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ADCY5 Dyskinesia

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Summary

Clinical characteristics

ADCY5 dyskinesia is a hyperkinetic movement disorder (more prominent in the face and arms than the legs) characterized by infantile to late-adolescent onset of chorea, athetosis, dystonia, myoclonus, or a combination of these. To date, affected individuals have had overlapping (but not identical) manifestations with wide-ranging severity. The facial movements are typically periorbital and perioral. The dyskinesia is prone to episodic or paroxysmal exacerbation lasting minutes to hours, and may occur during sleep. Precipitating factors in some persons have included emotional stress, intercurrent illness, sneezing, or caffeine; in others, no precipitating factors have been identified. In some children, severe infantile axial hypotonia results in gross motor delays accompanied by chorea, sometimes with language delays. The overall tendency is for the abnormal movements to stabilize in early middle age, at which point they may improve in some individuals; less commonly, the abnormal movements are slowly progressive, increasing in severity and frequency.

Diagnosis/testing

The diagnosis of *ADCY5* dyskinesia is established in a proband with a hyperkinetic movement disorder (in the absence of structural brain abnormalities) and a heterozygous pathogenic or likely pathogenic variant (or, rarely, biallelic pathogenic or likely pathogenic variants) in *ADCY5* identified by molecular genetic testing.

Management

Treatment of manifestations: Management by multidisciplinary specialists, including a neurologist or neurogeneticist, cardiologist, physical therapist, social worker, speech and language pathologist, and other specialists is recommended as needed. Anecdotally, medications have had variable effect in suppressing debilitating symptoms. Treatment should be determined by the individual's physician, taking into account potential risk/benefit, other medical conditions, allergies, and potential drug-drug interactions. Response to

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medication is difficult to evaluate because some individuals have long periods (weeks) of remission of the dyskinesia. Physical and occupational therapy may help maintain mobility and function. Speech and language therapy for dysarthria may include alternative communication methods. Cognitive impairment and psychiatric manifestations are managed per standard practice.

Surveillance: Routine follow up of neurologic involvement, dysarthria, oculomotor involvement, musculoskeletal involvement, activities of daily living, cognitive impairment, and psychiatric manifestations.

Pregnancy management: Potential teratogenic effects of medications given for treatment of *ADCY5* dyskinesia should be discussed with affected women of childbearing age, ideally prior to conception.

Genetic counseling

ADCY5 dyskinesia is typically inherited in an autosomal dominant (AD) manner. Autosomal recessive (AR) inheritance has been reported in two families.

AD inheritance. The majority of individuals diagnosed with *ADCY5* dyskinesia represent simplex cases (i.e., a single affected family member) and have the disorder as the result of a *de novo* pathogenic variant. Each child of an individual with *ADCY5* dyskinesia has a 50% chance of inheriting the pathogenic variant.

Both AD and AR inheritance. Once the *ADCY5* pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for *ADCY5* dyskinesia are possible.

Diagnosis

No consensus diagnostic guidelines for *ADCY5* dyskinesia have been published.

Suggestive Findings

Diagnosis of *ADCY5* dyskinesia **should be suspected** in individuals with the following clinical findings, neuroimaging, and family history.

Clinical findings

- Infantile to late-adolescent onset of choreiform, myoclonic, and/or dystonic movements that involve the limbs, neck, and/or face
- Familial benign chorea
- Alternating hemiplegia in childhood
- Myoclonus-dystonia
- Focal dystonia and tremor
- Spasticity and dystonia
- Sleep-related motor and behavior disorder

Neuroimaging. Brain MRI shows no evidence of structural abnormalities.

Family history is consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations) or, rarely, autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *ADCY5* dyskinesia **is established** in a proband with a hyperkinetic movement disorder (in the absence of structural brain abnormalities) and a heterozygous pathogenic or likely pathogenic variant (or, rarely, biallelic pathogenic or likely pathogenic variants) in *ADCY5* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *ADCY5* variant(s) of uncertain significance does not establish or rule out the diagnosis of this disorder.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing and multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of *ADCY5* dyskinesia has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *ADCY5* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected.

If no variant is detected by the sequencing method used, the next step typically is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications; however, because *ADCY5* dyskinesia occurs through a gain-of-function mechanism and large intragenic deletion or duplication has not been reported, testing for intragenic deletions or duplication is unlikely to identify a disease-causing variant.

Mosaicism of pathogenic variants has been reported.

A movement disorder multigene panel that includes *ADCY5* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *ADCY5* Dyskinesia

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
ADCY5	Sequence analysis [3]	100% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	None reported [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Chen et al [2012], Chen et al [2014], Chen et al [2015], Zech et al [2017], and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. In a simplex case (i.e., a single occurrence in a family), germline mosaicism for the pathogenic variant may complicate interpretation of sequencing results.
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. Because *ADCY5* dyskinesia occurs through a gain-of-function mechanism and large intragenic deletion or duplication has not been reported, testing for intragenic deletions or duplication is unlikely to identify a disease causing variant.

Clinical Characteristics

Clinical Description

The hallmark of *ADCY5* dyskinesia is infantile to late-adolescent onset of a hyperkinetic movement disorder characterized by chorea, athetosis, dystonia, myoclonus, or a combination which tends to be more prominent in the face and arms than the legs [Chen et al 2015]. Affected individuals identified to date have overlapping but not identical clinical manifestations with wide-ranging clinical severity. The facial movements are typically periorbital and perioral. The dyskinesia is prone to episodic or paroxysmal bouts of exacerbation lasting minutes to hours, and may occur during sleep. Precipitating factors have included emotional stress, intercurrent illness, sneezing, or caffeine [Vijiaratnam et al 2019]. In other affected individuals, no precipitating factors have been identified. In some children, severe infantile axial hypotonia results in gross motor delays accompanied by chorea, sometimes with language delays [Carecchio et al 2017]. The phenotypic spectrum of this disorder is still being elucidated.

ADCY dyskinesia was first identified in a single multigenerational family [Chen et al 2012]. Following that publication, more than 40 individuals representing simplex cases (i.e., a single occurrence in a family) and members of more than ten families with *ADCY5* dyskinesia have been reported [Chen et al 2015, Vijiaratnam et al 2019]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. *ADCY5* Dyskinesia: Frequency of Select Features

Feature	Frequency			Comment
	Nearly all	Common	Infrequent	
Dyskinesia	●			
Axial hypotonia		●		In children presenting in infancy
Spasticity		●		
Intellectual disability			●	
Epilepsy			●	

Table 2. continued from previous page.

Feature	Frequency			Comment
	Nearly all	Common	Infrequent	
Psychiatric disease			●	
Cardiomyopathy			●	

Neurologic Manifestations

All affected individuals reported to date have had episodes of choreiform, myoclonic, and/or dystonic movements that primarily affect the limbs, face, and/or neck. Typically the abnormal movements first appear during infancy, childhood, or early adolescence (range: neonatal period to age 19 years) [Chen et al 2015].

In those with milder manifestations, the abnormal movements involve the face and distal limbs (although minimally affecting function) and are socially debilitating. Some affected individuals may be described as "excessively clumsy."

In more severely affected infants, the earliest manifestations can include severe axial hypotonia resulting in developmental delays that lead to impairment in the ability to ambulate, requiring use of wheelchairs.

The abnormal movements are continual during waking hours, and have been noted to persist during sleep, particularly in infancy. Several affected individuals have noted severe, sleep-disrupting movements [Chen et al 2014, Chen et al 2015] that occurred during stages N2 and N3 of sleep, and were not associated with epileptiform discharges in one individual [Chen et al 2014].

A curious feature observed in some individuals is the occurrence of long periods (days to weeks) of remission.

The movements are often exacerbated by anxiety or stress and with drowsiness or sleep (although not by startle or alcohol). Less common triggers include intercurrent illness, fatigue, excitement, or caffeine, although one individual showed improvement with caffeine and other individuals have reported benefit [J Friedman, personal observation]. One woman reported that her choreiform movements were precipitated by enforced inactivity (e.g., as during a road trip), and could often be alleviated by voluntary movement.

Facial "twitches" (previously thought to be myokymia) involving the periorbital and/or perioral muscles may also be present. Twitches were also documented in limb muscles in one individual [Fernandez et al 2001].

Dysarthria and hypotonia have been reported in some affected individuals [Chen et al 2014, Chen et al 2015, Mencacci et al 2015].

Intellect and life span are usually normal. In severely affected individuals with onset in early childhood, intellectual disability may be present.

Neurologic examination can vary widely between individuals and in the same individual over time. Examination may reveal:

- A mixed movement disorder that may include prominent choreiform movements usually affecting the hands and/or feet, often characterized as piano playing movements [Vijiaratnam et al 2019];
- Myoclonic and dystonic movements [Friedman et al 2016];
- Non-myokymic facial twitching, hyperreflexia of the lower limbs, and intermittent head or limb tremors [Chen et al 2014];
- Axial hypotonia with limb and axial weakness including severe neck weakness [Chen et al 2014, Chen et al 2015];
- Alternating hemiplegia of childhood [Westenberger et al 2017];
- Progressive spasticity and dystonia with hyperreflexia [Dean et al 2019, Waalkens et al 2018].

Somatic mosaicism has been demonstrated in 43% of individuals with a *de novo* pathogenic variant [Raskind et al 2017] and in the founders of two multigenerational families, including one individual shown to be mosaic for the p.Met1029Lys variant who demonstrated considerable improvement during adulthood [Chen et al 2015].

Another individual, thought to be mosaic for p.Arg418Trp, exhibited significantly milder phenotypic features: fewer facial twitches, milder chorea, and no dysarthria [Mencacci et al 2015].

The natural history varies. In most, the abnormal movements are static or slowly progressive with increased severity and frequency. In some instances, choreiform movements have been more constant, and less paroxysmal, from the onset [Mencacci et al 2015]. The overall tendency is for the abnormal movements to stabilize in early middle age, at which point they may improve in some individuals.

Cardiac Complications

Chen et al [2011] reported that five individuals in a family with *ADCY5* dyskinesia also had congestive heart failure. Because *ADCY5* encodes a specific adenylyl cyclase that is highly expressed in both striatum and myocardium [Ho et al 2010], these observations suggest that pathogenic variants in *ADCY5* could contribute to cardiac pathology; further study is required.

Studies

Needle electromyogram (EMG) studies in two individuals with facial muscle twitching suggested centrally driven irregular muscle movements that were also observed in other muscles, including the orbicularis oculi, tongue, frontalis, and dorsal interosseous muscles. No fibrillations, fasciculations, myokymia, or myotonia were noted on EMG.

Brain imaging (MRI, CT) is normal.

Neuropathology. Gross pathology is normal. Detailed immunohistochemical analysis in one individual with molecularly confirmed *ADCY5* dyskinesia revealed increased immunoreactivity for ADCY5 in multiple brain regions as well as tau deposits in deep cortical sulci, the midbrain and hippocampus. Lewy bodies and amyloid pathology were absent [Chen et al 2019].

Genotype-Phenotype Correlations

In general, the number of individuals and families tested to date is too small to make reliable predictions of phenotypic features based on genotype; however, one missense variant, p.Ala726Thr, has been associated with a milder phenotype [Vijiaratnam et al 2019] (see Table 7).

Penetrance

In molecularly confirmed *ADCY5* dyskinesia, penetrance has been 100% in both men and women.

Nomenclature

ADCY5 dyskinesia has been previously described as:

- A variant of familial essential ("benign") chorea. Although the term "benign" was used to distinguish the movement disorder from progressive, neurodegenerative forms of chorea such as Huntington disease, *ADCY5* dyskinesia can be disabling and in some instances progressive, and, thus, use of the term "benign hereditary chorea" should be avoided.
- "Familial dyskinesia facial myokymia" because the prominent facial twitching was originally thought to be myokymia (see Clinical Description); however, more recently EMG studies of affected individuals have revealed that these twitches are not myokymia.

DYT-*ADCY5* may be an appropriate designation because dystonia is often a prominent feature [Marras et al 2012].

Prevalence

No data are available for the prevalence of *ADCY5* dyskinesia. It is likely underdiagnosed because of the variability in the clinical presentation and age of onset, and because of the high rate of *de novo* variants resulting in simplex cases (i.e., a single occurrence in a family) [Vijiaratnam et al 2019].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *ADCY5*.

Differential Diagnosis

Hereditary Disorders

Table 3. Genes of Interest in the Differential Diagnosis of *ADCY5* Dyskinesia

Gene(s)	DiffDx Disorder	MOI	Clinical Characteristics of DiffDx Disorder	
			Overlapping w/*ADCY5* dyskinesia	Distinguishing from *ADCY5* dyskinesia
ANO3	DYT-*ANO3* (See Hereditary Dystonia Overview.)	AD	Focal dystonia & tremor	Affects neck, laryngeal muscles, and arms
ATP1A3	Alternating hemiplegia of childhood (See *ATP1A3* Neurologic Disorders.)	AD	Alternating hemiplegia	Episodic hemiplegia assoc w/mvmt disorder
CHRNA2 *CHRNA4* *CHRNB2* *CRH* *DEPDC5* *KCNT1*	AD nocturnal frontal lobe epilepsy	AD	Sleep-related motor & behavioral disorders	On video-EEG: focal interictal epileptiform discharges arising from the frontal lobe; seizures recorded
GCH1	GTP cyclohydrolase 1-deficient dopa-responsive dystonia	AD	Dystonia	Dramatic response to treatment w/L-dopa
HTT	Huntington disease	AD	Chorea	• Mean onset age: 35-44 yrs • Choreiform mvmts become constant over time.
NKX2-1	Benign hereditary chorea (See *NKX2-1* Disorders.)	AD	Presents before age 5 yrs	• Manifestations often improve by late adolescence. • Pulmonary dysfunction & endocrine abnormalities, most commonly hypothyroidism (Note: Non-neurologic manifestations are rare in *ADCY5* dyskinesia.)
PDE10A	Infantile-onset limb & orofacial dyskinesia (OMIM 616921)	AR	Childhood onset chorea	• Diurnal fluctuation • Striatal lesions on brain MRI
PDE2A	*PDE10A* childhood-onset chorea [1]		Childhood onset chorea	Striatal lesions on brain MRI

Table 3. continued from previous page.

Gene(s)	DiffDx Disorder	MOI	Clinical Characteristics of DiffDx Disorder	
			Overlapping w/*ADCY5* dyskinesia	Distinguishing from *ADCY5* dyskinesia
PNKD	Familial paroxysmal nonkinesigenic dyskinesia	AD	• Unilateral or bilateral involuntary mvmts • Attacks are spontaneous or precipitated; involve dystonic posturing w/choreic & ballistic mvmts; may be accompanied by preceding aura; occur while awake; are not assoc w/seizures.	Consumption of alcohol or caffeine may precipitate attacks
PRRT2	Paroxysmal kinesigenic dyskinesia (PKD) (See *PRRT2* Paroxysmal Movement Disorders.)	AD	• Unilateral or bilateral involuntary mvmts precipitated by other sudden mvmts (e.g., standing up from sitting position; being startled; changes in velocity). • Attacks incl combinations of dystonia, choreoathetosis, & ballism; are sometimes preceded by an aura; do not involve loss of consciousness.	PKD is more common in men & is precipitated by voluntary mvmt.
SGCE	*SGCE* myoclonus-dystonia	AD	Myoclonus-dystonia	Improves w/alcohol consumption; psychiatric manifestations are more common.
SLC2A1	Paroxysmal choreoathetosis w/spasticity (See Glucose Transporter Type 1 Deficiency Syndrome.)	AD (AR)	Presents w/dystonic paroxysms affecting toes, legs, & arms; dysarthria; & changes in perioral sensation	No distinguishing clinical characteristics

AD = autosomal dominant; AR = autosomal recessive; DiffDx = differential diagnosis; DYT = dystonia; MOI = mode of inheritance
1. Mencacci et al [2016]

Mitochondrial disorders can present with dystonia or other abnormal movements.

Drug-Induced and Acquired Disorders

Tardive dyskinesia, a hyperkinetic movement disorder associated with long-term use of specific dopamine receptor blocking agents (including neuroleptics and certain antiemetics) [Aquino & Lang 2014], is often precipitated by a recent dose reduction or a change to a less potent drug.

Sydenham chorea, a manifestation of acute rheumatic fever, is the most common cause of acquired chorea in childhood, and typically presents between ages five and 12 years. Although carditis and arthritis are other manifestations of rheumatic fever, chorea may be the only clinical sign. Antistreptolysin O (ASO) titers are elevated in a significant proportion of affected individuals.

Multiple sclerosis can cause continuous facial myokymia in individuals with lesions impinging on the facial nerve as it courses in the dorsolateral pontine tegmentum. Other features – particularly abnormalities on brain MRI, which are disseminated in space and time – should assist in making the correct diagnosis.

Note: The hyperkinetic movements of *ADCY5* dyskinesia may be mistakenly thought to be epileptiform; however, normal EEGs, lack of impaired consciousness, and/or lack of response to antiepileptic medication distinguish epilepsy from *ADCY5* dyskinesia.

Management

Consensus clinical management recommendations for *ADCY5* dyskinesia have not been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *ADCY5* dyskinesia, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with *ADCY5* Dyskinesia

System/Concern	Evaluation	Comment
Neurologic involvement	By a neurologist	Assess: • Neurologic findings incl spasticity, dystonic posturing, sleep-related mvmts; • Response or lack of response to medications.
Oculomotor involvement	Complete ophthalmologic exam	Assess best corrected visual acuity; nystagmus, saccades & smooth pursuit; vertical & horizontal gaze limitation; ptosis.
Musculoskeletal	Orthopedics / physical medicine & rehab / PT/OT eval	To incl assessment of: • Gross motor & fine motor skills • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills) • Mobility, self-help skills, activities of daily living, & need for adaptive devices
DD / Cognitive impairment	Developmental behavioral pediatrician, neurologist, or geneticist	Children: To incl motor, adaptive, cognitive, & speech/language eval; eval for early intervention / special education
	Clinical psychologist	Adults: Assess for deficits in spatial working & episodic memory
Dysarthria	Speech & language assessment	Related to abnormal tongue & facial mvmts
Psychiatric manifestations	• Child psychiatrist • Clinical psychologist	Depression, psychosis w/delusions & auditory hallucinations, obsessive-compulsive symptoms, autistic-like behavior
Cardiac involvement	EKG, echocardiogram, cardiology eval	Dilated cardiomyopathy may be a manifestation.
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *ADCY5* dyskinesia in order to facilitate medical & personal decision making
Family support/ resources	Assess: • Use of community or online resources such as Parent to Parent; • Need for social work involvement for parental support; • Need for home nursing referral.	Disease severity may qualify some persons for disability &/or social security benefits.

DD = developmental delay; MOI= mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Management by multidisciplinary specialists, including a neurologist, or neurogeneticist, cardiologist, physical therapist, social worker, speech and language pathologist, and other specialists is recommended as needed.

Medication has been variably effective in suppressing debilitating manifestations. Treatment should be determined by the individual's physician, taking into account potential risk/benefit, other medical conditions, allergies, and potential drug-drug interactions. Response to medication is difficult to evaluate in an individual because some have long periods (weeks) of remission of the dyskinesia [Vijiaratnam et al 2019].

Table 5. Treatment of Manifestations in Individuals with *ADCY5* Dyskinesia

Manifestation/ Concern	Treatment	Considerations/Other
Chorea & dyskinesia	Acetazolamide	Up to 30 mg/kg/day
	Other potentially beneficial medications	• Trihexyphenidyl • Tetrabenazine • Clonazepam • Propranolol • Levocarnitine • Levetirracetam • Methylphenidate
	Medications that may worsen manifestations	Any of the above
	Deep brain stimulation	Improves mvmt disorder in some persons refractory to medical treatment [1]
Sleep-related movements	Clonazepam	Improves nocturnal dystonia & axial hypotonia in some
	Other potentially beneficial medications	Melatonin
Dysarthria	Speech/language eval	Consider alternative communication methods as needed (e.g., writing pads & digital devices).
Oculomotor involvement	Per treating ophthalmologist	
Musculoskeletal	Orthopedics / physical medicine & rehab / PT/OT	• To help maintain mobility & function • Walking aids incl canes or walkers when appropriate • Durable medical equipment & positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers) • Home adaptations for safety & function • Consider disability parking placard for care-givers.
Developmental delay	See Developmental Delay / Intellectual Disability Management Issues.	
Cognitive impairment	• Developmental eval • Individualized education plan	To identify degree of disability & provide resources for learning
Psychiatric manifestations	• Cognitive behavioral therapy • Medication • Mental health professionals	
Family support/ resources	Ensure appropriate social work involvement to: • Connect families w/local resources, respite, & support; • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	

1. Reported in fewer than 5 persons with overall beneficial effects [Dy et al 2016, Meijer et al 2017]

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- Individualized education plan (IEP) services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Surveillance

Table 6. Recommended Surveillance for Individuals with *ADCY5* Dyskinesia

System/Concern	Evaluation	Frequency
Neurologic involvement	Assess for new manifestations incl changes in tone, scoliosis, & mvmt disorders.	Annually
Dysarthria	Speech & language eval incl need for alternative communication methods	At each visit
Oculomotor involvement	Per treating ophthalmologist	As clinically indicated

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Musculoskeletal / Activities of daily living	PT/OT eval	At each visit
Developmental delay	Monitor developmental progress & educational needs.	
Cognitive impairment	Neuropsychological testing; developmental eval	
Psychiatric manifestations	Assess for changes in mood, attention, psychosis, or obsessive-compulsive disorder.	
Cardiac involvement	EKG, echocardiogram, cardiac MRI	As clinically indicated

OT = occupational therapy; PT = physical therapy

Agents/Circumstances to Avoid

The only exacerbating factor that is observed consistently across affected individuals is the presence of anxiety and exposure to typical life stressors. Further investigation is needed to determine whether stress management techniques or limitation of stressful activities may reduce the number and frequency of movements.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Potential teratogenic effects of medications given for treatment of *ADCY5* dyskinesia should be discussed with affected women of childbearing age, ideally prior to conception.

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

ADCY5 dyskinesia is typically inherited in an autosomal dominant manner, often as the result of a *de novo* pathogenic variant. Autosomal recessive inheritance of *ADCY5* dyskinesia has been reported in two families [Barrett et al 2017, Bohlega et al 2019].

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- The majority of individuals diagnosed with *ADCY5* dyskinesia represent simplex cases (i.e., a single affected family member) and have the disorder as the result of a *de novo* pathogenic variant [Vijiaratnam et al 2019].
- Some individuals diagnosed with *ADCY5* dyskinesia have the disorder as the result of a pathogenic variant inherited from a parent who may or may not have clinical manifestations of the disorder.
- Molecular genetic testing is recommended for the parents of a proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent several possibilities should be considered:
    - The proband has a *de novo* pathogenic variant. In a high percentage of individuals with an *ADCY5* *de novo* pathogenic variant, mutation occurred in later stages of embryogenesis resulting in somatic mosaicism for that variant [Vijiaratnam et al 2019] (Note: A pathogenic variant is reported as *de novo* if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity; if parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015]).
    - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism [Vijiaratnam et al 2019]. (Note: Testing of parental leukocyte DNA may not detect all instances of parental somatic mosaicism.)

      A parent with somatic and germline mosaicism for an *ADCY5* pathogenic variant may be mildly/minimally affected [Chen et al 2015].
- The family history of some individuals diagnosed with *ADCY5* dyskinesia may appear to be negative because of failure to recognize the disorder in family members or mild/late onset of the disease in a heterozygous parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has established that neither parent is heterozygous for the pathogenic variant identified in the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the *ADCY5* pathogenic variant identified in the proband, the risk to sibs of inheriting the pathogenic variant is 50%. All sibs who inherit an *ADCY5* pathogenic variant will most likely have clinical manifestations of the disorder (see Penetrance); however, the range of clinical manifestations may vary widely among heterozygous family members.
- If the *ADCY5* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent (or the parents are clinically unaffected but their genetic status is unknown), the recurrence risk to sibs is greater than that of the general population because of the possibility of parental mosaicism (which has been documented in *ADCY5* dyskinesia) [Chen et al 2015, Chen et al 2016].

Offspring of a proband. Each child of an individual with *ADCY5* dyskinesia has a 50% chance of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the pathogenic variant, the parent's family members may be at risk.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., presumed to be carriers of one *ADCY5* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that each parent is heterozygous for an *ADCY5* pathogenic variant and to allow reliable recurrence risk assessment. (*De novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)
- Individuals who are heterozygous for a pathogenic variant associated with autosomal recessive *ADCY5* dyskinesia are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an *ADCY5* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Individuals who are heterozygous for a pathogenic variant associated with autosomal recessive *ADCY5* dyskinesia are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Unless an individual with *ADCY5* dyskinesia has children with an affected individual or a carrier, his/her offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *ADCY5*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *ADCY5* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *ADCY5* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once the *ADCY5* pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for *ADCY5* dyskinesia are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **ADCY5.ORG**
  Phone: 858.882.7280

Email: info@adcy5.org
www.adcy5.org

- **Dystonia Medical Research Foundation**
  One East Wacker Drive
  Suite 1730
  Chicago IL 60601-1905
  Phone: 800-377-3978 (toll-free); 312-755-0198
  Fax: 312-803-0138
  Email: dystonia@dystonia-foundation.org
  Paroxysmal Dyskinesias
- **National Library of Medicine Genetics Home Reference**
  ADCY5-related dyskinesia

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. ADCY5 Dyskinesia: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
ADCY5	3q21.1	Adenylate cyclase type 5	ADCY5	ADCY5

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for ADCY5 Dyskinesia (View All in OMIM)

600293	ADENYLATE CYCLASE 5; ADCY5
606703	DYSKINESIA WITH OROFACIAL INVOLVEMENT, AUTOSOMAL DOMINANT; DSKOD

Molecular Pathogenesis

The adenylyl cyclase gene family encodes a number of proteins that convert adenosine triphosphate (ATP) to cyclic adenosine-3',5'-monophosphate (cAMP), a second messenger molecule that exerts a wide variety of effects via a number of intracellular signaling pathways [Halls & Cooper 2017].

ADCY5 encodes adenylyl cyclase type V (ADCY5), one of nine different membrane-bound adenylyl cyclases. ADCY5 converts adenosine triphosphate (ATP) to cyclic adenosine-3',5'-monophosphate (cAMP). Stimulation of ADCY5 by β-adrenergic agonists through a G-protein-coupled receptor induces a conformational change, aligning the two cytoplasmic domains such that they form a catalytic pocket in which ATP can bind [Chen et al 2014].

ADCY5 is highly expressed in striatum and myocardium. ADCY5 is especially prevalent in the nucleus accumbens, accounting for 80% of adenylate cyclase activation [Chen et al 2011].

Mechanism of disease causation. Gain-of-function missense pathogenic variants in *ADCY5* have been shown to increase intracellular cAMP, which could exert a myriad of effects at the cellular level [Chen et al 2014]. Presumably, increased ADCY5 activity affects either the signal transduction pathway following β-adrenergic stimulation or the interaction of the protein with other regulatory molecules [Mencacci et al 2015].

A loss-of-function (c.2088+1G>A) variant has been identified in a single family with hyperkinetic movements [Carapito et al 2015].

The mechanism by which contrasting gain of function and haploinsufficiency both result in a similar clinical presentation is currently unknown, but may result from the sum of ADCY effects on both stimulatory and inhibitory cellular pathways.

In mice, overexpression of ADCY5 leads to age-related cardiomyopathy and disruption protects against β-adrenergic-mediated cardiac stress [Ho et al 2010].

Table 7. Notable *ADCY5* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_183357.3 NP_899200.1	c.1252C>T	p.Arg418Trp [1]	Recurrent *de novo* pathogenic variants affecting the same residue [Chen et al 2014, Chen et al 2015, Chang et al 2016]
	c.1252C>G	p.Arg418Gly	
	c.1253G>A	p.Arg418Gln	
	c.1762G>A	p.Asp588Asn	Assoc w/autosomal recessive inheritance [Barrett et al 2017, Bohlega et al 2019]
NM_183357.3	c.2088+1G>A		Apparent loss-of-function variant w/unclear disease mechanism [Carapito et al 2015]
NM_183357.3 NP_899200.1	c.2176G>A	p.Ala726Thr	Assoc w/milder phenotype [Vijiaratnam et al 2019]
	c.3086T>A	p.Met1029Lys [2]	Assoc w/somatic mosaicism [Chen et al 2015]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. See Genotype-Phenotype Correlations.
2. See Clinical Description, Neurologic Manifestations.

Chapter Notes

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