Word limit: 2800 chars body no spaces/2800 characters,
including tables and graphs

Genotypic and Phenotypic Differences and Similarities Among Patients With Inherited Cardiovascular Diseases: Insights From a Genetic Testing Program

Andrew Keller,[1] Keyur Shah,[1] Diego Delgado,[2] Ajay Vallakati,[3] Olakunle Akinboboye,[4] Catherine Marti,[5] Jill Dolinsky,[6] Aaron Gabriel,[7] Arvind Narayana,[7] Kemi Olugemo[7]

[1]VCU Health Systems, Richmond, VA; [2]University Health Network, Toronto, ON, Canada; [3]The Ohio State University, Columbus OH; [4]Laurelton Heart Specialist PC, Rosedale, NY; [5]Piedmont Heart Institute, Athens, GA; [6]Ambry Genetics, Aliso Viego, CA; [7]Akcea Therapeutics, Boston, MA

Introduction: Hereditary transthyretin amyloidosis (hATTR/ATTRv) is a progressive, and fatal disease caused by mutations in the transthyretin gene (*TTR*). These mutations destabilize protein folding, resulting in amyloid deposits and causing multisystem dysfunction such as cardiomyopathy (CM), whose etiology may be attributed to traditional causes of cardiovascular diseases (CVDs). Genetic testing was recently added to the diagnostic armamentarium for ATTR CM.

Hypothesis: A molecular diagnostic program will help improve differential diagnosis and describe prevalence and characteristics of patients with *TTR* mutations versus patients with mutations associated with other inherited CV conditions.

Methods: Data from patients enrolled in the hATTR Compass Program, which provides confidential genetic testing to patients in the US, Canada, and Puerto Rico with possible hATTR with polyneuropathy or with a family history of hATTR,
were analyzed. DNA next-generation sequencing was performed using a panel of 92 genes associated with inherited CV conditions.

Results: A total of 978 patients under the care of cardiologists were referred for testing using this panel; 74 patients were positive for *TTR* mutations and 52 were positive for other non-*TTR* CV pathogenic mutations. The most common *TTR* mutation was p.V142I (V122I). Most patients (66.2%) with a *TTR* mutation did not have a family history of hATTR. Of patients with non-*TTR* mutations, 16 had mutations in the MYBPC3 locus, associated with CM. Patients with *TTR* mutations were older than those with non-*TTR* mutations (mean age, 67 vs 53 years). Both groups had similar proportions of heart disease (89% TTR vs 90% other CVD). Some key indicators of hATTR were more prevalent in patients with non-*TTR* versus *TTR* mutations: autonomic (21% vs 14%), motor (19% vs 12%), and gastrointestinal dysfunction (17% vs 8%, respectively); however, bilateral carpal tunnel syndrome (0% vs 26%) and sensory dysfunction (15% vs 28%) were more prevalent in patients with a *TTR* mutation. More patients with *TTR* mutations had other diagnostic tests (eg, PYP imaging, biopsy) than those with non-*TTR* mutations (34% vs 15%). A limitation of this analysis was that symptoms may have been underreported because of the simplified, voluntary nature of participation and data collection.

Word limit: 2800 chars body no spaces/2800 characters,
including tables and graphs

Conclusion: Despite newer imaging methods such as PYP imaging, hATTR is commonly undiagnosed. Because hATTR can progress rapidly, it is imperative that an accurate diagnosis be made early to institute appropriate therapy; genetic testing is key for obtaining an accurate diagnosis.