

Clinical and molecular characterization of SPG7 patients carrying the p.Ala510Val (A510V) variant

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Abstract (in English, max 250 words)

Background: The p.Ala510Val (A510V) is the most frequent pathogenic variant identified in SPG7 patients.

Aim of the study: Exploring SPG7 patients carrying the p.Ala510Val (A510V) variant.

Methods: We analysed 95 patients from SPATAX/BIOMOV cohorts (Paris Brain Institute) with biallelic SPG7 variants including at least one A510V variant. Proteomics and functional studies were performed.

Results: We identified 29 homozygous A510V and 66 compound heterozygous patients, including 18 with a second missense variant and 48 with a loss-of-function (LoF) variant. Age at onset differed significantly across group ($p=0.02$), being earliest in A510V/missense patients (mean 34.5 years), intermediate in A510V/LoF patients (38 years), and latest in A510V homozygotes (42 years). Signs at onset were similar across groups with ataxia more frequent (82%) than spasticity (26%). Ataxia severity was moderate in all groups (mean SARA score 12/40). Pyramidal syndrome was common (>85%), with spasticity more frequent in the LoF group (74%), followed by the homozygous (52%) and missense (33%) groups. Cerebellar atrophy was systematic in A510V/missense patients and observed in 60–70% of the other groups. Functional studies in fibroblasts from one A510V homozygous and four A510V heterozygous patients showed no detectable alteration in mitochondrial respiratory chain levels, consistent with

preliminary quantitative proteomic analysis (12 controls, 6 homozygous A510V, 7 A510V compound heterozygous), revealing no genotype-dependent differences in protein expression.

Conclusion: Homozygous A510V patients and compound heterozygous SPG7 patients showed a consistent clinical spectrum, with earlier onset in A510V/missense carriers. Mitochondrial function appeared preserved, and preliminary proteomic data did not identify genotype-dependent molecular differences.