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IRF2BPL mutations cause autosomal dominant dystonia with anarthria, slow saccades and seizures

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In the ever-expanding spectrum of genetic dystonia syndromes, the presence of associated clinical signs can provide useful clues to guide diagnostic reasoning and inform treatment approaches. We have previously delineated the range of known etiologies associated with dystonia and anarthria/aphonia, and provided an algorithmic approach to reach diagnosis [1]. Since then, mutations in the *KMT2B* gene have been added to this list and indeed, two of the patients we previously reported (cases 15 and 20)[1] were subsequently found to harbor pathogenic mutations in this gene. Here, we wish to highlight a novel genetic etiology, namely mutations in the *IRF2BPL* gene, recently reported to cause a broad phenotypic range of neurological syndromes [2–4], with a particular focus on the syndromic association of dystonia with anarthria/aphonia.

In 2013 we described an autosomal dominant dystonic syndrome in a female patient (index) and her son (Fig. 1A), with a characteristic phenotypic presentation consisting of leg-onset generalized dystonia, severe anarthria/aphonia, slow saccades and epilepsy, including photic myoclonus (video; with informed written consent from all individuals for online publication and dissemination of the videos; additional clinical information is to be found in original description) [5]. Thorough clinical, paraclinical and genetic investigations at the time, including exome sequencing had been unrevealing [5]. Brain MRI of the index patient revealed mild supratentorial and cerebellar brain atrophy (Fig. 1B), and neurophysiology showed axonal and demyelinating neuropathy of the peroneal and sural nerves. Due to newly performed trio-based exome analyses of the affected mother, the affected son and the unaffected brother of the index patient we filtered all common variants which were unique only in the affected family members. With this approach we identified a heterozygous nonsense variant (c.355C > T; p.Gln119*) within the gene *IRF2BPL*, which was confirmed by Sanger sequencing (Fig. 1C).

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2019.09.020.

IRF2BPL mutations were recently reported to cause a range of neurological syndromes, from progressive childhood-onset motor regression with severe speech abnormalities, including anarthria/aphonia, and photosensitive seizures, over to developmental epileptic encephalopathy [2–4]. Dystonia was reported in 9 cases and oculomotor abnormalities, including (horizontal) saccadic speed slowing, were also documented [2–4]. Onset of dystonia was variable. Indeed, in the 4 out of 7 cases reported by Macrogliese et al. dystonic symptoms developed between childhood and adolescence [2]. Remarkably, in one further patient symptoms of neurological degeneration were first noted at 17 years of age [4].

The cases we present here fit well within the phenotypic presentation of *IRF2BPL* mutation syndrome, but also provide important new aspects. First, all previously reported patients, where genetic evaluation of parents was available, harbored *de novo* mutations. In contrast, our cases show that *IRF2BPL* mutations could also manifest later in life and be, thereby, transmitted in an autosomal dominant manner. Importantly, they also reveal marked variability in the onset of symptoms (23 years for index vs early childhood for her son). Second, we believe that mutations at the IRF2BPL gene should be – to date – considered pathognomonic for the remarkably rare syndromic association of dystonia with anarthria/aphonia, slow (horizontal) saccades and seizures. Moreover, our patients had certain features, such as keratoconus (male) and gingival enlargement (index), which may prove to be further useful diagnostic clues. Third, we note the lack of treatment response to pallidal deep brain stimulation in the male patient.

To conclude, *IRF2BPL* mutations should be added to the long list of conditions that cause dystonia with anarthria/aphonia, particularly in cases were slow horizontal saccades and epileptic seizures, including photic myoclonus, are present.

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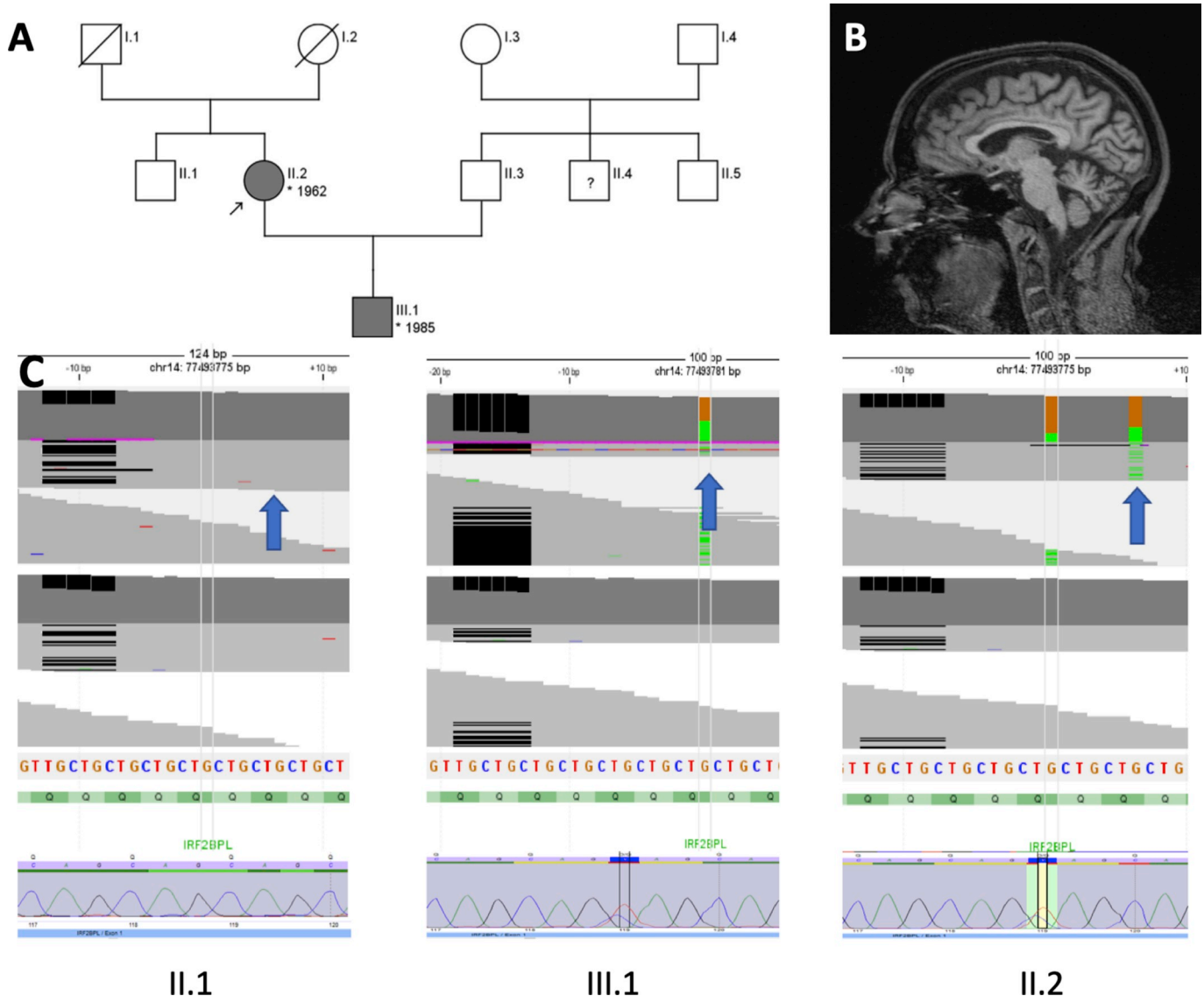

Fig. 1. A. Pedigree of the reported family (previously published and used with permission). **B**. Midsagittal plane of brain MRI of the index patient (II.2) at the age of 56 years demonstrating cerebellar atrophy. **C**. NGS (upper lane: family members; lower lane: wildtype references) and Sanger data of the region of interest of the *IRF2BPL* gene.

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Conflicts of interest

The authors disclose no conflicts of interest regarding this manuscript.

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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.2019.09.020.

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