P95

A novel variant in ANO3 presenting with autosomal dominant combined dystonia in an Italian family

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Introduction: Mutations in DYT-ANO3 are a rare cause of autosomal dominant isolated or combined dystonia, mainly presenting in the adulthood.

Objective: To describe the phenotype of an Italian family affected by autosomal dominant combined dystonia carrying a novel variant in ANO3.

Methods: Clinical and genetic data were collected. A next-generation sequencing (NGS) panel including 59 genes associated with dystonia was performed. All identified variants were validated by Sanger sequencing.

Results: A 21-year-old girl presented with a 10-year history of postural and rest tremor of her right hand, which worsened after orthopedic surgery. After two years she developed painful dystonic movements in her right arm, which impeded her writing and eating. The tremor then spread to her lower limbs, interfering with walking. Mild bradykinesia and rigidity in the right arm were observed. The patient suffers psychomotor delay, dyslexia, dysgraphia, and dyscalculia. A therapeutic attempt with topiramate, carbamazepine, propranolol, clonazepam, and levodopa were ineffective. Brain CT and MRI were normal. SPECT with FP-CIT excluded loss of striatal dopaminergic innervation. EMG documented dystonic tremor in the lower limbs during orthostatism. Family history was significative for psychomotor delay and postural tremor in the father and two sisters with an autosomal dominant pattern. A novel heterozygous variant in ANO3, c.17G>T p.G6V, was identified in the case index, in three affected and two asymptomatic relatives, showing incomplete penetrance. The variant was classified as likely pathogenic according to the latest ACMG criteria.

Conclusions: We described the phenotype associated with a novel variant in ANO3 and demonstrated the utility of NGS analysis in the differential diagnosis of combined dystonic syndromes with tremor and early-onset parkinsonism.