Parkinsonism and Related Disorders 133 (2025) 107319

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Short communication

Variable expressivity of *KMT2B* variants at codon 2565 in patients with dystonia and developmental disorders

Antonia M. Stehr [a,1], Jan Fischer [b,1], Nazanin Mirza-Schreiber [a,c,1], Katerina Bernardi [d,e], Joseph Porrmann [b], Philip Harrer [a,f], Frank Kaiser [g], Rami Abou Jamra [h], Juliane Winkelmann [a,f,i,j], Robert Jech [k], Anne Koy [e,l], Konrad Oexle [a,c,f], Michael Zech [a,f,m,*]

[a] *Institute of Human Genetics, Technical University of Munich, School of Medicine and Health, Munich, Germany*
[b] *Institute for Clinical Genetics, University Hospital Carl Gustav Carus at TUD Dresden University of Technology, Dresden, Germany*
[c] *Neurogenetic Systems Analysis Group, Institute of Neurogenomics, Helmholtz Munich, Neuherberg, Germany*
[d] *Department of Human Neurosciences, Sapienza University of Rome, Rome, Italy*
[e] *Department of Pediatrics, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany*
[f] *Institute of Neurogenomics, Helmholtz Zentrum München, Munich, Germany*
[g] *Institute of Human Genetics, Universitätsklinikum Essen, Essen, Germany*
[h] *Institute of Human Genetics, University of Leipzig Medical Center, Leipzig, Germany*
[i] *Munich Cluster for Systems Neurology (SyNergy), Munich, Germany*
[j] *DZPG, Deutsches Zentrum für Psychische Gesundheit, Munich, Germany*
[k] *Department of Neurology, Charles University, 1st Faculty of Medicine and General University Hospital in Prague, Prague, Czech Republic*
[l] *Center for Rare Diseases, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany*
[m] *Institute for Advanced Study, Technical University of Munich, Garching, Germany*

ARTICLE INFO

Keywords:
KMT2B
Recurrent variation
Episignature
Variable expressivity
Dystonia
Developmental disease

ABSTRACT

Introduction: Variable expressivity is an emerging characteristic of *KMT2B*-related dystonia. However, it remains poorly understood whether variants reoccurring at specific sites of lysine-specific methlytransferase-2B (KMT2B) can drive intra- and interfamilial clinical heterogeneity. Our goal was to ascertain independent families with variants affecting residue Arg2565 of KMT2B.

Methods: Whole-exome/genome sequencing, multi-site recruitment, genotype-phenotype correlations, and DNA methylation episignature analysis were performed.

Results: We report four individuals from two families harboring the variant c.7693C > G, p.Arg2565Gly. In an additional patient, a *de-novo* c.7693C > T, p.Arg2565Cys variant was identified. The observed phenotypic spectrum ranged from childhood-onset dystonia (N = 2) over unspecific intellectual disability syndromes (N = 2) to undiagnosed behavioral symptoms in adulthood (N = 1). Samples bearing p.Arg2565Gly had a *KMT2B*-typical episignature, although the effect on methylation was less pronounced than in carriers of loss-of-function *KMT2B* variants.

Conclusions: We established the existence of a KMT2B missense-mutation hotspot associated with varying degrees of disease severity and expression, providing information for patient counseling and elucidation of pathomechanisms.

1. Introduction

Heterozygous variants in *KMT2B* are responsible for *KMT2B*-related dystonia (DYT-*KMT2B*) [1,2]. Non-motor neurodevelopmental abnormalities are part of the phenotypic spectrum of this condition [3–5]. Although many hereditary dystonias are characterized by variable

* Corresponding author. Institute of Neurogenomics, Helmholtz Zentrum München, Deutsches Forschungszentrum für Gesundheit und Umwelt (GmbH), Ingolstädter Landstraße 1, 85764, Neuherberg, Germany.
E-mail address: michael.zech@mri.tum.de (M. Zech).
[1] These authors contributed equally as first authors.

https://doi.org/10.1016/j.parkreldis.2025.107319
Received 9 October 2024; Received in revised form 4 February 2025; Accepted 4 February 2025
Available online 5 February 2025

expressivity [6], the phenomenon is less well understood in DYT-*KMT2B*. The relationship between *KMT2B* variants and clinical presentations has been mostly examined in individuals ascertained as a result of specific, often movement disorder-focused phenotyping [3,4,7], potentially introducing a bias towards overestimation of disease severity. A few pedigrees have been described in which affected members either had progressive dystonia or milder neurodevelopmental disorders with no signs of dystonic features [1,8]. Moreover, a recent cohort study reported nine sporadic patients with *KMT2B* missense or loss-of-function variants who presented mild-to-profound developmental disturbances with no signs of dystonia [7]. No genotype-phenotype correlations explaining this variability in clinical expression have been identified [4], and it is unknown whether variants clustering at certain sites of lysine-specific methlytransferase-2B (KMT2B) are linked to only one or multiple phenotypic outcomes. A better delineation of the relationship between individual *KMT2B* genotypes and the observable set of associated disease characteristics is crucial to improving variant interpretation, family counseling, and the study of molecular mechanisms.

Herein, we highlight variable expressivity of a recurrently mutated amino-acid residue of KMT2B. We assembled a group of five patients with heterogeneous dystonic and non-dystonic features who each carried a missense variant at codon 2565 of *KMT2B*. Variant causality was confirmed by application of sequence classification guidelines [9] and DNA methylation analysis [10].

2. Patients and methods

Motivated by the identification of a KMT2B p.Arg2565Gly alteration in a family (family-A) from our Munich dystonia research program [10–12], we proposed a collaborative study for recruitment of patients with variants occurring exclusively at residue Arg2565 of KMT2B. A-II-1 from family-A has been included in the publication by Mirza-Schreiber and colleagues [10] without comprehensive clinical characterization, whereas A-I-1`s phenotypic abnormalities have not been reported so far. For details of the case-identification strategy and the involved centers and cohorts, see flow chart in Supplementary Figure. Existing exome-/genome-sequencing data and genetic testing reports were screened. Two other new patients (family-B) were identified by scrutiny of a repository of 500 neurodevelopmental disorder genome-sequencing datasets from the Institute for Clinical Genetics, Technical University Dresden, Germany. An additional previously unreported carrier (family-C) was enrolled from the outpatient clinic of the Center for Rare Diseases of University Hospital Cologne, Germany, following external genetic testing (see Supplementary Figure). Written informed consent was collected from all participants. The families underwent genetic investigation by exome or genome sequencing using family-based analysis designs (parent-child trio-exome sequencing in families-A/C, singleton genome sequencing followed by targeted sequencing of a twin brother in family-B) [11,13–15]. Prioritization of variants based on minor allele frequency and predicted impact were conducted as described [11–13,15,16]. Genome-wide peripheral blood DNA methylation profiles were generated with Illumina MethylationEPIC v2 BeadChip arrays. Data preprocessing, quality control, and derivation of methylation M-values were done using SeSAMe (https://git.bioconductor.org/packages/sesame) [17]. The *KMT2B* episignature scores of the samples were calculated using the previously published SVM classifier [10], but restricted to 97 of 113 CpG-sites overlapping between the EPIC v1 and v2 arrays. The pathogenicity of reported variants was evaluated according to American-College-of-Medical-Genetics-and-Genomics (ACMG) interpretation criteria [9], using the varsome interface (https://varsome.com/) [18].

3. Results

3.1. Molecular findings

Four individuals from families-A/B were found to share the recurrent transversion c.7693C > G (NM_014727.3), causing an arginine-to-glycine substitution at amino-acid position 2565 of KMT2B (p.Arg2565Gly) (Table 1; Fig. 1A). In the affected child from family-C, we identified a *KMT2B de-novo* c.7693C > T transition, resulting in an arginine-to-cysteine alteration at the same residue (p.Arg2565Cys) (Table 1; Fig. 1A). Variants affecting Arg2565 in KMT2B have not been listed in gnomAD v4.1.0 (neither missense/indel nor synonymous variants). The altered residue was phylogenetically conserved and localized in a highly mutation-intolerant sequence stretch (amino acids 2560–2576) [19] within the functionally important C-terminal region of KMT2B containing the FY-rich/C and SET domains [1] (Fig. 1B). Both variants were predicted to be deleterious according to machine-learned and other classifiers (p.Arg2565Gly: CADD = 24.6, REVEL = 0.8, AlphaMissense = 0.998; p.Arg2565Cys: CADD = 23.6, REVEL = 0.672, AlphaMissense = 0.997) [20–22]. To further proof a damaging effect of p.Arg2565Gly, we examined leukocyte DNA methylation in two patients from family-B (B-II-1, B-II-2; Fig. 1A). Indeed, both individuals showed a global increase in DNA methylation (not shown) and typical aberrations at the CpG sites of the DYT-*KMT2B* episignature [10] (Fig. 1C). The methylation aberrations in these subjects were more moderate than in samples bearing *KMT2B* loss-of-function mutations (Fig. 1C), consistent with previous results for family-A [10] and the observation that *KMT2B* missense variants sometimes cause 'milder' aberrations of episignature DNA methylation profiles [10]. Following ACMG rules [9], p.Arg2565Gly and p.Arg2565Cys were each categorized as 'likely pathogenic'.

3.2. Clinical phenotypes

Carrier individuals from family-A have been mentioned in a prior study but without comprehensive phenotype reports [10]. A-II-1 was a 13-year-old boy with normal developmental history, known for early-onset dystonia. Just before the age of 7, he started experiencing hand spasms and arm tremor, soon followed by progression to dystonic posturing of the trunk and all four limbs. At age 9, he additionally manifested laryngeal dystonia causing profound dysphonia. Testing of intellectual functioning (Wechsler Intelligence Scale for Children) provided results consistent with average cognitive ability. The remainder of the neurological examination was without significant findings, and there was no notion of physical abnormalities. In particular, there were no facial dysmorphic features or congenital anomalies. His brain MRI was normal. At last examination, he displayed generalized isolated dystonia with mild-to-moderate response to anticholinergic therapy. His 44-year-old father A-I-1 did not report any symptoms that impacted his daily life. There was no movement disorder. He had a history of learning difficulties and suspected ADHD-like features in childhood. In adulthood, he continued to have deficits in social motivation and episodes of anxiety.

In family-B, B-II-1 and his twin brother B-II-2 (15 years old) were under medical surveillance due to delayed psychomotor development and intellectual impairment. They had been placed in foster care. Family history was positive for dystonia on the maternal side but detailed information was unavailable. Clinical assessment at 15 months of age showed neurodevelopmental delays of both motor and language skills. Over time, mild dysmorphic facial features were noted in both individuals, including synophrys, smooth philtrum, broad nasal tip, and thin upper lip. B-II-1`s brain MRI at 6 years of age did not reveal any intracranial abnormalities. To date, the twins presented mild intellectual disability (Kaufman-Assessment-Battery-for-Children score of 60 for B-II-1) and speech abnormalities. Further, B-II-1 had cryptorchidism, plagiocephaly, and congenital talipes. In several examinations, there

Table 1
Clinical summary of patients with variants at codon 2565 of KMT2B.

Family/Patient	Family-A/A-II-1	Family-A/A-I-1	Family-B/B-II-1	Family-B/B-II-2	Family-C/C-II-1
KMT2B variant	NM_014727.3: c.7693C > G, NP_055542.1: p.Arg2565Gly	NM_014727.3: c.7693C > G, NP_055542.1: p.Arg2565Gly	NM_014727.3: c.7693C > G, NP_055542.1: p.Arg2565Gly	NM_014727.3: c.7693C > G, NP_055542.1: p.Arg2565Gly	NM_014727.3: c.7693C > T, NP_055542.1: p.Arg2565Cys
Gender	male	male	male	male	female
Current age	13 years	44 years	15 years	15 years	9 years
Developmental delay	no	not reported	yes – mild motor and cognitive delay	yes – mild motor and cognitive delay	yes - mild motor and cognitive delay
Dystonia age of onset	6 years	N/A	N/A	N/A	around 2–3 years
Dystonia site of onset	left upper extremity	N/A	N/A	N/A	lower extremities
Dystonia progression	yes	N/A	N/A	N/A	yes/variable
Dystonia sites involved (last exam)	upper and lower extremities, trunk, larynx	N/A	N/A	N/A	upper and lower extremities
Dystonia pattern	persistent	N/A	N/A	N/A	action-dependent, aggravated by voluntary movements
Dystonia treatment	anticholinergics, under evaluation for deep brain stimulation	N/A	N/A	N/A	anticholinergics
Hypotonia	no	not reported	not reported	not reported	yes – during early childhood
Intellectual impairment	no	borderline – learning difficulties in childhood	yes – mild, K-ABC score: 60	yes – mild	yes – mild
Speech impairment	yes – dysarthria	no	yes – mild expressive speech impairment	yes – mild expressive speech impairment	no
Dysmorphia	no	no	yes – synophrys, smooth philtrum, broad nasal tip, thin upper lip	yes – synophrys, smooth philtrum, thin upper lip	no
Behavioral deficits	no	yes – ADHD features in childhood, anxiety	no	no	autism spectrum disorder (Asperger)
Visual abnormalities	no	no	no	strabismus	no
Brain MRI abnormality	no	not performed	no	no	no
Other features	no	no	yes – cryptorchidism, plagiocephaly, clubfoot	no	potential episodes of epileptic activity, EEG normal

ADHD, attention deficit hyperactivity disorder; EEG, electroencephalography; K-ABC, Kaufman Assessment Battery for Children; KMT2B, lysine-specific methyltransferase-2B MRI, magnetic resonance imaging; N/A, not applicable.

were no signs of dystonia.

Patient C-II-1 was a 9-year-old girl with action-induced dystonia, mild intellectual disability, and suspected autism spectrum disorder. Her motor milestones and language development were delayed. Muscular hypotonia in infancy was also documented. Brain MRI conducted at 1 year of age was normal. Between her second and third birthday, her right foot started to turn inward while walking. At the age of 4, she came to medical attention because of increasing exercise intolerance. Detailed neurological gait assessment revealed dystonic postures of both legs worsened by action, which was interpreted as an exacerbation of dystonic features from baseline. There were no clinical signs of neuromuscular disease and creatine kinase was normal. Additional cardiac evaluation and pulmonary function tests did not reveal any abnormalities. Over the next few months, her parents noticed dystonia of upper and lower extremities with diurnal fluctuations. She was started on anticholinergic treatment with moderate effect. Currently, the girl`s examination showed mild dystonic posturing of the limbs mostly triggered by voluntary movements, without any impact on motor function.

4. Discussion

For the present study we collected patients carrying disease-causing variations at an identical amino-acid position of KMT2B and investigated the variability of their phenotypes. Likely pathogenic/pathogenic *KMT2B* variants published to date were mostly unique to single affected individuals, with high rates of non-recurrent *de-novo* mutations [3,4,7,23]. We have successfully identified a series of subjects from unrelated families with missense substitutions affecting only one residue (Arg2565) of KMT2B, establishing a previously unrecognized mutational hotspot for DYT-*KMT2B*. Despite the identical variant position, the phenotypic spectrum observed in the carrier individuals was unexpectedly broad, ranging from different types of dystonia (two patients) to non-dystonic neurodevelopmental conditions (two patients) and undiagnosed behavioral-disorder symptoms (one patient). The phenotype of A-II-1 (family-A) was consistent with 'classical', that is, DYT-*TOR1A*/DYT-*THAP1*-like isolated generalized dystonia [6], whereas patient C-II-1 (family-C) demonstrated more atypical dystonic features with multifocal distribution including signs not previously highlighted for DYT-*KMT2B* such as prominent exercise intolerance. By contrast, the twins from family-B had developmental-disease phenotypes similar to those previously reported in a few *KMT2B*-mutated cases without dystonia, such as variable intellectual disability and unspecific craniofacial morphological abnormalities [5,7]. We note that some aspects of the observed dysmorphic features such as smooth philtrum and thin upper lip are uncommon in DYT-*KMT2B*, at least according to current knowledge of this rare disease; on the other hand, the results of our molecular analyses with demonstration of variant recurrence at Arg2565 and an episignature pattern consistent with the pathogenicity of this variant are clearly indicative of a diagnosis of DYT-*KMT2B* in the twins. Finally, in case of patient A-II-1 (family-A) with isolated dystonia, the father was initially evaluated as clinically unaffected [10], but later found to manifest adult behavioral disturbances. Although an association of these abnormalities with the familial *KMT2B* variant seems to be likely, we cannot rule out that some clinical features are coincidental given that learning disorders and ADHD are among the most common unspecific neurodevelopmental traits in the general population [24]. The heterogeneous clinical spectrum seen in the herein investigated families is consistent with prior results from a large cohort of patients

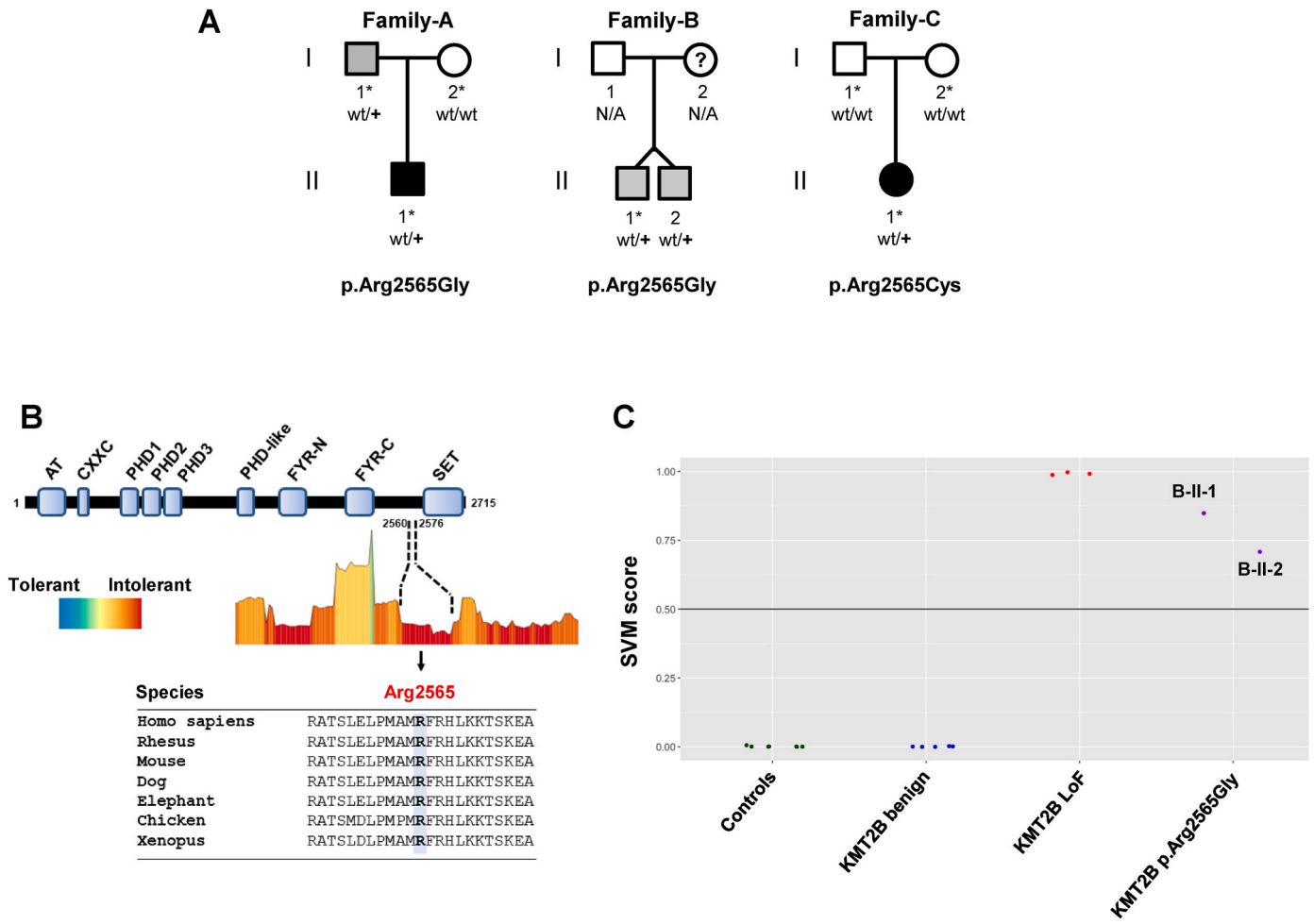

Fig. 1. *KMT2B* variants occurring exclusively at codon 2565 in patients with variable dystonic and non-dystonic phenotypes. (A) Pedigrees of three families with missense variants affecting Arg2565 of KMT2B. Patients with dystonia are indicated with filled black symbols and patients with neurodevelopmental symptoms but no dystonia with gray symbols. Phenotype of the mother in family-B was unknown (affected twins placed in foster care), with reported history of dystonia in a maternal relative. Individuals who underwent exome or genome sequencing are highlighted with asterisks. wt/+, variant carrier; wt/wt, individual homozygous for wild-type allele; N/A, genotyping unavailable. (B) Depiction of the domain structure of KMT2B and relative location of residue Arg2565 in the functionally important C-terminal part of the protein [1]. The magnified view illustrates the mutation intolerance of Arg2565 and its surrounding amino acid sequence, as defined by Wiel et al. [19]. Arginine at position 2565 was conserved in all organisms tested. (C) Results of episignature analysis [10,25] for samples carrying the variant p.Arg2565Gly. SVM probability scores of the individuals B-II-1 and B-II-2 from family-B with this variant (KMT2B p.Arg2565Gly) were determined and compared with the scores for samples with pathogenic *KMT2B de novo* loss-of-function mutations (KMT2B LoF; N = 3), benign *KMT2B* missense variants (KMT2B benign; N = 5), and controls, that is, individuals without a rare variant in *KMT2B* (N = 7). Technically, a score >0.5 indicates that a sample is more likely to carry a disease-causing *KMT2B* variant than not to carry such an alteration. Previous analyses showed that in individuals with missense variants scores may be between control and LoF levels and correlate with the age of dystonia onset [10,25]. Abbreviations: KMT2B, lysine-specific methlytransferase-2B; SVM, support vector machine.

with *KMT2B* variants described by Cif and colleagues [7], which reported variably expressed comorbid features in DYT-*KMT2B* such as cognitive difficulties in 48 % and dysmorphic features in 52 %. The results of our present study have several implications. First, our findings provide strong evidence for the causal character of the variants p.Arg2565Gly and p.Arg2565Cys, facilitating future interpretation of sequence changes that will be identified at the hotspot Arg2565 of KMT2B. Notably, p.Arg2565Gly was first regarded as a variant of uncertain significance according to ACMG criteria [9], but the insights from our episignature study allowed us to reclassify this variant as likely pathogenic. Second, the marked heterogeneity in phenotypic outcomes that we describe in families with variants affecting Arg2565 informs clinicians about the necessity of individualized care planning and careful counseling to ensure optimal management of affected families. We suggest to examine seemingly healthy parents and other relatives of patients with KMT2B Arg2565-involving variation for subtle signs of movement and developmental abnormalities. Third, the discovery of a mutation hotspot associated with diverse disease presentations can offer important possibilities to explore mechanisms of variable expressivity in DYT-*KMT2B*. While p.Arg2565Gly was associated with an episignature score that is diagnostic for DYT-*KMT2B* (family-B, see Fig. 1C, and family-A [10]), samples carrying this variant had lower scores than carriers of loss-of-function variants. This is in line with the existence of allelic series in DYT-*KMT2B* [10,25], and reminiscent of what has been described in some other monogenic disorders characterized by variable expressivity [26,27]. On the other hand, heterogeneity of dystonic and non-dystonic manifestations has also been observed within families positive for *KMT2B* loss-of-function variants and extreme episignature scores [1,10], suggesting that profiling of blood methylation alone will not always be sufficient to predict outcomes. Mosaicism is another possible cause of variable expressivity but is not typical of DYT-*KMT2B* [25]. Indeed, the patients in the present study also were unlikely to be mosaics since their variants were inherited or suspected to be inherited and the one *de novo* change had a variant allele frequency close to 50 %. Other potential causes of variability include differential effects of missense variants on protein stability and turnover [28], modifier genes,

sex, parent-of-origin, varying environmental influences, and random effects in early development [29]. Moreover, it is possible that variants specifically clustering in the pre-SET domain region (see. Fig. 1B) may confer a differential biological effect that is associated with heterogeneous outcomes. Additional research efforts are needed to better define how *KMT2B* variants, resulting methylation alterations, and downstream regulatory disruptions determine disease states and the associated severity of symptoms.

In summary, our present data underscore the notion that variable expressivity likely plays a greater than expected role in families with dominantly transmitted *KMT2B* variants. Inherited *KMT2B* variants, especially those reoccurring at specific sites, should not be disregarded in clinical curation, as they may represent under-appreciated causes of pleiotropic familial movement- and developmental-disorder phenotypes.

CRediT authorship contribution statement

Antonia M. Stehr: Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Jan Fischer:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Nazanin Mirza-Schreiber:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Katerina Bernardi:** Writing – review & editing, Formal analysis, Data curation. **Joseph Porrmann:** Writing – review & editing, Formal analysis, Data curation. **Philip Harrer:** Writing – review & editing, Formal analysis, Data curation. **Frank Kaiser:** Writing – review & editing, Formal analysis, Data curation. **Rami Abou Jamra:** Writing – review & editing, Formal analysis, Data curation. **Juliane Winkelmann:** Writing – review & editing, Formal analysis, Data curation. **Robert Jech:** Writing – review & editing, Formal analysis, Data curation. **Anne Koy:** Writing – review & editing, Formal analysis, Data curation. **Konrad Oexle:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Michael Zech:** Writing – original draft, Formal analysis, Data curation, Conceptualization.

Disclosures

None of the authors report disclosures concerning the present manuscript.

Declaration of competing interest

The authors state that they have nothing to declare.

Acknowledgements

This work was supported by funding from the EJP RD (EJP RD Joint Transnational Call 2022) and the German Federal Ministry of Education and Research (BMBF, Bonn, Germany), awarded to the project PreDYT (PREdictive biomarkers in DYsTonia, 01GM2302). This research was also supported by a "*Schlüsselprojekt*" grant from the Else Kröner-Fresenius-Stiftung (2022_EKSE.185). In addition, this study (M.Z.) has received funding from the Federal Ministry of Education and Research (BMBF) and the Free State of Bavaria under the Excellence Strategy of the Federal Government and the Länder, as well as by the Technical University of Munich - Institute for Advanced Study. J.W. and M.Z. receive research support from the German Research Foundation (DFG 458949627; WI 1820/14-1; ZE 1213/2-1). The work was also supported by the National Institute for Neurological Research, Czech Republic, Programme EXCELES, ID Project No. LX22NPO5107, funded by the European Union – Next Generation EU and also by the Charles University: Cooperatio Program in Neuroscience and by the Agency for Health Research of the Czech Republic (grant AZV CR: NW24-04-0006).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2025.107319.

References

[1] M. Zech, S. Boesch, E.M. Maier, I. Borggraefe, K. Vill, F. Laccone, V. Pilshofer, A. Ceballos-Baumann, B. Alhaddad, R. Berutti, W. Poewe, T.B. Haack, B. Haslinger, T.M. Strom, J. Winkelmann, Haploinsufficiency of KMT2B, encoding the lysine-specific histone methyltransferase 2B, results in early-onset generalized dystonia, Am. J. Hum. Genet. 99 (6) (2016) 1377–1387.

[2] E. Meyer, K.J. Carss, J. Rankin, J.M. Nichols, D. Grozeva, A.P. Joseph, N. E. Mencacci, A. Papandreou, J. Ng, S. Barral, A. Ngoh, H. Ben-Pazi, M. A. Willemsen, D. Arkadir, A. Barnicoat, H. Bergman, S. Bhate, A. Boys, N. Darin, N. Foulds, N. Gutowski, A. Hills, H. Houlden, J.A. Hurst, Z. Israel, M. Kaminska, P. Limousin, D. Lumsden, S. McKee, S. Misra, S.S. Mohammed, V. Nakou, J. Nicolai, M. Nilsson, H. Pall, K.J. Peall, G.B. Peters, P. Prabhakar, M.S. Reuter, P. Rump, R. Segel, M. Sinnema, M. Smith, P. Turnpenny, S.M. White, D. Wieczorek, S. Wiethoff, B.T. Wilson, G. Winter, C. Wragg, S. Pope, S.J. Heales, D. Morrogh, U. K. Consortium, S. Deciphering Developmental Disorders, N.B.R.D. Consortium, A. Pittman, L.J. Carr, B. Perez-Duenas, J.P. Lin, A. Reis, W.A. Gahl, C. Toro, K. P. Bhatia, N.W. Wood, E.J. Kamsteeg, W.K. Chong, P. Gissen, M. Topf, R.C. Dale, J. R. Chubb, F.L. Raymond, M.A. Kurian, Mutations in the histone methyltransferase gene KMT2B cause complex early-onset dystonia, Nat. Genet. 49 (2) (2017) 223–237.

[3] M. Zech, D.D. Lam, J. Winkelmann, Update on KMT2B-related dystonia, Curr. Neurol. Neurosci. Rep. 19 (11) (2019) 92.

[4] L. Abela, M.A. Kurian, KMT2B-Related dystonia, in: M.P. Adam, J. Feldman, G. M. Mirzaa, R.A. Pagon, S.E. Wallace, L.J.H. Bean, K.W. Gripp, A. Amemiya (Eds.), GeneReviews((R)), 1993. Seattle (WA).

[5] V. Faundes, W.G. Newman, L. Bernardini, N. Canham, J. Clayton-Smith, B. Dallapiccola, S.J. Davies, M.K. Demos, A. Goldman, H. Gill, R. Horton, B. Kerr, D. Kumar, A. Lehman, S. McKee, J. Morton, M.J. Parker, J. Rankin, L. Robertson, I. K. Temple, , S. Clinical Assessment of the Utility of, S. Evaluation as a Service, S. Deciphering Developmental Disorders, S. Banka, Histone lysine methylases and demethylases in the landscape of human developmental disorders, Am. J. Hum. Genet. 102 (1) (2018) 175–187.

[6] M. Thomsen, L.M. Lange, M. Zech, K. Lohmann, Genetics and pathogenesis of dystonia, Annu. Rev. Pathol. 19 (2024) 99–131.

[7] L. Cif, D. Demailly, J.P. Lin, K.E. Barwick, M. Sa, L. Abela, S. Malhotra, W.K. Chong, D. Steel, A. Sanchis-Juan, A. Ngoh, N. Trump, E. Meyer, X. Vasques, J. Rankin, M. W. Allain, C.D. Applegate, S. Attaripour Isfahani, J. Baleine, B. Balint, J.A. Bassetti, E.L. Baple, K.P. Bhatia, C. Blanchet, L. Burglen, G. Cambonie, E.C. Seng, S. C. Bastaraud, F. Cyprien, C. Coubes, V. d'Hardemare, S. Deciphering Developmental Disorders, A. Doja, N. Dorison, D. Doummar, M.E. Dy-Hollins, E. Farrelly, D.R. Fitzpatrick, C. Fearon, E.L. Fieg, B.L. Fogel, E.B. Forman, R.G. Fox, C. Genomics England Research, W.A. Gahl, S. Galosi, V. Gonzalez, T.D. Graves, A. Gregory, M. Hallett, H. Hasegawa, S.J. Hayflick, A. Hamosh, M. Hully, S. Jansen, S.Y. Jeong, J.B. Krier, S. Krystal, K.R. Kumar, C. Laurencin, H. Lee, G. Lesca, L. L. Francois, T. Lynch, N. Mahant, J.A. Martinez-Agosto, C. Milesi, K.A. Mills, M. Mondain, H. Morales-Briceno, N. BioResource, J.R. Ostergaard, S. Pal, J. C. Pallais, F. Pavillard, P.F. Perrigault, A.K. Petersen, G. Polo, G. Poulen, T. Rinne, T. Roujeau, C. Rogers, A. Roubertie, M. Sahagian, E. Schaefer, L. Selim, R. Selway, N. Sharma, R. Signer, A.G. Soldatos, D.A. Stevenson, F. Stewart, M. Tchan, N. Undiagnosed Diseases, I.C. Verma, B.B.A. de Vries, J.L. Wilson, D.A. Wong, R. Zaitoun, D. Zhen, A. Znaczko, R.C. Dale, C.M. de Gusmao, J. Friedman, V.S. C. Fung, M.D. King, S.S. Mohammad, L. Rohena, J.L. Waugh, C. Toro, F. L. Raymond, M. Topf, P. Coubes, K.M. Gorman, M.A. Kurian, KMT2B-related disorders: expansion of the phenotypic spectrum and long-term efficacy of deep brain stimulation, Brain 143 (11) (2020 Dec 5) 3242–3261, https://doi.org/10.1093/brain/awaa304.

[8] L. Dai, C. Ding, F. Fang, An inherited KMT2B duplication variant in a Chinese family with dystonia and/or development delay, Parkinsonism Relat. Disorders 63 (2019) 227–228.

[9] S. Richards, N. Aziz, S. Bale, D. Bick, S. Das, J. Gastier-Foster, W.W. Grody, M. Hegde, E. Lyon, E. Spector, K. Voelkerding, H.L. Rehm, A.L.Q.A. Committee, Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American college of medical genetics and genomics and the association for molecular pathology, Genet. Med. 17 (5) (2015) 405–424.

[10] N. Mirza-Schreiber, M. Zech, R. Wilson, T. Brunet, M. Wagner, R. Jech, S. Boesch, M. Skorvanek, J. Necpal, D. Weise, S. Weber, B. Mollenhauer, C. Trenkwalder, E. M. Maier, I. Borggraefe, K. Vill, A. Hackenberg, V. Pilshofer, U. Kotzaeridou, E.M. C. Schwaibold, J. Hoefele, M. Waldenberger, C. Gieger, A. Peters, T. Meitinger, B. Schormair, J. Winkelmann, K. Oexle, Blood DNA methylation provides an accurate biomarker of KMT2B-related dystonia and predicts onset, Brain 145 (2) (2022 Apr 18) 644–654, https://doi.org/10.1093/brain/awab360.

[11] M. Zech, R. Jech, S. Boesch, M. Skorvanek, S. Weber, M. Wagner, C. Zhao, A. Jochim, J. Necpal, Y. Dincer, K. Vill, F. Distelmaier, M. Stoklosa, M. Krenn, S. Grunwald, T. Bock-Bierbaum, A. Fecikova, P. Havrankova, J. Roth, I. Prihodova, M. Adamovicova, O. Ulmanova, K. Bechyne, P. Danhofer, B. Vesely, V. Han, P. Pavelekova, Z. Gdovinova, T. Mantel, T. Meindl, A. Sitzberger, S. Schroder, A. Blaschek, T. Roser, M.V. Bonfert, E. Haberlandt, B. Plecko, B. Leineweber,

S. Berweck, T. Herberhold, B. Langguth, J. Svantnerova, M. Minar, G.A. Ramos-Rivera, M.H. Wojcik, S. Pajusalu, K. Ounap, U.A. Schatz, L. Polsler, I. Milenkovic, F. Laccone, V. Pilshofer, R. Colombo, S. Patzer, A. Iuso, J. Vera, M. Troncoso, F. Fang, H. Prokisch, F. Wilbert, M. Eckenweiler, E. Graf, D.S. Westphal, K. M. Riedhammer, T. Brunet, B. Alhaddad, R. Berutti, T.M. Strom, M. Hecht, M. Baumann, M. Wolf, A. Telegrafi, R.E. Person, F.M. Zamora, L.B. Henderson, D. Weise, T. Musacchio, J. Volkmann, A. Szuto, J. Becker, K. Cremer, T. Sycha, F. Zimprich, V. Kraus, C. Makowski, P. Gonzalez-Alegre, T.M. Bardakjian, L. J. Ozelius, A. Vetro, R. Guerrini, E. Maier, I. Borggraefe, A. Kuster, S.B. Wortmann, A. Hackenberg, R. Steinfeld, B. Assmann, C. Staufner, T. Opladen, E. Ruzicka, R. D. Cohn, D. Dyment, W.K. Chung, H. Engels, A. Ceballos-Baumann, R. Ploski, O. Daumke, B. Haslinger, V. Mall, K. Oexle, J. Winkelmann, Monogenic variants in dystonia: an exome-wide sequencing study, Lancet Neurol. 19 (11) (2020) 908–918.

[12] I. Dzinovic, S. Boesch, M. Skorvanek, J. Necpal, J. Svantnerova, P. Pavelekova, P. Havrankova, E. Tsoma, E. Indelicato, E. Runkel, V. Held, D. Weise, W. Janzarik, M. Eckenweiler, S. Berweck, V. Mall, B. Haslinger, R. Jech, J. Winkelmann, M. Zech, Genetic overlap between dystonia and other neurologic disorders: a study of 1,100 exomes, Parkinsonism Relat. Disorders 102 (2022) 1–6.

[13] L. Gieldon, L. Mackenroth, A.K. Kahlert, J.R. Lemke, J. Porrmann, J. Schallner, M. von der Hagen, S. Markus, S. Weidensee, B. Novotna, C. Soerensen, B. Klink, J. Wagner, A. Tzschach, A. Jahn, F. Kuhlee, K. Hackmann, E. Schrock, N. Di Donato, A. Rump, Diagnostic value of partial exome sequencing in developmental disorders, PLoS One 13 (8) (2018) e0201041.

[14] M. Thiel, D. Bamborschke, W.G. Janzarik, B. Assmann, S. Zittel, S. Patzer, A. Auhuber, J. Opp, E. Matzker, A. Bevot, J. Seeger, A. van Baalen, B. Stuve, K. Brockmann, S. Cirak, A. Koy, Genotype-phenotype correlation and treatment effects in young patients with GNAO1-associated disorders, J. Neurol. Neurosurg. Psychiatry 94 (10) (2023) 806–815.

[15] R.T. Jauss, S. Schliesske, R. Abou Jamra, Routine diagnostics confirm novel neurodevelopmental disorders, Genes 13 (12) (2022).

[16] M. Zech, R. Jech, P. Havrankova, A. Fecikova, R. Berutti, D. Urgosik, D. Kemlink, T. M. Strom, J. Roth, E. Ruzicka, J. Winkelmann, KMT2B rare missense variants in generalized dystonia, Mov. Disord. 32 (7) (2017) 1087–1091.

[17] W. Zhou, T.J. Triche Jr., P.W. Laird, H. Shen, SeSAMe: reducing artifactual detection of DNA methylation by Infinium BeadChips in genomic deletions, Nucleic Acids Res. 46 (20) (2018) e123.

[18] C. Kopanos, V. Tsiolkas, A. Kouris, C.E. Chapple, M. Albarca Aguilera, R. Meyer, A. Massouras, VarSome: the human genomic variant search engine, Bioinformatics 35 (11) (2019) 1978–1980.

[19] L. Wiel, C. Baakman, D. Gilissen, J.A. Veltman, G. Vriend, C. Gilissen, MetaDome: pathogenicity analysis of genetic variants through aggregation of homologous human protein domains, Hum. Mutat. 40 (8) (2019) 1030–1038.

[20] M. Kircher, D.M. Witten, P. Jain, B.J. O'Roak, G.M. Cooper, J. Shendure, A general framework for estimating the relative pathogenicity of human genetic variants, Nat. Genet. 46 (3) (2014) 310–315.

[21] N.M. Ioannidis, J.H. Rothstein, V. Pejaver, S. Middha, S.K. McDonnell, S. Baheti, A. Musolf, Q. Li, E. Holzinger, D. Karyadi, L.A. Cannon-Albright, C.C. Teerlink, J. L. Stanford, W.B. Isaacs, J. Xu, K.A. Cooney, E.M. Lange, J. Schleutker, J. D. Carpten, I.J. Powell, O. Cussenot, G. Cancel-Tassin, G.G. Giles, R.J. MacInnis, C. Maier, C.L. Hsieh, F. Wiklund, W.J. Catalona, W.D. Foulkes, D. Mandal, R. A. Eeles, Z. Kote-Jarai, C.D. Bustamante, D.J. Schaid, T. Hastie, E.A. Ostrander, J. E. Bailey-Wilson, P. Radivojac, S.N. Thibodeau, A.S. Whittemore, W. Sieh, REVEL: an ensemble method for predicting the pathogenicity of rare missense variants, Am. J. Hum. Genet. 99 (4) (2016) 877–885.

[22] J. Cheng, G. Novati, J. Pan, C. Bycroft, A. Zemgulyte, T. Applebaum, A. Pritzel, L. H. Wong, M. Zielinski, T. Sargeant, R.G. Schneider, A.W. Senior, J. Jumper, D. Hassabis, P. Kohli, Z. Avsec, Accurate proteome-wide missense variant effect prediction with AlphaMissense, Science 381 (6664) (2023) eadg7492.

[23] M.J. Landrum, J.M. Lee, M. Benson, G. Brown, C. Chao, S. Chitipiralla, B. Gu, J. Hart, D. Hoffman, J. Hoover, W. Jang, K. Katz, M. Ovetsky, G. Riley, A. Sethi, R. Tully, R. Villamarin-Salomon, W. Rubinstein, D.R. Maglott, ClinVar: public archive of interpretations of clinically relevant variants, Nucleic Acids Res. 44 (D1) (2016) D862–D868.

[24] E. Magnin, A. Richard Mornas, I. Ryff, J. Monnin, O. Martinaud, S. Mouton, I. Bernard, S. Basaglia-Pappas, M. Sauvee, G.c.a.p.o.t. GRECO, Suspected neurodevelopmental disorders in adult patients of memory clinics: start at the beginning. GREDEV proposals for clinical practice, Rev. Neurol. (Paris) 179 (4) (2023) 297–307.

[25] K. Oexle, M. Zech, L.G. Stuhn, S. Siegert, T. Brunet, W.M. Schmidt, M. Wagner, A. Schmidt, H. Engels, E. Tilch, O. Monestier, A. Destree, B. Hanker, S. Boesch, R. Jech, R. Berutti, F. Kaiser, B. Haslinger, T.B. Haack, B. Garavaglia, P. Krawitz, J. Winkelmann, N. Mirza-Schreiber, Episignature analysis of moderate effects and mosaics, Eur. J. Hum. Genet. 31 (9) (2023) 1032–1039.

[26] M.A. Levy, H. McConkey, J. Kerkhof, M. Barat-Houari, S. Bargiacchi, E. Biamino, M.P. Bralo, G. Cappuccio, A. Ciolfi, A. Clarke, B.R. DuPont, M.W. Elting, L. Faivre, T. Fee, R.S. Fletcher, F. Cherik, A. Foroutan, M.J. Friez, C. Gervasini, S. Haghshenas, B.A. Hilton, Z. Jenkins, S. Kaur, S. Lewis, R.J. Louie, S. Maitz, D. Milani, A.T. Morgan, R. Oegema, E. Ostergaard, N.R. Pallares, M. Piccione, S. Pizzi, A.S. Plomp, C. Poulton, J. Reilly, R. Relator, R. Rius, S. Robertson, K. Rooney, J. Rousseau, G.W.E. Santen, F. Santos-Simarro, J. Schijns, G.M. Squeo, M. St John, C. Thauvin-Robinet, G. Traficante, P.J. van der Sluijs, S.A. Vergano, N. Vos, K.K. Walden, D. Azmanov, T. Balci, S. Banka, J. Gecz, P. Henneman, J. A. Lee, M. Mannens, T. Roscioli, V. Siu, D.J. Amor, G. Baynam, E.G. Bend, K. Boycott, N. Brunetti-Pierri, P.M. Campeau, J. Christodoulou, D. Dyment, N. Esber, J.A. Fahrner, M.D. Fleming, D. Genevieve, K.D. Kerrnohan, A. McNeill, L. A. Menke, G. Merla, P. Prontera, C. Rockman-Greenberg, C. Schwartz, S.A. Skinner, R.E. Stevenson, A. Vitobello, M. Tartaglia, M. Alders, M.L. Tedder, B. Sadikovic, Novel diagnostic DNA methylation episignatures expand and refine the epigenetic landscapes of Mendelian disorders, HGG Adv 3 (1) (2022) 100075.

[27] E.G. Bend, E. Aref-Eshghi, D.B. Everman, R.C. Rogers, S.S. Cathey, E.J. Prijoles, M. J. Lyons, H. Davis, K. Clarkson, K.W. Gripp, D. Li, E. Bhoj, E. Zackai, P. Mark, H. Hakonarson, L.A. Demmer, M.A. Levy, J. Kerkhof, A. Stuart, D. Rodenhiser, M. J. Friez, R.E. Stevenson, C.E. Schwartz, B. Sadikovic, Gene domain-specific DNA methylation episignatures highlight distinct molecular entities of ADNP syndrome, Clin. Epigenet. 11 (1) (2019) 64.

[28] S.A. Chakkalakal, J. Heilig, U. Baumann, M. Paulsson, F. Zaucke, Impact of arginine to cysteine mutations in collagen II on protein secretion and cell survival, Int. J. Mol. Sci. 19 (2) (2018).

[29] J. Zschocke, P.H. Byers, A.O.M. Wilkie, Mendelian inheritance revisited: dominance and recessiveness in medical genetics, Nat. Rev. Genet. 24 (7) (2023) 442–463.

Update

Parkinsonism and Related Disorders
Volume 134, Issue , May 2025, Page

DOI: https://doi.org/10.1016/j.parkreldis.2025.107795

Parkinsonism and Related Disorders 134 (2025) 107795

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Corrigendum to "Variable expressivity of *KMT2B* variants at codon 2565 in patients with dystonia and developmental disorders" [Parkinson. Relat. Disord. (2025) 133 107319]

Antonia M. Stehr [a,1], Jan Fischer [b,1], Nazanin Mirza-Schreiber [a,c,1], Katerina Bernardi [d,e], Joseph Porrmann [b], Philip Harrer [a,f], Frank Kaiser [g], Rami Abou Jamra [h], Juliane Winkelmann [a,f,i,j], Robert Jech [k], Anne Koy [e,l], Konrad Oexle [a,c,f], Michael Zech [a,f,m,*]

[a] *Institute of Human Genetics, Technical University of Munich, School of Medicine and Health, Munich, Germany*
[b] *Institute for Clinical Genetics, University Hospital Carl Gustav Carus at TUD Dresden University of Technology, Dresden, Germany*
[c] *Neurogenetic Systems Analysis Group, Institute of Neurogenomics, Helmholtz Munich, Neuherberg, Germany*
[d] *Department of Human Neurosciences, Sapienza University of Rome, Rome, Italy*
[e] *Department of Pediatrics, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany*
[f] *Institute of Neurogenomics, Helmholtz Zentrum München, Munich, Germany*
[g] *Institute of Human Genetics, Universitätsklinikum Essen, Essen, Germany*
[h] *Institute of Human Genetics, University of Leipzig Medical Center, Leipzig, Germany*
[i] *Munich Cluster for Systems Neurology (SyNergy), Munich, Germany*
[j] *DZPG, Deutsches Zentrum für Psychische Gesundheit, Munich, Germany*
[k] *Department of Neurology, Charles University, 1st Faculty of Medicine and General University Hospital in Prague, Prague, Czech Republic*
[l] *Center for Rare Diseases, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany*
[m] *Institute for Advanced Study, Technical University of Munich, Garching, Germany*

The authors regret < that in the original version of our article one grant number was incorrect. The correct number is: grant AZV NW24-04-00067>.

The authors would like to apologise for any inconvenience caused.

DOI of original article: https://doi.org/10.1016/j.parkreldis.2025.107319.

* Corresponding author. Institute of Neurogenomics, Helmholtz Zentrum München, Deutsches Forschungszentrum für Gesundheit und Umwelt (GmbH), Ingolstädter Landstraße 1, Neuherberg, 85764, Germany.
E-mail address: michael.zech@mri.tum.de (M. Zech).

[1] These authors contributed equally as first authors.

https://doi.org/10.1016/j.parkreldis.2025.107795

Available online 23 March 2025