





CLINICAL REPORT

A novel synonymous *KMT2B* variant in a patient with dystonia causes aberrant splicing

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Funding information

Paul Ainsworth Family Foundation

Abstract

Background: Heterozygous *KMT2B* variants are a common cause of dystonia. A novel synonymous *KMT2B* variant, c.5073C>T (p.Gly1691=) was identified in an individual with childhood-onset progressive dystonia.

Methods: The splicing impact of c.5073C>T was assessed using an in vitro exon-trapping assay. The genomic region of *KMT2B* exons 23–26 was cloned into the pSpliceExpress plasmid between exon 2 and 3 of the rat *Ins2* gene. The c.5073C>T variant was then introduced through site-directed mutagenesis. The *KMT2B* wild-type and c.5073C>T plasmids were transfected separately into HeLa cells and RNA was extracted 48 hours after transfection. The RNA was reverse transcribed to produce cDNA, which was PCR amplified using primers annealing to the flanking rat *Ins2* sequences.

Professor Marina Kennerson and Dr Kishore Raj Kumar should be considered joint senior author.

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Results: Sanger sequencing of the PCR products revealed that c.5073C>T caused a novel splice donor site and therefore a 5-bp deletion of *KMT2B* exon 23 in mature mRNA, leading to a coding frameshift and premature stop codon (p.Lys1692AsnfsTer7).

Conclusion: To our knowledge, this is the first report of a *KMT2B* synonymous variant associated with dystonia. Reassessment of synonymous variants may increase diagnostic yield for inherited disorders including monogenic dystonia. This is of clinical importance, given the generally favourable response to deep brain stimulation for *KMT2B*-related dystonia.

KEYWORDS

deep brain stimulation, dystonia, *KMT2B*, splicing, synonymous

1 | INTRODUCTION

Dystonia is characterised by involuntary muscle contractions and abnormal postures (Albanese et al., 2013). Heterozygous pathogenic variants in *KMT2B* (19q13.12; NM_014727.2, OMIM:# 606834), encoding lysine-specific histone methyltransferase 2B, cause a severe form of childhood-onset dystonia (DYT28; OMIM:#617284) (Meyer et al., 2017; Zech et al., 2016). Symptom onset is typically in the first decade, initially presenting as a lower-limb dystonia that progresses to a generalised dystonia with cranio-cervical involvement (Meyer et al., 2017; Zech et al., 2016).

A variety of *KMT2B* loss-of-function pathogenic mechanisms have been reported for *KMT2B*-related dystonia, including 19q13.11-19q13.12 microdeletions encompassing *KMT2B*, nonsense mutations, frameshift mutations, splice site mutations and missense mutations.^{2,3} *KMT2B* mutations have also recently been implicated in cerebellar ataxia (Damasio et al., 2021) and neurodevelopmental delay (Cif et al., 2020; Dai et al., 2019; Faundes et al., 2018; Reuter et al., 2017). To our knowledge, no disease-causing synonymous *KMT2B* variants have previously been reported.

We developed an in vitro splicing assay to assess a novel synonymous *KMT2B* variant, NM_014727.2:c.5073C>T [chr19:35,730,122C>T (hg38)], which was identified in an individual with progressive childhood-onset dystonia. Our assay demonstrated that the synonymous c.5073C>T variant introduced a novel 5' splice donor site that produced a null *KMT2B* allele. This finding is of key clinical relevance as *KMT2B*-related dystonia is characteristically responsive to DBS (Cif et al., 2020; Meyer et al., 2017; Tisch & Kumar, 2020), and synonymous variants are often overlooked when identifying pathogenic variants in genetic disease.

2 | MATERIALS & METHODS

2.1 | Commercial gene panel testing

The patient provided a saliva sample and total genomic DNA was extracted using a bead-based method. He underwent targeted sequencing of a dystonia panel in a commercial CLIA-accredited laboratory [Blueprint Genetics Dystonia (version 3) Panel Plus Analysis] including sequence analysis and copy number variation analysis of the following genes in the nuclear and mitochondrial genome (see Supplementary Material). The proband did not undergo whole genome sequencing or whole exome sequencing.

2.2 | In silico splicing analysis

In silico splicing assessment was conducted using Human Splice Finder 3.1 (HSF 3.1) (Desmet et al., 2009) (<https://hsf.genomnis.com/>), NNSplice 0.9 (Reese et al., 1997) (https://www.fruitfly.org/seq_tools/splice.html) and SpliceAI (<https://spliceailookup.broadinstitute.org/>) (Jaganathan et al., 2019).

2.3 | In vitro exon-trapping of *KMT2B*-pSpliceExpress vectors

The cloning procedure used to generate the wild type and c.5073C>T *KMT2B*-pSpliceExpress plasmids and subsequent exon-trapping procedures were adapted from published methods (Kishore et al., 2008) (see Supplementary Material).

3 | RESULTS

3.1 | Clinical phenotype

A 22-year-old male presented with childhood-onset, multi-focal dystonia with prominent craniocervical involvement. He is a single child to non-consanguineous parents of Bangladeshi origin, with no family history of neurological disorders.

He was the product of a normal pregnancy and delivery with normal early development, walking independently by 12 months and talking by 18 months. There was no history of feeding difficulties, failure to thrive or toe walking. Symptom onset was at 9–10 years with writer's cramp and speech disturbance. He was given levodopa therapy without benefit. He was then switched to trihexyphenidyl and botulinum toxin injections to the vocal cords with a marked transient improvement in speech. Between ages 10 to 20 years, he had a relatively stable course. While living overseas at age 20 years, he developed neck dystonia and difficulty breathing, associated with reduced oral intake and marked weight loss. He complained of dry throat, drooling, tongue and jaw stiffness and difficulty in chewing. He developed continuous involuntary neck movement and mild dystonic posturing of the left hand. He was trialled on gabapentin (300 mg tds) with an improvement in dystonic spasms. A subsequent trial of levodopa at 800 mg/day resulted in a clear clinical improvement but was not sustained beyond 12 months. He currently lives at home and is completing a university degree with no neuropsychiatric symptoms.

On examination at age 21 years, there was no short stature or microcephaly (height 165 cm and head circumference 55 cm). He had severe lingual dystonia with almost no voluntary movement of the tongue. He had moderate to high amplitude flexion dystonic movements of the neck (Supplementary video). Upper limb examination revealed mild dystonic posturing of the fingers with severe impairment of finger tapping on the left with mild impairment on the right. He had only a slightly dystonic gait with mildly reduced knee bend, which was not reversed by walking backwards, but he could run quite well and perform tandem gait. The remainder of his neurological examination was normal, including eye movements and other cranial nerves, and the motor and sensory examination of the upper and lower limbs. There were no Kayser–Fleischer rings.

Brain MRI performed at 10 years old was normal, with no hypointensity of the globus pallidus on T2-weighted sequences (a repeat MRI could not be performed due to involuntary head movements). Urine metabolic screen, lactate, ammonia, very long chain fatty acids, electroencephalogram, liver function tests, full blood count, transferrin isoforms, blood copper and caeruloplasmin were unremarkable. He had a negative testing of dystonia genes

TOR1A (OMIM:#605204), *THAP1* (OMIM:# 609520) and *PRKRA* (OMIM:# 603424) approximately 10 years ago (prior to the identification of *KMT2B* as a dystonia gene).

3.2 | Genetic analysis

Commercial diagnostic testing detected a single heterozygous synonymous variant of uncertain significance in *KMT2B* (NM_014727.2), c.5073C>T (p.Gly1691=) at chr19:35,730,122 (hg38). Sanger sequencing of blood-derived DNA confirmed the c.5073C>T variant was absent in the unaffected mother and father, (Figure 1a-b), however maternity and paternity could not be confirmed as another proband DNA sample could not be obtained. This variant was not identified in our dystonia whole genome sequencing database (n = 111 probands) (Kumar et al., 2019) or in a childhood movement disorder database of the Great Ormond Street Institute of Child Health (n > 400). The *KMT2B* c.5073C>T variant is also unreported in the gnomAD population database (Karczewski et al., 2020).

3.3 | In silico variant analysis

The *KMT2B* c.5073C>T variant was predicted to impact splicing in silico using all three tools (see Supplementary Materials).

3.4 | Exon-trapping of *KMT2B*-pSpliceExpress vectors

As patient tissue was unavailable for splicing analysis, we aimed to assess the impact of *KMT2B* c.5073C>T using an in vitro splicing exon-trapping assay. Wild-type (WT) *KMT2B*-pSpliceExpress and c.5073C>T *KMT2B*-pSpliceExpress vectors were separately transfected into HeLa cells, and the RT-PCR products were size fractionated. The gel-purified amplicons were Sanger sequenced and aligned to the WT *KMT2B* transcript sequence (Figure 1c). The sequenced PCR products showed that the exon-trapping WT *KMT2B* sequence (Figure 1cii) produced a correctly spliced *KMT2B* transcript at the exon: exon junction between *KMT2B* exon 23 (green) and exon 24 (blue). In contrast, the c.5073C>T variant caused a novel splice donor site, resulting in a 5-bp deletion of the 3' end of *KMT2B* exon 23 in mature mRNA (Figure 1ci: boxed red). The predicted novel coding sequence caused by the 5 bp deletion *KMT2B* exon 23 revealed a coding frameshift causing a premature stop codon (Figure 1d: red asterisk) which is predicted to result in a truncated and non-functional *KMT2B* protein (p.Lys1692AsnfsTer7).

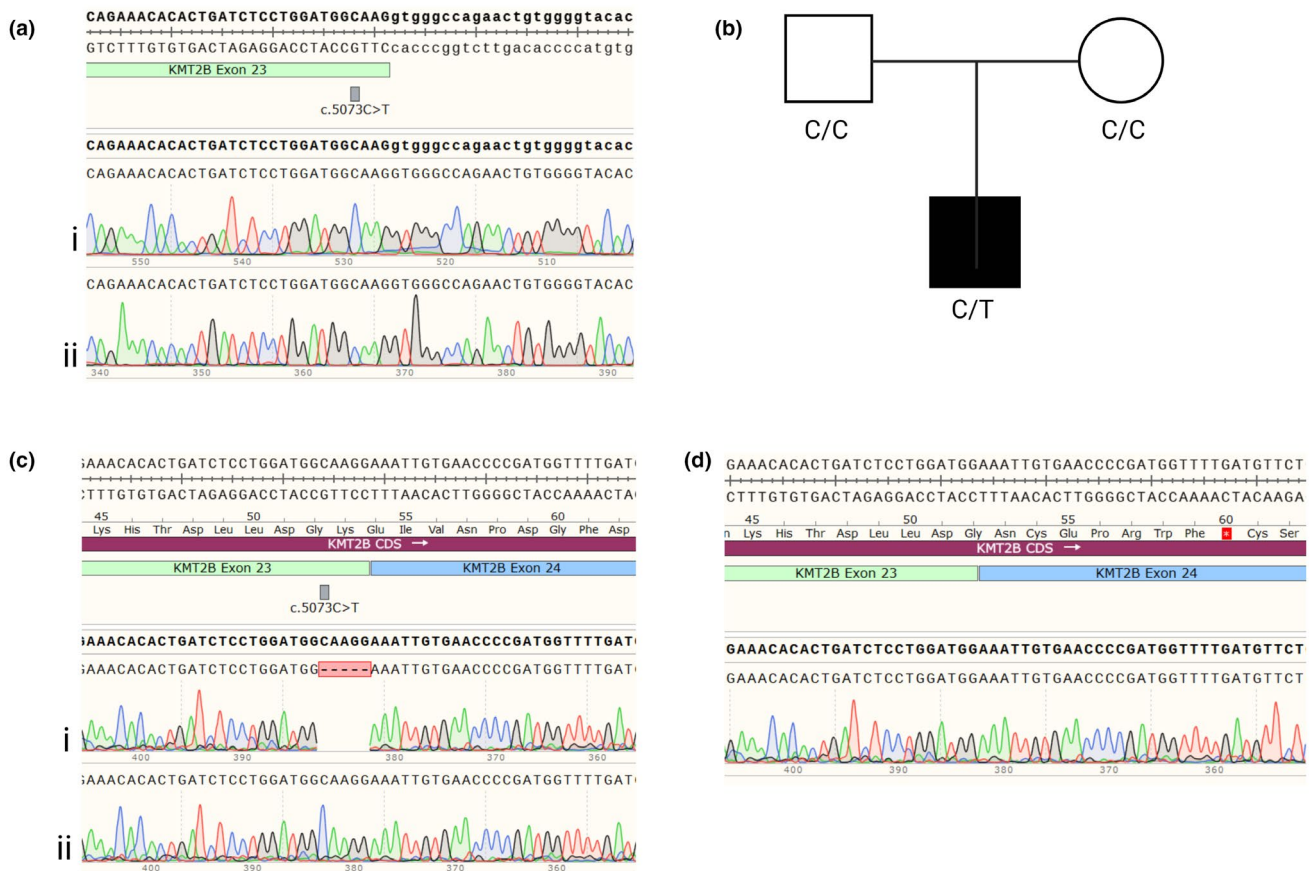


FIGURE 1 Exon-trapping assay using pSpliceExpress for the assessment of splicing changes due to the *KMT2B* c.5073C>T variant. a) Sanger sequencing of *KMT2B* in the unaffected mother (i) and unaffected father (ii) revealed absence of the c.5073C>T variant. b) A pedigree of the two-generation kindred and associated *KMT2B* c.5073C>T genotypes. c) Sanger sequencing of exon-trapped *KMT2B* c.5073C>T (i.) and WT *KMT2B* (ii) confirmed that the c.5073C>T variant (i.) produced a novel splice donor site resulting in a 5 bp deletion at the exon: Exon junction of exon 23 (green) and exon 24 (blue). Correct splicing was observed at the exon: Exon junction for the exon-trapped WT *KMT2B* (ii) transcript. d) Analysis of the novel coding sequence of the c.5073C>T transcript demonstrates that the 5 bp deletion of exon 23 produces a coding frameshift and premature stop codon (p.Lys1692AsnfsTer7) in exon 24 (blue), indicated by the red asterisk

This premature stop codon is not located in the last exon of *KMT2B*, nor in the last 50 base pairs of the penultimate exon of the gene, and therefore this transcript is likely subject to degradation by nonsense-mediated decay.

3.5 | Return of results

The patient was counselled on the likely outcome of pallidal DBS according to the literature on *KMT2B*-related dystonia and is considering this as a treatment option.

4 | DISCUSSION

Here, we report a novel de novo synonymous mutation, *KMT2B* NM_014727.2:c.5073C>T [chr19:35730122C>T (hg38)] in an individual with a severe childhood-onset dystonia. We used an exon-trapping assay to demonstrate

that the c.5073C>T variant introduced an aberrant 5' splice site which caused a 5 bp deletion in exon 23 of *KMT2B*. The coding frameshift resulted in a premature stop codon and therefore a null *KMT2B* allele (*KMT2B*:p.Lys1692AsnfsTer7). These results allow the reclassification of the *KMT2B* c.5073C>T variant as 'pathogenic' (Criteria: PVS1, PS3, PM2, PM6) according to ACMG-AMP guidelines (Richards et al., 2015). Our finding has important clinical implications as patients with *KMT2B* variants have a generally favourable response to DBS treatment, although laryngeal symptoms may only partially improve (Cif et al., 2020). Additionally, the patient in this report had a non-sustained response to levodopa and anticholinergic therapy, as expected from the literature (Abela & Kurian, 1993). To our knowledge, this is the first report to provide evidence of a synonymous variant in *KMT2B* associated with dystonia.

Synonymous variants are often assumed to be functionally neutral and are regularly excluded by variant filtering

methods. Therefore, it has been suggested that aberrant splicing caused by synonymous variants is likely an under recognised disease-causing mechanism in monogenic disease (Zeng & Bromberg, 2019). Our report highlights the value of reassessing synonymous variants in dystonia genes, with priority given to those which are predicted to affect splicing when assessed in silico. We conducted SpliceAI in silico analysis of all 92 reported synonymous variants on ClinVar (regardless of reported clinical significance). Six were predicted to possibly impact splicing, however, no phenotype data were reported for these variants (Supplementary Table 2). Notably, previous cohort studies aiming to detect pathogenic *KMT2B* variants have excluded synonymous variants during filtering (Meyer et al., 2017; Zech et al., 2016). A reassessment of these and other cohorts, as well as ongoing consideration of synonymous variants in dystonia-associated genes, may increase the reported low diagnostic rate in dystonia (Kumar et al., 2019).

Our in vitro approach for assessing splicing variants has several advantages. This method does not require patient tissue, and therefore is an ideal and non-invasive approach for assessing variants found in children with dystonia or in individuals who are unable to provide tissue. This in vitro assay also allows for the rapid assessment of predicted splicing variants in parallel, as each variant can be separately inserted using site-directed mutagenesis once the gene of interest has been cloned into pSpliceExpress. Therefore, this method is also ideal for assessing large cohorts where patient DNA or tissue cannot be obtained.

Confirmation of a genetic diagnosis in dystonia is of major clinical importance, as it can affect the choice of the most appropriate therapeutic strategy. Therefore, we suggest that the potential pathogenicity of synonymous variants is considered when screening dystonia-related genes.

ACKNOWLEDGEMENTS

Kishore Raj Kumar receives funding to study dystonia from the Paul Ainsworth Family Foundation.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

ETHICS

The proband and his parents gave written informed consent for this study which was conducted in accordance with the relevant guidelines and regulations from St Vincent's Hospital Human Research Ethics Committee (HREC2019/ETH12538, approval date 12/08/2020).

VIDEO CONSENT

The subject gave written consent to be videoed for publication both in print and online.

STATEMENT OF CONTRIBUTION

All authors have made substantial contributions to all of the following: (1) the conception and design of the study or acquisition of data or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

DATA AVAILABILITY STATEMENT

Data available in article supplementary material.

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SUPPORTING INFORMATION

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How to cite this article: Grosz, B. R., Tisch, S., Tchan, M. C., Fung, V. S., Darveniza, P., Fellner, A., Kurian, M. A., McLean, A., Tomlinson, S. E., Smyth, R., Devery, S., Wu, K. H., Kennerson, M. L. & Kumar, K. R. (2022). A novel synonymous KMT2B variant in a patient with dystonia causes aberrant splicing. *Molecular Genetics & Genomic Medicine*, *00*, e1923. <https://doi.org/10.1002/mgg3.1923>