Journal of the American Heart Association

ORIGINAL RESEARCH

Clinical Penetrance of the Transthyretin V122I Variant in Older Black Patients With Heart Failure: The SCAN-MP (Screening for Cardiac Amyloidosis With Nuclear Imaging in Minority Populations) Study

Avni Madhani, BA; Natalia Sabogal, BS; Daniel Massillon, BA; Ludwine D. Paul, MSN, ACNP-BC, AACC; Carlos Rodriguez, MD; Denise Fine, MS; Stephen Helmke, RDCS; Morgan Winburn, RDCS, MS; Damian Kurian, MD; Farbod Raiszadeh, MD, PhD; Sergio Teruya, MD; Elizabeth Cohn, PhD; Andrew J. Einstein, MD, PhD; Edward J. Miller, MD, PhD; Lawreen H. Connors, PhD; Mathew S. Maurer, MD; Frederick L. Ruberg, MD

BACKGROUND: Transthyretin amyloid cardiomyopathy (ATTR-CM) is an underdiagnosed cause of heart failure (HF) among patients ≥60 years of age. Although the V122I (valine to isoleucine substitution at position 122 of the transthyretin protein) variant associated with hereditary ATTR-CM is present in 3.4% of self-identified Black individuals in the United States (or 1.5 million people), the phenotypic penetrance is not known.

METHODS AND RESULTS: The SCAN-MP (Screening for Cardiac Amyloidosis With Nuclear Imaging in Minority Populations) study is a currently accruing prospective multisite study designed to determine the prevalence of ATTR-CM using technetium-99m-pyrophosphate imaging in older (≥60 years of age) self-identified Black and Hispanic individuals with HF. Calculations of the penetrance and prevalence of the V122I allele, along with analyses of functional, biochemical, and echocardiographic parameters, were performed for the first 278 Black participants in SCAN-MP. The prevalence of ATTR-CM was 6.8% (95% CI, 4.2–10.5; n=19 cases), of whom 63% were ATTR wild-type. The prevalence of V122I was 6.5% (n=18 carriers), of whom 7 had ATTR-CM, yielding a phenotypic penetrance of 39% (95% CI, 17–64). V122I carriers with ATTR-CM evidenced more advanced HF than carriers without ATTR-CM. Prealbumin concentration was lowest among V122I carriers with ATTR-CM (12.9 mg/dL) versus carriers without ATTR-CM (21.0 mg/dL) and HF controls (25.0 mg/dL, $P<0.0001$).

CONCLUSIONS: Among older Black individuals with HF and increased left ventricular wall thickness, of those with ATTR-CM, 63% had wild-type, and of those with V122I, the phenotypic penetrance of ATTR-CM was 39% (95% CI, 17–64), suggesting that genotype alone is insufficient for diagnosis. Prealbumin concentration may be useful to identify V122I carriers with ATTR-CM.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03812172.

Key Words: amyloid ■ biomarkers ■ cardiomyopathy ■ genetics ■ heart failure

See Editorial by Leedy et al.

Correspondence to: Frederick L. Ruberg, MD, Section of Cardiovascular Medicine, Boston Medical Center, 72 E Concord Street, Boston, MA 02118. Email: frruberg@bu.edu

This article was sent to Sula Mazimba, MD, MPH, Associate Editor, for review by expert referees, editorial decision, and final disposition.

For Sources of Funding and Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- We describe the prevalence and penetrance of the V122I (valine to isoleucine substitution at position 122 of the transthyretin protein) variant in a prospectively recruited cohort of older, self-identified Black patients with heart failure and increased left ventricular wall thickness using sensitive nuclear imaging.
- We identified that biochemical, functional, and echocardiographic parameters are indicative of more advanced heart failure in V122I carriers with transthyretin amyloid cardiomyopathy (ATTR-CM) when compared with V122I carriers without ATTR-CM.
- Lower prealbumin concentration, which suggests dissociation of the transthyretin protein, was observed before clinically evident cardiac amyloidosis in V122I carriers.

What Are the Clinical Implications?

- The availability of effective therapies for ATTR-CM necessitates early identification and genotyping of individuals to facilitate the optimal treatment choice.
- Our data suggest that among Black individuals with heart failure, determination of genotype alone is insufficient to infer the presence of ATTR-CM, because clinical penetrance was incomplete and additional cases of ATTR wild-type (normal genotype) were identified.
- Low prealbumin concentration can potentially be useful to increase suspicion of V122I ATTR-CM among variant carriers with heart failure.

Nonstandard Abbreviations and Acronyms

6MWD	6-minute walk distance
ATTR-CM	transthyretin amyloid cardiomyopathy
PYP	technetium-99m-pyrophosphate
SCAN-MP	Screening for Cardiac Amyloidosis With Nuclear Imaging in Minority Populations
TTR	transthyretin or prealbumin protein
V122I	valine to isoleucine substitution at position 122 of the transthyretin protein

Transthyretin amyloid cardiomyopathy (ATTR-CM) is caused by the misfolding and myocardial deposition of the TTR (transthyretin or prealbumin) protein.[1] ATTR-CM is an underdiagnosed cause of heart failure (HF) among older individuals and occurs in the context of both variant and wild-type *TTR* genetic sequences.[1] A single nucleotide polymorphism that results in substitution of valine for isoleucine at position 122 of the protein structure (Val122Ile, V122I, or pV142I) has been reproducibly demonstrated in approximately 3.4% of Black individuals in the United States through different population studies, yielding an estimated 1.5 million carriers. V122I is the most common cause of hereditary ATTR-CM.[1] The V122I allele is hypothesized to have a West African founder and was first identified in a Black man found to have cardiac amyloidosis in 1988.[2,3]

Although evidence strongly suggests that inheritance of the V122I allele increases the risk for incident HF,[4] there is vast discordance between the number of estimated carriers and recognized cases of ATTR-CM. A broad range of estimates of V122I penetrance exists, with previous estimates being as low as 7% based on echocardiography to as high as 100% based on autopsy/pathology in Black individuals >65 years of age.[5,6] The lack of consensus results from limited methods for disease ascertainment and varying penetrance of the allele with sex and increasing age.[1] Previous noninvasive testing estimates relied on retrospective analyses using insensitive diagnostic criteria.[5,6] Accordingly, the primary goal of this study was to determine the clinical penetrance of the V122I variant using contemporary noninvasive nuclear imaging in an interim analysis comprising 278 older, self-identified Black individuals with HF drawn from a prospectively recruited cohort as a part of the SCAN-MP (Screening for Cardiac Amyloidosis With Nuclear Imaging in Minority Populations) study. Given the paucity of granular biochemical, functional, and echocardiographic data from V122I carriers, we also sought to characterize differences between V122I carriers with ATTR-CM, V122I carriers without ATTR-CM, and controls with HF without ATTR-CM so as to identify clinically actionable features.

METHODS

SCAN-MP Overview

SCAN-MP (NCT03812172) is a National Institutes of Health/National, Heart, Lung, and Blood Institute–funded (R01 HL139671), currently accruing, multisite cohort study that includes Boston Medical Center/Boston University, Columbia University Irving Medical Center, Harlem Hospital, and Yale New Haven Hospital (M.S.M. and F.L.R. overall principal investigators). The primary aims of SCAN-MP are to determine the prevalence of ATTR-CM using nuclear imaging (technetium-99m-pyrophosphate [PYP]) in older (≥60 years of age), self-identified Black and Caribbean Hispanic individuals with HF and to improve knowledge of genotype–phenotype associations, especially

for V122I ATTR-CM. The study began in May 2019 with expected conclusion in March 2024 and a target recruitment of 800 participants, of whom 600 will be self-identified as Black race. This interim analysis of SCAN-MP included all self-identified Black participants who enrolled in SCAN-MP between September 20, 2019 and April 6, 2022. The Western Institutional Review Board, Boston Medical Center Institutional Review Board, and Columbia University Irving Medical Center Institutional Review Board approved SCAN-MP. Written informed consent was obtained from all participants. The data that support the findings of this study are available from the corresponding author upon reasonable request. In addition, at the conclusion of the SCAN-MP study, anonymized data and materials will be made publicly available at a National, Heart, Lung, and Blood Institute–supported repository.

SCAN-MP Inclusion and Exclusion Criteria

Participants included in the SCAN-MP study were Black or Hispanic of Caribbean origin and were ≥60 years of age. They had a diagnosis of HF by either modified criteria used by Rich et al[7] or National Health and Nutrition Examination Survey heart failure criteria with a score of ≥3,[8] had a left ventricular septal or inferolateral wall thickness ≥12 mm, and had an ejection fraction >30%. Because the study was designed to assess HF caused by ATTR-CM, patients with primary light chain amyloidosis or secondary AA amyloidosis (attributable to serum amyloid A protein) and patients with HF caused by severe left-sided valve disease or ischemic heart disease as determined by the investigators were excluded. Patients who were expected to survive <1 year due to a malignancy or nonamyloid disease were also excluded, because the study design included a 6- and 12-month follow-up. Due to the table weight limit of the cameras used for PYP imaging, weight >350 pounds precluded study participation. Additional key exclusion criteria were prior liver or heart transplantation, the presence of a ventricular assist device (or expectation of a device in 6 months from prospective enrollment), disabling dementia or other mental or behavioral disease, expected use of continuous inotropic therapy in 6 months, high risk for nonadherence determined during screening, or chronic kidney disease with estimated glomerular filtration rate <15 mL/min per 1.73 m^2. Participants could not have functional impairment from stroke, injury, or another medical disorder that prevented them from taking part in the study procedures.

SCAN-MP Study Procedures

Data collection for SCAN-MP participants included a baseline visit, a 6-month follow up, and a 12-month follow up. At the baseline visit, medical history and medical inventory were assessed, and a physical exam that included vital signs, height, and weight was performed. A 12-lead ECG was obtained on all participants. Laboratory testing comprised a basic metabolic panel, hepatic function panel, prealbumin, 4-exon *TTR* gene sequencing, cardiac biomarkers (B-type natriuretic peptide, NT-proBNP [N-terminal pro-B-type natriuretic peptide], high-sensitivity troponin I, high-sensitivity troponin T, and galectin-3 to be fully analyzed at the end of the study), vitamin A and retinol binding protein-4 in plasma and urine, TTR protein subunit exchange, and genetic ancestry. Functional testing included the 6-minute walk distance (6MWD) and Short Physical Performance Battery. The Short Physical Performance Battery, scored on a scale of 0 to 12, tests participants' standing balance, walking speed, and ability to stand after being seated in a chair.[9] The Short Physical Performance Battery scores were stratified into no functional deficit (scores of 10–12), mild functional deficit (scores of 7–9), and severe functional deficit (scores of 0–6). The Kansas City Cardiomyopathy Questionnaire and Short-Form Survey 12 were administered for quality-of-life assessments. Imaging by transthoracic echocardiography was acquired with analysis performed through the SCAN-MP echocardiography core laboratory (directed by F.L.R.), whereas PYP imaging was performed and analyzed through the PYP core laboratory (directed by A.J.E.). The presence of ATTR-CM was determined by PYP imaging with a Perugini score of 2 or 3 confirmed by single photon emission computed tomography (SPECT), with hybrid CT performed when available, following multisocietal consensus recommendations.[10] Light-chain amyloidosis was excluded by serum and urine testing for a monoclonal protein by free-light chain assay and immunofixation electrophoresis consistent with consensus recommendations.[11]

Statistical Analysis

Data from SCAN-MP participants were analyzed in the following groups: (1) PYP positive versus PYP negative and (2) V122I carriers without ATTR-CM versus V122I carriers with ATTR-CM. Differences in demographics and comorbidities as well as biochemical, functional, and echocardiographic parameters were determined using premutation testing for continuous variables or analysis of variance with post hoc testing using the Tukey multiple comparison test. A χ^2 or Fisher exact test (where appropriate) was used to determine differences in categorical variables. The prevalence of V122I and penetrance of ATTR-CM were determined by proportions with 95% CI estimates. For comparison of prealbumin levels, SCAN-MP participants were categorized in the following groups based upon *TTR* genotype and PYP scan result: (1) HF but without

ATTR-CM and with normal *TTR* genotype (HF controls), (2) V122I carriers without ATTR-CM (V122I carriers), (3) ATTR-CM but without a genetic variant of the *TTR* gene (ATTR wild-type), and (4) V122I carriers with ATTR-CM (ATTR V122I). Missing data were ≤10.1% for all variables reported unless specified as follows. Prealbumin data were available for 237 of 278 participants, with 9 out of 11 V122I carriers and 6 out of 7 ATTR-CM V122I having available prealbumin. In addition, because of the SCAN-MP study design to measure all cardiac biomarkers at the conclusion of the study, cardiac biomarker data (high-sensitivity troponin I and NT-proBNP) were available in only the first 140 recruited Black subjects; overall, 50% of the cohort did not have cardiac biomarker data. Missing data were similar across subject groups. 6MWD data were available in 87% of subjects, and global longitudinal strain data were available in 70% of the cohort but with similar missing data across subject groups. All tests were 2-sided and were considered statistically significant at a *P* value <0.05. Statistical analysis was performed using SAS Studio 3.8 (Enterprise Edition).

RESULTS

Overview of Study Participants With ATTR-CM

The first 278 self-identified Black participants in SCAN-MP were included in this analysis. As indicated in Table 1, 19 of the 278 participants had a positive PYP scan indicative of ATTR-CM, resulting in an overall population prevalence of ATTR-CM of 6.8% (95% CI, 4.2–10.5). Image examples of positive and negative planar and SPECT PYP scans can be found in Figure 1. When ATTR-CM was categorized by *TTR* genotype, of those with ATTR-CM by PYP imaging, there were 7 with V122I (37% of those with ATTR-CM) and 12 with normal *TTR* genotype (63% of those with ATTR-CM). PYP-positive participants were older, with a median age of 82 years (interquartile range [IQR], 77–86 years) when compared with PYP-negative participants with a median age of 69 years (IQR, 64–77 years; *P*<0.01). No significant difference in sex distribution was found between the 2 groups. The only significantly different preexisting comorbidity at study enrollment between the 2 groups was coronary artery disease, which had a prevalence of 21% in the PYP-negative group and a prevalence of 42% in the PYP-positive group (*P*<0.05).

High-sensitivity troponin I was significantly higher in the PYP-positive group (*P*<0.01, Table 2), and prealbumin was lower in the PYP-positive group (20 mg/dL) compared with the PYP-negative group (25 mg/dL, *P*<0.01). PYP-positive participants were impaired by functional assessments, as evidenced by a lower 6MWD score (160 versus 273 m, *P*<0.05). A higher proportion of PYP-positive participants had a Short Physical Performance Battery score, indicating severe functional deficit as compared with PYP-negative participants (56.3% versus 27.8%, *P*<0.05). PYP-positive individuals had echocardiographic features of more advanced cardiac functional and structural abnormalities than PYP-negative individuals. Notable echocardiographic findings in PYP-positive individuals were a greater wall thickness (1.5 versus 1.3 mm, *P*<0.01), lower stroke volume (56 versus 72 mL, *P*<0.01), lower cardiac output (4.0 L/min versus 4.9 L/min, *P*<0.01), lower mean e′ (4.1 versus 5.9 cm/s, *P*<0.01), higher E/e′ (19.0 versus 12.9, *P*<0.01), and worse global longitudinal strain (–10.7% versus –13.7%, *P*<0.05). Finally, as expected, heart to contralateral chest uptake ratio was higher in PYP-positive participants (1.7) than PYP-negative participants (1.1, *P*<0.01).

Table 1. Demographics and Comorbidities for Participants by ATTR-CM Status

Variable	PYP negative, n=259	PYP positive, n=19	*P* value
Age, y	69 (64, 77)	82 (77, 86)	<0.0001
Male sex	133 (51.4%)	13 (68.4%)	0.15
V122I variant	11 (4.3%)	7 (36.8%)	<0.0001
Comorbidities			
Atrial fibrillation/flutter	74 (28.6%)	7 (36.8%)	0.44
Coronary artery disease	55 (21.2%)	8 (42.1%)	0.047
Hypertension	247 (95.4%)	19 (100%)	1
Hyperlipidemia	186 (71.8%)	13 (68.4%)	0.75
Peripheral vascular disease	24 (9.3%)	3 (15.8%)	0.41
Stroke	36 (13.9%)	2 (10.5%)	1
Chronic kidney disease	82 (31.7%)	9 (47.4%)	0.16
Carpal tunnel syndrome	17 (6.6%)	2 (10.5%)	0.63
Spinal stenosis	21 (8.1%)	0 (0%)	0.38
Polyneuropathy	19 (7.3%)	0 (0%)	0.38
Malignancy	28 (10.8%)	4 (21.1%)	0.25

ATTR-CM indicates transthyretin amyloid cardiomyopathy; PYP, technetium-99m-pyrophosphate imaging; and V122I, valine to isoleucine substitution at position 122 of the transthyretin protein.

V122I Carriers Versus ATTR V122I

Out of the 278 participants, 18 had the V122I variant, resulting in an allele prevalence of 6.5%. Out of the 18 carriers, 7 had clinically evident ATTR-CM. Therefore, the overall clinical penetrance of the V122I variant was 39% (95% CI, 17–64). The median age of those with penetrant ATTR-CM was 82 years (IQR, 74–85 years), whereas the median age for carriers without penetrant ATTR-CM was 66 years (IQR, 64–77 years) (*P*=0.02, Table 3).

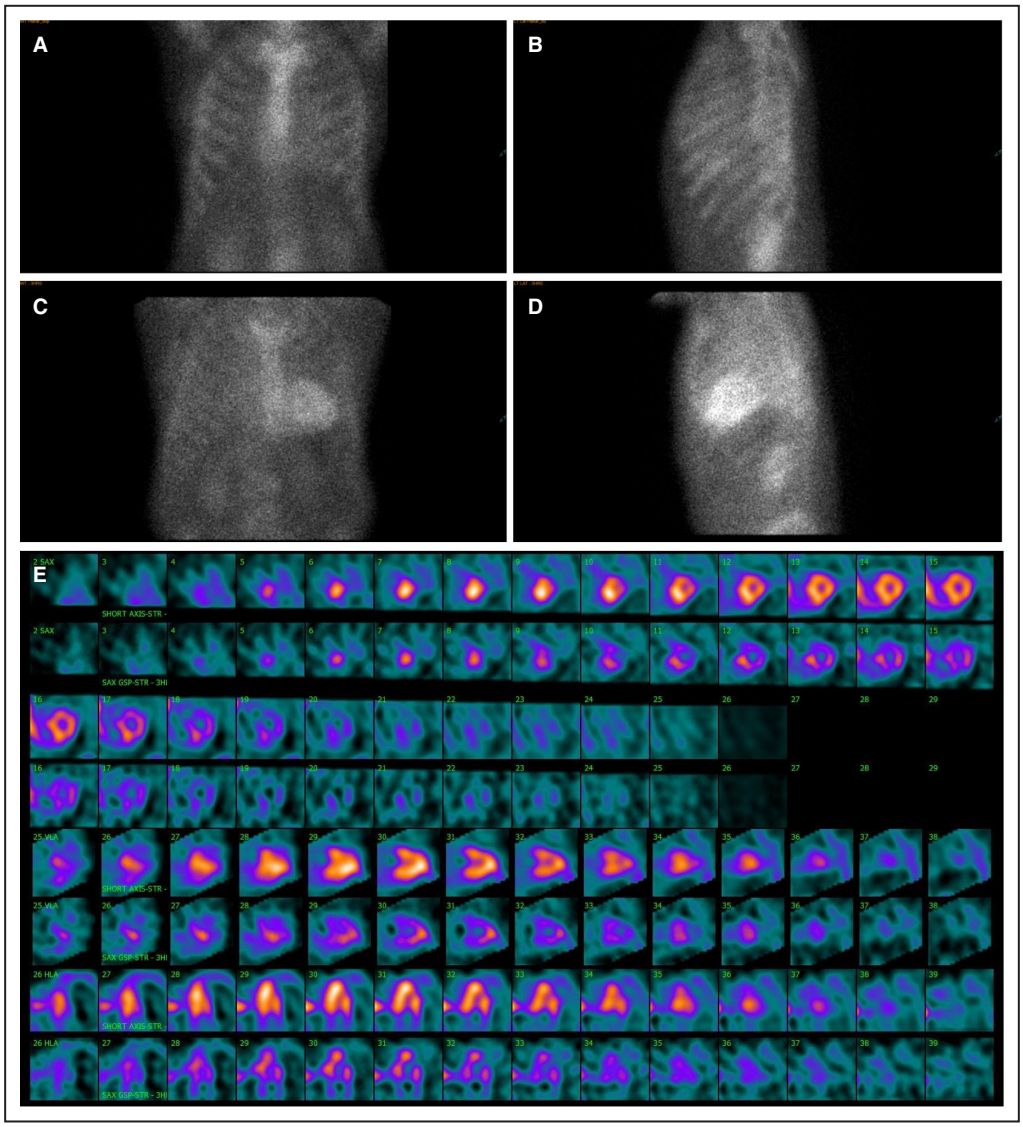

Figure 1. Technetium-99m-pyrophosphate planar and SPECT images for V122I carrier without ATTR-CM and V122I carrier with ATTR-CM.
A, Planar image, AP view for V122I carrier without ATTR-CM. **B**, Planar image, lateral view for V122I carrier without ATTR-CM. **C**, Planar image, AP view for V122I carrier with ATTR-CM. **D**, Planar image, lateral view for V122I carrier with ATTR-CM. **E**, SPECT image demonstrating myocardial uptake diagnostic of ATTR-CM. AP indicates anterior/posterior; ATTR-CM, transthyretin amyloid cardiomyopathy; and V122I, valine to isoleucine substitution at position 122 of the transthyretin protein.

When analyzed by age, 10 participants with the V122I mutation were <75 years of age, of whom only 2 had ATTR-CM. Penetrance for participants <75 years of age was 20% (95% CI, 3–56). Of the 8 participants ≥75 years of age, 5 had ATTR-CM, resulting in a penetrance for this subgroup of 63% (95% CI, 24–91). When analyzed by sex, 9 of the 18 participants with the V122I variant were men, of whom 5 had ATTR-CM. The penetrance for men in this group was 56% (95% CI, 21–86). Of the 9 women, 2 had ATTR-CM, resulting in a clinical penetrance for women of 22% (95% CI, 3–60). The only significantly different comorbidity between the 2 groups was the higher prevalence of chronic kidney disease in ATTR-CM V122I (57.1%) versus in V122I carriers (9.1%, P=0.047), but this difference may be due to chance as a result of testing multiple variables (Table 3).

Circulating biomarkers and imaging findings can be found in Table 4. NT-proBNP was higher in ATTR-CM V122I (2721 pg/mL) than in V122I carriers (708.8 pg/mL, P<0.05), whereas prealbumin was lower in ATTR-CM V122I (12.9 mg/dL) versus V122I carriers (21 mg/dL, P<0.05). 6MWD scores were significantly lower in ATTR-CM V122I (80 m) than in V122I carriers (273 m, P<0.05). ATTR-CM V122I evidenced significantly

Table 2. Biochemical, Functional, and Echocardiographic Parameters for Self-Identified Black Participants by ATTR-CM Status

Variable	PYP negative, n=259	PYP positive, n=19	*P* value
Laboratory			
NT-proBNP, pg/mL	402 (166.7 to 815.3)	1208.8 (841.6 to 2721)	0.18
hs-troponin I, ng/mL	11.7 (7.1 to 19.5)	81.7 (21.9 to 97.8)	0.008
Prealbumin, mg/dL	25 (21 to 29)	20 (15 to 24)	0.0002
eGFR, mL/min per 1.73 m^2	64.7 (47.2 to 77.9)	53.8 (41.4 to 75.8)	0.19
Functional assessments			
6-minute walk distance, m	273 (170 to 360)	160 (80 to 289.5)	0.04
SPPB score, 0–12	8 (6 to 10)	6 (3.5 to 10)	0.008
SPPB score, 3 categories			0.02
Severe functional deficit, 0–6	65 (27.8%)	9 (56.3%)	
Mild functional deficit, 7–9	100 (42.7%)	2 (12.5%)	
No functional deficit, 10–12	69 (29.5%)	5 (31.3%)	
Echocardiogram			
LV end diastolic dimension, mm	4.5 (4 to 5.1)	4.3 (3.7 to 4.6)	0.07
Maximal LV thickness, mm	1.3 (1.1 to 1.4)	1.5 (1.3 to 1.7)	0.0002
Left atrial volume, mL	76 (60 to 96)	83 (67 to 98)	0.95
Ejection fraction, %	60 (54 to 67)	53 (48 to 63)	0.38
Stroke volume, mL	72 (60 to 86)	56 (36 to 66)	0.003
Cardiac output, L/min	4.9 (4 to 5.8)	4.0 (3 to 4.9)	0.007
Mean e′, cm/s	5.9 (4.8 to 7.4)	4.1 (3.6 to 5.5)	0.005
E/e′	12.9 (9.8 to 16.6)	19 (14.5 to 27.6)	0.001
Global longitudinal strain, %	–13.7 (–16.9 to –11)	–10.7 (–13.7 to –7.9)	0.04
PYP scan			
H/CL ratio	1.1 (1 to 1.2)	1.7 (1.6 to 1.9)	<0.0001

ATTR-CM indicates transthyretin amyloid cardiomyopathy; eGFR, estimated glomerular filtration rate; H/CL, heart to contralateral chest uptake; hs-troponin I, high-sensitivity troponin I; LV, left ventricular; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PYP, technetium-99m-pyrophosphate imaging; and SPPB, Short Physical Performance Battery.

lower stroke volume (36 versus 80 mL, $P<0.05$) and worse global longitudinal strain (–7.6% versus –16.9%, $P=0.03$) than V122I carriers. As expected, heart to contralateral chest uptake ratio was higher in ATTR-CM V122I (1.6) versus V122I carriers (1.1, $P<0.01$).

Prealbumin in V122I Carriers Versus Controls

Prealbumin was lowest in ATTR-CM V122I, with a median value of 12.9 mg/dL (IQR, 10.0–17.0 mg/dL) versus V122I carriers (21.0 mg/dL; IQR, 18.0–22.0 mg/dL; Figure 2 and Table 4). Prealbumin in V122I carriers trended lower than the prealbumin in HF controls (25.0 mg/dL; IQR, 22.0–29.0 mg/dL) ($P=0.10$). Prealbumin in ATTR wild-type (24.0 mg/dL; IQR, 20.0–25.0 mg/dL) was similar to that of the HF controls.

DISCUSSION

In this study, we present data elucidating the clinical penetrance of the V122I variant in older, Black individuals with HF and increased left ventricular wall thickness. The principal findings are that (1) among the 18 carriers with V122I identified, the penetrance of ATTR-CM was 39% (95% CI, 17–64), with a median age of 82 years among those with clinically penetrant disease; (2) that among newly identified cases of ATTR-CM in this population, the majority (63%) were ATTR wild-type; and (3) that prealbumin trended lower in V122I carriers versus HF controls, affording a new clinical variable that could be used to identify those at risk for hereditary ATTR-CM. To our knowledge, these data are the first to be reported that inform clinical penetrance of V122I using a prospectively acquired study that in addition uses sensitive nuclear imaging for active ascertainment of ATTR-CM cases.

Clinical Penetrance of the V122I Variant in ATTR-CM

Our finding of a clinical penetrance of 39% (95% CI, 17–64) in older Black individuals with HF and increased left ventricular wall thickness is of importance given

Table 3. Demographics and Comorbidities for Participants by V122I and ATTR-CM Status

Variable	V122I carrier, n=11	V122I ATTR-CM, n=7	*P* value
Age, y	66 (64, 77)	82 (74, 85)	0.02
Male sex	4 (36.4%)	5 (71.4%)	0.33
Comorbidities			
Atrial fibrillation/flutter	5 (45.5%)	4 (57.1%)	1
Coronary artery disease	2 (18.2%)	3 (42.9%)	0.33
Hypertension	9 (81.8%)	7 (100%)	0.50
Hyperlipidemia	7 (63.6%)	6 (85.7%)	0.60
Peripheral vascular disease	0 (0%)	1 (14.3%)	0.39
Stroke	1 (9.1%)	0 (0%)	1
Chronic kidney disease	1 (9.1%)	4 (57.1%)	0.047
Carpal tunnel syndrome	0 (0%)	1 (14.3%)	0.39
Spinal stenosis	0 (0%)	0 (0%)	NA
Polyneuropathy	1 (9.1%)	0 (0%)	1
Malignancy	0 (0%)	1 (14.3%)	0.39

ATTR-CM indicates transthyretin amyloid cardiomyopathy; and V122I, valine to isoleucine substitution at position 122 of the transthyretin protein.

the frequency of the allele (1.5 million carriers) and suggests that V122I carriers with HF, who may have phenotypic overlap with ATTR-CM, do not necessarily have ATTR-CM as the cause of HF. Therefore, a clinical strategy of genotype screening for at-risk patients, a so-called genotype first approach, is insufficient

Table 4. Biochemical, Functional, and Echocardiographic Parameters for Self-Identified Black Participants by V122I and ATTR-CM Status

Variable	V122I carrier, n=11	V122I ATTR-CM, n=7	*P* value
Laboratory			
NT-proBNP, pg/mL	708.8 (410.8 to 1204.3)	2721 (1933 to 3612.7)	0.04
hs-troponin I, ng/mL	9.7 (3.4 to 45.9)	119.3 (73.4 to 273.1)	0.08
Prealbumin, mg/dL	21 (18 to 22)	12.9 (10 to 17)	0.04
eGFR, mL/min per 1.73 m^2	69.3 (50.9 to 83.6)	53.8 (29.1 to 82.6)	0.38
Functional assessments			
6-minute walk distance, m	273 (213 to 327)	80 (80 to 140)	0.046
SPPB score, 0–12	7 (5 to 9)	6 (5 to 8)	0.73
SPPB score, 3 categories			0.48
Severe functional deficit, 0–6	3 (33.3%)	3 (60%)	
Mild functional deficit, 7–9	5 (55.6%)	1 (20%)	
No functional deficit, 10–12	1 (11.1%)	1 (20%)	
Echocardiogram			
LV end-diastolic dimension, mm	4.4 (3.6 to 5.3)	4 (3.6 to 4.5)	0.68
Maximal LV thickness, mm	1.3 (1.1 to 1.5)	1.6 (1.3 to 1.7)	0.13
Left atrial volume, mL	73 (59 to 101)	79 (65 to 98)	0.77
Ejection fraction, %	62 (55 to 69)	52 (34 to 56)	0.06
Stroke volume, mL	80 (60 to 91)	36 (31 to 62)	0.03
Cardiac output, L/min	4.9 (4.2 to 6.1)	2.7 (2 to 4)	0.05
Mean e′, cm/s	5.8 (4.7 to 7.2)	4.3 (4 to 5.1)	0.05
E/e′	13.2 (9.8 to 15.6)	18.8 (12.6 to 30.3)	0.10
Global longitudinal strain, %	−16.9 (−20 to −11.2)	−7.6 (−9.1 to −7.1)	0.03
PYP scan			
H/CL ratio	1.1 (1.1 to 1.2)	1.6 (1.4 to 1.8)	0.001

ATTR-CM indicates transthyretin amyloid cardiomyopathy; eGFR, estimated glomerular filtration rate; H/CL, technetium-99m-pyrophosphate heart to contralateral chest uptake; hs-troponin I, high-sensitivity troponin I; LV, left ventricular; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PYP, technetium-99m-pyrophosphate imaging; SPPB, Short Physical Performance Battery; and V122I, valine to isoleucine substitution at position 122 of the transthyretin protein.

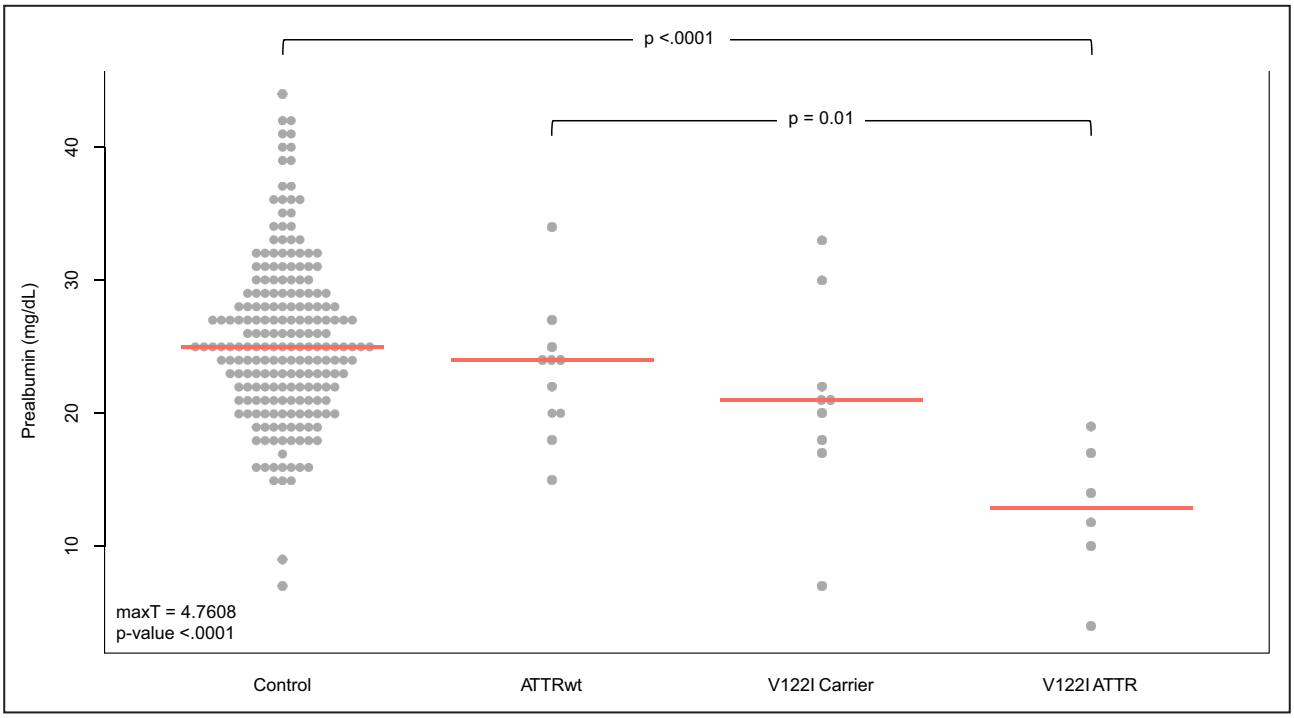

Figure 2. Bee swarm plot of prealbumin concentration (milligrams per deciliter) in heart failure controls without transthyretin cardiac amyloidosis (Control), participants with ATTRwt, V122I Carrier, and V122I ATTR.
ATTRwt indicates wild-type transthyretin cardiac amyloidosis; V122I, valine to isoleucine substitution at position 122 of the transthyretin protein; V122I ATTR, V122I carriers with transthyretin cardiac amyloidosis; and V122I Carrier, V122I carriers without transthyretin cardiac amyloidosis.

because there is not a 1:1 carrier to ATTR-CM concordance, and furthermore, such an approach will miss ATTR wild-type. Importantly, our HF control cohort appeared similar echocardiographically and by biomarkers to the V122I carriers, because both had features of left ventricular wall thickening, increased left ventricular filling pressures, and functional limitation. Although not achieving statistical significance due to the small sample size, we observed that penetrance was higher in participants ≥75 years of age and in men in particular, reaffirming the clinical impression of an age-dependent and sex-dependent penetrance drawn largely from retrospective cohort studies of referral populations.[1,12,13] Thus, our results provide clinically actionable information: V122I allele carriers with HF who are ≥75 years of age and men are at the highest risk of having ATTR-CM as the cause of their symptoms and should be tested for ATTR-CM by PYP imaging. Furthermore, we would suggest that because of the possibility of interval development of ATTR-CM with time, rescreening should be considered for individuals with the V122I variant as they age, even if initial presentation is not consistent with clinically penetrant disease. Our estimate of penetrance was constructed from a prospectively recruited cohort using active ascertainment of ATTR-CM from PYP imaging, which has higher diagnostic accuracy than does echocardiography for assessing disease penetrance as used in prior studies.[5] Similar imaging methods have demonstrated a 6% prevalence of wild-type ATTR-CM in older patients with HF, but in a cohort of White race individuals (96% of the cohort and 100% of identified cases).[14] It is important to emphasize the differences in racial identification among these cohorts, thereby altering the distribution of *TTR* variants and ATTR-CM prevalence, because V122I is extremely uncommon in White race individuals.

Biochemical, Echocardiographic, and Functional Differences

When comparing V122I carriers and ATTR-CM V122I, those with cardiac amyloidosis had higher NT-proBNP but lower prealbumin, 6MWD score, ejection fraction, stroke volume, and cardiac output. In addition to identifying more advanced heart failure due to V122I ATTR-CM, these parameters may be used to increase clinical suspicion for V122I ATTR-CM in known carriers. Our data are unique in the degree of characterization afforded, because biochemical, echocardiographic, and functional assessments of V122I carriers with and without ATTR-CM are generally not reported in prior studies. Instead, prior studies tend to assess differences in outcomes between V122I carriers and noncarriers,[5,15] likely due to the limited means available to

accurately establish penetrant ATTR-CM among V122I carriers in retrospective analyses.

Predictably, prealbumin was lower in V122I ATTR-CM than in V122I carriers. The finding that prealbumin trended lower in V122I carriers than in HF controls is important and suggests that dissociation of TTR resulting in lower circulating levels may occur before clinical detection of ATTR-CM. These data suggest that the stratification of prealbumin levels among these 3 groups can potentially be used in the future to suggest both the presence of the V122I variant, if a known family history of V122I ATTR-CM exists, and the clinical penetrance of the V122I variant.

Limitations

Our study is limited by the small number of carriers and cases of V122I ATTR-CM, thereby rendering a wide confidence interval for the point estimate of clinical penetrance. Because the criteria for SCAN-MP included ejection fraction >30%, age ≥60 years, and wall thickness ≥12 mm, the prevalence and penetrance of the V122I variant in our cohort is not representative of all Black individuals with HF (for example, those with ischemic heart disease or aortic stenosis). However, we sought to carefully enroll a population of patients with HF who would appear similar phenotypically and as such would comprise a clinically relevant population. Finally, the lack of invasive, confirmatory cardiac biopsy is another limitation but is not feasible in a screening study. All participants had ATTR-CM verified by the clinical practices at our experienced amyloidosis centers that adhere to established consensus recommendations.[11]

CONCLUSIONS

We determined that the phenotypic penetrance of the V122I allele among older allele carriers with HF symptoms is 39% (95% CI, 17–64). We also observed that among those with ATTR-CM, ATTR wild-type was present in 63%. These data suggest that genotype alone is insufficient to infer ATTR-CM as the cause of HF in this population. Our study also suggests that lower prealbumin concentration, alone or in conjunction with other biochemical, functional, and echocardiographic measures, may be useful to differentiate allele carriers with and without ATTR-CM from HF controls.

ARTICLE INFORMATION

Received January 20, 2023; accepted April 19, 2023.

Affiliations

Boston University Chobanian & Avedisian School of Medicine, Boston, MA (A.M.); Section of Cardiovascular Medicine, Department of Medicine, Boston University Chobanian & Avedisian School of Medicine, Boston Medical Center, Boston, MA (N.S., D.M., L.D.P., D.F., M.W., F.L.R.); Seymour, Paul, and Gloria Milstein Division of Cardiology, Department of Medicine, Columbia University Irving Medical Center, and New York-Presbyterian Hospital, New York, NY (C.R., S.H., S.T., A.J.E., M.S.M.); Division of Cardiology, Harlem Hospital Center, New York City Health and Hospital Corporation, New York, NY (D.K., F.R.); Hunter College, City University of New York, New York, NY (E.C.); Department of Radiology, Columbia University Irving Medical Center, and New York-Presbyterian Hospital, New York, NY (A.J.E.); Section of Cardiovascular Medicine, Department of Medicine, Yale School of Medicine, New Haven, CT (E.J.M.); Amyloidosis Center (L.H.C., F.L.R.), and Department of Pathology and Laboratory Medicine (L.H.C.), Boston University Chobanian & Avedisian School of Medicine, Boston, MA.

Acknowledgments

The cardiac biomarkers analysis (NT-proBNP and high-sensitivity troponin I) was performed by Abbott Laboratories through a separate in-kind biomarker substudy research grant.

Sources of Funding

SCAN-MP was funded by the National Institutes of Health/National Heart, Lung, and Blood Institute (HL 139671) to Drs Maurer and Ruberg.

Disclosures

Dr Ruberg acknowledges research grant funding from Pfizer, Alnylam, and Akcea/Ionis. Dr Maurer acknowledges consulting income from Eidos, Prothena, Ionis, Alnylam, Novo-Nordisk, and Intellia; and institutional support in the form of clinical trial funding from Pfizer, Attralus, Ionis, Eidos, and Alnylam. Dr Einstein acknowledges speaker fees from Ionetix; has received consulting fees from W. L. Gore & Associates; has received authorship fees from Wolters Kluwer Healthcare–UpToDate; and has received grants or grants pending to his institution from Attralus, Canon Medical Systems, Eidos Therapeutics, GE Healthcare, NeoVasc, Pfizer, Roche Medical Systems, and W. L. Gore & Associates. Dr Miller served as a consultant to Bracco, Pfizer, GE Healthcare, and Alnylam; he has received grant support from Bracco, Eidos, Alnylam, and Pfizer. The remaining authors have no disclosures to report.

REFERENCES

1. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin amyloid cardiomyopathy. *J Am Coll Cardiol*. 2019;73:2872–2891. doi: 10.1016/j.jacc.2019.04.003
2. Jacobson DR, Alexander AA, Tagoe C, Garvey WT, Williams SM, Tishkoff S, Modiano D, Sirima SB, Kalidi I, Toure A, et al. The prevalence and distribution of the amyloidogenic transthyretin (TTR) V122I allele in Africa. *Mol Genet Genomic Med*. 2016;4:4–556. doi: 10.1002/mgg3.231
3. Gorevic PD, Prelli FC, Wright J, Pras M, Frangione B. Systemic senile amyloidosis. Identification of a new prealbumin (transthyretin) variant in cardiac tissue: immunologic and biochemical similarity to one form of familial amyloidotic polyneuropathy. *J Clin Investig*. 1989;83:83–843. doi: 10.1172/JCI113966
4. Parcha V, Malla G, Irvin MR, Armstrong ND, Judd SE, Lange LA, Maurer MS, Levitan EB, Goyal P, Arora G, et al. Association of transthyretin Val122Ile variant with incident heart failure among black individuals. *JAMA*. 2022;327:1368–1378. doi: 10.1001/jama.2022.2896
5. Quarta CC, Buxbaum JN, Shah AM, Falk RH, Claggett B, Kitzman DW, Mosley TH, Butler KR, Boerwinkle E, Solomon SD. The amyloidogenic V122I transthyretin variant in elderly black Americans. *N Engl J Med*. 2015;372:21–29. doi: 10.1056/NEJMoa1404852
6. Jacobson DR, Pastore RD, Yaghoubian R, Kane I, Gallo G, Buck FS, Buxbaum JN. Variant-sequence transthyretin (isoleucine 122) in late-onset cardiac amyloidosis in black Americans. *N Engl J Med*. 1997;336:466–473. doi: 10.1056/NEJM199702133360703
7. Rich MW, Beckham V, Wittenberg C, Leven CL, Freedland KE, Carney RM. A multidisciplinary intervention to prevent the readmission of elderly patients with congestive heart failure. *N Engl J Med*. 1995;333:1190–1195. doi: 10.1056/NEJM199511023331806
8. Schocken DD, Arrieta MI, Leaverton PE, Ross EA. Prevalence and mortality rate of congestive heart failure in the United States. *J Am Coll Cardiol*. 1992;20:301–306. doi: 10.1016/0735-1097(92)90094-4
9. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, Scherr PA, Wallace RB. A Short Physical Performance Battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol*. 1994;49:M85–M94. doi: 10.1093/geronj/49.2.M85

10. Dorbala S, Ando Y, Bokhari S, Dispenzieri A, Falk RH, Ferrari VA, Fontana M, Gheysens O, Gillmore JD, Glaudemans AWJM, et al. ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI expert consensus recommendations for multimodality imaging in cardiac amyloidosis: part 1 of 2—evidence base and standardized methods of imaging. *J Nucl Cardiol*. 2019;26:2065–2123. doi: 10.1007/s12350-019-01760-6
11. Kittleson MM, Maurer MS, Ambardekar AV, Bullock-Palmer RP, Chang PP, Eisen HJ, Nair AP, Nativi-Nicolau J, Ruberg FL. Cardiac amyloidosis: evolving diagnosis and management: a scientific statement from the American Heart Association. *Circulation*. 2020;142:142–e22. doi: 10.1161/CIR.0000000000000792
12. Chandrashekar P, Alhuneafat L, Mannello M, Al-Rashdan L, Kim MM, Dungu J, Alexander K, Masri A. Prevalence and outcomes of p.Val142Ile *TTR* amyloidosis cardiomyopathy: a systematic review. *Circ Genom Precis Med*. 2021;14:e003356. doi: 10.1161/CIRCGEN.121.003356
13. Buxbaum JN, Ruberg FL. Transthyretin V122I (pV142I)* cardiac amyloidosis: an age-dependent autosomal dominant cardiomyopathy too common to be overlooked as a cause of significant heart disease in elderly African Americans. *Genet Med*. 2017;19:733–742. doi: 10.1038/gim.2016.200
14. AbouEzzeddine OF, Davies DR, Scott CG, Fayyaz AU, Askew JW, McKie PM, Noseworthy PA, Johnson GB, Dunlay SM, Borlaug BA, et al. Prevalence of transthyretin amyloid cardiomyopathy in heart failure with preserved ejection fraction. *JAMA Cardiol*. 2021;6:1267–1274. doi: 10.1001/jamacardio.2021.3070
15. Damrauer SM, Chaudhary K, Cho JH, Liang LW, Argulian E, Chan L, Dobbyn A, Guerraty MA, Judy R, Kay J, et al. Association of the V122I hereditary transthyretin amyloidosis genetic variant with heart failure among individuals of African or Hispanic/Latino ancestry. *JAMA*. 2019;322:2191–2202. doi: 10.1001/jama.2019.17935