GENEReviews

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Episodic Ataxia Type 2

[*Includes: CACNA1A-Related Episodic Ataxia Type 2, CACNB4-Related Episodic Ataxia Type 2*]

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Summary

Disease characteristics. Episodic ataxia type 2 (EA2) is characterized by paroxysmal attacks of ataxia, vertigo, and nausea typically lasting minutes to days in duration. Attacks can be associated with dysarthria, diplopia, tinnitus, dystonia, hemiplegia, and headache. About 50% of individuals with EA2 have migraine headaches. Onset is typically in childhood or early adolescence (age range 2-32 years). Frequency of attacks can range from once or twice a year to three or four times a week. Attacks can be triggered by stress, exertion, caffeine, alcohol, and phenytoin and can be stopped or decreased in frequency and severity by administration of acetazolamide. Between attacks, individuals may initially be asymptomatic but eventually develop interictal findings that can include nystagmus and ataxia.

Diagnosis/testing. The diagnosis of EA2 is most commonly made on clinical grounds. MRI can demonstrate atrophy of the cerebellar vermis. *CACNA1A* and *CACNB4* are the only genes known to be associated with EA2. *CACNA1A* molecular genetic testing is available on a clinical basis; *CACNB4* molecular genetic testing is available on a research basis only.

Management. *Treatment of manifestations:* Acetazolamide is effective in controlling or reducing the frequency and severity of attacks; typical starting dose is 125 mg a day given orally, but doses as high as 500 mg twice a day may be required; although generally well tolerated, the most common side effects are paresthesias of the extremities, rash, and renal calculi; acetazolamide does not appear to prevent the progression of interictal symptoms. *Surveillance:* annual neurologic examination. *Agents/circumstances to avoid:* Phenytoin has been reported to exacerbate symptoms.

Genetic counseling. EA2 is inherited in an autosomal dominant manner. Most individuals with a diagnosis of EA2 have an affected parent. The proportion of cases caused by *de novo* gene mutations is unknown. Offspring of affected individuals have a 50% chance of inheriting the disease-causing gene mutation. Prenatal testing is available for pregnancies at increased risk for *CACNA1A*-related episodic ataxia type 2 if the mutation has been identified in the family. Prenatal testing may be available for pregnancies at increased risk for *CACNB4*-related episodic ataxia type 2 through laboratories offering custom prenatal testing if the disease-causing mutation has been identified in the family.

Diagnosis

Clinical Diagnosis

The diagnosis of episodic ataxia type 2 (EA2) is most commonly made on clinical grounds based on the following:

- Attacks of gait ataxia and nystagmus lasting hours in duration, possibly associated with vertigo, nausea, and vomiting
- Presence of interictal ataxia and nystagmus
- Attacks that can be provoked by exercise, emotional stress, alcohol, and caffeine
- Attacks of ataxia that can be reduced in frequency or prevented by acetazolamide
- Absence of myokymia (fine twitching or rippling of muscles) clinically and electrographically (EMG)
- Family history consistent with autosomal dominant inheritance

Neuroimaging MRI can demonstrate atrophy of the cerebellar vermis [Vighetto et al 1988].

Nuclear magnetic spectroscopy has demonstrated abnormal cerebellar intracellular pH levels in individuals with EA2 not treated with acetazolamide [Bain et al 1992] and low cerebellar creatine [Harno et al 2005].

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.

Genes. *CACNA1A* and *CACNB4* are the only two genes known to be associated with EA2 [Ophoff et al 1996, Escayg et al 2000].

Clinical uses

- Confirmatory diagnostic testing
- Presymptomatic testing
- Prenatal testing

Clinical testing

Sequence analysis. Sequence analysis has identified a number of *CACNA1A* mutations [Yue et al 1998, Friend et al 1999, Denier et al 2001]. In the study of Jen et al (2004), nine of 11 families (82%) with episodic ataxia showed linkage to 19p; mutations in *CACNA1A* were identified in all nine families. In the same study, four of nine simplex cases (i.e., individuals with no family history of EA2) had identifiable *CACNA1A* mutations.

Research

Direct DNA. A mutation in *CACNB4* has been identified in one family with EA2 [Escayg et al 2000].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in EA2

Test Method	Mutations Detected	Proportion of EA2 Caused by Mutations in this Gene	Mutation Detection Frequency [1]	Test Availability
Sequence analysis	*CACNA1A* sequence variants	82%	>95% [2]	Clinical Testing
Direct DNA [3]	*CACNB4* sequence variants	Rare [4]	Unknown	Research only

1. Proportion of affected individuals with a mutation(s) as classified by gene and test method
2. In families linked to chromosome 19
3. Direct DNA methods may include mutation analysis, mutation scanning, sequence analysis, or other means of molecular genetic testing to detect a genetic alteration associated with EA2.
4. A mutation was identified in one of 71 families with episodic ataxia.

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

Genetically Related (Allelic) Disorders

Mutations in the *CACNA1A* gene can cause other disorders, including:

- **Familial hemiplegic migraine (FHM).** Approximately 50% of families with FHM, including all those with permanent cerebellar symptoms, have missense mutations in the *CACNA1A* gene (FHM1) [Ophoff et al 1996, Ducros et al 1999]. Two other FHM-causing genes have been identified; FHM2 is caused by mutations in *ATP1A2* [De Fusco et al 2003] and FHM3 by mutations in *SCN1A* [Dichgans et al 2005].

  FHM is characterized by an aura of hemiplegia that is always associated with at least one other aura symptom such as hemianopsia, hemisensory deficit, or aphasia. The aura is followed by a moderate to severe headache. Two clinical forms exist: pure FHM (80% of families), in which interictal examination is normal in all family members, and FHM with permanent cerebellar symptoms (20% of families), in which some family members show interictal nystagmus and/or ataxia [Ducros et al 2001]. Some individuals with FHM, primarily children and adolescents who sustain minor head trauma, develop uncontrollable cerebral edema [McCrory & Berkovic 1998]. Three individuals with delayed cerebral edema were shown to have the p.Ser218Leu missense mutation in *CACNA1A* [Kors et al 2001]. Inheritance is autosomal dominant.

- **Spinocerebellar ataxia type 6 (SCA6).** SCA6 is characterized by adult-onset, slowly progressive cerebellar ataxia, dysarthria, and nystagmus. SCA6 is associated with a CAG expansion in exon 47 of the *CACNA1A* gene [Zhuchenko et al 1997]. The normal number of CAG repeats ranges up to 18. Individuals with SCA6 have 20 to 33 CAG repeats [Matsuyama et al 1997]. Inheritance is autosomal dominant.

Their well-described phenotypes notwithstanding, clinical overlap exists among EA2, FHM, and SCA6, even within the same family.

- In a family with EA2, affected members had hemiplegia, and one affected member had migraine during episodes of ataxia [Jen et al 1999].
- In a study of 11 individuals with EA2 and documented *CACNA1A* mutations, four met IHS criteria for migraine, but none experienced hemiplegic migraine [Mantuano et al 2004].
- Members of a Portuguese family with a missense mutation (A>G substitution) in *CACNA1A* had either hemiplegic migraine with or without cerebellar signs or permanent ataxia without migraines [Alonso et al 2003].

- Individuals with SCA6 can present with episodic ataxia, mostly during the first years of the disorder. In one study, up to 33% of individuals with 21 or more CAG repeats in the *CACNA1A* gene had episodic features prominent enough to warrant the diagnosis of EA2 [Geschwind et al 1997]. In another family with a CAG repeat expansion, some members had episodic ataxia and others had progressive ataxia; in all affected members, the abnormal allele had 23 CAG repeats [Jodice et al 1997].

Clinical Description

Natural History

Episodic ataxia type 2 (EA2) demonstrates variable expressivity both between and within families [Denier et al 1999]. Episodic ataxia typically starts in childhood or early adolescence (age range 2-32 years) [Baloh et al 1997]. Onset as late as age 61 years has been reported [Imbrici et al 2005].

EA2 is characterized by paroxysmal attacks of ataxia, vertigo, and nausea typically lasting hours to days. Attacks can be associated with dysarthria, diplopia, tinnitus, dystonia, hemiplegia, and headache. One study reported vertigo and weakness accompanying the ataxia in more than half of individuals with genetically confirmed EA2 [Jen et al 2004]. Another report suggested that about 50% of individuals with EA2 have migraine headaches without loss of consciousness [Baloh et al 1997].

Frequency of attacks can range from one to two times per year to three to four times per week [von Brederlow et al 1995]. Attacks can be triggered by stress, exertion, caffeine, alcohol, and phenytoin. In one kindred, attacks could be provoked by fever or high environmental temperatures [Subramony et al 2003]. EA2 attacks can be stopped or decreased in frequency and severity by administration of acetazolamide [Griggs et al 1978]; attacks can recur within 48 to 72 hours of stopping the medication [von Brederlow et al 1995]. In some cases, attacks remit within one year after onset but in others, they can recur over a 50-year interval [Baloh et al 1997].

While individuals with EA2 may initially be asymptomatic between attacks, most eventually develop interictal permanent cerebellar symptoms. Ninety percent have nystagmus and about 80% have ataxia. Interictal dystonia has also been reported in two individuals with genetically confirmed EA2 [Spacey et al 2005].

Genotype-Phenotype Correlations

Specific *CACNA1A* mutations do not strictly predict the EA2 phenotype.

Allelic modifying factors such as number of CAG repeats in exon 47 of the *CACNA1A* gene do not appear to influence the severity of attacks or the persistence of neurologic symptoms between attacks [Denier et al 1999].

Three mutations (p.Arg1281X, p.Phe1406Cys, p.Arg1549X) have been associated with fluctuating weakness manifesting as a myasthenic syndrome in individuals with EA2 [Jen et al 2001].

Penetrance

Penetrance is estimated at 80%-90% [Jen et al 1999, Spacey et al 2005].

Anticipation

Anticipation is not observed.

Nomenclature

EA2 has also been known as periodic vestibulocerebellar ataxia and acetazolamide-responsive episodic ataxia.

Prevalence

EA2 is rare. The Consortium for Clinical Investigation of Neurological Channelopathies (CLINCH) has estimated the prevalence at lower than 1:100,000 population based on the cases seen by experts in regional centers.

Differential Diagnosis

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

Episodic ataxia can occur sporadically or in a number of hereditary disorders.

Sporadic Causes

Sporadic causes of episodic ataxia include multiple sclerosis, Arnold Chiari malformation, vertebral basilar insufficiency, basilar migraine, and labyrinthine abnormalities.

Hereditary Causes

Mitochondrial. Disorders of mitochondrial oxidative metabolism result in a number of neurologic conditions that are associated with episodic ataxia. The most common of these are pyruvate carboxylase deficiency [OMIM 266150] and pyruvate dehydrogenase deficiency [OMIM 208800]. Measurement of serum pyruvate and lactate concentrations following a 1.75 g/kg oral glucose load facilitates diagnosis. Definitive diagnosis requires studies of enzymatic activity in muscle, leukocytes, or fibroblasts. Molecular genetic studies may allow precise characterization of the molecular defects. (See Mitochondrial Diseases Overview.)

X-linked. Ornithine transcarbamylase (OTC) deficiency [OMIM 311250] is an inborn error of metabolism of the urea cycle that causes hyperammonemia (see Urea Cycle Disorders Overview). Diagnosis can be facilitated by measurement of serum ammonia concentration. Mutations in the structural gene for ornithine transcarbamylase may lead to partial deficiency in heterozygous females and to complete deficiency in hemizygous males. Severely affected males die in the neonatal period and females have varying clinical manifestations ranging from no symptoms to severe deficits. Symptoms can include episodic extreme irritability (100%), episodic vomiting and lethargy (100%), protein avoidance (92%), ataxia (77%), stage II coma (46%), delayed growth (38%), developmental delay (38%), and seizures (23%). OTC deficiency is treatable with supplemental dietary arginine and a low-protein diet.

Autosomal recessive

- **Hyperammonemias caused by deficiencies of urea cycle enzymes** include carbamoylphosphate synthetase deficiency [OMIM 237300], argininosuccinate synthetase deficiency (citrullinemia type 1) [OMIM 215700], arginosuccinase deficiency, and arginase deficiency [OMIM 207800]. See Urea Cycle Disorders Overview.

  Diagnosis is established by the identification of raised blood ammonia concentration. Immediate treatment is by hemodialysis and by IV sodium benzoate; long-term treatment is by a high-calorie, low-protein diet supplemented with essential amino acids.

The severe forms of the hyperammonemias present in the first few days of life with lethargy and possible focal and generalized seizures, ultimately leading to coma. The less severe forms develop in early childhood and are characterized by intermittent ataxia, dysarthria, vomiting, headache, ptosis, involuntary movements, seizures, and confusion. These episodes are precipitated by high protein loads and intercurrent illness. Children with arginosuccinase deficiency often have distinctive facial features and brittle hair.

- **Aminoacidurias,** including Hartnup disease, intermittent branched-chain ketoaciduria, and isovaleric acidemia, can be diagnosed by identification of increased excretion of amino acids in the urine and feces.
  - **Hartnup disease** [OMIM 234500] results from defective renal and intestinal transport of monoaminomonocarboxylic acids giving rise to intermittent ataxia, tremor, chorea, and psychiatric disturbances; mental retardation; and pellagra-like rash. Episodes are triggered by exposure to sunlight, emotional stress, and sulfonamide drugs. Attacks last about two weeks, followed by relative normalcy. The frequency of attacks diminishes with maturation. Treatment is oral administration of nicotinamide.
  - **Intermittent branched-chain ketoaciduria** [OMIM 248600] is characterized by intermittent transient ataxia, mental and physical retardation, feeding problems, and elevation of branched-chain amino acids and keto acids in the urine as well as a distinctive odor of maple syrup to the urine. This condition is treated by the elimination of branch chain amino acids (leucine, isoleucine, valine) from the diet. A variant of this condition may be effectively treated with thiamine. See Maple Syrup Urine Disease.
  - **Isovaleric acidemia** [OMIM 243500] occurs in two forms. The acute neonatal form is associated with urine that has a sweaty foot odor and massive metabolic acidosis in the first days of life followed by rapid death. The chronic form is associated with periodic attacks of severe ketoacidosis between asymptomatic periods. Treatment consists of protein restriction and supplementation with glycine and carnitine. See Organic Acidemias Overview.

Autosomal dominant

- **Episodic ataxia type 1 (EA1)** [OMIM 160120] is the result of mutations in the potassium channel gene *KCNA1* [Browne et al 1994], which has been mapped to chromosome 12p13 [Litt et al 1994]. EA1, also called ataxia with myokymia, is characterized by brief attacks (<15 minutes) of ataxia and dysarthria that can occur up to 15 times per day. Attacks can occur spontaneously or be triggered by anxiety, exercise, startle, and/or intercurrent illness. Onset is typically in late childhood and early adolescence; symptoms usually remit in the second decade. Between attacks, widespread myokymia of the face, hands, arms, and legs occurs [VanDyke et al 1975, Hanson et al 1977, Gancher & Nutt 1986]. Electromyographic studies reveal myokymia (neuromyotonia). Phenytoin can control symptoms; acetazolamide is also effective [Lubbers et al 1995].
- **Episodic ataxia type 3 (EA3)** [OMIM 606552] has been described in two Caucasian families from rural North Carolina [Farmer & Mustian 1963, Vance et al 1984]. A relationship between the two kindreds is suspected but has not been established. EA3 is characterized by attacks of vertigo, diplopia, and ataxia beginning in early adulthood. In some individuals, slowly progressive cerebellar ataxia occurs. This

condition does not link to loci identified with EA1, EA2, or spinocerebellar ataxia types 1, 2, 3, 4, and 5 [Damji et al 1996].

- **Episodic ataxia type 4 (EA4)** [OMIM 606554] has been described in a large Canadian Mennonite family [Steckley et al 2001]. EA4 is characterized by brief acetazolamide-responsive attacks of vestibular ataxia, vertigo, tinnitus, and interictal myokymia. Interictal nystagmus and ataxia were not identified. The age of onset is variable. EA4 does not link to the EA1 or EA2 loci.
- **Spinocerebellar ataxia type 6 (SCA6)** (See also Genetically Related Disorders.)

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with episodic ataxia type 2 (EA2), the following evaluations are recommended:

- Neurologic examination for signs of interictal ataxia and nystagmus
- Neuroimaging of the head, preferably MRI, to evaluate for structural lesions and to look for evidence of atrophy
- EMG to look for myokymia (associated with EA1)
- If family history is not clearly consistent with EA2, a metabolic work-up that includes serum ammonia concentration and assessment of urine amino acids

Treatment of Manifestations

Acetazolamide is effective in controlling or reducing the frequency and severity of attacks [Griggs et al 1978]. A trial of acetazolamide is worthwhile in any individual who has episodic ataxia and reports a family history of similar episodes. The typical starting dose is 125 mg a day given orally, but doses as high as 500 mg twice a day may be required. This medication is generally well tolerated; the most common side effects are paresthesias of the extremities, rash, and renal calculi. Treatment with acetazolamide does not appear to prevent the progression of interictal symptoms [Baloh & Winder 1991]. It is not clear how acetazolamide prevents attacks of EA2, although it is speculated that it acts by altering intra/intercellular pH.

Surveillance

Surveillance should include annual neurologic examination.

Agents/Circumstances to Avoid

Phenytoin has been reported to exacerbate symptoms.

Testing of Relatives at Risk

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

Therapies Under Investigation

In a single report, 4-aminopyridine, a potassium channel blocker, successfully prevented attacks in three individuals with EA2, two of whom had proven *CACNA1A* mutations. The mechanism by which 4-aminopyridine prevents attacks is unknown [Strupp et al 2004].

Scoggan et al (2006) reported an individual who responded to a combination of acetazolamide and valproic acid.

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

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

Episodic ataxia type 2 (EA2) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals with a diagnosis of EA2 have an affected parent.
- A proband with EA2 may have the disorder as the result of a *de novo* gene mutation. The proportion of cases caused by *de novo* gene mutations is unknown as the frequency of subtle signs of the disorder in parents has not been thoroughly evaluated and molecular genetic data are insufficient.
- Recommendations for the evaluation of parents of an individual with EA2 and no known family history of EA2 include clinical assessment.

Note: The family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, late onset of the disease in an affected parent, or incomplete penetrance.

Sibs of a proband

- The risk to the sibs of a proband depends upon the genetic status of the parents.
- If a parent of a proband is affected, the risk to the sibs is 50%.
- Since EA2 demonstrates incomplete penetrance, a clinically unaffected parent may have the disease-causing mutation and the sibs of the proband may still be at 50% risk.
- No instances of germline mosaicism have been reported, although it remains a possibility.

Offspring of a proband. Offspring of affected individuals have a 50% chance of inheriting the disease-causing mutation.

Other family members of a proband. The risk to other family members depends upon the genetic status of the proband's parents. If a parent is found to be affected, his or her family members are at risk.

Related Genetic Counseling Issues

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

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.

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 in situations in which the sensitivity of currently available testing is less than 100% or when molecular genetic testing is available on a research basis only. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk for *CACNA1A*-related episodic ataxia type 2 is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. The disease-causing allele of an affected family member 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.

No laboratories offering molecular genetic testing for prenatal diagnosis of *CACNB4*-related episodic ataxia type 2 are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing mutation has been identified. For laboratories offering custom prenatal testing, see Testing.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have 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 Episodic Ataxia Type 2

Gene Symbol	Chromosomal Locus	Protein Name
CACNA1A	19p13	Voltage-dependent P/Q-type calcium channel subunit alpha-1A
CACNB4	2q22-q23	Voltage-dependent L-type calcium channel subunit beta-4

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 Episodic Ataxia Type 2

108500	EPISODIC ATAXIA, TYPE 2; EA2
601011	CALCIUM CHANNEL, VOLTAGE-DEPENDENT, P/Q TYPE, ALPHA-1A SUBUNIT; CACNA1A
601949	CALCIUM CHANNEL, VOLTAGE-DEPENDENT, BETA-4 SUBUNIT; CACNB4

Table C. Genomic Databases for Episodic Ataxia Type 2

Gene Symbol	Entrez Gene	HGMD
CACNA1A	773 (MIM No. 601011)	CACNA1A
CACNB4	785 (MIM No. 601949)	CACNB4

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

Note: HGMD requires registration.

CACNA1A

Normal allelic variants: The *CACNA1A* gene consists of 47 exons. A polymorphic CAG repeat in the 3' end of the gene occurs within a portion of the gene previously thought to be only noncoding. The identification of expansions of this CAG repeat associated with SCA6 was accompanied by the recognition of a novel long spliceform of theα_{1A} mRNA in which the reading frame includes the CAG repeat translated into glutamine residues. The CAG repeats range from $(CAG)_4$ to $(CAG)_{18}$.

Pathologic allelic variants: More than 30 different *CACNA1A* mutations associated with EA2 have been described [Ophoff et al 1996, Yue et al 1997, Yue et al 1998, Denier et al 1999, Friend et al 1999, Denier et al 2001, van den Maagdenberg et al 2002, Matsuyama et al 2003, Subramony et al 2003, Jen et al 2004, Kaunisto et al 2004, Mantuano et al 2004, Spacey et al 2004, Spacey et al 2005]. The majority are nonsense mutations resulting in a truncated protein product. However, a number of non-truncating mutations that appear to cluster in the S5-S6 linkers and their borders have been described [Mantuano et al 2004, Spacey et al 2004]. Intronic mutations causing exon skipping and abnormal splicing have been reported [Wan, Carr et al 2005; Eunson et al 2005].

Normal gene product: The *CACNA1A* gene encodes an α_{1A} subunit that serves as the pore-forming subunit of a voltage-dependent P/Q-type calcium channel [Hofman et al 1994, Greenberg 1997]. Voltage-dependent calcium channels are made up of the pore-forming alpha1 subunit and accessory subunits alpha2-delta, beta, and gamma. Theα_{1A} subunits are membrane glycoproteins of approximately 2400 amino acids in length in which primary structure predicts the presence of four homologous domains, each consisting of six transmembrane domains and a pore-forming P loop. P/Q-type calcium channels are high voltage-activated calcium channels that are found primarily on neurons and are expressed at high levels in granule cells and Purkinje cells of the cerebellar cortex. Their principal role is believed to be in synaptic transmission.

The *CACNA1A* gene consists of 47 exons and gives rise to several alternatively spliced mRNAs of approximately 7-8 kb [Zhuchenko et al 1997]. In the long spliceform, inclusion of five additional nucleotides at the end of exon 46 eliminates a stop codon and places an additional 237 nucleotides of 3' sequence, including the polymorphic CAG repeat, in translational frame. The CAG repeat encodes a tract of glutamine residues, in which wild-type alleles range from four to 18 glutamates in length. The function of the different spliceforms of the *CACNA1A* gene products remains to be demonstrated, although differences have been measured in phosphorylation acceptor sites [Sakurai et al 1996].

Abnormal gene product: *CACNA1A* mutations appear to cause a loss of function. The p.Arg1820X nonsense mutation results in a premature stop and loss of the 1A wild-type (wt) carboxyl terminal tail region.

- **p.Arg1820X.** When expressed in Xenopus oocytes, P/Q-type channels containing the p.Arg1820X mutation do not form functional Ca^{2+} channels. However, although nonfunctional, the mutated channel was found to have a dominant-negative effect on co-expressed wtα_{1A} channels [Jouvenceau et al 2001].
- **p.Phe149Ser.** Electrophysiologic studies of the missense mutation p.Phe149Ser have also demonstrated nonfunctional channels, resulting in the hypothesis that *CACNA1A* mutations associated with EA2 lead to a complete loss of channel function [Guida et al 2001].
- **p.Gly293Arg.** In contrast, another study demonstrated that the mutation p.Gly293Arg was able to form functional channels when expressed in *X. laevis* oocytes, resulting in decreased inward mediated Ca^{2+}. However, there was failure of expression of this same mutant channel in mammalian systems (HEK 293 cells) [Wappl et al 2002].
- **p.His1736Leu.** The p.His1736Leu mutation, successfully expressed in a mammalian system, was found to cause a decrease in current density, an increased rate of inactivation, and a shift in the voltage dependence of activation to more positive values that would likely result in a decrease in inward-mediated current. However, the p.His1736Leu mutation also decreased inactivation-dependent current decay and increased the rate of recovery from inactivation. The apparent oppositional effects caused by this mutation have previously been observed with other *CACNA1A* mutations [Tottene et al 2002] and the impact of the p.His1736Leu mutation in vivo is likely the net effect of these changes. Because of the dramatic decrease in current density (>2.5-fold) for the p.His1736Leu mutant channel, it was concluded that the net effect of this mutation was a loss of function [Spacey et al 2004].

Mutations p.Cys287Tyr and p.Gly293Arg cause abnormal protein folding and trafficking [Wan, Khanna et al 2005].

Jeng et al (2006) have shown that in xenopus oocytes both nonsense and missense mutations in Cav2.1 channels have prominent dominant-negative effects.

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.

euro-ataxia (European Federation of Hereditary Ataxias)
Boherboy Dunlavin
Co Wicklow
Ireland
Phone: 045 401218
Fax: 045 401371
Email: mary.kearneyl@euro-ataxia.org
www.euro-ataxia.org

International Network of Ataxia Friends (INTERNAF)
www.internaf.org

National Ataxia Foundation
2600 Fernbrook Lane Suite 119
Minneapolis MN 55447
Phone: 763-553-0020
Fax: 763-553-0167
Email: naf@ataxia.org
www.ataxia.org

Spinocerebellar Ataxia: Making an Informed Choice about Genetic Testing
Booklet providing information about spinocerebellar ataxia
depts.washington.edu/neurogen/SpinoAtaxia.pdf

WE MOVE (Worldwide Education and Awareness for Movement Disorders)
204 West 84th Street
New York NY 10024
Phone: 800-437-MOV2 (800-437-6683)
Fax: 212-875-8389
Email: wemove@wemove.org
Dyskinesia (Paroxysmal)

Consortium for Clinical Investigations of Neurological Channelopathies (CINCH) Registry
Email: Barbara_Herr@URMC.Rochester.edu
CINCH Registry

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

American Society of Human Genetics and American College of Medical Genetics (1995) Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents.

National Society of Genetic Counselors (1995) Resolution on prenatal and childhood testing for adult-onset disorders.

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Chapter Notes

Revision History

- 17 December 2007 (cd) Revision: prenatal testing available for *CACNA1A*-related EA2
- 12 April 2007 (me) Comprehensive update posted to live Web site
- 21 January 2005 (me) Comprehensive update posted to live Web site
- 29 December 2003 (me) Revision: change in test availability
- 24 February 2003 (me) Review posted to live Web site
- 20 August 2002 (ss) Original submission