Movement Disorders
CLINICAL PRACTICE

CASE REPORT

Paroxysmal Dyskinesia with a Novel Variant in the Histone 3 Family 3B (H3-3B) Gene

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Heterozygous germline deleterious variants in the Histone 3 Family 3A and 3B genes *H3-3A* and *H3-3B* cause a neurodevelopmental disorder, characterized by developmental delay (DD)/intellectual disability (ID) and nonspecific craniofacial abnormalities.[1] Here we report a 13-year-old female with the previously undescribed phenotype of paroxysmal dyskinesia (PxD) and a de novo variant in *H3-3B*.

Case Report

A 13-year-old female was referred for episodes of PxD. She was born to non-consanguineous parents, with no family history of movement disorders (MDs).

She presented a history of DD, starting to walk at 2 years of age and experiencing language delay.

Since the age of 6 years old, she has experienced paroxysmal episodes of hyperventilation followed by dystonic posturing mainly on the right side of her body, accompanied by choreiform movements of the face and arms (Video 1). The episodes mostly occurred in the morning, lasting from a few seconds to a minute, with over 50 episodes a day. Speaking became difficult during more severe episodes. Episodes were more frequent in the mornings and triggered mainly by strong emotions, such as excitement or frustrations and sometimes by voluntary movements, such as getting up. No nocturnal episodes were reported.

She had appendicular hypotonia, ligamentous laxity, and buccolingual apraxia. The rest of the examination was normal with no MDs between episodes. A diagnosis of PxD was made at the age of 8.

Carbamazepine up to a dosage of 400 mg/day resulted in no improvement. Clonazepam (maximum 0.75 mg/day) initially reduced episode frequency and intensity but lost effectiveness over time and was discontinued. Similarly, trials with L-dopa (75 mg/day), Trihexyphenidyl (15 mg/day), Acetazolamide (375 mg/day), and Levetiracetam (1250 mg/day) were ineffective. Interestingly, she had a sustained partial benefit to Topiramate (TPM) with a more than 50% reduction in the frequency of episodes. Currently, the patient takes 130 mg/day of

Video 1. Hyperkinetic movements associated with *H3-3A* and *H3-3B*-related neurodevelopmental disorder. The videos capture the patient during typical paroxysmal events. The predominant phenomenology is chorea, that involves mainly the upper limbs, along with facial involvement, and neck extension dystonia.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.70236

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TPM. With this treatment, episodes occur about 3–4 times a day (versus over 50 episodes a day pre-treatment), lasting an average of 10 s.

Biochemical diagnostic testing was normal in blood (transaminases, uric acid, electrolytes, TSH, copper, ceruloplasmin, vitamin B12, folate, amino acids, lactate, ammonia) and cerebrospinal fluid (lactate, pyruvate, glucose, protein, amino acids and neurotransmitter metabolites). Brain magnetic resonance imaging (MRI) at 8 years of age showed a non-specific hyperintense T2/FLAIR lesion in the deep right-parietal white matter of unclear significance. The basal ganglia were normal, as was brain magnetic resonance spectroscopy. Routine awake EEG and a 4-h monitoring, which captured multiple episodes of dyskinesia, were normal.

Trio exome analysis revealed a heterozygous de novo variant, c.109A>G (p.Lys37Glu), in *H3.3B* (NM_005324.5).

This variant was designated as likely pathogenic because it fulfills criteria PS2, PM2 and PP3 of the consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. It was documented to be de novo (PS2), is absent in large population databases ExAc and 1000 Genomes (PM2) and multiple computational programs (SIFT, Polyphen-2, MutationTaster and CADD) concluded that it is disruptive (PP3): lysine 109 is evolutionarily conserved and the variant substitutes the negatively-charged amino acid lysine with a positively charged one, glutamic acid.

Discussion

The *H3-3A* and *H3-3B* genes are located on chromosomes 1q42.12 and 17q25.1, respectively, and encode proteins with identical protein sequences.[1] The c.109A>G variant occurs in the Lysine 37 codon of *H3-3B*. Confusingly, because the methionine 1 residue of histones is removed nearly immediately after transcription, the variant residue is typically designated lysine 36 (K36) in histone research. K36 is well documented to undergo trimethylation, an important epigenetic modification.[2] Intriguingly, an identical paralogous K36E substitution was described in *H3-3A*, among the original description of *H3-3A* and *H3-3B*-related neurodevelopmental disorder.[1]

We report a video-documented case of *H3-3B*-related neurodevelopmental disorder associated with PxD. The phenotype blurs the traditional classification between paroxysmal kinesiogenic versus paroxysmal non kinesiogenic dyskinesia. Interestingly, among 97 *H3-3A* and *H3-3B*-related neurodevelopmental disorder cases published to date,[1,3–6] dystonia was previously reported in four and oral dyskinesias in two (Table 1). *H3.3A* and *H3.3B* may therefore be emerging genes for MDs, the prevalence of which may be underestimated. A recent review of the phenotypic spectrum of *H3-3A* and *H3-3B*-related neurodevelopmental disorder[3] emphasize the importance of repeated phenotyping due to the lack of longitudinal follow-up for most individuals, considering this disorder as a possible neurodegenerative condition. Interestingly, in three of the seven

TABLE 1 *Comparison of our case with previously reported Bryant-Li-Bhoj neurodevelopmental syndrome associated with movement disorders*

Paper	Gene	Variant	Gender	Age at last evaluation	Brain imaging	Movement disorder(s)
Layo-Carris et al[3]	*H3-3A*	c.34A>G (p.Thr12Ala)	F	5 y 2 m	Callosal dysgenesis with possible mild left colpocephaly	Dystonia
Layo-Carris[3]	*H3-3A*	c.73G>A (p.Ala25Thr)	M	15 y 9 m	Mild prominence of spinal central canal	Lower limb spasticity with some dystonic posturing from age 5 y, slowly progressive (right side affected first)
Bryant et al[1]	*H3-3A*	c.137C>T (p.Thr46Ile)	F	4 y 6 m	Mild enlargement of cisterna magna with a thin corpus callosum	Dystonia and oral dyskinesia
Bryant et al[1]	*H3-3A*	c.377A>G (p.Gln126Arg)	F	15 y	Hypomyelination, thin corpus collosum	Oral dyskinesia
Hojo et al[6]	*H3-3A*	c.143C>G (p.Ala48Gly)	F	20 y	Normal	Neonatal myoclonus (unclear origin)
This report	*H3-3B*	c.109A>G (p.Lys37Glu)	F	13 y	Non-specific hyperintense T2/FLAIR lesion in the deep right-parietal white matter of unclear significance	Paroxysmal dyskinesia (right more than left)
Bryant et al[1]	*H3-3B*	c.440C>A (p.Ser147Ter)	M	15 y	Progressively diminishing volume of putamen and caudate on the right side with hyperintense T2 signal. Hypointense T2 signal of globus pallidus.	Progressive hemidystonia (left side), first signs at 9 y

Abbreviations: F, female; M, male; m, months; y, years.

patients associated with MDs (including our case), the initial manifestations appear to be asymmetric, and, in one of these (*H3-3B* c.440C>A, p.Ser147Ter),[1] MRI showed progressive reduction of the volume of the putamen and caudate on one side.

Additionally, although PxD are relatively uncommon among NDDs, an increasing number of NDD-associated genes, such as *KCNMA1*, *ATP1A3*, *ADCY5*, *PDE2A*, and *SLC2A1*, have recently been linked to PxD phenotypes.[7–9] More rarely, *PRRT2* mutations have also been associated with neurodevelopmental impairment.[8] These observations suggest that a PxD-NDD syndrome may represent an underrecognized clinical entity. It is interesting to note that topiramate can act as an histone deacetylase inhibitor.[10] We can speculate that the patient's improvement with this treatment may in part relate to this action.

In conclusion, this case history illustrates the early occurrence of movement disorders in *H3-3A* and *H3-3B*-related neurodevelopmental disorder; similar observations are increasingly described in many neurodevelopmental disorders, an important consideration because many of them might benefit from targeted treatments.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution. (2) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

G.D'.O.: 1A–C, 2A,B.

S.P.: 1C, 2B.

G.M.: 1C, 2B.

I.M.: 1A–C, 2B.

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Disclosures

Ethical Compliance Statement: This study was performed in line with the principles of the Declaration of Helsinki and procedures were in accordance with the ethical standards of our Institution. Written informed consent was obtained from the legal guardian of the patient, for the publication of the case history and the video included in this article, authorizing the offline and/or online distribution of the video material. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. ■

References

1. Bryant L, Li D, Cox SG, et al. Histone H3.3 beyond cancer: germline mutations in histone 3 family 3A and 3B cause a previously unidentified neurodegenerative disorder in 46 patients. *Sci Adv* 2020;6(49):eabc9207. https://doi.org/10.1126/sciadv.abc9207.
2. Xiao C, Fan T, Tian H, et al. H3K36 trimethylation-mediated biological functions in cancer. *Clin Epigenetics* 2021;13(1):199. https://doi.org/10.1186/s13148-021-01187-2.
3. Layo-Carris DE, Lubin EE, Sangree AK, et al. Expanded phenotypic spectrum of neurodevelopmental and neurodegenerative disorder Bryant-Li-Bhoj syndrome with 38 additional individuals. *Eur J Hum Genet* 2024;32:928–937. https://doi.org/10.1038/s41431-024-01610-1.
4. Maver A, Čuturilo G, Ruml SJ, Peterlin B. Clinical next generation sequencing reveals an H3F3A gene as a new potential gene candidate for microcephaly associated with severe developmental delay, intellectual disability and growth retardation. *Balkan J Med Genet* 2019;22(2):65–68. https://doi.org/10.2478/bjmg-2019-0028.
5. Okur V, Chen Z, Vossaert L, et al. De novo variants in H3-3A and H3-3B are associated with neurodevelopmental delay, dysmorphic features, and structural brain abnormalities. *NPJ Genom Med* 2021;6(1):104. https://doi.org/10.1038/s41525-021-00268-8.
6. Hojo M, Soma N, Yamada K, et al. Neonatal myoclonus in Bryant-Li-Bhoj syndrome associated with a novel H3F3A variant. *Hum Genome Var* 2024;11(1):45. https://doi.org/10.1038/s41439-024-00303-x.
7. Zhang ZB, Tian MQ, Gao K, Jiang Y-W, Wu Y. De novo KCNMA1 mutations in children with early-onset paroxysmal dyskinesia and developmental delay. *Mov Disord* 2015;30(9):1290–1292. https://doi.org/10.1002/mds.26216.
8. Gardiner AR, Jaffer F, Dale RC, et al. The clinical and genetic heterogeneity of paroxysmal dyskinesias. *Brain* 2015;138(Pt 12):3567–3580. https://doi.org/10.1093/brain/awv310.
9. Doummar D, Dentel C, Lyautey R, et al. Biallelic PDE2A variants: a new cause of syndromic paroxysmal dyskinesia. *Eur J Hum Genet* 2020;28(10):1403–1413. https://doi.org/10.1038/s41431-020-0641-9.
10. Eyal S, Yagen B, Sobol E, Altschuler Y, Shmuel M, Bialer M. The activity of antiepileptic drugs as histone deacetylase inhibitors. *Epilepsia* 2004 Jul;45(7):737–744. https://doi.org/10.1111/j.0013-9580.2004.00104.x.