



## Case Report

# Genotype-Phenotype Correlation of a Rare Transthyretin Variant Causing Amyloidosis

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### ABSTRACT

Left ventricular hypertrophy is a common entity with a broad differential diagnosis. We present a case of a middle-aged woman with left ventricular hypertrophy and neuropathy caused by a rare transthyretin variant in the absence of a family history or regional reports of hereditary transthyretin amyloidosis. This report outlines the diagnosis and management of patients with a mixed phenotype of hereditary transthyretin amyloidosis and enriches clinical data supporting the pathogenicity of a rare variant of transthyretin.

### RÉSUMÉ

L'hypertrophie ventriculaire gauche est une entité clinique fréquente pour laquelle le diagnostic différentiel est vaste. Nous décrivons le cas d'une femme d'âge moyen présentant une hypertrophie ventriculaire gauche et une neuropathie, causées par un variant rare de la transthyréline en l'absence d'antécédents familiaux ou de cas régionaux déclarés d'amylose héréditaire à transthyréline. Le présent article décrit le diagnostic et la prise en charge des patients qui présentent un phénotype mixte d'amylose héréditaire à transthyréline, et il alimente le bassin de données cliniques sur la pathogénicité d'un variant rare de la transthyréline.

Hereditary transthyretin amyloidosis (hATTR) is an increasingly recognized cause of left ventricular hypertrophy (LVH) and heart failure (HF). The overlap in the spectrum of causes of LVH and the unknown prevalence of hATTR in many ethnic groups pose a diagnostic challenge.<sup>1-3</sup>

Although many transthyretin (*TTR*) variants implicated in hATTR are well-characterized with respect to pathogenicity and epidemiology, some variants are rare and represent gaps in

our knowledge. Different geographic regions and ethnicities may harbor such variants and enhance our knowledge of the epidemiology, classification, treatment, and screening of hATTR.<sup>3,4</sup>

We report a case of an Arab woman with a rare variant of *TTR* (c.239C>T;p.Thr80Ile) who presented with LVH, severe HF, and polyneuropathy in the absence of a family history or regional reports for hATTR. This case provides a clear genotype-phenotype correlation that supports the pathogenicity of a rare *TTR* variant and highlights the approach and controversies in diagnosing and treating hATTR associated with a mixed phenotype.

### Clinical Presentation

A 58-year-old Saudi Arabian woman was referred to our centre for further evaluation of HF. She had upper abdominal pain, anorexia, and weight loss of 15 kg over 3 years. She was

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**Ethics Statement:** The research reported has adhered to the relevant ethical guidelines.

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See page 1035 for disclosure information.

### Novel Teaching Points

- The c.239C>T;p.Thr80Ile *TTR* variant is associated with a mixed phenotype of cardiac amyloidosis, sensorimotor polyneuropathy, and bilateral carpal tunnel syndrome. This rare variant previously had incomplete phenotypic characterization in public databases, and this case enriches the clinical data to support its pathogenicity.
- The cardiomyopathy associated with the p.Thr80Ile *TTR* variant dominates the clinical presentation of ATTR and can cause advanced HF refractory to conservative therapy, highlighting the importance of early diagnosis and intervention.
- hATTR can present in older individuals in the absence of family history and in ethnicities not known for the disease.

initially investigated for gastrointestinal and hepatobiliary diseases, and she received treatment for *Helicobacter pylori* and gallstone disease. She had had insidious onset of dyspnea for at least 2 years, which was later associated with orthopnea and lower-limb edema. Her edema, orthopnea, and abdominal pain improved with diuretic therapy, but she remained dyspneic on a less-than-ordinary activity, in New York Heart Association (NYHA) functional class III. She also complained of tingling in the fingertips of both hands and in her feet. An echocardiogram at the referring hospital showed that the septal and posterior wall thickness were each 14 mm, with a normal left ventricle size.

She had a history of bilateral carpal tunnel syndrome occurring 3 years earlier. She had no history of hypertension or renal failure. A younger brother had experienced palpitations but had not received a specific diagnosis. She had no established family history for cardiomyopathy or sudden cardiac death.

### Examination

Her heart rate was 75 beats per minute, and her blood pressure was 103/55 mm Hg without orthostatic changes. Her jugular venous pressure was elevated to the angle of the jaw while sitting. Cardiac, chest, abdominal, cutaneous, and lower-extremity examination was unremarkable. Neurologic examination showed positive Tinel sign in the left wrist. The remainder of the neurologic examination was normal.

Hypertensive heart disease, aortic stenosis, athlete's heart, and myocardial edema are common causes of LVH, but these were unlikely based on the patient's presentation and initial investigations. Other possibilities were conventional hypertrophic cardiomyopathy (HCM), cardiac amyloidosis, and genetic systemic disorders. The latter group includes the following: (i) glycogen storage disease type III, which usually causes childhood hypoglycemia and short stature; (ii) mitochondrial cardiomyopathies, which present at a young age with proximal myopathy, ocular myopathy, or ataxia as in Friedrich's ataxia; (iii) lysosomal storage diseases. This latter category includes (i) Danon's disease and (ii) Pompe's disease,

both of which are associated with skeletal myopathy; (iii) mucopolysaccharidoses, which cause valvular thickening and coarsening of skin and facial features; and (iv) Fabry's disease, an X-linked disorder that can mimic conventional HCM in adults. Heterozygous female patients with Fabry's disease could still exhibit symptoms because of normal X-chromosome silencing, including hypohidrosis, hypertension, renal failure, and angiokeratomas.<sup>2</sup> Features specific to these systemic genetic disorders were absent. HCM and cardiac amyloidosis remained possible etiologies. Sensory neurologic symptoms favoured amyloidosis.

### Investigations

Complete blood cell count and renal function were normal. Her N-terminal pro-brain natriuretic peptide (NT-proBNP) level was 1866 pg/mL, and her troponin T level was 55.2 ng/L (normal < 14 ng/L). The electrocardiogram demonstrated conduction abnormalities and reduced voltages relative to the degree of LVH. (Fig. 1A). The echocardiogram demonstrated mild global left ventricular systolic dysfunction, with a left ventricular ejection fraction of 45%, severe concentric LVH, and an apex-base gradient by strain assessment (Fig. 1, B and C). These findings narrowed the differential diagnosis of her LVH to amyloid light chain (AL) and ATTR cardiomyopathy (ATTR-CM). Light chains were in the normal range. A bone scan showed grade 3 cardiac uptake for pyrophosphate (Fig. 2A). Cardiac magnetic resonance imaging demonstrated abnormally reversed gadolinium kinetics with diffused late gadolinium enhancement (Fig. 2, B and C).

An invasive hemodynamic assessment and trans-jugular right ventricular biopsy were performed after escalation of diuretic therapy. Mean right atrial pressure was 10 mm Hg; mean pulmonary capillary wedge pressure was 14 mm Hg; cardiac output was 3.02 L/min by thermodilution; and cardiac index was 1.94 L/min per m<sup>2</sup>. The cardiac biopsy samples stained for Congo red and demonstrated apple green birefringence (Fig. 2, D-F). Nerve conduction studies showed a length-dependent, axonal mixed sensorimotor polyneuropathy, with evidence of bilateral moderate median nerve entrapment at the wrist.

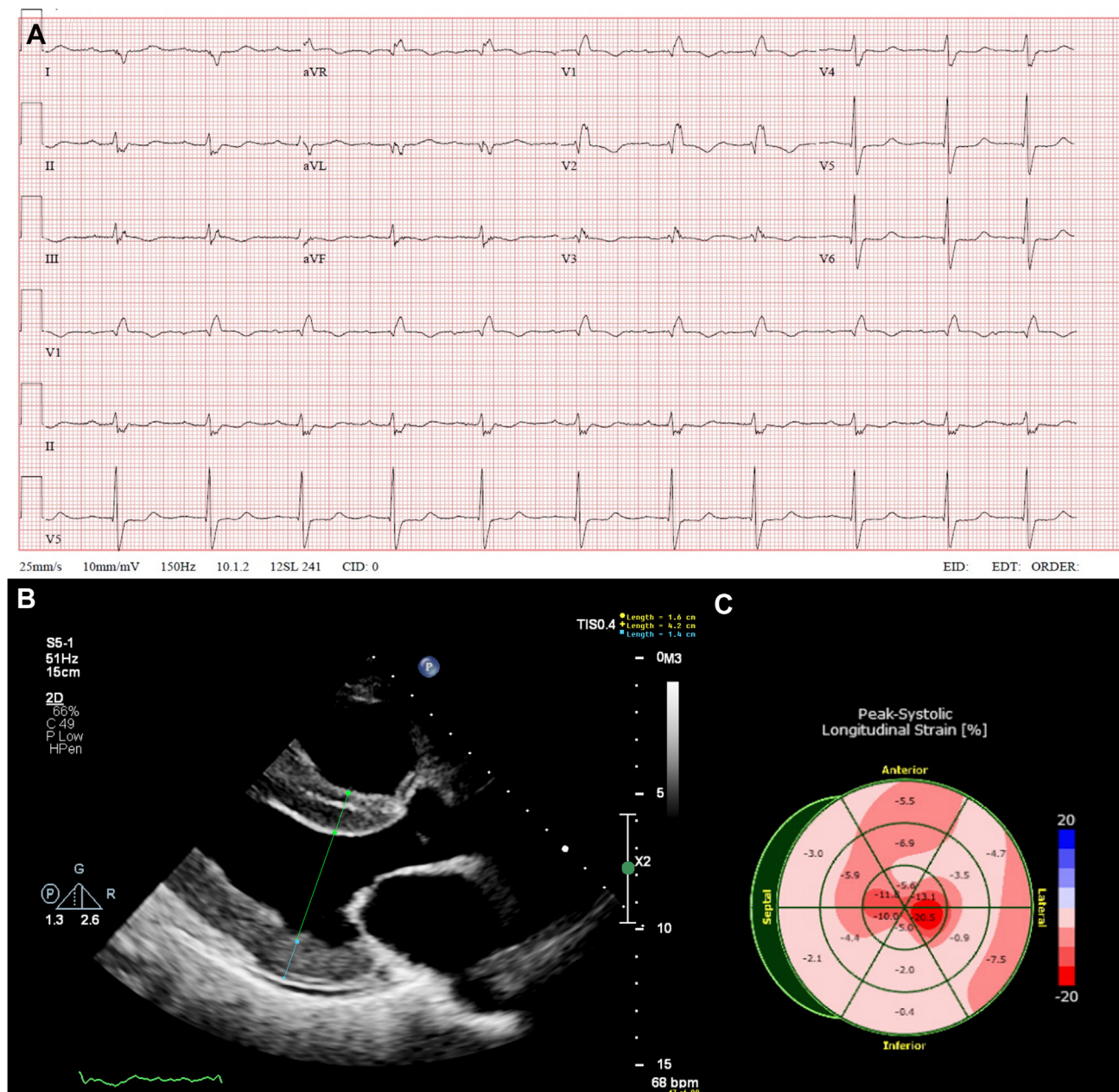
### Genetic Tests

An HCM gene panel using next-generation sequencing showed the c.239C>T;p.Thr80Ile heterozygous variant in the *TTR* gene. Targeted *TTR* gene testing using Sanger sequencing confirmed this finding.

### Management

Because the patient presented with a predominant cardiac phenotype and had NYHA functional class III symptoms, treatment of *TTR* deposition with tafamidis was deemed an appropriate initial strategy. Family members were offered predictive genetic testing and clinical screening for the disease.

After 9 months of treatment at our centre, the patient required admission for intravenous diuretics and had persistent NYHA functional class IIIB symptoms. She was referred for heart and liver transplant evaluation.

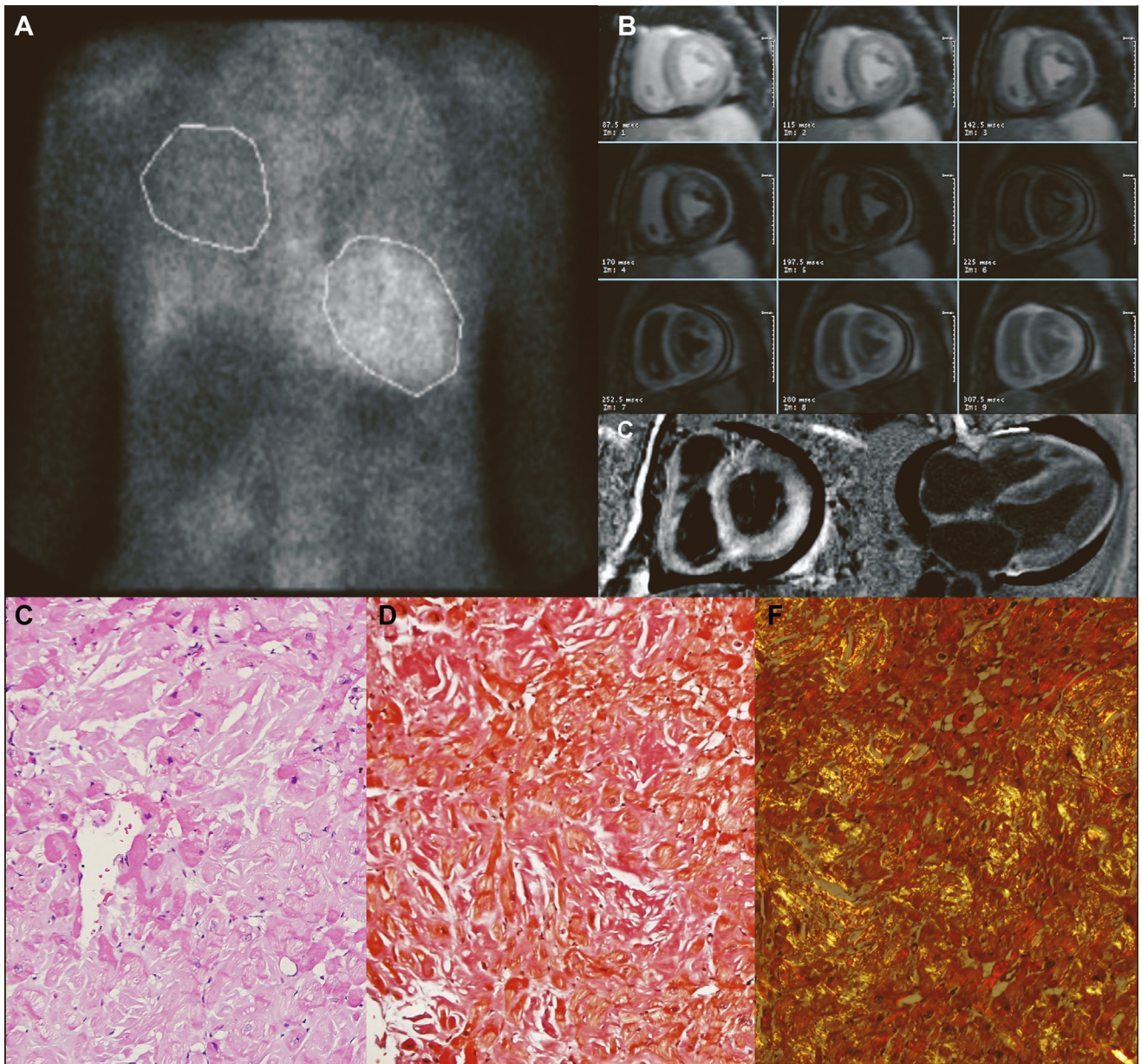


**Figure 1.** (A) A12-lead electrocardiogram demonstrates sinus rhythm with a first-degree atrioventricular block, right bundle branch block, right-axis deviation, and reduced voltages in limb leads and precordial leads relative to the degree of left ventricular hypertrophy. (B) A 2-dimensional parasternal long-axis echocardiographic view demonstrates symmetric wall thickness of 14 mm, relative wall thickness of 0.65, left ventricular mass index of 147 g/m<sup>2</sup>, consistent with severe concentric left ventricular hypertrophy. (C) A bullseye plot demonstrates global longitudinal peak strain reduction (−6.4) with relatively preserved peak systolic strain in the apical segments and significantly reduced values in the mid and basal segments

## Discussion

We present a case of LVH and severe HF from amyloidosis with cardiac, neurologic, and soft tissue involvement, supported by clinical, laboratory, imaging, and pathology data typical for ATTR. Genetic tests of the proband demonstrated that the disease was secondary to a rare variant of *TTR*. This variant previously had limited phenotypic characterization and lacked functional data.<sup>4,5</sup>

LVH is common with a broad differential diagnosis. Despite advancements in diagnostic methods, delay in diagnosing cardiac amyloidosis is a vexing problem in clinical cardiology.<sup>1</sup> This delay can be attributed partly to a low perceived prevalence of the disease and insufficient attention to its features in the early stages. In this case, bilateral carpal tunnel syndrome preceded all symptoms and was an important clinical clue to ATTR-CM.<sup>3</sup> A key electrocardiogram



**Figure 2.** (A) A nuclear bone scan demonstrates high-grade cardiac uptake for pyrophosphate, with a heart-to-contralateral ratio of 1.92 ( $> 1.5$  consistent with amyloidosis), and a semiquantitative visual score of 3/3. (B) A series of inversion time scout images demonstrate abnormally reversed gadolinium kinetics with the myocardium nulling (hypo-intense dark signal) occurring prior to the blood pool nulling. (C) Images in the short-axis and 4-chamber planes demonstrate diffuse late gadolinium enhancement in the lateral, inferior, and septal basal segments, the right ventricular septal subendocardium, and both atria. (D) Cardiac muscle with interstitial and perimyocytic deposition of pale, finely fibrillar eosinophilic material (hematoxylin and eosin, original magnification  $\times 200$ ). (E, F) Congo red stain demonstrates apple green birefringence under polarized light microscopy (original magnification  $\times 200$ ), consistent with amyloidosis.

feature that distinguished cardiac amyloidosis from other causes of LVH was the presence of relatively low voltages for the degree of LVH. The presence of conduction abnormalities and an apex-base strain gradient was suggestive of cardiac amyloidosis.<sup>3</sup> Although amyloid light chain and hATTR could have been implicated in our patient because of her age and a history of neuropathy, the combination of normal light chains and high-grade cardiac uptake of pyrophosphate was highly specific for ATTR.<sup>3</sup> A positive gene test supported the diagnosis of hATTR.

Practice guidelines no longer require histologic proof for the routine diagnosis of ATTR because noninvasive tests can be diagnostic. An endomyocardial biopsy therefore is primarily indicated when results of bone scintigraphy are equivocal amid an ongoing suspicion for ATTR-CM.<sup>3</sup> However, high-grade cardiac uptake on bone scintigraphy in conditions other than ATTR, including a few recently reported cases of HCM, suggests that the range of indications for endomyocardial biopsy could be broader than is currently proposed.<sup>6</sup> Tissue sampling provides a definitive diagnosis for

reporting purposes and the opportunity for proteomic analysis if required. Cardiac magnetic resonance imaging and endomyocardial biopsy were therefore performed to complete the phenotypic picture and dispel any ambiguity with respect to the diagnosis. We pursued a cardiac biopsy as opposed to the fat pad because an invasive hemodynamic assessment was required, and the yield and safety level of cardiac biopsy in amyloidosis are high.<sup>3</sup>

Hereditary ATTR is an autosomal dominant disease with varying age of onset, ethnic clustering, and a clinical spectrum that includes cardiomyopathy, peripheral neuropathy, central nervous system selective syndromes, soft tissue infiltration causing nerve entrapment, nephropathy, and ocular disease.<sup>3,7</sup> The phenotype of hATTR is determined by its genotype, among other factors that affect disease penetrance and expression. The p.Thr80Ile *TTR* variant identified in our case was reported in the Mutations in Hereditary Amyloidosis database as being amyloidogenic based on a single unpublished case.<sup>8</sup> The variant was interpreted in the ClinVar genomics database as being likely pathogenic or pathogenic, based on interpretations of the limited reports submitted for this variant.<sup>5</sup> A large regional study exploring the prevalence of established and candidate variants of *TTR* in 13,906 unrelated Saudi Arabian individuals using data mining identified 2 subjects with c.239C>T;p.Thr80Ile *TTR*, corresponding to an allele frequency of 0.00007191. The clinical manifestations of these subjects were not known or reported.<sup>4</sup>

A closely related missense pathogenic variant (c.238A>G;p.Thr80Ala) was primarily associated with polyneuropathy and frequently cardiomyopathy, further supporting the clinical significance of the p.Thr80 amino acid residue.<sup>5</sup> Computational algorithms have predicted the potential of both p.Thr80Ala and p.Thr80Ile to cause disease.<sup>5</sup> One ClinVar case provided clinical data: HF and polyneuropathy associated with compound heterozygous c.239C>T;p.Thr80Ile and c.424G>A;p.Val142Ile *TTR* variants. Because the p.Val142Ile *TTR* variant is pathogenic, the isolated significance of the p.Thr80Ile *TTR* variant could not be fully ascertained.<sup>5</sup> Our patient had only the p.Thr80Ile *TTR* variant and demonstrated predominant cardiac involvement resulting in severe HF. Nevertheless, variability in the phenotypic spectrum among carriers of this variant is possible because factors beyond the *TTR* gene could influence disease expression.<sup>9</sup>

Tafamidis, a kinetic stabilizer of TTR, is the only approved therapy for ATTR-CM. It was shown to reduce the progression of ATTR-CM and improve survival when compared with placebo. Tafamidis was less effective in subjects with advanced HF symptoms, highlighting the importance of early diagnosis. Because only 24% of patients in the pivotal trial of tafamidis had hATTR, variability in its effectiveness among specific variants cannot be entirely excluded.<sup>3</sup>

Patisiran and inotersen are ribonucleic acid silencing (RNAs) agents that were effective in halting and possibly regressing symptoms in patients with hereditary polyneuropathy.<sup>3</sup> In a prespecified analysis of the pivotal trial of patisiran, the subset of patients with hereditary polyneuropathy who had cardiomyopathy and were randomized to receive patisiran showed improvement in cardiac indices and HF biomarkers, and on post-hoc analysis experienced better clinical outcomes.<sup>3</sup> These results raise the possibility that RNAs might be more effective and better suited for patients

across the severity spectrum of HF, compared with tafamidis. Ongoing clinical event-driven trials of RNAs should provide more definitive answers.<sup>3</sup>

In conclusion, we report a case of LVH due to amyloidosis caused by a rare variant of hATTR. This case highlights the importance of a careful and timely evaluation for the various etiologies of LVH, and consideration of genetic causes, regardless of age, family history, or prevalence in a given ethnic group. The clear phenotypic characterization in this case supplements the existing body of evidence supporting the pathogenicity of a rare variant. Individuals identified with this variant warrant screening for cardiac and neurologic disease, and they could benefit from genetic counseling and therapeutic intervention if the disease is identified in its early stages.

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## Disclosures

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