



Ataxia with Vitamin E Deficiency

Synonyms: Ataxia with Isolated Vitamin E Deficiency, AVED

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Summary

Clinical characteristics

Untreated ataxia with vitamin E deficiency (AVED) generally manifests between ages five and 15 years. The first manifestations include progressive ataxia, clumsiness of the hands, loss of proprioception, and areflexia. Other features often observed are dysdiadochokinesia, dysarthria, positive Romberg sign, head titubation, decreased visual acuity, and positive Babinski sign. Although age of onset and disease course are more uniform within a given family, disease manifestations and their severity can vary even among sibs.

When lifelong high-dose vitamin E supplementation is initiated in presymptomatic individuals, manifestations of AVED do not develop.

Diagnosis/testing

The diagnosis of AVED is established in a proband with suggestive findings and biallelic pathogenic variants in *TTPA* identified by molecular genetic testing.

Management

Targeted therapy: Lifelong targeted therapy with high-dose oral vitamin E supplementation (that brings plasma vitamin E concentrations into the high-normal range) initiated in presymptomatic individuals (e.g., younger sibs of an index case) prevents the manifestations of AVED. Vitamin E supplementation early in the disease course of a symptomatic individual may to some extent reverse ataxia and mental deterioration.

Supportive care: Supportive care for those with ataxia and related findings is the same multidisciplinary care for individuals with ataxia of other causes.

Surveillance: Monitor plasma vitamin E concentration in treated individuals – particularly children – every six months. For symptomatic individuals, regular evaluations to monitor the individual's response to supportive care and to identify emergence of new manifestations.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of all sibs of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of treatment. Timely treatment with vitamin E supplementation may completely avert the clinical manifestations of the disease.

Genetic counseling

AVED is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *TTPA* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial pathogenic variants. Once the *TTPA* pathogenic variants have been identified in an affected family member, carrier detection for at-risk family members, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for ataxia with vitamin E deficiency (AVED) have been published.

Suggestive Findings

AVED **should be suspected** a proband with the following clinical and laboratory findings and family history.

Clinical features

- Onset between ages five and 15 years
- Progressive cerebellar findings including the following:
 - Gait ataxia
 - Clumsiness of the hands
 - Loss of proprioception (especially distal joint position and vibration sense)
 - Dysdiadochokinesia
 - Positive Romberg sign
 - Head titubation
- Lower motor neuron involvement. Areflexia
- Upper motor neuron involvement. Positive Babinski sign
- Ophthalmologic involvement. Decreased visual acuity due to macular degeneration, pigmentary retinopathy

Supportive laboratory findings

- Normal lipid and lipoprotein profile
- Very low plasma vitamin E (alpha-tocopherol, or α -tocopherol) concentration

Note: There is no universal normal range of plasma vitamin E concentration, as it depends on the test method and varies among laboratories.

In Finckh et al [1995], the normal range lies between 9.0 and 29.8 $\mu\text{mol/L}$ (SD 2). In El Euch-Fayache et al [2014], the normal range is given as 16.3-34.9 $\mu\text{mol/L}$, while individuals with AVED had vitamin E levels between 0.00 and 3.76 $\mu\text{mol/L}$ (mean 0.95 $\mu\text{mol/L}$, SD 1.79 $\mu\text{mol/L}$; n=132). In individuals with AVED, the plasma vitamin E concentration is generally lower than 4.0 $\mu\text{mol/L}$ (<1.7 mg/L) [Cavalier et al 1998, Mariotti et al 2004].

Because oxidation of α -tocopherol by air may invalidate test results, the following precautions with a blood sample 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, or using a black or light-shielded Eppendorf tube
- Shipment of the sample to the test laboratory in dry ice

Electrophysiologic findings

- No electrophysiologic findings (motor nerve conduction velocities, compound muscle action potentials, or nerve sensory action potentials) are specific to or diagnostic of AVED; even the presence of a severe neuropathy does not exclude the diagnosis of AVED. See Clinical Description for more details.
- Somatosensory evoked potentials show increased central conduction time between the segment C1 (N13b) and the sensorimotor cortex (N20) and increased latencies of the N20 (median nerve) and P40 (tibial nerve) waves. The P40 wave may be missing completely [Schuelke et al 1999].

Neuroimaging

- Cerebellar atrophy [Mariotti et al 2004] is present in approximately half of reported individuals.
- Small T₂ high-intensity spots in the periventricular region and the deep white matter [Usuki & Maruyama 2000] are inconsistent findings in some individuals.

Note: No radiologic findings are specific to or diagnostic of AVED.

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

Establishing the Diagnosis

The diagnosis of AVED is **established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *TTPA* identified by molecular genetic testing (see Table 1).

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

Molecular genetic testing approaches can include **gene-targeted testing**, which requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas **comprehensive genomic testing** does not (see Option 2).

Option 1

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

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

Option 2

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

For an introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).

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

Gene ¹	Method	Proportion of Pathogenic Variants ² Detectable by Method
<i>TTPA</i>	Sequence analysis ³	>97% ⁴
	Gene-targeted deletion/duplication analysis ⁵	1 reported ⁶

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on variants detected in this gene.

3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).

4. Ouahchi et al [1995], Hentati et al [1996], Cavalier et al [1998], Schuelke [personal observation], and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]

5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

6. A single whole-gene deletion has been reported [Kara et al 2008].

Clinical Characteristics

Clinical Description

The phenotype and disease severity of untreated ataxia with vitamin E deficiency (AVED) vary widely. Although age of onset and disease course tend to be more uniform within a given family, clinical findings and disease severity can vary among sibs [Shorer et al 1996]. Untreated AVED generally manifests in late childhood or the early teenage years, between ages five and 15 years; however, the range may be from age two to 37 years as reported in a series of 132 North African individuals [El Euch-Fayache et al 2014].

When vitamin E treatment is initiated in presymptomatic individuals (e.g., younger sibs of an index case), manifestations of AVED do not develop (see Management, Targeted Therapy).

The following description of the phenotypic features associated with untreated individuals with AVED is based on findings in 132 individuals of North African descent [El Euch-Fayache et al 2014].

Table 2. Ataxia with Vitamin E Deficiency: Frequency of Select Features in Untreated Individuals

Feature ¹	% of Persons w/Feature	
Cerebellar involvement	Gait impairment	93.4%
	Dysarthria	61.8%
	Head titubation	33%
	Nystagmus	5.3%

Table 2. continued from previous page.

Feature ¹	% of Persons w/Feature	
Lower motor neuron involvement	Areflexia	94.7%
	Deep sensory disturbances	67.1%
Upper motor neuron involvement	Babinski sign	85.5%
	Urinary urgency	22.4%
Pigmentary retinopathy		2.3%
Cardiomyopathy		1.5%

Based on findings in 132 individuals of North African descent [El Euch-Fayache et al 2014]

Untreated Individuals

Neurologic findings. The first manifestations in untreated individuals include progressive ataxia, clumsiness of the hands, and loss of proprioception, especially of vibration and joint position sense. Affected individuals have difficulty walking in the dark and often have a positive Romberg sign. Handwriting deteriorates. Many individuals have cerebellar signs such as dysdiadochokinesia and dysarthria with a scanning speech pattern. One third of individuals have a characteristic head tremor (head titubation).

Tendon reflexes of the lower extremities are generally absent, and the plantar reflexes (Babinski sign) increase in intensity.

Arm or cervical dystonia may be seen on rare occasion [Becker et al 2016].

No electrophysiologic findings (motor nerve conduction velocities, compound muscle action potentials, or nerve sensory action potentials) are specific to or diagnostic of AVED. The following are the results from a neurophysiologic study of 45 individuals (from a cohort of 132 individuals) with AVED from North Africa that included median and peroneal nerve motor conduction velocity, compound muscle action potential, median and saphenous nerve sensory action potential, and sensory action potential [El Euch-Fayache et al 2014].

- 9% had normal findings.
- 47% had mild neuropathy (at least 1 parameter 70%-100% of lower limit of normal [LLN]).
- 27% had moderate neuropathy (at least 1 parameter 30%-70% of LLN).
- 17% had severe neuropathy (at least 1 parameter <30% of LLN or no response).
- Neuropathy was either purely sensory (34%), purely motor (24%), or combined (42%).

Ophthalmologic. A high percentage of affected individuals (e.g., 8/11 individuals in one series) experience decreased visual acuity [Benomar et al 2002].

Intellectual decline / behavioral issues. In some persons, psychotic episodes and intellectual decline have been described. In rare individuals, school performance declines secondary to loss of intellectual capacities.

Histopathologic findings. See [pdf](#).

Natural history in untreated individuals. 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].

Genotype-Phenotype Correlations

To date, only two pathogenic variants have shown clear-cut genotype-phenotype correlations:

- The pathogenic variant **p.His101Gln** is associated with late-onset disease (age >30 years) with a mild disease course, and increased risk for pigmentary retinopathy. This variant is primarily reported in individuals of Japanese descent [Gotoda et al 1995].
- The pathogenic variant **c.744delA** is associated with early onset and a more severe disease course, and slightly increased risk for cardiomyopathy. However, disease severity may vary considerably, and even in persons from the same family the onset of manifestations may vary between ages three and 12 years [Cavalier et al 1998, Marzouki et al 2005]. This variant is mainly observed in individuals of Mediterranean or North African descent.

A less clear genotype-phenotype correlation can be seen for other pathogenic variants, particularly when homozygous.

Preliminary genotype-phenotype correlations related to variant and age of onset of disease include:

- **Early onset (generally before or around age ten years).** p.Arg59Trp, p.Arg134Ter, p.Glu141Lys, p.Arg221Trp, c.486delT, c.513_514insTT, c.530_531delAGinsGTAAGT (See Table 3.)
- **Late onset (generally after age 20 years).** p.Ala120Thr [Cavalier et al 1998] (See Table 3.)

Pathogenic missense variants that cause substitutions in non- or semi-conserved amino acids (e.g., p.His101Gln, p.Ala120Thr, p.Arg192His, or p.Gly246Arg) are associated with a mild phenotype, whereas substitutions in highly conserved amino acids are associated with early onset and severe symptoms (e.g., p.Arg59Trp, p.Asp64Gly, p.Glu141Lys, p.Leu183Pro, p.Arg221Trp) (see Table 3).

Nomenclature

AVED was first called "Friedreich ataxia phenotype with selective vitamin E deficiency" [Ben Hamida et al 1993]. Subsequent names for AVED include "Friedreich-like ataxia" and "familial isolated vitamin E deficiency."

Prevalence

The *TTPA* pathogenic founder variant c.744delA has been identified in individuals of Tunisian ancestry.

Several restricted population-based studies have been performed.

Gotoda et al [1995] found one *TTPA* pathogenic variant (p.His101Gln) in 21 of 801 randomly selected inhabitants of a Japanese island on which one individual had previously been diagnosed with AVED. This would amount to a calculated prevalence of one homozygous individual per 1,500 inhabitants. This pathogenic variant was not detected in 150 unrelated individuals from Tokyo.

Of 29 individuals from Morocco with a Friedreich ataxia-like phenotype, 13 had AVED and the remainder had Friedreich ataxia [Benomar et al 2002].

In a population study in southeast Norway, 1 in 171 individuals with hereditary ataxia had AVED, suggesting a prevalence of 0.6:1,000,000 [Elkamil et al 2015].

Anheim et al [2010] evaluated 102 individuals with suspected autosomal recessive cerebellar ataxia; in 57 individuals (56%) a molecular diagnosis could be established, and of those, one individual had AVED. From their findings, the authors infer a prevalence for AVED in the Alsace region of France of approximately 1:1,800,000.

Zortea et al [2004] performed an epidemiologic study of inherited ataxias in the Italian province of Padua and found a prevalence of 3.5:1,000,000 for AVED.

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Friedreich ataxia (FRDA). The age of onset is similar in ataxia with vitamin E deficiency (AVED) and FRDA; however, only in AVED are plasma vitamin E concentrations low [Benomar et al 2002]. Certain clinical signs may also help distinguish the two disorders; however, the distinction cannot be made on clinical grounds alone. FRDA is caused by biallelic pathogenic variants in *FXN* and is inherited in an autosomal recessive manner.

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](#)).

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 disease). The symptoms are similar to AVED. Although such individuals should be supplemented with oral preparations of vitamin E, they do not need the high doses necessary for treatment of AVED.

Management

No clinical practice guidelines for ataxia with vitamin E deficiency (AVED) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with a hereditary ataxia, the evaluations summarized in [Hereditary Ataxia Overview](#), [Table 6](#), are recommended.

Treatment of Manifestations

Targeted Therapy

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

The treatment of choice for AVED is lifelong high-dose oral vitamin E supplementation. With treatment, plasma vitamin E concentrations can become normal.

Presymptomatic individuals. When vitamin E treatment is initiated in presymptomatic individuals (e.g., younger sibs of an index case), manifestations of AVED do not develop [Amiel et al 1995, El Euch-Fayache et al 2014].

No large-scale therapeutic studies have been performed to determine optimal vitamin E dosage and to evaluate outcomes. The reported vitamin E dose ranges from 800 mg to 1,500 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 et al 2000b, Gabsi et al 2001, Mariotti et al 2004].

One of the following vitamin E preparations is used:

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

It is currently unknown whether affected individuals should be treated with *all-rac-α*-tocopherol acetate or with *RRR-α*-tocopherol. It is known that alpha-tocopherol transfer protein (α -TTP) stereoselectively binds and transports *2R-α*-tocopherols [Weiser et al 1996, Hosomi et al 1997, Leonard et al 2002]. For some *TTPA* pathogenic variants, 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.

Symptomatic individuals. Some manifestations (e.g., ataxia and intellectual deterioration) can be reversed in symptomatic individuals if treatment is initiated early in the disease process [Schuelke et al 1999].

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, El Euch-Fayache et al 2014].

Supportive Care

The goals of supportive care in those with manifestations of AVED are to maximize function and reduce complications. Depending on the clinical manifestations, it is recommended that each individual be managed by a multidisciplinary team of relevant specialists such as neurologists, occupational therapists, physical therapists, physiatrists, orthopedists, nutritionists, speech-language pathologists, pulmonologists, and mental health specialists (see Hereditary Ataxia Overview, [Table 7](#)).

Surveillance

Targeted Therapy

For those on vitamin E therapy, the plasma vitamin E concentration should be measured at regular intervals (e.g., every 6 months), especially in children. Ideally the plasma vitamin E concentration 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 appears to be the best surrogate marker for clinical improvement [Schuelke et al 1999]. Discontinuation of vitamin E supplementation, even temporarily, leads to a drop in plasma vitamin E concentration within two to three days and to a prolonged drop in TRAP, even after reinitiating vitamin E supplementation [Kohlschütter et al 1997, Schuelke et al 2000b].

Symptomatic Individuals

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Hereditary Ataxia Overview, [Table 8](#), are recommended.

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];
- Occupations requiring quick responses or good balance.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of all sibs of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of treatment. Timely treatment with vitamin E supplementation may completely avert the clinical manifestations of the disease.

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

Pregnancy Management

Because reduced vitamin E levels are associated with low fertility and embryo resorption in mice [Traber & Manor 2012] and α -tocopherol transfer protein is highly expressed in the human placenta [Müller-Schmehl et al 2004], it is advisable for women with AVED to maintain vitamin E levels in the high-normal range during pregnancy.

Therapies Under Investigation

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://clinicaltrialsregister.eu) in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

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

Mode of Inheritance

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 presumed to be heterozygous for a *TTPA* pathogenic variant.
- Molecular genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for a *TTPA* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
 - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
 - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *TTPA* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial pathogenic variants.
- Clinical findings and disease severity can vary among affected sibs with the same *TTPA* pathogenic variants (see Clinical Description).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Unless an affected individual's reproductive partner also has AVED or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *TTPA* (see **Family planning**).

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

Carrier Detection

Molecular genetic carrier testing for at-risk relatives requires prior identification of the *TTPA* pathogenic variants in the family.

Note: 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

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Predictive testing of at-risk family members. Because vitamin E treatment initiated in presymptomatic individuals can prevent the findings of AVED [Amiel et al 1995], predictive testing of all sibs of the proband is appropriate.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.
- Carrier testing for the reproductive partners of known carriers and for the reproductive partners of individuals affected with AVED should be considered, particularly if both partners are of the same ethnic background (see Table 3).

Prenatal Testing and Preimplantation Genetic Testing

Once the *TTPA* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for AVED are possible.

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

Resources

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

- **MedlinePlus**
[Ataxia with vitamin E deficiency](#)
- **National Organization for Rare Disorders (NORD)**
Phone: 203-744-0100
Fax: 203-263-9938
[Ataxia with Vitamin E Deficiency](#)
- **Ataxia UK**
United Kingdom
Phone: 0800 995 6037; +44 (0) 20 7582 1444 (from abroad)
Email: help@ataxia.org.uk
ataxia.org.uk
- **euro-ATAXIA (European Federation of Hereditary Ataxias)**
United Kingdom
Email: ageorgousis@ataxia.org.uk
euroataxia.org
- **National Ataxia Foundation**
Phone: 763-553-0020
Email: naf@ataxia.org
ataxia.org

Molecular Genetics

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

Table A. Ataxia with Vitamin E Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
TTPA	8q12.3	Alpha-tocopherol transfer protein	TTPA database	TTPA	TTPA

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

Table B. OMIM Entries for Ataxia with Vitamin E Deficiency ([View All in OMIM](#))

277460	ATAXIA WITH VITAMIN E DEFICIENCY; AVED
600415	TOCOPHEROL TRANSFER PROTEIN, ALPHA; TTPA

Molecular Pathogenesis

TTPA encodes the alpha-tocopherol transfer protein (α -TTP). This cytosolic 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 [Kaempf-Rotzoll et al 2003, Müller-Schmehl et al 2004].

Liver α -TTP incorporates α -tocopherol from the chylomicrons into very low-density lipoproteins (VLDLs), which are then secreted into the circulation [Traber et al 1990] – a stereoselective process that favors 2R- α -tocopherols [Weiser et al 1996, Leonard et al 2002]. In the absence of α -TTP, α -tocopherol is rapidly lost into the urine [Schuelke et al 2000a]. Alpha-TTP appears 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 hepatocytes, α -TTP appears 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* pathogenic variants (p.Arg59Trp, p.Arg221Trp, p.Ala120Thr), vitamin E did not travel to the plasma membrane and remained trapped in the lysosomes [Qian et al 2006]. The effect of the pathogenic variant on protein stability appears to be directly related to the clinical phenotype [Qian et al 2006].

Mechanism of disease causation. Loss of function

Table 3. Notable *TTPA* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000370.2 NP_000361.1	c.175C>T	p.Arg59Trp	See Genotype-Phenotype Correlations.
	c.191A>G	p.Asp64Gly	
	c.358G>A	p.Ala120Thr	
	c.400C>T	p.Arg134Ter	See Genotype-Phenotype Correlations.
	c.421G>A	p.Glu141Lys	
	c.486delT	p.Trp163GlyfsTer13	
	c.530_531delAGinsGTAAGT	p.Lys177SerfsTer3	
	c.548T>C	p.Leu183Pro	
	c.575G>A	p.Arg192His	
	c.661C>T	p.Arg221Trp	
	c.736G>C	p.Gly246Arg	
	c.744delA	p.Glu249AsnfsTer15	Founder variant among persons of Mediterranean or North African descent (Tunisia, Libya, Morocco, Algeria, Italy) [El Euch-Fayache et al 2014]; see Genotype-Phenotype Correlations.

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.

GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See [Quick Reference](#) for an explanation of nomenclature.

Chapter Notes

Revision History

- 16 March 2023 (bp) Comprehensive update posted live
- 13 October 2016 (sw) Comprehensive update posted live
- 2 November 2010 (me) Comprehensive update posted live
- 4 September 2007 (me) Comprehensive update posted live
- 20 May 2005 (me) Review posted live
- 4 October 2004 (ms) Original submission

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