Clinical features

Transthyretin gene (TTR) mutations are associated with an autosomal dominant disease leading to clinical symptoms through amyloid deposits, especially in the heart, but also in the lungs, blood vessels, and kidneys. Hereditary transthyretin amyloidosis must be suspected in adults with slowly progressive sensorimotor and/or autonomic neuropathy, cardiomegaly, conduction block, arrhythmia, anginal pain, congestive heart failure and sudden death.

The phenotype of Hereditary Transthyretin amyloidosis (ATTR) depends on the specific TTR mutation where some common mutations have been predominantly associated with cardiac involvement. The missense variant V142I is by far the most common cause of cardiac ATTR in African-Americans.

The disease usually begins with sensory neuropathy in the lower extremities with paresthesias and hypesthesias of the feet, or autonomic neuropathy (orthostatic hypotension, constipation alternating with diarrhea, attacks of nausea and vomiting, delayed gastric emptying, sexual impotence, anhidrosis, and urinary retention or incontinence). Currently, more than 150 different mutations in the gene have been described.

Most of the TTR gene mutations that cause transthyretin amyloidosis are thought to alter the structure of transthyretin, impairing its ability to bind to other transthyretin proteins and altering its normal function. For reasons that are unclear, the transthyretin protein abnormally begins to form protein deposits.

In elderly people, deposits of amyloid protein cause a condition called senile systemic amyloidosis. People with this condition do not have a mutation in the TTR gene.

The most common place for amyloidosis in people with this condition is the heart, causing slowly progressive heart failure. Other sites of amyloidosis may include the lungs, blood vessels, and kidneys. It is estimated that 10 to 25 percent of people older than 80 have senile systemic amyloidosis (Connors et al., 2016).
Differential diagnosis

A total of 35 amyloidogenic proteins including transthyretin (TTR) have been identified in human amyloidosis, and among the hereditary amyloidosis, familial TTR amyloidosis is the most prevalent. Other amyloidosis to consider in the differential diagnosis of Hereditary Transthyretin (ATTR) amyloidosis are neuropathic amyloidosis and systemic amyloidosis.

Neuropathic amyloidosis includes Gelsolin amyloidosis and Apo AI amyloidosis. Systemic amyloidosis include wild type transthyretin amyloidosis (senile systemic amyloidosis), and Immunoglobulin amyloidosis.

Diagnostic strategy

We offer the following assay selection for diagnosing TTR associated hypertrophic cardiomyopathy:

- Sequence analysis/mutation scanning of entire coding and flanking intronic regions of the gene with NGS single gene sequencing (confirmation of low quality variants and all insertions/deletions by Sanger)

- If no mutation is identified, deletion/duplication analysis will be performed using qPCR

Referral reasons

The following individuals are candidates for this particular gene testing:

- Individuals with a family history of ATTR and presentation of the most common symptoms

- Individuals without a positive family history, but with symptoms resembling this disease

- Individuals with a negative but suspected family history, in order to perform proper genetic counseling

Test utility

Sequencing and deletion/duplication testing of this gene as well as related genes should be performed in all individuals suspected for this particular phenotype. In parallel, other genes reported to be related with this clinical phenotype should also be analyzed for the presence of mutations, due to the overlap in many clinical features caused by those particular genes. Confirmation of a clinical diagnosis through genetic testing can allow for genetic counseling and may direct medical management.

Genetic counseling can provide a patient and/or family with the natural history of the condition, identify at-risk family members, provide reproductive risks as well as preconceptional options, and allow for appropriate referral for patient support and/or resources.

REFERENCES