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Childhood onset progressive myoclonic dystonia due to a de novo *KCTD17* splicing mutation

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Myoclonus-dystonia syndrome (MDS) is a young-onset inherited movement disorder related to mutations in epsilon sarcoglycan (*SGCE*) [1]. In 2015, two families were reported with MDS and a dominant mutation in the potassium channel tetramerization domain containing 17 (*KCTD17*) [2].

Here we report a 19-year-old man born at term after a normal pregnancy and perinatal period. Parents were healthy and non-consanguineous, and originated in Argentina. The boy presented with infantile hypotonia and motor delay followed by generalized dystonic movements (video part A). Non-epileptic myoclonic jerks were recorded on electroencephalographic at age 11 years and he was diagnosed with MDS. Diagnostic work-up for childhood-onset dystonia included metabolic screening in blood and urine, neurotransmitters in cerebrospinal fluid, ophthalmological examination, visual and auditory evoked potentials, cerebral CT and magnetic resonance imaging, all reported as normal.

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Insidious progressive course led to speech deterioration and he needed to repeat himself several times in order to be understood. He had also some difficulties with eating and swallowing solid foods and occasional choking. Fine motor skills were also affected; he could not use pieces of cutlery accurately and preferred to use his hands for self-feeding. He was clumsy for dressing and hygiene, and needed help for some activities. Occasional falls were preceded by bilateral foot inversion. He attended high school with good academic performance.

Examination at 17 years revealed normal growth, intelligence and behavior. He had generalized dystonia with prominent oro-lingual-laryngeal involvement (Video Part B). Action myoclonus was observed in the face, neck and upper limbs. Tendon reflexes were normal and there was distal lower limb hypertonia. After several ineffective drug trials (clonazepam, L-dopa, tetrabenazine, zonisamide, pimozide and trihexyphenidyl), bilateral GPi (Medtronic, Activa PC) was implanted at 18 years. Four months later, a clear improvement was observed, especially in the fluency and intelligibility of his speech, and in tongue and mandibular dystonia (stimulation parameters: 1(−) 4V, 60 ms, 130Hz; 9(−) 3,8V, 60 ms, 130Hz) (video Part C). Burke-Fahn-Marsden rating scale score dropped from 46 to 23.

Whole exome sequencing identified a novel de novo mutation affecting a highly conserved splicing acceptor position of *KCTD17* gene (NM_001282684: c.508-1G > C).

To confirm pathogenicity of the variant, total RNA was isolated from skin biopsy fibroblasts and cDNA was sequenced (see supplementary material). Results showed that c.508-1G > C impaired splicing of exon 5, thus deleting its first 35 nucleotides. As a consequence, a frameshift was generated (p.Leu170Argfs*73) resulting in a truncated protein of 240 aminoacids (Fig. 1). Real-time PCR analysis did not show differences in RNA levels between patient and control fibroblasts, suggesting that RNA stability is not affected by nonsense mediated decay mechanism.

Previously, p.Arg145His mutation in *KCTD17* was detected in two British and German families with childhood onset MDS [1]. A founder allele was reasonably ruled out on the basis of microsatellite analysis of the two pedigrees. Here we confirm allelic heterogeneity by reporting a second mutation in *KCTD17* gene.

KCTD17 is involved in post-synaptic dopaminergic signaling and intracellular calcium homeostasis in the putamen and globus pallidus. KCTD17 dysfunction could impair endoplasmic reticulum calcium signaling, a common mechanism in genetic dystonias.

We present a distinct KCTD17-related phenotype characterized by infantile onset generalized dystonia and motor delay, and a progressive course with prominent speech involvement and upper limb and neck myoclonic jerks. Our patient has some overlapping features with SGCE-related MDS, however he does not meet the proposed diagnostic criteria for MDS [1,2]. Importantly, no associated psychiatric disorder or sensitivity of myoclonus to alcohol was observed. Clinical similarities with THAP1- and KMT2B-related dystonia was also evident, with progressive dystonia affecting the oro-lingual-laryngeal region [4,5].

The excellent response to pallidal stimulation in KCTD17-related MDS was already reported by Mencacci et al. [3]. We emphasize the improvement in orolingual dyskinesia and speech, which is usually non responsive to DBS [6]. Our results underline the relevance of the genotype in predicting DBS response in patients with inherited dystonia [7].

In conclusion, our results confirm that *KCTD17* is a disease causing gene in patients with MDS. The c.508-1G > C splicing mutation identified in our patient changes the sequence and length of KCTD17 protein and affects the C-terminal domain, possibly leading to an early onset and more severe phenotype in our patient compared to initially

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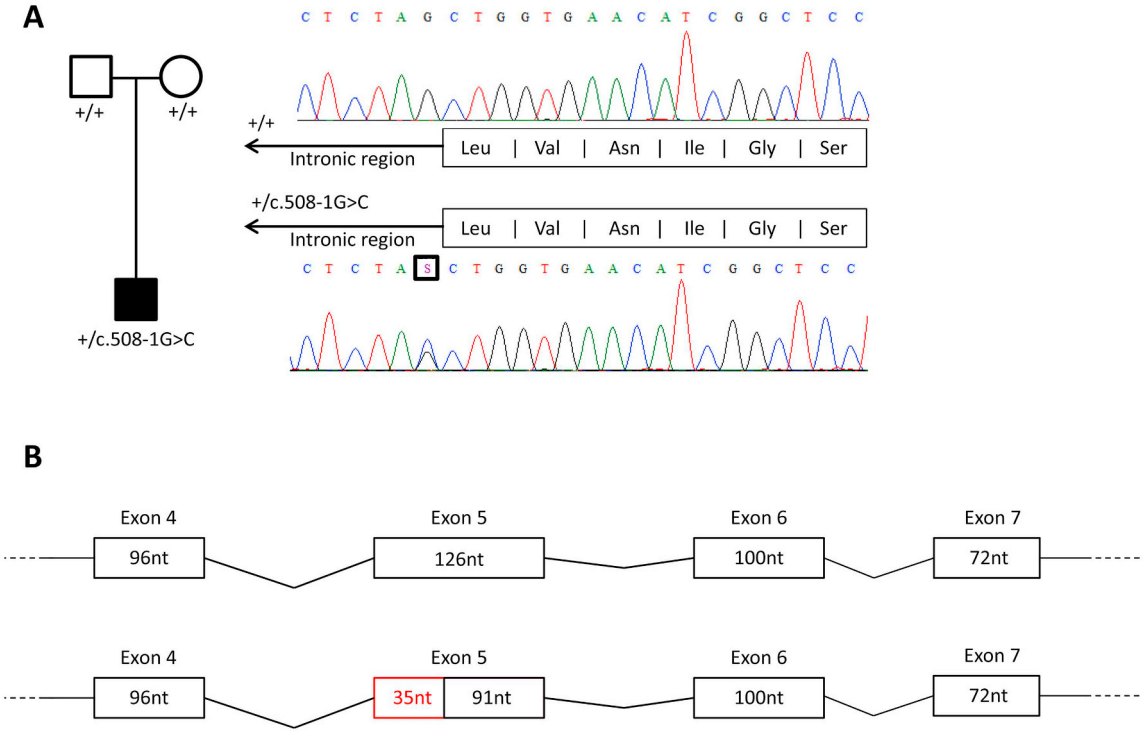

Fig. 1. A. Pedigree and electropherogram of patient and his unaffected parents confirmed the de novo nature of the c.508-1G > C mutation, which is placed upstream the exon 5 of the gene. The variant was not reported neither in general population (ExAC, gnomAD) or specific disease databases (ClinVar, HGMD). Moreover, *in silico* predictors classify the detected mutation as disease causing (Mutation Taster) and potentially affecting splicing (Human Splice Finder 3.0).**B**. cDNA sequencing results showed that c.508-1G > C affects correct splicing of exon 5 deleting the first 35 nucleotides of the exon. This might be due to the activation of a cryptic acceptor site placed inside the wildtype exon. This generates a frameshift which modifies aminoacid sequence and reduces KCTD17 protein length in 81 residues.

reported pedigrees harboring inherited heterozygous missense variants. Importantly, after the submission of our manuscript we were informed by the editor that an independent group had described an 8-years old girl with developmental coordination disorder and myoclonic dystonia harboring a novel KCTD17 variant in an adjacent nucleotide (c.508-2A > T) within the same splice site, also causing a truncating protein [8]. This manuscript had not been published yet at the time we first submitted. Therefore, these two reports independently replicate and confirm the pathogenicity of KCTD17 mutations for MDS.

Contributions

HB, MV, MC and TMR were responsible for the collection and analysis of clinical data. MC was responsible for the video editing. TMR was in charge of deep brain stimulation therapy. AMG participated in the analysis of whole exome sequencing and segregation studies. AMG and SFA performed the analysis of cDNA in fibroblasts. BPD conceived the idea for the study, designed and supervised the study. AMG, AM and BPD participated in the analysis and interpretation of data and drafting of the manuscript. All authors read and approved the final manuscript.

Disclosures

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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.2019.01.004.

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