Expanding the Phenotypic Spectrum of *FAT2*-Associated Disorders: An Italian Case Series

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Objectives

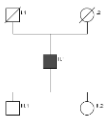
Spinocerebellar ataxias (SCAs) are a clinically and genetically heterogeneous group of autosomal dominant neurodegenerative disorders with more than 50 distinct subtypes described to date. Among them, SCA45, associated with *FAT2* gene mutations, was first described in 2017. Reported cases are rare and typically exhibit a pure cerebellar phenotype with late onset. *FAT2* is highly expressed in cerebellar granule cells and is thought to play a role in neuronal migration and cerebellar development. We describe four patients from three unrelated families, expanding the clinical spectrum of SCA45, with two cases showing additional pyramidal involvement.

Methods

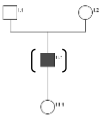
Three patients were evaluated at the Neurogenetics Clinic of Polo Pontino/ICOT, Sapienza University of Rome, and one at the IRCCS Stella Maris Foundation. Genetic analyses were performed via targeted NGS panels.

Results

We identified four patients with adult-onset gait disturbances and rare heterozygous *FAT2* variants.
P1: Ataxic gait after age 60; cerebellar atrophy on MRI; c.8218C>T (p.Phe2740Leu).
P2: Spastic-paretic gait after 50; cerebellar atrophy and axonal neuropathy; c.5240A>G (p.Asp1747Gly).
P3: Sister of P2; ataxic gait after 60; same variant c.5240A>G.
P4: Spastic-paretic gait, hyperreflexia; SPRS 28/52, SARA 17/40, SPATAX stage 5, FARS 4.0, FARS-ADL 15/36; c.5416G>A (p.Glu1806Lys).


P1


P3 P2


P4

Conclusions

These cases broaden the phenotypic spectrum of *FAT2*-related ataxia, highlighting the possible presence of spasticity and pyramidal signs in addition to cerebellar features. *FAT2* variants should be considered in patients with adult-onset cerebellar ataxia, especially when common SCA repeat expansions are excluded.

No conflicts of interest

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