Novel CLN6 Variant in **Autosomal Recessive Adult-Onset Neuronal Ceroid Lipofuscinosis** with **Drug-Resistant Epilepsy:** *Expanding the Phenotypic Spectrum*

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Case description

A 23-year-old female, onset at age 19 of generalized tonic-clonic seizures preceded by dysphasia and tremor. She developed drug-resistant epilepsy, currently with monthly seizures, progressive dysarthria, cerebellar ataxia, gait impairment, and cognitive decline with mild intellectual disability (verbal domains). Previously in treatment with cenobamate (worsened cerebellar symptoms) and lamotrigine (ineffective). Current therapy: levetiracetam 2250 mg, perampanel 8 mg, valproate 1000 mg.

Investigations

MRI: cerebellar atrophy.

EEG-polymiography: photoparoxysmal response (PPR), frequent bilateral parieto-temporo-occipital abnormalities, bilateral distal upper limbs myoclonus on voluntary motor activation.

NGS showed compound heterozygous CLN6 variants:

- c.17G>C (p.Arg6Thr), maternal, VUS (ACMG 3), rare (gnomAD: 0.00001227)
- **c.243dup (p.Gly82TrpfsTer50)**, paternal, likely pathogenic (ACMG 4), absent in population databases

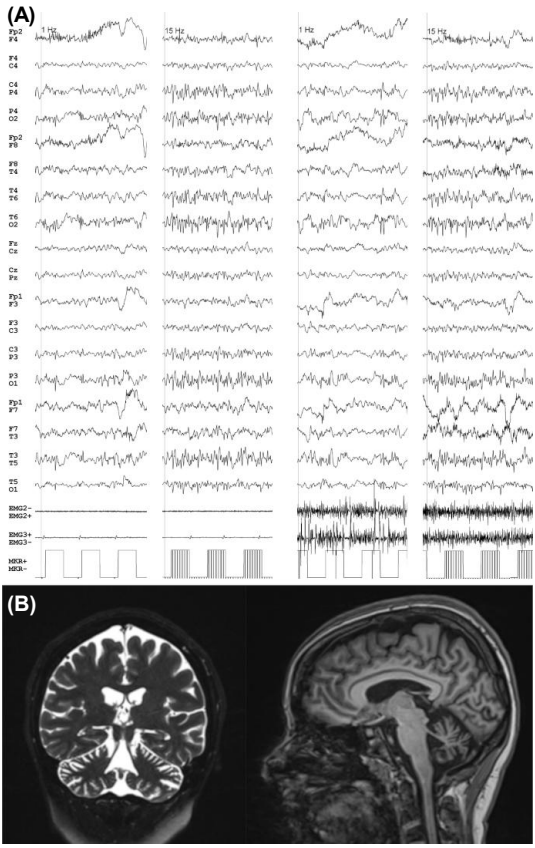

Figure 1: (A) Electroencephalogram (EEG)-polymyography (EMG2: left deltoid, EMG3: right deltoid) showing: on the left, PPR during intermittent light stimulation (ILS) at 1 and 15 Hz, on the right bilateral distal myoclonus on voluntary motor activation (arms extension) during ILS. (B) Magnetic resonance imaging (MRI) (left to right: coronal T2 w.i. and sagittal T1 w.i.) performed at 22 years shows cerebellar atrophy

Discussion and conclusions

CLN6 mutations cause Kufs disease type A (adult-onset CLN) with progressive myoclonic epilepsy, cognitive decline, and cerebellar ataxia without visual loss [1][2]. PPR and multifocal EEG abnormalities are typical markers [2]. The p.Arg6Thr variant has been reported in Kufs, while the novel frameshift p.Gly82TrpfsTer50 supports a loss-of-function mechanism, pathogenic in CLN6 disease. The absence of visual involvement and adult onset distinguish this case from infantile forms, and this novel CLN6 variant could represent a possible contributor to the phenotypic variability observed.

References:

1. Arsov T et al. Kufs Disease, the Major Adult Form of Neuronal Ceroid Lipofuscinosis, Caused by Mutations in CLN6. *Am J Hum Genet*. 2011;88:566-573.
2. Canafoglia L et al. Electroclinical spectrum of the neuronal ceroid lipofuscinoses associated with CLN6 mutations. *Neurology*. 2015;85:316-324.