

TTR Gene Analysis for Transthyretin Amyloidosis: Familial Amyloid Polyneuropathy and Familial Amyloid Cardiomyopathy

Disorder also known as: Amyloid polyneuropathy, amyloid cardiomyopathy (Cardiac amyloidosis), leptomeningeal amyloidosis, hyperthyroxinemia, Familial amyloid polyneuropathy (FAP), TTR amyloid neuropathy, oculoleptomeningeal amyloidosis

Clinical Features:

Transthyretin (TTR) amyloidosis is an autosomal dominant disorder caused by the deposition of insoluble amyloid fibrils around peripheral nerves and in various tissues, including the heart muscle. Based on the predominant organ involvement, several distinct subtypes have been reported.

Familial amyloid polyneuropathy (FAP) aka TTR amyloid neuropathy is characterized by slowly progressive, peripheral sensorimotor polyneuropathy and autonomic dysfunction. Disease onset is usually in the third to fourth decade of life. Sensory neuropathy starts in the lower extremities with paresthesia, impaired pain and temperature sensation, followed by loss of motor function. Autonomic neuropathy usually manifests with orthostatic hypotension, constipation alternating with diarrhea, vomiting, impotence or hypohidrosis. Unrelated to neuropathy, other organs manifestations may include cardiomyopathy, vitreous opacities and CNS amyloidosis.

Leptomeningeal amyloidosis aka oculoleptomeningeal amyloidosis affects predominantly the central nervous system, sometimes combined with visual impairment.

Cardiac amyloidosis usually manifests in the sixth decade of life with progressive left ventricular hypertrophy and restrictive cardiomyopathy. In a subset of families with cardiac amyloidosis, peripheral neuropathy may be completely absent or very mild.

Treatment: Currently, the only effective treatment for FAP is an orthotopic liver transplant to stop production of misfolded amyloid protein. In patients with severe amyloid cardiomyopathy, a heart transplant may be necessary. Different drugs designed to prevent or alleviate accumulation of TTR amyloid protein (transthyretin amyloidosis inhibitors) are currently under investigation.¹⁻³

Inheritance Pattern/Genetics:

Autosomal dominant

Transthyretin (TTR) amyloidosis is due to pathogenic variants in the TTR gene located at chromosome 18q12.1. TTR consists of four coding exons and is predominantly expressed in the liver, the choroids plexuses of the brain and the retinal pigment epithelium of the eye, but also in the pancreas and heart. The active protein is a homotetramer that is thought to mediate the transport of thyroid hormones T3 and T4 (thyroxine), and retinol-binding protein coupled to

vitamin A. All studied disease-associated TTR variants are less stable than wild type transthyretin, indicating that a tetramer containing an abnormal TTR monomers is more easily dissociated into amyloidogenic monomers than the wild type protein.¹⁻³

Test Methods:

Using genomic DNA obtained from the submitted biological material, bi-directional sequence of the coding region (exons 1 – 4) and corresponding splice junctions of the TTR gene is obtained and analyzed. Variants identified in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

Test Sensitivity:

TTR is the only gene associated with transthyretin amyloidosis. The vast majority of individuals with transthyretin amyloidosis (forms with polyneurogenic as well as cardiomyopathy) are expected to have a variant in TTR that is detectable by DNA sequence analysis. If a variant is present in the TTR gene, sequence analysis as performed at GeneDx is expected to detect >99% of the variants identifiable by sequencing.

References:

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