BRAIN
LETTER TO THE EDITOR

RAB3A variants in ataxia and other neurodegenerative disorders

Marco Percetti,[1,2] Edoardo Monfrini,[2] Roberto Del Bo,[1] Margherita Canesi,[3] Francesco Cavallieri,[4] Giulia Di Rauso,[4,5] Valentina Fioravanti,[4] Eleonora Del Prete,[6] Daniela Frosini,[6] Giovanni Palermo,[6,7] Roberto Ceravolo,[6,7] Giorgio Sacilotto[8] and Alessio Di Fonzo[2]

1 Dino Ferrari Center, Neuroscience Section, Department of Pathophysiology and Transplantation, University of Milan, Milan 20122, Italy
2 Neurology Unit, Department of Neuroscience and Mental Health, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan 20122, Italy
3 Department of Neurological Rehabilitation, Parkinson's Disease and Movement Disorders Center, Moriggia-Pelascini Hospital, Gravedona ed Uniti 22015, Italy
4 Neurology Unit, Neuromotor and Rehabilitation Department, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia 42122, Italy
5 Clinical and Experimental Medicine PhD Program, University of Modena and Reggio Emilia, Modena 42121, Italy
6 Center for Neurodegenerative Diseases, Parkinson's Disease and Movement Disorders Unit of Neurology, Department of Neuroscience, University of Pisa, Santa Chiara Hospital, Pisa 56126, Italy
7 Department of Clinical and Experimental Medicine, University of Pisa, Pisa 56126, Italy
8 Parkinson Institute, ASST G.Pini-CTO, Milan 20122, Italy

Correspondence to: Dr Alessio Di Fonzo
Neurology Unit, Department of Neuroscience and Mental Health, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via Francesco Sforza 35, Milan 20122, Italy
E-mail: alessio.difonzo@policlinico.mi.it

We read with great interest the recent article by Hengel and colleagues[1] in *Brain*, reporting monoallelic variants in the *RAB3A* gene as a novel cause of autosomal dominant cerebellar ataxia.

The authors reported 18 patients with cerebellar ataxia from 10 unrelated families, each carrying a rare heterozygous *RAB3A* variant. Notably, the p.Arg83Trp variant recurred in nine families. Affected carriers predominantly presented with adult-onset, isolated cerebellar ataxia. Furthermore, three unrelated families with neurodevelopmental disorders were found to carry *de novo* or nonsense *RAB3A* variants.

Thereafter, Mouraux and colleagues[2] screened *RAB3A* in a cohort of 1235 individuals with cerebellar ataxia and/or spastic paraplegia who underwent whole exome sequencing (WES). They identified 10 heterozygous carriers from five unrelated families. The p.Arg83Trp variant recurred in three families with autosomal dominant cerebellar ataxia. The p.Arg41Cys variant was identified in two siblings with dominant spastic paraplegia, whereas the p.Asp181Tyr was detected in one patient with spastic paraplegia and parkinsonism.

Prompted by these findings, we screened for *RAB3A* variants in our in-house WES and whole genome sequencing dataset of unsolved index cases from Italy with cerebellar ataxia ($n = 116$), spastic ataxia ($n = 15$), and spastic paraplegia ($n = 27$). Owing to the observation of parkinsonism in a *RAB3A* affected carrier, we also searched for *RAB3A* variants in patients with Parkinson's disease (PD) ($n = 958$) (Supplementary Table 2). The search was extended to a control dataset of 1686 unrelated healthy Italians (Network for Italian Genomes—Exomes from ITaly, freely available online at http://nigdb.ext.cineca.it/).

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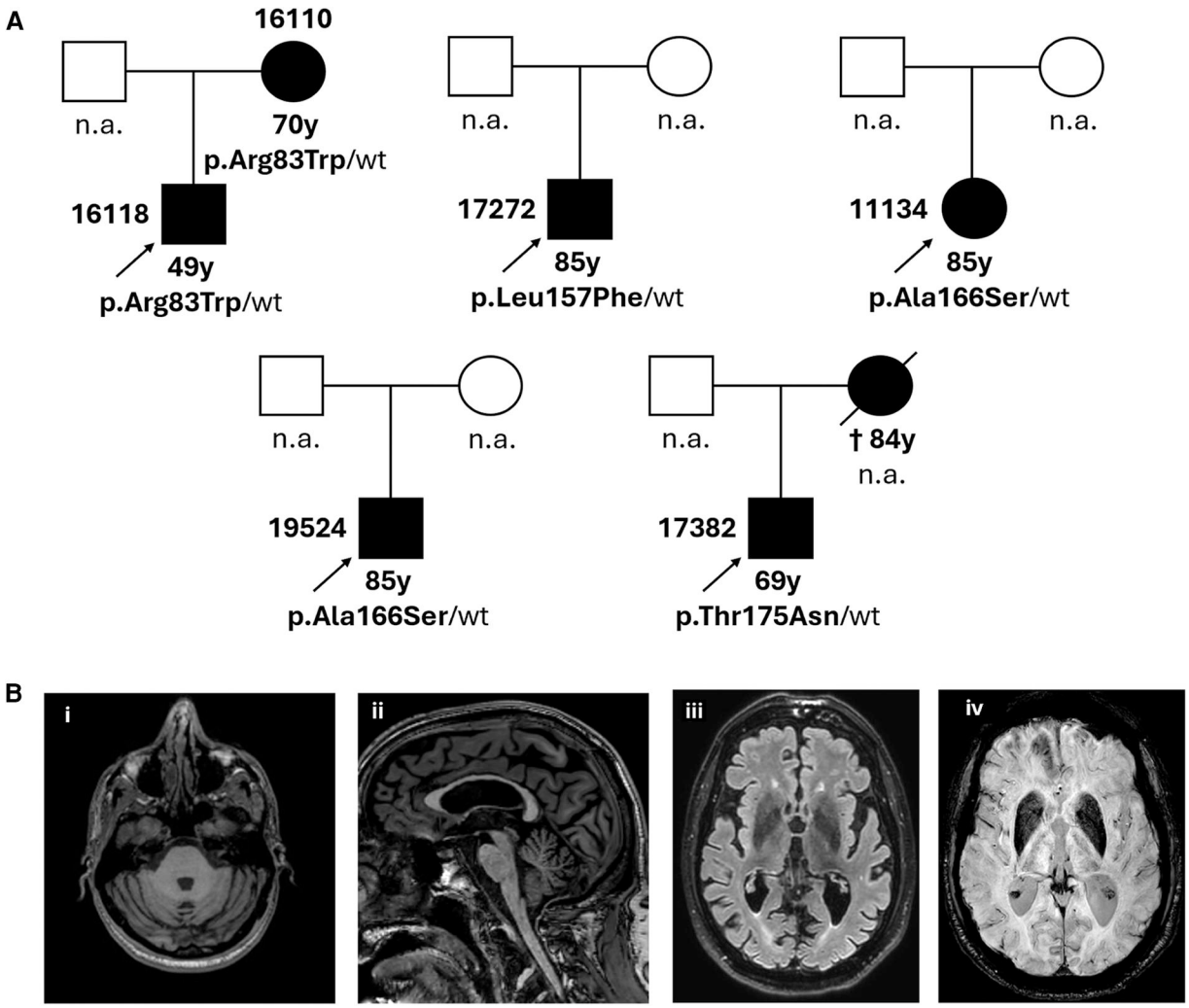

Figure 1 Pedigrees and brain MRI of *RAB3A* carriers. (**A**) Pedigrees of *RAB3A* carriers. The arrow indicates the proband. Square = male, circle = female, black square/circle = affected, crossed = deceased. n.a. = not available for genetic testing, wt = wild type. [**B(i)**]. Brain MRI of Patient II.1 showing cerebellar atrophy (T1 axial). [**B(ii–iv)**] Brain MRI of patient 19524 showing cerebellar atrophy (**ii**, T1 sagittal), leukoaraiosis (**iii**, FLAIR axial), and bilateral lenticular paramagnetic deposits (**iv**, SWI axial). FLAIR = fluid-attenuated inversion recovery, SWI = susceptibility weighted imaging.

We identified four *RAB3A* variants (p.Arg83Trp, p.Leu157Phe, p.Ala166Ser and p.Thr175Asn) in heterozygous state in five unrelated patients (2 of 116 ataxia, 1.7%; 3 of 958 PD, 0.8%). None of these variants were detected in healthy controls (Supplementary Table 3).

The p.Arg83Trp variant was identified in a patient with autosomal dominant cerebellar ataxia and co-segregated with the disease in her affected son (Fig. 1, Table 1 and Supplementary Table 1). Both patients developed slowly progressive gait ataxia beginning in their fourth decade of life, and displayed cerebellar atrophy at brain MRI. Another patient with sporadic late-onset ataxia and mild parkinsonism carried the rare p.Ala166Ser variant. Remarkably, the ^{123}I-FP CIT SPECT was negative. The same variant was identified in a patient with familial late-onset PD. Finally, the

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Table 1 Demographic-clinical data of RAB3A carriers

	Patient 16110	Patient 16118	Patient 17272	Patient 11134	Patient 19524	Patient 17382
RAB3A variant (het)	c.247C>T p.(Arg83Trp)	c.247C>T p.(Arg83Trp)	c.469C>T p.(Leu157Phe)	c.496G>T p.(Ala166Ser)	c.496G>T p.(Ala166Ser)	c.524C>A p.(Thr175Asn)
Sex	Female	Male	Male	Female	Male	Male
First symptom (AaO, years)	Gait ataxia (33 y)	Gait ataxia (31 y)	Tremor, motor slowness (76 y)	Right hand tremor (65 y)	Gait ataxia (59 y)	Motor slowness (63 y)
Cerebellar features	+	+	–	–	+	–
Spasticity	+	–	–	–	–	–
Extrapyramidal features	–	–	+	+	+	+
Levodopa response	n.a.	n.a.	+	+	n.a.	+
Sensorial deficits	–	–	–	–	+	–
Visual impairment	+	+	–	–	–	+
Seizures	–	–	–	–	–	–
Neuropsychiatric features	+	+	+	+	–	–
Cognitive deficits	+	–	+	–	–	+
Neuroimaging findings	n.a.	MRI: cerebellar vermis atrophy, bilateral lenticular T1 hyperintensity	MRI: cortical atrophy, leukoaraiosis	n.a.	MRI: cortical atrophy, cerebellar vermis atrophy, leukoaraiosis, bilateral lenticular paramagnetic deposits ^{123}I-FP-CIT SPECT: negative ^{18}F-FDG-PET: cortical and cerebellar hypometabolism	MRI: cortical atrophy ^{123}I-FP-CIT SPECT: dopaminergic presynaptic denervation

A more detailed version of the table is available in Supplementary Table 1. +/– = present/absent; ^{123}I-FP-CIT SPECT = single-photon emission computed tomography with DaTscan (^{123}I-FP-CIT); AaO = age at onset; n.a. = not available.

p.Leu157Phe and p.Thr175Asn variants were found in two sporadic unrelated PD patients. None of these PD patients harboured pathogenic variants in PD genes.

The observation here reported of *RAB3A* variants in PD patients is noteworthy and deserve further investigations. This finding is supported by functional studies showing impaired synaptic vesicle trafficking due to the interaction of α-synuclein with RAB3A and phosphorylation of RAB3A by PD-related *LRRK2* mutations.[3-5]

Our findings confirm that monoallelic *RAB3A* variants occur in patients with cerebellar ataxia and suggest that *RAB3A* may be associated with parkinsonism.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

References

1. Hengel H, Hannan SB, Reich S, et al. Heterozygous RAB3A variants cause cerebellar ataxia by a partial loss-of-function mechanism. *Brain*. 2025;148:2812-2826.
2. Mouraux C, Méreaux JL, Davoine CS, et al. Expanding the clinical spectrum of RAB3A: From cerebellar ataxia to spastic paraplegia. *Brain*. 2025;148:e96-e99.
3. Dalfó E, Barrachina M, Rosa JL, Ambrosio S, Ferrer I. Abnormal α-synuclein interactions with rab3a and rabphilin in diffuse Lewy body disease. *Neurobiol Dis*. 2004;16:92-97.
4. Gitler AD, Bevis BJ, Shorter J, et al. The Parkinson’s disease protein α-synuclein disrupts cellular Rab homeostasis. *Proc Natl Acad Sci U S A*. 2008;105:145-150.
5. Dou D, Aiken J, Holzbaur ELF. RAB3 phosphorylation by pathogenic LRRK2 impairs trafficking of synaptic vesicle precursors. *J Cell Biol*. 2024;223:e202307092.

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