Ceroid lipofuscinosis type 5: novel pathogenic variants, and unexpected phenotypic findings

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Background: Neuronal ceroid lipofuscinoses (NCLs) are a heterogeneous group of genetic disorders affecting the brain and the retina. *CLN5* pathogenic variants were described mainly in Caucasians. Here we describe 17 South American patients harboring ten pathogenic variants in *CLN5*, five of them novel variants, and one with a founder effect.

Methods: This is a multicenter case series. Patients were identified through a search for homozygous/compound heterozygous pathogenic *CLN5* variants in the database of a commercial laboratory (Mendelics) and by contacting reference centers from all South America for CLN5 disease confirmed cases.

Results: Seventeen patients were reported. All patients presented with cognitive and motor decline, cerebellar ataxia, and seizures. Three patients had no visual loss until the last visit. One patient had an unusual late onset at his forties with visual loss, dementia, spasticity and ataxia. We have found six missense variants, two frameshift variants, two nonsense variants and one splicing site variant. The variant p.Arg63Cys was found in a homozygous state in six patients and as compound heterozygous in one. The same haplotype was present in all Brazilian samples, suggesting a possible founder effect.

Conclusions: We present a large series of South American patients with CLN5 disease with a recurrent missense variant with a possible founder effect. This study broadens the phenotypic and genotypic spectrum associated with CLN5 disease, with early-onset seizures presenting in patients with this new recurrent variant. No other genotype-phenotype correlation was found.

We also described an unusual late-onset case with hypogonadotropic hypogonadism, dementia and higher-order visual symptoms.