Reply to: "Childhood Onset Chorea Caused by a Recurrent De Novo DRD2 Variant"

van der Weijden, Marlous C M; Rodriguez-Contreras, Dayana; Neve, Kim A; Verbeek, Dineke S; Tijssen, Marina A J

Published in:
Movement Disorders

DOI:
10.1002/mds.28635

affects an amino acid residue completely conserved across species down to invertebrates (Fig. 1), and is predicted pathogenic by all in silico prediction tools. It was interpreted as likely pathogenic according to American College of Medical Genetics and Genomics guidelines.[3]

Analysis of data from both family trios did not identify any other potential candidate variants, including other de novo or biallelic likely pathogenic variants or variants in other genes linked to monogenic movement disorders.

Supporting its pathogenic role, p.Met374Arg is located in the protein sixth transmembrane domain, which forms part of the binding pocket core for D2R agonists. A mutation at this residue (p.Met374Leu) was shown to determine a shift of the ligand-free D2R toward the active state,[4] suggesting a similar mechanism may apply to p.Met374Arg. The p.Ile212Phe variant was also shown to cause increased agonist potency and constitutive activation,[1] suggesting that pathogenic *DRD2* variants are gain-of-function.

In conclusion, these cases highlight that variants in *DRD2* should be included in the diagnostic workup of genetically unexplained early-onset hyperkinetic movement disorders. Compared with the previously reported cases, our series expands the age of onset to as early as 4 months and shows that developmental delay, myoclonus, and cognitive and neuropsychiatric dysfunction can be part of the phenotype.

Niccolò E. Mencacci, MD, PhD,[1] Dora Steel, MD,[2,3] Francesca Magrinelli, MD,[4,5] Jerry Hsu, MD,[1] Ignacio Juan Keller Sarmiento, MD,[1] Mónica Troncoso Schifferli, MD,[6] Daniela Muñoz, MD,[6] Leonidas Stefanis, MD, PhD,[7] Steven J. Lubbe, PhD,[1] Nicholas W. Wood, PhD,[4] Manju A. Kurian, PhD,[2,3] and Maria Stamelou, MD[7,8,9*]

[1]*Ken and Ruth Davee Department of Neurology and Simpson Querrey Center for Neurogenetics, Northwestern University, Feinberg School of Medicine, Chicago, Illinois, USA,* [2]*Molecular Neurosciences, Developmental Neurosciences, University College London Great Ormond Street Institute of Child Health, London, United Kingdom,* [3]*Department of Neurology, Great Ormond Street Hospital, London, United Kingdom,* [4]*Department of Clinical and Movement Neurosciences, University College London Queen Square Institute of Neurology, University College London, London, United Kingdom,* [5]*Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy,* [6]*Child Neurology Service, Clinical Hospital San Borja Arriarán, Faculty of Medicine, University of Chile, Santiago, Chile,* [7]*1st Neurology Clinic, Eginition Hospital, National and Kapodistrian University of Athens, Medical School, Athens, Greece,* [8]*Parkinson's Disease and Movement Disorders Department, HYGEIA Hospital, Athens, Greece, and* [9]*School of medicine, European University of Cyprus, Nicosia, Cyprus*

References

1. van der Weijden MCM, Rodriguez-Contreras D, Delnooz CCS, et al. A gain-of-function variant in dopamine D2 receptor and progressive chorea and dystonia phenotype. Mov Disord 2021;36(3):729–739.
2. Carecchio M, Mencacci NE, Iodice A, et al. ADCY5-related movement disorders: frequency, disease course and phenotypic variability in a cohort of paediatric patients. Parkinsonism Relat Disord 2017;41:37–43.
3. 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(5):405–424.
4. Yin J, Chen KM, Clark MJ, et al. Structure of a D2 dopamine receptor-G-protein complex in a lipid membrane. Nature 2020;584(7819):125–129.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Reply to: "Childhood Onset Chorea Caused by a Recurrent De Novo DRD2 Variant"

We read the letter by Mencacci and colleagues with great interest, describing two unrelated cases with a childhood-onset chorea caused by a recurrent de novo variant c.1121T>G, p.Met374Arg in *DRD2*. In our article,[1] we reported a gain-of-function missense mutation c.634A>T, p.Ile212Phe in *DRD2* carried by subjects with progressive chorea and dystonia inherited in a dominant manner in a large Dutch family. We have now confirmed that the mother of the index patient with a comparable phenotype carried the same mutation (II:7, Fig. 1).

The two unrelated cases described by Mencacci et al. both suffered from childhood-onset chorea accompanied with myoclonic movements, dystonia of the left foot, and ocular motor apraxia; behavioral, psychiatric, and cognitive problems (Case 1 only); myoclonic jerks; and global developmental delay (Case 2 only).

The choreatic presentation in Case 1 is quite similar to that of the cases reported by us, but the dystonia in our five patients affected the neck and/or upper extremities and not the foot. In two out of five cases, cervical dystonia was part of the presenting symptoms next to chorea. The occasional myoclonus in the neck and upper limbs seen in Cases 1 and 2 was also sporadically seen in our cases but was considered part of the chorea based on electromyographic examination. Orofacial involvement was also seen in our patients, but in the eyebrows rather than the tongue, and only in a later disease stage. The ocular motor apraxia was seen in three out of five cases.

*Correspondence to: Prof. Marina A.J. Tijssen, Expertise Center Movement Disorders Groningen, University Medical Center Groningen, Antonius Deusinglaan 1, 9713 AV, Groningen, the Netherlands; E-mail: m.a.j.de.koning-tijssen@umcg.nl

Relevant conflicts of interest/financial disclosures: Nothing to report.

Marlous C.M. van der Weijden and Dayana Rodriguez-Contreras are co-first authors.

Dineke S. Verbeek and Marina A.J. Tijssen are co-last authors.

Received: 13 April 2021; **Accepted:** 14 April 2021

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.28635

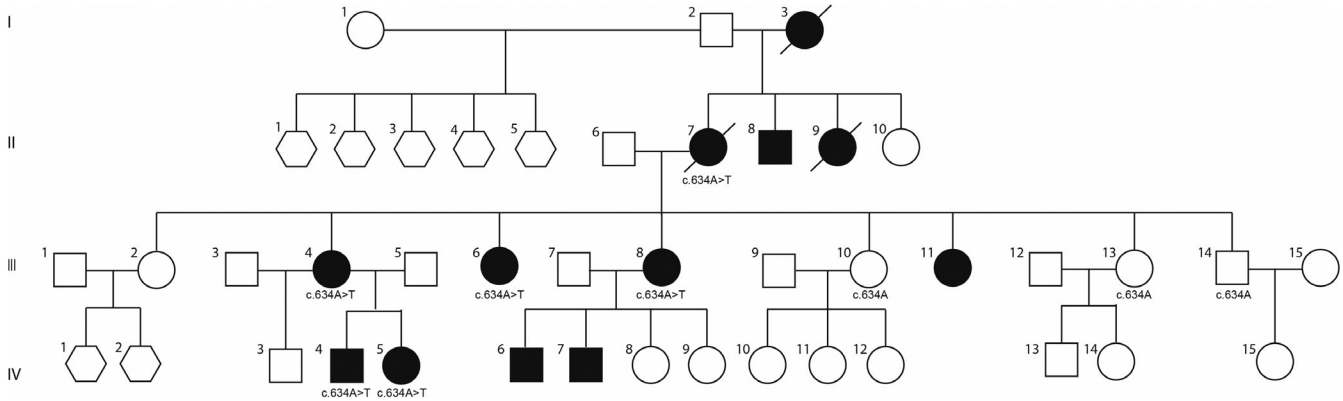

FIG. 1. Four-generation pedigree carrying the missense variant c.634A > T, p.Ile212Phe in DRD2. Male = square, female = circle, sex unknown = hexagon. Filled symbols = affected. Open symbols = unaffected.

The non-motor symptoms as described in Cases 1 and 2 were less present in our cases. However, three out of five cases suffered from anxiety problems. We hypothesize that the difference in non-motor symptoms may be caused by the difference in disease age-at-onset because dopamine (including the dopamine D2 receptor) plays an important role in neurodevelopment, and early disruption of dopamine signaling has been implicated in psychiatric and behavior diseases.[2]

Given the location of the two mutations at the cytoplasmic face of transmembrane domains 5 and 6, together with the reported functional evidence for the p.Ile212Phe mutation, we also support the hypothesis that both phenotypes may be the result of constitutive activation of the dopamine D2 receptor. Nevertheless, the question remains how the *de novo* missense variant p.Met374Arg in *DRD2* causes a childhood-onset disease compared with mutation p.Ile212Phe causing an adolescent-onset disease. One possibility is that D2-Met374Arg is simply more constitutively active and exhibits more enhanced G protein-mediated signaling than D2-Ile212Phe. Alternatively, the Met374Arg mutation may affect arrestin binding very differently compared with the Ile212Phe mutation, so that the balance between G protein- and arrestin-regulated cellular processes is altered in a way that is deleterious for neurodevelopment.

Overall, the work of Mencacci et al. further supports the notion that variants in *DRD2* can cause hyperkinetic disorders. This work is important for clinicians who treat patients with chorea, with either a pediatric onset or adolescent onset, as in addition to screening for Huntington and Huntington-like genes, screening for mutations in *DRD2* should be considered.

Marlous C.M. van der Weijden, MD,[1,2]
Dayana Rodriguez-Contreras, PhD,[3]
Kim A. Neve, PhD,[3,4] Dineke S. Verbeek, PhD,[1,2] and
Marina A.J. Tijssen, MD, PhD[2,5]*

[1]*Department of Genetics, University Medical Center Groningen, Groningen, the Netherlands,* [2]*Expertise Center Movement Disorders Groningen, University Medical Center Groningen, Groningen, the Netherlands,* [3]*Department of Behavioral Neuroscience, Oregon Health & Science University, Portland, Oregon, USA,* [4]*Research Service, VA Portland Health Care System, Portland, Oregon, USA, and* [5]*Department of Neurology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands*

References

1. van der Weijden MCM, Rodriguez-Contreras D, Delnooz CCS, et al. A gain-of-function variant in dopamine D2 receptor and progressive chorea and dystonia phenotype. Mov Disord 2020;36(3):729–739.
2. Money KM, Stanwood GD. Developmental origins of brain disorders: roles for dopamine. Front Cell Neurosci 2013;7:260.