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ORIGINAL COMMUNICATION

ANO10 mutational screening in recessive ataxia: genetic findings and refinement of the clinical phenotype

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Abstract

Autosomal recessive cerebellar ataxia type 3 (ARCA3) is a rare inherited disorder caused by mutations in the *ANO10* gene. The disease is characterized by slowly progressive spastic ataxia variably associated with motor neuron involvement, epilepsy, and cognitive decline. We performed mutational screening in 80 patients with sporadic or autosomal recessive adult-onset ataxia. We identified 11 *ANO10* gene variants in 10 patients from 8 families (10%): 4 mutations were previously described and 7 were novel. Age at onset ranged between 27 and 53 years. All patients presented ataxia, pyramidal signs and cerebellar atrophy at brain MRI. Additional signs were bradykinesia (7/10), mild vertical gaze paresis (5/10), pes cavus (4/10), and sphincteric disturbances (3/10). Six patients, with normal MMSE score, failed several neuropsychological tests rating executive functions. Three patients had giant somatosensory evoked potentials and epileptic spikes in EEG without clinical evidence of seizures. Our observational study indicates a high frequency of ARCA3 disease in sporadic patients with adult-onset cerebellar ataxia. We extended the *ANO10* mutational spectrum with the identification of novel gene variants, and further defined the clinical, cognitive, and neurophysiological features in a new cohort of patients. These findings may contribute to the refinement of the complex ARCA3 phenotype and be valuable in clinical management and natural history studies.

Keywords ARCA3 · SCAR10, recessive ataxia · Dysexecutive cognitive syndrome · Somatosensory evoked potentials · Spastic ataxia

Introduction

Autosomal recessive ataxias are rare genetic diseases primarily characterized by progressive gait and limb cerebellar ataxia, often associated with other neurological or non-neurological symptoms [1]. Classification of these forms has been largely revised in the recent years, and different acronyms have been proposed for the numerous genetically characterized entities. Autosomal recessive cerebellar ataxia type 3 (ARCA3) and spinocerebellar ataxia recessive type 10 (SCAR10) describe the same genetic form associated with mutations in the *ANO10* gene [2]. This gene encodes a transmembrane protein, named anoctamin 10, which is a member of a family of calcium-activated chloride channels [3].

The clinical phenotype of patients with ataxia caused by *ANO10* mutations was originally described in three affected siblings of a Dutch consanguineous family. These subjects presented a slowly progressive cerebellar syndrome, brisk

Lorenzo Nanetti and Elisa Sarto equally contributed to this study.

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reflexes, lower limb muscle fasciculations, and cerebellar atrophy [3]. Genetic screening for causative *ANO10* gene mutations led to the identification of more than 40 additional ARCA3/SCAR10 families worldwide, and an estimated frequency of the disease ranging from 0.4 to 5% in sporadic or autosomal recessive ataxic patients [3–15].

The phenotype of ARCA3/SCAR10 patients has been expanded with additional features described in some of the patients and including epilepsy, cognitive decline, deficit of coenzyme Q10, and elevated serum alphafetoprotein [4, 5, 7, 8, 11, 12]. In the present study, we describe ten patients carrying recurrent and novel *ANO10* gene mutations, and revised the literature to further refine the clinical spectrum of ARCA3 phenotype.

Subjects and methods

We evaluated 80 adult index patients with progressive cerebellar ataxia, family history compatible with sporadic or autosomal recessive transmission, and cerebellar atrophy at brain MRI. The diagnostic workup excluded acquired causes of ataxia, and the most frequent genetic causes of hereditary ataxia or spastic ataxia (spinocerebellar ataxia types 1, 2, 3, 6, 7, 17, Friedreich ataxia, and spastic paraplegia type 7). We performed a mutational screening with a next-generation sequencing (NGS) approach using either a probe-based customized panel (Nextera Rapid Capture Custom Kit, Illumina) covering > 100 known genes associated with cerebellar ataxia ($n = 39$ patients) or a single-gene ultradeep amplicon sequencing ($n = 41$ patients) (Nextera XT, Illumina). Genetic variants were classified according to the consensus recommendation of the American College of Medical Genetics (ACMG). This recommendation describes a method for classifying sequence variants into five categories using standardized criteria and available evidence (such as frequency in the population, computational data, and segregation data) [16]. The criteria are combined according to specific scoring rules to assign to each variant a classification from the five-tier system: "pathogenic" (Class 5), "likely pathogenic" (Class 4), "uncertain significance" (Class 3), "likely benign" (Class 2), and "benign" (Class 1).

The patients carrying either homozygous or compound heterozygous *ANO10* mutations underwent detailed clinical and neuroimaging examinations. The clinical scale for assessment and rating of ataxia (SARA) and a battery of cognitive tests for cerebellar cognitive abilities were administered. The tests included Mini Mental State Examination (MMSE), Rey Verbal Learning Test, Rey–Osterrieth Complex Figure (ROCF) Task, Trail Making Test A and B (TMT-A, B), Symbol Digit Modalities Test (SDMT), and Semantic and Phonemic verbal fluency tests.

Standard 1.5T brain MRI was performed in all cases. Nerve conduction studies, electromyography, motor, visual, and auditory brainstem evoked potentials were performed by standard procedures. EEG polymyography and nap EEG were recorded using Ag/AgCl electrodes placed in accordance with the International 10–20 system; corticomuscular coherence (CMC) was measured according to previously reported methods [17, 18] to assess the relationship between EEG and muscular activity. Upper limb somatosensory evoked potentials (SEPs) were elicited by electrically stimulating the right and left median nerves at wrist [19]. Cortical SEPs were considered "giant" if one of the amplitudes of the N20–P25 and/or P25–N33 components exceeded the mean value + 3SD obtained in healthy subjects (12.3 μV for N20P25, and 8.6 μV for P25N33) in our laboratory [20].

Patients gave written informed consent for all clinical and genetic tests performed during the study, in agreement with the procedures approved by the Local Ethics Committee.

Results

Eight out of the 80 index ataxic patients were diagnosed as ARCA3 (10%) (Table 1). Seven families were of Italian origin and one from Romania. We identified eleven *ANO10* sequence variants (Fig. 1). Six patients were compound heterozygous and two cases were homozygous for *ANO10* mutations. Nine sequence variants were classified as "pathogenic" (Class 5) according to ACMG guidelines [16], including four variants previously described in ARCA3 patients [4, 15], four novel truncating variants, and one splice site variant (c.337 + 1G > A) (Table 1).

The novel splice site variant c.337 + 1G > A was classified as pathogenic according to the following combined criteria: (a) null variant (within ± 2 of canonical splice site), (b) multiple in silico predictions supporting a deleterious effect ("break/abolish the donor site": Human Splicing Finder, NNSPLICE version 9), (c) ExAC allele frequency of 0.006%, and (d) recently reported as pathogenic in ClinVar [16].

Both novel missense variants (c.815G > C; c.1664G > C) were classified as "likely pathogenic" for (a) very low allele frequency in public databases, (8×10^{-4}, ExAC, website), (b) missense variant in a gene with low rate of benign missense variation, (c) detected *in trans* with a pathogenic variant, and (d) predicted as "probably damaging" (Polyphen-2-HumDiv score = 1), and "deleterious" (SIFT score = 0) (Table S1).

Clinical features of patients with ARCA3/SCAR10

All our ARCA3 diagnosed patients presented a progressive cerebellar syndrome with pyramidal signs and onset

Table 1 Clinical and genetic findings in ARCA3 patients

Family	1		2		3	4	5	6	7	8
cDNA variants[a]	c.[289delA]; [289delA]		**c.[1088_1093 delinsTCCTT]; [1088_1093 delinsTCCTT]**		c.289delA(;) **518delT**	**c.1418delA(;) 337 + 1G > A**	c.[(1797 + 1_17981)_(1913 + 1_1914-1)del]; **[815G > C]**	c.132dupA(;) 1291C > T	**c.[1418delA]; [1664G > C]**	c.(1797 + 1_17981)_(1913 + 1_1914-1)del(;) **1558dupG**
Variant class[b]	5; 5		5; 5		5; 5	5; 5	5; 4	5; 5	5; 4	5; 5
Patients	1.1	1.2	2.1	2.2	3	4	5	6	7	8
Age/sex	58/F	62/F	50/M	54/F	62/F	47/M	55/M	31/F	70/F	41/M
Onset of ataxia	51	53	40	41	38	41	33	27	40	38
Disease duration	7	11	10	13	24	6	22	4	30	3
SARA score	9	10	10	15	17.5	16.5	20	8	22	9
Nystagmus	+	+	−	+	++	+	+	+	+	+
Vertical ophthalmoparesis	−	−	+/−	+	+	−	+	−	+++	−
Dysphagia	++	++	++	+	+	−	+	−	+++	−
Increased DTR	+	+	+	+	+	+	+	+	+	−
Ankle clonus	+	+	−	−	+	−	−	−	+	−
LL spasticity	+	+	−	−	+	−	−	−	+	+
Babinski sign	−	+	−	+	+	−	−	−	+	−
Pes cavus	−	−	+	+	−	+	−	+	−	−
Bradykinesia	+	+	+	+	+	+	−	−	++	−
Urinary incontinence	+	−	−	−	++	−	−	−	++	−
MRI cerebellar atrophy	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
MRI cortical atrophy	+	+	−	−	+	−	−	−	++	−
Sensory evoked potentials (SEPs)	Giant SEPs	Giant SEPs					Giant SEPs			
EEG	Epileptic spikes	Epileptic spikes		Epileptic spikes						
Other features	Tremor	Tremor		Conjunctive eye vessel tortuosity	Tremor	Left acoustic neurinoma	Tremor		Cognitive decline, behavioral abnormalities	

[a]In bold are described novel *ANO10* genetic variants

[b]See reference [16]

SARA Scale for Assessment and Rating of Ataxia, *F* female, *M* male, *DTR* deep tendon reflexes, *LL* lower limb, *SEPs* sensory evoked potentials, (−) absent, (+) mild, (++) moderate, (+++) severe, *Na* not available

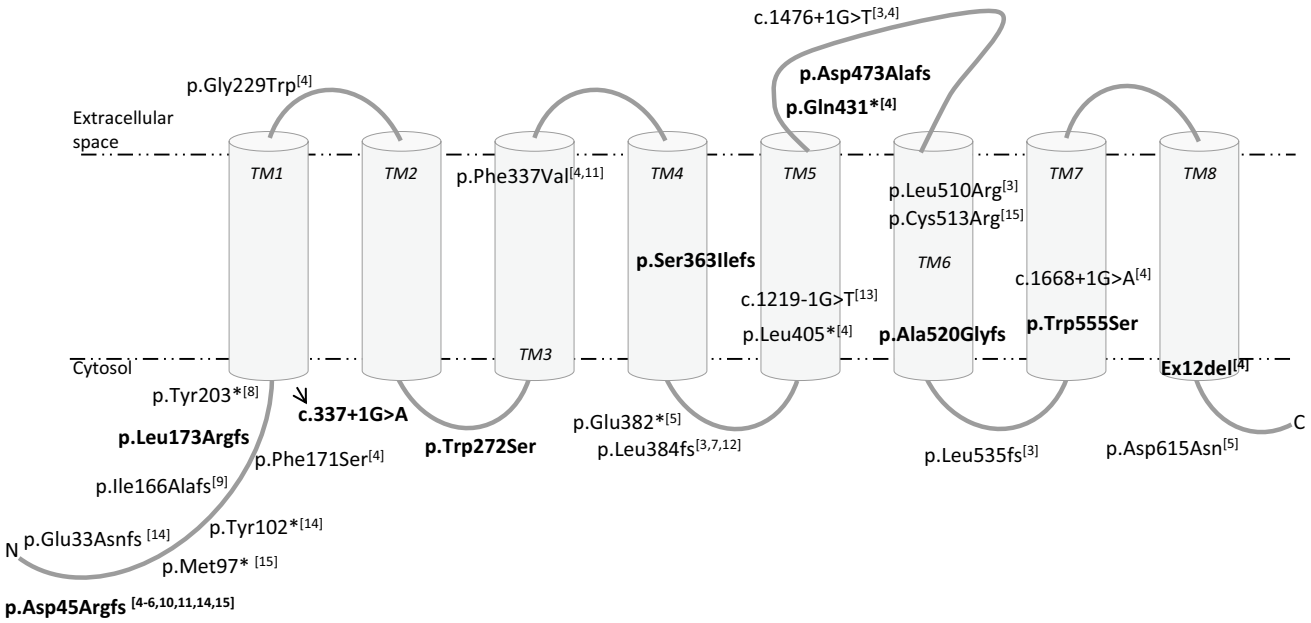


Fig. 1 Graphical representation of identified *ANO10* mutations. Schematic representation of *ANO10* mutations reported in the literature and identified in the present study in ARCA3 patients, in either homozygous or compound heterozygous form. The novel mutations described in this study are highlighted in bold. TM, transmembrane domain

in adulthood, between 27 and 53 years (Table 1). The progression of the disease was slow in all cases. Three patients needed constant gait support at age 47, 48, and 52, and only one patient was wheelchair-bound at age 70, after 30 years of disease duration. The SARA score ranged from 8 to 22 and correlated with the disease duration ($\rho = 0.80$; $p = 0.009$). In addition to cerebellar signs, we also found bradykinesia (7/10), mild vertical gaze paresis (5/10), pes cavus (4/10) and sphincteric disturbances (3/10). Fundus was evaluated in two patients and tortuosity of conjunctive eye vessels was demonstrated in one. None of the tested patients ($n = 3$) had increased serum alphafetoprotein or deficit of coenzyme Q10.

MMSE scores were within the normal range except in two patients (MMSE = 17.5 and 23.8) (Table 2). In subjects with normal MMSE ($n = 6$), cognitive evaluations showed deficits in different domains related to cerebellar cognitive abilities. The SDMT score was deficient in all tested patients (100%), and the ROCF test revealed deficit in both the copy (7/8) and delayed recall tasks (6/8). Low scores were also found with TMT-A (5/8) and B tests (6/8), and in phonemic fluency test (5/8).

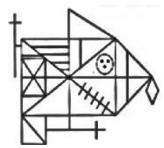
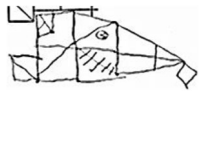
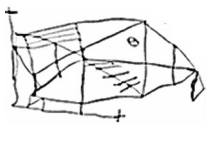
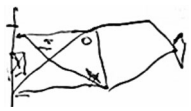
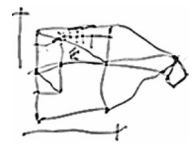
Electrophysiological evaluations excluded the presence of peripheral neuropathy and conduction abnormalities in motor, visual, and auditory central pathways. The EEG occipital background activity was normal in all patients, but sequences of diffuse slow waves on fronto-temporal regions were observed (Fig. 2a). In three patients, nap EEG showed epileptic spikes on central and parietal regions, which were asymmetric and often asynchronous on the hemispheres (Fig. 2c). EMG polygraphy during posture maintenance demonstrated repetitive tremor bursts mostly asynchronous on antagonist muscles at about 9 Hz. CMC values did not differ from the pattern and amplitudes detectable in healthy subjects (Fig. 2b). Somatosensory evoked potentials were normal except in three patients (Table 1), who presented "giant" SEPs with N20–P25 amplitude ranging from 20.3 to 28.6 μV, and P25–N33 amplitude ranging from 12.1 to 20.5 μV (Fig. 2d).

Brain MRI scans consistently demonstrated cerebellar atrophy and dentate nuclei faintly visible as mildly hyperintense regions in T2-weighted images. Diffuse supratentorial cortical atrophy, more pronounced in the anterior fronto-parietal regions, was detected in four patients aged 58–70 years (Fig. 2e–g).

Discussion

In this study, we revised the literature and described one of the largest series of patients with pathogenic mutation in the *ANO10* gene (Table S2). In our patient population, ARCA3 appears to be one of the most common recessive ataxia along with ARCA1 (*SYNE1*, SCAR8) [21]. The majority of our patients carried *ANO10* truncating mutations. In two unrelated families, we identified the c.289delA, which represented the most frequent mutation in our cohort (3/16 alleles, 19%). On the contrary, we

Table 2 Cognitive and neuropsychological tests in ARCA3 subjects

Family/patient	1.1	1.2	2.1	2.2	3	4	5	6
Age/education (years)	58/5	62/5	50/10	54/8	62/8	47/11	55/17	31/15
Cognitive tests[a]								
MMSE[a] (> 24)[b]	**23.8**	25.3	25	27	**17.5**	24.9	30	26.9
Rey Verbal Test[c]								
Immediate recall (> 28.5)	**19.8**	29.4	66.2	**17.2**	29.3	28.8	**26.2**	47.3
Delayed recall (> 4.69)	**0**	5.2	15	6.4	9.7	**3.2**	7	11.2
Verbal fluency[d]								
Semantic (> 23.6)	**23.2**	32	39	28.2	32.8	28	33.8	35.7
Phonemic (> 17)	**10**	30	**16**	**11**	**16**	24	**14**	19
SDMT[e] (> 35.8)	**10**	**3**	**20**	**8**	np	np	**19**	**29**
TMT[f]								
Part A (< 93)	**206**	**201**	51	**134**	np	np	86	60
Part B (< 282)	**400**	**400**	**400**	**400**	np	np	219	114
Rey–Osterrieth Complex Figure Test[g]								
Copy score (> 28.88)	**17.3**	**22.5**	**27.8**	**19.5**	**0**	**16**	32.5	**3.8**
									
Delayed recall (> 9.47)	**7.5**	9.8	**5.8**	**5**	**0**	**8.5**	14.3	**2.3**
								

np not performed

[a]In parenthesis cut-off score in healthy. The values in bold represent scores below the cut-off limit, according to normative. References for: [b]MMSE total score Folstein et al., 1975; [c]Rey Verbal Learning Test, Italian validation, Carlesimo et al., 1996; [d]Verbal fluency, Zarino et al. 2014; [e]Symbol Digit Modalities Test, Sheridan et al., 2006; (5) [f]Trail Making Test, Giovagnoli et al. 1996); [g]Rey–Osterrieth Complex Figure Test (Caffarra et al. 2002)

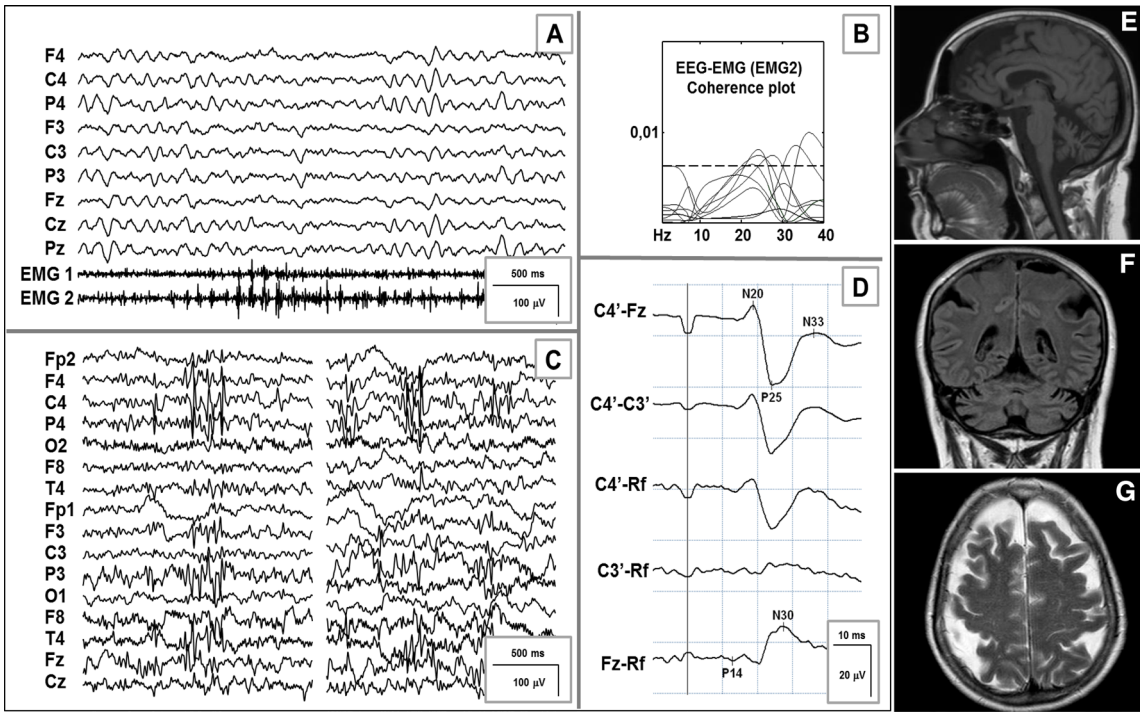


Fig. 2 Neurophysiological and neuroimaging findings. Neurophysiological findings and brain MRI in patient 1.2. **a** EEG–EMG recording fragment showing quasi-rhythmic EMG bursts synchronous on left wrist flexor (EMG 1) and left wrist extensor (EMG 2). **b** EEG–EMG (left wrist flexor) coherence plot showing scattered peaks. **c** EEG segment of NREM sleep showing bilateral or asymmetric spikes on centro-parietal regions. **d** SEPs elicited of the left median nerve showing remarkable increase of cortical response ("giant" SEP). Brain MRI T1-weighted sagittal (**e**), coronal (**f**), and T2-weighted axial (**g**) images of the same patient showing cerebellar and fronto-parietal cortical atrophies

found only one allele carrying the c.132dupA that is the most frequent recurrent mutation previously described in families of European ancestry [4–6, 10, 11, 14, 15]. The seven novel *ANO10* gene mutations were found across different exons and domains, confirming that *ANO10* gene has no mutational "hot spots".

Gait instability was noticed in our patients between the 4th and the 6th decades, except in one patient, who presented ataxic gait at the age of 27. This patient was compound heterozygote for a truncating and a missense mutation, which argues against the hypothesis that patients with at least one missense mutation may have a later age at onset in comparison with subjects carrying two truncating mutations [4, 10].

We confirm in our study that an adult-onset slowly progressive cerebellar ataxia syndrome associated with signs of pyramidal system involvement characterizes the clinical phenotype of ARCA3 patients (Fig. 3).

Extensive cognitive tests were previously performed only in three patients who had several deficits across different cognitive domains, intellectual disability, and low MMSE scores (range 19–21) [7]. In our patients, a normal score in the MMSE score was associated with several dysfunctions in specific test for executive, linguistic, and visuospatial domains. The most critical tasks for ARCA3 patients were the ROCF and the SDMT. The ROCF test has already been used for patients affected by genetic cerebellar ataxias, and, despite the fact that it requires motor ability to draw correctly, the scores are only slightly influenced by motor performances [22]. These types of alterations have been previously recognized in patients with cerebellar ataxic disorders and were demonstrated to be unrelated to dysarthria or limb incoordination [23]. In addition to the difficulties in the ROCF, all our patients also failed the SDMT test. A recent study in Friedreich ataxia demonstrated that the patients without cognitive decline had significantly lower SDMT scores than healthy controls even after with a normalization applied to reduce the impact of neurological disability [24]. We hypothesized that the association of cerebellar atrophy and frontal cortical degeneration, as observed in the MRI of patients with long disease duration, may contribute to the development of the selective cognitive defects. We also observed the presence of slow EEG activity prevalent on fronto-temporal regions and epileptic spikes on central regions compatible with the anterior cortical impairment. None of our patients had seizures, but we detected giant SEPs in 3/6 patients. The neurophysiological features reminded those observed in progressive myoclonus epilepsies (i.e., Lafora body disease, ceroidolipofuscinosis),

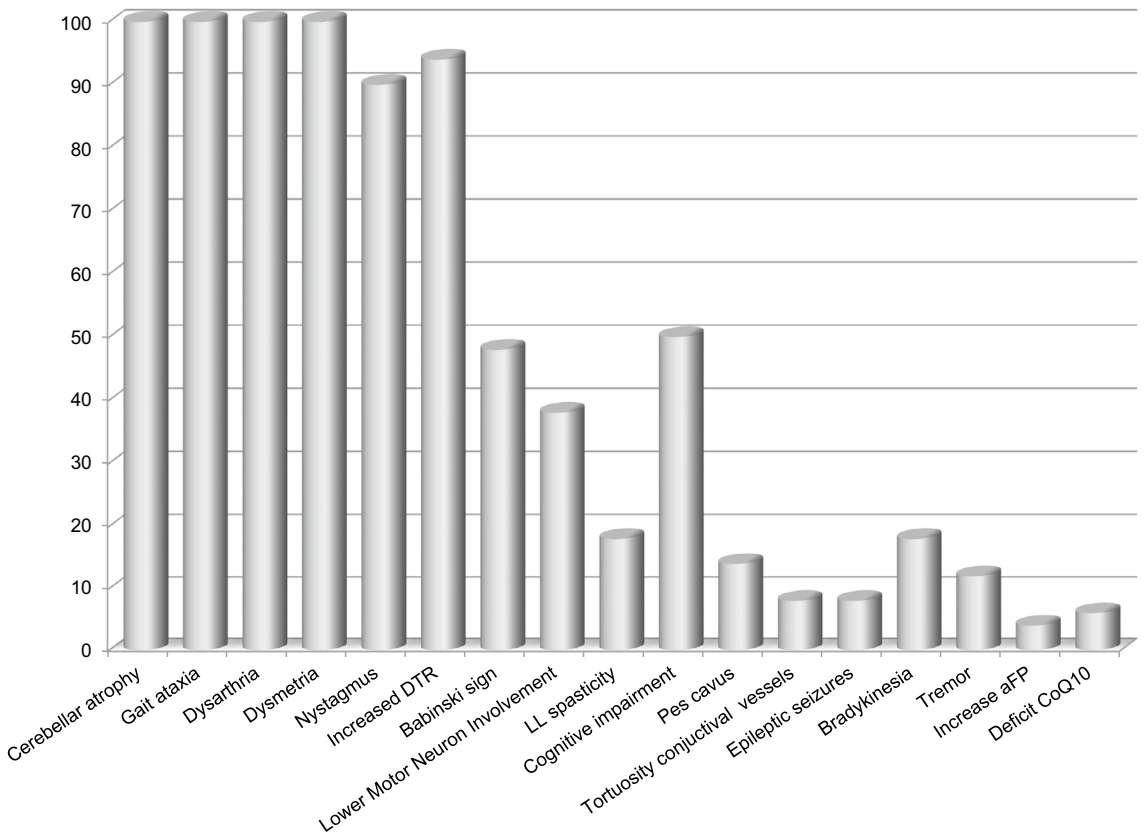


Fig. 3 Phenotypic spectrum in recessive cerebellar ataxia caused by *ANO10* mutations. Graph summarizing the percentage of clinical signs and symptoms in ARCA3 patients described in the literature and this study. Cerebellar, pyramidal, and cognitive deficits are the most frequent neurological features

and indicated hyperexcitability of the sensorimotor cortex, even if cortical reflex myoclonus was not generated and CMC was normal. Such condition is not specific for ataxic or ARCA3 patients, as isolated giant SEPs have also been described in patients with multiple sclerosis, cerebrovascular strokes, hydrocephalus, multiple-system atrophy or progressive supranuclear palsy [25, 26]. Giant SEPs were not previously described in ARCA3. Our observation may represent either a coincidental finding or a less frequent disease-related clinical feature. The presence of enlarged SEPs represents a marker of primary sensory cortex involvement and may indicate a possible widespread cortical degeneration including both the motor and the sensory cortex [27]. We could speculate a possible implication of anoctamin 10 protein in cortical excitability, but the role of the mutated protein and the pathogenic mechanism of the disease are not yet fully elucidated.

Our findings confirm the essential cerebellar features of ARCA3, and suggest a progressive sensory–motor cortical impairment during the course of the disease. Although extensive phenotype characterization may not be essential for diagnosis in the NGS era, the comprehensive definition of the common and rare clinical features of a specific genetic disease may be useful for studies on the natural history, prognosis, and clinical management of the patients.

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Compliance with ethical standards

Conflicts of interest All authors declare that they have no conflict of interest.

Ethical standard All patients gave written informed consent for the clinical and genetic tests in agreement with the procedures approved by the Local Ethic Committee. The consent forms routinely used in our Hospital specifically enquire the patient consent for diagnostic and research purposes. Ethics committee approval is not required for retrospective anonymized observational studies.

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