Movement Disorders
CLINICAL PRACTICE
LETTER: GENOTYPE AND PHENOTYPE

STUB1-Associated Autosomal-Recessive Spinocerebellar Ataxia Type 16 (SCAR16) Presenting with Gordon–Holmes Syndrome Caused by Maternal Uniparental Isodisomy

Habibah A.P. Agianda, MD,[1] Amy Tam, BSc,[1] Avaneesh Kunta, BSc,[2] Umar Zubair, cand.med,[1] Afshin Saffari, MD,[1] Joshua Rong, BSc,[1] Michelle Crough, MD,[1] Rasha Srouji, CPNP,[1] Vicente Quiroz, MD,[1] Kathryn Yang, MBChB, FRCPC,[1] Luca Schierbaum, MD,[1] and Darius Ebrahimi-Fakhari, MD, PhD[1,*]

Gordon–Holmes syndrome (GHS) is a clinical syndrome characterized by cerebellar ataxia, cognitive decline, endocrinopathies, and psychiatric comorbidities. Biallelic variants in *STUB1* have been linked to GHS[1] and are known to cause autosomal-recessive spinocerebellar ataxia 16 (SCAR16, ATX-*STUB1*).[2] *STUB1* encodes CHIP (C-terminus of HSC70-interacting protein), a key E3 ubiquitin ligase and co-chaperone implicated in several neurodegenerative diseases.[3] Here, we describe a case of SCAR16 with GHS due to a novel biallelic variant in *STUB1* inherited through maternal uniparental isodisomy (UPiD(16)mat).

The case is a 20-year-old woman who was referred for evaluation of gait ataxia, first noted 5 years prior when she presented with an increasing frequency of falls and unsteadiness, leading to difficulty with running and climbing stairs. Gait and coordination deteriorated significantly, ultimately necessitating the use of a walker for ambulation. She also developed dysarthria and experienced cognitive challenges with routine tasks.

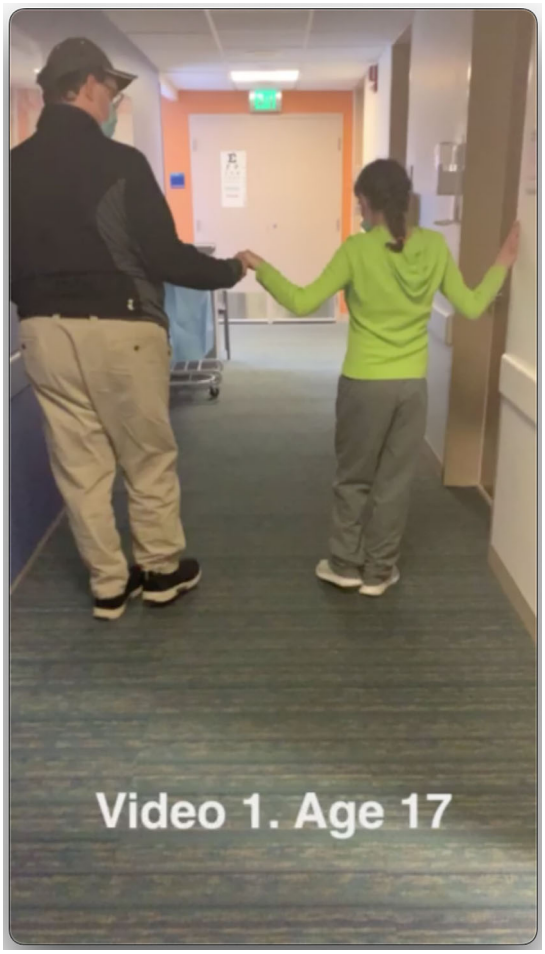
The patient was born at term and was diagnosed with cleft lip and palate postnatally, with no other perinatal complications. The parents are of mixed Northern European ancestry, with an unremarkable family history. After repair for her cleft palate, she was noted to have speech delays at 24 months. She was found to be toe-walking, which corrected with orthopedic braces. Diagnoses of autism spectrum disorder, attention deficit hyperactivity disorder, and anxiety disorder were made in early childhood. At age 14, she was diagnosed with hypothyroidism and started on levothyroxine. At age 16, she was also diagnosed with growth hormone deficiency and prescribed somatropin, with laboratory tests also showing mild hypogonadotropic hypogonadism. Around the same time, she experienced onset of generalized tonic–clonic seizures that responded to levetiracetam.

Upon presentation to our clinic at 17 years of age, her height was 151 cm (less than third percentile) and weight was 43 kg (less than third percentile). She was alert but had a short attention span and appeared anxious, frequently fidgeting and wringing her fingers. Extraocular movements were intact, though she exhibited slow and hypometric horizontal saccades and moderately dysarthric speech. Muscle strength was full, and axial and appendicular tone were normal. She displayed impaired rapid alternating movements and bilateral dysmetria in both upper and lower limbs. Reflexes were brisk in the lower extremities, with no clonus and a normal plantar flexor reflex. Most notably, she exhibited significant gait ataxia, with a Brief Ataxia Rating Scale (BARS) score of 17/30. Specifically, she had a gait score of 4/8, knee-tibia test 3/4 bilaterally, finger-to-nose test 2/4 bilaterally, dysarthria 2/4, and oculomotor abnormalities 1/2 (Video 1). At age 18, her ataxia had worsened, with a BARS score of 19/30 (Video 2), including a gait score of 6/8. Therapy with 4-aminopyridine was initiated, and follow-up at age 20 showed a stable BARS score (Video 3).

A diagnosis of GHS was made based on clinical presentation. Exome sequencing revealed the absence of heterozygosity regions on chromosome 16, suggestive of uniparental isodisomy, which spanned a private (absent from gnomAD, version 4.1.0), maternally inherited homozygous splice variant in *STUB1* (NM_005861.2, c.612 + 11C > G) predicted to lead to a donor gain (SpliceAI DG 0.9) and increased MaxEntScan score (6.15). This variant was classified as a variant of uncertain significance (ACMG criteria: PM2, BP4), but considering the patient's clinical features was deemed diagnostic. A retrospective review of brain magnetic resonance imaging (MRI) scans confirmed mild volume loss of the cerebellar hemispheres and vermis at age 12.

[1]*Movement Disorders Program, Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts, USA;* [2]*University of Central Florida College of Medicine, Orlando, Florida, USA*

***Correspondence to:** Dr. Darius Ebrahimi-Fakhari, Movement Disorders Program, Department of Neurology, Boston Children's Hospital, Harvard Medical School, 3 Blackfan Circle, Boston, MA 02115, USA; E-mail: darius.ebrahimi-fakhari@childrens.harvard.edu
Habibah A.P. Agianda, Amy Tam and Avaneesh Kunta have contributed equally to this article.
Received 19 September 2024; revised 23 November 2024; accepted 8 December 2024.
Published online 00 Month 2024 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mdc3.14322



Video 1. Video taken at age 17 years. The patient walks with assistance from 1 person and occasionally relies on the wall for balance. Truncal ataxia and an ataxic gait are observed. Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.14322

Video 2. Video taken at age 18 years. Speech exhibits a nasal quality with mild dysarthria. The patient struggles to complete the Archimedes spiral. Gait assessment reveals dependence on a walker for balance with significant ataxia. Brisk deep tendon reflexes are noted in the lower limbs. Finger-to-nose testing demonstrates moderate dysmetria during postural tasks, and rapid alternating movements are impaired. Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.14322

Follow-up at age 17 revealed progression to severe diffuse cerebellar atrophy (Fig. 1).

This report highlights that SCAR16, an ultrarare form of recessive ataxia, can be caused by UPiD(16)mat and exhibit features consistent with GHS. In uniparental isodisomy, an individual inherits 2 identical copies of a chromosome or chromosomal region from 1 parent, a scenario that can unmask recessive conditions. The presence of progressive cerebellar ataxia, cognitive decline, and endocrinopathies directed our investigation toward *STUB1*, though other genes, such as *RNF216*, *OTUD4*, and *PNPLA6*, have been associated with GHS.[4] From a movement disorders perspective, SCAR16 presents with a broad spectrum ranging from progressive cerebellar ataxia to dystonia, chorea, and myoclonus.[5] Absent in our case were sensory neuropathy,[6,7] chorea, or dystonia.[5,8]

Exome sequencing identified 2 copy-neutral regions of absence of heterozygosity on chromosome 16, consistent with UPiD(16)mat, covering a homozygous variant in *STUB1*. The biallelic variant, c.612 + 11C > G, is novel and is predicted to lead to a loss of function. Brain MRI confirmed cerebellar volume loss, supporting the diagnosis. This finding underscores the importance of considering UPD in the differential diagnosis of recessive ataxias. It is noteworthy that heterozygous variants in *STUB1* cause autosomal-dominant SCA48[9] and have been implicated in a digenic inheritance pattern with intermediate-length expansions in the *TBP* gene in an ataxia-dementia phenotype,[10] underscoring the complexity of phenotypes associated with this gene. Notably, repeat expansion analysis in *TBP* in our patient revealed repeats of 33 and 37, respectively, below the threshold. Future studies are needed to assess the frequency of

Video 3. Video taken at age 20 years. Finger-to-nose testing shows segmented elbow movements with moderate dysmetria in both upper limbs. Heel-to-shin testing reveals lateral deviations bilaterally. Deep tendon reflexes remain brisk. The patient can ambulate only with a walker and exhibits significant gait ataxia.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.14322

UPD in recessive, early-onset ataxias, and potential genotype–phenotype correlations.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical analysis: A. Design, B. Execution, C. Review and critique; (3) Manuscript: A. Writing of the first draft, B. Review and critique.

H.A.P.A.: 1A, 1B, 1C, 3A
A.T.: 1C, 3A, 3B
A.K.: 1C, 3A, 3B
U.Z.: 1C, 3B
A.S.: 1C, 3B
J.R.: 1C, 3B
M.C.: 1C, 3B
R.S.: 1C, 3B
V.Q.: 1C, 3B
K.Y.: 1C, 3B
L.S.: 1B, 1C, 3B
D.E.-F.: 1A, 1B, 1C, 3A

Acknowledgments

We thank the patient and her family for supporting this research.

Disclosures

Ethical Compliance Statement: This patient was identified through the HSP Genomic Sequencing Initiative (NCT05354622),

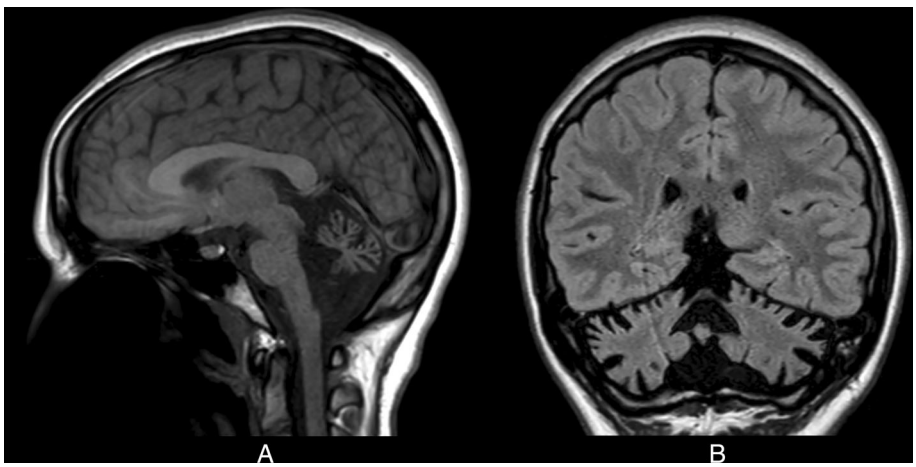


FIG. 1. Brain MRI (magnetic resonance imaging) at the age of 18 years. (**A**) Sagittal T1-weighted image shows diffuse cerebellar volume loss. (**B**) Coronal T2-FLAIR (fluid-attenuated inversion recovery) image reveals significant atrophy of the cerebellar vermis and hemispheres.

part of the Children's Rare Disease Cohorts at Boston Children's Hospital. This study is approved by the Boston Children's Hospital Institutional Review Board (IRB-P00039630). Written consent was obtained. 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.

Funding Sources and Conflicts of Interest: This project was supported by the Boston Children's Hospital Children's Rare Disease Cohorts (CRDC). Research in the Ebrahimi-Fakhari Laboratory is supported by the Spastic Paraplegia Foundation, the Boston Children's Hospital Translational Research Program, and the National Institutes of Health/National Institute of Neurological Disorders and Stroke (K08NS123552-01). Vicente Quiroz is supported by a fellowship from the International Parkinson and Movement Disorder Society. Luca Schierbaum is supported by a fellowship from the German Research Foundation (536105452). The authors declare that there are no conflicts of interest relevant to this work.

Financial Disclosures for the Previous 12 Months: Vicente Quiroz reports a fellowship from the Movement Disorders Society—Pan America Section. Luca Schierbaum reports a fellowship from the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation, 536105452). Darius Ebrahimi-Fakhari served as a consultant to the University of Texas Southwestern, the German Center for Neurodegenerative Diseases, and Guidepoint LLC; received honoraria from the Movement Disorders Society; holds a patent related to hereditary spastic paraplegia (US Patent no.: 63/503,262, Compounds for treating hereditary spastic paraplegia); and has received research funding from the National Institutes of Health/National Institute of Neurological Disorders and Stroke, CureAP4 Foundation, CureSPG50 Foundation, Spastic Paraplegia Foundation, Tom Wahlig Foundation, Un raggio di Sole per Martina, Manton Center for Orphan Disease Research, BCH Office of Faculty Development, and BCH Translational Research Program and Astellas Pharmaceuticals.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. ■

References

1. Shi CH, Schisler JC, Rubel CE, et al. Ataxia and hypogonadism caused by the loss of ubiquitin ligase activity of the U box protein CHIP. *Hum Mol Genet* 2014;23(4):1013–1024.
2. Lange LM, Gonzalez-Latapi P, Rajalingam R, et al. Nomenclature of genetic movement disorders: recommendations of the International Parkinson and Movement Disorder Society task force: an update. *Mov Disord* 2022;37(5):905–935.
3. Pratt WB, Gestwicki JE, Osawa Y, Lieberman AP. Targeting Hsp90/Hsp70-based protein quality control for treatment of adult onset neurodegenerative diseases. *Annu Rev Pharmacol Toxicol* 2015;55:353–371.
4. Gonzalez-Latapi P, Sousa M, Lang AE. Movement disorders associated with hypogonadism. *Mov Disord Clin Pract* 2021;8(7):997–1011.
5. Olszewska DA, Kinsella JA. Extending the phenotypic Spectrum associated with STUB1 mutations: a case of dystonia. *Mov Disord Clin Pract* 2020;7(3):318–324.
6. Synofzik M, Schule R, Schulze M, Gburek-Augustat J, Schweizer R, Schirmacher A, et al. Phenotype and frequency of STUB1 mutations: next-generation screenings in Caucasian ataxia and spastic paraplegia cohorts. *Orphanet J Rare Dis* 2014;9:57.
7. Heimdal K, Sanchez-Guixe M, Aukrust I, Bollerslev J, Bruland O, Jablonski GE, et al. STUB1 mutations in autosomal recessive ataxias-evidence for mutation-specific clinical heterogeneity. *Orphanet J Rare Dis* 2014;9:146.
8. Kawarai T, Miyamoto R, Shimatani Y, Orlacchio A, Kaji R. Choreoathetosis, dystonia, and myoclonus in 3 siblings with autosomal recessive spinocerebellar ataxia type 16. *JAMA Neurol* 2016;73(7):888–890.
9. Genis D, Ortega-Cubero S, San Nicolas H, Corral J, Gardenyes J, de Jorge L, et al. Heterozygous STUB1 mutation causes familial ataxia with cognitive affective syndrome (SCA48). *Neurology* 2018;91(21):e1988–e1998.
10. Nanetti L, Magri S, Fichera M, et al. Complex ataxia-dementia phenotype in patients with digenic TBP/STUB1 spinocerebellar ataxia. *Mov Disord* 2023;38(4):665–675.