Hereditary Transthyretin Amyloidosis and Other Neuromuscular Diseases

Authors: Sami Khella,1 Urvi Desai,2 Meghan Towne, 3 Arvind Narayana,4 Kemi Olugemo4

Affiliations: 1University of Pennsylvania, Philadelphia, PA, USA; 2Atrium Health Neurosciences Institute, Charlotte, NC, USA; 3Ambry Genetics, Aliso Viejo, CA, USA; 4Akcea Therapeutics, Boston, MA, USA

Introduction: Hereditary transthyretin amyloidosis (hATTR or ATTRv [variant]) is a progressive, fatal disease caused by mutations in the transthyretin gene (TTR) and results in multisystem dysfunction. Early diagnosis, which can be facilitated with genetic testing, is key to achieving optimal patient outcomes.

Methods: This analysis utilised data from patients enrolled in hATTR Compass, a genetic testing programme for patients in the United States and Canada suspected of having or with a family history of hATTR with polyneuropathy. Next-generation sequencing was performed using an 81-gene panel associated with inherited neuromuscular disorders.

Results: A neurology specialist referred 188 patients who tested positive for a mutation and had a negative family history of hATTR. Of the 188 patients, 14 had a TTR mutation and 174 had non-TTR mutations. The most common TTR mutation was p.V142I (57%), which is typically associated with a cardiomyopathy phenotype. The most common non-TTR mutation was in the PMP22 gene (30%); this mutation is responsible for neuropathy arising from myelination errors in peripheral neurons. Compared to those with TTR mutations, the non-TTR mutation group had lower proportions of heart disease (29% vs 2%); bilateral carpal tunnel syndrome (43% vs 3%); and sensory (86% vs 21%), motor (64% vs 17%), and autonomic (43% vs 6%) dysfunction.

Conclusion: Diagnosis of hATTR is challenging because it can present similarly to other diseases. It is critical that clinicians recognise symptoms of hATTR and refer patients for genetic testing to facilitate diagnosis and initiate disease-modifying therapy for this fatal disease.