NR4A2 Mutations Can Cause Intellectual Disability and Language Impairment With Persistent Dystonia-Parkinsonism

Silvia Jesús, MD, PhD,* Isabel Hinarejos, MSc,* Fátima Carrillo, MD, PhD, Dolores Martínez-Rubio, PhD, Daniel Macías-García, MD, Ana Sánchez-Monteagudo, PhD, Astrid Adarmes, MD, Vincenzo Lupo, PhD, Belén Pérez-Dueñas, MD, PhD, Pablo Mir, MD, PhD,* and Carmen Espinós, PhD*

Neurol Genet 2021;7:e543. doi:10.1212/NXG.0000000000000543

Correspondence

Dr. Mir
pmir@us.es
or Dr. Espinós
cespinos@cipf.es

The *NR4A2/NURR1* gene (MIM*601828) has recently been associated with autosomal-dominant early-onset dystonia-parkinsonism with intellectual disability.¹ *NR4A2* codifies for a nuclear transcription factor and is expressed mainly in the substantia nigra, ventral tegmental area, and limbic areas.² To date, 14 different alterations in *NR4A2* have been described associated with various clinical phenotypes, mainly with neurodevelopment disorders (table e-1, links.lww.com/NXG/A371). We describe here an interesting case suffering a persistent dystonia-parkinsonism syndrome (DPS) with motor tics, which expands the clinical phenotype of *NR4A2*-associated DPS.

MORE ONLINE

▶ Video

This is a 30-year-old man with no family history of neurologic disease who was born after a normal pregnancy and childbirth. He started walking with support at 13 months, but his gait was clumsy, resulting in numerous falls during childhood. At 2 years old, the patient presented attention deficit. He began to speak at 3 years of age but with impaired fluency, vocabulary, and articulation. The patient required special education to learn basic writing and arithmetic skills. At the age of 7 years, his intelligence quotient was 77. At 16 years old, he presented trichotillomania, and he began to experience motor tics characterized by an urge to move his right shoulder upward, an urge that was relieved after performing the movement. He was satisfactorily treated with atomoxetine. He also noticed an abnormal backward-cervical deviation. This clinical situation remained stable for 10 years, although motor tics tended to improve with age.

At 28 years old, the patient complained of slowness, walking difficulties, and a worsening abnormal craniocervical posture. He presented marked jaw-opening dystonia and parkinsonian features, with rigidity and a progressive reduction in the amplitude and frequency of repetitive movements in the left hemibody. The gait difficulties manifested with dragging steps, mainly in the left hemibody (Video 1). The patient also presented nonmotor symptoms such as gastrointestinal and sleep-related symptoms, with the mobility and communication domains affecting his quality of life the most (figures e-1 and e-2, links.lww.com/NXG/A371).

The results of supplementary and neuroimaging tests were normal (figure 1, table e-2, links.lww.com/NXG/A371), whereas ¹²³FP-CIT-single photon emission CT revealed reduced bilateral (predominantly right sided) uptake in both striatum (figure e-1).

A genetic analysis using a custom gene panel of 498 genes involved in movement disorders (MovDisord-498)³ revealed no causative mutations (appendix e-1, links.lww.com/NXG/A371). The proband and healthy parents (trio) then underwent whole exome sequencing

*These authors contributed equally to this work.

From the Unidad de Trastornos del Movimiento (S.J., F.C., D.M.-G., A.A., P.M.), Servicio de Neurología y Neurofisiología Clínica, Instituto de Biomedicina de Sevilla, Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Spain; Centro de Investigación Biomédica en Red Enfermedades Neurodegenerativas (CIBERNED) (S.J., F.C., D.M.-G., A.A., P.M.), Spain; Unit of Genetics and Genomics of Neuromuscular and Neurodegenerative Disorders (I.H., D.M.-R., A.S.-M., V.L., C.E.), Centro de Investigación Príncipe Felipe (CIPF), Valencia, Spain; Joint Units INCLIVA and IIS La Fe Rare Diseases (I.H., D.M.-R., A.S.-M., V.L., C.E.), Centro de Investigación Príncipe Felipe (CIPF), Valencia, Spain; Department of Pediatric Neurology (B.P.-D.), Hospital Universitari Vall d'Hebron, Barcelona, Spain; and Universitat Autònoma de Barcelona (B.P.-D.), Spain.

Go to Neurology.org/NG for full disclosures. Funding information is provided at the end of the article.

The Article Processing Charge was funded by FISEVI CIF: ESG-41918830 Edificio de Laboratorios 6 º planta Hospital Virgen del Rocío Avda. Manuel Siurot, s/n, 41013 Sevilla.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND), which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

(A) ^{123}FP -CIT-SPECT revealed bilateral uptake reduction with impairment of the caudate and putamen and a predominance in the right hemisphere and both putamen. (B and C) Normal ^{18}FDG -PET coronal and axial images. (D) Normal cranial MRI T2 axial image. ^{18}FDG = 18-fluorodeoxyglucose.

(WES) using the Whole Exome Family Plus test (Blueprint Genetics, Helsinki, Finland). WES data were filtered as previously described⁴ and 3 candidate disease-causing changes were found (table e-3). We further investigated the detected changes by Sanger sequencing in all the available relatives (figure e-3). The *KCNQ2* c.1807-5A>T resulted to be a false-positive result. The proband, his parents, and his brother carried the *CEP170* c.2375C>A (p.S792*) change in heterozygosis, and therefore, this variant was discarded as disease-causing mutation. Regarding the *NR4A2* c.956G>A (p.R319Q) substitution, only the patient harbored it, and consequently, this mutation was de novo. Moreover, 2 frameshift mutations in *NR4A2* were recently described in 2 patients with DPS.¹ R319 is an evolutionarily conserved amino acid (data not shown) located on the essential domain Zf-C4/DBD (figure e-4). The variant was considered likely pathogenic according to the American College of Medical Genetics and Genomics classification, based mainly on the PS2 and PM2 criteria, although the *NR4A2* c.956G>A mutation also meets the PP3 and PM1 criteria.⁵

Consistent with previous descriptions of *NR4A2* subjects,¹ our patient also presented craniocervical dystonia with parkinsonian features that started in early adulthood, with previous intellectual disability and language impairment. In our proband, however, the dystonia was persistent and worsened in stressful situations, contrasting with the previously reported paroxysmal dystonic episodes.¹ Clinicians should therefore be aware of paroxysmal and persistent dystonia features related to *NR4A2*.

Our proband also shared with previously reported cases, clear signs, and symptoms of dopaminergic degeneration,¹ suggesting a relationship between the role of *NR4A2* and dysfunction of the dopaminergic nigrostriatal network. Of interest, our patient also experienced motor tics and attention deficit during childhood. Previous reports have shown the involvement of gross deletions in *NR4A2* in autism spectrum disorders, with some patients manifesting “restlessness” during childhood.⁶ To date, however, there have been no reported data on the

comorbidity with motor tics, which are therefore a novel feature associated with the *NR4A2* phenotype, a feature that will become clearer as more cases are reported.

In *NR4A2*, there seems to be no association between the mutation type and the resulting phenotype, except for patients with complex neurodevelopmental disorders that are caused by large deletions. In fact, diverse *NR4A2*-related phenotypes can even be caused by the same mutation.⁷ In this case study, we presented the first patient with DPS caused by a missense *NR4A2* mutation, the p.R319Q. *NR4A2*-associated DPS can therefore be caused by more than just loss-of-function mutations.

In conclusion, motor tics and persistent dystonia in *NR4A2*-associated DPS should be included within its phenotypic description along with early-onset parkinsonism and intellectual disability with language impairment. The description of new cases may help to improve the correlation between *NR4A2* and its clinical picture, which, so far, is mainly relevant for neurodevelopmental disorders.

Study Funding

This work was supported by the Health Institute Carlos III—General Subdirector for Research Evaluation and Promotion (PI16/01575, PI18/01898, PI18/00147, PI19/01576), the Spanish Ministry of Economy and Competitiveness (SAF2007-60700), the Ministry of Economy, Innovation, Science and Business of the Government of Andalucía (CVI-02526, CTS-7685), the Ministry of Health and Social Welfare of the Government of Andalucía (PI-0459-2018, PE-0210-2018, PE-0186-2019) and by the Valencian Government (PROMETEO/2018/135), within the framework of the National Research and Development Plan co-funded with European Regional Development Funds. Part of the equipment employed in this study was funded by the Valencian Government and co-financed with European Regional Development Funds (OP ERDF of Valencian Community 2014-2020). I. Hinarejos has a PFIS-PhD fellowship (FI19/00072), S. Jesús has a contract “Acción B Clínicos-

Investigadores” (Action B Clinicians-Researchers) contract (B-0007-2019) funded by the Ministry of Health and Family of the Government of Andalucía, and D. Macías-García has a Río Hortega contract (CM18/00142) funded by the Health Institute Carlos III.

Disclosure

S. Jesús has received honoraria from AbbVie, Bial, Merz, UCB, Italfarmaco and Zambon. F. Carrillo has received honoraria from AbbVie, Bial, and Zambon. A. Adarmes has received honoraria from AbbVie and Italfarmaco. D. Macías-García has received honoraria from AbbVie. P. Mir has received honoraria from AbbVie, Abbott, Allergan, Bial, Merz, UCB, and Zambon. All other authors report no conflicts of interest. Go to [Neurology.org/NG](https://www.neurology.org/NG) for full disclosures.

Publication History

Received by *Neurology: Genetics* July 18, 2020. Accepted in final form November 6, 2020.

Appendix Authors

Name	Location	Contribution
Silvia Jesús, MD, PhD	Biomedical Institute of Seville/University Hospital Virgen del Rocío, Spain	Clinically described and supervised the patients. Wrote the study/first draft. Reviewed and critiqued the manuscript.
Isabel Hinarejos, MSc	Research Centre Príncipe Felipe (CIPF), Valencia, Spain	Performed/interpreted the genetic study. Wrote the study/first draft. Reviewed and critiqued the manuscript.
Fátima Carrillo, MD, PhD	Biomedical Institute of Seville/University Hospital Virgen del Rocío, Spain	Clinically described and supervised the patients. Reviewed and critiqued the manuscript.
Dolores Martínez-Rubio, MSc	Research Centre Príncipe Felipe (CIPF), Valencia, Spain	Conceived and designed the study. Performed/interpreted the genetic study. Reviewed and critiqued the manuscript.
Daniel Macías-García, MD	Biomedical Institute of Seville/University Hospital Virgen del Rocío, Spain	Clinically described and supervised the patients. Reviewed and critiqued the manuscript.

Appendix (continued)

Name	Location	Contribution
Ana Sánchez-Monteagudo, MSc	Research Centre Príncipe Felipe (CIPF), Valencia, Spain	Performed/interpreted the genetic study. Reviewed and critiqued the manuscript.
Astrid Adarmes, MD	Biomedical Institute of Seville/University Hospital Virgen del Rocío, Spain	Clinically described and supervised the patients. Reviewed and critiqued the manuscript.
Vincenzo Lupo, PhD	Research Centre Príncipe Felipe (CIPF), Valencia, Spain	Conceived and designed the study. Performed/interpreted the genetic study. Reviewed and critiqued the manuscript.
Belén Pérez-Dueñas, MD, PhD	Hospital Universitari Vall d'Hebron, Barcelona, Spain	Conceived and designed the study. Reviewed and critiqued the manuscript.
Pablo Mir, MD, PhD	Biomedical Institute of Seville/University Hospital Virgen del Rocío, Spain	Clinically described and supervised the patients. Wrote the study/first draft. Reviewed and critiqued the manuscript.
Carmen Espinós, PhD	Research Centre Príncipe Felipe (CIPF), Valencia, Spain	Conceived and designed the study. Performed/interpreted the genetic study. Wrote the study/first draft. Reviewed and critiqued the manuscript.

References

1. Wirth T, Mariani LL, Bergant G, et al. Loss-of-function mutations in NR4A2 cause dopa-responsive dystonia Parkinsonism. *Mov Disord* 2020;35:880–885.
2. Sakurada K, Ohshima-Sakurada M, Palmer TD, Gage FH. Nurr1, an orphan nuclear receptor, is a transcriptional activator of endogenous tyrosine hydroxylase in neural progenitor cells derived from the adult brain. *Development* 1999;126:4017–4026.
3. Correa-Vela M, Lupo V, Montpeyo M, et al. Impaired proteasome activity and neurodegeneration with brain iron accumulation in FBXO7 defect. *Ann Clin Transl Neurol* 2020;7:1436–1442.
4. Sanchez-Monteagudo A, Alvarez-Saucó M, Sastre I, et al. Genetics of Wilson disease and Wilson-like phenotype in a clinical series from eastern Spain. *Clin Genet* 2020;97:758–763.
5. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015;17:405–424.
6. Levy J, Grotto S, Mignot C, et al. NR4A2 haploinsufficiency is associated with intellectual disability and autism spectrum disorder. *Clin Genet* 2018;94:264–268.
7. Ramos LLP, Monteiro FP, Sampaio LPB, et al. Heterozygous loss of function of NR4A2 is associated with intellectual deficiency, rolandic epilepsy, and language impairment. *Clin Case Rep* 2019;7:1582–1584.

Neurology[®] Genetics

***NR4A2* Mutations Can Cause Intellectual Disability and Language Impairment With Persistent Dystonia-Parkinsonism**

Silvia Jesús, Isabel Hinarejos, Fátima Carrillo, et al.

Neurol Genet 2021;7;

DOI 10.1212/NXG.0000000000000543

This information is current as of January 21, 2021

Neurol Genet is an official journal of the American Academy of Neurology. Published since April 2015, it is an open-access, online-only, continuous publication journal. Copyright Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology.. All rights reserved. Online ISSN: 2376-7839.

Updated Information & Services	including high resolution figures, can be found at: http://ng.neurology.org/content/7/1/e543.full.html
References	This article cites 7 articles, 1 of which you can access for free at: http://ng.neurology.org/content/7/1/e543.full.html##ref-list-1
Citations	This article has been cited by 1 HighWire-hosted articles: http://ng.neurology.org/content/7/1/e543.full.html##otherarticles
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): Clinical neurology examination http://ng.neurology.org/cgi/collection/clinical_neurology_examination Dystonia http://ng.neurology.org/cgi/collection/dystonia Genetic linkage http://ng.neurology.org/cgi/collection/genetic_linkage Parkinson's disease/Parkinsonism http://ng.neurology.org/cgi/collection/parkinsons_disease_parkinsonism Tics http://ng.neurology.org/cgi/collection/tics
Permissions & Licensing	Information about reproducing this article in parts (figures,tables) or in its entirety can be found online at: http://ng.neurology.org/misc/about.xhtml#permissions
Reprints	Information about ordering reprints can be found online: http://ng.neurology.org/misc/addir.xhtml#reprintsus

Neurol Genet is an official journal of the American Academy of Neurology. Published since April 2015, it is an open-access, online-only, continuous publication journal. Copyright Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology.. All rights reserved. Online ISSN: 2376-7839.