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LETTER TO THE EDITORS

Adult-onset ataxia or developmental disorder with seizures: two sides of missense changes in CACNA1A

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Dear Sirs,

Spinocerebellar ataxia type 6 (SCA6), familiar hemiplegic migraine (FHM), and episodic ataxia type 2 (EA2) are allelic disorders linked to *CACNA1A* mutations. *CACNA1A* encodes the alpha-1A subunit of neuronal voltage-dependent P/Q-type Ca^{2+} channels [1]. Some genotype-phenotype correlation has been observed with FHM usually caused by missense, EA2 by premature stop mutations, and SCA6 by CAG trinucleotide repeat expansions [2]. However, there is ample clinical overlap [3] and high intrafamilial phenotypic variability [4, 5]. Also, clinical manifestations beyond the "classical" phenotypes have recently been described including seizures and intellectual disability (ID) [6].

We report two patients with different missense mutations in *CACNA1A,* one presenting with an adult-onset SCA6-like phenotype, the other with infantile epilepsy, ID, ataxia, and myoclonus.

A 32-years-old male Portuguese patient (Patient 1) had a 3-year history of gradually developing diplopia, slurring speech and gait instability. The patient's father was reported to have similar impairment commencing in his fifties. On examination, the patient had mild dysarthria, prominent cerebellar oculomotor dysfunction, limb and truncal ataxia with gait instability, but no additional signs. The score on the scale for the assessment and rating of ataxia (SARA) increased within 1 year by two points to 7/40. cMRI showed pancerebellar atrophy. SCA was considered but repeat expansions were not found in SCA1-3, 6–8, 12, and 17. Mutations in *TTBK2*, *KCN3*, *PRKCG*, *FGF14* and *AFG3L2* were likewise excluded. Exome sequencing in the patient and his father detected a heterozygous, likely pathogenic variant in *CACNA1A* (c.2416C>A [NM_023035]; p.Arg806Ser; chr19:13410043G>T). This variant has previously not been reported in a patient, is extremely rare in the Exome Aggregation Consortium database (ExAC) (6/33262 Europeans) [7], and predicted to be deleterious [Combined Annotation Dependent Depletion (CADD) Score: 25.8] [8].

A 17-year-old boy (Patient 2) had a history of postnatal absence-seizures evolving into self-limiting generalised tonic–clonic seizures at the age of 2 years, which were fully suppressed by carbamazepine treatment. At the age of 5 years, anti-convulsive therapy was stopped and seizures recurred. There was global developmental delay. He started to walk at the age of 3 years and attended a school for mentally handicapped children. The patient was consecutively treated with different medication (Table 1) with Levetiracetam and Oxcarbacepine being most effective initially. In adolescence, attack frequency increased with having seizures twice a week. He presented to our center because of newly developed generalized myoclonus. On examination, he had mild dysmetria, gait ataxia, generalised spontaneous and action-induced myoclonus including perioral muscles, and mild dystonic posturing of the arms but no other neurological signs. Both parents were asymptomatic. Karyotype and array-CGH were normal.

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Table 1 Clinical features in Patient 1 in comparison to the typical SCA6 phenotype and Patient 2 compared to two previously reported patients with the p.A713T mutation

	Patient 1	Typical SCA6 [9]	Patient 2	Other patients with p.A713T mutation [6]
Mutation	c.2416C>A; p.Arg806Ser	>19 CAG repeats	c.2137G>A; p.A713T	c.2137G>A; p.A713T
Onset (years)	29	19–71	Birth	Birth
Ataxia	+	100%	+	1/2
Dysarthria and oculomotor dysfunction	+	100%	−	1/2
Intellectual disability, myoclonus and epilepsy	−	−	+	2/2
Hyperreflexia	−	40–50%	−	2/2
Dystonia	−	up to 25%	+	0/2
Episodic symptoms	−	up to 33%	+	2/2
Current and previous treatment	4-Aminopyridin (recently initiated)		OCBZ, LCM, TPM, LEV, VPA, SUL, CBZ, ZNS	LTG, TPM, LEV, PB, VPA, AZD, CZP, CLB, ETX MDZ, CLZ, PHT, lignocaine, pyridoxine, propranolol, pyridoxal-phosphate

Current treatment is underlined

AZD acetazolamide; *CBZ* carbamazepine; *CZP* clonazepam; *ETX* ethosuxamide; *LCM* lacosamide; *LEV* levetiracetam; *LTG* lamotrigine; *OCBZ* oxcarbacepine; *PB* phenobarbitone; *SUL* sultiame; *STP* stiripentol; *TPM* topiramate; *VPA* valproate; *ZNS* zonisamide

There were no mutations in *ADCY5, POLG, SCN1A, PEO1, SCN2A, SCN1B, GABRAG2, GABRD, CSTB,* and *MECP2*. Exome sequencing of the patient and his parents (trio analysis) revealed a likely pathogenic, de-novo *CACNA1A* mutation (c.2137G>A; p.A713T; chr19:13414398C>T) that was confirmed by Sanger sequencing. This variant was predicted to be deleterious (CADD-Score: 31), absent from public databases, and previously found in two similarly affected patients (Table 1) [6].

These two patients with strikingly different phenotypes (classical SCA6 vs. complex neurodevelopmental syndrome with epilepsy and ID) illustrate the broad phenotypic spectrum of missense mutations in *CACNA1A* and underline the necessity for tailoring genetic testing of *CACNA1A* mutations. In the setting of late-onset cerebellar ataxia as in Patient 1 (SCA phenotype), testing for common repeat expansions should probably be the first choice but, if negative, *CACNA1A* sequencing to detect point mutations should subsequently be considered. In the context of a complex, unspecific syndromes as in Patient 2, exome sequencing, ideally of the parent-offspring trio to enable detection of de-novo mutations, should be preferred to single gene sequencing.

In conclusion, these cases highlight the manifold clinical presentation of *CACNA1A* mutations that may affect children as well as adults.

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Compliance with ethical standards

Conflicts of interest The authors have no disclosures relevant to the manuscript.

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Ethical standards Ethical approval for this study was obtained from the local ethics committee (Ref. 11-021).

Informed consent informed consent was obtained from each involved patient.

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