Correction to: Novel mutations in *KMT2B* offer pathophysiological insights on childhood-onset progressive dystonia

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The authors noticed nomenclature errors in the publication. The description of the identified variant for patient 2 was not appropriate according to the most recent HGVS nomenclature regulations. In patient 2, the correct description of the variant in *KMT2B* shall be c.3602dupC, p.M1202Dfs*22. In the legend for Figure 3 there was a typographical error, it shall be Y2488 and in the labeling of the Figure 3B it shall be C2488, since the variant was correctly described in our paper as c.7463A>G, p.Y2488C. These corrections do not alter the results and scientific interpretation as discussed in the paper. The authors apologize for the incomppliance with the HGVS nomenclature regulations. The corrected Abstract, Figure 1, Figure 2, and Table 1 were updated and are as follows.

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ABSTRACT

Rapid progress has recently been made in the elucidation of the genetic basis of childhood-onset inherited generalized dystonia (IGD) due to the implementation of genomic sequencing methodologies. We identified four patients with childhood-onset IGD harboring novel disease-causing mutations in lysine-specific histone methyltransferase 2B gene (*KMT2B*) by whole-exome sequencing. The main focus of this paper is to gain novel pathophysiological insights through understanding the molecular consequences of these mutations.

The disease course is mostly progressive, evolving from lower limbs into generalized dystonia, which could be associated with dysarthria, dysphonia, intellectual disability, orofacial dyskinesia, and sometimes distinct dysmorphic facial features. In two patients, motor performances improved after bilateral implantation of deep brain stimulation in the globus pallidus internus (GPi-DBS). Pharmacotherapy with trihexyphenidyl reduced dystonia in two patients.

We discovered three novel *KMT2B* mutations. Our analyses revealed that the mutation in patient 1 (c.7463 A > G, p.Y2488C) is localized in the highly conserved FYRC domain of *KMT2B*. This mutation holds the potential to alter the inter-domain FYR interactions, which could lead to *KMT2B*

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Fig. 1 Pedigree and chromatogram of the variants in *KMT2B* in our three patients. **a** Pedigree and chromatogram of the variant in *KMT2B* in patient 1. The parents are healthy. The patient showed a single base exchange (c.7463A>G, p.Y2488C). **b** Pedigree and chromatogram of the variant in *KMT2B* in patient 2. The parents are healthy. The patient showed a duplication and frame shift (c.3602dupC, p.M1202Dfs*22).

We show the strand as it is mutated in the patient (above) and also without the mutation (below) for comparison. **c** Pedigree and chromatogram of the variant in *KMT2B* in patient 3. The parents were not available for molecular genetic diagnoses. The patient showed a deletion (c.4229delA, p.Q1410Rfs*12).

Fig. 2 Overview of *KMT2B* variants and FYRC domain conservation between *KMT2B* homologs. **a** *KMT2B* locus. Gene structure (NM_014727.1) with 37 exons is represented. Variants found in our four patients are labeled in red. **b** *KMT2B* protein structure (Q9UMN6) with domains. Positions of frameshift or missense mutations are located in important protein domains, which are labeled in red. AT-Hook: DNA-binding motif consisting of a conserved, palindromic, core sequence of proline–arginine–glycine–arginine–proline binding to AT (adenosine, tyrosine). Zf-CXXC: domain containing eight conserved cysteine residues binding to two zinc ions. PHD: plant homeodomain (PHD) finger is a C4HC3 zinc-finger-like motif found in nuclear proteins. Bromo ALL: an ~110-amino-acid protein domain recognizing acetylated lysine residues like the N-terminal tails of histones. FYRN and FYRC: "FY-rich" domain N-terminal (FYRN)

and "FY-rich" domain C-terminal (FYRC) sequence motifs are two poorly characterized phenylalanine/tyrosine-rich regions of around 50 and 100 amino acids found in a variety of chromatin-associated proteins. SET: a 130–140 amino acid, evolutionarily well-conserved sequence motif that was initially characterized in the *Drosophila* proteins Su(var)3-9, Enhancer-of-zeste and Trithorax. Pro-SET: domain in the immediate vicinity to the SET domain. **c** Sequence alignment of top FYRC domains between *KMT2B* homologs, performed in CLC genomics workbench tool (protein accessions Human NP_055542.1; Mouse NP_001277502.1; Monkey XP_014979183.1; Cattle XP_015322911.1; Dog XP_003432729.3; Western Clawed Frog XP_002940678.2; Zebra Fish XP_009290151.1; Fruit Fly NP_599108.1; TBRG1 (model template NP_116200.2)).

Table 1 Patient characterization with age/gender, genetic *KMT2B* variant, symptoms at initial onset, exacerbation, current condition, and therapeutic strategy

Patient	Age (years), gender	KMT2B variant	Initial symptoms and age at onset	Symptoms, age, and trigger at exacerbation	Current symptoms		Neuro-imaging abnormalities	Additional symptoms	Therapy and response	
					Bilateral LL involvement (years)	Bilateral UL involvement (years)			Medication	Deep brain stimulation
#1	18, F	c.7463A>G, p.Y2488C	Nightly hyperkinesia of the head and trunk (6 years)	Severe myalgia and impairment of independent ambulation during viral infection (7 years)	Pes equinus in supination ($l > r$); retropulsion	Variable muscle tone	Dysarthria, dysphonia, torticollis, retrocollis (10 years), orofacial dyskinesia, hyperlordosis, scoliosis	None	Anticholinergics, botox injections, benzodiazepines with mild benefit	GPI-DBS at 7 years; good response with restoration of independent ambulation, severe worsening when the device was switched off
#2	8, F	c.3602dupC, p.M1202Dfs*22	Muscle cramps and ventral deviation of the right hand with deterioration of manual function (2.5 years), slight limp (4 years)	Bilateral LL increased muscle tone and fixed pes equinus ($r > l$), loss of independent ambulation, hyperlordosis, scoliosis, intern. opisthotonus (6 years)	External rotation of feet, intermittent toe walking ($r > l$)	Hyperkinesia	Dysarthria, orofacial dyskinesia, torticollis, hyperlordosis, scoliosis	Severe stress, mood instability, depressive episodes	Benzodiazepines; anticholinergics with good response (BFMDRS 75.5 –>51) (independent ambulation)	Under evaluation
#3	47, M	c.4229delA, p.Q1410Rfs*12	Transient post-OP right-sided increase in muscle tone (6 weeks)	Abnormal gait with legs turned outwards (4 years)	Gait impairment (3 years), retropulsion (43 years)	Hyperkinesia	Dysarthria (4 years), torticollis and laterocollis (43 years)	None	Anticholinergics, L-dopa, botox injections; mild benefit	n/a
#4	11, F	c.4966_4968TCCdel, p.S1656del	Right-handed dystonic tremor and myocloni spreading to the legs and left hand (4 years)	Impaired ambulation with frequent falls (6 years)	Pronation	Dystonic posturing in hands	Torticollis and scoliosis	Reduction of short-term memory and concentration (due to anticholinergics)	Anticholinergics initially very successful, pramipexole inefficient	GPI-DBS at 10 years; good response with improvement of gait, torticollis and scoliosis (BFMDRS-M 43–28)

LL lower limbs, UL upper limbs, DBS deep brain stimulation, n/a not available

instability. The mutations in patients 2 and 3 (c.3602dupC, p.M1202Dfs*22; c.4229delA, p.Q1410Rfs*12) lead to predicted unstable transcripts, likely to be subject to degradation by non-sense-mediated decay.

Childhood-onset progressive dystonia with orofacial involvement is one of the main clinical manifestations of

KMT2B mutations. In all, 26% (18/69) of the reported cases have T2 signal alterations of the globus pallidus internus, mostly at a younger age. Anticholinergic medication and GPi-DBS are promising treatment options and shall be considered early (Figs. 1, 2 and Table 1).