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Adult onset familiar dystonia-plus syndrome: A novel presentation of IRF2BPL-associated neurodegeneration

A B S T R A C T

Pathogenic variants of the *IRF2BPL* gene have been mostly associated with early onset epileptic encephalopathy. Movement disorders such as dystonia and ataxia were also reported, with symptoms mainly developing between childhood and adolescence. Here we describe a family with several members affected by a late onset dystonic and ataxic progressive syndrome, caused by a novel heterozygous pathogenic variant in the *IRF2BPL* gene.

Heterozygous pathogenic variants in the *IRF2BPL* gene have been associated with a range of neurological conditions. A progressive neurodevelopmental disorder characterized by severe regression, speech abnormalities, and an epileptic encephalopathy with onset usually in the first years of life is the most documented phenotype [1]. Movement disorders such as dystonia and ataxia were also reported, with symptoms mainly developing between childhood and adolescence [1]. Nearly all variants have arisen *de novo*, yet in a single published family the proband had inherited the pathogenic variant from his father, who developed the first signs of the disease at age 23 years [1]. Here we further expand the *IRF2BPL*-associated phenotypic spectrum by reporting a large family with several affected individuals, with onset as late as in the early fifth decade of life. The reported family originates from the North West of Italy and comprises seven affected members: three of them (the proband, her daughter and sister) could be directly examined and genetically tested, while the other four (the proband's father, two paternal uncles and paternal grandmother) were deceased at the time of examination, but were reported to be affected by a progressive neurological disease similar to that presented by living affected individuals (Fig. 1A). The clinical presentation in all subjects was that of a late onset, progressive syndrome characterized by gait ataxia, dystonia with severe dysarthria, extrapyramidal and pyramidal signs, cognitive and psychiatric symptoms (Supplementary material). Genetic testing for trinucleotide repeat expansion disorders, including the commonest spinocerebellar ataxias, DRPLA, Huntington Disease and Friedreich Ataxia, were all negative. Whole exome sequencing (Twist Human Core Exome Kit, Twist Bioscience) was performed on the proband's DNA on a NovasSeq6000 platform (Illumina, San Diego, CA). Variant filtering and prioritization led to identify the heterozygous frameshift variant c.584delG; p.(Gly195Alafs*17) in the *IRF2BPL* gene (NM_024496.3). The variant is absent in the population database gnomAD and is classified as pathogenic according to ACMG guidelines [2]. Sanger sequencing confirmed segregation of the variant with the disease (Fig. 1B). This study was approved by the institutional review board of University of Modena e Reggio Emilia, and all participants provided written informed consent.

The clinical presentation of the several affected members fits well and further expands the phenotypic spectrum associated to *IRF2BPL*. Indeed, the vast majority of *IRF2BPL* variants published to date have arisen *de novo* in sporadic pediatric patients presenting a neurodevelopmental disorder with severe regression and epileptic encephalopathy [1]. Very few cases have been reported featuring a later-onset phenotype, and only two inherited case are known, with onset in the early third decade [3,4]. The family reported here illustrates how *IRF2BPL*-related disorders may also manifest later in adult life, from the third to the fifth decade, leading to dominant inheritance along consecutive generations. Of note, the penetrance of *IRF2BPL* variants seems to be very high, as all three brothers in the second generation and both sisters in the third generation manifested signs of the disease. However, this observation requires further validation in additional families. Moreover, this family contributes to delineate the *IRF2BPL*-associated phenotype, which is characterized by a complex neurological condition mainly featuring ataxia, dystonia and anarthria/aphonia that relentlessly progress with worsening of all capacities, likely due to an underlying neurodegenerative process. Gait ataxia and limb dystonia are usually the symptoms of onset, which are followed in time by oro-mandibular dystonia, pyramidal signs, peripheral nerve involvement, cognitive decline and psychiatric symptoms. In contrast to previous reports [3,5], none of the patients in the present family presented ophthalmologic defects (such as keratoconus) nor epilepsy, which had been consistently reported in all adult cases so far. This phenotypic variability is a common finding in neurogenetic disorders, suggesting the existence of yet unknown genetic or epigenetic modifiers.

In conclusion, *IRF2BPL*-related disorder should be added to the long list of conditions that cause adult onset progressive ataxia with dystonia and anarthria. We suggest *IRF2BPL* to be included in all custom gene panels designed for ataxic syndromes, movement disorders and neurodegenerative disorders, and emphasize the importance of the genotype-first approach to increase the diagnostic yield in patients with complex phenotypes.

Ethics

All patients provided informed consent for publication.

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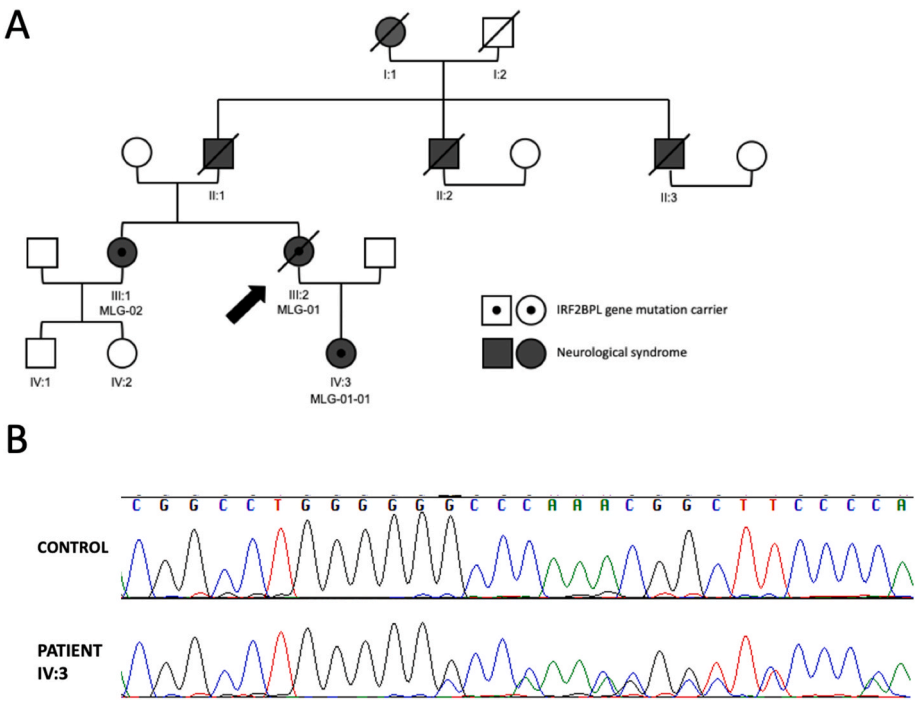

Fig. 1. A) Pedigree of the family; B) Sequencing chromatogram: Sanger chromatogram of IV:3 respect to reference sequence shows the presence of frameshift variant c.584delG only in the proband, confirming the NGS variant call.

Author contributions

Francesca Antonelli: design of the study, acquisition of data, interpretation of data, drafting the manuscript; Gaetano Grieco: analysis and interpretation of data, revising the manuscript for intellectual content; Francesco Cavallieri: interpretation of data, revising the manuscript for intellectual content; Antonella Casella: analysis and interpretation of data, revising the manuscript for intellectual content; Enza Maria Valente: design of the study, acquisition of data, interpretation of data, revising the manuscript for intellectual content. All authors approved the final manuscript.

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Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2021.10.033.

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