KMT2B-related dystonia

KMT2B-related dystonia is a recently discovered hereditary dystonia that mostly occurs in childhood. This dystonia usually progresses to generalized dystonia with cervical, cranial, pharynx, and larynx involvement.

A study summarizes genotype-phenotype features and deep brain stimulation (DBS) efficacy observed with KMT2B-related dystonia patients in China.

Li et al. identified 20 patients with KMT2B variations from dystonia samples with a gene panel and whole exome sequencing. Genetic, clinical, and treatment analyses of these patients with KMT2B mutations were further conducted.

They summarized the genotype and phenotypic characteristics of KMT2B-related patients in China, including 16 sporadic patients and 3 pedigrees (including 4 patients). Thirty-five percent (7/20) of patients had been published previously. The age of onset was between 1 month and 24 years (average 6.90 ± 5.72 years). Sixty-five percent (13/20) of patients had onset from lower limbs. Upper limbs or larynx accounted for 15% (3/20) and 20% (4/20) of patients, respectively. In the same family, male patients tended to have more severe symptoms than female patients. Carriers of KMT2B variants may present with nonmotor symptoms without dystonia. Abnormal endocrine metabolism could also be seen in our patients, including advanced bone age that had never been reported previously. Nine of the patients underwent DBS surgery. The mean follow-up time was 4.9 (range 1.3-16) months after DBS, and perceptible improvement of clinical symptoms was observed.

The genotypic and phenotypic spectra of Chinese KMT2B-related dystonia patients were further expanded. DBS surgery might be the preferred option for severe KMT2B-related dystonia patients till now [1].

Histone lysine methylation, mediated by mixed-lineage leukemia (MLL) proteins, is now known to be critical in the regulation of gene expression, genomic stability, cell cycle and nuclear architecture. Despite MLL proteins being postulated as essential for normal development, little is known about the specific functions of the different MLL lysine methyltransferases. Here we report heterozygous variants in the gene KMT2B (also known as MLL4) in 27 unrelated individuals with a complex progressive childhood-onset dystonia, often associated with a typical facial appearance and characteristic brain magnetic resonance imaging findings. Over time, the majority of affected individuals developed prominent cervical, cranial and laryngeal dystonia. Marked clinical benefit, including the restoration of independent ambulation in some cases, was observed following deep brain stimulation (DBS). These findings highlight a clinically recognizable and potentially treatable form of genetic dystonia, demonstrating the crucial role of KMT2B in the physiological control of voluntary movement [2].

Case reports

A 28-year-old woman developed generalized dystonia with developmental delay, microcephaly, short stature, and cognitive decline. She was diagnosed with KMT2B- related dystonia using whole-exome sequencing with a heterozygous frameshift insertion of c.515dupC (p.T172fs) in the KMT2B gene. Oral

medications and botulinum toxin injection were not effective. The dystonia markedly improved with bilateral pallidal DBS (the Burke-Fahn-Marsden Dystonia Rating Scale score was reduced from 30 to 5 on the dystonia movement scale and from 11 to 1 on the disability scale), and she could walk independently. From this case, we suggest that bilateral globus pallidus internus DBS can be an effective treatment option for patients with KMT2B-related generalized dystonia [3].

1)
Li XY, Dai LF, Wan XH, et al. Clinical phenotypes, genotypes, and treatment in Chinese dystonia patients with KMT2B variants [published online ahead of print, 2020 Jun 9]. Parkinsonism Relat Disord. 2020;77:76-82. doi:10.1016/j.parkreldis.2020.06.002
2)
Meyer E, Carss KJ, Rankin J, Nichols JM, Grozeva D, Joseph AP, Mencacci NE, Papandreou A, Ng J, Barral S, Ngoh A, Ben-Pazi H, Willemsen MA, Arkadir D, Barnicoat A, Bergman H, Bhate S, Boys A, Darin N, Foulds N, Gutowski N, Hills A, Houlden H, Hurst JA, Israel Z, Kaminska M, Limousin P, Lumsden D, McKee S, Misra S, Mohammed SS, Nakou V, Nicolai J, Nilsson M, Pall H, Peall KJ, Peters GB, Prabhakar P, Reuter MS, Rump P, Segel R, Sinnema M, Smith M, Turnpenny P, White SM, Wieczorek D, Wiethoff S, Wilson BT, Winter G, Wragg C, Pope S, Heales SJ, Morrogh D; UK10K Consortium.; Deciphering Developmental Disorders Study.; NIHR BioResource Rare Diseases Consortium., Pittman A, Carr LJ, Perez-Dueñas B, Lin JP, Reis A, Gahl WA, Toro C, Bhatia KP, Wood NW, Kamsteeg EJ, Chong WK, Gissen P, Topf M, Dale RC, Chubb JR, Raymond FL, Kurian MA. Mutations in the histone methyltransferase gene KMT2B cause complex early-onset dystonia. Nat Genet. 2016 Dec 19. doi: 10.1038/ng.3740. [Epub ahead of print] PubMed PMID: 27992417.
3)
Mun JK, Kim AR, Ahn JH, et al. Successful Pallidal Stimulation in a Patient with KMT2B-Related Dystonia. J Mov Disord. 2020;13(2):154-158. doi:10.14802/jmd.19087