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ATTR Epidemiology, Genetics, and Prognostic Factors

REVIEW

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ABSTRACT

Transthyretin amyloid cardiomyopathy (ATTR-CM) is an underdiagnosed disease and an underestimated cause of both heart failure and conduction abnormalities. It is characterized by pathologic accumulation of extracellular protein arising from unstable transthyretin (TTR) tetramers, which dissociate into monomers that misfold, aggregate, and form insoluble fibrils that are resistant to proteolysis. Cardiac amyloidosis appears in two distinct forms: hereditary and wild-type. There is considerable heterogeneity in the clinical presentation of ATTR, ranging from primarily cardiac, primarily neuropathic, or mixed cardiac and neuropathic disease. Pathogenic variants in the *TTR* gene that predominantly involve the heart include Val122Ile, Leu111Met, and Ile68Leu. The wild-type form of ATTR is also predominantly cardiac. Phenotypic heterogeneity is linked to differences among specific pathogenic *TTR* variants, geography, and the subtype of endemic versus nonendemic disease. Factors contributing to wild-type ATTR are largely unknown, but similar factors likely influence the penetrance of hereditary ATTR. Recognition of ATTR-CM is improving due to the increased use of cardiac scintigraphy as a noninvasive diagnostic tool, and early recognition of cardiac infiltration is crucial to optimize long-term prognosis.

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