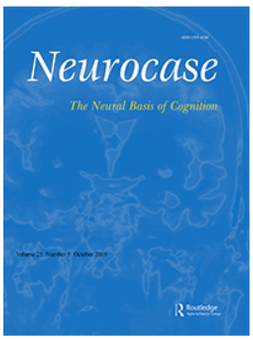

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The Neural Basis of Cognition

ISSN: 1355-4794 (Print) 1465-3656 (Online) Journal homepage: https://www.tandfonline.com/loi/nncs20

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To cite this article: Antonieta Nieto, Javier Pérez-Flores, Marc Corral-Juan, Antoni Matilla-Dueñas, Francisco Martínez-Burgallo & Fernando Montón (2019) Cognitive characterization of SCAR10 caused by a homozygous c.132dupA mutation in the ANO10 gene, Neurocase, 25:5, 195-201, DOI: 10.1080/13554794.2019.1655064

To link to this article: https://doi.org/10.1080/13554794.2019.1655064

NEUROCASE
2019, VOL. 25, NO. 5, 195–201
https://doi.org/10.1080/13554794.2019.1655064

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Cognitive characterization of SCAR10 caused by a homozygous c.132dupA mutation in the ANO10 gene

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ABSTRACT

Autosomal recessive spinocerebellar ataxia type 10 (SCAR10) caused by a homozygous c.132dupA mutation in the anoctamin 10 gene is infrequent and little is known about its cognitive profile. Three siblings (1 male) with this mutation were assessed with a neuropsychological battery measuring multiple cognitive domains. The deficits observed in one patient were in executive functions whereas the other two patients showed deficits in practically all the functions. Cognitive impairment seems to be a characteristic of the SCAR10 produced by this mutation, with a range from mild impairment, especially involving prefrontal systems, to a severe cognitive impairment suggesting widespread cerebral involvement.

ARTICLE HISTORY
Received 13 November 2018
Accepted 5 August 2019

KEYWORDS
ANO10 gene; autosomal recessive spinocerebellar ataxia; SCAR10 cognitive impairment; cerebellum

Introduction

Homozygous or compound heterozygous mutations in the anoctamin 10 (*ANO10*) gene in chromosome 3p21.33, cause autosomal recessive spinocerebellar ataxia type 10 (SCAR10) (Vermeer et al., 2010). *ANO10* gene codes for an eight transmembrane putative chloride channel and spans 2.7 kb containing 13 exons, 12 of which are coding. ANO10 protein expression is higher in the whole adult brain, followed by the retina and heart (Vermeer et al., 2010). SCAR10 is a neurodegenerative disease, with the onset in the teenage or young adult years, of gait and limb ataxia, dysarthria, and nystagmus, occasional involvement of lower associated motor neurons and marked cerebellar atrophy on brain imaging. Some patients have low levels of coenzyme Q10 (CoQ10) in muscle and may show some clinical improvement with CoQ10 treatment (Balreira et al., 2014). The cognitive status of SCAR10 is reported as normal or with cognitive impairment (Balreira et al., 2014; Mišković et al., 2016; Renaud et al., 2014; Vermeer et al., 2010), although a few studies describe the cognitive profile (Chamard, Sylvestre, Koenig, & Magnin, 2016; Chamova et al., 2012).

The c.132dupA mutation is regarded as the most common *ANO10* mutation in SCAR10 (Renaud et al., 14; Koenig, Tranchant, & Anheim, 2015). In the study of Renaud et al. (2014), all patients with this mutation were compound heterozygotes, however Minnerop and Bauer (2015) reported a female presenting a homozygous c.132dupA mutation in *ANO10* and a mild clinical phenotype. To the best of our knowledge, there are no previous studies of cognitive functioning in patients with this mutation. The aim of this study is to characterize the cognitive profile of three patients from a remote consanguineous family with a homozygous c.132dupA mutation in the *ANO10* gene.

Methods

Three of six siblings born to consanguineous parents were studied. They carry the homozygous *ANO10* mutation (c.132dupA) causing a frame shift and introducing a premature stop codon (p. Asp45ArgfsTer9). Sequencing found an average coverage of 498x and 99% reads on target, and 99.5% of target regions of these 119 genes covered at least 20x. No other family members presented symptoms. Asymptomatic family members did not undergo genetic testing.

All three patients showed a progressive degenerative disorder with ataxia, dysarthria, nystagmus, brisk reflexes and cerebellar atrophy on neuroimaging. The disease duration was 15 years (patient 1, male), 18 years (patient 2, female) and 21 years (patient 3, female). The females also presented restless legs syndrome without ferropenic anemia, and the EMG showed a mild axonal sensitive neuropathy in one of these females (patient 2). Q10 plasma levels were measured with tandem mass spectrometry coupled to liquid chromatography (LC/MS/MS). Although all values were in the normal range (0.5–1.8,mg/L; internal lab reference), the values were at the lower end in the case of the females (0.57 and 0.56 mg/L) (see Table 1).

Ataxia NGS custom panel and analysis

DNA quality and quantity of total from patient 1 were determined with a Nanodrop-1000 (Thermo Fisher Scientific, Waltham, MA) by agarose gel electrophoresis and Qubit 3.0 (Thermo Fisher Scientific). Sequencing was performed using a custom targeted NGS approach designed to study 119 related ataxia genes using SureSelect Capture Library reagents

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Table 1. Clinical feature of patients.

	Case 1 Male Age: 43	Case 2 Female Age: 51	Case 3 Female Age: 55
Age at onset	28 y	30 y	37 y
Age at examination			
Evolution	15 y	21 y	18 y
RLS	0	+	+
Tendon reflexes/ plantar response	Brisk Flexor	Brisk Flexor	Brisk Flexor
SARA scale	12	20	24
MRI	Cerebellar atrophy	Cerebellar atrophy	Cerebellar atrophy
Plasm Q10 levels	1,35 mg/L	0,56 mg/L	0,57 mg/L
Normal: 0,5–1,8 mg/L			
Nerve conduction and EMG studies	N.P.	Normal	Mild axonal sensory neuropathy
SSEP, ATEP, EVP	Normal	Normal	N.P.

Note. BAEPs: brainstem auditory evoked potentials; N.P.: not performed; RLS: restless legs syndrome; SSEP: somatosensory evoked potential; VEP: visual evoked potential.

(Agilent Technologies, Santa Clara, CA) and probes custom designed to capture coding exons, following Agilent protocols and recommendations. DNA Library quality and quantity were assessed with a TapeStation4200, High Sensitivity assay (Agilent Technologies). Library was sequenced by paired-end sequencing (100×2) with an Illumina HiSeq 2500 sequencer (Illumina, San Diego, CA). Phred was used to calculate quality values (Ewing & Green, 1998). A specific custom pipeline was used for the bioinformatics analysis. Briefly, Burrows-Wheeler Aligner (Li & Durbin, 2009) and in-house scripts were implemented to map the readings against the human reference genome version GRCh38/hg38. Variant calling was performed using a combination of two different algorithms: VarScan (Koboldt et al., 2009) and GATK (McKenna et al., 2010). In-house scripts were developed to combine and filter variants, which were annotated using the Ensembl database (Kersey et al., 2016). The methodology was validated in a cohort of 500 neurological patients. Variants were filtered out, prioritized and classified to obtain a list of variants with a minor allele frequency regarding their minor allele frequency (MAF) ≤0.01 in 1000 Genomes 1000 Genomes (http://www.ncbi.nlm.nih.gov/variation/tools/1000genomes/), Exome Variant Server (EVS) (http://evs.gs.washington.edu/EVS/), ExAC Browser (http://exac.broadinstitute.org/), the variant position in the gene, the variant effect and the pathogenesis prediction by 3 different prediction algorithms (Condel, SIFT, PolyPhen2 and Mutation Taster) (Adzhubei et al., 2010; González-Pérez & López-Bigas, 2011; Kumar, Henikoff, & Ng, 2009; Schwarz, Cooper, Schuelke, & Seelow, 2014) for missense variations. Candidate variant identified by NGS was verified and segregated in patient 2 and 3 by Sanger sequencing following PCR amplification of the respective coding exon and adjacent intronic sequence.

Neuropsychological assessment

A detailed neuropsychological assessment was performed. Neuropsychological tests were administered by an experienced clinical neuropsychologist over two sessions. Tests were chosen to examine cognitive functioning in various cognitive domains: speed of processing, attention, working memory, declarative memory, executive functions and conceptualization, visuoperceptual and visuoconstructive functions and language. The neuropsychological battery was composed of subtests from WAIS-IV (Wechler, 2008, 2012). Reaction Times Tasks, the Continuous Performances Test-Identical Pairs task, the Logical Memory subtest of the WMS-IV (immediate and delayed free recall and recognition of two prose passages) (Wechler, 2008), Spanish adaptation of the California Verbal Learning Test (learning over a five-trial presentation of a 16-word list, free and cued delayed recall, recognition) (Benedet, Alejandre, & Pamos, 1998; Delis, Kramer, Kaplan, & Thompkins, 1987), Verbal fluency tasks (phonemic, semantic and actions fluency) (Benton, Hamsher, & Sivan, 1989; Piatt, Fields, Paolo, & Tröster, 1999), Facial Recognition test (Benton, Sivan, Hamsher, Varney, & Spreen, 1983), and language screening. Only non-standard procedures will be described here

Reaction Times: Simple and choice reaction time tasks from the Reaction Unit/Vienna System (RT) were used (Schuhfried, 1992). This system allows the dissociation of the cognitive component, Decision Time (DT) and the motor component, Motor time (MT). Simple reaction time: A yellow light appeared randomly, at which time the subject was instructed to remove his/her index finger of the dominant hand from a rest button and press another key as quickly as possible. Choice reaction time: A red light appeared randomly in a background of distractor stimuli. Decision Time (DT) is the time interval between the appearance of the stimuli and release of the finger. Motor Time is the time interval between release of the finger and depression of the second key. Decision Time is a cognitive measure of information processing speed. Motor time shows motor and coordination deficit (Wollmann, Barroso, Monton & Nieto; Nieto et al., 2012).

Continuous Performance Test-Identical pairs (CPT-IP) paradigm: a computerized version of the paradigm was administered in order to measure sustained attention (Erlenmeyer-Kimling et al., 1995). One hundred fifty digits were auditorily presented with an interstimuli interval of 1 sec. The subjects were instructed to press the response button every time two identical letters appeared consecutively (15% target stimuli). The total number of correct responses and omission and commission errors were collected.

Language screening: A brief non-standardized screening was used to assess length of sentences, grammatical form, paraphasias, object naming, word and phrase repetition and orders/phrases comprehension. Items were selected from the Addenbrooke´s Cognitive Examination-Revised (Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006; Nieto, Galtier, Hernández, Velasco, & Barroso, 2016) and the Profile of Speech characteristics (Goodglass, Kaplan, Weintraub, & Barresi, 2001).

In addition, a modification to the standard administration procedure was used in the case of the Block Design subtest of WAIS-IV: if the design was not correctly completed within the standard administration time, the subject was allowed to work on the problem for one extra minute, and was discontinued after three consecutive failures. The number of correct blocks was recorded without any kind of speed credits to take into account the motor deficits of the patients.

Raw scores were converted into age-corrected standard scores using published normative data. Scaled scores were used (Mean = 10; SD = 3) for the WAIS-IV subtests, CVLT and Logical Memory Composite scores were used (Mean = 100, SD = 15) for the WAIS-IV Indexes. In the case of the Reaction Time Tasks, CPT-IP and Fluency the T scores (Mean = 50, SD = 10) were obtained by comparing individual performance with an age-matched control sample (N = 68; 30 males/38 females; Age mean = 51 years SD = 6). In all cases, low scores indicate a poor performance.

This study had institutional and ethical review board approval and all the patients gave their informed consent.

Results

Patient 1

Patient 1 was a 43 year old male. The results of the neuropsychological assessment are summarized in Tables 2 and 3. He had a high Decision and Motor Time in the Simple Reaction task with scores below 2 SD of the mean. In the Choice Reaction Time task, the Motor time was markedly high and the Decision Time was in the borderline range. This impairment in processing speed was also confirmed by the Processing Speed Index from the WAIS-IV in which Patient 1 had an extremely low score (composite score = 69)

Performance in CPT-IP, a measure of sustained and focused attention, was preserved. All targets were correctly detected, and no commission errors were executed.

A scaled score in the Digit subtest (WAIS-IV) indicates a borderline performance. A more detailed analysis of the different modalities showed a borderline performance in Digit Span Forward, but a performance within the normal range in Digit Span Backward and Digit Span Sequencing. These results indicate a reduced attention span without deficits in working memory. In fact, the Working memory Index (WAIS-IV) was within the average range (composite score = 94).

Results in the Similarities subtest (WAIS-IV) revealed a notable deficit in concept formation. Verbal fluency was preserved in all the assessed modalities.

Patient 1 demonstrated a normal word list learning capacity, as assessed by the CVLT, but he had a poor performance in immediate recall of List B indicating an increased susceptibility to proactive interference. Free delayed recall and recognition in the CVLT were preserved. In contrast, he had an impaired performance in immediate and delayed recall of stories (Text Memory, WMS-IV).

Performances in the Facial Recognition test and Picture Completion were in the normal range indicating that visuoperceptive functioning was preserved. In contrast, he showed marked abnormalities in the modified Block-Design Test. A normal performance was observed in the language screening.

The results in WAIS-IV indicated a borderline intellectual functioning (Full scale intellectual quotient; FIQ = 72). The General Ability Index (GAI), a summary score less sensitive than the FIQ to the influence of processing speed and working memory, was extremely low. This result indicates that impaired FIQ was not attributable to the slowed processing or working memory capacity. Patient 1 had an extremely low Verbal Comprehension Index (VCI) and Processing Speed Index (PSI). In contrast, Working Memory Index was in the average range and Perceptual Reasoning Index was within a low average range. The difference between VCI/PSI and WMI/PRS were significant according to the comparative standards outlined in the WISC-IV manual ($p < 0.05$).

His behavior during the evaluation was correct and adapted to the context. His attitude was positive and had communicative intention which was demonstrated by the questions he asked and the spontaneous comments he made about his daily life.

Patient 2

Patient 2, a 51 year old female, had extremely high Motor and Decision times independently of the task used (Table 2). This slow processing was also observed in WAIS-IV performance which gave an extremely low Processing Speed Index (composite score = 50) (Table 3).

She showed marked abnormalities in CPT-IP performance: only one target out of a total of 23 was correctly detected and, consequently, a high number of omission errors were recorded. Commission errors were high but in a lower proportion. As in the case of Patient 2, instructions were repeated and she answered correctly when asked to say what she should say according to the instructions.

All modalities of the Digit subtest were impaired indicating an important deficit in working memory. The performance in other components of executive functions, concepts formation and fluency, were also impaired.

The immediate recall in the first trial of CVLT was low. Her performance ameliorated with the successive presentations but total learning was impaired. Recall was markedly impaired, especially in the case of long delay recall. Recognition was not examined. She was extremely uncomfortable when asked to recall the story of The Memory Text and the task was not continued.

Patient 2 had an impaired performance in the FRT and Picture Completion subtest indicating a deteriorated visuoperceptual ability. Visuoconstructive ability was also low as demonstrated by her performance in the modified Block-Design Test, both the standard and extended time.

Language screening revealed reduced speech and difficulties in comprehension of relatively complex phrases.

Overall intellectual functioning as shown by the Full IQ obtained in the WASI-IV was extremely low (FIQ = 40), even when the influence of limitations in processing speed and working memory were considered (GAI = 40). All index scores were in the extremely low range.

Her behavior was correct during the evaluation. However, she tended to show inactivity and her lack of communicative intent made the assessment process difficult.

Table 2. Neuropsychological tests scores.

	Patient 1			Patient 2			Patient 3		
	Raw Score	Standard Score (T/Ss)	Descriptive classification	Raw Score	Standard Score (T/Ss)	Descriptive classification	Raw Score	Standard Score (T/Ss)	Descriptive classification
Simple Reaction Time task									
Motor Time (ms)	452	T 21	Impaired	1163	T < 0	Impaired	1078	T < 0	Impaired
Decision Time (ms)	429	T 26	Impaired	670	T < 0	Impaired	529	T 6	Impaired
Choice Reaction Time task									
Motor Time (ms)	537	T < 0	Impaired	1684	T < 0	Impaired	1007	T < 0	Impaired
Decision Time (ms)	555	T 35	Bordeline	951	T < 0	Impaired	962	T < 0	Impaired
CPT-IP									
Hits	23	T 58	Preserved	1/23	T < 0	Impaired	13/23	T 27	Impaired
Omissions errors	0	T 58	Preserved	22	T < 0	Impaired	2	T 27	Impaired
Comission Errors (falses alarmes)	0	T 52	Preserved	6	T < 0	Impaired	32	T < 0	Impaired
Digits Span (WAIS-IV)	18	Ss 5	borderline	3	Ss 1	impaired		4	Ss 1
Digit Span Forward	6	Ss 5	Borderline	3	Ss 2	Impaired	4	Ss 3	Impaired
Digit Span Backward	6	Ss 7	Preserved	0	Ss 1	Impaired	0	Ss 1	Impaired
Digit Span Sequencing	6	Ss 6	Preserved	0	Ss 1	Impaired	0	Ss 1	Impaired
Similarities (WAIS-IV)	10	Ss 2	Impaired	2	Ss 1	Impaired		0	Ss 1
Verbal Fluency									
Phonetic	40	T 58	Preserved	3	T 25	Impaired	4	T 26	Impaired
Semantic	18	T 41	Preserved	5	T 21	Impaired	7	T 25	Impaired
Actions	14	T 51	Preserved	4	T 30	Impaired	1	T 22	Impaired
California Verbal Learning test									
Trial 1	5	T 39	Preserved	2	T 24	Impaired	3	T 32	Borderline
Trial 5	13	T 48	Preserved	9	T 34	Borderline	8	T 29	Impaired
Total Learning	52	T 46	Preserved	28	T 29	Impaired	24	T 22	Impaired
List B	3	T 32	Borderline	0	T 24	Impaired	2	T 29	Impaired
Free short delay	13	T 53	Preserved	0	T 13	Impaired	4	T 26	Impaired
Cued short delay	10	T 41	Preserved	1	T 10	Impaired	4	T 25	Impaired
Free long delay	11	T 43	Preserved	0	T 3	Impaired	0	T 5	Impaired
Cued long delay	10	T 37	Preserved	0	T 1	Impaired	0	T 5	Impaired
Recognition-Hits	15	T 48	Preserved	–	–		–	–	–
Recognition-False alarms	0	T 56	Preserved	–	–		–	–	–
Text Memory (WMS-IV)									
Inmediate Recall	11	Ss 2	Impaired	–	–		–	–	–
Delayed racall	4	Ss 1	Impaired	–	–	–	–	–	–
Facial Recognition test	21	T 41	Preserved	16	T 18	Impaired		17	T 22
Picture Completion (WAIS-IV)	7	Ss 6	Preserved	2	Ss1	Impaired		1	Ss1
Block Design (Modified WAIS-IV)	24	Ss 5	Borderline	1	Ss1	Impaired		4	Ss1
Standard Time		T 4	Impaired		T < 0	Impaired		T < 0	Impaired
Extended Time		T 29	Impaired		T 8	Impaired		T 12	Impaired

Note. T: T scores: Mean = 50, SD = 10; Ss: Scaled Scores: Mean = 10; SD = 3.

Table 3. Composites scores obtained on WAIS-IV (Mean = 100; SD = 15).

	Patient 1			Patient 2			Patient 3		
Scale	Composite Score	Confidence Interval	Classification	Composite Score	Confidence Interval	Classification	Composite Score	Confidence Interval	Classification
Full Scale IQ	72	67–80	Borderline	40	37–49	Impaired	57	53–65	Impaired
General Ability Index	60	56–68	Impaired	40	37–49	Impaired	50	46–59	Impaired
Verbal Comprehension Index	69	64–78	Impaired	50	46–61	Impaired	56	52–66	Impaired
Perceptual Reasoning Index	89	83–97	Preserved	52	48–63	Impaired	75	70–84	Borderline
Working Memory Index	94	87–102	Preserved	50	46–62	Impaired	66	61–76	Impaired
Processing Speed Index	62	58–76	Impaired	50	47–65	Impaired	52	49–67	Impaired

Patient 3

Patient 3 was a 55 year old female. Reaction times of Patient 3 were extremely high in both the motor and cognitive components (Table 2). This slowed processing was evident in the Simple and Choice tasks and was also confirmed by the Processing Speed Index (WAIS-IV) in which she obtained an extremely low score (composite score = 52) (Table 3)

Her performance in CPT-IP was impaired. Given the low performance observed, the task was stopped three times and instructions were repeated. She answered correctly when asked to say what she should say according to the instructions. Despite a seemingly good understanding, she correctly identified 13 of 23 targets. In addition, she made a high number of commission errors. These results indicate an impairment in attention.

There were clear working memory problems in her performance in the Digit Subtest where all modalities were impaired. Other executive function components, such as concept formation and fluency, were also impaired. In the case of Fluency tasks not only was a reduction in productivity observed, but a high number of rule breaks (intrusions) was also observed.

Patient 3 had a markedly impaired learning curve in the CVLT. The first immediate recall was in the borderline range. Repeated presentations of the word list helped to improve recall performance, but this improvement was limited. She only recalled 8 words out of 16 after five trials. Immediate recall of List B and all measures of delayed recall were impaired. A recognition trial was not applied given the discomfort shown by the patient. In the Memory Text subtest, she did not recall any item from the first text and was clearly unable to perform the task.

Her performance in the Facial Recognition test was borderline and impaired in the Picture Completion subtests. Her scores in the modified Block-Design Test were markedly low. Language screening revealed reduced speech and difficulties in comprehension of relatively complex phrases, which was taken into account during assessment, and instructions were simplified and repeated when necessary.

Her results in WAIS-IV revealed an extremely low overall intellectual functioning (FIQ = 57). The General Ability Index was also extremely low, and the result was the same when the influence of processing speed and working memory deficits was reduced. Index scores were in the borderline to extremely low range. Her Perceptive Reasoning Index was significantly higher than her Verbal Comprehension Index ($p < 0,05$) suggesting that non-verbal reasoning and perceptual organization was proportionally less affected than verbal reasoning and comprehension.

Her behavior was appropriate and adapted to the evaluation situation. However, she showed little communicative intention. Her spontaneous interactions were limited to a few smiles and nods. Despite this, her general attitude was positive during evaluation.

Discussion

The c.132dupA mutation is the most frequent *ANO10* mutation in heterozygosity (Koenig et al., 2015; Renaud et al., 2014). The homozygous c.132dupA mutation found in the patients here is infrequent. To the best of our knowledge, only a few patients have been reported as having autosomal recessive spinocerebellar ataxia type 10 with a homozygous c.132dupA mutation in *ANO10* (Fogel et al., 2014; Minnerop & Bauer, 2015). The neurological picture of the three homozygous patients was characterized by ataxia, dysarthria, nystagmus, brisk reflexes and cerebellar atrophy with neuroimaging. This phenotype is similar to that previously reported for this mutation in heterozygosity and homozygosity (Koenig et al., 2015; Minnerop & Bauer, 2015; Renaud et al., 2014).

A detailed neuropsychological evaluation showed cognitive impairment in the three patients in the present study. Patient 1 showed a marked reduction of cognitive processing speed in addition to motor slowing. His attention span was slightly reduced but sustained and focused attention was preserved. He showed problems in concept formation and normal verbal fluency. Word learning and recall were preserved except for a significant susceptibility to proactive interference. In contrast to the good performance in word list memory, story recall was impaired. This difference between the two memory tasks is evidence of difficulties when the task demands the use of organizing strategies for encoding the abundant information contained in the texts. The presence of concept formation problems, the susceptibility to interference and the difficulties in the use of organizing strategies suggest an impaired executive functioning. This executive problem may also contribute to his defective performance in the visuoconstructive task. On the other hand, visuoperceptual and language functions were preserved. In summary, the performance observed in Patient 1 may be especially related to a prefrontal dysfunction.

Patients 2 and 3 showed a more impaired performance than Patient 1. Testing revealed a marked cognitive and motor slowing but also problems in attention, executive functions, memory, visuoperceptual and visuoconstrutive abilities. These results suggest a widespread cerebral dysfunction.

The cognitive state of patients with homozygous c.132dupA *ANO10* mutation has not been previously studied although there are reports of cognitive impairment in patients with

heterozygous c.132dupA *ANO10* mutation. Renaud et al. (2014) reported a mild intellectual disability in one patient and normal cognition in the other three studied patients. No information about the procedure used to assess cognition was reported. Chamard et al. (2016) studied two patients with heterozygous c.132dupA mutation with a neuropsychological battery. The authors concluded that patients showed executive and attention impairments, but results of the neuropsychological assessment were not reported.

The cognitive profiles observed in the present study show that the homozygous c.132dupA *ANO10* mutation is associated with cognitive impairment. These results are consistent with previous reports supporting the notion that the cerebellum is not only involved in motor functions but also contributes to cognition (Schmahmann, 2013). In fact, most of the human cerebellum maps to association areas including those associated with cognitive control and the default network (Buckner, 2013). Therefore, cerebellar damage may disrupt the cerebellar-cortical network and, consequently, cause impairment in several cognitive domains (Nieto et al., 2012; Schmahmann, 2013; Selvadurai, Harding, Corben, & Georgiou-Karistianis, 2018).

The severity of the cognitive impairment is variable among the studied patients. The deficits observed in Patient 1 were in executive functions whereas the other two patients showed deficits in practically all the assessed functions. In terms of IQ, Patient 1 has borderline intellectual functioning (FIQ = 72), with a Working Memory Index and Perceptual Reasoning Index in the average to low average range, whereas Patients 2 and 3 have extremely low overall intellectual functioning (FIQ = 57, FIQ = 40, respectively). The differences in cognitive impairment between Patient 1 and Patients 2 and 3 cannot be attributed to differences in age at onset or duration of disease. The cerebellar atrophy observed in MR was also similar in all three patients. The most relevant difference was found in Q10 plasma levels which was lower in Patients 2 and 3. In addition, the severity of ataxia was also greater in Patients 2 and 3. Interestingly, the three previously reported compound heterozygous *ANO10* patients with low levels of CoQ10 were also females (Balreira et al., 2014; Chamard et al., 2016). Sex-related differences in phenotype severity in the case of *ANO10* mutations or in other genetic CoQ10 deficiencies related with ataxia have not been described (Emmanuele et al., 2012; Mišković et al., 2016; Renaud et al., 2014), therefore, we still cannot ensure the clinical significance of the observations here.

In summary, cognitive impairment seems to be a clinical characteristic of the SCAR10 produced by a homozygous c.132dupA mutation of *ANO10*, with a range from mild impairment, specifically involving prefrontal systems, to a severe and widespread cerebral involvement. The relationship between plasma CoQ10 levels and phenotype severity requires further investigation.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

The research of this work was funded by the Ministerio de Economia y Competitividad grant PSI2015-67514-P (to AN), the Spanish Health Institute Carlos III grants CP08/00027 and CPII14/00029 (to AM-D), and FIS PI14/00136 and PI17/00534 (to AM-D). Antoni Matilla Dueñas was a Miguel Servet Investigator in Neuroscience supported by the Spanish Health Institute Carlos III (ISCIII; CPII14/00029).

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