedreich's ataxia and mitochondrial disease due to *POLG1* mutations) causes (2). More recently biallelic AAGGG expansion in Replication Factor complex subunit 1 have been identified as a major cause of sensory ataxia neuropathy, often with cerebellar and vestibular involvement (CANVAS) (3,4). However, a significant fraction of patients with a sensory ganglionopathy remain genetically undiagnosed.

In 2004 Valdamanis et al. identified a heterozygous p.Arg199Cys mutation in *Ring Finger Protein 170 (RNF170)* responsible for a rare form of sensory ataxia in two families from eastern Canada sharing a founder haplotype(5–7). Affected cases showed progressive sensory loss and ataxia due to degeneration of the posterior columns, but normal sensory nerve conduction.

By exome-sequencing we have identified the same p.Arg199Cys *RNF170* mutation in an Ecuadorian family affected by an autosomal dominant late-onset progressive sensory ganglionopathy. Unlike the previously reported cases from Eastern Canada, affected members showed evidence of ganglionic/post ganglionic involvement of the sensory peripheral nerves. Also, bilateral vestibular areflexia was identified in the index case, mimicking CANVAS.

Case presentation

The index case (III-3, **figure 1A**) is a 57-year old woman with onset of poor balance at the age of 47 years, followed by dysaesthesia and sensory loss in her feet and hands. At the age of 57 she was referred for neurological evaluation, by which time she required a walking aid. Her past medical history was notable for rheumatic fever and gastro-oesophageal reflux. A sister had similar symptoms and her father and paternal grandmother both reporting progressive unsteadiness since the age of 60. (**figure 1A**). Neurological examination in III-3 at the age of 60 revealed an ataxic gait (**supplemental video**). Romberg's was positive. There was no dysarthria, saccadic and pursuit eye movements were normal. Head impulse test showed a bilaterally impaired vestibular-ocular reflex. Cranial nerve examination was otherwise unremarkable. Muscle bulk, tone and strength were normal. Deep-tendon reflexes were reduced in the upper limbs and absent in the lower limbs. Babinski was absent. Pinprick sensation was reduced to the elbow and to the hip. Vibration was reduced to the metacarpal-phalangeal joints and to the anterior-superior iliac spine. Position sense was normal in the upper limbs and reduced to the knees in the lower limbs. Coordination testing was altered in all limbs, but significantly worse in the lower extremities. Pseudo-athetotic arm movements could also be observed.

Nerve conduction studies (NCS) showed absent sensory action potentials throughout. Motor nerve conduction was normal. Brain MRI was normal and in particular there was no cerebellar atrophy. MRI of the cervical spine showed reduced volume and increased T2 signal of the posterior columns (**figure 1B-C**). Vestibular testing showed a bilateral VOR gain impairment at the video Head Impulse test (**figure D-E**). Notably VOR testing only showed borderline changes when performed three years before. Autonomic testing was within normal limits. Screening for autoimmune, neoplastic, toxic and metabolic causes was negative.

Her older sister (III-1), now aged 62, reported progressive unsteadiness since the age of 50 resulting in multiple falls and a fracture of her right tibia and fibula. She has been using a stick to walk since the age of 55. Neurological examination revealed a severe ataxic gait requiring aids to walk. Cranial nerves were normal. VOR was not assessed. Muscle bulk, tone and power was

normal throughout except for minimal weakness of right foot dorsiflexion. Deep-tendon reflexes were present in the upper limbs but absent in the lower limbs. Superficial sensation was intact. Vibration sensation was reduced in the upper limbs and absent in the lower limbs to the costal margin. Position sense was normal in the upper limbs and reduced to the knees in the lower limbs. Coordination testing was altered with eyes closed in the upper limb and grossly impaired in the lower extremities.

NCS showed normal motor conduction parameters. Sensory action potentials had decreased amplitudes in the upper limbs and were absent in the lower limbs.

Because of the presence of sensory neuropathy and vestibular areflexia gene testing for RFC1 expansion was performed and resulted negative ($(AAAAG)_{11}/(AAAAG)_{exp}$). Therefore, we performed focused exome sequencing in III-3 which identified a c.595C>T, p.Arg199Cys variant in *RNF170*. Segregation of the mutation with disease in III-1 was confirmed by Sanger sequencing (**figure 1A**). Two sisters III-2 and III-4, aged 58 and 49, are reportedly unaffected but given the late onset of the disease were not considered for segregation analysis. There were no additional pathogenic variants in genes associated with neuropathy or ataxia. We concluded that this is the likely cause of the autosomal dominant sensory ataxic neuropathy in the family.

Discussion

Our patients show remarkable similarities with the previously reported families from Maritime Canada including a predominantly sensory ataxic phenotype, without evidence of cerebellar or autonomic involvement and no significant foot ulcerations or pain. However, in contrast to the two previously reported families, both our patients had reduced or absent sensory action potentials in the four limbs. This finding, together with the MRI evidence of degeneration of posterior column, point to a primary involvement of sensory dorsal root ganglia, leading to degeneration of both central and peripheral branches of sensory neurons. There is no clear explanation which can account for the phenotypic differences. We hypothesize that the diverse genetic background could play a role.

Similar to RFC1 CANVAS, the vestibular system was also affected in the index case, suggesting a common susceptibility of sensory neurons in spinal, cranial and Scarpa's ganglia to the neurodegenerative processes underlying this expanding group of inherited sensory ataxic disorders. As opposed to autosomal recessive RFC1 CANVAS, cerebellar involvement, cough and retained/brisk reflexes are absent RNF170 related syndrome, mode of inheritance is autosomal dominant, and the vestibular areflexia may be observed only in more advanced disease stages.

RNF170 is a ubiquitin E3 ligase involved in endoplasmic reticulum-associated protein degradation (ERAD) and calcium signalling. Notably, biallelic nonsense mutation in *RNF170* were recently identified to cause of autosomal recessive hereditary spastic paraparesis (HSP)(8). However, both the clinical phenotype, with primary involvement of upper motor neurons vs dorsal root ganglia sensory neurons, and the disease-causing mechanism, loss-of-function vs toxic gain-of-function, differ between RNF170 HSP and autosomal dominant sensory ataxia, respectively. Indeed, despite previous evidence of reduced stability and expression level of mutant Arg199Cys RNF170 haploinsufficiency is unlikely to be the primary disease since heterozygous carriers of nonsense variants in *RNF170* were later shown to be unaffected (8–10). Although the exact mechanism remains elusive, a toxic gain of function seems plausible and is supported by the dose-dependent toxicity of RNF170 Arg199Cys in zebrafish larvae (7).

Our report expands the phenotypic spectrum of *RNF170* to encompass sensory ataxic neuropathy with bilateral vestibular impairment. Therefore, we recommend considering *RNF170* in the diagnostic work-up of patients affected by sensory ataxic neuropathies and RFC1 negative CANVAS-like patients, particularly if there is a dominant family history.

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Ethics: The Ethic Committee of San Matteo Hospital, Pavia, Italy, approved study protocol, and all subjects signed informed consent form.

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FIGURE LEGEND

Figure 1. A) Pedigree of autosomal dominant family carrying c.595C>T, p.Arg199Cys mutation in *RNF170*. The black arrow indicates the index case. A representative chromatogram from a healthy control (left) and III-3 (right) are shown. The c.595C>T mutation is indicated by a red arrow. **B)** Sagittal T2 Short tau inversion recovery and **C)** axial T2 turbo spin echo of the cervical spine showing a slight T2 dorsal bilateral hyperintensity (blue arrows) at the level of C6. **D-E)** Head velocity (black line), and eye velocity (blue and red lines) profiles respectively of repetitive head turns rightward (D) and leftward (E) in a healthy individual (top lane) and in an affected case (III-3; bottom lane). Note the presence of catch up saccades in the bottom graphs which are performed to compensate for impaired vestibular ocular

Figure 1.

