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An atypical case of early-onset dystonia with a novel missense variant in *KMT2B*

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Recently, lysine-specific methyltransferase 2B (*KMT2B*) was reported as a novel gene responsible for early-onset generalized dystonia. Typically, *KMT2B*-associated dystonia had limb symptoms at onset and gradually progressed to generalized dystonia with cervical, cranial, or laryngeal involvement [1]. Here, we report an atypical case of isolated dystonia with only lower-limb and trunk symptoms with a novel de novo mutation of p. Arg1597Trp (NP_055542.1). Consent for publication (including online publication) was provided by the patient's parents.

This 19-year-old female patient of Chinese Han was the only child of her heathy non-consanguineous parents. The patient first presented with involuntary movement in the right toes at the age of 4. She also displayed dystonic gait on the right side during walking. The disease progressed slowly, and at the age of 15, she had her trunk affected. Slight dystonic posturing of her trunk was observed (Supplementary video). However, there was no evidence of cervical, oromandibular, or laryngeal involvement. Also, no additional neurological features including intellectual impairments, microcephaly, seizures and spasticity were found, nor any systemic features. On physical examination, the patient developed well. She may have had a mildly bulbous nasal tip (video), reported previously in *KMT2B*-related disease [1], but had no other or obvious dysmorphic features. Brain MRI was also unremarkable.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2018.09.020.

Genetic testing was performed in the proband by a gene panel containing over 4000 known disease-associated genes (Supplementary materials). The mean depth of the sequencing was 137.4x and the coverage was 99.2%. The percentage of the target region with mean depth > 20x was 98.6%. After the variants screening, a novel missense variant (c.4789C > T, chr19-36220069; p. Arg1597Trp) in *KMT2B* was detected with depth of 93X. Sanger sequencing was performed in the proband and her parents and found the variant de novo (Fig. 1 A, B, C). The family refused to take a paternity test and thus, de novo status has not been formally proven. The variant was absent from GenomeAD (http://gnomad.broadinstitute.org) and ExAC (http://exac.broadinstitute.org), and was predicted to be disease-causing by Mutationtaster (http://www.mutationtaster.org). The variant was further investigated in 200 seniors with no neurological diseases from the community by Sanger sequencing and was not detected. According to the ACMG guideline, the variant was rated as likely pathogenic: one PS2 (de novo variant) and one PM2 (absent from population databases) [2].

The disclosed variant occurred in the residue located on the surface of the PHD-like domain. The domain works together with PHD1 to stabilize the N terminal fragments of *KMT2B* through intramolecular interaction with C terminal fragments [3]. In comparison with the wild type, both hydrophobicity and charge of the residue were altered (http://www.cmbi.ru.nl/hope/) (Fig. 1 D, E). Consequently, the intramolecular interaction may be disturbed. Notably, several *KMT2B* variants in reported patients and families are clustered in the PHD-like domain (Fig. S1, Table S2).

Of note, the patient appeared to have less severe clinical features than most reported cases. Though the patient finally progressed to generalized dystonia 11 years after onset, she had no cervical, oromandibular or laryngeal dystonia. It is possible that the patient may develop dystonia in these parts in the future, but duration until upper body involvement would be much longer than in the reported cases (mean 4 and maximum 11 years after onset [1,4,5]). Further, the patient's symptoms were relatively mild because some reported cases with involvement of trunk and lower extremities have become wheelchair-bound at adolescent [1,6]. Other DYT-*KTM2B* cases without cranial, cervical or laryngeal involvement have been described recently, but many of these had mild intellectual impairments or microcephaly [5]. Our patient had no additional neurological or systemic manifestations. Finally, while hypointensity of the globus pallidi or white matter abnormalities on MRI were observed in some cases [1,7], no positive neuroimaging results were found in our patient.

KMT2B dystonia is thus clinically heterogeneous. Different variants in *KMT2B* can lead to distinctive clinical symptoms, even individuals carrying identical variant may have diverse clinical manifestations. Genotype has a remarkable but limited influence on clinical manifestations in *KMT2B* dystonia. Other accompanied genetic and epigenetic modifications, as well as the environment, also play an important role.

In conclusion, the case we reported expanded the clinical spectrum of *KMT2B* dystonia and also demonstrated the clinical heterogeneity of *KMT2B* dystonia.

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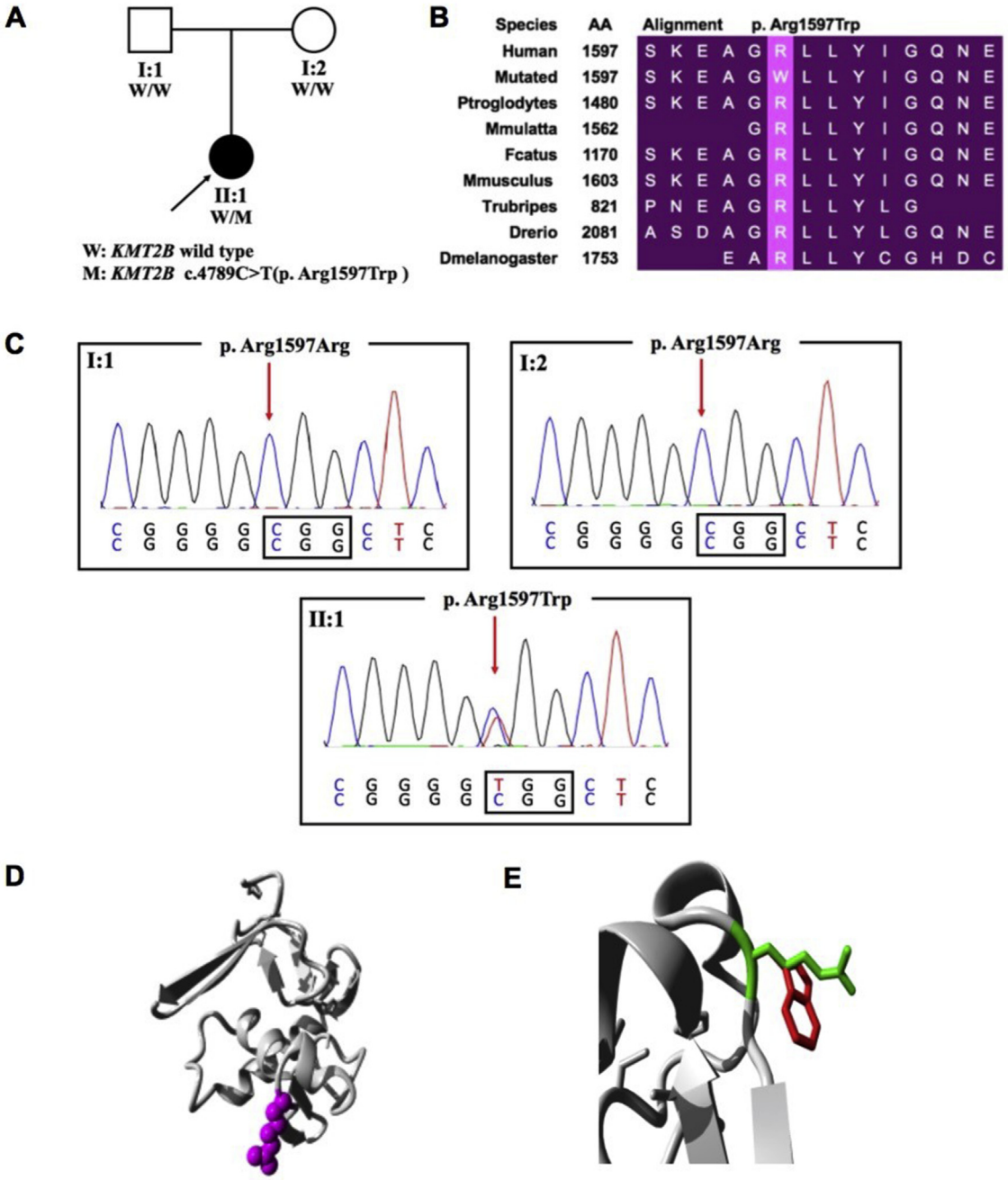

Fig. 1. Pedigree chart, results of Sanger sequencing and bioinformatics analyses. (A) Pedigree chart. The affected individual was portrayed in solid symbol. The arrow indicated the proband (II:2). Genotypes of the family members were shown below the symbols.
(B) Conservation analysis of the variant residue.
(C) Sanger sequences of the mutation in *KMT2B* in the proband and her parents. The variant site detected in the proband (c.4789C > T, chr19-36220069; p. Arg1597Trp) was indicated by an arrow, while there was no abnormality detected at the same site (also indicated by an arrow) in the proband's parents.
(D) Overview of the protein. The protein is illustrated in grey, the side chain of the variant residue was shown as small balls highlighting in magenta.
(E) Comparison of the side chains in the wild type and variant residue. The protein is illustrated in grey, and the wild-type and variant side chains were highlight in green and red respectively. The variant from Arg to Trp at the position 1597 turned the charge of the residue from positive to neutral, and at the same time made the residue more hydrophobic than the wild-type. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Conflicts of interest

The authors report no conflicts of interest.

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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.2018.09.020.

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