Clinical/Scientific Notes

Rubina Dad, MPhil
Susan Walker, PhD
Stephen W. Scherer, PhD
Muhammad Jawad Hassan, PhD
Suk Yun Kang, MD, PhD
Berge A. Minassian, MD

Neurol Genet
2017;3:e189; doi: 10.1212/NXG.0000000000000189

HYPERVENTILATION-ATHETOSIS IN *ASXL3* DEFICIENCY (BAINBRIDGE-ROPERS) SYNDROME

OPEN

The protein product of the *Drosophila additional sex combs-like (Asx)* gene was shown to be a regulator, both a suppressor and an activator, of *Hox* developmental genes. Mammals, including humans, possess 3 *Asx* orthologs: 2 expressed ubiquitously, while the third, *ASXL3*, is predominantly expressed in the brain. All 3 are involved in transcriptional regulation of many genes through direct actions or epigenetically via histone modifications. Specific genes regulated by *ASXL3* have not been identified.[1,2]

The clinical phenotype associated with heterozygous loss of *ASXL3* function was first described in 2013 (Bainbridge-Ropers syndrome; OMIM 615485) and subsequently expanded through a total of 27 patients to date. Key clinical features are as follows: intellectual disability with profound speech impairment, severe early feeding difficulty, autistic behaviors, failure to thrive, severe muscular hypotonia, and a characteristic long face with arched eyebrows, downslanting palpebral fissures, and poor expressivity.[3–6] We describe a new case with a striking phenotype, namely hyperventilation-induced athetosis.

The patient is the 16-year-old son of unrelated Korean parents. His birth weight was 3.2 kg. In the neonatal period, he had episodes of apnea, for which EEG did not support an epileptic cause. He subsequently exhibited severe delays in all aspects of development. He walked at 9 years. He is short of stature and has microcephaly (head circumference <third percentile), hypertelorism, and a hypoplastic face (figure, A). He has severe intellectual disability and cannot understand or express any language. He has no eye contact, has never focused on any object, and is considered blind. Brainstem auditory evoked potentials obtained recently were normal. He does not have feeding or swallowing difficulties. Current examination reveals scoliosis and postural instability. He has an ataxic wide-based and staggering gait, which has been gradually deteriorating. He is not presently hypotonic, and motor strength and sensory functions appear to be normal, as are his deep tendon and plantar reflexes. Brain MRI and several EEGs have been normal.

Since age 10, the patient has been exhibiting frequent daily episodes of deep and constant hyperventilation. His neurodevelopmental presentation places him at the severe end of the autism spectrum. The hyperventilation escalates with any nervousness, and as it builds, he develops athetotic movements of both upper extremities, especially of the hands (videos 1 and 2 at Neurology.org/ng). The young man also hyperventilates in bed prior to falling asleep again developing the athetoid movements (video 3). Both hyperventilation and movements cease with sleep.

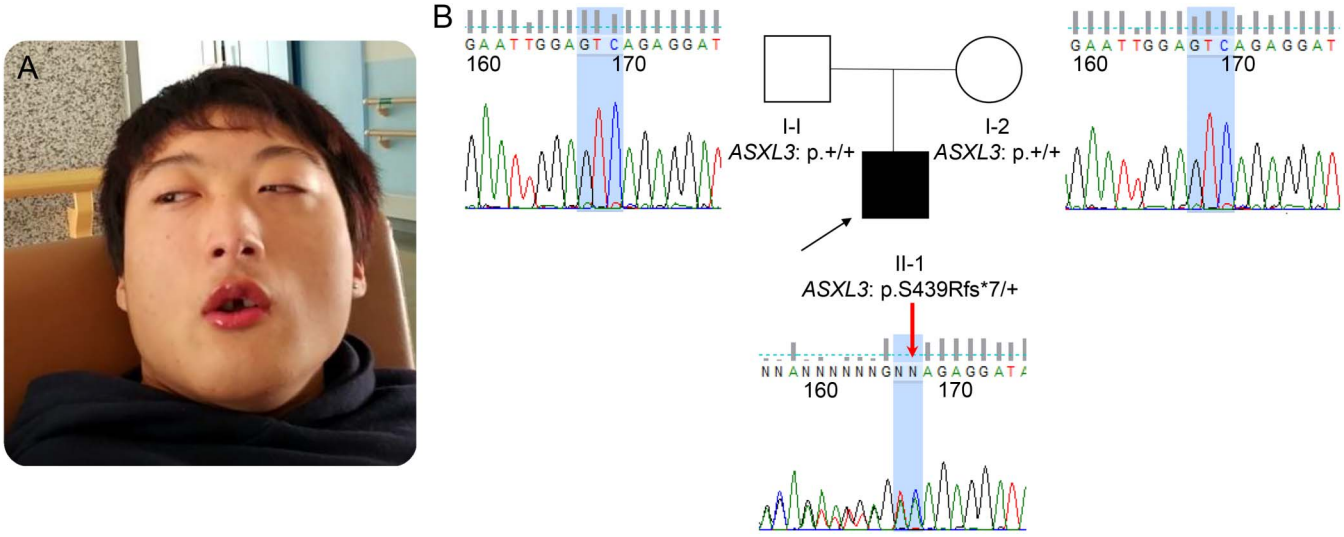
Written informed consent was obtained from the family for participation in the study and showing the video recordings. Whole-exome sequencing was performed on the patient's DNA using the Agilent SureSelect Human All Exon V5 target enrichment kit followed by sequencing on Illumina HiSeq 2500. Bases were called using bcl2fastq v2.17 and reads mapped to the hg19 reference sequence using the Burrows-Wheeler Aligner backtrack algorithm (v0.5.9). A previously unreported heterozygous substitution-deletion mutation in the *ASXL3* gene was identified (NM_030632; exon11: c.1314_1316delinsA; p. S439Rfs*7), resulting in frameshift and predicted premature truncation. Sanger sequencing confirmed the mutation in the patient (figure, B) and its absence in his parents.

Specific loci for which transcription is regulated by the *ASXL3* are not known, nor which of these target genes underlie the resultant neurodevelopmental outcome. One study in patient fibroblasts identified 564 misregulated genes (approximately half up and the rest downregulated), most of which had known functions in development and proliferation, or were themselves transcriptional regulators, suggesting that ASXL3 may function in upstream modulation of neurodevelopmental regulator genes.[2] ASXL3 is clearly critical to brain development, and profound developmental disturbance manifested in patients resulting from the loss of 1 of the 2 copies of the gene suggests haploinsufficiency as the likely mechanism.

Athetosis with hyperventilation is seen in the present case; however, only hyperventilation was previously reported in 2 cases.[4,5] Hyperventilation in the context of severe neurodevelopmental disturbance is seen in several neurogenetic disorders, including Rett, Joubert, Pitt-Hopkins, and Pallister-Killian syndromes. Recent

Supplemental data at Neurology.org/ng

Figure **Facial appearance and the mutation of the patient with Bainbridge-Ropers syndrome**



(A) Patient photograph: microcephaly (head circumference <third percentile), hypertelorism, and facial hypoplasia. (B) Electropherograms from exon 11 of the *ASXL3* gene showing de novo heterozygous deletion of 2 base pairs (shaded area) and a substitution (arrow) of a third (C>A) resulting in frameshift/premature termination (*ASXL3* NM_030632: c.1314_1316delinsA; p.S439Rfs*7).

work in Rett syndrome mice revealed that expression of *Mecp2* broadly in the medulla, rather than in any particular medullary nucleus or pathway, is required for normal breathing.[7] Similar future work in autopsy and animal models of the other above diseases, and in Bainbridge-Ropers disease, will gradually uncover the pathways, systems, and functions involved in the neurodevelopmental symptoms in affected patients and aid in the understanding of normal brain development and function. Our particular case suggests a neural connection, in the context of ASXL3 deficiency, between pathways of respiration and of motor control.

From the Atta-ur Rahman School of Applied Biosciences (R.D., M.J.H.), National University of Sciences and Technology (NUST), Islamabad, Pakistan; Program in Genetics and Genome Biology (R.D.) and The Centre for Applied Genomics, Genetics and Genome Biology (S.W., S.W.S.), The Hospital for Sick Children, Department of Molecular Genetics (S.W.S.), and McLaughlin Centre (S.W.S.), University of Toronto, Ontario, Canada; Department of Neurolgy (S.Y.K.), Dongtan Sacred Heart Hospital, Hallym University College of Medicine, Hwaseong, Gyeonggi-do, Republic of Korea; Program in Genetics and Genome Biology (B.A.M.), Division of Neurology, Department of Pediatrics, The Hospital for Sick Children, University of Toronto, Ontario, Canada; and Departments of Pediatrics, Neurology, and Neurotherapeutics (B.A.M.), University of Texas Southwestern, Dallas.

Author contributions: study concept and design by Berge A. Minassian and Suk Yun Kang. Acquisition of clinical data by Suk Yun Kang. Acquisition of genetic data by Rubina Dad, Susan Walker, and Stephen W. Scherer. Analysis and interpretation of data by Rubina Dad and Susan Walker. Study supervision by Berge A. Minassian and Muhammad Jawad Hassan. Critical revision of the manuscript for intellectual content by Berge A. Minassian and Suk Yun Kang.

Acknowledgement: The authors are thankful to the family members for participation in the study. Rubina Dad gratefully acknowledges her funding by the Higher Education Commission of Pakistan under the International Research Support Initiative Program (HEC-IRSIP). This work was funded by the Ontario Brain Institute and Genome Canada. Berge A. Minassian holds the University of Toronto Michael Bahen Chair in Epilepsy Research and the University of Texas Southwestern Jimmy Elizabeth Westcott Distinguished Chair in Pediatric Neurology.

Study funding: No targeted funding reported.

Disclosure: R. Dad has received research support from the Higher Education Commission of Pakistan. S. Walker reports no disclosures. S.W. Scherer has served on the editorial boards of Genomic Medicine, Genes, Genomes, Genetics, *the* Journal of Personalized Medicine, *the* Open Genomics Journal, *the* Hugo Journal, Genome Medicine, *the* Journal of Neurodevelopmental Disorders, Autism Research, PathoGenetics, Comparative and Functional Genomics, BioMed Central Medical Genomics, *and* Cytogenetics and Genome Research*; and has received research support from the Genome Canada/Ontario Genomics Institute, the Canadian Institutes of Health Research, the Canadian Institute for Advanced Research, the McLaughlin Centre, the Canada Foundation for Innovation, the government of Ontario, the NIH, Autism Speaks, and the SickKids Foundation. M.J. Hassan reports no disclosures. S.Y. Kang has served on the editorial board of the* Journal of Clinical Neurology. *B.A. Minassian holds patents for diagnostic testing of the following genes: EPM2A, EPM2B, MECP2, and VMA21; has received research support from the NINDS of the NIH; and receives license fee payments/royalty payments from patents for diagnostic testing of the following genes: EPM2A, EPM2B, MECP2, and VMA21. Go to Neurology.org/ng for full disclosure forms. The Article Processing Charge was funded by the authors.*

Received April 13, 2017. Accepted in final form July 25, 2017.

Correspondence to Dr. Minassian: berge.minassian@utsouthwestern.edu

1. Micol JB, Abdel-Wahab O. The role of additional sex combs-like proteins in Cancer. Cold Spring Harb Perspect Med 2016;6:a026526.

2. Srivastava A, Ritesh KC, Tsan YC, et al. De novo dominant ASXL3 mutations alter H2A deubiquitination and transcription in Bainbridge-Ropers syndrome. Hum Mol Genet 2016;25:597–608.
3. Bainbridge MN, Hu H, Muzny DM, et al. De novo truncating mutations in ASXL3 are associated with a novel clinical phenotype with similarities to Bohring-Opitz syndrome. Genome Med 2013;5:11.
4. Kuechler A, Czeschik JC, Graf E, et al. Bainbridge-Ropers syndrome caused by loss-of-function variants in ASXL3: a recognizable condition. Eur J Hum Genet 2017;25: 183–191.
5. Balasubramanian M, Willoughby J, Fry AE, et al. Delineating the phenotypic spectrum of Bainbridge-Ropers syndrome: 12 new patients with de novo, heterozygous, loss-of-function mutations in ASXL3 and review of published literature. J Med Genet 2017;54:537–543.
6. Dinwiddie DL, Soden SE, Saunders CJ, et al. De novo frameshift mutation in ASXL3 in a patient with global developmental delay, microcephaly, and craniofacial anomalies. BMC Med Genomics 2013;17:32.
7. Huang TW, Kochukov MY, Ward CS, et al. Progressive changes in a distributed neural circuit underlie breathing abnormalities in mice lacking MeCP2. J Neurosci 2016;36:5572–5586.