Movement Disorders
CLINICAL PRACTICE

LETTER: GENOTYPE AND PHENOTYPE

Causative Role of the *SLC6A1* p.Asp451Gly Variant in a Patient with Combined Dystonia and Neurodevelopmental Disorder

Luigi M. Romito, PhD,[1,2,] Fabiana Colucci, PhD,[1,3] Valentina Leta, MD,[1,4] Celeste Panteghini, MS,[5] Roberta Telese, MD,[1,6] Gianluca Tolva, MD,[7] Roberta Villa, MD,[7] Antonio E. Elia, PhD,[1] Roberto Eleopra, MD,[1] Angela Peron, PhD,[8] Barbara Garavaglia, PhD,[5] and Maria Iascone, MS[9]*

The Solute Carrier Family 6 gene (*SLC6A1*, OMIM #137165) encodes voltage-dependent γ-aminobutyric acid (GABA) transporter 1 (GAT-1),[1] which plays a crucial role in the reuptake of GABA from synapses and in its removal from the extracellular space.[2]

Pathogenic variants in *SLC6A1* cause a wide spectrum of neurodevelopmental disorders (*SLC6A1*-NDD) characterized by developmental delay/intellectual disability (ID), epilepsy with myoclonic atonic seizures, movement disorders, and behavioral manifestations. Tremors, stereotypies, and ataxia are the most common abnormal movements that have been described in *SLC6A1*-NDD patients.[3,4]

Herein, we report a clinical case of *SLC6A1*-NDD with child-onset progressive combined dystonia, providing insight into the prognosis and neurotherapeutic approaches.

The patient is a 32-year-old Caucasian (Italian) man who was first born to nonconsanguineous parents and who presented with severe ID with absent speech, epilepsy, aggressiveness, and movement disorders.

Epilepsy started at the age of 30 months and was characterized by atonic seizures. Since then, seizures have been sufficiently controlled by carbamazepine (500 mg/day). At the age of 6 years, the patient was diagnosed with cervical dystonia with right torticollis and antecollis; the focal dystonia has become generalized with a prominent axial distribution and has been associated with tics, stereotypies, and mannerisms since onset (Video 1). He developed an effective neck sensory trick allowing him to straighten his head from anteflexion to direct his gaze forward. Interspersed between possible mannerisms of the fingers (left>right), a distinctive "behavioral-sensory trick" was established by the patient: this trick consisted of outstretching the right arm to overcome gait hesitation, especially when associated with lip and left-hand fingers snapping, to provide himself with a sort of metronomic timing in the preparation of this action (Video 1).

Since the age of 15 pregabalin and clonazepam were tried without significant benefits on dystonia. At age 24, delta-9-tetrahydrocannabinol (THC) (33 mg/day) + cannabidiol (CBD) (16 mg/day) was added, resulting in optimal seizure control and a significant reduction in trunk-neck dystonia. The introduction of clozapine (50 mg/day) was efficacious at controlling behavioral disorders since the age of 30. The brain MRI scan was unremarkable. Physical examination revealed the presence of a slender habitus, mild dysmorphic craniofacial features, a long and broad neck with bilateral *pterygium colli*, and severe lumbar scoliosis.

The patient's high-resolution karyotype and test for fragile X syndrome were normal. Trio-based whole-exome sequencing (WES) of the family revealed a de novo heterozygous missense variant in *SLC6A1* [NM_003042.4]: c.1352A > G; (p.Asp451Gly). This variant is classified as likely pathogenic [*SLC6A1* Portal, https://slc6a1-portal.broadinstitute.org/][3] [in silico scores: MTR-score 0.556, Paraz-score 0.88, Fold enrichment of pathogenic variants (log2) 2.85805; GABA uptake (vs *wild type*) 4.22–9.06] and has already been mentioned in ClinVar to be associated with epilepsy with myoclonic-astatic epilepsy (EMAS)[https://www.ncbi.nlm.nih.gov/clinvar/variation/224107/].[5]

[1]*Parkinson and Movement Disorders Unit, Department of Clinical Neurosciences, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy;* [2]*Department of Health Sciences, Università degli Studi di Milano, Milan, Italy;* [3]*Department of Neuroscience and Rehabilitation, University of Ferrara, Ferrara, Italy;* [4]*Parkinson's Centre of Excellence at King's College Hospital and King's College London, London, UK;* [5]*Medical Genetics and Neurogenetics Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy;* [6]*Department of Neuroscience, Università Degli Studi di Milano-Bicocca, Milan, Italy;* [7]*Medical Genetics Unit, ASST Santi Paolo e Carlo, Milan, Italy;* [8]*Division of Medical Genetics, Meyer Children's Hospital IRCCS, Florence, Italy and Department of Clinical and Experimental Biomedical Sciences "Mario Serio", Università degli Studi di Firenze, Florence, Italy;* [9]*Laboratorio di Genetica Medica, ASST Papa Giovanni XXIII, Bergamo, Italy*

***Correspondence to:** Dr. Luigi Romito, Parkinson and Movement Disorders Unit, Department of Clinical Neurosciences, Fondazione IRCCS Istituto Neurologico Carlo Besta, Via G. Celoria, 11, 20133 Milano, Italy; E-mail: luigi.romito@istituto-besta.it

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Luigi M. Romito, Fabiana Colucci, and Valentina Leta contributed equally to this work as first authors.

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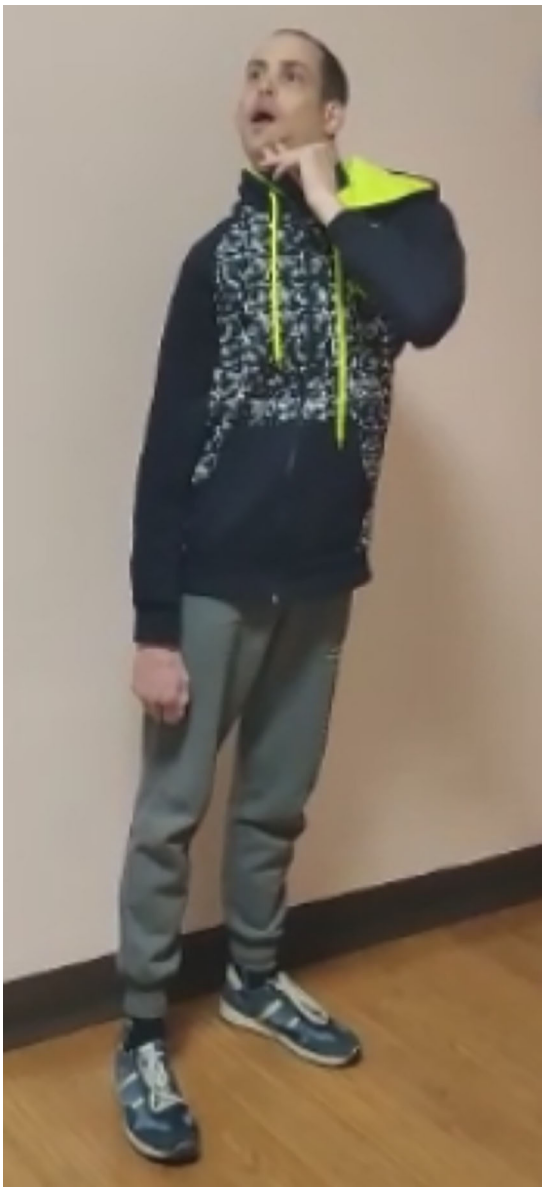

Video 1. The Video shows a right torticollis with a right sagittal shift of the neck, improved by a sensory trick for straightening the head from anteflexion and aligning the gaze with the surroundings; during the action, a residual retrocollis with a left tilt of the head is shown. Trunk dystonia with left deviation and predominantly a dorsolumbar fulcrum (similar-scoliotic) with activation of extensor truncal dystonia (retro-truncus) during walking is also shown. Mannerisms of the fingers are more prominent on the left hand, and cranial and shoulder tics are present. The patient snaps his lips and fingers of the left hand not only in the context of motor mannerisms but also possibly to provide himself with a sort of metronomic timing in preparation for the action. In addition, the patient exhibited a "point trick"—he outstretches his right upper limb—possibly a behavioral-sensory trick helping him to start walking.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.14246

EMAS is a rare form of epilepsy associated with ID.[6] Numerous affected individuals have behavioral problems, such as aggressive behavior/irritability, attention deficit disorder, hand stereotypies/automatisms, and autistic features.[7] Motor abnormalities, including verbal dyspraxia, slowness, dysarthria, ataxia, tremor, and chorea/dyskinesia, have also been reported.[4] In addition to the core phenotype presented by our patient (epilepsy responsive to carbamazepine and THC/CBD, ID with absent speech, autistic traits, and aggressive behavior), the associated dystonic features since childhood have not been described.[3,4] The only case of dystonia due to *SLC6A1* mutation was described by Zech et al in a German female presenting with adolescence-onset.[8]

We speculated that this pathogenic variant might be related to a peculiar abnormal molecular function leading to the neuropsychiatric and neurological phenotype we described. *SLC6A1* regulates the reuptake of GABA.[2] Several studies have suggested that altered GABA function in individuals with autism mainly reduces sensorimotor GABA levels, provoking somatosensory network abnormalities: GABA influences behavioral measures of inhibition.[7] These findings are also reported in dystonia: patients with dystonia have lower GABA levels in plasma and CSF and an altered distribution of GABA receptors in the cortex and cerebellum.[9] Furthermore, sensory tricks to improve dystonia are well known; similarly, one could argue that the presence of "behavioral-sensory tricks" in autism could improve actions. GABA agonist treatment might improve both clinical aspects underpinned by shared pathophysiology; indeed, this patient benefited from cannabidiol, which modulates the GABAergic system, by controlling behavioral aspects and dystonia.[10] We also hypothesize that *SLC6A1*-NDD subcortical cortico-cerebellar abnormalities due to an altered dendritic GABAergic system might contribute to aphonia, as reported in other genetic disorders.[11]

In conclusion, these preliminary observations expand the genetic and clinical spectrum of *SLC6A1*-NDD and provide a possible pathogenetic link between *SLC6A1* and dystonia, prompting movement disorder specialists to suspect *SLC6A1* variants in patients with epilepsy, behavioral disorders, and combined dystonia.[8] Such rare conditions, which often go unrecognized until different specialties become involved, should encourage continuous dialogue among pediatricians, neurologists, and geneticists, among other professionals, encompassing different life stages and medical subspecialties. Finally, as in our case, the motor phenotype can often change over time, and longitudinal video recordings could prove useful to facilitate the multidisciplinary discussion mentioned above and to better codify the natural history of these rare pathologies as a function of specific genetic variants.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical analysis: A. Study design, B. Study

execution, C. Review and critique; (3) Manuscript preparation: A. Writing of the first draft, B. Review and critique.

L.M.R.: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B.
F.C.: 1B, 1C, 2B, 3A.
V.L.: 1A, 1B, 3B.
C.P.: 1B, 1C, 3B.
R.T.: 1B, 1C, 3B.
G.T.: 1A, 1B, 1C, 3B.
R.V.: 1A, 1B, 1C, 3B.
A.E.E.: 1B, 1C, 3B.
R.E.: 1B, 1C, 3B.
A.P.: 1A, 1B, 1C, 3C.
B.G.: 1B, 1C, 2B, 3B.
M.I.: 1B, 1C, 2B, 3A, 3B

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Disclosures

Ethical Compliance Statement: The authors confirm that the approval of an institutional review board was not required for this work. 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. The manuscript was submitted for publication following the ethical standards of the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from the patient's legal representative for the publication of this case report and all iconographic and video materials.

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Data Availability Statement

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

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