Parkinsonism and Related Disorders 63 (2019) 227–228

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Correspondence

An inherited *KMT2B* duplication variant in a Chinese family with dystonia and/or development delay

Dear editor

Dystonia is a hyperkinetic movement disorder characterized by sustained or intermittent muscle contractions causing repetitive twisting movements and disabling postures [1]. Since 2016, *KMT2B*, a gene encoding lysine methyltransferase 2B, has been reported to be an important cause of childhood-onset progressive generalized dystonia with or without pre-existing development delay [2–4]. The presence of both symptomatic and asymptomatic carriers and relatives suggests incomplete penetrance, and symptomatic parents appear to have later onset dystonia with fewer systemic features than their children [5,6]. Most *KMT2B* variants reported are de novo. To our knowledge, there are no previous reports of multiple patients with the same *KMT2B* variant with dystonia and development delay in one family. However, there is evidence of other relatives within the family having isolated development delay without dystonia. We describe a Chinese family with an inherited *KMT2B* duplication variant.

The family gave written informed consent and the local ethics committee approved the study. The proband (III-1), who is a 10-year-old boy, is the second child of a nonconsanguineous marriage with a healthy father (II-2) and was delivered at term after an uneventful pregnancy. He presented with moderate-to-severe global psychomotor delay. His movement disorder started at the age of 2 years, 6 months with progressive action-induced lower limb and trunk dystonia, which rapidly spread to muscles of the arms, neck and tongue; however, he could walk without assistance. The symptoms were worsened by fever or respiratory infections. At the age of 9 years, dysphonia was causing progressive speech impairment, and the patient was unable to walk independently or talk clearly. There was no evidence of abnormal facial features, cerebellar signs, or Babinski sign. Brain MRI, electroencephalogram and metabolism results were normal. Both his mother (II-3) and older sister (III-2) displayed motor development delay before 3 years of age, with moderate-to-severe intellectual disability and dysmorphic features of short stature, broad nasal base and bulbous nasal tip but without dystonia until 42 and 14 years of age, respectively. The 60-year-old maternal grandmother (I-2) has the same clinical manifestations as her daughter. The mother's younger brother (II-1) suffered from the same moderate-to-severe global psychomotor delay and dystonia as the proband, but he can walk independently today at 37 years of age (Fig. 1).

Whole-exome sequencing was conducted on the proband's father and four patients, except for the mother's younger brother (individuals subjected to exome sequencing were highlighted with an asterisk in Fig. 1). Whole-exome sequencing was performed on DNA from peripheral blood. All human exons and the 50 bp bases in their adjacent introns were captured by a SeqCap EZ Med Exome Enrichment Kit (Roche NimbleGen). The DNA library was generated by post-capture amplification and purification and then sequenced by the Illumina HiSeq sequencing platform. Sequence data alignments to the human reference genome (hg19) and variant calls were made using NextGene V2.3.4 software to obtain the coverage and mean read depth of the target regions. The mean read depth was 151.24 × and even reached 20 × for 97.95% of the target sequences. Meanwhile, annotation information, including the conservation of nucleotide bases and amino acids, predictions of biological functions, frequency of the normal populations (1000 Genomes Project, ExAC, dbSNP database and locus-specific databases) and data from HGMD, Clinvar and OMIM, was investigated using NextGene V2.3.4 and scripts from our own lab. We used Sanger sequencing to validate the probable pathogenic variations. An inherited heterozygous duplication variant at c.1656dupC (p.Lys553Glnfs*46) of *KMT2B* was identified in this family (Fig. 1), which was reported as the disease-causing variant [7]. No variant was found in other candidate genes.

KMT2B is an important epigenetic regulator gene that is essential for normal development. It is highly expressed in both embryonic and adult human brains. To our knowledge, 43 different KMT2B variants have been reported in 48 patients with early-onset progressive dystonia, which typically begins in the lower limbs and occurs with or without other neurological or systemic manifestations [4–7].

To the best of our knowledge, our KMT2B variant family is the first family reported with two male patients with dystonia and development delay, as well as three female patients with isolated development and growth retardation without dystonia until juvenile to older ages. This is the first example of a recurrent KMT2B variant. The various phenotypes may be associated with gender or varying penetrance. Levodopa and clonazepam therapies were initiated in our proband without beneficial effect. He will undergo deep brain stimulation, which showed good clinical responses in KMT2B-dystonia5. Our findings expand the clinical spectrum of KMT2B. Future investigations are needed to elucidate the pathomechanism of the KMT2B variant causing dystonia and development delay.

Financial disclosures/conflicts of interest concerning the research related to the manuscript

None for all authors.

Acknowledgments

We are grateful to the family members for their cooperation and permission to publish this case. This work was funded by The National Key Research and Development Program of China (No. 2016YFC1306203).

https://doi.org/10.1016/j.parkreldis.2018.08.021
Received 23 May 2018; Received in revised form 29 July 2018; Accepted 28 August 2018

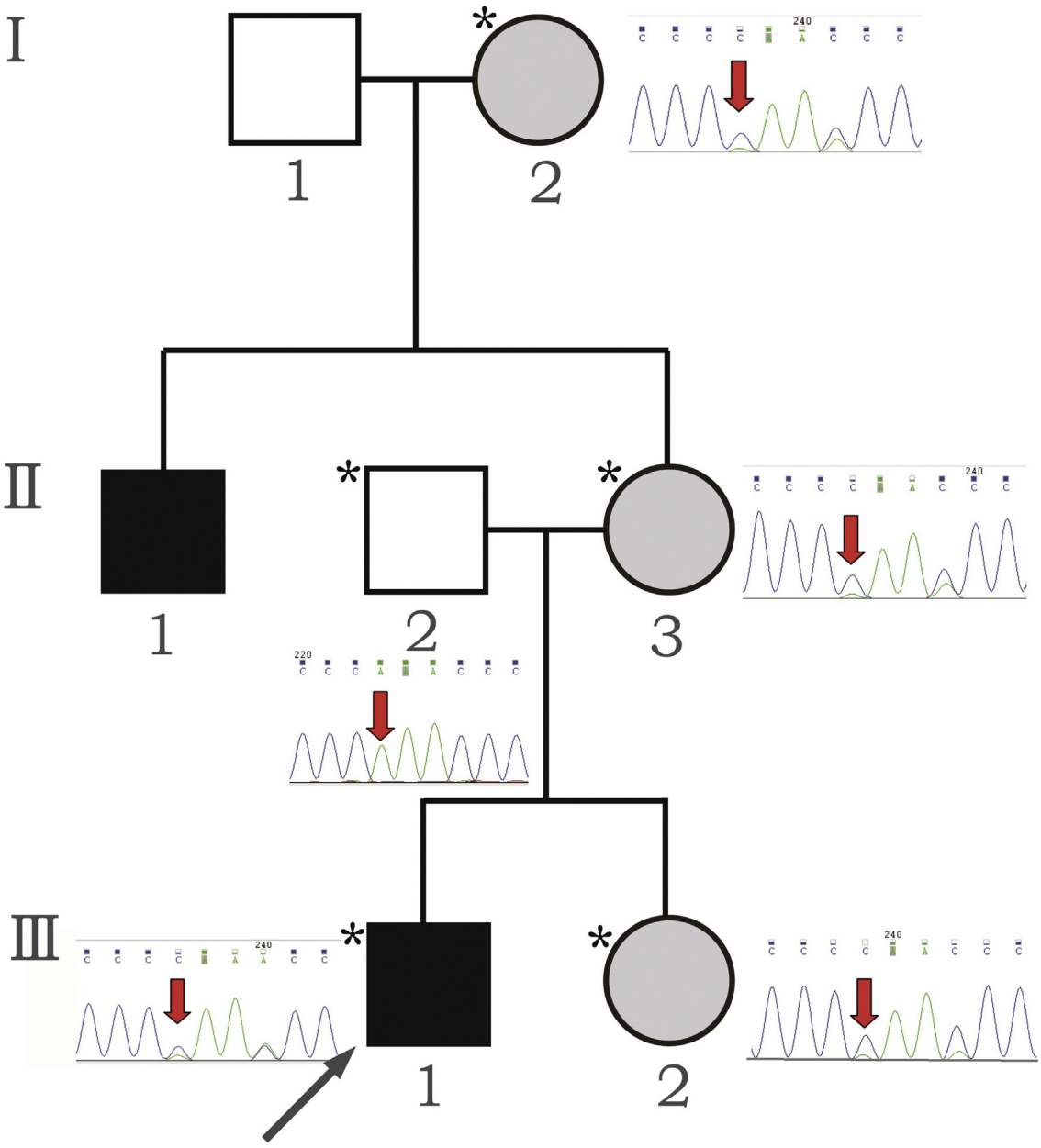

Fig. 1. Family pedigree. The proband is depicted in arrow pointing. Two male patients having dystonia with development delay are in black. Three female patients having isolate development and growth retardation without dystonia are in gray. Sequencing chromatograms demonstrate the inherited duplication variant c.1656dupC (p.Lys553Glnfs*46) of *KMT2B* on the proband's father and four patients (individuals were highlighted with an asterisk).

References

[1] D.E. Lumsden, H. Gimeno, J.P. Lin, Classification of dystonia in childhood, Park. Relat. Disord. 33 (2016) 138–141.
[2] M. Zech, S. Boesch, E.M. Maier, et al., Haploinsufficiency of KMT2B, encoding the lysine specific histone methyltransferase 2B, results in early-onset generalized dystonia, Am. J. Hum. Genet. 99 (2016) 1377–1387.
[3] J.F. Baizabal-Carvallo, M. Alonso-Juarez, Generalized dystonia associated with mutation in the histone methyltransferase gene KMT2B (DYT28) and white matter abnormalities, Park. Relat. Disord. 49 (2018) 116–117.
[4] V. Faundes, W.G. Newman, L. Bernardini, et al., Histone lysine methylases and demethylases in the landscap of human developmental disorders, Am. J. Hum. Genet. 102 (2018) 175–187.
[5] K.M. Gorman, E. Meyer, M.A. Kurian, Review of the phenotype of early-onset generalised progressive dystonia due to mutations in KMT2B, Eur. J. Paediatr. Neurol. 22 (2018) 245–256.
[6] E. Meyer, K.J. Carss, J. Rankin, et al., Mutations in the histone methyltransferase gene KMT2B cause complex early-onset dystonia, Nat. Genet. 49 (2017) 223–237.
[7] T. Kawarai, R. Miyamoto, E. Nakagawa, et al., Phenotype variability and allelic heterogeneity in KMT2B-Associated disease, pii: S1353-8020, Park. Relat. Disord. 18 (2018) 30137–30138 Epub ahead of print).

Lifang Dai, Changhong Ding[*,1], Fang Fang[**,1]
Department of Neurology, Beijing Children's Hospital, Capital Medical University, National Center For Children's Health, China, Nanlishi Road No 56, Xi Strict, Beijing, 100045, China
E-mail addresses: dingchanghong@bch.com.cn (C. Ding), fangfang@bch.com.cn (F. Fang)

[*] Corresponding author.
[**] Corresponding author.
[1] These authors contributed equally to this work.