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***RNF170*-related hereditary spastic paraplegia: confirmation by a novel mutation**

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Background:

Spastic paraparesis and biallelic variants functionally characterized as deleterious in the *RNF170* gene have recently been reported by Wagner et al.¹, strongly supporting the involvement of this gene in Hereditary Spastic Paraplegia (HSP).

Objectives, Methods:

Exome sequencing were performed on 6 HSP families previously tested on HSP specific panel.

Results:

We describe here a novel HSP family with four affected members carrying a homozygous p.(Tyr114*) stop gain variant in *RNF170*.

Conclusions:

We confirm the involvement of biallelic truncating variants in *RNF170* in a novel form of HSP.

This gene encodes RNF170, a ubiquitin E3 ligase belonging to the Endoplasmic Reticulum Associated protein Degradation pathway², a cellular pathway already known to be involved in pathophysiology of HSP with ERLIN2 (SPG18)³, ARL6IP1 (SPG61), and ERLIN1 (SPG62)⁴.

Biallelic loss-of-function variants in *RNF170* have been involved in a novel form of HSP with a phenotype associating early-onset HSP with optic atrophy¹.

The four new patients described here are siblings of a distantly related couple from Guinea (Fig. 1). Their phenotypes (Table 1) correspond to those previously reported, except for optic atrophy which has not been explored.

This family was selected for whole exome sequencing after the negativity of genetic investigations on individual 2 with a HSP specific panel used in our diagnostic laboratory, according to Morais et al.⁵.

Whole exome sequencing was performed on DNA extracted from blood-derived leukocytes of the four affected individuals and their two parents using SeqCap EZ MedExome Target

Enrichment Kit (Roche, Basel, Switzerland). Sequencing was carried out as paired-end 151 bp reads on a NextSeq500 (Illumina, San Diego, USA). Raw data were analyzed using in-house annotation and analysis pipelines based on the hg19 human genome reference as described elsewhere⁶.

Briefly, only non-synonymous coding and splicing variants found in the four siblings were considered. Variant filtering was performed according to the mode of transmission based on the parents' genotypes (de novo, autosomal recessive and X-linked), the frequency of the variant in the gnomAD database (< 0.01% and < 50 heterozygous carriers or < 5 homo/hemizygous carriers) and in our in-house database of n = 866 exomes (< 1 homozygous occurrence).

Four candidate variants were identified through filtering in the *SMIM19*, *SULF1*, *RNF170* and *RPI* genes. Only one (*RNF170*) was absent from the general population database, including Africans (gnomAD). The other three were two intronic variants and one missense, all with very mild in-silico prediction effects. The very rare variant in *RNF170* was carried by all four affected siblings and was a homozygous stop-gain variant NM_030954.3:c.342C>G; p.(Tyr114*) (see Fig. 1) in exon 5 of *RNF170*. This variant is predicted to be degraded by the nonsense mediated decay according to the 50 bp rule⁸. Moreover, the involvement of several downstream truncating variants in this HSP phenotype (p.Ala109Asnfs*9; p.Arg173Asnfs*49, Fig. 1B) strongly supports the pathogenic role of the p.(Tyr114*) variant.

The homogeneous clinical spectrum of this new *RNF170*-related HSP family is consistent with those previously described, including an early age of onset (< 5 y). The age of loss of independent walking is earlier in our family. Optical coherence tomography was not

performed but no severe visual defect nor aggravation was detected and the eye fundus performed at the age of 12 years in individual 2 was considered normal. This new family emphasizes a possible genotype-phenotype correlation regarding the variability of cerebellar impairments found between distinct families. All four individuals in our new family are carriers of a variant probably targeted by NMD and are free of any cerebellar defect, which brings significance to the hypothesis of a toxic gain-of-function. Indeed, the presence of cerebellar defects seems to be correlated with variants probably escaping NMD (Cys102Arg and Arg173Asnfs*49, n=6 cases from Wagner et al) and their absence is associated with transcript deleting variants (via prohibited transcription: delEx4_7, n=1 from Wagner et al; or via NMD-targeted variants: Tyr114*, n=4 from our study).

Interestingly, the p.Ala109Asnfs*9 variant reported by Wagner et al. was described as partially escaping NMD, and although no ataxia was found in the two affected individuals, they have been reported as having a saccadic oculomotricity, suggesting a potential minor cerebellar alteration.

In conclusion, the description of this new family case confirms the involvement of bi-allelic variants in the *RNF170* gene in this new autosomal recessive form of HSP. This new clinico-genetic entity is a rare form of hereditary spastic paraplegia since only one affected family was identified among the 141 HSP families of our local reference center (69 exomes, 72 NGS genes panel including *RNF170*) and has not been found in a cohort of 344 recessive ataxias or in 865 other neurological cases analyzed by exome in our center.

Other case reports are needed to precisely define the clinical spectrum of this HSP entity and validate the genotype-phenotype correlations.

Authors roles:

J.M. de Sainte Agathe, whole exome sequencing execution and analysis, writing of the first draft of the manuscript

S. Mercier, main clinical description, manuscript review and critique

J.Y. Mahé, clinical description

Y. Péréon, clinical description, manuscript review and critique

J. Buratti, informatical pipeline designer for the sequencing analysis

L. Tissier, technical sequencing adviser

B. Kol, technical sequencing adviser

S. Ait Said, research project conception and organization

É. Le Guern, research project conception and organization, manuscript review and critique

G. Banneau, research project conception and organization, manuscript review and critique

G. Stevanin, research project conception, main manuscript reviewing and critique

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The authors declare no conflict of interest.

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All other authors declare no conflict of interest and all have received salary from the state as part of their public employment.

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Table 1: Clinical characteristics of a new family affected by *RFN170* related HSP. *Moi* mode of inheritance, *UL* upper limb, *LL* lower limb, *y* years, *n.d.* not done. * vibration/joint position/surface/temperature.

ID	1	2	3	4
Variant	c.342C>G	c.342C>G	c.342C>G	c.342C>G
	Tyr114* (hom)	Tyr114* (hom)	Tyr114* (hom)	Tyr114* (hom)
moi/gender	AR/M	AR/F	AR/F	AR/M
Age at onset (y)	3	3	3	3
Age at exam (y)	20	17	13	10
Age at loss of independent walking	10	10	10	still walking
Delayed motor development	–	–	–	–
Cognitive deficits	–	–	–	–
Visual system	refractive anomaly	refractive anomaly (normal eye fundus at 12 y)	refractive anomaly	refractive anomaly
Oculomotor abnormalities	–	–	–	–
Dysarthria/ dysphagia	–/–	–/–	–/–	–/–
UL/LL spasticity	+/+	+/+	+/+	+/+
UL/LL tendon reflexes	Brisk/brisk	Brisk/brisk	brisk/brisk	brisk/brisk
UL/LL weakness	–/+ (proximal)	–/+ (proximal)	–/+ (distal)	–/+ (distal)

ID	1	2	3	4
Muscle atrophy	+ (LL, severe)	+ (LL, severe)	+ (LL, severe)	+ (LL, severe)
Extensor plantar response	-	mild	+	-
Sensory deficits*	n.d.	n.d.	n.d.	n.d.
Ataxia	-	-	-	-
Extrapyramidal involvement	-	-	-	-
Urinary/fecal urgency or incontinence	-/-	-/-	+/-	-/-
Nerve conduction studies	n.d.	normal	n.d.	n.d.
Motor evoked potentials	n.d.	delayed LL pyramidal response	n.d.	n.d.
Sensory evoked potentials	n.d.	n.d.	n.d.	n.d.
Visually evoked potentials	n.d.	n.d.	n.d.	n.d.
MRI	n.d.	Cranium and cervical spine normal	n.d.	n.d.

