GENEReviews

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Ataxia with Vitamin E Deficiency

[*AVED, Ataxia with Isolated Vitamin E Deficiency, Familial Isolated Vitamin E Deficiency, Friedreich-Like Ataxia*]

Markus Schuelke, MD
Department of Neuropediatrics
Charité, University Medical School Berlin
markus.schuelke@charite.de

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Summary

Disease characteristics. Most individuals with ataxia with vitamin E deficiency (AVED) present at puberty; common characteristics of the disease include progressive ataxia, clumsiness of the hands, loss of proprioception (especially of vibration and joint position sense), and areflexia. Other features often observed are dysdiadochokinesia, positive Romberg sign, head titubation, decreased visual acuity, and positive Babinski sign. The phenotype and disease severity vary widely among families with different mutations; age of onset and disease course are more uniform within a given family, but symptoms and disease severity can vary even among sibs.

Diagnosis/testing. Presently, no consensus diagnostic criteria for AVED exist; the principal criterion for diagnosis is a Friedreich ataxia-like neurologic phenotype associated with markedly reduced plasma vitamin E (α-tocopherol) concentration in the absence of known causes of malabsorption. In most cases, molecular analysis of *TTPA*, the gene encoding α-tocopherol transfer protein and the only gene known to be associated with AVED, allows confirmation of the diagnosis by demonstrating the presence of pathogenic mutations.

Management. *Treatment of manifestations:* lifelong high-dose oral vitamin E supplementation to normalize plasma vitamin E concentrations; treatment early in the disease process may reverse ataxia and mental deterioration. *Prevention of primary manifestations:* Vitamin E therapy in presymptomatic children prevents development of symptoms. *Testing of relatives at risk:* evaluation of relatives at risk, especially younger sibs of a proband, for vitamin E deficiency. *Agents/circumstances to avoid:* smoking; occupations requiring quick responses or good balance. *Other:* before learning to drive a car, assessment to determine if abnormal position sense in the extremities presents a danger.

Genetic counseling. AVED is inherited in an autosomal recessive manner. The parents of an affected child are obligate heterozygotes and carry one mutant allele; heterozygotes are asymptomatic. At conception, each sib of an affected individual has 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. Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3. Carrier detection for at-risk family members and prenatal diagnosis for pregnancies at increased risk are available once the disease-causing mutations in the family have been identified.

Diagnosis

Clinical Diagnosis

Presently no consensus diagnostic criteria for ataxia with vitamin E deficiency (AVED) exist; the principal criterion for diagnosis is the presence of a Friedreich ataxia-like neurologic phenotype associated with markedly reduced plasma vitamin E (α-tocopherol) concentration in the absence of known causes of malabsorption. In most cases, molecular analysis of the *TTPA* gene allows confirmation of the diagnosis by demonstrating the presence of pathogenic mutations.

Characteristic clinical findings. Most individuals present at the beginning of puberty with the following [Burck et al 1981, Harding et al 1985]:

- Progressive ataxia
- Early loss of proprioception (especially distal joint position and vibration sense)
- Areflexia
- Dysdiadochokinesia
- Positive Romberg sign
- Head titubation
- Decreased visual acuity
- Positive Babinski sign

Electrophysiologic findings [Zouari et al 1998, Schuelke et al 1999, Gabsi et al 2001]

- Normal motor conduction velocity (MCV), normal muscle action potential (MAP) amplitude
- Normal sensory conduction velocity (SCV), decreased sensory action potential (SAP)
- Somatosensory evoked potentials (SSEP): increased central conduction time between the segment C1 (N13b) and the sensomotor cortex (N20), increased latencies of the N20 (median nerve) and P40 (tibial nerve) waves. The P40 wave may be missing completely.

Note: All electrophysiologic findings are neither specific to nor diagnostic of AVED.

Testing

Characteristic laboratory findings

- Normal lipid and lipoprotein profile
- Very low plasma α-tocopherol concentration

Note: (1) No universal normal range of plasma vitamin E concentration can be given as it depends on the specific method used and varies among laboratories. In Finckh et al (1995), the normal range lies between 9.0 and 29.8 µmol/L (mean: ±2 SD). In individuals with AVED, the plasma α-tocopherol concentrations are generally lower than 4.0 µmol/L (<1.7 mg/L) [Cavalier et al 1998, Mariotti et al 2004]. (2) Because oxidation of α-tocopherol by air may invalidate test results, the following precautions should be taken:

- Centrifugation of the EDTA-blood soon after venipuncture
- Quick separation of plasma from blood cells after centrifugation and subsequent flash freezing of the plasma in liquid nitrogen

- Filling the space above the plasma with an inert gas (e.g., argon or nitrogen)
- Protecting the sample from light by wrapping the container in aluminum foil
- Shipment of the sample to the test laboratory in dry ice

Heterozygotes. Although the plasma vitamin E concentration is generally within the normal range [Harding et al 1985, Amiel et al 1995], it is on average 25% lower than normal in heterozygotes [Gotoda et al 1995].

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. *TTPA*, the gene encoding the α-tocopherol transfer protein, is the only gene known to be associated with AVED [Arita et al 1995].

Clinical testing

- **Sequence analysis.** Sequencing the five exons and flanking intron sequences of *TTPA* genomic DNA detects mutations in more than 90% of individuals with AVED [Ouahchi et al 1995; Hentati et al 1996; Cavalier et al 1998; Schuelke, personal observation]. Sequence analysis identified at least one abnormal allele in 23 of 25 individuals with AVED who had clearly reduced plasma vitamin E concentration [Schuelke, personal observation].

  Sometimes mutations in intron sequences create a cryptic splice site that can cause abnormal splicing, leading to abnormal RNA transcripts and thus abnormal proteins. These kinds of splice-site mutations may be overlooked if sequencing is only done on the exon and flanking intron sequences on the genomic DNA level.

  Most individuals are homozygous or compound heterozygous for one of the known mutations. See Table 3 (pdf).

Research testing

- **Targeted mutation analysis.** Restriction fragment length polymorphism (RFLP) analysis can be used to verify or to exclude the presence of a specific mutation; in a study of 33 individuals of Mediterranean or North African descent, the 744delA mutation was identified by RFLP analysis on both alleles in 11 individuals and on one allele in one individual [Cavalier et al 1998].
- Sequencing can be done on cDNA from EBV immortalized lymophoblastoid cells (LCL) to detect splicing errors [Schuelke et al 1999].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Ataxia with Vitamin E Deficiency

Test Method	Mutations Detected	Mutation Detection Frequency [1]	Test Availability
Sequence analysis	Point mutations or small insertions/deletions in *TTPA*, splice-site mutations	>90%	Clinical Testing
Targeted mutation analysis	744delA in *TTPA*	~80% of individuals of Mediterranean or North African descent	Research only

1. Proportion of affected individuals with a mutation(s) as classified by gene/locus, phenotype, population group, and/or test method

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

Testing Strategy

To confirm the diagnosis in a proband

1. Clinical examination with attention to symptoms described in Table 2
2. Measurement of serum vitamin E concentration and the lipoprotein profile
3. Molecular genetic testing of the TTPA gene by direct sequence analysis
4. Exclusion of diseases that cause fat malabsorption

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

Note: Carriers are heterozygotes for an autosomal recessive disorder and are not at risk of developing the disorder.

Predictive testing for at-risk asymptomatic adult family members requires prior identification of the disease-causing mutations in an affected family member.

Prenatal diagnosis for at-risk pregnancies requires prior identification of the disease-causing mutations in the family.

Genetically Related (Allelic) Disorders

No other phenotypes are associated with mutations in *TTPA*.

Clinical Description

Natural History

The phenotype and disease severity of ataxia with vitamin E deficiency (AVED) vary widely. Although age of onset and disease course tend to be more uniform within a given family, symptoms and disease severity can vary among sibs [Shorer et al 1996].

AVED generally manifests in late childhood or early teens between ages five and 15 years. First symptoms include progressive ataxia, clumsiness of the hands, and loss of proprioception, especially of vibration and joint position sense. The handwriting deteriorates. In rare cases, school performance declines secondary to loss of intellectual capacities. Tendon reflexes of the lower extremities are generally absent and the plantar reflexes increase in intensity. Affected individuals have difficulty walking in the dark and often have a positive Romberg sign. A high percentage of affected individuals (e.g., 8/11 individuals in a series) experience decreased visual acuity [Benomar et al 2002].

In many individuals, cerebellar signs such as dysdiadochokinesia and dysarthria with a scanning speech pattern are present. One third of individuals have a characteristic head tremor (head titubation). In some persons, psychotic episodes, intellectual decline, and dystonic episodes have been described.

Most untreated individuals become wheelchair dependent as a result of ataxia and/or leg weakness between ages 11 and 50 years [Harding et al 1985, Ouahchi et al 1995, Hentati et al 1996, Cavalier et al 1998, Gabsi et al 2001, Benomar et al 2002, Mariotti et al 2004].

Neuroimaging

- Cerebellar atrophy [Aoki et al 1990, Gabsi et al 2001, Mariotti et al 2004], present in approximately half of reported individuals
- Dilatation of the cisterna magna [Shimohata et al 1998], single case report
- Small T_2-high intensity spots in the periventricular region and the deep white matter [Amiel et al 1995, Usuki et al 2000], inconsistent finding in some individuals

Note: All radiologic findings are neither specific to nor diagnostic of AVED.

Pathologic findings [Larnaout et al 1997, Yokota et al 2000]

- Spinal sensory demyelination with neuronal atrophy and axonal spheroids
- Dying back-type degeneration of the posterior columns
- Neuronal lipofuscin accumulation in the third cortical layer of the cerebral cortex, thalamus, lateral geniculate body, spinal horns, and posterior root ganglia
- Retinal atrophy
- Mild loss of Purkinje cells

Genotype-Phenotype Correlations

Except for the following two mutations, no clear-cut genotype-phenotype correlations have been identified:

- **303T>G (p.His101Gln):** Late-onset disease (age >30 years), mild course, increased risk for pigmentary retinopathy; mainly described in individuals of Japanese descent
- **744delA:** Early-onset, severe course, increased risk for cardiomyopathy; mainly observed in individuals of Mediterranean or North African descent. However, disease severity may vary considerably, and even in persons from the same family the onset of symptoms may vary between ages three and 12 years [Cavalier et al 1998, Marzouki et al 2005].

A less clear genotype-phenotype relation can be seen for the following mutations if they occur in homozygous form. Manifestation of disease:

- **Before age ten years.** p.Arg59Trp, p.Arg134X, p.Glu141Lys, 486delT, 530AG>6, 513insTT
- **After age ten years.** p.Arg221Trp, p.Ala120Thr [Cavalier et al 1998]

Penetrance

AVED shows nearly complete penetrance in individuals who are homozygous or compound heterozygous for a *TTPA* mutation.

Nomenclature

AVED was first called "Friedreich ataxia phenotype with selective vitamin E deficiency" [Ben Hamida et al 1993].

Prevalence

With one exception, no population-based studies have been performed. Gotoda et al (1995) found one mutant allele of *TTPA* (303T>G) in 21 of 801 randomly selected inhabitants of a Japanese island on which an individual had previously been diagnosed with AVED. This mutation was not detected in 150 unrelated individuals from Tokyo.

In a Moroccan study, AVED was diagnosed in 20% of individuals with a Friedreich ataxia-like phenotype [Benomar, personal communication].

Differential Diagnosis

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

Friedreich ataxia. The age of onset is similar in ataxia with vitamin E deficiency (AVED) and Friedreich ataxia (FRDA); however, only in AVED are plasma vitamin E concentrations low [Benomar et al 2002].

Although certain clinical symptoms help distinguish the two disorders (Table 2), the distinction cannot be made on clinical grounds alone.

Table 2. Clinical Symptoms that Help Distinguish FRDA from AVED

Clinical Symptom	FRDA	AVED
Cavus foot	+	Rare
Peripheral neuropathy	+	Mild
Diabetes mellitus type I	+	(+)
Head titubation	Rare	+
Amyotrophy	+	–
Babinski sign	+	(+)
Retinitis pigmentosa	–	(+)
Reduced visual acuity	Rare	+
Cardiac conduction disorder	+	Rare
Cardiomyopathy	+	(+)
Muscle weakness	+	–

+ symptom generally present
(+) symptom present only with certain mutations
– symptom generally absent

FRDA can be diagnosed based on molecular genetic testing and AVED based on plasma α-tocopherol concentration and molecular genetic testing of the *TTPA* gene.

Abetalipoproteinemia (Bassen-Kornzweig) and hypobetalipoproteinemia (OMIM 200100). Features include retinitis pigmentosa, progressive ataxia, steatorrhea, demyelinating neuropathy, dystonia, extrapyramidal signs, spastic paraparesis (rare), and acanthocytosis together with vitamin E deficiency, which is secondary to defective intestinal absorption of lipids. The serum cholesterol concentration is very low, and serum β-lipoproteins are absent.

Low-density lipoproteins (LDLs) and very low-density lipoproteins (VLDLs) cannot be synthesized properly. Abetalipoproteinemia is caused by mutations in the gene *MTTP*, which encodes microsomal triglyceride transfer protein. Hypobetalipoproteinemia is caused by mutations in the gene *APOB*, which encodes the protein apolipoprotein B.

Malnutrition/reduced vitamin E uptake. To become vitamin E deficient, healthy individuals have to consume a diet depleted in vitamin E over months. This is sometimes seen in individuals, especially children, who eat a highly unbalanced diet (e.g., Zen macrobiotic diet), but is most often observed in chronic diseases that impede the resorption of fat-soluble vitamins in the distal ileum (e.g., cholestatic liver disease, short bowel syndrome, cystic fibrosis, Crohn's disease). The symptoms are similar to AVED [Harding et al 1982, Weder et al 1984]. Although such individuals should be supplemented with oral preparations of vitamin E, they do not need the high doses necessary for treatment of AVED.

Refsum disease (OMIM 266500). Findings are retinitis pigmentosa, chronic polyneuropathy, deafness, and cerebellar ataxia. Many individuals have cardiac conduction disorders and ichthyosis. In Refsum disease, the degradation of phytanic acid is impeded because of mutations in the gene encoding phytanoyl-CoA hydroxylase *(PHYX)* or the gene encoding peroxin 7 *(PEX7)*. High serum concentration of phytanic acid differentiates Refsum disease from AVED.

Charcot-Marie-Tooth disease 1A (CMT1A) (OMIM 118220). Findings are sensorimotor neuropathy with areflexia, cavus foot, and muscle wasting and weakness, especially in the lower legs and of the interdigital muscles. Neuropathy can be verified by presence of reduced NCVs (<38 m/s). CMT1A is caused by duplication of the gene encoding peripheral myelin protein 22 *(PMP22)*. The plasma vitamin E concentrations in CMT1A are normal. Inheritance is autosomal dominant.

Ataxia-oculomotor apraxia type 1 (AOA1) (OMIM 208920). Findings are oculomotor apraxia, cerebellar ataxia, peripheral neuropathy, and choreoathetosis. Hypoalbuminemia and hypercholesterolemia may occur. AOA1 neurologically mimics ataxia-telangiectasia, but without telangiectasias or immunodeficiency. No information is available regarding plasma vitamin E concentrations. AOA1 is caused by mutations in the gene encoding aprataxin *(APTX)*. Inheritance is autosomal recessive.

Ataxia-oculomotor apraxia type 2 (AOA2) (OMIM 606002). Findings are spinocerebellar ataxia and, rarely, oculomotor apraxia. Serum concentrations of creatine kinase, γ-globulin, and α-fetoprotein (AFP) are increased. AOA2 is caused by mutations in the gene encoding senataxin *(SETX)*. No information is available on the plasma concentration of vitamin E in this disorder. Inheritance is autosomal recessive.

Other ataxias. Because AVED typically presents with ataxia or clumsiness in late childhood, AVED should be included in the differential diagnosis of all ataxias with the same age of onset (see Hereditary Ataxia Overview, Palau & Espinos 2006), including the following:

- **Ataxia-telangiectasia** (OMIM 208900). Findings are cerebellar ataxia, seizures, nystagmus, conjunctival telangiectasias, hypogonadism, immunodeficiency, frequent pulmonary infections, and neoplasia. Inheritance is autosomal recessive.
- **Marinesco-Sjögren syndrome** (OMIM 248800). Findings are cerebellar ataxia, mental retardation, dysarthria, cataracts, short stature, and hypergonadotropic hypogonadism. Inheritance is autosomal recessive.
- **Congential cataracts, facial dysmorphism, neuropathy (CCFDN)** (OMIM 604168). Clinical findings are congenital cataracts, cerebellar ataxia, cavus foot

deformity, facial dysmorphisms, delayed motor development, and pyramidal signs. The affected individuals are of Gypsy origin and share the same mutation in intron 1 of the *CTDP1* gene.

- **Pyruvate decarboxylase deficiency** (OMIM 312170). Findings are episodic ataxia, mental retardation, hypotonia, cerebellar atrophy, dystonia, and lactic acidosis. The inheritance is X-linked. A high proportion of heterozygous females manifest severe symptoms.
- **Sideroblastic anemia and ataxia** (OMIM 301310). Findings are early-onset non-progressive cerebellar ataxia, hyperreflexia, tremor, dysdiadochokinesia, and hypochromic microcytic anemia. Inheritance is X-linked.
- **Cayman-type cerebellar ataxia** (OMIM 601238). Findings are cerebellar ataxia with wide-based gait, psychomotor retardation, intention tremor, and dysarthria. Inheritance is autosomal recessive.
- ***SYNE1*-related autosomal recessive cerebellar ataxia** (OMIM 610743) (also known as autosomal recessive spinocerebellar ataxia [SCAR8] and autosomal recessive cerebellar ataxia type 1 [ARCA1]). Findings are adult-onset cerebellar ataxia and/or dysarthria. Dysmetria, brisk lower-extremity tendon reflexes, and minor abnormalities in ocular saccades and pursuit can be seen. ARCA1 has not been observed outside of Quebec, Canada.
- **Joubert syndrome (JBTS)** (OMIM 213300). Findings are truncal ataxia, developmental delays, and episodic hyperpnea or apnea and/or atypical eye movements or both. Cognitive abilities range from severe mental retardation to normal. Variable features include retinal dystrophy, renal disease, ocular colobomas, occipital encephalocele, hepatic fibrosis, polydactyly, oral hamartomas, and endocrine abnormalities. The characteristic finding on MRI is the "molar tooth sign" in which hypoplasia of the cerebellar vermis and accompanying brain stem abnormalities resemble a tooth. Four causative genes have been identified: *AHI1* (JBTS3, OMIM 608629), *NPHP1* (JBTS4, OMIM 609583), *CEP290* (JBTS5, OMIM 610188), and *TMEM67 (MKS3)* (JBTS6, OMIM 610688). Two other loci have been mapped: JBTS2 *(CORS2)* and *JBTS1*. Inheritance is autosomal recessive.
- **Cerebrotendineous xanthomatosis** (OMIM 213700). Clinical features include xanthomas of the Achilles and other tendons, cerebellar ataxia beginning after puberty, juvenile cataracts, early atherosclerosis, and progressive dementia. The disease is caused by mutations in *CYP27*, the gene encoding sterol 27-hydroxylase.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with ataxia with vitamin E deficiency (AVED), the following evaluations are recommended:

- Clinical neurologic examination; particularly reflex status, vibratory and position sense, gait, Babinski sign, tremor, dsyarthria
- Ophthalmologic examination for evidence of retinitis pigmentosa and decreased visual acuity; electroretinogram
- Cardiac examination; echocardiography and ECG to assess for cardiomyopathy
- Neurophysiologic examination; nerve conduction velocity (NCV) and somatosensory potentials (especially the central conduction time [Schuelke et al 1999]), which are good objective measures of neurologic improvement after vitamin E supplementation

Treatment of Manifestations

The treatment of choice for AVED is lifelong high-dose oral vitamin E supplementation. Some symptoms (e.g., ataxia and mental deterioration) can be reversed if treatment is initiated early in the disease process. In older individuals, disease progression can be stopped, but deficits in proprioception and gait unsteadiness generally remain [Gabsi et al 2001, Mariotti et al 2004]. With treatment, plasma vitamin E concentrations can become normal.

No therapeutic studies have been performed on a large cohort to determine optimal dosage and evaluate outcomes. Reported doses of vitamin E range from 800 mg to 1500 mg (or 40 mg/kg body weight in children) [Burck et al 1981; Harding et al 1985; Amiel et al 1995; Cavalier et al 1998; Schuelke et al 1999; Schuelke, Finckh et al 2000; Gabsi et al 2001; Mariotti et al 2004].

The following vitamin E preparations are used:

- The chemically manufactured racemic form, *all-rac*-α-tocopherol acetate

  OR

- The naturally occurring form, *RRR*-α-tocopherol

It is not currently known whether affected individuals should be treated with *all-rac*-α-tocopherol acetate or with *RRR*-α-tocopherol. It is known that ATTP stereoselectively binds and transports 2R-α-tocopherols [Weiser et al 1996, Hosomi et al 1997, Leonard et al 2002]. For some *TTPA* mutations, this stereoselective binding capacity is lost and affected individuals cannot discriminate between *RRR*- and *SRR*-α-tocopherol [Traber et al 1993, Cavalier et al 1998]. In this instance, affected individuals would also be able to incorporate non-*2R*-α-tocopherol stereoisomers into their bodies if they were supplemented with *all-rac*-α-tocopherol. Since potential adverse effects of the synthetic stereoisomers have not been studied in detail, it seems appropriate to treat with *RRR*-α-tocopherol, despite the higher cost.

Prevention of Primary Manifestations

If vitamin E treatment is initiated in presymptomatic individuals (e.g,. younger sibs of an index case), findings of AVED do not develop [Amiel et al 1995].

Surveillance

During vitamin E therapy, plasma vitamin E concentration should be checked at regular intervals (e.g., every six months), especially in children. Ideally the plasma concentration of vitamin E should be maintained in the high normal range.

Some protocols call for measuring the total radical-trapping antioxidant parameter of plasma (TRAP). Although α-tocopherol only contributes 5%-10% to TRAP, this parameter best reflects clinical improvement [Schuelke et al 1999]. Discontinuation of vitamin E supplementation — even temporarily — leads to a fall of vitamin E plasma concentration within two to three days and to a prolonged fall of TRAP, even after reinitiation of vitamin E supplementation [Kohlschütter et al 1997; Schuelke, Finckh et al 2000].

Agents/Circumstances to Avoid

Individuals with AVED should avoid smoking because it considerably lowers TRAP and reduces plasma vitamin E concentrations [Sharpe et al 1996].

Individuals with AVED should avoid occupations requiring quick responses or good balance.

Testing of Relatives at Risk

Predictive testing should be offered to all sibs of an index patient, as timely treatment with vitamin E supplementation may completely avert the clinical manifestation of the disease.

All relatives at risk, especially younger sibs of a proband, should be evaluated for vitamin E deficiency. If plasma vitamin E concentration is low, the person should be tested for presence of the *TTPA* mutations found in the proband so that homozygotes can be treated promptly with vitamin E supplementation.

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

Because of abnormal position sense in the extremities, an individuals with AVED may have difficulty riding a bicycle or driving a car. Before attempting to drive a car, the individual needs to be tested by a physician to determine whether he/she can safely drive.

Genetics clinics, staffed by genetics professionals, provide 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 may include disease-specific and/or umbrella support organizations.

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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

Ataxia with vitamin E deficiency (AVED) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband

- At conception, each sib of an affected individual has 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.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. The offspring of an individual with AVED are obligate heterozygotes (carriers) for a disease-causing mutation in the *TTPA* gene.

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

Carrier Detection

- Carrier testing for at-risk family members is available on a clinical basis once the mutations have been identified in the family.
- The moderately lowered plasma vitamin E concentration in heterozygotes is not a sensitive enough measure to distinguish between heterozygous carriers and non-carriers.

Related Genetic Counseling Issues

Presymptomatic testing of at-risk family members. Because vitamin E treatment initiated in presymptomatic individuals can prevent the findings of AVED [Amiel et al 1995], testing of at-risk family members (particularly younger sibs of the proband) is appropriate. See Testing of Relatives at Risk for information on testing at-risk relatives for the purpose of early diagnosis and treatment.

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal 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.

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%. See DNA Banking for a list of laboratories offering this service.

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 about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. Both disease-causing

alleles in the family must be identified before prenatal testing can be performed and both parents must be verified to be carriers.

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

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 Ataxia with Vitamin E Deficiency

Gene Symbol	Chromosomal Locus	Protein Name
TTPA	8q13.1-q13.3	Alpha-tocopherol transfer protein

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 Ataxia with Vitamin E Deficiency

277460	VITAMIN E, FAMILIAL ISOLATED DEFICIENCY OF; VED
600415	TOCOPHEROL TRANSFER PROTEIN, ALPHA; TTPA

Table C. Genomic Databases for Ataxia with Vitamin E Deficiency

Gene Symbol	Entrez Gene	HGMD
TTPA	7274 (MIM No. 600415)	TTPA

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

Note: HGMD requires registration.

Normal allelic variants: The *TTPA* gene consists of five uniformly spliced exons with an open reading frame of 834 bp.

Pathologic allelic variants: Disease-causing mutations of *TTPA* comprise nonsense, missense, and splice-site mutations as well as small deletions, insertions, and indeletions (i.e., simultaneous deletion and insertion) (see Table 3 [pdf]). Most affected individuals have private mutations. Only the 744delA and the 513-514insTT mutations occur more often, especially in individuals of Mediterranean or North African descent. In a study of 33 individuals with AVED, the 744delA mutation was found on both alleles in 11 individuals and on one allele in one individual [Cavalier et al 1998]

For more information, see Genomic Databases table.

Normal gene product: The transcript encodes the 278 amino acid protein, α-tocopherol transfer protein (ATTP). This cytosolic 31.7-kd protein is mainly expressed in liver cells [Sato et al 1993], but also in the pyramidal cells of the cerebellum [Hosomi et al 1998, Copp et al 1999] and in the placenta [Kfaempf-Rotzoll et al 2003, Muller-Schmehl et al 2004].

Liver-ATTP incorporates the α-tocopherol from the chylomicrons into VLDLs, which are then secreted into the circulation [Traber et al 1990]. This is a stereoselective process that favors 2R-α-tocopherols [Weiser et al 1996, Leonard et al 2002]. In the absence of ATTP, α-tocopherol is rapidly lost into the urine [Schuelke, Elsner et al 2000]. ATTP seems to have two

functions that can be tested separately: (1) the stereoselective binding of 2R-α-tocopherols and (2) the transfer of α-tocopherol between membranes [Gotoda et al 1995, Morley et al 2004]. In the hepatocytes, ATTP seems to direct vitamin E trafficking from the endocytic compartment to transport vesicles that deliver the vitamin to the site of secretion at the plasma membrane. In the presence of *TTPA* mutations (p.Arg59Trp, p.Arg221Trp, p.Ala120Thr), vitamin E did not travel to the plasma membrane and remained trapped in the lysosomes. The authors also reported that the impact of the mutation on protein stability seems to be directly related to the clinical phenotype [Qian et al 2006].

ATTP has two CRAL-TRIO domains (AA 11-83 and 89-275). These domains were first described in the cellular retinaldehyde-binding protein (CRALBP) and the trifunctional protein (TRIO) [Crabb et al 1988, Debant 1996]. Other proteins of this family comprise a phosphatidyl inositol/phosphatidyl choline transfer protein (Sec14p) of yeast [Sha et al 1998] and the tocopherol-associated protein (TAP or SEC14 like 2) [Zimmer et al 2000]. Mutations in caytaxin, another CRAL-TRIO protein, cause ataxia in humans (Cayman ataxia) as well [Bomar et al 2003].

Abnormal gene product: Nine out of 18 known mutations in *TTPA* lead to a truncated protein through missplicing or generation of a premature termination codon. Missense mutations that cause substitutions in non- or semi-conserved amino acids (p.His101Gln, p.Arg192His) cause a mild phenotype, whereas substitutions in highly conserved amino acids are associated with early onset and severe symptoms (p.Arg59Trp, p.Glu141Lys, p.Arg221Trp).

Through the x-ray crystallographic structure of ATTP [Meier et al 2003, Min et al 2003], the impact of some mutations on the protein structure and function may be explained. Of the nine missense mutations, only one (p.Leu183Pro) is located in the α-tocopherol binding pouch. There is a highly positively charged arginine cluster on the surface of the protein, where ATTP probably interacts with other binding partners. Mutations of these conserved amino acids (Arg59, Arg221) cause a severe AVED phenotype.

Biochemical investigations of the in vitro capacity of ATTP to bind and to transfer α-tocopherol revealed a reduction in both functions for the p.Arg59Trp, p.Glu141Lys, p.Arg221Trp mutations. In contrast, the mutations associated with the mild AVED phenotype (p.His101Gln, p.Ala120Thr) do not have a pronounced effect on ATTP in vitro function. It has been hypothesized that the pathology of these mutations may derive from other as-yet-unknown ATTP functions [Morley et al 2004]. Both types of mutations may impair the ability of ATTP to facilitate the secretion of vitamin E from cells where it remains trapped in lysosomes [Qian et al 2006].

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.

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

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
www.wemove.org

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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

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Chapter Notes

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