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AUTOSOMAL RECESSIVE INHERITANCE OF ADCY5-RELATED GENERALIZED DYSTONIA AND MYOCLONUS

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Monoallelic *ADCY5* mutations have been associated with a benign hereditary chorea-like phenotype and a mixed hyperkinetic syndrome with dystonia, chorea, and myoclonus.^{1–4} We report 2 siblings with generalized dystonia and myoclonus associated with biallelic pathogenic variants in *ADCY5* inherited in an autosomal recessive pattern.

Case report. A 27-year-old woman presented with a movement disorder. She was born full term. She walked at 18 months, and speech development was delayed. Involuntary movements were first noted at 3 years with walking and increased in amplitude over time. Dystonia was first diagnosed at age 3. She had frequent falls due to involuntary myoclonic movements in the setting of lower extremity dystonia. Movements lessened with sleep and did not improve with alcohol or caffeine. Trihexyphenidyl, levodopa, clonazepam, and amantadine failed to provide benefit. On examination, she was found to have generalized dystonia with superimposed myoclonus. See video at Neurology.org/ng. Chromosomal microarray was negative. Alpha-fetoprotein and vitamin E levels were normal. Her 24-year-old brother was born at term and walked prior to 1 year. His speech development was delayed. After age 8, he developed cramping in his hands and neck. His gait worsened at age 15 secondary to worsening lower extremity dystonia following a growth spurt. Levodopa, clonazepam, gabapentin, propranolol, primidone, and topiramate did not provide benefit. His neurologic examination revealed generalized dystonia with superimposed myoclonus. See video. Creatine kinase, lactic acid, comprehensive metabolic panel, ceruloplasmin, and 24-hour urine copper levels were normal. No pathogenic variants or large deletions/duplications were found in *SGCE*. Brain MRI was unremarkable. There were no other siblings. Neither parent nor other relatives had a history of a movement disorder.

Because of familial juvenile-onset generalized dystonia with myoclonus and previous negative

evaluations, trio exome sequencing was pursued to establish a definitive diagnosis (Ambry Genetics Corp., Aliso Viejo, CA). Testing revealed the presence of a maternally inherited frameshift variant (c.409_428del20; p.G137Cfs*184) and a paternally inherited missense variant (c.3037C>T; p.R1013C) in *ADCY5* (NM_183357). These alleles were confirmed in the proband's brother using Sanger sequencing.

Discussion. *ADCY5* mutations are believed to be inherited in an autosomal dominant fashion based on observations from the original pedigree: there were affected individuals in all 5 generations, complete penetrance in males and females, and evidence of male-to-male transmission.⁵ Subsequent reported families confirmed autosomal dominant inheritance.^{3,4} In addition, mutations described in *ADCY5*-related dyskinesia are recurrent, with the p.R418W and the p.A726T mutation described in multiple unrelated individuals.^{1–3,6} Subsequent functional analysis characterized the effect of these mutations as gain of function: there was increased adenylyl cyclase activity in cells containing mutant *ADCY5* compared with wild type.⁶ However, in a previously reported family affected with autosomal dominant chorea and dystonia, a c.2088+1G>A splice site mutation segregated with disease.⁴ Functional studies showed no expression of the variant allele and reduced expression of *ADCY5* messenger RNA. It appears that both gain of function and haploinsufficiency may result in *ADCY5*-related dyskinesia.

Here, we report 2 siblings with a phenotype of generalized dystonia and myoclonus associated with biallelic pathogenic variants in *ADCY5*. A phenotype of autosomal dominant myoclonus dystonia has been reported with *ADCY5* mutations, and dystonia and myoclonus have been reported in other published cases.⁷ Our cases differ from previously published cases because they inherited 2 pathogenic variants from unaffected parents, a paternally inherited missense variant and a maternally inherited frameshift variant. There is evidence supporting a role for both these variants in the clinical manifestation of disease. The paternal p.R1013C variant occurs at an evolutionarily conserved residue, is predicted to be damaging by PolyPhen and deleterious by scale-invariant

Supplemental data at
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feature transform, and is not present in over 60,000 individuals in the Exome Aggregation Consortium browser. These data together with cosegregation with the movement disorder phenotype suggest that p.R1013C is not a normal population variant and has clinical significance. We interpret the maternally inherited 20 base-pair deletion as a loss of function allele because it results in an early stop codon after 184 amino acids.

In this family, both variants appear to be required for a movement disorder phenotype. The missense variant may result in a change in the function of adenylate cyclase that does not result in a phenotype in the presence of a wild-type allele. However, in the presence of a null allele, the mutant protein is insufficient to maintain adequate cyclic adenosine monophosphate levels resulting in dystonia and myoclonus. Autosomal recessive inheritance has also been reported for other genes typically associated with autosomal dominantly inherited dystonia, specifically *THAP1* and *GNAL*.^{8,9} This family expands the understanding of *ADCY5*-related dyskinesia by showing that certain pathogenic variants inherited in an autosomal recessive pattern may produce a phenotype identical to autosomal dominant mutations.

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