JACC: CASE REPORTS VOL. 29, 2024

CASE REPORT

CLINICAL CASE SERIES

ATTR Gene Variants in HCM

Anthony J. Kanelidis, MD, Jeremy A. Slivnick, MD, Rachel Campagna, MS, CGC, Bryan Smith, MD, Sara Kalantari, MD, Nitasha Sarswat, MD, Gene Kim, MD

ABSTRACT

Hypertrophic cardiomyopathy is the most common inherited cardiomyopathy, with a prevalence of 1:200 to 1:500. Cardiac amyloidosis, another cardiomyopathy caused by myocardial deposition of abnormally folded TTR protein, can be acquired or hereditary. The presence of pathogenic TTR gene variants in patients with phenotypic HCM is an underrecognized and clinically important entity. (J Am Coll Cardiol Case Rep 2024;29:102236) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiomyopathy, with a prevalence of 1:200 to 1:500, that requires a nuanced approach for diagnosis, combining clinical evaluation, cardiac imaging, and often genetic testing.[1] Most genetic causes of HCM are due to changes in sarcomeric genes, particularly cardiac myosin binding protein C (*MYBPC3*) and myosin heavy chain (*MYH7*). HCM is a diagnosis of exclusion and must be differentiated from other cardiomyopathies with left ventricular (LV) hypertrophy such as hypertensive heart disease, valvular disease, transthyretin (TTR) cardiac amyloidosis (ATTR-CA), and storage diseases.[1] ATTR-CA, in particular, is an increasingly recognized cause of heart failure triggered by myocardial deposition of abnormally folded TTR protein that can be acquired or occur in the presence of a pathogenic *TTR* variants (ATTRv).[2] Certain *TTR* variants, such as the Val142Ile variant, appear to be quite common, with a prevalence as high as 3% to 4% in Black adults.[3] Yet, despite the relatively high prevalence of both disorders, the concept of potential overlap between HCM and ATTRv-CA remains poorly understood.

LEARNING OBJECTIVES

- To recognize the presence of pathogenic *TTR* gene variants in hypertrophic cardiomyopathy with genetic testing.
- To be able to differentiate hypertrophic cardiomyopathy from transthyretin cardiac amyloidosis with multimodality imaging in the presence of pathogenic *TTR* gene variants and rule out concomitant disease.

We performed a retrospective medical record review of all patients with confirmed phenotypic HCM referred for genetic testing at our institution between 2008 and 2023. Phenotypic HCM was defined according to guidelines as the presence of asymmetric LV hypertrophy unexplained by alternative cardiac, systemic, or metabolic causes.[1] All genetic testing was performed for clinical purposes after a diagnosis of HCM was made by the patients' cardiologist in conjunction with counseling by a certified genetic counselor. As testing was completed in a clinical setting, panel testing of 30 to 100 genes was ordered based on patients' insurance eligibility criteria and availability of sponsored testing. Informed consent for genetic testing was obtained and documented in

From the University of Chicago Medicine, Chicago, Illinois, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received July 24, 2023; revised manuscript received January 8, 2024, accepted January 12, 2024.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2024.102236

ABBREVIATIONS AND ACRONYMS

ATTR-CA = transthyretin cardiac amyloidosis

ATTRv = pathogenic variant transthyretin cardiac amyloidosis

CMR = cardiac magnetic resonance imaging

HCM = hypertrophic cardiomyopathy

ICD = implantable cardiac defibrillator

LGE = late gadolinium enhancement

LV = left ventricular

MYBPC3 = cardiac myosin binding protein C

MYH7 = myosin heavy chain

NSVT = nonsustained ventricular tachycardia

Tc-PyP = technetium pyrophosphate scintigraphy

TTR = transthyretin

the patients' medical records, including additional informed consent for sponsored testing if selected. Buccal or saliva samples were collected at the time of consent and sent to a CAP/CLIA-certified lab for analysis and retention based on laboratory policies. Within our cohort, the prevalence of both phenotypic HCM and *TTR* Val142Ile variant was 4.7%. A description of clinical, phenotypic, and cardiac imaging findings for the 4 patients are summarized in **Figure 1**. This study was approved by the institutional review board, who agreed to waive informed consent.

CASE 1

Patient 1 is a 34-year-old African American man with a history of mid-ventricular phenotypic HCM and found to have a Val142Ile variant. He was diagnosed at age 16 years and had an implantable cardiac defibrillator (ICD) implanted in his 20s due to nonsustained ventricular tachycardia (NSVT). A cardiac magnetic resonance imaging (CMR) before device implantation showed severe, asymmetric septal hypertrophy with maximal wall thickness of 30 mm and an apical aneurysm. Late gadolinium enhancement (LGE) imaging demonstrated striking mid-myocardial LGE involving the right ventricular insertion points as well as transmural LGE within the apical aneurysm in a pattern typical of HCM with an estimated scar burden of 16%.[4] Native T1 and gadolinium kinetics were normal, suggesting against cardiac amyloidosis in light of the *TTR* Val142Ile variant. A technetium pyrophosphate scan (Tc-PyP) was obtained to assess for evidence of ATTR-CA, which was negative for myocardial involvement. There were no reported additional features associated with systemic involvement of TTR protein deposition, including neuropathy, carpal tunnel syndrome, spinal stenosis, or autonomic dysfunction to date.

CASE 2

Patient 2 is a 65-year-old African American woman with newly diagnosed basal septal phenotypic HCM discovered after episodes of NSVT for which an ICD was placed. Her CMR pre-ICD implantation showed asymmetric basal septal hypertrophy (17 mm) with diffuse, mid-myocardial LGE involving the septum corresponding to the regions of greatest hypertrophy, suggestive of HCM, with an estimated LGE burden of 20%. Precontrast T1 relaxation times were minimally elevated at 1,100 ms (normal <1,100 ms). In addition to the *TTR* Val142Ile variant, she was also noted to have a variant of uncertain significance in *MYBPC3* (c.505G>A; p.Gly169Ser). This *MYBPC3* variant was highly suspicious and met multiple pathogenic American College of Medical Genetics and Genomics criteria. It was also studied using a minigene assay and shown to impact mRNA splicing leading to the loss of protein expression, a well-described mechanism of HCM.[5] A Tc-PyP scan was negative, and she did not report any signs or symptoms related to amyloidosis.

CASE 3

Patient 3 is a 57-year-old African American woman with a history of basal septal phenotype HCM diagnosed at age 21 years due to the detection of a heart murmur. Her CMR demonstrated asymmetric septal hypertrophy (maximum wall thickness 19 mm) with systolic anterior motion of the mitral valve and moderate mitral regurgitation. Precontrast T1 relaxation times were mildly elevated at 1,119 ms (normal <1,100 ms). There was prominent mid-myocardial LGE involving the basal septum and both right ventricular insertion points corresponding to the regions of greatest hypertrophy, a pattern typical of HCM (estimated LGE burden 10%). An ICD was placed due to detection of NSVT. Her genetic testing had revealed multiple pathogenic variants including *MYBPC3* (c.3286G>T; p.Glu1096*) and *PTPN11* (c.844A>G; p.Ile282Val), along with the *TTR* Val142Ile variant. She did not report any signs or symptoms of amyloidosis, and a Tc-PyP scan was negative.

CASE 4

Patient 4 is an 18-year-old African American man with a new diagnosis of apical phenotype HCM that was discovered after a presyncopal episode while playing basketball. An abnormal electrocardiogram led to a transthoracic echocardiogram, which revealed concentric LV hypertrophy. CMR demonstrated apical hypertrophy (maximum wall thickness 13 mm) with no LGE. Family history was positive for an uncle with a diagnosis of HCM. Genetic testing revealed a *TTR* Val142Ile variant. The patient reports no signs or symptoms of amyloidosis, and Tc-PyP scan is pending.

DISCUSSION

In our cohort of patients with phenotypic HCM undergoing genetic testing, the overall prevalence of

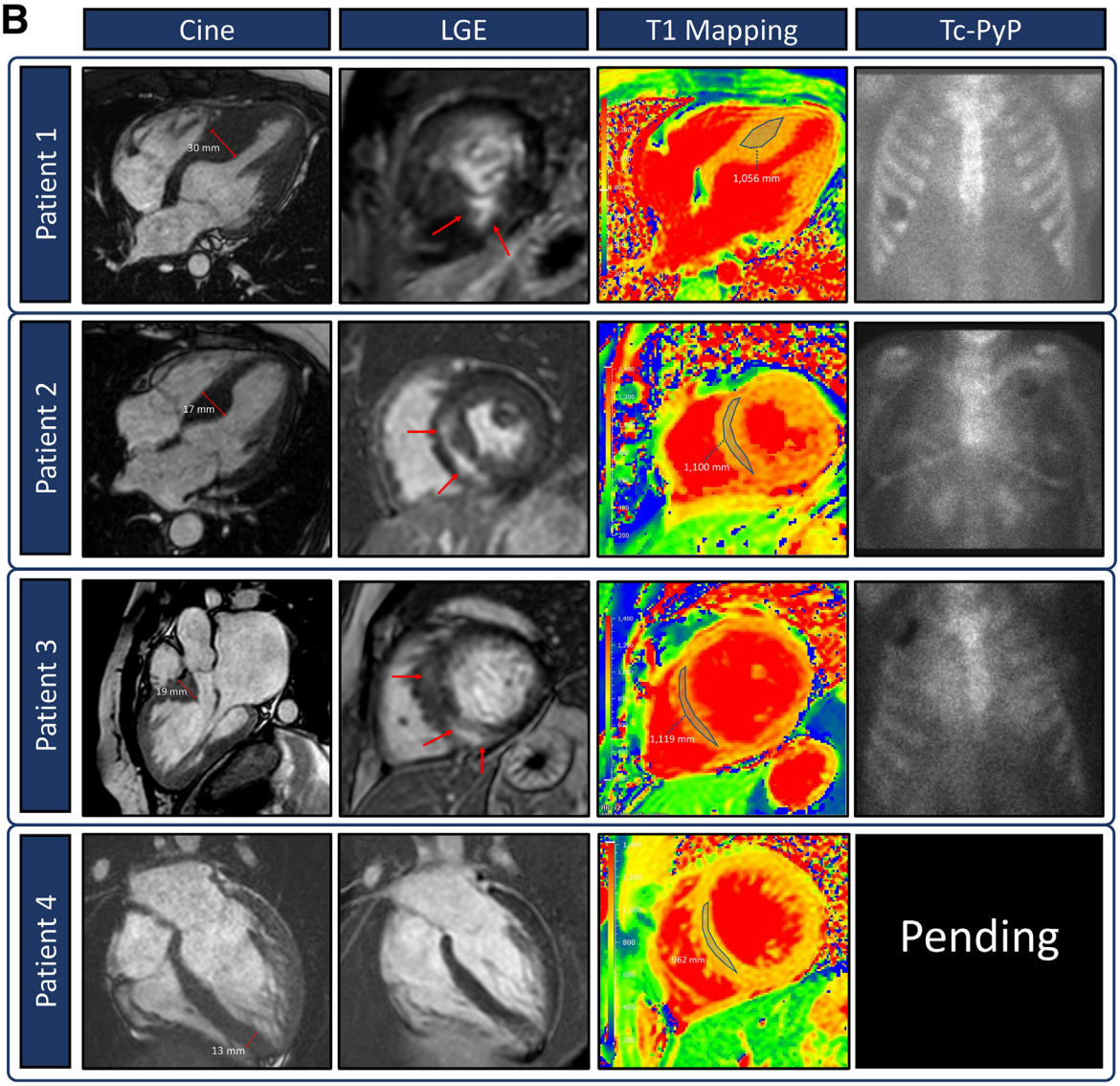
FIGURE 1 **Case Series of 4 Patients With Phenotypic HCM and Val142Ile *TTR* Variants**

A description of Val142Ile HCM patients within the cohort.

Patient	Age at Diagnosis (years)	Genetic Testing	HCM Phenotype	LGE Pattern	LGE Burden	Rhythm Monitoring	Tc-PyP Grade
Patient 1	34	Val142Ile	Mid-ventricular	Non-ischemic (mid-myocardial)	16%	NSVT	Grade 0
Patient 2	65	Val142Ile	Basal Septal	Non-ischemic (mid-myocardial)	20%	NSVT	Grade 0
Patient 3	58	MYBPC3, Val142Ile	Basal Septal	Non-ischemic (mid-myocardial)	10%	NSVT	Grade 0
Patient 4	18	Val142Ile	Apical	N/A	None	Pending	Pending

HCM, hypertrophic cardiomyopathy; LGE, late gadolinium enhancement; Tc-PyP; technetium pyrophosphate.

B



(A) Description of patients including age, phenotypic pattern on cardiac magnetic resonance imaging, late gadolinium enhancement (LGE) pattern, LGE burden, rhythm monitoring, and technetium pyrophosphate scintigraphy (Tc-PYP) scan grade is shown. (B) Additionally, representative images of each patient's cardiac magnetic resonance imaging and Tc-PYP scan are shown. NSVT = nonsustained ventricular tachycardia; TTR = transthyretin.

concomitant *TTR* Val142Ile variant was 4.7%. Although this overlap is underrecognized, it is not altogether surprising given the relatively high prevalence of both disorders in the general population.[3] This issue is likely of particular concern in the Black population where the prevalence of the *TTR* Val142Ile variant is highest.[3] Accordingly, all 4 patients with *TTR* Val142Ile variants in our cohort were Black. Conversely, in an observational study of patients with HCM out of London, United Kingdom, the prevalence of concomitant pathogenic *TTR* variants were much lower at <1%; this discrepancy is likely explained by an overall lower prevalence of Black patients in their study as compared with ours (11% vs 39%).[6] Further population studies are ideally needed to better establish the true prevalence of ATTRv in patients with phenotypic HCM.

Current guidelines for ATTR-CA discuss clinical monitoring for those identified to have asymptomatic ATTRv on family member screening, which includes repeat clinical testing every three to five years.[7,8] Of note, these recommendations are based on expert opinion and formal screening intervals still need to be established. Also, they do not address screening for ATTRv carriers who have a pre-existing cardiovascular phenotype such as HCM. Given the potential morbidity and mortality associated with concomitant ATTR-CA and HCM, we recommend that these patients be systematically screened for myocardial ATTR involvement, which may involve more frequent monitoring. There may be a synergistic risk of atrial and ventricular arrhythmias, as well as diastolic and systolic dysfunction, given the deposition of amyloid fibrils in a background of myocardial disarray when concomitant ATTR-CA and HCM exists.

Initial screening would include a Tc-PyP to rule out concomitant ATTR-CA; if uncertainty exists, it would be reasonable to pursue an endomyocardial biopsy. At our institution, we recommend annual clinic follow-up to assess for cardiac symptoms, transthoracic echocardiography with strain or CMR every 2 years, and a Tc-PYP scan every 3 to 5 years beginning 10 years before the age of the proband (if one exists) or expected age of onset based on the identified variant. These recommendations are adapted from recent consensus documents regarding optimal screening intervals for ATTR variant carriers.[7,8]

There are no guidelines to address treatment for coexistent HCM and ATTR-CA, but it would be reasonable to start a TTR stabilizer and/or TTR silencer for treatment of concomitant ATTR-CA. This may mitigate progression of heart failure. Thus, systematic screening and early recognition of concomitant disease is important to promptly start treatment and avoid progression of disease.

CONCLUSION

The presence of pathogenic *TTR* gene variants in patients with phenotypic HCM is an underrecognized and clinically important entity. These patients require a tailored approach in the initial diagnosis, as well as ongoing surveillance for ATTR deposition, that integrates genetic testing, cardiac imaging, and when necessary, tissue biopsy. Ongoing, long-term longitudinal assessment for both the development and progression of cardiac amyloidosis is warranted.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Gene Kim, Advanced Heart Failure and Cardiac Transplantation, Section of Cardiology, University of Chicago, 5841 South Maryland Street, A621, Chicago, Illinois 60637, USA. E-mail: gkim1@bsd.uchicago.edu.

REFERENCES

1. Ommen SR, Mital S, Burke MA, et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2020;76(25):3022-3055. https://doi.org/10.1016/j.jacc.2020.08.044

2. Ruberg FL, Grogan M, Hanna M, et al. Transthyretin amyloid cardiomyopathy: JACC state-of-the-art review. *J Am Coll Cardiol*. 2019;73(22):2872-2891. https://doi.org/10.1016/j.jacc.2019.04.003

3. Parcha V, Malla G, Irvin MR, et al. Association of transthyretin val122ile variant with incident heart failure among black individuals. *JAMA*. 2022;327(14):1368-1378. https://doi.org/10.1001/jama.2022.2896

4. Chan RH, Maron BJ, Olivotto I, et al. Prognostic value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy. *Circulation*. 2014;130(6):484-495. https://doi.org/10.1161/CIRCULATIONAHA.113.007094

5. Suay-Corredera C, Pricolo MR, Herrero-Galan E, et al. Protein haploinsufficiency drivers identify MYBPC3 variants that cause hypertrophic cardiomyopathy. *J Biol Chem*. 2021;297(1):100854. https://doi.org/10.1016/j.jbc.2021.100854

6. Lopes LR, Futema M, Akhtar MM, et al. Prevalence of TTR variants detected by whole-exome sequencing in hypertrophic cardiomyopathy. *Amyloid*. 2019;26(4):243-247. https://doi.org/10.1080/13506129.2019.1665996

7. Conceição I, Damy T, Romero M, et al. Early diagnosis of ATTR amyloidosis through targeted follow-up of identified carriers of TTR gene mutations. *Amyloid*. 2019;26(1):3-9. https://doi.org/10.1080/13506129.2018.1556156

8. Kittleson MM, Ruberg FL, Ambardekar AV, et al. 2023 ACC expert consensus decision pathway on comprehensive multidisciplinary care for the patient with cardiac amyloidosis: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2023;81(11):1076-1126. https://doi.org/10.1016/j.jacc.2022.11.022

KEY WORDS **cardiac amyloidosis, genetics, hypertrophic cardiomyopathy, infiltrative cardiomyopathy, *TTR* gene**