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De-novo KMT2B mutation in a consanguineous family: 15-Year follow-up of an Afghan dystonia patient

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According to recent statistics from the United Nations High Commissioner for Refugees (https://www.unhcr.org/figures-at-a-glance.html), there are > 25 million refugees worldwide which represents the highest levels of displacement on record. Many refugees from the Middle East, especially Syria and neighbouring countries, arrive in Europe. These countries are known to have relatively high rates of consanguinity leading to growing awareness of recessive movement disorders that frequently lack a positive family history and are usually caused by biallelic mutations. On the other hand, advances in large-scale mutation testing have confirmed another important cause of genetic disease in patients without a positive family history, i.e. heterozygous de-novo mutations, which have been found to account for a striking 68% of patients with mutations causing dominant diseases [1].

We here report a 31-year-old female patient of Afghan origin and daughter of consanguineous parents. The patient gave written permission to distribute the videos for scientific purpose including online publication. She developed gait problems at the age of 7 years. These were attributed by the family to two car accidents followed by unspecified operations of the feet in Afghanistan, as well as to the exhaustive exercise that the patient underwent when she had to walk very long distances as a refugee. Family history was negative. Upon neurologic examination in Germany, aged 15 years, the patient showed generalized dystonia, predominantly in the lower extremities and trunk, initially largely sparing the face and neck (Video, Segment 1). Speech was limited due to reduced speech production and dysarthria. The dystonia continuously worsened including the development of severe cervical dystonia until the age of 31 years when she presented to us (Video, Segment 2). Although not formally tested, the patient appeared to suffer mild intellectual disability including dyscalculia. The remainder of the neurological examination was normal. Treatment with botulinum toxin and trihexyphenidyl resulted in mild symptomatic improvement; the patient declined to undergo deep brain stimulation. The patient gave written informed consent and the local ethics committee approved the study.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2019.03.018

Panel sequencing excluded rare variants in *TOR1A, THAP1, GNAL, ANO3, GCH1*, and *SGCE* but disclosed a heterozygous variant in the *KMT2B* gene, resulting in a frameshift and premature protein truncation (chr19:36216157GGCCTGAGTGT > G; c.3568_3577delCTGAGTGTGC; p.Leu1190fs161X), which was absent in both parents and thus occurred de novo. To our knowledge, this variant has not previously been reported and is absent from large databases such as GnomAD (genome aggregation consortium at https://gnomad.broadinstitute.org/region/19-36216147-36216167). Heterozygous *KMT2B* mutations have recently been identified as a form of early-onset, generalized dystonia with dysmorphic features and mild intellectual disability in a subset of patients [2,3] but otherwise broad phenotypic overlap with isolated dystonia such as DYT-*TOR1A*.

To investigate the effect of the frameshift mutation in Exon 11 (of 37), we tested for expression of *KMT2B*, *TOR1A*, and *THAP1*, as alterations of expression of all three genes have previously been suggested in *KMT2B* mutation carriers [2]. We used cDNA generated from a blood sample and fibroblast culture of the patient, included another recently reported in-frame mutation carrier [4] and compared expression to four (blood) and two (fibroblast) unrelated controls, respectively, using four different reference genes (*ACTB, YWHAZ, FLAD1, FPGS*). We, indeed, detected a significantly reduced expression of *KMT2B* in both patients' fibroblasts (Figure 1C). This observation, along with the previous description of whole *KMT2B* deletions in dystonia patients [2], clearly suggests a loss-of-function mechanism of *KMT2B* in dystonia. It may be hypothesized that the reduction of mRNA levels in our patient with the frameshift mutation is due to nonsense-mediated mRNA decay (NMD). However, since the same reduction was also observed in the patient with a non-frameshift deletion, this is a rather unlikely mechanism in this case. Further, we observed reduced expression of *THAP1* and *TOR1A* in both patients in blood (Figure 1D) but not in fibroblasts (data not shown). The presumably downstream ex-

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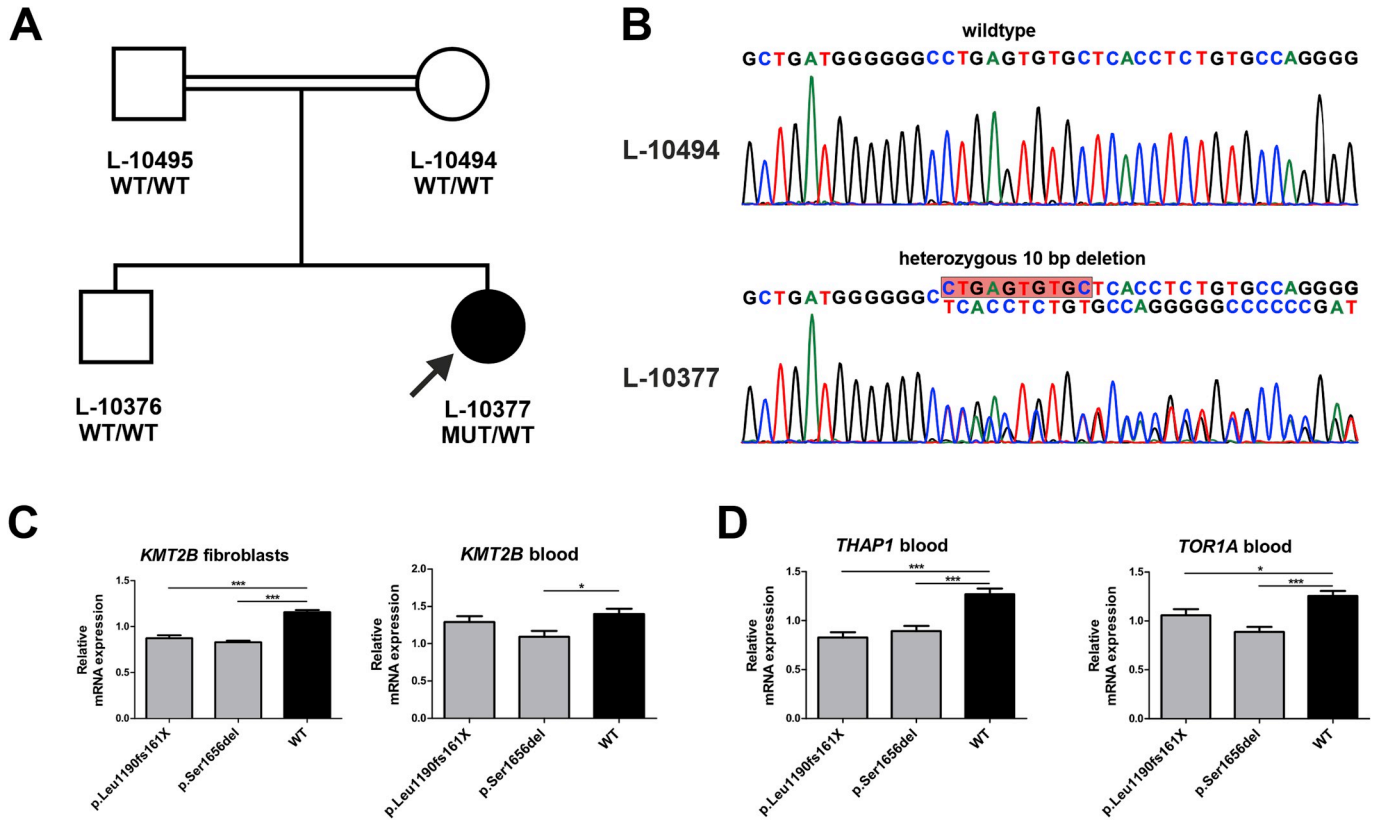

Fig. 1. *Genetic findings in a consanguineous family with a de-novo KMT2B mutation.* **(A)** Pedigree of the family. The parents are second degree cousins (indicated by the double line). Sample identifier (L code) and genetic status (WT: wildtype; MUT: mutation) is given below the symbols for each individual. The index patient (highlighted by an arrow) is the only affected (black filled symbol) in the family. **(B)** Electropherogram of Sanger sequencing in the mother and the patient. The ten heterozygously deleted base pairs are boxed. **(C)** Results of expression analysis of *KMT2B* in the index patient (p.Leu1190fs161X) and a recently reported *KMT2B* mutation carrier (p.Ser1656del) compared to the mean of four controls (in blood, left panel) and two controls (in fibroblasts, right panel). The mean expression with the standard error of the mean (SEM) normalized to four different reference genes is displayed. All experiments were independently carried out four times. **(D)** Results of expression analysis of *THAP1* (left panel) and *TOR1A* (right panel) in the two *KMT2B* mutation carriers compared to the mean of four controls in blood. The mean expression and SEM normalized to four different reference genes is displayed. For statistical analysis, a one-way ANOVA was performed using Bonferroni post-hoc test. One asterisk indicates $p < 0.05$; three asterisks indicate $p < 0.001$.

pressional changes of *TOR1A* and *THAP1* might be mediated by altered density of chromatin packaging due to reduced histone-methylation in *KMT2B* mutation carriers and thus impact on the expressional activity of *THAP1* and *TOR1A*.

In conclusion, although the clinical presentation of our patient is fully in keeping with DYT-*KMT2B*, environmental or recessive causes of dystonia had primarily been considered based on patient history. Thus, consanguinity should not distract from searching for de-novo mutations causing dominant movement disorders.

Authors' roles

Christine Klein: Organization (Research project), Review and Critique (Statistical Analysis), Writing of the first draft (Manuscript).

Hauke Baumann: Execution (Research project), Design (Statistical Analysis), Review and Critique (Manuscript).

Luisa Olschewski: Execution (Research project), Execution (Statistical Analysis), Review and Critique (Manuscript).

Henrike Hanssen: Execution (Research project), Review and Critique (Statistical Analysis), Review and Critique (Manuscript).

Alexander Münchau: Organization (Research project), Review and Critique (Statistical Analysis), Review and Critique (Manuscript).

Andreas Ferbert: Organization, Execution (Research project), Review and Critique (Statistical Analysis), Review and Critique (Manuscript).

Norbert Brüggemann: Execution (Research project), Review and Critique (Statistical Analysis), Review and Critique (Manuscript).

Katja Lohmann: Conception (Research project), Review and Critique (Statistical Analysis), Writing of the first draft (Manuscript).

Financial disclosure/Conflict of interest

None of the authors have any conflicts of interest to declare related to this work.

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