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Cerebellar ataxia associated with IRF2BPL pathogenic variant

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Introduction and objective: Cerebellar ataxias represent a group of disorders with heterogeneous clinical presentation consisting in a pure cerebellar phenotype or various combinations with extracerebellar signs. We report a case of ataxia associated to IRF2BPL gene variant, an intronless gene mapped to 14q24.3 chromosome that codes for the interferon-regulatory-factor-2-binding-like-protein [1].

Materials: A 24-year-old woman came to clinical observation because of the appearance of myoclonic jerks and unsteady gait with frequent falls a few months before. Clinical examination showed multifocal myoclonic jerks, adult-onset intention tremor in the four limbs, and gait ataxia. The patient also reported a mild neuro-developmental disorder with regression and memory lapses starting when she was 7.

Methods: MRI brain-scan revealed six small T2/Flair-hyperintense supratentorial, bilateral gliotic lesions. Metabolic and genetic (SCA1, 2, 3, 6, 7, 17 and HTT genes) investigations resulted normal. Levetiracetam and Clonazepam consistently reduced the frequency of myoclonic jerks. Whole exome sequencing (WES) followed by Sanger sequencing revealed a de novo heterozygous pathogenetic variant (c.364C> T, p.Gln122Ter) in the IRF2BPL gene. WES performed in the parents of the patient didn't reveal any mutation. In addition to our case, a review of the literature identified 27 further patients carrying IRF2BPL variants was performed. Developmental delay and/or motor/speech regression of variable severity were present in all 28 patients, whereas ataxia was observed in 10.

Conclusions: The IRF2BPL mutation is to be added to the increasing number of genes implicated in cerebellar ataxias. The IRF2BPL variants should be considered in the diagnostic work up of patients with ataxia and extracerebellar signs, even though the condition is apparently sporadic. The absence of a family history should not preclude diagnosis because the great majority of previously reported probands had the disorder as the result of a de novo pathogenic variant.

References:

[1] Seizure 2022 Jul;99:12-15. doi: 10.1016/j.seizure.2022.04.010.