A Novel Frameshift *CACNA1A* Mutation Causing Episodic Ataxia Type 2

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Introduction

The alpha-1A subunit of neuronal voltage-dependent P/Q-type Ca^{2+} channels is encoded by the *CACNA1A* gene, and mutations in *CACNA1A* result in channelopathies originally thought to cause distinct, well-known allelic disorders: Spinocerebellar ataxia type 6 (SCA6), familial hemiplegic migraine (FHM), and episodic ataxia type 2 (EA2) [4]. Certain *CACNA1A* mutation types are more frequently associated with distinct phenotypes: missense mutations with FHM, mutations resulting in a premature stop with EA2, and an exonic CAG trinucleotide repeat expansion with SCA6 (<http://www.hgmd.cf.ac.uk/ac/gene.php?gene=CACNA1A>). Recent reports, however, revealed an extensive clinical overlap between these three phenotypes [1, 9] and a high intrafamilial phenotypic variability [5, 7]. In addition, new phenotypes including seizures and mental retardation have been reported [1].

Here, we describe the identification and functional characterization of a novel *CACNA1A* mutation in a patient with EA2. We highlight that mutations in genes being associated with paroxysmal disorders may be overlooked as the symptomatology may be misclassified as psychogenic especially when the family history is negative.

The genetic study was approved by the ethics committee of the University of Luebeck.

Case Report

A 27-year-old male patient was referred to our movement disorders outpatient clinic with a 10-year history of episodic double and blurred vision, dysarthria, clumsiness, nausea, and rotating vertigo being triggered by physical exercise and alcohol lasting for minutes to hours. Apart from intermittent occipital headache, the patient was completely asymptomatic and reported no other signs between the attacks. EEG, cMRI, and ECG were normal. The first attack occurred at the age of 13 years when the patient was swimming during school class requiring assistance to leave the pool. Subsequent attacks were thus considered panic attacks (ICD10 F41.0) as a consequence of the event of near-drowning. Neither behavioral therapy nor the administration of an SSRI for 2 to 3 months was successful. Treatment with acetazolamide, however, resulted in a clear improvement with regard to the frequency of the attacks.

Family history was negative for movement disorders and headaches. His mother was reported to suffer from multiple sclerosis since young adulthood and his brother had an inborn hydrocephalus.

On examination, the patient showed slightly hypometric horizontal saccades, mild action-induced perioral jerks, a slightly dysmetric finger-to-nose test with his left hand, and ataxic spiral drawing (SARA score 0.5/40, [video](#)). He displayed no nystagmus, and the remaining examination was otherwise normal. Given the frequency and length of the reported attacks and very mild interictal cerebellar signs, episodic ataxia type 2 (EA) was considered as clinical diagnosis and genetic testing was initiated demonstrating a novel, heterozygous, pathogenic variant in *CACNA1A* (c.3901delC; p.Leu1301Sefs*19) [6]. This variant has previously not been linked to any *CACNA1A*-related disorder, was absent in the server of the Genome Aggregation Database (gnomAD; <http://gnomad.broadinstitute.org/variant/>

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the large age range of disease manifestation calls for close collaboration of pediatric neurologists, neurologists, and human geneticists.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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