ADCY5 mutations are another cause of benign hereditary chorea

ABSTRACT

Objective: To determine the contribution of ADCY5 mutations in cases with genetically undefined benign hereditary chorea (BHC).

Methods: We studied 18 unrelated cases with BHC (7 familial, 11 sporadic) who were negative for NKX2-1 mutations. The diagnosis of BHC was based on the presence of a childhood-onset movement disorder, predominantly characterized by chorea and no other major neurologic features. ADCY5 analysis was performed by whole-exome sequencing or Sanger sequencing. ADCY5 and NKX2-1 expression during brain development and in the adult human brain was assessed using microarray analysis of postmortem brain tissue.

Results: The c.1252C>T; p.R418W mutation was identified in 2 cases (1 familial, 1 sporadic). The familial case inherited the mutation from the affected father, who had a much milder presentation, likely due to low-grade somatic mosaicism. The mutation was de novo in the sporadic case. The clinical presentation of these cases featured nonparoxysmal generalized chorea, as well as dystonia in the most severely affected, but no facial myokymia. We observed significant progression of symptoms in ADCY5 mutation carriers, in contrast to BHC secondary to NKX2-1 mutations. The difference in the clinical course is mirrored by the brain expression data, showing increasing ADCY5 expression in the striatum during brain development, whereas NKX2-1 shows an opposite trend.

Conclusions: Our study identifies mutations in ADCY5, the gene previously linked to familial dyskinesia with facial myokymia, as a cause of familial and sporadic BHC. ADCY5 genetic analysis should be performed in cases with a benign choreiform movement disorder even in the absence of facial myokymia.

GLOSSARY

ADCY5 = adenylate cyclase 5 gene; BHC = benign hereditary chorea; FDFM = familial dyskinesia with facial myokymia; mRNA = messenger RNA; OMIM = Online Mendelian Inheritance in Man; WES = whole-exome sequencing.

Benign hereditary chorea (BHC) (OMIM 118700) is a rare and poorly delineated syndrome, clinically characterized by onset of symptoms in infancy or early childhood, relatively little clinical progression, and absence of other major neurologic deficits, in particular prominent cognitive decline.1,2

Mutations in the NKX2-1 gene (OMIM 600635) were identified in 2002 as a major cause of familial and sporadic BHC.3,4 However, a number of families with BHC do not carry mutations in NKX2-1, suggesting that other genes may be responsible for this syndrome.5–8

Familial dyskinesia with facial myokymia (FDFM) (OMIM 606703) was first described by Fernandez et al.9 in 2001. They reported a 5-generation kindred with 18 members affected with an autosomal dominant movement disorder, mainly characterized by childhood or early adolescent onset of hyperkinetic movements and perioral and periorbital myokymia. The disease locus was

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subsequently mapped to chromosome 3p21-3q21,10 and recently a missense variant in the adenylate cyclase 5 gene (ADCY5; OMIM 600293) was identified by next-generation sequencing as the causative mutation.11

Of note, before the identification of facial myokymia as one of the core features, individuals from the original FDFM kindred had been described as affected with familial essential (“benign”) chorea.12 Given the phenotypic overlap between FDFM and BHC, we wondered whether ADCY5 mutations could be detected in cases clinically diagnosed with BHC but lacking mutations in NKX2-1. We therefore performed a comprehensive mutational analysis of ADCY5 in a cohort of NKX2-1-negative cases with a BHC phenotype.

METHODS Standard protocol approvals, registrations, and patient consents. The study was approved by the UCL ethics committee (UCLH project 06/N076), and written informed consent was obtained from all participants.

Patients. All cases included in this study were evaluated in the Movement Disorder Center of the National Hospital for Neurology and Neurosurgery, Queen Square, London. We studied 18 consecutive unrelated cases, including 7 with an autosomal dominant family history and 11 sporadic. All participants in the study were assessed by neurologists with significant expertise in movement disorders (N.Q. and K.P.B.). BHC was clinically diagnosed based on the presence of a movement disorder, with onset before the age of 20 years, predominantly characterized by chorea in the absence of other major neurologic features (i.e., cognitive decline, ataxia, spasticity, or peripheral neuropathy). Medical history was negative for toxin exposure and drugs known to cause chorea.

Basic diagnostic evaluations, including MRI of the brain, CSF analysis, acanthocytes, antistreptolysin titer, copper, ceruloplasmin, and α-fetoprotein, were unremarkable. All cases were negative for mutations in the NKX2-1 and the Huntington disease triplet repeat expansion. DRPLA, SCA17, and HDL2 expansions were excluded in familial cases. SGCE mutations were excluded when myoclonus-dystonia was suspected due to the presence of dystonic features.

Genetic analysis. After informed consent was given, DNA was extracted from peripheral lymphocytes following a standard protocol. DNA of patients was analyzed either by whole-exome sequencing (WES) or by direct Sanger sequencing of the 21 coding exons and flanking intronic regions of ADCY5 (RefSeq accession number NM_183357). WES and Sanger sequencing methods are detailed in the supplementary methods (appendix e-1 on the Neurology® Web site at Neurology.org). Variants identified by WES were confirmed by Sanger sequencing. Segregation analysis was performed in parents and other relatives in mutation-positive cases.

Expression profiling of ADCY5 and NKX2-1 in brain tissue. Regional distribution of ADCY5 and NKX2-1 messenger RNA (mRNA) expression in the normal adult human brain was determined using microarray analysis of human postmortem brain tissue from the UK Human Brain Expression Consortium as previously described.13 This dataset is based on exon array profiling of 1,231 samples from 10 brain areas originating from 134 control individuals. ADCY5 and NKX2-1 mRNA expression changes during the course of human brain development were assessed by accessing the data available through the Human Brain Transcriptome database.14,15

RESULTS Identification of ADCY5 mutations. Analysis by WES or Sanger sequencing of the ADCY5 coding sequence revealed 4 different heterozygous mutations.

The pathogenic c.1252C>T; p.R418W variant was identified in 2 unrelated cases. This amino acid change has been previously reported in association with FDFM,16 is absent in all publicly available datasets of population controls (dbSNP, 1000 Genomes project, NHLBI exome variant server and Exome Aggregation Consortium), and is consistently predicted pathogenic by in silico prediction tools (PolyPhen-2, SIFT, and MutationTaster).

Another novel missense variant (c.2117C>T; p.A706V) was identified in the index case of a pedigree with autosomal dominant BHC. The mutation was predicted benign and tolerated respectively by PolyPhen-2 and SIFT, but disease-causing by MutationTaster. Segregation analysis in the family showed that the mutation was absent in the affected mother and had been inherited from the unaffected father, ruling out any pathogenic relevance.

Finally, a variant in the 5’ untranslated region (c.1-5G>C) together with the missense variant c.29C>T; p.P10L (rs143905423) was detected in a sporadic case of African ancestry (unknown phase of the 2 mutations). Both variants are reported with a minor allele frequency ≥1% in control individuals of African ancestry as reported by the Exome Aggregation Consortium, suggesting that both variants are likely to be neutral.

Clinical presentations of cases with pathogenic ADCY5 mutations. Clinical information of the patients with pathogenic ADCY5 mutations identified in this study and of those previously reported in the literature is summarized in the table.

Family 1. The clinical description of this pedigree has been previously reported.17 The index case is a 36-year-old British man (subject III-1; figure 1A). His birth and early development throughout infancy were normal. Around age 1, he progressively developed brief choreic movements at rest, affecting the face and the 4 limbs (video 1, segment 1A). Movements were markedly exacerbated by excitement, stress, or tiredness. Around the age of 18, he also developed painful spasms of the 4 limbs, particularly frequent and severe upon awakening. Symptoms progressed over the years and clinical examination at the age of 28 (video 1, segment 1B) revealed dystarthric speech and severe abnormal involuntary movements comprising generalized chorea with facial
## Table

Clinical features of cases with pathogenic ADCYS5 mutations described in this study and reported in the literature

<table>
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<tr>
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<th>This study</th>
<th>Literature</th>
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<tbody>
<tr>
<td></td>
<td>Family 1/subject II-1</td>
<td>Family 1/subject III-1</td>
</tr>
<tr>
<td>Ethnic origin</td>
<td>UK-Caucasian</td>
<td>UK-Caucasian</td>
</tr>
<tr>
<td>Age at onset</td>
<td>1 y</td>
<td>1 y</td>
</tr>
<tr>
<td>Age at examination, y</td>
<td>64</td>
<td>36</td>
</tr>
<tr>
<td>Symptoms at onset</td>
<td>Chorea</td>
<td>Chorea</td>
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<tr>
<td>Developmental milestones</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Facial dyskinesias</td>
<td>Few facial twitches</td>
<td>Chorea</td>
</tr>
<tr>
<td>EMG</td>
<td>No myokymia</td>
<td>No myokymia</td>
</tr>
<tr>
<td>Chorea</td>
<td>Yes, mild</td>
<td>Yes, severe and worsened by action and anxiety</td>
</tr>
<tr>
<td>Dystonia</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Other features</td>
<td>Gaze impersistence, difficulty initiating saccades</td>
<td>Gaze impersistence, difficulty initiating saccades</td>
</tr>
<tr>
<td>Paroxysmal events</td>
<td>Ballistic episodes and spasms upon awakening</td>
<td>Ballistic episodes and spasms at night</td>
</tr>
<tr>
<td>Gait</td>
<td>Mild difficulty on tandem walking</td>
<td>Abnormal due to lower limb choreo-dystonia</td>
</tr>
<tr>
<td>Extraneural involvement (cardiac, respiratory, or thyroid)</td>
<td>No</td>
<td>No</td>
</tr>
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Abbreviations: FDFM = familial dyskinesia with facial myokymia; NA = not available.
grimacing and marked dystonic elements. Both chorea and dystonia were present at rest, but action significantly exacerbated movements in the limbs. Eye movements were abnormal with gaze impersistence and use of head thrust to initiate saccades. Gait was unsteady with both choreic and dystonic features, but cerebellar testing was normal. He never displayed facial myokymia and EMG of periorbital and perioral regions failed to show either myokymia or other signs of motor neuron hyperexcitability. Over the years, different medications were tried without major improvements, including trihexyphenidyl, tetrabenazine, baclofen, levodopa, and clonazepam. He is currently on a combination of trihexyphenidyl (3 mg/d) and tetrabenazine (75 mg/d), which he finds helpful in reducing the intensity and frequency of the spasms.

His 64-year-old father (subject II-1; figure 1A) also developed involuntary movements in the first year of life. His involuntary movements mainly consisted of generalized chorea, with no dystonic posturing and overall he has always been much less affected than the son (video 1, segments 1A and 2). Besides chorea, on examination, he had marked ocular and motor impersistence and tandem walking difficulties. Cerebellar testing was otherwise normal. At the last follow-up, when he was 61, occasional twitches were observed in the periorbital areas (video 1, segment 2), but an EMG performed on the same day did not show myokymia. A low dose of tetrabenazine was tried but was not tolerated because of the development of depression. He is currently taking trihexyphenidyl (7.5 mg/d), with satisfactory control of...
of the dyskinesias. Higher doses were not tolerated because of the occurrence of cognitive difficulties.

There was no history of movement disorders in other family members, including both paternal grandparents of the index case.

The heterozygous ADCY5 c.1252C>T; p.R418W mutation was found by WES and confirmed by direct sequencing in subject III-1. No other possibly pathogenic variants in genes linked to chorea or other movement disorders were observed.

Sanger sequencing unexpectedly failed to detect the mutation in the affected father (figure 1A). Mosaicism has been previously reported in patients with mild presentation of mendelian disorders.\(^{18}\) We therefore suspected that Sanger sequencing might have missed the mutation in the father because of low-grade somatic mosaicism.

Because next-generation sequencing has been shown to be a more sensitive method to detect this type of mutation,\(^{18,19}\) WES was performed also in subject II-1.

Of note, this revealed the presence of the mutated allele in 9 of 110 sequence reads (approximately 8% vs 40% in his son; figure 1A), demonstrating the presence of low-level somatic mosaicism. This suggests that possibly the mutation arose in the father during early stages of embryogenesis. The unaffected mother and sister of the index case were wild-type by Sanger sequencing analysis.

**Family 2.** This is a 22-year-old man of Pakistani ethnicity (subject II-1; figure 1B). He is the son of a consanguineous marriage (parents are first-degree cousins) and he is the first of 4 siblings. He is the only affected member in the family. He had delayed motor milestones with walking at approximately 20 months. Since then, his gait has always been abnormal, being mainly characterized by arcing of the trunk, walking on tiptoes, and inversion of both feet. Around the age of 2, he developed constant involuntary movements involving all 4 limbs and trunk, which became progressively more evident over the years. Movements were largely exacerbated by stress and anxiety. Around the age of 10, he developed “fits” of violent hyperkinetic movements and painful spasms of all 4 limbs, mainly occurring at night. A polysomnographic study performed to investigate their nature excluded any epileptic activity and showed that the attacks occurred when the patient was fully awake.

On examination (video 2), he had moderate generalized chorea at rest and intermittent distal dystonic posturing in the 4 limbs. The hyperkinetic movements were dramatically increased by action. Gait was unsteady, but cerebellar testing was otherwise normal. Cranial nerve examination showed ocular impersistence, and frequent facial choreic movements were also observed. The patient declined an EMG of the facial muscles. He is currently taking trihexyphenidyl (30 mg/d) and tetrabenazine (50 mg/d), which partially reduced the intensity of the dyskinesias and the frequency of the spasms.

WES and subsequent Sanger sequencing analysis showed the presence in the affected case of the ADCY5 c.1252C>T; p.R418W change in the heterozygous state (figure 1B). The mutation had likely occurred de novo, as Sanger sequencing showed its absence in both healthy parents and in the 3 unaffected siblings. Mutations in other genes associated with chorea or other movement disorders were excluded.

**Brain expression data.** To investigate the differences in the phenotype and clinical course between BHC due to ADCY5 and NKX2-1 mutations, we analyzed and compared expression of the 2 genes across multiple brain regions and during the course of development.

Consistent with the observed phenotype, mainly characterized by chorea and dystonia with preserved cognition and no other major neurologic features, both ADCY5 and NKX2-1 mRNA expression profiling in 10 brain regions showed the highest expression in the putamen relative to other brain regions (figure 2A). When comparing ADCY5 with NKX2-1 expression, we observed that ADCY5 has a much higher expression in adult striatum. Furthermore, longitudinal analysis of mRNA expression during brain development showed opposite trends for ADCY5 and NKX2-1, with ADCY5 expression progressively increasing in the striatum from 50 to 500 days postconceptionalization and NKX2-1 progressively decreasing (figure 2D).

**DISCUSSION** Recently, a gain-of-function heterozygous missense mutation in ADCY5 (c.2176G>A; p.A726T) was recognized as the genetic cause in the original FDFM pedigree.\(^{11}\) The phenotype of the affected members of this family consisted of hyperkinetic movements starting from early childhood to late adolescence. A distinctive feature of this disorder was the presence of prominent periorbital and perioral facial myokymia.\(^{9}\)

After the identification of ADCY5 as the responsible gene in the original FDFM pedigree, the same group described a second pathogenic missense variant in ADCY5 (c.1252C>T; p.R418W), which occurred de novo in 2 unrelated individuals with a sporadic complex hyperkinetic movement disorder.\(^{14}\) The phenotype of these cases shared some features with the original FDFM pedigree, but it was more severe and further encompassed delayed motor milestones, axial hypotonia, and progressive gait difficulties in one case. More recently, a splice-site mutation in ADCY5 was identified in a family with autosomal dominant early-onset chorea, dystonia, and pyramidal signs.\(^{20}\)
We report here the results of the ADCY5 mutational analysis in a cohort of NKX2-1-negative sporadic and familial cases with a BHC-like presentation. These cases had previously been extensively investigated for genetic and acquired causes of chorea, without reaching a conclusive diagnosis. We identified 3 cases from 2 unrelated pedigrees bearing the same pathogenic change c.1252C>T;
p.R418W. The clinical phenotype of these cases predominantly featured generalized chorea, although with significant intra- and interfamilial phenotypic variability.

As previously observed in other cases with the ADCY5 p.R418W mutation, 2 of the 3 subjects with the mutation (individual III-1 from family 1 and individual II-1 from family 2) presented with severe choreo-dystonic dyskinesias, which were significantly more disabling than those of individuals carrying the p.A726T mutation from the original FDFM pedigree.

Subject II-1 from family 1 had conversely a milder presentation, with little functional impact from the dyskinesias. Furthermore, he had isolated chorea and no dystonic features. Of note, this milder presentation was reflected by the WES data, showing in the latter case a significantly reduced number of reads carrying the mutated allele. This suggests low-level somatic mosaicism as the likely explanation for the mitigated phenotype.

In some of the previously described cases with ADCY5 mutations, dyskinesias were reported as paroxysmal in the initial phase of the disease.\(^\text{9,16}\) Conversely, we show that dyskinesias were not paroxysmal, but constantly present from the onset of symptoms in the 3 cases we report, albeit markedly influenced by emotional states and action. It is of interest that all 3 cases developed episodes of violent ballistic movements and spasms later during the disease course. The episodes were particularly frequent at night or upon awakening. Similar episodes were also reported by Chen et al.\(^\text{16}\) in individual ID1 (carrier of the p.R418W mutation), suggesting that this may be a specific feature of the ADCY5-related movement disorder.

Facial myokymia has been suggested to be a distinctive feature of ADCY5-related disorder. However, an EMG study of the facial muscles performed in both affected subjects from family 1 (both presenting facial involuntary movements) did not show myokymia or other signs of motor neuron hyperexcitability. Although the subject from family 2 refused to undergo EMG, his facial hyperkinesias were clinically deemed to be choreiform in nature (video 2). This indicates that patients with ADCY5 mutations may present facial choreiform movements in the absence of myokymia. Consistent with this, facial myokymia was neither described in affected members from the original FDFM kindred nor recognized as a prominent feature in the other ADCY5 mutation carriers who were subsequently reported (table).

Even though the clinical presentation of patients with ADCY5 mutations is consistent with the clinical definition of BHC, some clinical clues may help to recognize and differentiate ADCY5 mutation carriers from BHC cases due to mutations in NKX2-1.

First, although both conditions can have extraneuronal involvement, NKX2-1 carriers often present with pulmonary symptoms or evidence of endocrine defects,\(^\text{21}\) whereas cardiac heart failure has been observed in some affected individuals from the original FDFM pedigree.\(^\text{11}\) ADCY5 overexpression has also been shown to lead to cardiomyopathy in a mouse model.\(^\text{22}\)

Second, the clinical progression between the 2 disorders seems to be different. BHC cases secondary to NKX2-1 mutations tend to remain relatively mildly affected and often improve after childhood,\(^\text{21}\) while we show here that ADCY5 mutation carriers may present significant progression of symptoms, at least until adult age. This difference in the clinical progression is nicely mirrored by the brain transcriptome data. The analysis and comparison of ADCY5 and NKX2-1 mRNA regional brain expression showed that, although both genes are most highly expressed in the adult striatum, ADCY5 levels progressively increase during brain development whereas NKX2-1 levels show an opposite trend.

Third, prominent dystonic posturing is present in the most severely affected cases with ADCY5 mutations and may dominate the clinical picture as the disease progresses (video 1, section 1B). Mild dystonic features can also be observed in some NKX2-1 cases,\(^\text{23,24}\) but they are generally not as severe as we observed in ADCY5 mutation carriers. Lastly, ADCY5-related dyskinesias are dramatically worsened by action, excitement, or stress. This feature likely reflects the biological role of adenyl cyclase 5. This enzyme catalyzes the formation of cAMP (cyclic adenosine monophosphate) upon β-adrenergic receptor stimulation via G proteins in striatal cells, and pathogenic mutations seem to increase the cyclase activity.\(^\text{16}\)

Our study demonstrates that ADCY5 mutations are responsible for familial and sporadic BHC and further delineates the phenotype associated with ADCY5 mutations. A diagnosis of ADCY5-related disorder should be suspected when evaluating patients with a BHC-like presentation, regardless of the presence of facial myokymia. Differences in the clinical presentation may be attributed to distinct molecular effects of different mutations, although somatic mosaicism may explain intrafamilial phenotypic variability, as shown in family 1. We also suggest that the term FDMD should not be used to refer to ADCY5-related movement disorder because myokymia may often not be part of the phenotype.

Given the possible reported association of ADCY5 mutations with cardiac involvement, it will be fundamental to closely follow up ADCY5 mutation carriers in order to prevent or adequately treat potential cardiac complications.

We confirm the usefulness of WES in the molecular diagnosis of rare and genetically heterogeneous
movement disorders, such as BHC. WES should be considered in the diagnostic workup of BHC after the exclusion of acquired causes in sporadic cases and mutations in the genes most frequently associated with choreic syndromes. In particular, repeat expansions (e.g., Huntington disease, SCA17 [spinocerebellar ataxia 17], DRPLA [dentatorubral-pallidolusian atrophy]) should be ruled out before performing WES because these mutations are not easily detected with this technology.

AUTHOR CONTRIBUTIONS
Niccolo E. Mencacci: drafting the manuscript for content, including medical writing for content, study concept and design, analysis and interpretation of data, acquisition of data. Roberto Erro: drafting the manuscript for content, including medical writing for content, study concept and design, analysis and interpretation of data, acquisition of data. Sarah Wierhoff: revising the manuscript for content, including medical writing for content, analysis and interpretation of data, acquisition of data. Joshua Hershenson: revising the manuscript for content, including medical writing for content, analysis and interpretation of data, acquisition of data. Minia Ryten: revising the manuscript for content, including medical writing for content, study concept, interpretation of data. Christina Ho: revising the manuscript for content, including medical writing for content, study concept and design, analysis and interpretation of data, acquisition of data. Christos Ganos: revising the manuscript for content, including medical writing for content, interpretation of data, supervision. Nicholas W. Wood: revising the manuscript for content, including medical writing for content, supervision. Kailash P. Bhatia: revising the manuscript for content, including medical writing for content, study concept, interpretation of data, acquisition of data, supervision.

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