https://doi.org/10.14802/jmd.24080 / J Mov Disord 2024;17(3):354-356
pISSN 2005-940X / eISSN 2093-4939

LETTER TO THE EDITOR

Tremulous Dystonia Due to *GNAL* Haploinsufficiency Caused by 18p Deletion Syndrome

Arianna Braccia,[1]* Miryam Carecchio,[2,3]* Francesca Luisa Sciacca,[4] Anna Castagna,[5] Antonio Emanuele Elia,[1] Luigi Michele Romito[1,6]

[1]Department of Clinical Neurosciences - Parkinson and Movement Disorders Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy
[2]Parkinson and Movement Disorders Unit, Department of Neuroscience, University of Padua, Padua, Italy
[3]Study Center for Neurodegeneration (CESNE), University of Padua, Padua, Italy
[4]Department of Diagnostics and Applied Technology, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy
[5]IRCCS Don Gnocchi Foundation, Milan, Italy
[6]Department of Pathophysiology and Transplantation, Milan University, Milan, Italy

Dear Editor,

We read with great interest the Letter by Di Rauso and colleagues.[1] The authors described an individual with adult-onset dystonia-parkinsonism with nigrostriatal denervation carrying a deletion of chromosome 18p encompassing *GNAL* (OMIM# 615073) and speculated that *GNAL* could play a significant role not only in dystonia but also in degenerative parkinsonism.[1]

The phenotypes of chromosome 18p deletion syndrome[2,3] vary widely among individuals due to differences in the size of breakpoints and genes involved in the deletion[3] and may include generalized dystonia and tremor.[4]

Here, we highlight our experience with the heterogeneous phenotypic presentation of 18p syndrome by reporting two unrelated patients who presented with vigorous tremulous dystonia associated with monosomy 18p[5] that caused protein subunit alpha L (*GNAL*) gene[6] haploinsufficiency. A detailed map of the deleted 18p regions obtained by array-comparative genomic hybridization (aCGH) is also provided for both patients (Figure 1).

Patient 1 (P1) was a 67-year-old man who presented with neurological manifestations characterized by adult-onset generalized dystonia involving the face, larynx, upper limbs, and right lower limb and subsequently developed slight hypokinesia (Supplementary Video 1 in the online-only Data Supplement). After age 40, he manifested progressive jerky tremors of the upper limbs (more severe in the right hand, with the additional development of mild rest tremors), and tremulous voice dystonia developed at the age of 54 after cholecystectomy. He later developed eyelid dystonia (apraxia of lid opening). His gait was characterized by mild action-dystonia of the right lower limb. Brain magnetic resonance imaging (MRI) revealed a slight T2-weighted hyperintensity of the left internal pallidum (Figure 1), while the DaT (I-123 ioflupane) scan suggested normal presynaptic dopaminergic terminals. The patient's response to levodopa was limited to a moderate benefit for limb hypokinesia/clumsiness. The nonneurological clinical manifestations were typical of 18p deletion syndrome and included short stature, craniofacial dysmorphism (triangular face with mid-hypoplasia, low-set ears, and bilateral eyelid ptosis), moderate intellectual disability, autoimmune thyroiditis, and pernicious anemia. A neuropsychological evaluation at age 58 confirmed the presence of moderate mental retardation (global Wechsler Adult Intelligence Scale-Revised score of 62 with a verbal score of 62 and a performance score of 68). Genetic analysis revealed a deletion of 13.33–13.37 Mb in the 18p11.32p11.21region: arr[hg19] 18p11.32p11.2

Received: March 29, 2024 **Revised:** May 1, 2024 **Accepted:** May 13, 2024
✉ **Corresponding author:** Luigi Michele Romito, MD, PhD
Parkinson and Movement Disorders Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Via Giovanni Celoria 11, Milan 20133, Italy / **Tel:** +39-02-23942552 / **Fax:** +39-02-23942539 / **E-mail:** luigi.romito@istituto-besta.it
*These authors contributed equally to this work.

(118729x2, 118788_1346377x1,13496784x2) (Figure 1, P1).

Patient 2 (P2) was a 59-year-old woman who presented with neurological manifestations characterized by multifocal adult-onset dystonia, which started in the left leg (thigh flexion) and progressed to the left arm with cervical and laryngeal (vocal cord hyperadduction) involvement; the laryngeal involvement caused mild dysphagia. Since the age of 33, her gait stability was severely affected (Supplementary Video 1 in the online-only Data Supplement). She was treated with botulinum toxin injections in the left upper limb (in the biceps, brachioradialis and radial extensor carpi), to which she showed a good response for many years. A brain MRI scan performed due to behavioral alterations (psychomotor agitation due to hallucinations) demonstrated marked diffuse cerebellar atrophy and chronic vascular encephalopathy. Her syndromic features included severe intellectual disability (intelligence quotient 47), short stature, short webbed neck, microcephaly, and bilateral eyelid ptosis[7] treated with blepharoplasty. Genetic analysis revealed a deletion of 14.19–14.22 Mb in the 18p11.32p11.21region: arr[hg19] 18p11.32p11.21 (14275_14206245x1,14220801x2) (Figure 1, P2).

Our study significantly expands the complex phenotypic spectrum of *GNAL* haploinsufficiency caused by 18p deletion.[8] P1 developed clumsiness and slow hand movements resembling mild hypokinesia at a later point in a very long follow-up period (more than 15 years after onset); in contrast to the patient reported by Di Rauso et al.,[1] our patient had a normal DaT scan. Moreover, both reports support the concept of extensive clinical diversity and different motor circuitry involvement in 18p syndrome patients.[3-5,7,9]

The brain MRI of P1 revealed left globus pallidus internus (GPi) hyperintensity; this finding was not previously described, and it is possible that these alterations may be aspecific and that an acquired left GPi lesion may have worsened the dystonic tremor of the right limb in our patient. The brain MRI of P2 revealed marked diffuse cerebellar atrophy, which is a unique finding not previously reported in patients affected by 18p deletion syndrome. The pathogenesis of cerebellar involvement is not clear. One possibility is that this finding may be related to dysfunction of the *LAMA1* gene (deleted in both patients), which plays a role in the development of the cerebellum; therefore, mutations of this gene may be associated with cerebellar ataxia.[10] On the other hand, the long-term disease course and the possible evolution of brain imaging in patients with 18p deletion syndrome are not well known; therefore, some characteristics may have not been reported to date, as the literature includes only cross-sectional studies.

In conclusion, there are important practical implications for diagnostics based on the lessons learned from these studies. We suggest that *GNAL* haploinsufficiency should also be suspected in tremulous dystonia patients with or without combined hypokinesia/akinesia when the phenotype of 18p deletion syndrome is observed[3] independently from dopaminergic system image results. In addition, we recommend that aCGH analysis should be performed to identify chromosomal breakpoints and deleted

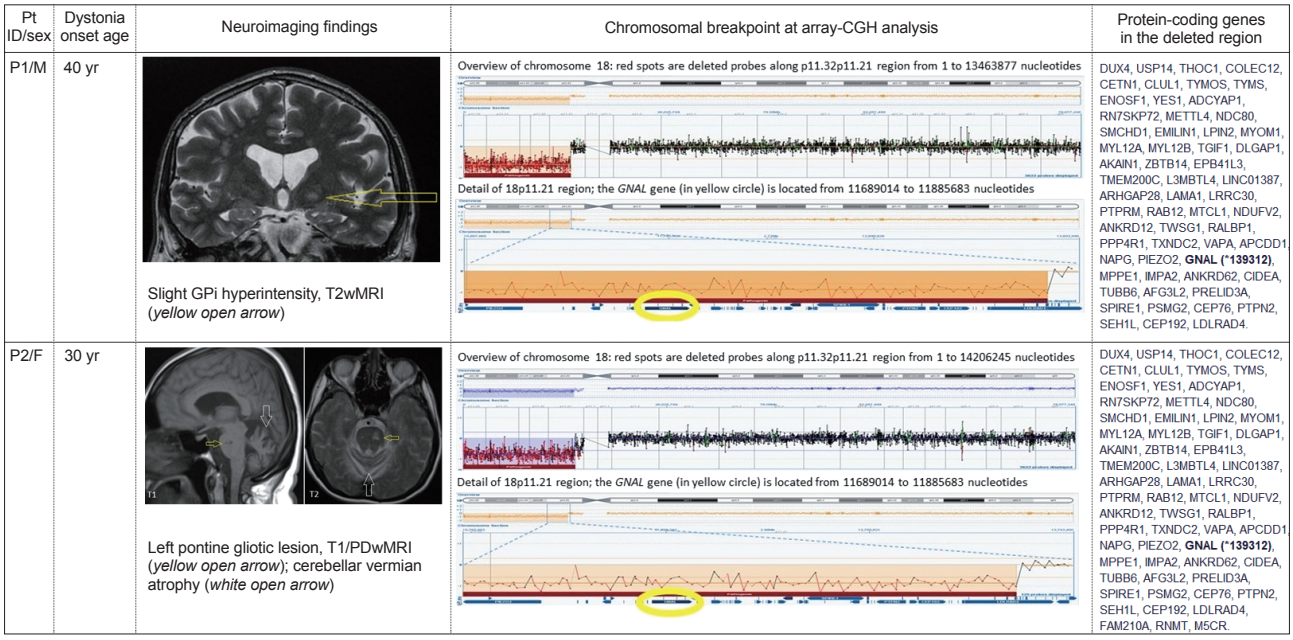

Figure 1. Neuroimaging findings, chromosomal breakpoints from array-CGH analysis, and protein-coding genes in the deleted region of the two patients. P1, patient 1; P2, patient 2; M, male; F, female; CGH, comparative genomic hybridization; GPi, globus pallidus internus; T2wMRI, T2 weighted magnetic resonance imaging; T1/PDwMRI, T1/PD weighted magnetic resonance imaging; PD, Parkinson's disease.

genes; however, when aCGH analysis is not available, diagnostic technologies such as next-generation sequencing for hyperkinetic disorders or a whole-exome sequencing read-depth-based algorithm[9] should be used.

Ethics Statement

Approval from the local ethical committee to conduct this study was not required because the diagnostic procedures were part of Neurological Institute Carlo Besta, Milan, Italy current standard of care/standard of diagnosis. Informed consent was obtained from the patient for genetic testing, video publication (both in print and online), and case reports. The authors certify that this article complies with the Principles of Ethical Publishing of the *Journal of Movement Disorders* and declare that they acted following ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Supplementary Video Legends

Video 1. Segment 1: The patient presented with mild dysarthria, severe dystonic jerky tremors (more severe in the right hand), clumsiness/hypokinesia of the limb movements, and task-specific right lower limb dystonia during gait. Captions are embedded into the video. Segment 2: The patient had multifocal dystonia, prevalent on the left side of the body with cranial (oromandibular, eyelids), cervical (retrocollis), and laryngeal involvement; her gait was marked by axial and lower limb dystonia. Captions are embedded into the video.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.14802/jmd.24080.

Conflicts of Interest

The authors have no financial conflicts of interest.

Funding Statement

None

Acknowledgments

We would like to thank our patients and their relatives who permitted us to acquire thewhole medical documentation and who gave permission to publish this manuscript and the videos.

Author Contributions

Conceptualization: Arianna Braccia, Miryam Carecchio, Luigi Michele Romito. Data curation: all authors. Investigation: all authors. Methodology: Miryam Carecchio, Francesca Luisa Sciacca, Anna Castagna, Antonio Emanuele Elia, Luigi Michele Romito. Project administration: Miryam Carecchio, Luigi Michele Romito. Visualization: Arianna Braccia, Miryam Carecchio, Luigi Michele Romito. Writing—original draft: Arianna Braccia, Miryam Carecchio, Anna Castagna, Antonio Emanuele Elia, Luigi Michele Romito. Writing—review & editing: all authors.

ORCID iDs

Arianna Braccia	https://orcid.org/0000-0003-1119-7518
Miryam Carecchio	https://orcid.org/0000-0002-0755-5477
Francesca Luisa Sciacca	https://orcid.org/0000-0002-7411-4567
Anna Castagna	https://orcid.org/0000-0003-0216-8205
Antonio Emanuele Elia	https://orcid.org/0000-0002-5917-7578
Luigi Michele Romito	https://orcid.org/0000-0002-6772-1035

REFERENCES

1. Di Rauso G, Cavallieri F, Monfrini E, Fraternali A, Fioravanti V, Grisanti S, et al. A case of 18p chromosomal deletion encompassing GNAL in a patient with dystonia-parkinsonism. J Mov Disord 2024;17:236-238.
2. Thieffry S, Arthuis M, de G, Lamy M, Salmon C. [Deletion of the short arms of chromosome 17-18: complex deformities with oligophrenia]. Arch Fr Pediatr 1963;20:740-745. French
3. Wester U, Bondeson ML, Edeby C, Annerén G. Clinical and molecular characterization of individuals with 18p deletion: a genotype-phenotype correlation. Am J Med Genet A 2006;140:1164-1171.
4. Postma AG, Verschuuren-Bemelmans CC, Kok K, van Laar T. Characteristics of dystonia in the 18p deletion syndrome, including a new case. Clin Neurol Neurosurg 2009;111:880-882.
5. Crosiers D, Blaumeiser B, Van Goethem G. Spectrum of movement disorders in 18p deletion syndrome. Mov Disord Clin Pract 2018;6:70-73.
6. Fuchs T, Saunders-Pullman R, Masuho I, Luciano MS, Raymond D, Factor S, et al. Mutations in GNAL cause primary torsion dystonia. Nat Genet 2013;45:88-92.
7. Chen CP, Lin SP, Chern SR, Wu PS, Chen SW, Lai ST, et al. A 13-year-old girl with 18p deletion syndrome presenting Turner syndrome-like clinical features of short stature, short webbed neck, low posterior hair line, puffy eyelids and increased carrying angle of the elbows. Taiwan J Obstet Gynecol 2018;57:583-587.
8. Esposito F, Addor MC, Humm AM, Vingerhoets F, Wider C. GNAL deletion as a probable cause of dystonia in a patient with the 18p- syndrome. Parkinsonism Relat Disord 2014;20:351-352.
9. Mouraux C, Depierreux F. Late diagnosis of 18p syndrome with movement disorders by whole exome sequencing read-depth based algorithm. Mov Disord Clin Pract 2023;10:1557-1558.
10. Sun H, Wan N, Wang X, Chang L, Cheng D. Genotype-phenotype analysis, neuropsychological assessment, and growth hormone response in a patient with 18p deletion syndrome. Cytogenet Genome Res 2018;154:71-78.