




# CLINICAL CHARACTERIZATION OF A NOVEL DE NOVO MUTATION IN THE CACNA1A GENE (C.3277DEL) ASSOCIATED WITH MIGRAINE WITHOUT AURA AND EPISODIC ATAXIA

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**Background.** Hemiplegic migraine (HM) is a rare form of migraine with motor aura, associated with pathogenic variants in genes involved in ion transport, including CACNA1A, which encodes the α1A subunit of the voltage--gated P/Q-type calcium channel. Variants in CACNA1A are responsible for a spectrum of paroxysmal neurological disorders, including familial hemiplegic migraine type 1, episodic ataxia type 2, and spinocerebellar ataxia type 6, now considered a clinical continuum rather than distinct nosological entities.

**Methods.** A 42-year-old man with a long-standing history of episodic vertigo, transient dysarthria, gait disturbance, and migraine without aura was evaluated. Targeted next-generation sequencing (NGS) of SCN1A, CACNA1A, SCN2A, ATP1A2, and ATP1A3 was performed, with complete coverage of exons and flanking intronic regions. The identified variant was confirmed by Sanger sequencing, and segregation analysis was performed in four first-degree relatives (parents and two brothers).

**Results.** Neurological examination revealed inexhaustible horizontal and vertical gaze-evoked nystagmus, while brain MRI and prolonged video-EEG were unremarkable. Paroxysmal episodes occurred in clusters of up to six per month, while migraine attacks were daily. NGS analysis identified a heterozygous frameshift variant in CACNA1A, c.3277del (p.Ser1093Alafs*93), resulting in protein truncation and loss of function of the P/Q-type channel. Segregation analysis confirmed the de novo origin of the variant, which was absent in both parents. Based on ACMG/AMP criteria, the variant was classified as pathogenic due to loss-of-function mechanism, absence from population databases (gnomAD v4.1), location within a CACNA1A hotspot region, and de novo origin. Initial preventive therapy with acetazolamide, poorly tolerated, was replaced with topiramate with partial benefit; subsequent reintroduction of acetazolamide, in combination with topiramate, resulted in a further reduction in attack frequency.

**Conclusions.** This case expands the phenotypic spectrum associated with CACNA1A-related channelopathies, showing how migraine without aura and episodic ataxia may represent atypical manifestations within the same clinical continuum. Recognition of such presentations, even in the absence of overt motor aura, is relevant for early diagnosis and for guiding personalized therapeutic strategies.