PLP1 gene mutations cause spastic paraplegia type 2 in three families

Li Yao [1] [2], Zeyu Zhu [1], Chao Zhang [2], Wotu Tian [1], Li Cao [1]

Affiliations expand

PMID: 36622199 PMCID: PMC10014006 DOI: 10.1002/acn3.51722

Abstract

Objective: Spastic paraplegia type 2 (SPG2) is an X-linked recessive (XLR) form of hereditary spastic paraplegia (HSP) caused by mutations in proteolipid protein 1 (PLP1) gene. We described the clinical and genetic features of three unrelated families with PLP1 mutations and reviewed PLP1-related cases worldwide to summarize the genotype-phenotype correlations.

Methods: The three probands were 23, 26, and 27 years old, respectively, with progressively aggravated walking difficulty as well as lower limb spasticity. Detailed physical examination showed elevated muscle tone, hyperreflexia, and Babinski signs in lower limbs. Brain MRI examinations were investigated for all cases. PLP1 mutations were identified by whole exome sequencing, followed by Sanger sequencing, family co-segregation, and phenotypic reevaluation.

Results: A total of eight patients with SPG2 were identified in these three families. The probands additionally had cognitive impairment, urinary or fecal incontinence, ataxia, and white matter lesions (WML) in periventricular regions, with or without kinetic tremor. Three hemizygous mutations in PLP1 were identified, including c.453+159G>A, c.834A>T (p.*278C), and c.434G>A (p.W145*), of which c.834A>T was first associated with HSP.

Interpretation: We identified three families with complicated SPG2 due to three PLP1 mutations. Our study supports the clinically inter-and intra-family heterogeneity of SPG2. The periventricular region WML and cognitive impairment are the most common characteristics. The kinetic tremor in upper limbs was observed in 2/3 families, suggesting the spectrum of PLP1-related disorders is still expanding.