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Transthyretin Amyloidosis

[*Includes: Familial Amyloid Cardiomyopathy, Familial Amyloid Polyneuropathy Type I (Portuguese-Swedish-Japanese Type), Familial Amyloid Polyneuropathy Type II (Indiana/Swiss or Maryland/German Type), Leptomeningeal Amyloidosis, Familial Oculoleptomeningeal Amyloidosis (FOLMA)*]

Yoshiki Sekijima, MD, PhD
Division of Clinical and Molecular Genetics
Shinshu University Hospital
Matsumoto
sekijima@hsp.md.shinshu-u.ac.jp

Kunihiro Yoshida, MD, PhD
Division of Clinical and Molecular Genetics
Shinshu University Hospital
Matsumoto
kyoshida@hsp.md.shinshu-u.ac.jp

Takahiko Tokuda, MD, PhD
Division of Clinical and Molecular Genetics
Shinshu University Hospital
Matsumoto

Shu-ichi Ikeda, MD, PhD
Division of Clinical and Molecular Genetics
Shinshu University Hospital
Matsumoto

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Summary

Disease characteristics. Transthyretin (TTR) amyloidosis is characterized by a slowly progressive peripheral sensorimotor neuropathy and autonomic neuropathy as well as non-neuropathic changes of nephropathy, cardiomyopathy, vitreous opacities, and CNS amyloidosis. Onset is usually in the third or fourth decade, but may be later. Typically, sensory neuropathy starts in the lower extremities as paresthesia and hypesthesia of the feet and is followed by motor neuropathy within a few years. Autonomic neuropathy may be the first symptom of the disease; findings include orthostatic hypotension, constipation alternating with diarrhea, attacks of nausea and vomiting, delayed gastric emptying, sexual impotence, anhidrosis, and urinary retention or incontinence. Cardiac amyloidosis is mainly characterized by progressive cardiomyopathy. Individuals with leptomeningeal amyloidosis show CNS signs and symptoms including dementia, psychosis, visual impairment, headache, seizures, motor paresis, ataxia, myelopathy, hydrocephalus, or intracranial hemorrhage.

Diagnosis/testing. Traditionally, diagnosis of TTR amyloidosis relied upon either tissue biopsy to document the presence of amyloid using Congo red staining (and immunocytochemical study if Congo red staining was negative), or mass spectrometry to detect serum TTR protein variants. However, molecular genetic testing of the entire *TTR* gene can be performed efficiently because the gene consists of only four exons, and all the hitherto-identified mutations exist in exons 2, 3, or 4. Sequence analysis detects more than 99% of

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disease-causing (amyloidogenic) mutations. Such testing is available clinically. Molecular genetic testing is less invasive and more sensitive than biopsy for diagnosis.

Management. Treatment for transthyretin amyloidosis includes carpal tunnel release surgery for carpal tunnel syndrome and vitrectomy for vitreous involvement. Orthotopic liver transplantation (OTLX) is the only effective therapy for the neuropathy. OTLX is recommended in individuals: (1) younger than 50 years, (2) with disease duration less than five years, (3) with polyneuropathy restricted to the lower extremities or with autonomic neuropathy alone, and (4) with no significant cardiac or renal dysfunction. Surveillance of affected individuals includes serial nerve conduction studies to monitor polyneuropathy. Molecular genetic testing of at-risk relatives of a family member in whom a disease-causing mutation is identified ensures early diagnosis and treatment; clinical evaluations ensure early treatment if the disease-causing mutation is not known.

Genetic counseling. Transthyretin amyloidosis is inherited in an autosomal dominant manner. About one-third of probands have an affected parent and about two-thirds have the disorder as the result of a *de novo* mutation. Each child of an affected individual has a 50% risk of inheriting the *TTR* mutation. For individuals homozygous for *TTR* mutations, (1) each sib is at a 50% risk of inheriting one *TTR* mutation and a 25% risk of inheriting two *TTR* mutations; (2) all offspring will inherit a mutation. Prenatal testing for fetuses at 50% risk is possible if a disease-causing mutation has been identified in an affected family member. Requests for prenatal testing for adult-onset conditions such as TTR amyloidosis that do not affect intellect and have some treatment available are not common.

Diagnosis

Clinical Diagnosis

The diagnosis of transthyretin amyloidosis is suspected in adults with slowly progressive sensorimotor and/or autonomic neuropathy frequently accompanied by cardiac conduction blocks, cardiomyopathy, nephropathy, and/or vitreous opacities. Family history consistent with autosomal dominant inheritance supports the diagnosis.

Testing

Tissue biopsy. Deposition of amyloid in tissue can be demonstrated by Congo red staining of biopsy materials. With Congo red staining, amyloid deposits show a characteristic yellow-green birefringence under polarized light. Tissues suitable for biopsy include subcutaneous fatty tissue of the abdominal wall, skin, gastric or rectal mucosa, sural nerve, and peritendinous fat from specimens obtained at carpal tunnel surgery. Sensitivity of endoscopic biopsy of gastrointestinal mucosa is around 85%; biopsy of the sural nerve is less sensitive because amyloid deposition is often patchy [Hund et al 2001, Koike et al 2004, Vital et al 2004].

Serum variant TTR protein. TTR protein normally circulates in serum or plasma as a soluble protein having a tetrameric structure [Kelly 1998, Rochet & Lansbury 2000]. The plasma TTR concentration is 20-40 mg/dL (0.20-0.40 mg/mL).

Pathogenic mutations in the *TTR* gene cause conformational change in the TTR protein molecule, disrupting the stability of the TTR tetramer, which is then more easily dissociated into pro-amyloidogenic monomers [Sekijima et al 2005]. Small amounts of TTR monomer (0.28-0.56 µg/mL) can be detected in the plasma of individuals with transthyretin amyloidosis and normal controls [Sekijima et al 2001].

After immunoprecipitation with anti-TTR antibody, serum variant TTR protein can be detected by mass spectrometry [Kishikawa et al 1996, Tachibana et al 1999]. Approximately 90% of

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TTR variants so far identified are confirmed by this method, but care must be taken because TTR undergoes extensive post-translational modification, causing mass shift in both wild-type and variant proteins. Mass shift associated with each variant TTR protein is indicated [Connors et al 2003].

Molecular Genetic Testing

Molecular Genetic Testing —Gene. *TTR* is the only gene associated with transthyretin amyloidosis.

Molecular genetic testing: Clinical uses

- Diagnosis
- Predictive testing
- Prenatal diagnosis

Molecular genetic testing: Clinical methods

- **Targeted mutation analysis.** The most frequent pathogenic mutation, V30M, has been identified in many kindreds with different ethnic backgrounds. This mutation can be easily identified by PCR-RFLP.
- **Sequence analysis.** Sequence analysis of the entire *TTR* gene can be performed efficiently because it consists of only four exons, and all the hitherto-identified mutations are present in exons 2, 3, or 4. Direct sequencing detects more than 99% of disease-causing (amyloidogenic) mutations.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Transthyretin Amyloidosis

Test Methods	Mutations Detected	Mutation Detection Rate	Test Availability
Targeted mutation analysis	V30M mutation	Unknown [1]	Clinical Testing
Sequence analysis	*TTR* sequence alterations	>99%	

1. Found in large clusters in Portugal, Sweden, and Japan

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

Testing Strategy for a Proband

Traditionally, diagnosis relied upon either 1) tissue biopsy to document the presence of amyloid using Congo red staining (and immunocytochemical study if Congo red staining was negative), 2) identification of the specific amyloid protein using immunohistochemical staining of biopsy material, or 3) mass spectrometry to detect serum TTR protein variants. However, molecular genetic testing of *TTR* for diagnosis is less invasive and more sensitive than these other test types.

Genetically Related (Allelic) Disorders

Familial euthyroid hyperthyroxinemia is caused by non-amyloidogenic mutations in *TTR*, including G6S, A109T, A109V, and T119M [Benson & Uemichi 1996, Nakazato 1998, Benson 2001, Saraiva 2001]. The TTR protein binds about 15% of serum thyroxine.

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Clinical Description

Natural History

Clinical features of transthyretin amyloidosis can include peripheral sensorimotor neuropathy and autonomic neuropathy as well as non-neuropathic changes (nephropathy, cardiomyopathy, vitreous opacities and CNS amyloidosis) (see Table 2).

Table 2. Phenotypes Associated with Transthyretin Amyloidosis

Phenotype		Genotype
Type	**Features**	**Mutations in *TTR***
TTR amyloid neuropathy [formerly familial amyloid polyneuropathy type I (Portuguese-Swedish-Japanese type) and familial amyloid polyneuropathy type 2 (Indiana/Swiss; Maryland/German)]	Early • Sensorimotor polyneuropathy of the legs • Carpal tunnel syndrome • Autonomic dysfunction • Constipation/ diarrhea • Impotence Late • Cardiomyopathy • Vitreous opacities • Nephropathy	• V28M • V30M • L58H • L58R • K70N • Y78F • I84S • Y114H
Cardiac amyloidosis	• Cardiomegaly • Arrhythmia • Anginal pain • Congestive heart failure • Sudden death	• D18N • D18E • V20I • P24S • E42D • A45T • T49P • S50I • H56R • I68L • A81T • Q92K • R103S • L111M • V122I
Leptomeningeal/ CNS amyloidosis	• Dementia • Ataxia • Spasticity • Seizures • Hemorrhage (intracerebral and/or subarachnoid) • Psychosis • Hydrocephalus	• L12P • D18G • A25T • V30G • A36P • G53E • F64S • Y69H • Y114C

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Neuropathy. The cardinal feature of TTR-familial amyloid polyneuropathy type I is slowly progressive sensorimotor and autonomic neuropathy [Benson 2001, Hund et al 2001, Ando et al 2005]. Typically, sensory neuropathy starts in the lower extremities, and is followed by motor neuropathy within a few years. The initial sign of this sensory neuropathy is paresthesia (sense of burning, shooting pain), and hypesthesia of the feet. Temperature and pain sensation are impaired earlier than vibration and position sensation. By the time sensory neuropathy progresses to the level of the knees, the hands have usually become affected. At the full-blown stage of the disease, sensory loss, muscle atrophy, and weakness of the extremities show a glove and stocking distribution. Footdrop, wristdrop, and disability of the hands and fingers are frequent symptoms of motor neuropathy.

Autonomic neuropathy may occur as the first clinical symptom of the disease (Table 3). The symptoms of autonomic dysfunction include orthostatic hypotension [Vita et al 2005], constipation alternating with diarrhea, attacks of nausea and vomiting, delayed gastric emptying, sexual impotence, anhidrosis, and urinary retention or incontinence. Because of sensory loss and autonomic dysfunction, trophic ulcers on the lower extremities are common. Frequently the autonomic neuropathy produces the most significant morbidity of the disorder.

Table 3. Symptoms at Presentation of Familial Amyloid Polyneuropathy

Symptoms		% of Individuals	
		From Coelho et al 1994	From Ikeda et al 1987
Sensory (lower limbs)	Most commonly parathesias	80%	49%
Autonomic	Vomiting	3%	
	Constipation	21%	18%
	Constipation alternating with diarrhea	12%	
	Diarrhea	17%	4%
	Impotence	24%	9%
	Orthostatic fainting		7%
Motor		7%	7%

The disease usually begins in the third or fourth decade, but the onset of symptoms may be later. For Japanese individuals with the V30M mutation, the mean age at onset is 40.1 ±12.8 years (range 22-74 years) [Nakazato 1998]. For Portuguese individuals with the V30M mutation, the mean age is 33.5 ±9.4 years (range 17-78 years) [Sousa et al 1995]. Japanese individuals with V30M who are unrelated to two large endemic foci show much later onset of the disease (mean age 62.7 ±6.6 years; range 52-80 years) [Misu et al 1999, Ikeda et al 2002]. These data show that the age at onset varies greatly even within ethnically identical populations with the same mutation in the *TTR* gene. The mean age at onset in individuals of Swedish, French, or British ancestry is much later than that in individuals of Japanese or Portuguese ancestry [Sousa et al 1993; Reilly, Adams, Davis et al 1995; Planté-Bordeneuve et al 1998]. Sensorimotor and autonomic neuropathy progress over ten to 20 years. Various types of cardiac conduction block frequently appear. Cachexia is a common feature at the late stage of the disease. Affected individuals usually die of cardiac failure, renal failure, or infection.

TTR-familial amyloid polyneuropathy type II (or the Indiana/Swiss or Maryland/German type) starts in the upper extremities as carpal tunnel syndrome in association with specific *TTR* mutations (e.g., L58H, L58R, K70N, I84S, Y114H) [Benson & Uemichi 1996, Nakazato 1998, Connors et al 2000, Benson 2001, Hund et al 2001, Connors et al 2003]. Sensorimotor

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and autonomic neuropathy is accompanied by visceral involvement. Cardiomyopathy or nephropathy is frequently seen in the advanced stage of the disease.

Non-neuropathic amyloidosis. Individuals with TTR amyloidosis do not necessarily present with polyneuropathy. Cardiac amyloidosis and leptomeningeal amyloidosis are well-known non-neuropathic forms of TTR amyloidosis that are associated with specific *TTR* mutations. In these types of TTR amyloidosis, polyneuropathy is absent or less evident if present. Approximately one-third of the TTR protein variants (including those resulting from a V30M mutation) are accompanied by vitreous opacities [Benson & Uemichi 1996, Connors et al 2000, Benson 2001, Connors et al 2003, Kawaji et al 2004].

Cardiac amyloidosis. Cardiac amyloidosis is mainly characterized by progressive cardiomyopathy and has been reported to be caused by mutations V20I, P24S, A45T, I68L, L111M, or V122I [Benson & Uemichi 1996, Nakazato 1998, Connors et al 2000, Benson 2001, Saraiva 2001, Connors et al 2003, Hattori et al 2003]. In some families with specific *TTR* mutations such as V20I or L111M, cardiomyopathy without peripheral neuropathy is a main feature of the disease. Cardiac amyloidosis is usually late onset. Most individuals develop cardiac symptoms after age 50 years; cardiac amyloidosis generally presents with restrictive cardiomyopathy. The typical electrocardiogram shows a pseudoinfarction pattern with prominent Q wave in leads II, III, $_{a}V_{F}$, and V_{1}-V_{3}, presumably resulting from dense amyloid deposition in the anterobasal or anteroseptal wall of the left ventricle. The echocardiogram reveals left ventricular hypertrophy with preserved systolic function. The thickened walls present "a granular sparkling appearance."

Among the mutations responsible for cardiac amyloidosis, V122I is notable for its prevalence in African-Americans. About 3.0-3.9% of African-Americans are heterozygous for V122I [Jacobson et al 1996, Yamashita et al 2005]. The high frequency of V122I partly explains the observation that in individuals in the US over the age of 60, cardiac amyloidosis is four times more common among blacks than whites [Jacobson et al 1997].

Leptomeningeal (oculoleptomeningeal) amyloidosis. Amyloid deposition is seen in the pial and arachnoid membrane, and in the walls of vessels in the subarachnoid space associated with *TTR* mutations such as L12P, D18G, A25T, V30G, A36P, G53E, F64S, Y69H, or Y114C [Benson & Uemichi 1996, Garzuly et al 1996, Petersen et al 1997, Nakazato 1998, Brett et al 1999, Mascalchi et al 1999, Uemichi et al 1999, Connors et al 2000, Benson 2001, Ellie et al 2001, Saraiva 2001, Ikeda et al 2002, Blevins et al 2003, Connors et al 2003, Hammarström et al 2003, Sekijima et al 2003]. Amyloid in the blood vessels disappears as the vessels penetrate the brain parenchyma.

Individuals with leptomeningeal amyloidosis show CNS signs and symptoms including dementia, psychosis, visual impairment, headache, seizures, motor paresis, ataxia, myelopathy, hydrocephalus, or intracranial hemorrhage.

When associated with vitreous amyloid deposits, this type of amyloidosis is known as familial oculoleptomeningeal amyloidosis (FOLMA) [Goren et al 1980, Uitti et al 1988, Garzuly et al 1996, Herrick et al 1996, Petersen et al 1997, Jin et al 2004].

Protein concentration in the cerebrospinal fluid is usually high, and gadolinium-enhanced MRI typically shows extensive enhancement of the surface of the brain, ventricles, and spinal cord in individuals with leptomeningeal amyloidosis [Goren et al 1980, Uitti et al 1988, Garzuly et al 1996, Herrick et al 1996, Brett et al 1999].

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Although meningeal biopsy is necessary to confirm amyloid deposition in the meninges, characteristic MRI findings and *TTR* gene mutations strongly suggest this pathology [Mitsuhashi et al 2004].

Other. Vitreous opacification has been reported in approximately 20% of families with various *TTR* mutations (V30M, E54K, L58R, Y114C). In one case report,vitreous opacification was the only evidence of amyloid deposit caused by the W41L mutation [Yazaki et al 2002]. Four out of 43 individuals with the V30M mutation developed vitreous amyloidosis as the first manifestation of transthyretin amyloidosis [Kawaji et al 2004].

Involvement of muscle producing a myopathic phenotype has been reported [Yamashita et al 2005].

Anemia with low erythropoietin has been reported in 25% of cases [Beirao et al 2004].

Moderate to severe renal involvement is described [Haagsma et al 2004, Lobato et al 2004].

Genotype-Phenotype Correlations

With expanding lists of mutations in the *TTR* gene, genotype-phenotype correlations have been intensively investigated, but they still remain unclear. In subsets of families with V30M, considerable variation in phenotypic manifestations and age of onset is observed. It is hypothesized that genetic modifiers and non-genetic factors contribute to the pathogenesis and progression of TTR amyloidosis [Holmgren et al 1997, Misu et al 1999, Munar-Qués et al 1999, Sobue et al 2003].

It has been clinically and experimentally demonstrated that T119M has a protective effect on amyloidogenesis in individuals who have the V30M mutation [Coelho et al 1996, Alves et al 1997, Sebastião et al 2001, Hammarström et al 2001].

Most of the more than 80 mutations in the *TTR* gene result in classic peripheral and autonomic neuropathy. But some mutations are considered to be associated with unique phenotypes of TTR amyloidosis, in which peripheral or autonomic neuropathy is clinically absent or less prominent:

- Cardiac amyloidosis is caused by D18N, V20I, P24S, E42D, A45T, T49P, H56R, I68L, Q92L, R103S, L111M, or V122I [Benson & Uemichi 1996, Nakazato 1998, Connors et al 2000, Benson 2001, Saraiva 2001, Connors et al 2003].
- Leptomeningeal amyloidosis is associated with L12P, A18G, A25T, V30G, A36P, G53E, F64S, Y69H, or Y114C [Benson & Uemichi 1996, Garzuly et al 1996, Petersen et al 1997, Nakazato 1998, Brett et al 1999, Mascalchi et al 1999, Uemichi et al 1999, Connors et al 2000, Benson 2001, Ellie et al 2001, Saraiva 2001,Ikeda et al 2002, Blevins et al 2003, Connors et al 2003, Hammarström et al 2003, Sekijima et al 2003].

The vast majority of individuals with TTR amyloidosis are heterozygous for a *TTR* mutation; however, at least 18 homozygous individuals have been reported [Munar-Qués et al 2001]. Fifteen developed symptoms after age 50 years, indicating that the dosage effect of the mutant gene does not significantly modify the clinical phenotype [Munar-Qués et al 2001, Ikeda et al 2002], although amyloid deposition may be widespread [Yoshinaga et al 2004].

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Penetrance

Since the penetrance for transthyretin amyloidosis is not 100%, an individual with a *TTR* mutation may be symptom free until late adulthood. The penetrance may vary by mutation, geographical region, or ethnic group.

It is generally accepted that the penetrance is much higher in individuals in endemic foci than outside of endemic foci [Misu et al 1999]. In Portugal, 87% of individuals with the V30M mutation develop symptoms of transthyretin amyloidosis before 40 years of age [Sousa et al 1995], but in Sweden, disease penetrance is only 2%, and some V30M homozygotes remain asymptomatic [Holmgren et al 1994].

Anticipation

Genetic anticipation is observed in families with TTR amyloid polyneuropathy from endemic areas [Drugge et al 1993, Tashima et al 1995, Yamamoto et al 1998, Soares et al 1999, Misu et al 2000]. In Japanese families with the V30M mutation, which originated from one of two endemic foci, it was reported that affected children with maternal transmission showed more profound anticipation than those with paternal transmission, especially when the children were male [Yamamoto et al 1998].

Nomenclature

The neuropathy associated with *TTR* mutations, now called TTR amyloidosis, was formerly referred to as one of the following:

- Familial amyloid polyneuropathy type I (or the Portuguese-Swedish-Japanese type)
- Familial amyloid polyneuropathy type II (or the Indiana/Swiss or Maryland/German type)

Prevalence

Well-known large foci of V30M TTR amyloidosis are present in Portugal, Sweden, and Japan. Numerous families with various mutations have also been identified in Ireland, Spain, France, Finland, Germany, and Greece. Thus, the prevalence of TTR amyloidosis varies greatly in different ethnic groups.

The frequency of TTR amyloidosis caused by the mutation V30M is estimated to be one in 538 in northern Portugal (Povoa do Varzim and Vila do Conde), where the largest cluster of individuals with TTR amyloidosis exists worldwide [Sousa et al 1995].

In Caucasians in the United States, the frequency of V30M TTR amylodosis is estimated to be one in 100,000 [Benson 2001].

The frequency of the V122I allele in the African-American population is 3.0-3.9%; most heterozygous individuals develop late-onset cardiac amyloidosis. Over 5.0% of the population in some areas of West Africa are heterozygous for this mutation. In the US, the frequency of the V122I allele in the white and Hispanic populations is 0.44 and 0.0%, respectively [Jacobson et al 1996, Jacobson et al 1997, Yamashita et al 2005].

Differential Diagnosis

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

A total of 20 amyloidogenic proteins including TTR have been identified in human amyloidoses [Buxbaum & Tagoe 2000]. Among the hereditary amyloidoses, TTR amyloidosis

is the most prevalent. Other hereditary amyloidoses are summarized in Table 4 [Benson 2001, Hund et al 2001, Benson 2005].

Table 4. Other Hereditary Amyloidoses

Type	Disease Name	Phenotype	Protein Name
Neuropathic	Apo AI amyloidosis [formerly familial amyloid polyneuropathy-III (Iowa type)]	Early • Nephropathy • Gastric ulcers • Polyneuropathy	Apolipoprotein A-I
	Gelsolin amyloidosis [formerly familial amyloid polyneuropathy-IV (Finnish-Danish type)]	• Cranial neuropathy • Corneal lattice dystrophy • Polyneuropathy • Carpal tunnel syndrome	Gelsolin
Non-neuropathic	Fibrinogen A α-associated amyloidosis	• Nephropathy • Petechiae	Fibrinogen A α
	Lysozyme-associated amyloidosis	• Nephropathy	Lysozyme
	Familial Mediterranean fever	• Nephropathy • Peritonitis • Periodic fever	Pyrin (marenostrin)
	Apo AII amyloidosis	• Nephropathy • Gastrointestinal hemorrhage	Apolipoprotein A-II
Cerebral	Alzheimer disease type 3	• Dementia	Presenilin 1
	Alzheimer disease type 4		Presenilin 2
	Alzheimer disease type 1 (Swedish, London, Florida, Flemish, Arctic, Iowa type)		Amyloid precursor protein
	Hereditary cerebral hemorrhage with amyloid (Dutch type)	• Cerebral hemorrhage	Amyloid precursor protein
	Cystatin C amyloidosis (Icelandic type)	• Cerebral hemorrhage	Cystatin C
	Familial British dementia	• Dementia • Ataxia • Spastic palsy • Cataract • Hearing loss	BRI
	Familial Danish dementia		

Non-hereditary systemic amyloidoses include immunoglobulin (AL) amyloidosis, reactive (secondary, AA) amyloidosis, and ß2-microglobulin (dialysis-associated) amyloidosis.

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Senile systemic amyloidosis (SSA) (earlier called senile cardiac amyloidosis). Senile systemic amyloidosis (SSA) results from the pathologic deposition of wild-type TTR, predominantly in the heart. Pathologic deposits are also seen in the lungs, blood vessels, and the renal medulla of kidneys [Westermark et al 2003]. SSA mainly affects the elderly, but is rarely diagnosed during life. Thus, the precise prevalence of SSA is still unknown, but the examination of autopsy samples revealed the prevalence was 22-25% in the elderly (>80 years of age) [Westermark et al 1979, Cornwell et al 1983, Westermark et al 1990]. SSA is typically asymptomatic or manifest by cardiac symptoms. Some individuals with SSA present with carpal tunnel syndrome. SSA should be distinguished from TTR amyloidosis with variant TTR or other forms of amyloidosis such as primary (AL) amyloidosis. In contrast to the rapid progression of heart failure in AL amyloidosis, SSA results in slowly progressive heart failure [Ng et al 2005]. Westermark et al (2003) have indicated that the lung may be a more reliable tissue for amyloid detection than the heart.

Other acquired and familial causes of neuropathy need to be considered (see Charcot-Marie-Tooth Hereditary Neuropathy Overview). Non-hereditary, non-amyloidotic causes of neuropathy such as chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), Crow-Fukase syndrome [POEMS (plasma cell neoplasia with polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes)], diabetic neuropathy, or Shy-Drager syndrome should be considered, particularly when family history is negative and when the disease is in the early stage.

If cardiomyopathy or CNS manifestations are prominent instead of sensorimotor or autonomic neuropathy, a wide variety of diseases should be considered. Cardiac amyloidosis should be differentiated from HFE-associated hereditary hemochromatosis, glycogen storage diseases (e.g., Pompe disease), Fabry disease, cardiac sarcoidosis, and mitochondrial cytopathy (MELAS), all of which may present with restrictive cardiomyopathy.

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

- Complete neurologic assessment including baseline nerve conduction studies
- Evaluation of the heart:
  - Echocardiogram, the most useful noninvasive test for cardiac amyloidosis, for visualization of ventricular wall thickness, ventricular septal thickness, and hyperrefractile myocardial echoes (so called "granular sparkling appearance")
  - Electrocardiogram (ECG) to show characteristic findings of cardiac amyloidosis including low voltage in the standard limb leads and QS pattern in the right precordial leads with or without conduction blocks
  - Myocardial technetium-99m-pyrophosphate scintigraphy to visualize amyloid deposition in heart [Ikeda 2004]
- Gadolinium-enhanced MRI of the brain and spinal cord to evaluate CNS amyloidosis [Mitsuhashi 2004]
- Ophthalmologic evaluation
- Evaluation of renal function

Treatment of Manifestations

- Carpal tunnel release surgery for carpal tunnel syndrome

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- Vitrectomy for vitreous involvement

Prevention of Primary Manifestations

Orthotopic liver transplantation (OLTX). The only effective therapy for the neuropathy of TTR amyloidosis is orthotopic liver transplantation (OLTX), which removes the main production site of the amyloidogenic protein. Successful OLTX results in rapid disappearance of variant TTR protein from the serum, and thus halts the progression of peripheral and/or autonomic neuropathy. It has been shown by pre- and postoperative sural nerve biopsy that myelinated nerve fibers regenerate after OLTX [Ikeda et al 1997].

Recommended clinical criteria for OLTX in individuals with TTR amyloid polyneuropathy [Takei et al 1999, Adams et al 2000] include the following:

- Age younger than 50 years
- Less than five years since the onset of the disease
- Either polyneuropathy that is restricted to the lower extremities or autonomic neuropathy alone
- No significant cardiac or renal dysfunction

As of the end of November 2005, 1146 individuals with TTR amyloid polyneuropathy, approximately 80% of whom were heterozygous for the V30M mutation, had undergone liver transplantation [Ericzon et al 2000, Ikeda et al 2003, Herlenius et al 2004, Stangou & Hawkins 2004]. The five-year survival rate was significantly higher in individuals with the V30M mutation than in those with other mutations (80% vs 57%, p=0.001) [Ericzon et al 2000, Ikeda et al 2003]. The most common causes of postoperative death were cardiovascular events (29%) and septicemia (26%) [Ikeda et al 2003].

Poor outcomes of transplanted individuals based on ten years' experience [Ikeda et al 2003] include:

- Poor nutritional condition (mean body mass index <600)
- Severe polyneuropathy (Norris score <55/81)
- Permanent urinary incontinence
- Marked postural hypotension
- A fixed pulse rate

OLTX is not effective in the non-neuropathic forms of TTR amyloidosis [i.e., cardiac amyloidosis, leptomeningeal amyloidosis, and familial oculoleptomeningeal amyloidosis (FOLMA)].

Cardiomyopathy was reported to progress after OLTX in some individuals with specific non-V30M mutations (A36P, Glu42G, S77Y) [Dubrey et al 1997, Stangou et al 1998, Yazaki et al 2000, Hornsten et al 2004]. It is presumed that amyloid cardiomyopathy may accelerate after OLTX by progressive deposition of wild-type TTR on a template of amyloid derived from variant TTR [Yazaki et al 2000, Hornsten et al 2004]. Therefore, it is critical to assess the severity of cardiac amyloidosis when considering OLTX [Coutinho et al 2004, Juneblad et al 2004].

Individuals with leptomeningeal involvement may not be candidates for liver transplantation because amyloidogenic TTR variants that cause intracranial amyloid deposits are considered to derive from the choroid plexus [Benson 1996, Herrick et al 1996].

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Vitreous opacities may also progress after OLTX, possibly as the result of *de novo* production of variant TTR in the retinal epithelium.

Note: Because liver involvement in TTR amyloidosis is minimal, the liver of an individual with TTR amyloidosis can be grafted into an individual with liver cancer or end-stage liver disease (so-called "domino" liver transplantation). Since 1995, more than 330 domino liver transplantations have been performed. Stangou et al (2005) recently reported that an individual who had received a liver graft from a V30M heterozygote with TTR amyloidosis developed systemic amyloidosis eight years after the domino liver transplantation. Also, subclinical cutaneous TTR deposits were reported in five other recipients of domino liver grafts [Sousa et al 2004].

Surveillance

Serial nerve conduction studies can be used to objectively monitor the course of the polyneuropathy.

Testing of Relatives at Risk

It is appropriate to offer molecular genetic testing to at-risk relatives if the disease-causing mutation is identified in an affected family member, so that morbidity and mortality can be reduced by early diagnosis and treatment.

If the disease-causing mutation in the family is not known, it is appropriate to offer clinical diagnostic evaluations to identify those family members who will benefit from early treatment.

Therapies Under Investigation

Strategies of potential molecular therapies for TTR-amyloidosis include the following [Saraiva 2002, Ando 2003]:

- Inhibition of synthesis of variant TTR
- Stabilization of variant TTR
- Inhibition of aggregation of amyloidogenic intermediates
- Disruption of insoluble amyloid fibrils

Drugs that stabilize TTR tetramer and prevent dissociation into monomers or drugs that disrupt TTR amyloid fibrils into amorphous materials have been designed [Saraiva 2002, Miller et al 2004, Almeida et al 2005].

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

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.

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Mode of Inheritance

Transthyretin amyloidosis is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Approximately one-third of probands with TTR amyloidosis have an affected parent [Coelho et al 1994; Reilly, Adams, Booth et al 1995; Planté-Bordeneuve & Said 2000] and about two-thirds have the disorder as the result of a *de novo* gene mutation.
- A large number of mutations in the *TTR* gene indicates that the gene is very prone to be mutated; thus, *de novo* mutations are common.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include molecular genetic testing if the disease-causing *TTR* gene mutation has been identified in the proband.

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, or late onset of the disease in the affected parent.

Sibs of a proband

- The risk to sibs depends on the genetic status of the parents.
- Sibs of an affected individual have a 50% chance of inheriting a mutation in the *TTR* gene if one parent has a mutation.
- Munar-Qués et al (2001) reported homozygous mutations in some affected individuals. In this circumstance, sibs of the proband have a 50% chance of inheriting one *TTR* mutation and a 25% chance of inheriting two *TTR* mutations.
- If the disease-causing mutation found in the proband cannot be detected in the DNA of either parent, the risk to sibs is low, but greater than that of the general population because although no instances of germline mosaicism have been reported, it remains a possibility.

Offspring of a proband

- Every child of an affected individual has a 50% risk of inheriting a mutation in the *TTR* gene.
- If the proband is homozygous for a *TTR* mutation, all offspring will inherit the mutation.

Other family members. 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.

Testing of at-risk asymptomatic adults. Testing of at-risk asymptomatic adults for TTR amyloidosis is available using the same techniques described in Molecular Genetic Testing.

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This testing is not useful in predicting age of onset, severity, type of symptoms, or rate of progression in asymptomatic individuals. When testing at-risk individuals for TTR amyloidosis, an affected family member should be tested first to confirm that the disorder in the family is actually TTR amyloidosis.

Testing for the disease-causing mutation in the absence of definite symptoms of the disease is predictive testing. At-risk symptomatic adult family members may seek testing in order to make personal decisions regarding reproduction, financial matters, and career planning. Others may have different motivations including simply the "need to know." Testing of asymptomatic at-risk adult family members usually involves pretest interviews in which the motives for requesting the test, the individual's knowledge of TTR amyloidosis, the possible impact of positive and negative test results, and neurologic status are assessed. Those seeking testing should be counseled about possible problems that they may encounter with regard to health, life, and disability insurance coverage, employment and educational discrimination, and changes in social and family interaction. Other issues to consider are implications for the at-risk status of other family members. Informed consent should be procured and records kept confidential. Individuals with a positive test result need arrangements for long term follow-up and evaluation.

Related donors for liver transplantation. In Japan, where liver transplantation from living, related donors is the generally accepted therapy of TTR amyloid polyneuropathy I and II, molecular genetic testing for asymptomatic adults is inevitably performed on family members seeking to be donors.

Testing of at-risk asymptomatic individuals during childhood. Consensus holds that individuals at risk for adult-onset disorders should not have testing during childhood in the absence of symptoms. The principal arguments against testing asymptomatic individuals during childhood are that it removes their choice to know or not know this information, it raises the possibility of stigmatization within the family and in other social settings, and it could have serious educational and career implications [Bloch & Hayden 1990, Harper & Clarke 1990]. Children who are symptomatic usually benefit from having a specific diagnosis established. (See also the National Society of Genetic Counselors statement on genetic testing of children and the American Society of Human Genetics and American College of Medical Genetics points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents).

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy. Similarly, decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made 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%. 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 10-12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

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

Requests for prenatal testing for adult-onset conditions such as TTR amyloidosis that do not affect intellect and have some treatment available are not common. Differences in perspective may exist among medical professionals and in families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) has been reported [Almeida et al 2005] and may be available for families in which the disease-causing mutation has been identified in an affected family member in a research or clinical laboratory. 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 Transthyretin Amyloidosis

Gene Symbol	Chromosomal Locus	Protein Name
TTR	18q11.2-q12.1	Transthyretin

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 Transthyretin Amyloidosis

176300	TRANSTHYRETIN; TTR

Table C. Genomic Databases for Transthyretin Amyloidosis

Gene Symbol	Entrez Gene	HGMD
TTR	7276 (MIM No. 176300)	TTR

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

Molecular Genetic Pathogenesis

The main component of amyloid is protein fibrils. In TTR amyloidosis, the fibrils are mainly composed of self-aggregated TTR protein. TTR protein is potentially amyloidogenic because of its extensive beta-sheet structure. The key factor in amyloidogenesis in TTR amyloid polyneuropathy is the stability of the TTR protein [Kelly 1998, Rochet & Lansbury 2000]. The TTR protein normally circulates in plasma as a soluble protein having a tetrameric structure. The amyloidogenic process is considered to need two steps: soluble TTR tetramers dissociate into pro-amyloidogenic monomers, which in turn polymerize into amyloid fibrils in certain tissues [Kelly 1998, Rochet & Lansbury 2000]. Pathogenic mutations in the *TTR* gene cause significant conformational change in TTR protein molecules, in turn disrupting the stability of the TTR tetramer. In other words, a tetramer containing variant TTR monomers is more easily dissociated into pro-amyloidogenic monomers than is a normal TTR tetramer [Sekijima et al 2005].

It has been demonstrated that all disease-associated TTR variants are energetically (thermodynamically and kinetically) less stable than wild-type TTR. On the other hand, suppressor mutations (T119M and R104H) are more stable than wild-type TTR. In vitro

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amyloidogenicity correlates very well with protein stability. However extremely destabilized (highly amyloidogenic in vitro) TTR variants do not induce severe systemic amyloidosis because serum concentrations of these TTR variants are very low. The low serum concentration of highly destabilized TTR variants is a result of degradation by endoplasmic reticulum (ER) quality control system (ERAD) of the hepatic cells. The most pathogenic TTR variant (L55P) exhibiting the earliest disease onset is the most destabilized variant that can be secreted at levels comparable to the wild type, barely avoiding ERAD. TTR variants that predominantly induce CNS amyloidosis are the least stable variants. The choroid plexus secretes highly destabilized TTR variants more efficiently than hepatic cells, thus, it is thought, accounting for CNS selective amyloid deposition [Sekijima et al 2003, Hammarström et al 2003, Mitsuhashi et al 2005, Sekijima et al 2005]

Normal allelic variants: The human *TTR* gene contains four exons and spans approximately 7 kb [Sasaki et al 1985, Tsuzuki et al 1985]. All exons but exon 1 consist of fewer than 200 base pairs. Exon 1 encodes a signal peptide and the first three amino acids of the mature protein. Non-pathogenic mutations or normal polymorphisms have been described in individuals of various ethnic backgrounds (A74H, H90N, P102R, R104C, T119N) [Benson & Uemichi 1996, Nakazato 1998, Benson 2001, Saraiva 2001, Connors et al 2003].

Pathologic allelic variants: To date, more than 80 point mutations and one in-frame microdeletion have been identified in exons 2-4 in the *TTR* gene in individuals with TTR amyloidosis [Benson & Uemichi 1996, Connors et al 2000, Benson 2001, Saraiva 2001, Connors et al 2003]. No mutation has been described in exon 1, which encodes amino acids 1 through 3.

The V30M mutation, found worldwide, is the most widely studied *TTR* variant and is responsible for the well-known large foci of individuals with TTR amyloid polyneuropathy in Portugal, Sweden, and Japan. Several haplotypes are associated with V30M in different ethnic groups, suggesting that multiple founders spontaneously occurred in each group [Yoshioka et al 1989; Ii & Sommer 1993; Reilly, Adams, Davis et al 1995].

V122I, present in 3.0-3.9% African-Americans and over 5.0% of the population in some areas of West Africa, is the most common amyloid-associated *TTR* variant worldwide [Jacobson et al 1996, Jacobson et al 1997, Yamashita et al 2005].

Normal gene product: The human *TTR* cDNA encodes a 127-amino acid protein with molecular mass 14 kd. TTR is a normal plasma protein synthesized predominantly by the liver. TTR is secreted into plasma as a tetrameric form (Mr = 55 kd) composed of four identical monomers; its plasma half-life is no more than 15 hours. TTR concentration in plasma normally ranges from 20 to 40 mg/dL.

TTR is considered to transport thyroxine and retinol-binding protein (RBP) coupled to vitamin A. TTR binds virtually all of serum RBP and about 15% of serum thyroxine. In the cerebrospinal fluid, TTR is required for transport of serum thyroxine across the blood-brain barrier.

The choroid plexus is the source of the cerebrospinal fluid TTR. The TTR concentration in cerebrospinal fluid ranges from ten to 40 µg/mL.

The other site of synthesis is the retina.

Abnormal gene product: It is speculated that amyloidogenic TTR variants reduce the stability of the physiologic TTR tetramer, and consequently produce a pro-amyloidogenic monomer

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more easily than normal TTR (see Molecular Genetic Pathogenesis) [Kelly 1998, Rochet & Lansbury 2000, Saraiva 2002, Sekijima et al 2005].

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.

Amyloidosis Support Group
Phone: 866-404-7539; 630-350-7538
www.amloidosissupport.com

American Liver Foundation
75 Maiden Lane, Suite 603
New York, NY 10038
Phone: 800-GO-LIVER (800-465-4837)
Fax: 212-483-8179
Email: info@liverfoundation.org
liverfoundation.org

The Neuropathy Association
P. O. Box 26226
New York, NY 10117-3422
Phone: 800-247-6968; 212-692-0662
Email: info@neuropathy.org
www.neuropathy.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

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Chapter Notes

Revision History

- 15 March 2006 (me) Comprehensive update posted to live Web site
- 2 March 2005 (cd) Revision: mutation scanning and sequencing of select exons no longer clinically available
- 5 March 2004 (ky) Revision: molecular genetic testing
- 9 January 2004 (me) Comprehensive update posted to live Web site
- 5 November 2001 (me) Review posted to live Web site
- 25 June 2001 (ky) Original submission