GENEReviews

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Rapid-Onset Dystonia Parkinsonism

[*DYT12*]

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Summary

Disease characteristics. Rapid-onset dystonia-parkinsonism (RDP) is characterized by abrupt onset of dystonia with parkinsonism (primarily bradykinesia and postural instability); a clear rostra-caudal (face>arm>leg) gradient of involvement; bulbar involvement; and absence of response to an adequate trial of L-dopa therapy. Often triggering events such as fever, physiologic stress or alcoholic binges occur prior to the onset of symptoms. The symptoms often stabilize with little improvement after initial appearance with occasional second episodes of abrupt worsening of symptoms. Anxiety, depression, and seizures have been reported. The age of onset of symptoms ranges from four to 55 years.

Diagnosis/testing. Diagnosis of RDP is based on clinical findings. *ATP1A3* is the only gene known to be associated with RDP. Molecular genetic testing of *ATP1A3* is available on a research basis only. It is unclear if mutations in genes at other loci are also causative.

Management. *Treatment of manifestations:* high-dose benzodiazepines; standard treatment for seizures, depression and anxiety, and dysphagia. *Prevention of secondary complications:* physical therapy to prevent contractures in the hands and feet. *Agents/circumstances to avoid:* triggers of abrupt onset of RDP, such as alcohol, fever, psychological stress, excessive exercise; possibly digoxin.

Genetic counseling. RDP is inherited in an autosomal dominant manner. Many individuals with RDP have an affected parent; the proportion of cases caused by a *de novo* mutation is unknown. Each child of an individual with RDP has a 50% chance of inheriting the mutation. Prenatal diagnosis for pregnancies at increased risk is possible if the disease-causing mutation in the family is known.

Diagnosis

Clinical Diagnosis

Diagnosis of rapid-onset dystonia-parkinsonism (RDP) is based on clinical findings in individuals with mutations in *ATP1A3*, the only gene known to be associated with RDP.

Findings in 36 individuals from ten families with *ATP1A3* mutations established the following minimal diagnostic criteria for RDP [Brashear et al 2007]:

- Abrupt onset of dystonia with features of parkinsonism over a few minutes to 30 days
- A clear rostra-caudal (face>arm>leg) gradient of involvement
- Prominent bulbar findings on examination
- Absence of response to an adequate trial of L-dopa therapy (e.g., carbidopa/levodopa 25/100 one pill 3x/day)
- Family history consistent with autosomal dominant inheritance

Note: One of the 11 individuals without an *ATP1A3* mutation who also met these criteria had an exquisite response to anticholinergic medication that is not seen in RDP.

In addition to the minimal criteria, other features suggestive of RDP include the following:

- Minimal or no tremor at onset
- Occasional mild limb dystonia prior to the abrupt onset of dystonia
- Triggers (such as running, childbirth, emotional stress, or alcoholic binges) associated with the abrupt onset of symptoms
- Stabilization of symptoms within a month
- Rare "second onsets" or abrupt worsening of symptoms later in life
- Minimal improvement overall, but with limited improvement in gait

Testing

Brain imaging (MRI, CT) has been normal when performed.

Position emission tomography (PET) studies using the dopamine transporter imaging agent [^{11}C]β-CFT did not show a decrease in dopamine reuptake sites [Brashear et al 1999] (see Figure 1).

Cerebral blood flow was similar in persons with RDP when compared with age-matched controls [Brashear et al 1999].

Low cerebrospinal fluid concentration of the dopamine metabolite homovanillic acid in symptomatic individuals with an *ATP1A3* mutation increased after L-dopa treatment, but did not correlate with clinical improvement.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. Mutations in *ATP1A3*, which encodes the alpha 3 subunit of the Na K ATPase, is the only gene known to be associated with RDP [de Carvalho Aguiar et al 2004, Brashear et al 2007, Lee et al 2007, McKeon et al 2007] (see Table 1).

Other loci. Although no other genes have been identified as causing RDP, a German family with eight affected members does not have a mutation in *ATP1A3* and does not show linkage to the *ATP1A3* locus on chromosome 19, suggesting the presence of at least one additional locus for RDP. It should also be noted that five of the eight affected members have concurrent

renal disease, which has not been seen in families with *ATP1A3* mutations [Kabakci et al 2005].

Research testing

- **Sequence analysis** identified mutations in ten out of 21 families referred with "possible" RDP, including four *de novo* mutations. Six mutations have been identified to date (see Table 3).

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Rapid-Onset Dystonia Parkinsonism

Gene Symbol	Proportion of RDP Attributed to Mutations in This Gene	Test Method	Mutation Detection Frequency by Test Method	Test Availability
ATP1A3	Unknown [1]	Sequence analysis	Unknown	Research only [2]

1. No other genes or loci are known to be associated with RDP; however, not all individuals with a phenotype consistent with RDP have mutations in *ATP1A3*. Therefore, it is possible that mutations in another gene or genes cause RDP.
2. No laboratories offering clinical molecular genetic testing for this disorder are listed in the GeneTests Laboratory Directory. However, clinical confirmation of mutations identified in research laboratories may be available for families in which a disease-causing mutation has been identified in a research laboratory. For laboratories offering such testing, see Testing.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

Establishing the diagnosis in a proband. Diagnosis of RDP is based on clinical findings in individuals with mutations in *ATP1A3*.

Carrier testing for at-risk relatives requires prior identification of the disease-causing mutations in the family.

Note: No laboratories offering clinical molecular genetic testing for this disorder are listed in the GeneTests Laboratory Directory. However, clinical confirmation of mutations identified in research laboratories may be available for families in which a disease-causing mutation has been identified in a research laboratory. For laboratories offering such testing, see Testing.

Genetically Related (Allelic) Disorders

RDP is the only phenotype known to be associated with mutations in *ATP1A3*.

Clinical Description

Natural History

The study of the clinical manifestations of rapid-onset dystonia-parkinsonism (RDP) has focused on the dystonia/parkinsonism [Dobyns et al 1993; Brashear et al 1996; Brashear et al 1997; Brashear, Butler, Ozelius et al 1998; Kramer et al 1999; Pittock et al 2000; Linazasoro et al 2002; de Carvalho Aguiar et al 2004; Zaremba et al 2004; Kamphuis et al 2006; Brashear et al 2007; McKeon et al 2007].

The clinical presentation of RDP includes the following:

- Rapid onset of dystonia with parkinsonism (primarily bradykinesia and postural instability) over hours to days to weeks

- Appearance of symptoms after triggering events such as running, childbirth, emotional stress, or alcoholic binges
- Stability of the phenotype with little improvement after its initial appearance
- Low concentration of dopamine metabolites in cerebrospinal fluid
- Absence of other features, such as pill-rolling tremor, diurnal fluctuation, and responsiveness to standard medications for parkinsonism

To date, all affected individuals have sought medical attention after developing motor symptoms. Of those with motor symptoms and *ATP1A3* mutations, most presented with a rostra-caudal gradient, rapid onset in less than 30 days, and no response to dopaminergic medications. Many had an identifiable trigger, such as fever, physiologic stress, or alcohol consumption. One individual had antecedent parkinsonism, and at least two had fluctuating symptoms before the deficit became permanent.

Motor findings. The clinical stages of RDP include: antecedent symptoms, primary onset, and occasional second episodes of worsening.

Antecedent symptoms have included nonspecific symptoms of dystonia, usually in the hands and arms. Some individuals reported mild limb cramping, most often involving the hands, prior to development of typical RDP following a physiologic stressor. One individual presented with one year of parkinsonism, not dystonia, followed by abrupt onset of oromandibular dystonia with dysarthria.

The primary onset in individuals with an identified *ATP1A3* mutation is usually paroxysmal or abrupt over hours to several weeks. All affected individuals in two large US families stopped progressing at or before one month after onset. Many reported specific triggers consisting of either physical or psychological stress. Alcohol was a trigger in many but not all.

The bulbar and arm symptoms rarely improve after the primary onset, although four individuals reported mild improvement in leg symptoms.

A few individuals report episodes of abrupt worsening of symptoms one to nine years after the initial onset. Because only a few affected individuals have been serially examined, documentation of the second events is incomplete. The second events resemble the primary onset, with worsening of bulbar, arm, and leg symptoms over a similar time course. Except for these second events, little change is reported over many years in those affected individuals on whom such information is available.

Non-motor features, including anxiety, depression, and seizures, have been reported. It is not clear whether these features are part of the phenotype.

Other. Although RDP is the first human disease to be associated with mutations in *ATP1A3*, three neurologic diseases have been associated with mutations in the *ATP1A2* subunit: infantile seizures, familial hemiplegic migraine (FHM), and, more recently, familial common migraine [De Fusco et al 2003, Vanmolkot et al 2003, Bassi et al 2004, Kaunisto et al 2004, Swoboda et al 2004, Ambrosini et al 2005, Todt et al 2005]. This suggests that the phenotypic spectrum associated with mutations in *ATP1A3* may be broader.

Pathophysiology. The non-motor features may have a biochemical basis considering findings of abnormal dopamine, serotonin, and norepinephrine metabolites in cerebrospinal fluid of affected individuals and individuals with an *ATP1A3* mutation who are asymptomatic [Brashear, Butler, Hyland et al 1998]. The presence of psychological symptoms and seizures

fits with the localization of α3 in neurons and suggests that RDP many have a phenotype beyond motor manifestations.

Genotype-Phenotype Correlations

Genotype-phenotype correlations were reported by Brashear et al (2007) based on *ATP1A3* sequence analysis in 49 persons from 21 families referred with "possible" RDP (Table 2, Table 3). Mutations were identified in 36 persons from ten families, including four *de novo* mutations. No mutations were found in 13 persons from 11 families.

Comparison of onset, gradient (i.e., rostra-caudal or vice versa), and presence of bulbar symptoms, tremor, and pain in mutation-positive and mutation-negative individuals demonstrated that:

- All 36 individuals with rapid-onset ($p=0.002$), rostra-caudal gradient ($p<0.001$), and bulbar symptoms ($p<0.001$) were mutation-positive.

  Note: These three findings were also found in 1/13 mutation-negative persons. Unlike mutation-positive persons, this individual responded to anticholinergic therapy, making it likely that this person's findings represent a phenocopy.
- None of the mutation-positive individuals reported tremor ($p=0.003$) or complained of severe pain (0/36, $p=0.051$).
- Four of 13 mutation-negative individuals reported tremor at onset and 2/11 reported pain (data not available on two). Pain and tremor in mutation-negative persons are important distinguishing features.

  Note: It is not clear if this is an absolute distinction because tremor was reported later in life in a few affected individuals in two families.

Table 2. Genotype-Phenotype Correlation

Citation	#	Mutation	Average Age at Onset (Range)	Reported Triggers	Bulbar Symptoms	F>A>L Gradient [1]	Time for Stable
Kamphuis et al 2006	1	p.Ile274Thr	37	None	+	+	24 hours
de Carvalho Aguiar et al 2004	1*	p.Glu277Lys	20	Fever, head trauma	+	+	1 week
Linazasoro et al 2002	1*	p.Thr613Met	17	None	+	+	30 days
Zaremba et al 2004	4	p.Thr613Met	20 (16-28)	Head trauma	+	+	Hours
de Carvalho Aguiar et al 2004	13	p.Ile758Ser	23 (14-43)	Running, childbirth, fever	+	+	1 day - 1 year
de Carvalho Aguiar et al 2004	2	p.Phe780Leu	25 (16-35)	Running in one subject	+	+	2 days-30 days
de Carvalho Aguiar et al 2004	4	p.Asp801Tyr	17 (12-22)	Overheated	+	+	30 mins - 3 days
Pittock et al 2000	8	p.Thr613Met	22 (4-55)	Psych, minor fall	+	+	Days
Brashear et al 2007	1*	p.Thr613Met	22	Psych	+	+	4 days
Brashear et al 2007	1	p.Glu277Lys	22	None	+	+	**Gradually progressive

Adapted from Brashear et al 2007
= number of affected individuals
+ = present
– = absent
* = *de novo* mutation
** = abrupt onset
Psych = psychological stress
1. Rostro-caudal gradient of face>arm>leg

Penetrance

Penetrance is reduced. The small number of families studied to date limits the estimate of penetrance; however, several members of the larger reported families have had an *ATP1A3* mutation but were asymptomatic [Kramer et al 1999, de Carvalho Aguiar et al 2004, Zaremba et al 2004].

Anticipation

Anticipation has not been specifically observed in RDP. However, preliminary findings in one family warrant further study [Pittock et al 2000, McKeon et al 2007].

Nomenclature

Rapid-onset dystonia-parkinsonism was first recognized and named by Dobyns et al (1993) in a 15-year-old girl with an abrupt onset of dystonia with severe bulbar symptoms.

Prevalence

The prevalence of RDP is not known.

RDP has been described in individuals and families from the US, Europe, and Korea [Webb et al 1999, de Carvalho Aguiar et al 2004, Zaremba et al 2004, Brashear et al 2007, Lee et al 2007].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

In comparing symptomatic persons with and without an *ATP1A3* mutation, the presence of tremor at onset of symptoms, a reversed rostra-caudal gradient, and significant limb pain exclude a diagnosis of rapid-onset dystonia-parkinsonism (RDP) [Brashear et al 2007].

The physician must exclude more common and treatable forms of dystonia-parkinsonism (see Dystonia Overview and Parkinson Disease Overview). The testing should include brain MRI, a trial of L-dopa, *TOR1A(DYT1*) gene testing, and evaluation for Wilson disease. In all cases of RDP, the MRI should be normal and the response to L-dopa should be minimal or none.

The differential diagnosis of RDP includes the following:

- **Dopa-responsive dystonia (DRD).** RDP differs from DRD as the response to L-dopa in RDP is minimal in contrast to DRD [Bressman et al 2002, Kabakci et al 2005, Geyer & Bressman 2006]. DRD also typically presents in the leg; and, in some cases, has been reported to be confused with cerebral palsy [Nygaard et al 1994].
- **DYT1 dystonia**. DYT1 dystonia has a more caudal to rostral gradient than RDP. Onset of DYT1 dystonia in older individuals is rare, whereas RDP may present abruptly after age 30 years.

- **Young-onset parkinsonism.** Individuals with young-onset parkinsonism may have limb dystonia as an early manifestation but, unlike RDP, should have a significant and sustained response to L-dopa. Other recently described genetic forms of Parkinson disease should be considered.
- A kindred with eight individuals with RDP with no mutations identified in *ATP1A3* and not linked to chromosome 19q in the DYT12 region is an apparent phenocopy [Kabakci et al 2005]. The proband presented at age six years with overnight onset of dysphonia, dysphagia, orofacial dystonia, and dystonia of all four limbs, findings which meet the diagnostic criteria for RDP. However, five of the affected individuals in this family had concurrent renal disease consisting of hypoplasia, cysts, or end-stage renal disease (ESRD), which has not been observed in individuals with RDP with *ATP1A3* mutations. This suggests that there is a second locus for RDP.

As in all persons with young-onset movement disorders, Wilson disease must be considered.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with rapid-onset dystonia-parkinsonism (RDP), evaluation using the RDP severity scale [de Carvalho Aguiar et al 2004] is recommended.

Treatment of Manifestations

Symptomatic benefit has been noted with high-dose benzodiazepines.

Standard therapies for the following are appropriate:

- Seizures
- Dysphagia
- Depression and anxiety

Prevention of Secondary Complications

Physical therapy to prevent contractures in the hands and feet is appropriate.

Agents/Circumstances to Avoid

Triggers associated with the abrupt onset of RDP that should be avoided include (but are not limited to) the following:

- Alcohol
- Fever
- Psychological stress
- Excessive exercise (such as running track)

Testing of Relatives at Risk

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

Therapies Under Investigation

Search ClinicalTrials.gov 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.

Other

Levodopa and dopamine agonists provide little benefit.

The abrupt onset of symptoms cannot be prevented. During the abrupt onset, no acute treatment is available other than symptomatic relief of dystonia.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Rapid-onset dystonia-parkinsonism (RDP) is inherited in an autosomal dominant manner.

Risk to Family Members

This section is written from the perspective that molecular genetic testing for this disorder is available on a research basis only and results should not be used for clinical purposes. This perspective may not apply to families using custom mutation analysis. —ED.

Parents of a proband

- Many individuals diagnosed with rapid-onset dystonia-parkinsonism (RDP) have an affected parent.
- A proband with RDP may have the disorder as the result of a new gene mutation. Of ten families in which mutations were identified, four probands had *de novo* mutations [Brashear et al 2007].
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include obtaining a detailed medical and family history, and examination by a movement disorder specialist.
- Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of failure by health care professionals to recognize the syndrome, a milder phenotypic presentation, or complete lack of symptoms (reduced penetrance). Therefore, an apparently negative family history cannot be confirmed until appropriate evaluations have been performed.

Note: If the parent is the individual in whom the mutation first occurred, s/he may have somatic mosaicism for the mutation and may be mildly/minimally affected.

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, the risk to the sibs is 50%.
- The sibs of a proband with clinically unaffected parents are still at increased risk for the disorder because of the possibility of reduced penetrance in a parent. When the parents are clinically unaffected because of reduced penetrance, the parents should undergo molecular testing to determine if they have the mutation.

Offspring of a proband. Each child of an individual with RDP has a 50% chance of inheriting the mutation.

Other family members of a proband. The risk to other family members depends on the status of the proband's parents. If a parent is found to be affected, his or her family members may be at risk. If the parent is unaffected, they could still carry the mutation but not express the disorder.

Related Genetic Counseling Issues

Issues unique to RDP. As a result of the sudden onset of symptoms, at-risk individuals may become hypervigilant about symptoms. Serious psychological issues have been reported in families [Brashear, personal observation].

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has a disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. Possible non-medical explanations including alternate paternity or maternity (i.e., with assisted reproduction) or undisclosed adoption could also be explored.

Family planning. The optimal time for determination of genetic risk 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.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant when molecular genetic testing is available on a research basis only. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. The disease-causing allele in the family must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Requests for prenatal testing for conditions such as RDP are not common. Differences in perspective may exist among medical professionals and within families regarding the use of

prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers consider decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Rapid-Onset Dystonia Parkinsonism

Gene Symbol	Chromosomal Locus	Protein Name
ATP1A3	19q12-q13.2	Sodium/potassium-transporting ATPase subunit alpha-3

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Rapid-Onset Dystonia Parkinsonism

128235	DYSTONIA 12; DYT12
182350	ATPase, Na+/K+ TRANSPORTING, ALPHA-3 POLYPEPTIDE; ATP1A3

Table C. Genomic Databases for Rapid-Onset Dystonia Parkinsonism

Gene Symbol	Entrez Gene	HGMD
ATP1A3	478 (MIM No. 182350)	ATP1A3

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

The Na,K-ATPases convert metabolic energy by moving Na^+ ions out of the cell and K^+ ions into the cell, restoring the ion gradients reduced by the activity of ion channels and Na^+-dependent carriers. In the central nervous system (CNS), the Na,K-ATPase is harnessed for reuptake of glutamate and other transmitters; extracellular K^+ buffering; extrusion of Ca^{2+} by Na^+:Ca^{2+} exchange; and the regulation of cell volume. Because it transports three Na^+ ions out of the cell for every two K^+ ions transported in, it is electrogenic and makes a small direct contribution to membrane potential.

Na,K-ATPase has three types of subunits (alpha, beta, and gamma) and each subunit has multiple isoforms. The catalytic alpha subunit has three isoforms (alpha 1, 2, and 3) that are expressed in the CNS by three distinct genes [Moseley et al 2003]. The alpha 3 isoform is expressed exclusively in neurons in the CNS, although it is found in a few peripheral cell types as well. There are also three beta subunits expressed in the CNS that are required for Na,K-ATPase function. The gamma subunit regulates and modifies the properties of the complex; at least three gamma subunits are expressed in the CNS [McGrail et al 1991].

Interestingly, mutations in a gene for another α subunit of the Na,K-ATPase, *ATP1A2*, are associated with familial hemiplegic migraine [De Fusco et al 2003] and benign familial infantile convulsions [Vanmolkot et al 2003], as well as episodic events with severe mental retardation [Vanmolkot et al 2006].

Knockout mice exist for all three alpha subunits. Alpha 1 knockouts die early in embryogenesis. Alpha 2 and alpha 3 homozygous knockout mice are born at full term but do not survive for more than a few hours. Heterozygote mice survive and demonstrate slowed gait, learning impairments, and symptoms after stress [Moseley et al 2007].

Animal models include the following:

- *Drosophila*: mutations in Na^+ pumps cause neuronal dysfunction and degeneration [Palladino et al 2003].
- Mouse:
  - *Atp1a2*$^{-/-}$ mice have akinesia and poor generation of respiratory rhythm in newborns [Moseley et al 2003].
  - *Atp1a2*$^{+/-}$ mice (heterozygotes) have degeneration in the amygdala and enhanced anxiety behavior [Ikeda et al 2003].
  - *Atp1a3*$^{+/-}$ mice (heterozygotes) have spatial learning difficulties [Moseley et al 2007].

Normal allelic variants: The normal *ATP1A3* gene comprises 23 exons. Several common coding SNPs are reported in dbSNP, as well as one common synonymous SNP c.2487G>A at amino acid 829 (rs45606534), the frequency of which is unknown.

In the course of sequencing, three variants were identified in multiple people [Author, personal observation]; two variants do not change an amino acid and occur in individuals with other known *ATP1A3* mutations.

Pathologic allelic variants: The six mutations described to date (Table 3) are located in only three of the 23 exons (exons 8, 14, and 17); all are missense changes [de Carvalho Aguiar et al 2004,Brashear et al 2007,Lee et al 2007,McKeon et al 2007]. The p.Glu277Lys mutation in exon 8 and the p.Thr613Met mutation in exon 14 are recurrent. Both occurrences of p.Glu277Lys were *de novo*. The p.Thr613Met mutation occurred as both *de novo* mutations and inherited mutations [de Carvalho Aguiar et al 2004,Brashear et al 2007,Lee et al 2007,McKeon et al 2007].

Table 3. *ATP1A3* Pathologic Allelic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequence
c.821T>C	p.Ile247Thr	NM_152296.3 NP_689509.1
c.829G>A	p.Glu277Lys	
c.1838C>T	p.Thr613Met	
c.2273T>G	p.Ile758Ser	
c.2338T>C	p.Phe780Leu	
c.2401G>T	p.Asp801Tyr	

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

Normal gene product: *ATP1A3* encodes the alpha 3 subunit of the sodium/potassium-transporting ATPase (Na,K-ATPase), which comprises 1013 amino acid residues.

Abnormal gene product: Both functional studies and structural analysis of the alpha 3 subunit of the Na,K-ATPase suggest that missense mutations impair enzyme activity or stability [de

Carvalho Aguiar et al 2004]. However, it is not known whether this loss of function occurs by haploinsufficiency or dominant negative effects.

Biochemical study of two different mutations in mice revealed that both are partially active (~25%) and both are functionally altered with reduced affinity for Na^+ on the cytoplasmic side of the membrane [Rodacker et al 2006]. The authors theorized that reduced Na^+ affinity coupled with low pump activity may be a major factor in the development and pathology of familial RDP.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Dystonia Medical Research Foundation
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Rapid-Onset Dystonia Parkinsonism

RDP (Rapid-onset Dystonia Parkinsonism) Study Web Site
www.rdpstudy.org

American Parkinson Disease Association Inc.
135 Parkinson Ave
Staten Island NY 10305
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Fax: 718-981-4399
Email: apda@apdaparkinson.org
www.apdaparkinson.org

National Parkinson Foundation
1501 N.W. 9th Avenue
Bob Hope Road
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Phone: 800-327-4545; 305--243-6666
Fax: 305-243-5595
Email: contact@parkinson.org
www.parkinson.org

WE MOVE (Worldwide Education and Awareness for Movement Disorders)
204 West 84th Street
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www.wemove.org

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Suggested Readings

Tarsy D, Simon DK. Dystonia. N Engl J Med. 2006;355:818–29. [PubMed: 16928997]

Chapter Notes

Author Notes

Web site: rdpstudy.org

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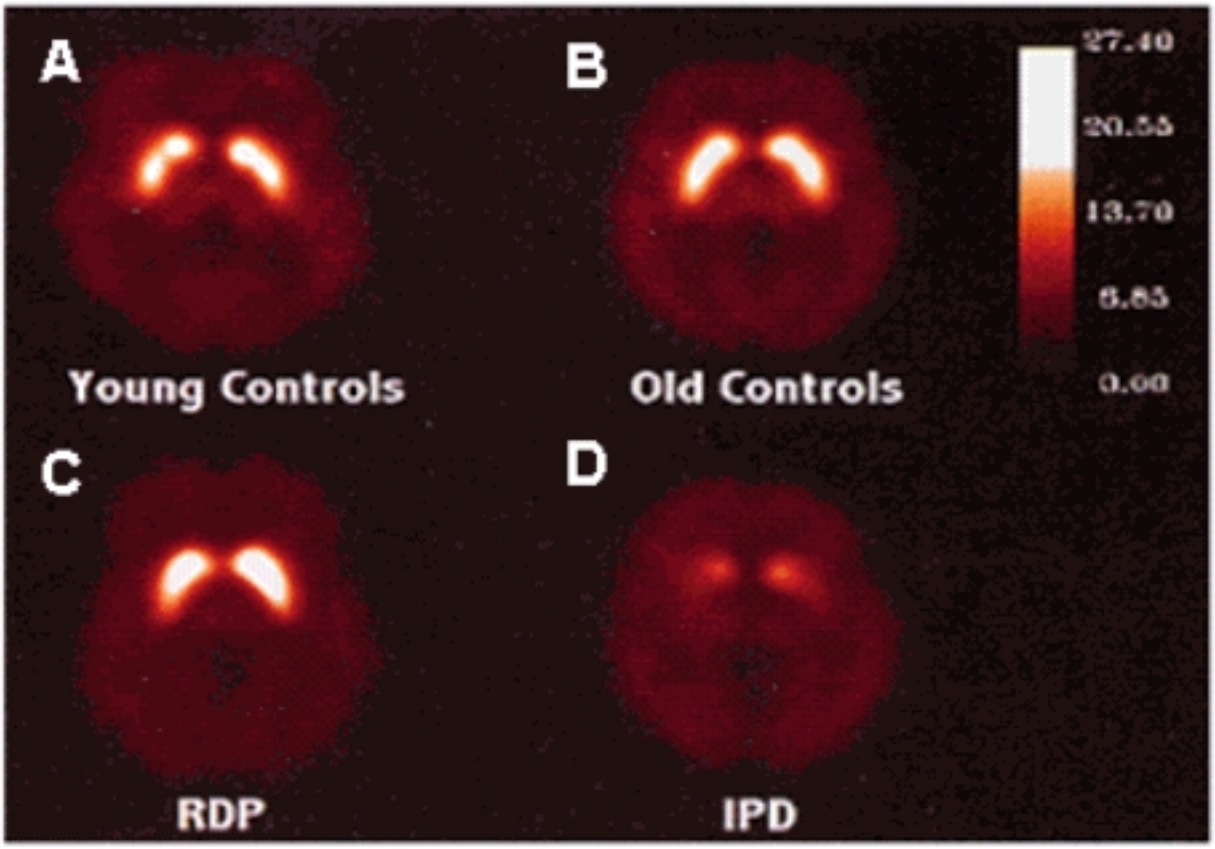

Figure 1. Position emission tomography (PET) images showing the distribution of the dopamine transporter imaging agent [^{11}C]β-CFT in **(A)** young controls, **(B)** old controls, **(C)** RDP, and **(D)** idiopathic Parkinson disease (IDP). Each transverse section image is a quantitative map of the [^{11}C]β-CFT volume of distribution calculated on a pixel-by-pixel basis by using a rapid linear least-squares search algorithm. The color bar on the right of the figure shows the quantitative scale used to display each of these images (from top to bottom: 27.40, 20.35, 13.70, 5.85, 0.00).
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