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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

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Abstract

Since the identification of a valine-to-isoleucine substitution at position 122 (TTR V122I; pV142I) in the transthyretin (TTR)-derived fibrils extracted from the heart of a patient with late-onset cardiac amyloidosis, it has become clear that the amyloidogenic mutation and the disease occur almost exclusively in individuals of identifiable African descent. In the United States, the amyloidogenic allele frequency is 0.0173 and is carried by 3.5% of community-dwelling African Americans. Genotyping across Africa indicates that the origin of the allele is in the West African countries that were the major source of the slave trade to North America. At autopsy, the allele was found to be associated with cardiac TTR amyloid deposition in all the carriers after age 65 years; however, the clinical penetrance varies, resulting in substantial heart disease in some carriers and few symptoms in others. The allele has been found in 10% of African Americans older than age 65 with severe congestive heart failure. At this time there are potential forms of therapy in clinical trials. The combination of a highly accurate genetic test and the potential for specific therapy demands a greater awareness of this autosomal dominant, age-dependent cardiac disease in the cardiology community.

Keywords

African American; amyloidosis; autosomal dominant; cardiomyopathy; transthyretin

Isolated amyloidosis of the heart was described at autopsy in the mid-nineteenth century.[1] Later studies distinguished atrial (composed of fibrils derived from atrial natriuretic peptide) from ventricular deposition.[2,3] Congestive heart failure and arrhythmias occurred

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DISCLOSURE

J.N.B. has been a paid consultant for Foldrx pharmaceuticals, Pfizer pharmaceuticals, Alnylam Pharmaceuticals, Isis (now Ionis) Pharmaceuticals, and Prothena Pharmaceuticals, all of which have drugs in development or in clinical trials for the transthyretin amyloidoses. F.L.R. has received consulting honoraria from Prothena Pharmaceuticals and Alnylam Pharmaceuticals.

almost exclusively in subjects with significant ventricular deposition. In contrast to the mutant forms of transthyretin (TTR) comprising the fibrils in tissue deposits in familial amyloidotic polyneuropathy (FAP) with significant cardiomyopathy (OMIM 1105210.0009),[4] molecular studies of hearts performed during autopsies of elderly Swedish subjects with congestive heart failure established that the amyloid deposits were composed of wild-type TTR.[5,6]

ATTR V122I (PV142I)

Amyloid fibrils extracted from the heart of an elderly patient with isolated cardiac amyloidosis and no family history were composed of TTR with a substitution of isoleucine for valine at position 122 (TTR V122I; pV142I).[7] DNA from the subject demonstrated homozygosity of the C → G transition, which caused the substitution, suggesting recessive inheritance; however, subsequent reports of similarly affected patients revealed homozygous and heterozygous V122I mutations, indicating dominant heredity.[6]

THE TTR GENE AND PROTEIN

TTR is a 55-kDa homotetramer with binding sites for thyroxine (T4) and retinol binding protein charged with retinol.[8] In humans, it is the major serum carrier of retinol bound to retinol binding protein and a minor serumT4 transporter. It is the only carrier of T4 in the cerebrospinal fluid, which provides the hormone to the CNS during development.[9] TTR is encoded by a conserved single gene on chromosome 18.[10] Most of the circulating protein is synthesized by hepatocytes, but there is also synthesis by retinal and choroid plexus epithelial cells, pancreatic α-cells, Schwann cells, and neurons under stress.[11–13] Mice with both copies of the gene silenced display a behavioral abnormality throughout life, and it has been suggested that they exhibit a physical developmental delay that normalizes in young adults.[14–16]

THE MECHANISM OF TTR AMYLOID FIBRIL FORMATION

Biophysical studies with purified recombinant TTR V122I revealed that, in contrast to the thermodynamically unstable FAP mutant TTR's V30M and L55P, its tetramer was kinetically unstable relative to the wild-type, i.e., the rate of tetramer dissociation was high enough to provide a pool of misfolded monomers capable of aggregating under physiologic conditions (Figure 1).[17]

POPULATION GENETICS IN THE UNITED STATES

The first three TTR V122I probands were African Americans, suggesting that the allele might be enriched in populations of African descent. Table 1 summarizes the results of studies of *TTR* V122I carrier prevalence in African Americans. The combined allele frequency is 0.0173, with a predicted occurrence in homozygotes of 3×10^{-4} by approximating the number found in population studies, which is consistent with Hardy-Weinberg equilibrium. Two studies of African-American newborns did not reveal significant differences in the allele frequency between infants and adults, suggesting that in the United States there was no selective advantage or disadvantage of the allele for reaching adulthood;

this observation replicated in Ghana.[18] Because V122I-associated disease typically occurs in the seventh or eighth decade of life in heterozygotes, it is unlikely to affect reproductive fitness. Genotyping for the allele across Africa revealed the highest prevalence in West Africa, which is the ancestral home of African slaves transported to North America (Figure 2).[19]

In the United States, the allele frequency in individuals without documented African origin is very low.[20] However, allele carriers of uncertain African descent have been identified in the United Kingdom, Italy, and France. Studies designed to establish their ancestry are in progress.[21–23]

The V122I amino acid variant is encoded in the genome in the single-nucleotide polymorphism rs76992529. The G → A transition resulting in the amyloidogenic TTR allele involves a CpG dinucleotide, a structure suggested to be a mutational “hot spot”; therefore, it is possible that non-African relatives carry mutations that originated independently.[24]

DISEASE ASSOCIATIONS

Case studies

Case reports of homozygous and heterozygous TTR V122I carriers (including a family with a homozygous parent and heterozygous child) indicated that homozygous individuals became symptomatic in their late 50s and early 60s, whereas heterozygotes developed congestive heart failure between the ages of 60 and 80.[25,26] The cardiac amyloid was usually identified at autopsy.

Autopsy series

Investigation of material from 52,000 autopsies performed at the Los Angeles County–USC Medical Center (1949–1982) revealed that isolated cardiac amyloidosis was twice as common in elderly African Americans as in comparably aged Caucasians and was 10 times more common than in Hispanics of Mexican origin.[27] Ninety-five percent of hearts with isolated amyloid deposition contained TTR.[28] All of the Caucasians were presumed to be of the V122V wild-type TTR genotype. Six of the 12 African-American hearts that were genetically evaluable were positive for TTR V122I, suggesting that the allele was responsible for at least half of the late-onset cardiac TTR amyloidosis in this population. However, for these subjects identified in the pre-echocardiographic era, there was insufficient information to determine clinical penetrance.

In the same study, tissues from 112 consecutive autopsies of African Americans aged 65 or over that were performed at the same institution between 1984 and 1985 were genotyped for the TTR V122I encoding allele. Four of the samples (3.6%, a figure remarkably close to the prevalence in living African Americans) were positive for the amyloidogenic allele. Re-examination of the hearts by pathologists blinded to the genotyping revealed TTR amyloid deposition in the four independently identified TTR V122I carriers, suggesting that TTR V122I had an absolute anatomic risk for cardiac amyloidosis after age 65.

Retrospective

Retrospective series of patients with TTR V122I cardiac amyloidosis have been reported by amyloid referral centers (Table 2). Most of the patients had severe congestive heart failure at the time of presentation and, hence, were late in the course of their disease. A comparison of African Americans with documented cardiac amyloidosis due to amyloid derived from immunoglobulin light chain (AL) with those whose deposits consisted of V122I TTR fibrils by the Amyloid Treatment and Research Program at Boston University revealed later onset in the TTR patients (70 vs. 57 years) with greater male preponderance (78 vs. 58%[29]). In their population (i.e., African Americans referred to an established amyloid treatment center with a diagnosis of cardiac amyloidosis), every individual had an equal chance of having AL or ATTR V122I deposition despite the higher frequency of AL in African Americans. Carpal tunnel involvement was more frequent in the ATTR group, whereas the AL subjects showed more renal and peripheral nerve deposition. Five of the 32 TTR V122I carriers were homozygous.

A retrospective analysis of 25 patients, all with some degree of cardiac failure and found to carry the TTR V122I encoding allele, referred to the National Amyloidosis Centre at the Royal Free Hospital in London for evaluation of cardiac amyloidosis found a spectrum of ethnic origins, including one Caucasian, several Nigerians, and a majority of subjects described as Afro-Caribbean, which is consistent with prior data regarding the association of African heritage with the allele.[30] Three were homozygous for the amyloidogenic allele and had a significantly lower mean age of onset than the heterozygous carriers (61 vs. 70 years). Again, the presence of congestive failure indicated advanced disease at the time of referral.

Prospective studies

A small, prospective, multicenter collaborative study (Transthyretin Amyloidosis Cardiac Study) of subjects with confirmed TTR cardiac amyloidosis recruited 11 patients with TTR V122I and 18 patients with wild-type TTR deposition.[31] The V122I patients were younger, although not significantly so ($P = 0.06$). All had significant congestive heart failure. Those with V122I had much higher mortality rates than the wild-type subjects for the duration of the study. Because of their mode of ascertainment, as in the Boston and London series, it is likely that they were late in the course of their disease at the time of entry into the study (i.e., with diminished systolic ejection fractions).

In a unique study using a prospective case–control design, 25 TTR V122I carriers were identified by genotyping consenting African-American subjects older than age 60 who were referred for echocardiography (21/25) or were in the general population of a Department of Veterans Affairs Hospital (4/25).[32] Each allele carrier was matched for age, gender, ethnicity, and blood pressure level with two homozygous wild-type TTR individuals. Although those referred for cardiac ultrasound were being investigated for either congestive heart failure or hypertensive heart disease, none had a clinical diagnosis of cardiac amyloidosis. The frequency of the allele was greater, but not statistically significantly so, in subjects referred for cardiac evaluation than in the general hospital population (5.5 vs. 4.5%).

When studied with echocardiography and electrocardiography, the allele carriers differed significantly from the TTR wild-type individuals in resting heart rate, frequency of conduction abnormalities, and the presence of Q waves; they frequently showed a pseudo-infarction pattern. Echocardiography revealed differences in the mean thickness of the interventricular septal and posterior ventricular walls, frequency of right ventricular hypertrophy, mitral deceleration time, and occurrence of granular sparkling.[33] The two groups did not differ regarding estimated left ventricular mass, ejection fraction, or left atrial diameter.

The ultrasound data were quite different from those presented in the retrospective studies of allele carriers in which all the subjects came to the attention of amyloid referral centers with known cardiac amyloidosis and congestive heart failure. In the latter group, the septal- and ventricular-wall dimensions were much greater. The left atrial cavity was more dilated and right ventricular hypertrophy was more common. In addition, the mean ejection fraction was well below 50% (Table 2). These observations suggest that ascertainment by genotyping is a high-yield and useful procedure identifying patients at risk before they are severely ill and possibly more likely to be responsive to specific therapy if and when treatments become available. The study also indicated that 75% of the allele carriers had anatomic (by echocardiogram) evidence of cardiac amyloidosis and that congestive heart failure (primarily diastolic) and/or atrial fibrillation were twice as common as in the age-, gender-, and ethnically matched allele-negative subjects. These observations support the notion that the amyloidogenic allele is clinically highly penetrant in elderly allele carriers referred for cardiac evaluation.[32]

The argument for aggressive genotyping is also supported by an analysis of the frequency of TTR V122I carriers in the Beta-Blocker Evaluation Survival Trial (BEST), which included 5,500 individuals (670 African Americans) above age 35 with New York Heart Association grade III or IV congestive heart failure.[34] DNA was available from 1,000 participants, including 207 African Americans. A diagnosis of cardiac amyloidosis excluded patients from the study. Nonetheless, in subjects older than 60, 10% of the congestive heart failure patients carried the amyloidogenic allele (compared with 2.12% of a community-based sample of African Americans older than age 65). The difference was highly significant, particularly because African-American subjects older than 60 were underrepresented in the DNA cohort compared to the entire study group. These data suggest that allele carriers with significant cardiac amyloidosis are overrepresented among elderly African Americans with severe congestive heart failure. The data also indicate that the diagnosis is not easily made even by cardiac physicians responsible for enrolling patients in a therapeutic trial. Among the BEST African-American subjects younger than 60 years with severe heart failure, the frequency of TTR V122I was 3.5%, which is not different from that of the African-American population at large and is consistent with the age dependence of the clinical phenotype.

A recent study from five cardiology clinics in France revealed that, of 300 consecutive patients with a diagnosis of hypertrophic cardiomyopathy who underwent exomic sequencing of their TTR genes, 15% had a pathogenic TTR variant. Surprisingly, the most

common mutation was TTR V122I.[21] The ethnic origin of the V122I-positive subjects is under investigation.

Outcomes

Because TTR V122I cardiac amyloidosis appears to be age-dependent, the prevalence of the allele in an "at-risk" population should reflect the mortality effect (if any) of the condition. To address this question, the allele frequency was determined in DNA samples from two populations selected to demographically represent the African-American community at large, one older than 65 (Cardiovascular Health Study; CHS) and one younger than 65 (Atherosclerosis Risk in Communities; ARIC). If the TTR V122I allele behaves as a disease-causing or disease-associated gene with age-dependent penetrance, then the frequency of the allele in the younger population should be similar or identical to that found in population studies and should be lower in the older cohort, reflecting an impact of the allele on mortality. The allele frequencies differed considerably between the two populations (ARIC 0.016 vs. CHS 0.011). Kaplan-Meier plots of the two populations showed a statistically significant impact on mortality in the older male subjects. In CHS females no effect was seen, suggesting a strong protective effect of gender, the mechanism of which is unknown. Higher relative risks were observed in allele carriers of congestive heart failure, particularly after age 70; higher risk of death was observed for 9 years after inception of CHS, after which the cumulative frequency of death in the amyloidogenic and wild-type allele carriers approached equity. Further, the differences in median values for some echocardiographic features of cardiac amyloidosis in allele carriers compared with nonallele carriers approached statistical significance, despite a very small number of TTR V122I allele carriers in the sample. This is particularly striking when one compares the same parameters in allele and nonallele carriers in the larger ARIC cohort comprising those younger than 65, in which no differences were detectable in any of the relevant parameters, again suggesting that TTR V122I disease is autosomal dominant with age-dependent penetrance.

A follow-up analysis of TTR V122I allele carriers in the ARIC population indicated that clinical penetrance of the allele may be lower than estimated in the case–control study.[35] The authors proposed that the high frequency of congestive failure and arrhythmia reported earlier may have reflected a degree of ascertainment bias because the allele carriers were identified among male patients undergoing cardiac ultrasonography for suspected heart disease. In the more recent study, congestive heart failure and findings consistent with cardiac amyloidosis were increased in the carrier males. However, differences in overall mortality were not statistically significant. Age and gender, previously found to be significant covariates of penetrance, could not be documented to play a role, perhaps because in the surviving population and those available for evaluation females were highly overrepresented. The data sets remain to be fully reconciled.

Open questions

The reported autopsy study showed that after age 65, all TTR V122I carriers had some degree of cardiac amyloid deposition. The extent of clinical penetrance is less certain. Studies of penetrance of other *TTR* mutations suggest that gene–gene or gene–environment interactions play a role in age of onset of clinical disease.[36]

The case–control analysis indicated that echocardiographic evidence of amyloid deposition was present in three-quarters of the allele carriers at the time of analysis (mean age, 73). At the same time, congestive heart failure, as manifested by diastolic dysfunction or arrhythmia, was present in approximately half of those showing echocardiographic abnormalities. It is unclear whether the 20–25% of TTR V122I–positive subjects older than 70 who had no abnormalities will ever show any evidence of disease or whether their age of onset will be later.

TTR V122I patients are underrepresented or absent from many reports describing large numbers of patients with hereditary cardiac amyloidoses, even from centers evaluating subjects with disease related to TTR mutations. One reason is geographic. Many of the TTR mutations occur in a single family member or a small number of relatives; they are generally recognized by the presence of polyneuropathy, a more blatant clinical presentation than early cardiomyopathy, and occur in confined geographic foci. The most common polyneuropathic mutation (TTRV30M) was described independently in three locations where there was little African representation: Portugal, Japan, and northern Sweden.[4,37,38] Over time, it became clear that many of these subjects also had cardiomyopathy. The first mutations with predominant cardiac clinical phenotypes Met111 and Ala60 were also described in kindreds of northern European origin (Denmark and Ireland).[39,40] Similarly, recent comprehensive studies of a large number of Italian TTR mutation carriers have provided much insight into disease pathogenesis but involved few subjects of African origin.

The second factor resulting in a lack of representation of TTR V122I carriers in a large series, particularly in the United States, was socioeconomic in that amyloid referral centers that had accumulated a sufficient number of cardiomyopathy patients to report did not serve patient populations likely to have significant numbers of subjects of West African descent. As physicians in centers with larger, more economically diverse patient populations have become aware of the disease, larger numbers of affected TTR V122I carriers have been identified and included in more recent clinical analyses (Table 2).[29,30]

Diagnosis

The first principle of diagnosis of TTR V122I cardiac amyloidosis or any amyloidosis is to consider the possibility. Without thinking of the diagnosis, it is unlikely that the definitive test (i.e., subcutaneous fat aspiration or endomyocardial biopsy) will be performed.[41,42] The manifestations of the disease(s) reflect the patient’s physiologic status and may be indistinguishable from those with cardiomyopathy of any cause, including cases of hypertensive, hypertrophic, or coronary artery disease in which diastolic dysfunction appears early. Hence, understanding the epidemiology and the clinical history is critical in forming one’s initial set of diagnostic possibilities. The case–control study cited above suggests that when presented with a male individual over age 60 of known African descent with symptoms and signs of diastolic dysfunction confirmed by echocardiography, the possibility of TTR V122I cardiac amyloidosis should be considered, particularly in the presence of interventricular septal and left ventricular posterior-wall thickening. These findings are of moderate sensitivity (57%) but good specificity (90%, Figure 3a). In that same study, neither the presence of hypertension nor the absence of low voltage on the electrocardiogram

eliminated a diagnosis of cardiac amyloid deposition. Many affected patients have cardiac-wall thickening that is incorrectly attributed to hypertensive disease. A low-voltage ECG in the setting of increased ventricular-wall thickness is reasonably specific for amyloid; however, it is not highly sensitive and is even less so in TTR than in AL cardiac deposition.[23,43,44]

In recent years, studies have reported Doppler longitudinal systolic strain measurements and cardiac magnetic resonance findings that appear to be characteristic of cardiac amyloidosis and that the nuclear bone-avid tracers Tc^{99}DPD or PYP can distinguish between AL and TTR cardiac deposition[45–48] (Figure 3b,c). The findings from the case–control study cited above, which preceded the availability of these more current techniques, suggest that in that particular clinical setting, genotyping for the TTR V122I allele may be equally informative. Once the diagnosis of cardiac amyloidosis is established, the nature of the precursor can be ascertained by either subcutaneous fat aspiration or endomyocardial biopsy with mass spectrometry of the sample or staining of the tissue with Congo red and antibodies specific for individual precursors (i.e., anti-TTR, anti-κ, or anti-λ) that are most likely to be responsible in this age group.[49] Because immunohistochemistry expertise varies greatly across institutions, mass spectrometry has been suggested as a more reliable standard. It is important to note that subcutaneous fat aspirate identifies amyloid deposition by Congo red staining in approximately 70% of cases; therefore, a negative aspirate does not preclude the diagnosis of ATTR V122I.[40] Involvement of other organ systems can also suggest amyloid type because AL is more likely to be associated with renal disease and peripheral neuropathy than cardiac TTR amyloid deposition.[29]

It appears that in elderly men, TTR V122I deposition precedes wild-type TTR deposition by approximately a decade.[28] Many studies have indicated the characteristic echocardiographic findings associated with restrictive cardiomyopathy and diastolic dysfunction in cardiac amyloidosis.[50] The argument regarding the relevance of late-stage diagnosis in amyloid referral centers is clear from the data shown in Table 2. Comparison of the conventional echocardiographic and electrocardiographic features of cardiac amyloidosis in TTR V122I carriers identified by preemptive genotyping of African Americans older than age 60 referred for echocardiography in a general hospital with those reported from amyloid referral centers revealed lesser amounts of amyloid deposition and diastolic dysfunction and no evidence of left ventricular dysfunction in the patients first identified as TTR V122I carriers. Hence, the diagnosis of early disease should come to mind using age and African origin, with evidence of diastolic dysfunction and septal thickening as filters for genotyping in this clinical setting. Although the population yield may be small (5–10%), the clinical impact on the individual allele carriers and their families will be high, particularly as effective therapies become available.

There is now sufficient experience with cardiac magnetic resonance imaging to be able to readily detect amyloid deposition and measure progression using a combination of late gadolinium enhancement (Figure 3d) and parametric quantification of T1 and T2 relaxation times.[46,51,52] These studies have suggested that sensitivity and specificity of cardiac magnetic resonance approaches 90% for identifying cardiac amyloidosis. Recent results indicate that TTR cardiac amyloid deposition can be distinguished from that of AL by

scanning with ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) in Europe[53] or with ^{99m}Tc-PYP (pyrophosphate) in the United States.[54] Although minimal uptake is seen in cardiac AL deposition, greater uptake is seen in TTR; hence, the magnitude of cardiac tracer uptake relative to bone as one suggested standard, or the contralateral chest as another standard, can be diagnostic. ^{99m}Tc-DPD or ^{99m}Tc-PYP scans are on the verge of widespread clinical adaptation owing to their ease of performance and interpretation, low cost, and high sensitivity and specificity for ATTR as compared to AL and other nonamyloid cardiomyopathies. A large, international, multicenter experience with ^{99m}Tc-DPD, ^{99m}Tc-PYP, and ^{99m}Tc-HMDP suggests that ATTR can be reliably and accurately differentiated from AL and other wall-thickening processes, perhaps bypassing the requirement for a positive tissue biopsy result. The second US-based multicenter experience with ^{99m}Tc-PYP reported excellent cross-center test validity and prognostic value ascribed to a positive test result (heart-to-contralateral chest ratio >1.6).[55] With a positive scan, subsequent genetic testing showing V122I would therefore confer diagnosis. For these reasons, these scans hold great promise for increasing ATTR recognition without having to resort to endomyocardial biopsy.

Therapy

For many years, the diagnosis of cardiac amyloidosis of any etiology was neglected on two grounds. First, it was thought to be largely without functional import. Second, even if the diagnosis could be established, there were no options for therapy; the main therapeutic consideration was avoidance of compounds reported to have toxic effects in such patients, notably digoxin-related glycosides and calcium channel blockers, both of which had been reported to bind to amyloid fibrils.[56–58] With the additional realization that stroke volume was relatively fixed in such patients, the use of agents such as high-dose β-blockers, which restricted cardiac rate and thereby compromised the response to increased demand, as well as high-dose ACE (angiotensin-converting enzyme) inhibitors have been avoided. Therefore, evidence-based interventions for other causes of heart failure are not helpful and can even be harmful in TTR V122I. The mainstay of therapy for all forms of cardiac amyloidosis has been diuretics. The adaptation of chemotherapeutic protocols effective in multiple myeloma for the treatment of AL has been reasonably successful. Thus, distinguishing between cardiac AL and TTR diseases has become essential for appropriate patient management.[58]

Since the early 1990s, liver transplantation has been the only therapy available for patients with TTR mutations. The procedure provided a crude form of gene therapy in which the source of the mutant protein was replaced by a liver producing only wild-type protein. More than 2,000 liver transplantations have been performed in patients carrying a variety of TTR mutations, predominantly TTR V30M.[59] Once experience defined criteria for patient selection and the particulars of pre- and perioperative management, the procedure resulted in arrest of disease progression in approximately 60% of patients with prolonged survival relative to nontransplanted gene carriers. There is early improvement, stabilization in approximately 20%, and progression, usually cardiac, in 20%. In terms of 10-year survival, TTR V30M subjects do better than carriers of other mutations; subjects with early-onset disease have better survival than those who present later in life. Because of their advanced age at the time of diagnosis, no patients with TTR V122I have received liver transplants.

There are two reports of cardiac transplantation with apparently good success, but the follow-up periods in these cases have been short.[60] Several patients with cardiac involvement with other mutations have undergone combined liver and heart transplantation.[61]

There has been an intense effort to develop other modes of therapy for the TTR amyloidoses because an increasing number of TTR V30M carriers are becoming symptomatic late in life (and are thus not optimal candidates for liver transplantation); the largest number of potential patients with cardiac TTR deposition are the *TTR* V122I carriers and elderly subjects who develop wild-type TTR deposition in their 70s and 80s. Although the acceptable age for liver transplantation has been gradually increasing, according to current criteria (age younger than 70) few of these patients would be candidates. In addition, the limited availability of suitable livers is a chronic problem; the late complication of continuing cardiac deposition of wild-type TTR after liver transplantation compromises the success of the procedure.[62]

The most fruitful therapeutic approach to date was based on the observation that occupation of the T4 binding site of the TTR molecule kinetically stabilized the native tetramer, preventing its dissociation and thus inhibiting fibril formation (Figure 1).[63] Several compounds were found to be effective in vitro. Tafamidis is a compound that has been approved by the European Medicines Agency for use in patients with early-onset FAP after a clinical trial in which the compound arrested progression of neuropathy at a rate similar to that seen in patients with liver transplants.[64] No cardiac efficacy results were reported from that study.[65] Current trials are assessing its effect in subjects with cardiac disease.

A recently completed 12-month open-label trial of tafamidis involving 21 subjects with a variety of mutations suggested stabilization of cardiac function in some patients during the period of the trial; however, the results are subject to the limitations of such trials, such as the small number of subjects, relatively short duration, and the open-label design.[66] It remains to be seen whether cardiac TTR deposition can be arrested or reversed by this approach.

Diflunisal, a nonsteroidal, anti-inflammatory drug (NSAID), also has a structure that allows it to fit in the T4 binding pocket and inhibit TTR dissociation and misfolding. Like any NSAID, it has inherent side effects of decreased renal function, volume retention, and gastrointestinal irritation, potentially limiting its utility in patients with advanced heart failure. Nonetheless, a controlled clinical trial in which FAP patients with a variety of mutations were treated with the drug has shown efficacy in arresting progression of peripheral neuropathy.[67] Limited cardiac data have been reported.

Alternative therapies not dependent on TTR stabilization attempt to suppress TTR production by liver cells. One method utilizes parenteral administration of TTR-specific small interfering RNAs shown to be effective in decreasing serum TTR concentrations in TTR transgenic mice.[68] These agents—patisiran and revusiran—also lower serum TTR levels in human mutation carriers. The early results of the patisiran trial suggest stabilization of the polyneuropathy, but the data regarding the effects on TTR cardiomyopathy caused by

any precursor are too preliminary to evaluate. The revusiran trial has recently been discontinued because of an unfavorable risk-to-benefit ratio.

A parallel approach using antisense TTR RNA administered parenterally has been shown to suppress TTR expression in mice transgenic for TTR I84S as well as to lower serum TTR levels in subjects with TTR mutations.[69] A phase III clinical trial is in progress.[70]

Based on animal and in vitro experiments, the antibiotic doxycycline and the catechin, epigallocatechin-3-gallate (EGCG), a polyphenol component of green tea, appear to be able to cause dissociation of amyloid fibrils. A single, small, uncontrolled 1-year study of EGCG either in capsule form or as a large volume of green tea in a heterogeneous group of 19 subjects with TTR cardiac deposition showed slight improvement in cardiac function as determined by echocardiography and some startling anecdotal results. Further animal experiments and phase II clinical studies are in progress.[71]

Preliminary studies in TTR transgenic mice suggested that doxycycline and tauroursodeoxycholic acid might be effective mobilizers of TTR deposits. Twenty patients with various forms of TTR neuropathy and cardiomyopathy were treated with oral doxycycline (100 mg b.i.d.) and tauroursodeoxycholic acid (250 mg t.i.d.) for 1 year. Although the results were reported before the completion of the full course of treatment, the regimen appeared to be well tolerated, with only two dropouts due to adverse effects. The patients appeared to be stable through the course of the study, but the published data are too limited to determine whether there was any benefit.[72]

Additional approaches using antibodies that specifically bind to TTR fibrils or other components of tissue amyloid deposits, notably serum amyloid P-component (SAP), which are designed to induce a host inflammatory reaction potentially capable of dissolving the amyloid fibrils, are entering clinical trials.[73,74] Whether they will achieve resolution of preexisting deposits and restore normal tissue function remains to be seen.

Successful development of pharmacologic therapy for V122I ATTR, whether tetramer stabilization, suppression of precursor synthesis, or dissolution of extant deposits, is critical given that the advanced age of affected patients precludes liver transplantation. The success of any or all of these approaches may also permit potential antiamyloid prophylaxis in at-risk individuals who carry an amyloidogenic TTR mutation as primary therapy and perhaps eliminate the need for liver transplantation. The fact that each treatment, if successful, works by a different mechanism offers the possibility of combined therapies. With their availability, the responsibility for making the diagnosis of this disorder early enough to impact outcome rests with the first physician to see the patient, typically a cardiologist. The diagnostic tools are now available. We just have to use them appropriately.

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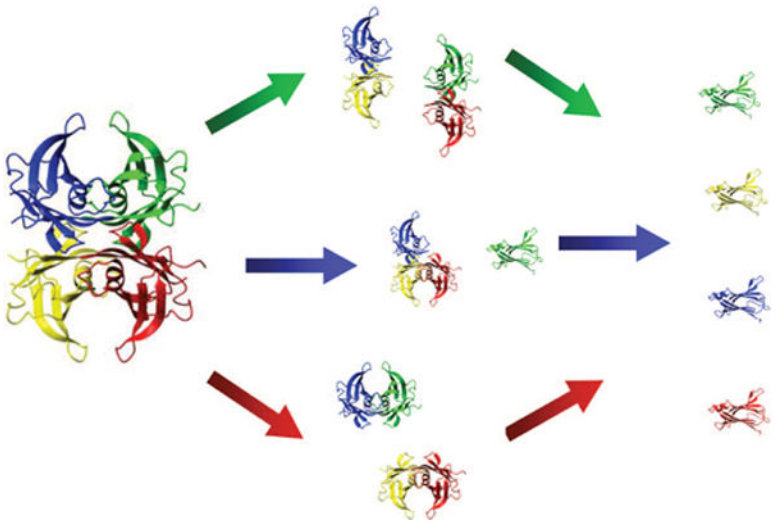

Figure 1. Possible dissociation pathways of human transthyretin tetramer

The TTR homotetramer dissociates into homodimers and then monomers, which represent the fibril precursor. The most likely dissociation pathway is shown by the red arrows. The rates of misfolding and aggregation of the monomers into oligomers, protofibrils, and then fibrils are very slow under physiologic conditions. The process is accelerated by mutations in the transthyretin gene or posttranslational changes in the peptide, including proteolysis or some forms of oxidation. (Reprinted by permission from ref. 75.)

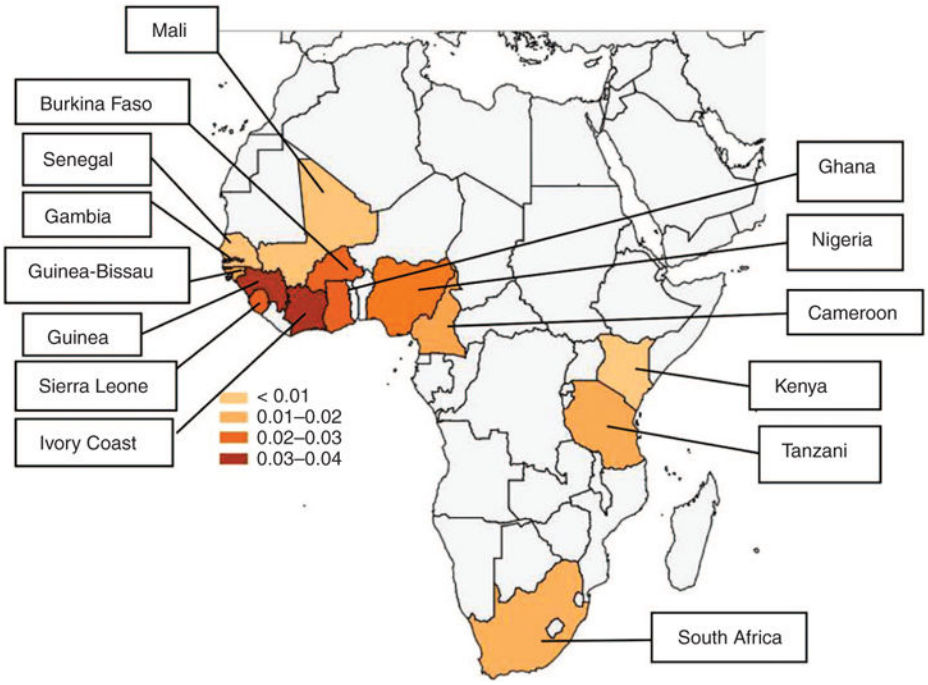

Figure 2. The distribution of the TTR V122I allele in Africa

DNA obtained from 2,700 subjects in various locales in Africa was genotyped for the V122I allele by either PCR single-nucleotide polymorphism analysis or complete exome sequencing. The color coding shows the greater frequency of the allele in the countries of coastal West Africa. TTR, transthyretin. (Reprinted by permission from ref. 18.)

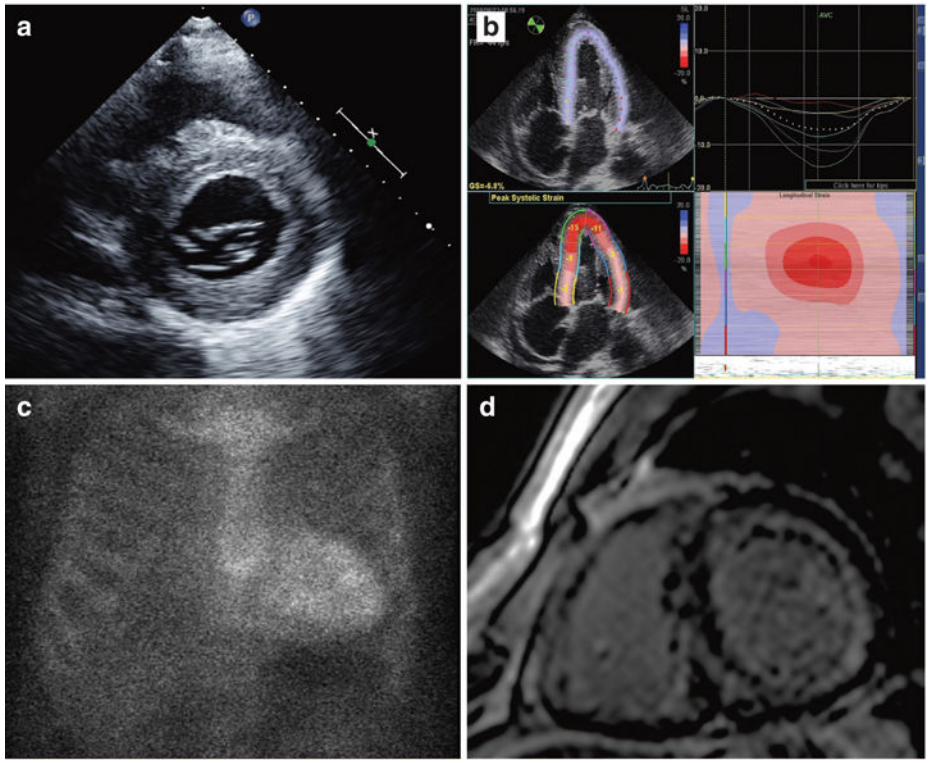

Figure 3. Multimodal imaging diagnosis of TTR V122I

(**a**) Standard echocardiogram shows increased wall thickness (distance between each fiduciary dot is 10 mm, the upper limit of normal). (**b**) Echocardiographic longitudinal systolic strain illustrates the characteristic reduced basal strain. (**c**) Nuclear imaging with Tc99m-PYP shows diffuse grade 3 uptake. (**d**) Cardiac magnetic resonance imaging shows diffuse subendocardial late gadolinium enhancement. TTR, transthyretin.

Table 1

Prevalence of transthyretin V122I in African Americans

Population	Prevalence
Convenience	65/1,688 (3.9%)[28]
Newborns, New York State	40/1,219 (3.3%), Buxbaum et al., unpublished data
Newborns, Indiana	30/1,000 (3.0%)[20]
Arteriosclerosis Risk in Communities Study (<65)	119/3,687 (3.4%)[34]
Jackson Heart Study	152/4,460 (3.4%), Buxbaum et al., unpublished data
Dallas Heart Study[b]	52/1,485 (3.5%)
Cardiovascular Health Study (>65)	17/802 (2.12%)[34]
Health ABC (70–79)	26/1,000 (2.6%), Liu and Buxbaum, unpublished data

The data in this table were obtained from the cited publications except for those from the Dallas Heart Study, which were graciously made available by Mark Drazner. The unpublished studies of the prevalence in New York State newborns and the Jackson Heart Study were analyzed in the Buxbaum laboratory using the methods described in refs. 24 and 26 or collaboratively with James Wilson of the University of Mississippi Medical Center and the Jackson Heart Study. The difference between the prevalence in subjects <65 (ARIC) and > 65 (Cardiovascular Health Study and Health ABC) was significant $P = 0.034$.

[a] M. Drazner, personal communication; difference between <65 and >65 (Cardiovascular Health Study, Health ABC), $P = 0.034$

Table 2

Echocardiographic features of patients with transthyretin V122I cardiac amyloidosis

Feature	NYVA (23)[32]	BU (30)[29]	TRACS (11)[31]	Mayo (19)[a]	Columbia (28)[b]	UK (64)[23]
Age	73	70	71	68	71	74
Ejection fraction (%)	58.7	37.9	50.4	36.3	24.8	35
Interventricular septum (cm)	1.35	1.68	1.85	1.9	1.74	1.7
Posterial-wall thickness (cm)	1.30	NA	1.80	1.80	1.78	1.7
Right ventricular hypertrophy	6/23	26/26	NA	NA	NA	NA
Mitral deceleration time (ms) Left atrial size (cm)	174	NA	NA	NA	NA	NA
	4.43	25/27↑	6.3	NA	4.64	4.6

NA, not available.

The data in this table were extracted from refs. 23, 29, 31, 32 or graciously provided by the cited investigators at the Mayo Clinic and Columbia University College of Physicians and Surgeons.

[a] S. Zeldenrust, personal communication;

[b] M.S. Maurer, personal communication.