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ADCY5-related movement disorders: Frequency, disease course and phenotypic variability in a cohort of paediatric patients

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ABSTRACT

Introduction: *ADCY5* mutations have been recently identified as an important cause of early-onset hyperkinetic movement disorders. The phenotypic spectrum associated with mutations in this gene is expanding. However, the *ADCY5* mutational frequency in cohorts of paediatric patients with hyperkinetic movement disorders has not been evaluated.
Methods: We performed a screening of the entire *ADCY5* coding sequence in 44 unrelated subjects with genetically undiagnosed childhood-onset hyperkinetic movement disorders, featuring chorea alone or in combination with myoclonus and dystonia. All patients had normal CSF analysis and brain imaging and were regularly followed-up in tertiary centers for paediatric movement disorders.
Results: We identified five unrelated subjects with *ADCY5* mutations (11% of the cohort). Three carried the p. R418W mutation, one the p. R418Q and one the p. R418G mutation. Mutations arose *de novo* in four cases, while one patient inherited the mutation from his similarly affected father. All patients had delayed motor and/or language milestones with or without axial hypotonia and showed generalized chorea and dystonia, with prominent myoclonic jerks in one case. Episodic exacerbations of the baseline movement disorder were observed in most cases, being the first disease manifestation in two patients. The disease course was variable, from stability to spontaneous improvement during adolescence.
Conclusion: Mutations in *ADCY5* are responsible for a hyperkinetic movement disorder that can be preceded by episodic attacks before the movement disorder becomes persistent and is frequently

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misdiagnosed as dyskinetic cerebral palsy. A residual degree of neck hypotonia and a myopathy-like facial appearance are frequently observed in patients with *ADCY5* mutations.

1. Introduction

Adenyl cyclase 5, encoded by *ADCY5*, is a striatal-specific enzyme that converts adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP), an intracellular second messenger crucial for several molecular pathways [1].

The role of pathogenic mutations in *ADCY5* was first recognized in 2012, when a segregating missense change in the gene was discovered in a large dominant kindred with multiple affected members presenting with an early-onset hyperkinetic movement disorder named Familial Dyskinesia with Facial Myokymia (FDFM; OMIM 600293) [1,2]. *A* second *de novo* mutation (p.R418W) in *ADCY5* was subsequently found in two unrelated patients presenting with childhood-onset chorea and dystonia [3] and mutation-positive subjects were also found in a cohort of patients with a clinical diagnosis of benign hereditary chorea (BHC) but no *NKX2-1* mutations [4]. The clinical phenotype associated with *ADCY5* mutations includes in most cases childhood-onset chorea with episodic exacerbations observed more frequently upon awakening, when falling asleep or during intercurrent illnesses [5–8]. Besides chorea, various hyperkinetic movement disorders such as myoclonus and dystonia have been described in *ADCY5* positive subjects, but the prevalence of *ADCY5* mutations in such patients is unknown.

The aim of this study was to establish the contribution of *ADCY5* mutations in a multi-centric cohort of patients with early-onset hyperkinetic movement disorder who lacked a definite genetic diagnosis.

We identified six new European cases with pathogenic *ADCY5* mutations belonging to five different families, showing the clinical course of disease at different ages, phenotypic heterogeneity and variability of movement disorder.

2. Materials and methods

In this study, we included patients displaying paediatric onset hyperkinetic movement disorder featuring chorea alone or in combination with myoclonus and dystonia, including patients diagnosed with dyskinetic cerebral palsy (CP). Patients with secondary movement disorders, such as documented hypoxic injury at birth or with detectable structural brain lesions were not included. Patients enrolled had previously undergone extensive metabolic screening (plasma and urinary aminoacids and organic acids, lactate/pyruvate, cerebrospinal fluid analysis including neurotransmitters and biopterins dosage) and multiple MRI brain scans that were unrevealing. Mutations in the *NKX2-1* gene, a significant though rare cause of childhood-onset chorea, were excluded in all of these patients [9].

44 unrelated patients were included from five different European Centers (IRCCS C. Besta Neurological Institute, Milan; IRCCS Santa Maria Nuova Hospital, Reggio Emilia; Movement Disorders Department, HYGEIA Hospital, Athens; Second Department of Neurology, Attikon Hospital, University of Athens; First Paediatric Clinic, University of Athens, Agia Sofia Hospital, Athens). Details on clinical history were obtained by direct interviewing the patients and their relatives; in some cases, home-made videos were retrieved and reviewed by the authors to better define the clinical phenotype at earlier disease stages.

After obtaining informed consent (parental consent for minors where applicable), patients were blood sampled and DNA was extracted from peripheral blood lymphocytes according to standard procedures. *ADCY5* exons 2 and 10, in which mutations have been identified in most of the families published to date, were Sanger sequenced. Samples without mutations in these two exons were submitted for Whole Exome Sequencing (WES), which was performed as previously reported [10]. Segregation analysis in available family members was performed in all positive cases.

3. Results

Five out of 44 unrelated patients (11%) carried *ADCY5* mutations. Four patients were sporadic and carried *de novo* changes, while one had an autosomal dominant family history and inherited the mutation from his 47-year-old father, who also suffered from childhood-onset generalized chorea and dystonia. All mutations detected were located in *ADCY5* exon 2, at amino acidic residue 418 (p.R418W in 3 patients, p. R418G and p. R418Q in one each). Analysis of WES data did not reveal any additional mutation in *ADCY5* located outside exons 2 and 10 in the remainder 39 patients.

Clinical features of positive patients are summarized in Table 1.

Patient 1 (p.R418W; *de novo* mutation) is a 15-year-old girl born pre-term from healthy parents. She presented with axial hypotonia (**Video 1 - Segment 1**) and delayed language. Around 11 months she developed abrupt brief generalized dystonic attacks when falling asleep. Between age 1 and 2, generalized chorea also appeared during attacks, that occurred in clusters on a weekly basis. Around 18 months of age she developed generalized chorea with a slowly progressive course until age 13 (**Video 1 - Segment 2**), and subsequent spontaneous improvement; at age 9 she developed left foot dystonia (in-turning). Due to chorea and severe axial hypotonia she could walk independently only at age 5; residual neck hypotonia is still present to date. Routine EEG and sleep studies did not show cortical correlates of movement disorder and brain MRI was unremarkable. She initially received a diagnosis of dyskinetic CP. On examination at age 15 (**Video 1 – Segment 3**), her mouth was slightly open, she showed generalized chorea involving also perioral muscles, dystonic posturing of upper and lower limbs, head drop and severe dysarthria with saliva drooling. Her total IQ (84) was in the borderline range (WISC). During teen age, episodic exacerbations of chorea and dystonia during sleep became shorter and less frequent and are now present about once a month. Episodic exacerbations also occur during the day with two distinct patterns: 1) sudden give-way of legs with falls to the ground with preserved consciousness and 2) generalized dystonic-choreic attacks favored by tiredness and narrow passages. Trihexyphenidyl up to 32 mg/day did not improve significantly motor symptoms.

Supplementary video related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2017.05.004.

Patient 2 (p.R418Q; *de novo* mutation) is an Italian 18-year-old boy born from healthy parents. He presented with delayed motor milestones and a tendency to tiptoe walking at 18 months. Since 6 months of age, nocturnal attacks of generalized dystonia with inconsolable crying, lasting up to some hours, disrupted his sleep. During infancy he developed generalized chorea and mild