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*

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

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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.

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 ^{123}FP-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.

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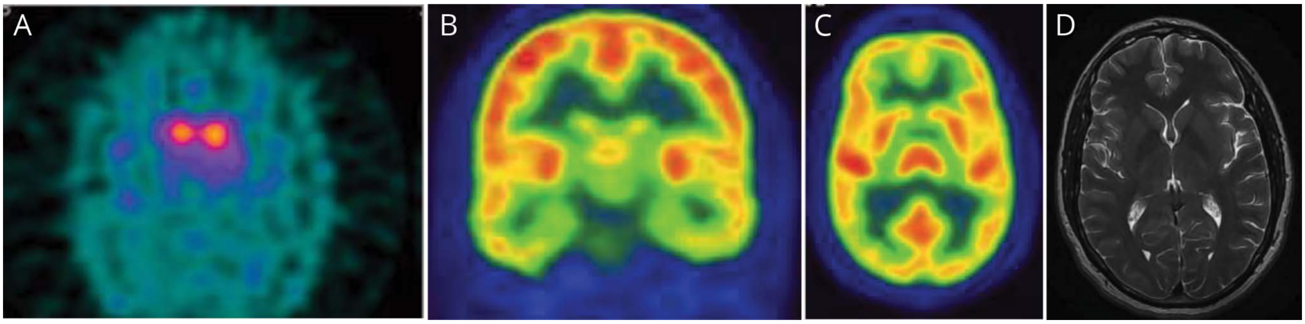
Figure 1 Functional and Structural Brain Images



(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 described[4] 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.

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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 for full disclosures.

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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.
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 of 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.

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