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A novel *KCTD17* mutation is associated with childhood early-onset hyperkinetic movement disorder

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KCTD17 [potassium channel tetramerization domain (KCTD)-containing protein 17] is a member of KCTD family [1], a group of soluble non-channel proteins involved in a wide spectrum of cell functions, including regulation of cellular proliferation, gene transcription, cytoskeleton organization [2], protein degradation targeting via the ubiquitin-proteasome system, and regulation of G protein-coupled receptors [3]. In particular, KCTD17 contributes to synaptogenesis and brain development via the ubiquitin-proteasome machinery, acting as an adaptor for the CUL3-RING E3 ligase [4]. Protein is highly expressed into the basal ganglia and in particular in the putamen where it participates to endoplasmic reticulum-dependent calcium signalling [5].

To date, only a single rare heterozygous missense pathogenic variant in the *KCTD17* gene (MIM: 616398) has been reported in eight adult individuals from two European families with a new form of autosomal dominant myoclonus-dystonia phenotypically distinct from cases due to SGCE mutations. Indeed, all the affected family members initially showed jerks or a jerky tremor, with mild dystonic features presenting later in life, and increasing severity of symptoms and spreading from the cranio-cervical region to other sites [5].

Here, we describe a heterozygous loss of function *KCTD17* mutation in a patient showing early-onset hyperkinetic movements disorders. This 8-years patient is the first daughter of non-consanguineous Italian healthy parents. She was born with caesarean section at 40 gestational weeks after an uneventful pregnancy. She had a regular adaptation to extra-uterine life. Developmental milestones were acquired with evidence of “clumsiness” in walking, difficulties in learning motor tasks, sequencing sounds and fine-motor problems. A diagnosis of developmental coordination disorder was set at the age of 3 years and physical therapy was started with a global improvement of motor skills. The last movement assessment battery performed (Movement ABC-2 Test) showed a score below the 5th percentile denoting a significant movement difficulty. A non-verbal estimation of fluid intelligence was also administrated (CPM, Coloured Progressive Matrices) showing a cognitive level in the normal-lower range (25–50%).

When she was referred to the Movement Disorder Clinic of Bambino Gesù Children's Hospital, neurological examination revealed a hyperkinetic movement disorder characterized by subtle myoclonic jerks in the upper and lower limbs, with dyskinetic movements and dystonia mainly in the upper limbs with mirror movements and overflow dystonia (Video 1). A diagnosis of complex movement disorder was made predominantly myoclonic (jerky) dystonia with associated dyskinesias. A full diagnostic work-up was performed including blood tests, extensive metabolic screening, hearth ultrasound and brain MRI resulting normal. A polymyography was performed using a standardized protocol (rest, postural maintenance, finger to nose movements, rapid alternating movements of hands, voluntary movements, writing and drawing - Archimedes spiral). EMG activity was recorded with surface electrodes and myoclonus with superimposed dystonia was recorded. Back averaging was performed; myoclonus was of subcortical origin lasting 100–110 ms.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2018.12.001.

We assessed our patient with a deep-sequencing NGS targeted panel comprising 103 known movement disorders related genes (Supplementary Table 1) on DNA extracted from peripheral blood. We identified a novel heterozygous variant (c.508-2A > T) affecting the acceptor splice site of exon 5 in the *KCTD17* gene. This variant is not reported in any publicly available human variation resources (i.e. dbSNP146, 1000 Genomes, Exome Aggregation Consortium (ExAC), NHLBI Exome Sequencing Project (ESP) Exome Variant Server and gnomAD) and is predicted to be damaging by different available bioinformatics tools (i.e Mutation Taster and Human Splicing Finder). Patient's parents resulted wild-type, suggesting a *de novo* origin of the variant. Other known genes including *SGCE* gene (*DYT11*), and those related to hereditary choreas (*NKX2.1*, *ADCY5*, *MBIP*, *PDE10A*, *PDE2A* and *SLC16A2*) were sequenced and no pathogenic variants were identified. To investigate if the mutant allele is expressed and to map the alternative splice acceptor site, RT-PCR was performed on RNA isolated from cultured fibroblasts (Fig. 1A–C). By 2% agarose gel we observed a single band of 343bp in a healthy control subject and the presence of a second smaller band of 308bp in the index patient (Fig. 1B). Sanger sequencing showed that this second band corresponds to an aberrantly spliced *KCTD17* transcript from the mutant allele, in which an alternative acceptor splice site 34bp downstream of the mutated site is used, resulting in the skipping of the first 35 nucleotides of exon 5. This results in a shift of the reading frame and in a premature stop codon introduction in exon 7 (Fig. 1C). This heterozygous mutation induced about 50% (2 fold) reduction of KCTD17 protein expression levels in

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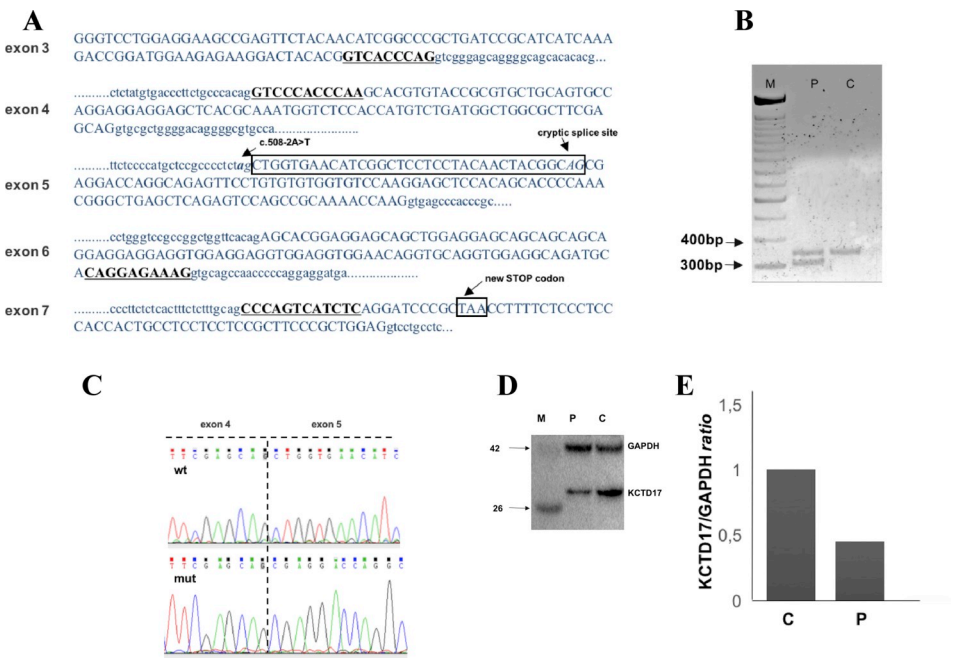

Fig. 1. Legend *KCTD17* analysis. **Panel A**: genomic DNA sequence of *KCTD17*. Intron sequences are in lowercase letters, exon sequences are in uppercase. The 5'-3′ sequences of primers used to perform RT-PCR are in bold and underlined. Arrowheads indicate the position of the heterozygous variant (c.508-2 A > T), the cryptic splice site activated in the mutant allele and the new stop codon. The hollow rectangle in the exon 5 sequence includes the first 35bp of exon 5 skipped from mutated transcript. **Panel B**: RT-PCR of *KCTD17* mRNA between exons 3 and 7 shows the presence of a 343bp band in a healthy control (C), as expected, and a second band of 308bp in the patient (P); A marker of 1 Kb is indicated as M. **Panel C**: electropherogram confirms the skipping of the first 35bp of exon 5 in mutant allele. **Panel D**: western blot showing KCTD17 and GAPDH expression in fibroblasts from patient (P) and healthy control (C). M indicates the marker. **Panel E**: quantitative analysis of KCTD17 protein expression shows a 50% reduction in patient (P) compared to control (C). Data are expressed as KCTD17/GAPDH ratio.

patient's fibroblasts when compared to wild-type control (Fig. 1D and E). To assess the stability of the mutant *KCTD17* mRNA we performed qPCR (see Methods in Supplementary data). We observed no differences in *KCTD17* mRNA expression levels in our patient compared with those of normal control suggesting that the loss of protein levels is due to reduced post-translational protein stability.

Herein, to our knowledge, we describe the first independent confirmation of the pathogenic role of *KCTD17* mutations as a genetic cause of myoclonus-dystonia of *KCTD17* after the original publication by Mencacci et al. [5]. Based on those cases already described, the phenotype of *KCTD17*, is consistent with a clinical diagnosis of myoclonus-dystonia, but is distinct in many ways from the usual phenotype of subjects with *SGCE* mutations. Dystonia is the main sign in the clinical picture and shows a progressive course over time while myoclonus, despite being the presenting symptom in most cases, is overall mild and not as disabling as in *SGCE*-mutated subjects. Our case seems to partially confirm the *KTCD17* phenotype. Indeed, myoclonus is mild and is not disabling, while dystonia is presenting since the beginning in the history of our patient, whereas in cases described by Mencacci et al. [5] dystonia occurred later in the life. Moreover, our patient had an history of developmental delay classified as "motor coordination disorder". Her difficulties in fine and gross motor skills, some years before the development of current clinical picture, as well as her low-normal range in cognitive level. We hypothesize that these additional clinical features along together with new genetic mechanism observed (haploinsufficiency), expand the phenotype of *KTCD17* related disorders and suggest a role of this gene in normal developing brain.

Authors' contributions

Federica Graziola, study concept and design, writing the first draft.

Fabrizia Stregapede, study concept and design, writing the first draft, acquisition of the data.

Lorena Travaglini, study concept, acquisition and interpretation of the data.

Giacomo Garone, acquisition and interpretation of the data.

Margherita Verardo, acquisition and interpretation of the data.

Luca Bosco, acquisition and interpretation of the data.

Stefano Pro, acquisition and interpretation of the data.

Enrico Bertini, study concept, critical revision of the manuscript.

Paolo Curatolo, critical revision of the manuscript.

Federico Vigevano, supervision and critical revision of manuscript.

Alessandro Capuano, study concept, interpretation of the data, critical revision of the manuscript.

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Informed consent

Parents gave their written informed consent for video publication including online publication and dissemination.

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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.2018.12.001.

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