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Expanding the *ADCY5* phenotype toward spastic paraparesis

A mutation in the M2 domain

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Patients with an *ADCY5* gene mutation reveal a heterogenous clinical presentation including axial hypotonia, motor milestone delay, fluctuating dyskinesias, dystonia, and/or myoclonus with episodic exacerbations during drowsiness and sleep.[1,2] Phenotype-genotype correlations and somatic mosaicism are suggested to explain the wide phenotypic spectrum.[1]

The *ADCY5* gene encodes 1 of 9 membrane-bound adenyl cyclases converting adenosine triphosphate to cyclic adenosine-3′, 5′-monophosphate, the second messenger in a range of cellular activities.[3] The *ADCY5* protein contains 2 transmembrane domains, M1 and M2, and 2 bipartite cytoplasmic domains, C1 and C2. Pathogenic mutations have been described in domains C1 and C2.[1,2] Mutations are likely to have a gain-of-function effect based on increased cyclic adenosine-3′, 5′-monophosphate accumulation.[4]

The present report describes 3 cases of *ADCY5* dyskinesia to further illustrate the clinical spectrum: a new phenotype, i.e., spastic paraparesis due to a mutation located in the M2 domain; case 1, case 2, and case 3 show previously described mutations in the C1 domain of the *ADCY5* protein. Their phenotypes show important similarities to previous cases, with the addition of the psychiatric symptoms of the patient in case 3.

Case 1

A 40-year-old woman was referred to our clinic with a 6-year history of progressive fatigue, painful movements, and muscle weakness of the lower limbs. History revealed delayed ability to sit independently until the age of 2 years, most likely due to early axial hypotonia, with subsequent catching up of motor development. Family history revealed no movement disorders. Neurologic examination showed spastic paraparesis, with hyperreflexia, hypertonia in the legs, and extensor plantar reflexes. There was mild dystonic posturing of the right foot while walking and writer's cramp of the right hand. As the dystonic features were not recognized as such before, the age at onset is not clear. MRI of the brain and spine and metabolic blood examination were unremarkable.

Whole-exome sequencing revealed a c.2722G>A, p.(Glu908Lys) mutation in the *ADCY5* gene. Her mother is mosaic for the mutation in peripheral blood (proportion mutation: wild type about 1:3) without a relevant medical history or current complaints.

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Case 2

A 1.5-year-old girl was presented to our clinic with motor milestone delay and dyskinesias. Pregnancy and delivery were unremarkable. Hypotonia and involuntary movements were first noticed at the age of 9 months. Family history was negative. Neurologic examination showed axial hypotonia and generalized chorea, more pronounced by action, with facial involvement. There was hyperreflexia without spasticity. Mother described exacerbations of dyskinesia during sleep. Genetic testing revealed a "de novo" previously reported c.1252C>T p.(Arg418Trp) mutation in the *ADCY5* gene.[1,2]

Case 3

A 16-year-old young woman was presented to the outpatient's clinic in Barcelona with episodic dyskinesias with oral involvement since the age of 18 months. At this age, she started walking independently with frequent falls. From 12 years of age, she developed tics, coprolalia, and prominent obsessive compulsive and anxiety disorder with phobias. At the age of 16 years, she presented with nonfluent speech, myoclonus, and chorea of the face and upper limbs and mild dystonic posturing of the limbs with episodic exacerbations. Family history revealed no movement, behavioral of psychiatric disorders. Genetic testing, using a dystonia panel, i.e., combined "next-generation" and Sanger sequencing method, showed a previously described c.1253G>A p.(Arg418Gln) mutation in the *ADCY5* gene.[1,2]

The 3 new *ADCY5* cases support the wide phenotypic presentation of *ADCY5* gene mutations in the literature. We add another phenotype, i.e., spastic paraparesis due to a mutation in the M2 domain of the *ADCY5* protein (case 1). This mutation is predicted pathogenic by in silico prediction tools and is absent in available data sets of population controls.

Spasticity, hyperreflexia, and bilateral extensor plantar reflexes were mentioned as additional features in several cases with mutation(s) in a cytoplasmic (C) domain.[2,5,6] The somatic mosaicism present in the index's mother demonstrates that mosaicism can lead to a (much) milder to no phenotype at all.[1] Future studies are of interest to detect the relevance of *ADCY5* mutations in patients with paraparesis.

Cases 2 and 3 show mutations in the C1 domain of the *ADCY5* gene. These 2 mutations have been previously described with comparable dyskinetic phenotypes[1,2]; however, case 3 patient's (prominent) psychiatric symptoms are distinctive. If the psychiatric manifestations can be ascribed to the *ADCY5* phenotype remains unclear, given these prevalence of psychiatric disorders in the general population. An association between *ADCY5* mutations and psychiatric symptoms is conceivable.

Our 3 cases further support the conclusion of a heterogenous phenotype and a possible phenotype-genotype correlation as suggested in *ADCY5*-mutation–associated disease.

Author contributions

Anne J.E. Waalkens: article design and data description. Fleur Vansenne and Annemarie H. van der Hout: critical revision of the manuscript for intellectual content. Rodi Zutt: acquisition of patient data and critical revision of the manuscript for intellectual content. Jeroen Mourmans: acquisition of patient data. Eduardo Tolosa and Tom J. de Koning: acquisition of patient data and critical revision of the manuscript for intellectual content. Marina A.J. Tijssen: data supervision, acquisition of patient data, and critical revision of the manuscript for intellectual content.

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