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Phenotypes Associated With the Val122Ile, Leu58His, and Late-Onset Val30Met Variants in Patients With Hereditary Transthyretin Amyloidosis

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Abstract

Background and Objectives

Hereditary transthyretin amyloidosis (hATTR) is a rare autosomal dominant systemic disease with variable penetrance and heterogeneous clinical presentation. Several effective treatments can reduce mortality and disability, though diagnosis remains challenging, especially in the United States where disease is nonendemic. Our aim is to describe the neurologic and cardiac characteristics of common US ATTR variants V122I, L58H, and late-onset V30M at presentation.

Methods

We conducted a retrospective case series of patients with a new diagnosis of ATTRv between January 2008 and January 2020 to characterize features of prominent US variants. The neurologic (examination, EMG, and skin biopsy), cardiac (echo), and laboratory assessments (pro b-type natriuretic peptide [proBNP] and reversible neuropathy screens) are described.

Results

A total of 56 patients with treatment-naïve ATTRv with symptoms/signs of peripheral neuropathy (PN) or cardiomyopathy and confirmatory genetic testing presenting with Val122Ile (N = 31), late-onset Val30Met (N = 12), and Leu58His ATTRv (N = 13) were included. The age at onset and sex distributions were similar (V122I: 71.5 ± 8.0, V30M: 64.8 ± 2.6, and L58H: 62.4 ± 9.8 years; 26, 25, 31% female). Only 10% of patients with V122I and 17% of patients with V30M were aware of an ATTRv family history, while 69% of patients with L58H were aware. PN was present in all 3 variants at diagnosis (90%, 100%, and 100%), though neurologic impairment scores differed: V122I: 22 ± 16, V30M: 61 ± 31, and L58H: 57 ± 25. Most points (deficits) were attributed to loss of strength. Carpal tunnel syndrome (CTS) and a positive Romberg sign were common across all groups (V122I: 97%, 39%; V30M: 58%, 58%; and L58H: 77%, 77%). ProBNP levels and interventricular septum thickness were highest among patients with V122I (5,939 ± 962 pg/mL, 1.70 ± 0.29 cm), followed by V30M (796 ± 970 pg/mL, 1.42 ± 0.38 cm) and L58H (404 ± 677 pg/mL, 1.23 ± 0.36 cm). Atrial fibrillation was present among 39% of cases with V122I and only 8% of cases with V30M and L58H. Gastrointestinal symptoms were rare (6%) among patients with V122I and common in patients with V30M (42%) and L58H (54%).

Discussion

Important clinical differences exist between ATTRv genotypes. While V122I is perceived to be a cardiac disease, PN is common and clinically relevant. Most patients with V30M and V122I were diagnosed de novo and therefore require clinical suspicion for diagnosis. A history of CTS and a positive Romberg sign are helpful diagnostic clues.

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Glossary

ANOVA = analysis of variance; **CTS** = carpal tunnel syndrome; **GFR** = glomerular filtration rate; **GI** = gastrointestinal; **hATTR** = hereditary transthyretin amyloidosis; ***ICD-10*** = *International Classification of Diseases, 10th Revision*; **IENFD** = intraepidermal nerve fiber density; **NCV** = nerve conduction velocity; **NIS** = neuropathic impairment score; **PN** = peripheral neuropathy; **proBNP** = pro b-type natriuretic peptide; **PYP** = pyrophosphate; **TTR** = transthyretin.

Hereditary transthyretin amyloidosis (hATTR or ATTRv) is a rare autosomal dominant systemic disease with variable presentation that prominently involves cardiac, peripheral nerve, and gastrointestinal (GI) systems. More than 120 pathogenic variants have been described, and the global prevalence is estimated at 50,000 cases.[1,2] The pathogenesis of ATTRv and nonhereditary ATTR involves a cascade of transthyretin (TTR) tetramer dissociation, TTR monomer misfolding, and aggregation and deposition of TTR amyloid fibrils that results in tissue dysfunction. Pathogenic variants involve single amino acid substitutions that destabilize the TTR tetramer.[3,4] The factors responsible for the initiation of TTR amyloid deposition and why certain organs are preferentially involved in different patients remain incompletely understood.

Globally, the most common genetic variants are Val30Met and Thr60Ala, and most clinical characterizations of ATTRv are from endemic regions where presentations are often stereotypical.[5] By contrast, Val122Ile is the most common variant in the United States with a prevalence of 3%–4% in the Black population, though penetrance is low. The presentation of the Val122Ile variant is reported to be predominantly cardiac;[2] however, peripheral nerve involvement is observed. In this study, we describe the clinical characteristics of 3 common genetic variants seen at our institution: Val122Ile, Leu58His, and late-onset Val30Met.

Methods

Study Population

Treatment naïve, symptomatic patients with ATTRv with V122I, V30M, or L58H were seen at the Johns Hopkins Amyloid Center between 2008 and 2020. Patients with evidence of active disease (peripheral neuropathy [PN] or cardiomyopathy) who underwent comprehensive evaluations and were treatment naïve were included. All patients referred to the clinic completed standardized neurologic intake questionnaires that cover medical history, cardiac, GI, and neurologic symptoms. The Romberg test was performed at all clinical visits. Participant race and ethnicity were self-reported in the electronic health records and included the following categories: Hispanic or Latino, non-Hispanic Asian (hereafter, Asian), non-Hispanic Black or African American (hereafter, Black), and non-Hispanic White (hereafter, White). We recorded these data, given that different ATTR variants have been linked to specific global regions. All patients were examined by a single neurologist (M.P.), and all investigations were performed under a uniform protocol. Cardiac assessments were performed under supervision of a board-certified cardiologist with expertise in heart failure (F.H.S., J.V., or D.J.).

Assessment

For the purposes of this study, *peripheral nerve involvement* was defined as having an abnormal nerve conduction or skin biopsy result and/or having been prescribed medication for neuropathic symptoms. *Cardiac involvement* was defined as having an interventricular septum >1.1 cm, a positive pyrophosphate (PYP) scan, or positive endomyocardial biopsy. *GI involvement* was defined as daily diarrhea or frequent constipation that represented a consequential change for the patient and required treatment and/or behavioral modifications. Patients were classified by their initial testing leading to diagnosis of ATTRv, including cardiac testing (positive PYP scan or cardiac biopsy) or neurologic testing (abnormal nerve conduction velocity [NCV] or intraepidermal nerve fiber density [IENFD] or genetic testing inspired by neuropathic symptoms). The year of symptom onset for each system involved was defined as the earliest abnormal test result or earliest reported symptoms from chart review. Onset of median neuropathy at the wrist (carpal tunnel syndrome, CTS) was defined as the year of diagnosis with CTS or 1 year before carpal tunnel release surgery if date of diagnosis was unknown. If disease manifestation for multiple systems began within 1 year of each other, onset was defined as simultaneous. Neuropathic symptom duration was calculated as the number of years from patient-reported PN symptom onset to initial presentation to the neurologist. Rate of neuropathy progression was calculated by dividing the patient's first visit neuropathic impairment score (NIS) by their neuropathic symptom duration value.

Limbs were warmed to 31°C for NCV studies. Sural and radial sensory nerve responses were measured antidromically stimulating at the calf 11 cm proximal to the lateral malleolus and stimulating at the forearm while recording at the lateral malleolus and first metacarpal, respectively. Ulnar and median sensory nerve responses were measured orthodromically stimulating at the finger and recording at the wrist. Peroneal, ulnar, and median motor nerve responses were obtained when recording from the extensor digitorum brevis, abductor polis brevis, and abductor digiti minimi while stimulating at the distal leg and wrist.

Patients were determined to have lumbar stenosis if they were diagnosed by a neurologist or neurosurgeon, and there was supporting imaging. For Romberg assessment, patients were asked to stand straight with feet together and arms at their side. They were then instructed to close their eyes. If they were not able to maintain balance, staggered, and opened their eyes, the test was determined to be positive. Gentle swaying was not characterized as a positive test.

Statistical Analysis

Continuous variables are presented as mean ± SD or as median (interquartile range) if not normally distributed and compared between variant groups using analysis of variance (ANOVA) and post hoc pairwise Welch *t* tests (2-tailed). Frequency data are presented as number (%) and compared across variant groups using the Fisher exact test. *p* Values <0.05 were considered significant for primary tests (ANOVA and Fisher exact), while *p* values below the Bonferroni-corrected α level of 0.017 (0.05/3) were considered significant for post hoc pairwise comparisons. Statistical analyses were performed in Python using the SciPy library version 1.7.2 and the Pandas module version 1.0.5. In instances where glomerular filtration rate (GFR) was recorded as >60 mL/min, a value of 60 was used. All figures were generated using Python matplotlib package version 3.4.3.

Standard Protocol Approvals, Registrations, and Patient Consents

Ethical approval was received from the Johns Hopkins University Institutional Review Board, under approved protocol IRB00282978. Informed consent was not required because of retrospective data collection from electronic medical records.

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

Baseline Demographics

A total of 75 patients were referred to the neurologist for evaluation of potential PN. Some, but not all, were referred with suspicion of amyloid. Nineteen patients were excluded from the study: 7 were genetic carriers without penetrant disease, and 12 had incomplete clinical records. Fifty-six patients with complete records remained: 31 with V122I, 12 with late-onset V30M, and 13 with L58H. Their clinical charts were abstracted for presenting neuropathic and cardiac symptoms and initial diagnostic test results including echocardiogram, EMG/NCV tests, laboratory studies and skin biopsies obtained for IENFD,[6,7] sweat gland nerve fiber density,[8] and Congo Red staining[9] through established protocols.

Patients with V122I were, on average, 6–7 years older than patients with V30M and L58H during presentation to the neurologist, and there was a male predominance across the 3 groups. Most of the patients with V122I (97%) were Black, and 1 patient (3%) identified as Hispanic or Latino. More than half of the patients with V30M (67%) were White, 17% were Asian, and 17% were Hispanic or Latino. All patients with L58H were White. Notably, patients with V122I and V30M were rarely aware of a family ATTRv diagnosis (10% and 17% of patients, respectively). Therefore, diagnosis required clinical suspicion (Table 1).

Table 1 Demographics

	V122I	V30M	L58H	*p* Value
N	31	12	13	NA
Female, n (%)	8 (26)	3 (25)	4 (31)	0.92
Age at presentation, y, mean (SD)	72.5 (8.4)	64.7 (2.6)	66.6 (7.8)	<0.01[aa]
Aware of genetic variant before diagnosis, n (%)	3 (10)	2 (17)	9 (69)	<0.01
Basis of diagnosis, n (%)				
Neurologic	1 (3)	8 (73)	11 (92)	<0.01
Cardiac	30 (97)	2 (18)	1 (8)	
Other[1]	0 (0)	1 (9)	0 (0)	
Cumulative multisystem involvement,[2] n (%)				
Peripheral nerve	29 (94)	12 (100)	13 (100)	1
Cardiac	29 (94)	10 (83)	4 (31)	<0.01
Gastrointestinal	2 (6)	5 (42)	7 (54)	<0.01
Neurologic function				
Neuropathic impairment score, points, mean (SD)	22 (16)	61 (31)	60 (28)	<0.01[a,bb]
Neuropathic symptom duration, y, mean (SD)	4 (6)	4 (3)	5 (4)	0.73
Neuropathy progression, NIS points per year, mean (SD)	10 (9)	20 (10)	20 (13)	<0.01
Renal function				
Creatinine, mg/dL, mean (SD)	1.7 (1.3)	0.9 (0.3)	0.9 (0.3)	0.03[a,b]
Glomerular filtration rate, mL/min, mean (SD)	54 (18)	67 (18)	64 (19)	0.06
Common comorbidities				
CTS, n (%)	30 (97)	7 (58)	10 (77)	<0.01
Bilateral CTS, n (%)	26 (84)	7 (58)	7 (54)	0.07
CTS preceded diagnosis, n (%)	13 (42)	4 (33)	4 (31)	0.81
CTS preceded diagnosis by > 7 y, n (%)	9 (30)	2 (17)	3 (23)	0.84
Lumbar stenosis, n (%)	8 (26)	3 (25)	7 (54)	0.17

Abbreviation: CTS = carpal tunnel syndrome; NA = not applicable.
[1] Diagnosed after vitreous detachment.
[2] "Cumulative multisystem involvement" refers to system involvement found through follow-up visits through July 2021, all other measures are reported during initial presentation to the neurologist.
V122I vs V30M: a: $p < 0.017$; aa: $p < 0.001$.
V122I vs L58H: b: $p < 0.017$; bb: $p < 0.001$.
V30M vs L58H: c: $p < 0.017$; cc: $p < 0.001$.

Initial Presentation

Nine patients had other potential causes for PN (such as diabetes or hypothyroidism). In all instances, the other cause was well controlled and not felt to be responsible for the patients' PN. For example, the mean A1c among the 4 patients with diabetes was 6.2 ± 0.48, and neuropathy severity was not statistically different among those with or without diabetes. Although severity differed, all groups showed clinically significant peripheral nerve involvement (94%/100%/100% V122I/V30M/L58H); despite this, most of the patients with V122I were diagnosed based on cardiac disease, while most of the patients with V30M and L58H were diagnosed based on neurologic involvement. Three patients with V122I had evidence of cardiomyopathy but tested normally on peripheral nerve assessment. The V122I cohort showed the highest rates of cardiac involvement (94%), followed by patients with late-onset V30M (83%), while patients with L58H showed the highest level of GI involvement with 54% of patients affected. Patients with V122I had the most severe renal impairment (Table 1). Fewer patients in the V122I cohort (5/31) had GFR recorded as >60 compared with the V30M (7/12) and L58H cohorts (5/13), which likely underestimates the difference between the groups.

CTS and lumbar stenosis were common comorbidities across variants, though CTS was most common among patients with V122I (97% affected, 84% with bilateral CTS), while lumbar stenosis was most common among patients with L58H (54%) (Table 1). One patient with V122I presented with pronounced PN (NIS = 66) with no structural cardiac involvement after amyloid was identified by sural nerve biopsy. Conversely, 1 patient with L58H was diagnosed by an endomyocardial heart biopsy.

While most patients with V122I were diagnosed by cardiac evaluation, more than 60% reported that their neuropathy symptoms began concurrently with or even proceeded cardiac symptoms (Figure 1), though symptoms of peripheral and focal neuropathies were not investigated until after ATTRv diagnosis by a cardiologist.

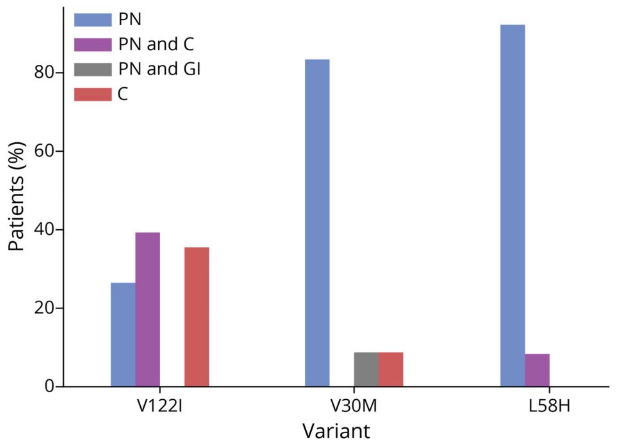
Assessment of Neurologic Disease Burden

NISs (Table 2) show that all 3 groups had PN. The relative breakdown between sensory, strength, and reflex abnormalities followed a similar pattern, with most of the points (deficits) accrued from loss of strength. In part, this is due to the NIS measure being weighted toward motor function. As summarized in Table 1, patients with V122I progressed at approximately half the rate of patients with V30M and L58H.

Numbness, weakness, and neuropathic pain were uniform complaints across all variants, while painless injuries were less common, especially in the V122I cohort. Of interest, there was a high prevalence of positive Romberg sign, which was common in all groups, especially in the L58H cohort. A positive Romberg was observed among 39% patients with V122I despite having milder neuropathy (Figure 2). NCV studies showed that patients with V30M experienced the greatest reduction in both sensory and motor nerve amplitudes, followed by patients with L58H. Patients with V122I had milder involvement, but still showed significant reductions relative to age-matched/sex-matched healthy controls (Figure 3A).

Skin biopsies revealed significantly decreased nerve fiber densities at all sites relative to age-matched/sex-matched

Figure 1 Patient-Reported Initial Symptoms



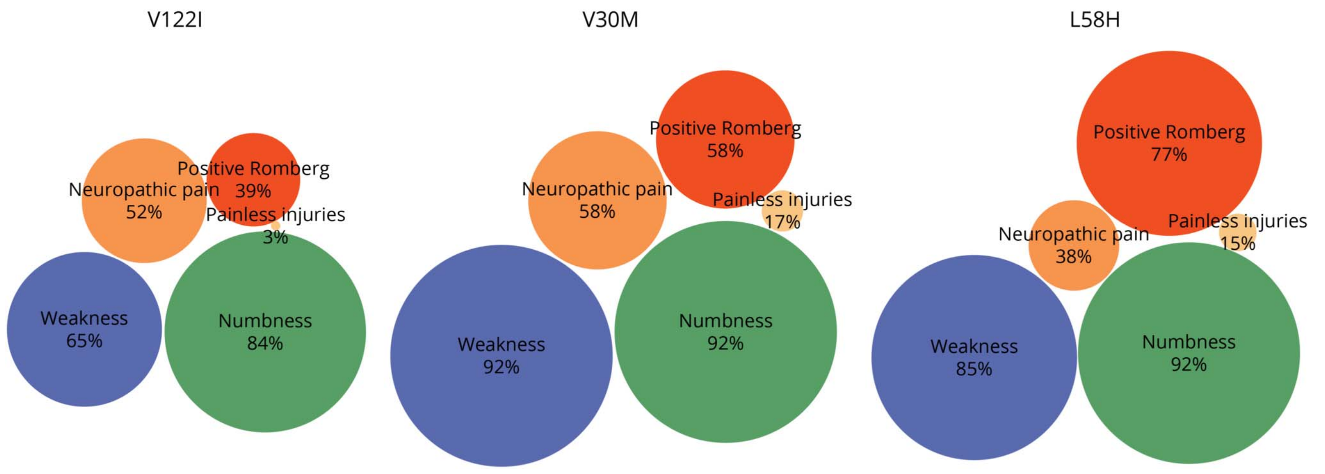
C = cardiac; GI = gastrointestinal; PN = peripheral nerve.

Table 2 Neurologic Examination

	V122I	V30M	L58H	*p* Value
NIS, mean (SD)				
NIS total	22 (16)	61 (31)	60 (28)	<0.01[a,bb]
NIS strength	9 (13)	29 (22)	32 (17)	<0.01[bb]
NIS reflexes	5 (4)	11 (5)	11 (6)	<0.01[b]
NIS sensation	7 (5)	18 (8)	17 (7)	<0.01[a,bb]
NIS vibration: Fingers	1 (1)	1 (1)	1 (1)	0.09
NIS vibration: Toes	3 (2)	4 (1)	4 (1)	0.06[a,b]
Rydel tuning fork, mean (SD)				
Digit II	12 (3)	10 (5)	7 (5)	0.02
Knee	7 (4)	8 (4)	6 (6)	0.57
Ankle	6 (4)	4 (6)	4 (4)	0.58
Great toe	3 (4)	2 (5)	1 (2)	0.24[b]

Abbreviation: NIS = neuropathic impairment score.
V122I vs V30M: a: $p < 0.017$; aa: $p < 0.001$.
V122I vs L58H: b: $p < 0.017$; bb: $p < 0.001$.
V30M vs L58H: c: $p < 0.017$; cc: $p < 0.001$.

Figure 2 Frequency of Neurologic Signs and Symptoms by Genotype



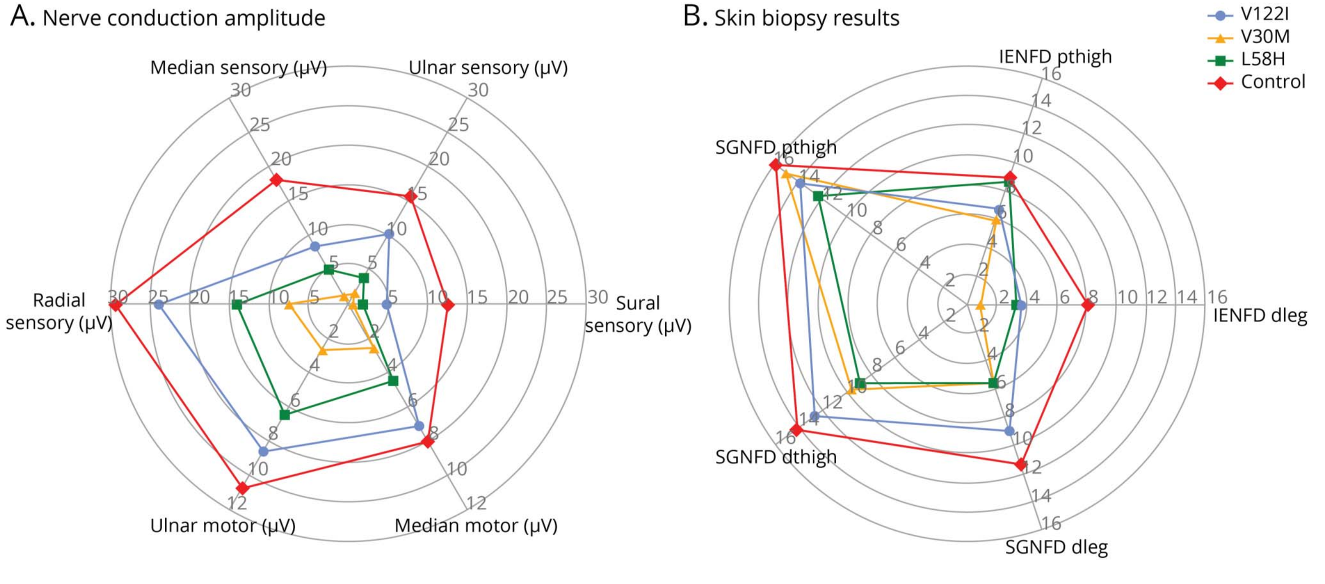
*Circle area is proportional to the percentage of patients of that group showing each sign or symptom.

controls with impairment of both sensory and sudomotor nerves associated with all 3 variants (Figure 3B). Nerve fiber density at the ankle was reduced in 71% of patients with V122I, 100% of patients with V30M, and 82% of patients with L58H. Skin biopsies were Congo red positive in 40%, 73%, and 83% of patients with V122I, V30M, and L58H tested, respectively, confirming systemic involvement (Figure 4).

Assessment of Cardiovascular Disease Burden

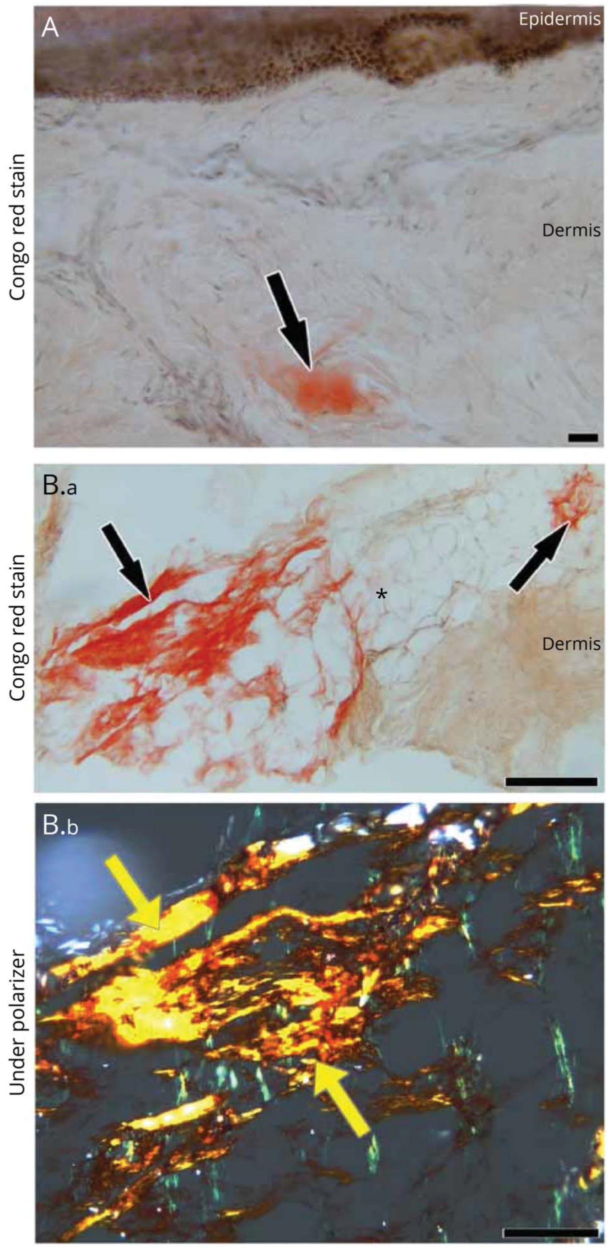
Cardiac parameters are described in all 3 variants (Table 3) and most pronounced in patients with V122I, as shown by the increased interventricular septal thickness, increased left ventricular wall thickness, most frequent use of loop diuretics, and the highest rate of atrial fibrillation. Patients with V122I also had a greater reduction in ejection fraction, which is suggestive of more advanced cardiac involvement of the disease. Among laboratory tests, N-terminal pro b-type natriuretic peptide (proBNP), a cardiac biomarker released by the heart in response to ventricular stretch as occurs in heart failure, was highest among patients with V122I. To our surprise, all 3 variants had similar blood pressures. We had hypothesized that increased cardiac involvement would be associated with lower blood pressure.

Figure 3 Measures of Peripheral Neuropathy: (A) Nerve Conduction Results and (B) Skin Biopsy Results



(A) Radar plot showing sensory (μV) and motor nerve (mV) amplitudes by hATTR genotype with age-matched/sex-matched controls. (B) Radar plot demonstrating unmyelinated sensory (fibers/mm) and sudomotor nerve fiber (nerve fiber length/mm^3) involvement at different leg sites. hATTR = hereditary transthyretin amyloidosis; IENFD = intraepidermal nerve fiber density; SGNFD = sweat gland nerve fiber density.

Figure 4 Skin Sections Stained With Congo Red



Representative 50 µm distal leg skin section from a patient with hATTR peripheral neuropathy. (A, B) Congo red staining demonstrates amyloid deposition (arrows) in the superficial dermis and in the deep dermis infiltrating subcutaneous fatty tissue (*). Amyloid is confirmed by the presence of birefringence (yellow arrows) under polarizer. Scale bar: 50 µm. hATTR = hereditary transthyretin amyloidosis.

Discussion

We report the clinical findings of 3 ATTRv genetic variants commonly seen at our institution: V122I, late-onset V30M, and L58H. Each of these have distinct clinical profiles, and in 2 of these, V122I and L58H, peripheral nerve involvement is not well known. We observed several notable patterns. First, while 97% of patients with V122I were identified based on cardiac symptoms, many had clinically meaningful PN that preceded or was contemporaneous with cardiac symptoms. Second, patients with L58H presented predominantly with neuropathy and little cardiac involvement but often had GI involvement and spinal stenosis. Finally, all patients with V30M presented after the age of 50 years, had advanced PN during diagnosis, and showed a variable pattern of presentation. These patterns underscore the variability in ATTRv and highlight the importance for clinical suspicion to make a diagnosis.

Patients with V122I were diagnosed at a later age, were the least likely to be aware of a family history of amyloidosis, and had the most pronounced cardiac involvement among the 3 variants. In addition, patients with V122I were less likely to have a history of lumbar stenosis and had lower baseline renal function—likely a manifestation of their cardiac involvement.[10] Surprisingly, there was no difference among the 3 variants with systolic or diastolic blood pressures as we hypothesized that because patients with V122I have more prominent cardiac involvement, they would have lower blood pressures. V122I is the most common pathogenic variant in the United States[11] affecting 3%–4% of Black individuals.[12] Consistent with these reports, all but one of our patients with V122I identified as Black. Most of our patients with V122I had PN and identified neuropathy as a presenting or copresenting feature (with cardiac involvement) of their amyloidosis. We observed that V122I-PN was milder than PN related to Leu58His or Val30Met. These findings are consistent with smaller studies or case reports.[13-16] The neuropathy predominantly affects sensory nerve fibers by NCV testing though most of the deficits were attributed to weakness by the NIS assessment, which is weighted toward strength. The progression of PN severity was slower among patients with V122I, approximately half that of patients possessing the L58H or V30M variants. Nearly all patients had symptomatic median neuropathy at the wrist (84% bilateral), and CTS preceded their ATTRv diagnosis by ≥7 years in nearly one-third of cases. These rates are higher than what has been reported in other variants.[17-19] Often, this was associated with prominent motor axon loss and hand weakness for which patients never sought medical attention and was identified only after the ATTRv diagnosis. Therefore, an opportunity for early diagnosis of penetrant V122I ATTRv is to educate target populations about CTS and its link to ATTRv. Polyneuropathy prevalence among V122I carriers between is reported as 2.1%–9.0% across 3 large biobanks based on *International Classification of Diseases, 10th Revision* (*ICD-10*) codes.[12] The variable estimates of PN among patients with the V122I allele observed in that study could be due to differences in ICD codes or a relative lack of a formal peripheral nerve evaluation similar to what we observed with CTS. Small, unmyelinated—both sensory and sudomotor—and large myelinated axons were equally affected, a pattern that stands out compared with other common forms of PN and early-onset V30M ATTRv, which often has a small fiber predominant presentation.[20,21]

Pain was reported in 52% of cases, and Congo Red staining in skin biopsies of the leg was detected in 40% of cases. This was

Table 3 Cardiac Assessments

	V122I	V30M	L58H	*p* Value
Echocardiogram				
Ejection fraction, %, mean (SD)	41.5 (11.8)	63.0 (5.7)	59.8 (7.0)	<0.01[aa,b]
Left ventricular wall thickness, cm, mean (SD)	4.25 (0.77)	3.76 (0.57)	4.36 (0.51)	0.12
Interventricular septum thickness, cm, mean (SD)	1.70 (0.29)	1.42 (0.38)	1.23 (0.36)	<0.01
Medications				
Loop diuretic, n (%)	26 (84)	1 (8)	1 (8)	<0.01[aa,bb]
Furosemide dose equivalent, mean (SD)	2 (2)	0.5	2	0.72
Mineralocorticoid antagonist, n (%)	7 (23)	1 (8)	1 (8)	0.42
Blood pressure, mm Hg, mean (SD)				
Systolic	116 (14)	121 (14)	123 (18)	0.40
Diastolic	72 (13)	71 (4)	76 (12)	0.53
Other				
NT-proBNP, pg/mL, mean (SD)	5,939 (9,621)	796 (970)	404 (677)	0.05[a,b]
Atrial fibrillation, n (%)	12 (39)	1 (8)	2 (15)	0.09

Abbreviation: NT-proBNP = N-terminal pro b-type natriuretic peptide.
V122I vs V30M: a: $p < 0.017$; aa: $p < 0.001$.
V122I vs L58H: b: $p < 0.017$; bb: $p < 0.001$.
V30M vs L58H: c: $p < 0.017$; cc: $p < 0.001$.
1 furosemide dose equivalent = 40 mg furosemide = 20 mg torsemide = 1 mg bumetanide.

a less common finding than with the other variants, which is consistent with our previous observation that amyloid burden correlates with neuropathy severity.[9,22] Patients with V122I had markedly thicker interventricular septum, higher pro-BNP values, and higher rates of arrythmia than the other variants, reflecting the prominent cardiac involvement of V122I and the cardiologist-based referral pattern of our patients with V122I. The interventricular septum thickness for our patients with V122I was similar to that reported for the cardiac subgroup of the APOLLO study (1.63 vs 1.70 cm), though our patients with V122I had higher proBNP levels (837 vs 5,939 pg/mL).[23,24] Taken together, these results not only demonstrate the cardiac predominant involvement of the V122I variant but also show that a sensory predominant PN is a common complication and is associated with a positive Romberg sign.

Patients with V30M from our cohort all had late-onset (after the age of 50 years) disease and severe PN with prominent upper and lower extremity involvement that limited walking and independence. Most of the patients with V30M (10/12, 83%) were diagnosed de novo, and family history was identified only retrospectively. PN was the presenting symptom among nearly all patients with V30M and was the most severe among the 3 variants we studied. Neuropathy severity was more pronounced than described in European and Japanese late-onset cohorts.[25,26] For example, the sural and ulnar sensory amplitudes in our patients were 0.5 ± 1.8 μV and 1.5 ± 3.7 μV compared with 4.1 ± 3.9 μV and 5.8 ± 3.9 μV, respectively, in the French late-onset group, and peroneal motor amplitudes were 0.2 ± 0.5 mV vs 1.3 ± 1.4 mV, respectively. In our cohort, even radial sensory nerve amplitudes were reduced at 7.5 ± 9.8, and a Romberg sign was present in 58% of patients. The increased neuropathy severity observed among our V30M cohort might be attributable to differences in the rate of disease progression or a longer delay in diagnosis, given the nonendemic nature of ATTRv in the United States. Pain was common, but relatively mild and demyelinating features were observed in only 1 patient in contrast to European reports where hATTR can present as a demyelinating neuropathy in 20%–25% of cases.[27,28] There were similar degrees of sensory and motor fiber involvement consistent with other late-onset V30M cohorts from in Europe and Japan.[25,26] Cardiac involvement was common though milder when compared with our patients with V122I.

The Leu58His ATTR variant is common in Western Maryland among families of German descent. Our patients with Leu58His had prominent PN with sensory loss and weakness. The severity was intermediate between the V30M and V122I cohorts. Neuropathic pain and symptomatic heart failure were relatively uncommon, though diarrhea and constipation were common. A family history was appreciated among most of our patients with L58H and was facilitated by extended families living in close proximity.

A positive Romberg sign was a common finding in all 3 genetic variants, even patients with V122I who had milder neuropathy. In many cases, this was out of proportion to neuropathy severity and may reflect amyloid deposition along the entire nerve length and dorsal root ganglion that results in dysfunction and variable degrees of axon loss.[29-31] It is also possible that other factors such as lumbar stenosis or dorsal column involvement as described in other forms of amyloidosis contributed.[32] This clinical examination sign along with a history of CTS, which was a common finding across variants, can serve as clinical clues to diagnosis.

There are several notable limitations to our study. Patients were diagnosed through different routes, and this may lead to an ascertainment bias. Despite identifying neuropathy as a presenting complication of disease, most patients with V122I were diagnosed on the basis of cardiac involvement. Syncope or exertional dyspnea likely prompt more rapid evaluation compared with limb numbness and weakness. This combined with cardiac assessments that facilitate diagnosis (altered echogenicity, strain imaging and thickened interventricular septum on echocardiogram) contribute to patients with V122I being diagnosed while their PN is milder. In addition, several of our patients with Leu58His were suspicious that they had penetrant disease based on family history awareness, but only sought medical attention after clinical trials were available.

We describe the peripheral nerve and cardiac features of patients with ATTRv at diagnosis including those with V122I (most prevalent variant in the United States), V30M (most prevalent globally), and L58H (poorly described to date). Taken together, this report highlights the challenge of diagnosing ATTRv in the United States. There is a broad heterogeneity of presentation within and between variants that delays diagnosis of a rare disorder in nonendemic areas. Symptoms of PN and CTS were common presenting features across variants, even among patients with V122I who were diagnosed only after developing cardiac involvement. Screening for symptoms across all systems affected (cardiac, peripheral nerve, GI, and musculoskeletal) and for imbalance (which disproportionately affects our patients) can improve diagnosis of this rare, progressive, but now treatable disease.

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