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

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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.  

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, suggesting a similar mechanism may apply to p.Met374Arg. The p.Ile212Phe variant was also shown to cause increased agonist potency and constitutive activation, 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.

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References


Supporting Data

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

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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.

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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.

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References