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The genetics of cardiac amyloidosis

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Abstract
Heritable cardiac amyloidosis (CA) is an underrecognized cause of morbidity and mortality in the USA. It results from the accumulation of the misfolded protein transthyretin within the myocardium, resulting in amyloid transthyretin-associated cardiomyopathy (ATTR-CM). Over 150 different pathologic point mutations within the transthyretin gene have been identified, each carrying variable clinical phenotypes and penetrance. In the USA, the most common cause of hereditary ATTR is the Val122Ile point mutation, with a prevalence of 3.4–4.0% in North Americans of African and Caribbean descent. Among Caucasians with hereditary ATTR-CM, the V30M mutation is the most commonly identified variant. Overall, the incidence of ATTR disease in the USA has been increasing, likely due to an increase in practitioner awareness, utilization of new non-invasive imaging technologies for ATTR diagnosis, and the growth of multidisciplinary amyloid programs across the country. Yet significant numbers of patients with evidence of left ventricular thickening on cardiac imaging, senile aortic stenosis, and/or symptoms of heart failure with preserved ejection fraction likely have undiagnosed CA, especially within the African American population. With the emergence of new disease-modifying therapies for ATTR, recognition and the prompt diagnosis of CA is important for patients and their potentially affected progeny. Herein, we review the genetics of heritable CA as well as the importance of genetic counseling and testing for patients and their families.

Keywords: Amyloid, Cardiomyopathy, Genetics, Phenotype, Genotype, Inheritance.

Overview of heritable amyloidosis

Heritable amyloidosis represents the fraction of amyloid diseases driven by genetic mutations, occurring most commonly within the transthyretin (TTR) gene. Other much rarer heritable forms of amyloidosis can be found in patients with mutations in the fibrinogen A alpha chain, apolipoprotein A1 and A2, gelsolin, LECT2, and cystatin C genes [1–6]. However, all heritable amyloidoses follow an autosomal dominant manner of transmission. The number of amyloidosis cases in the USA has risen dramatically in the past 25 years, with the greatest rise in the heritable and senile amyloidosis diagnoses over the past decade. These changes are more likely related to improved practitioner awareness, increased patient screening, better non-invasive imaging techniques, and the availability of disease-modifying treatment options [7]. Though heritable amyloid is still rare, it is a phenotypically diffuse disease with inconsistent penetrance that makes its diagnosis challenging; understanding its molecular and genetic basis is important for prompt diagnosis, testing, and counseling of patients and their families.

The transthyretin gene

Transthyretin (TTR, also called pre-albumin), the predominant source of heritable cardiac amyloidosis, is a 127 amino acid, 56 kDa homo-tetrameric transport protein encoded by the TTR gene on human chromosome 18q12.1. TTR is transcribed mainly within cells of the liver but can also be found in the choroid plexus, pancreatic islet cells, various parts of the brain, and the retina [8]. Its primary role in humans is to TRANSport THYroxine and RETINol bindign protein, the roles of which were used to derive the protein's name. TTR is present in all vertebrates and is integral for the function of multiple organ systems, including the eyes, nerves, heart, bone, and muscle.

Over 150 different mutations have been found in the TTR gene, most of which have been pathologically linked to

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heritable TTR amyloid (hATTR) [9]. The amyloidogencity of a particular mutation stems from the resultant protein's secretion efficiency and the ability of a given mutation to destabilize the homo-tetrameric structure of TTR, resulting in fibril accumulation within organs [10, 11]. Hereditary ATTR phenotypes vary greatly between mutation types, leading to differences in organ selectivity, disease severity, and patient prognosis. The vast majority of hATTR mutations are gain of function mutations and thus transmit in an autosomal dominant manner. However, phenotype and penetrance can be highly variable even within cohorts carrying the same mutation. Rare families with duplications or codon deletions within TTR have also been reported [12, 13], as have patients with homozygous and mixed heterozygous pathogenic genotypes [13–15].

Because hATTR is a genetic disease, geographical and ethno-racial clustering is noted across the world. The most common hATTR mutation globally is Val30Met, responsible for familial autonomic neuropathy (FAP) type I, predominantly found in Europe. In the USA, however, the most common form of hATTR, Val122Ile, is almost exclusively found in those of African and Caribbean descent. The diversity of the USA and the variable presentation of heritable amyloidosis warrant discussion of the several key hATTR mutations outlined in Table 1.

Transthyretin mutations most associated with heritable cardiac amyloidosis in the USA

Val122Ile cardiac amyloidosis

Val122Ile (also known as pV142I) is a point mutation in the TTR gene, resulting in the substitution of isoleucine for valine at position 122. It confers a similar phenotype to wild-type ATTR and is the most common subtype in the U.S. [13, 16–18]. While allele frequency for V122I in the U.S. is 0.0173, 3.4–4.0% of US individuals of Afro-Caribbean descent are believed to be carriers—between one and two million Americans [19, 20]. These patients are underrepresented in the Southern U.S. despite having larger populations of self-identified African Americans, almost certainly reflective of American healthcare disparities and CA underdiagnosis [21]. Although the true phenotypic penetrance of the Val122Ile mutation is not yet known, 10% of African Americans over age 60 with heart failure are estimated to be ValI122Ile positive [22], and carriers of the V122I mutation are 2 to 3 times more likely to develop heart failure compared to age, gender, and racially matched controls [12, 19].

The disease onset in all affected V122I patients is late—almost always after the age of 60—though it is unknown what factors influence who will be affected [19, 24, 25]. Despite its low penetrance, all V122I carriers 65 years and greater accumulate myocardial amyloid to some degree. The severity of accumulation, however, varies substantially between individuals, leaving some with severe heart disease while others are left with no or mild symptoms. Men are more than three times as likely to be affected than women despite carrying the mutation at equal frequencies; this is the case for nearly all ATTR subtypes, albeit in different ratios [12, 19].

Unlike other mutations, Val122Ile carriers display fewer and less debilitating neurologic complications; autonomic dysfunction in these patients is either absent or subtle. This is in stark contrast to V30M/FAP type 1 patients who often present with severe sensorimotor and automatic neuropathies. Many V122I patients have no neurologic symptoms, but among those who do, carpal tunnel syndrome (CTS) and spinal stenosis are most common. This represents only 20–30% of amyloid patients, but the diagnosis of CTS can precede amyloidosis development by 5 to 9 years [26]. Diagnosis in an older patient, especially when bilateral, confers a 12-fold risk for a future CA diagnosis and should prompt concern [27, 28]. Other signs or symptoms that warrant further work-up include biceps or Achilles tendon rupture, gastrointestinal dysmotility, glaucoma, and new-onset cardiac conduction disorders.

As mentioned, V122I hATTR is very similar to senile amyloidosis, though there are important distinctions. Patients with V122I hATTR-CA present a median of 5 years younger than most wild-type ATTR cardiomyopathy patients

Table 1 Several key hATTR mutations

Mutation	Penetrance	Frequency/area	Ethnicity	Neuropathy	Cardiac	Onset
Wild-type	NA	NA	Caucasian	No	HFpEF	> 70 y
V122I	Low	3.4–4%	African/Caribbean American	Mild or rare	HFpEF	> 60 y
V30M early	High	< 0.2%	Portuguese, Japanese	Severe	Arrhythmia	> 30 y
V30M late	Low	1–2%	Swedish, Japanese	Frequent	HFpEF > arrhythmia	> 50 y
T60A	Low	~ 1%	Irish, US Appalachian	Frequent	HFpEF	> 60 y

Frequency/area indicates frequency specific to endemic areas. Ref: [13, 19, 30, 75, 76]

[18, 23, 24]. They tend to have greater septal thickness and are more likely to have right-sided hypertrophy as well [19, 25]. Epidemiologic data have also indicated that the mutant phenotype has worse outcomes, worse quality of life, and likely worse survival when compared to wild-type ATTR-CA patients [18, 23]. However, given that V122I disease (unlike wild-type ATTR) disproportionately affects African Americans, it is difficult to discern if this difference reflects the disease process per se, or the overall poorer healthcare outcomes for people of color in the USA [29].

Thr60Ala amyloidosis

The second most common hATTR genotype in the USA is the Thr60Ala mutation [17]. T60A is the most common isoform in the UK, predominantly affects Caucasians, and confers a phenotype with features of V122I and Val30Met, the mutation responsible for familial amyloid neuropathy type I (discussed below) [30]. Populations of Thr60Ala patients are found throughout the USA; however, the carrier frequency is highest in Donegal County of Northern Ireland, affecting about 1% of the population (Table 1) [17, 30, 31]. Carriers in the USA have been found in Appalachia, New York, and the Mid-West, the families of whom likely originally immigrated from Europe through a common founder [17, 32, 33]. As with other forms of amyloidosis, spontaneous mutant ATTR cases of T60A have also been reported [34, 35].

Like V122I, T60A also has a low penetrance with a late-onset presentation. The disease usually occurs after age 60 and also has a male predominance, with a phenotypic ratio of 2:1 as opposed to 3:1 in V122I [12, 19]. However, these patients present with both cardiac disease and neuropathy, the latter of which usually affects somatic and autonomic fibers [30, 31]. Neurologic manifestations tend to be less severe than in Val30Met disease, though T60A patients have comparatively more cardiac manifestations, which is consistent with their somewhat higher mortality than V122I cohorts [30, 32].

Val30Met: familial amyloid neuropathy

The most common amyloid mutation worldwide, Val30Met, is responsible for familial amyloid neuropathy type I [13, 15, 36]. FAP is a rare disease worldwide and uncommon in North America, predominantly affecting US residents of Portuguese, Swedish, and Japanese descent with a 2: 1 male phenotypic predominance [37]. The Val30Met mutation is strongly penetrant in most kindreds (> 69%), and affected individuals experience severe, progressive, degenerative sensory, autonomic, and motor neuropathy. Rather than heart failure, Val30Met patients are more likely to suffer from cardiac conduction disturbances and syncope attributed to autonomic dysfunction [38–41].

There are several distinct populations of FAP patients that, despite a common genotype, have distinct phenotypes that can be further categorized into early- and late-onset FAP.

The Portuguese- and Japanese-predominant forms have an early age of onset (30 s) and a higher penetrance than the Swedish variant, the latter of which occurs later in life with a much lower penetrance and more indolent course [38, 40–42]. Both variants are more likely to manifest cardiac conduction disturbances than heart failure; however, late-onset FAP is more associated with heart failure with preserved ejection fraction (HFpEF) than early-onset disease (Table 1) [43, 44].

The explanation for differences between late-onset and early-onset phenotypes is unclear. As in wild-type and V122I disease, there are also sex-specific differences in phenotype that influence the age of disease onset [45]. Portuguese women with the V30M mutation demonstrate an older age of onset compared to male carriers and are more likely to pass along disease to their sons, who then present with symptoms at an increasingly earlier age of onset [45]. Anticipation is also apparent in early- and in some late-onset (> 50 years) cohorts among Spanish and Japanese kindreds, though this has not been reported with V122I carriers [46–49].

There also appears to be greater penetrance in carriers who have inherited the TTR mutation from their mothers than from their fathers [40, 44]. This may be influenced by mitochondrial inheritance; however, the mechanism for gender-based differences remains an open question [50, 51]. Finally, a second mutation, T119M, has been identified in a small proportion of patients with the V30M mutation who have no or mild disease, yielding a mixed heterozygous genotype (V30M/T119M) that appears protective. T119M stabilizes tetrameric TTR, slowing amyloid fibril formation and was a key impetus in the development of tafamidis [12].

Amyloidosis: the role of epigenetics and the environment

Epigenetics may play a significant role in determining which carriers will ultimately develop clinically significant hATTR disease and when [52, 53]. Epigenetics is the study of extra-genomic, potentially heritable processes that alter the expression of a gene and phenotype through biochemical modification of the nucleotide backbone or its associated chromatin. In addition to the variable penetrance and sex-based differences in phenotype among ATTR patients, monozygotic twins who carry hATTR mutations have also shown marked discordance in the expression of cardiac amyloid disease, necessitating the involvement of either epigenetic, trans-regulatory, and/or environmental factors [54, 55]. Epigenetic studies of hATTR patients have shown

differences in methylation profiles between Val30Met and Val122Ile carriers and their respective wild-type controls—changes which can be inherited [56, 57]. However, it is unclear at this time what causative role these differences may have in amyloid pathology [56, 57]. Epigenetic modifications of cardiac myocyte DNA (commonly through methylation) have been shown to be dynamic during development and into adulthood. Individuals with heart failure have demonstrated DNA methylation leading to transcriptional reprogramming, and such changes may also account for some of the phenotypic variability in amyloidosis [58, 59].

Hereditary ATTR, irrespective of genotype, also occurs on a heterogeneous genetic background of patients who may have other risk factors for diastolic dysfunction, including hypertension, obesity, and diabetes [60, 61]. Environmental stimuli and aging can influence gene expression through trans-regulatory elements in animal models [62, 63]. However, it is unknown how environmental stimuli, such as stress or hypertension, can influence the disease course of CA—if at all. Alzheimer's disease, also an amyloidopathy, has been linked to hypertension and smoking in the decades prior to disease onset [64–66]. Risk factors for heart disease may similarly influence the age of onset and penetrance of both mutant and wild-type ATTR-CA, though this has yet to be demonstrated among ATTR cohorts.

Role for genetic testing and counseling

Patients diagnosed with ATTR amyloidosis should be offered the opportunity to undergo genetic testing, regardless of family history, especially if they have progeny or siblings who are at risk for heritable disease [22]. The utility of genetic testing in patients with non-AL forms of amyloid (hereditary or wild-type TTR amyloid) who lack biological siblings or children is less clear, but it may be helpful when other testing is inconclusive or mixed amyloid disease (e.g., AL and hereditary amyloid) is of concern. Wild-type and V122I-ATTR are often clinically indistinguishable diseases, and while a detailed family history is obligatory, that alone is insufficient for identifying familial ATTR or a subtype [22, 30, 35]. Moreover, the presence of a pathogenic amyloid mutation has important implications for asymptomatic biological family members as discussed below.

When testing patients, it is important to consider that there are numerous mutations associated with hATTR and undoubtedly additional mutations are likely to be discovered. While most patients with hATTR will be heterozygous for a single mutation, patients with homozygous mutations have been identified. Such patients do not necessarily fare worse than those carrying a single mutant copy, but homozygosity has important implications for genetic counseling [14, 67, 68]. Patients can also be double heterozygous for different hATTR mutations, and duplications have been reported in ATTR as well [13, 15, 69]. Fortunately, genetic testing for known pathologic missense mutations is rapid and can be undertaken using blood, saliva, or buccal specimens with increasingly approved coverage by payors. In patients for which a provider has a high clinical suspicion for hATTR despite negative or ambiguous genotype results, more sophisticated genetic testing can be undertaken to detect deletions or duplications, or more commonly, tissue samples can be sent for mass spectrometry proteomic analysis, which can differentiate mutant ATTR protein from wild-type or other amyloid deposits in tissue [8].

The process of genetic counseling

Once a pathologic mutation has been identified, the implications for that person's family can be a difficult process to navigate and replete with ethical and financial issues. Thus, genetic counseling should accompany all decisions to obtain hATTR testing and should predate sample acquisition in both patients and blood relatives [70, 71]. Genetic counseling can be done formally, via a licensed individual, or informally by experienced hATTR practitioners. The genetic counseling encounter is a shared decision-making process that mandates an interactive, bidirectional discussion between the patient and the provider/counselor. The provider/counselor shares information appropriate to a patient's educational level about the disease process, its heritability, and the potential risks and benefits of testing. Additionally, the provider/counselor should highlight the equally important emotional considerations about genotyping, including intrapersonal stress regarding potential transmission of a mutation to offspring and anxiety offspring may face when confronted with an affected family member's diagnosis. Teach back should be used to ensure patients and families comprehend the information offered. The counseling visit should also discuss the protections and risk associated with genetic testing, and informed consent should be obtained prior to sending samples for analysis.

When the decision to genotype a patient has been made, samples should be sent to institutions or companies accredited by the College of American Pathologists (CAP) and with Clinical Laboratory Improvement Amendments (CLIA) certification. Both positive and negative results warrant further discussion, offering an opportunity to answer additional questions and address the timing and decision to disclose positive results to first degree relatives. It is often beneficial for the provider or genetic counselor to assist in leading these complex discussions. The availability of virtual encounters can afford several family members the opportunity to learn about hATTR screening and local resources for amyloid evaluation and genetic

testing as appropriate. It is important to emphasize that (1) the presence of a mutation is *not* equivalent to diagnosing amyloid disease, (2) a mutation in TTR does not necessarily determine the severity or distribution of amyloid, and (3) not all mutations causing amyloid have been detected.

For relatives of a patient who undergo testing for hATTR and return genotype-positive, many will have no phenotypic expression of the disease. However, the disclosure of a pathogenic genotype to patients and at-risk family members has the potential to produce anxiety about their future or trigger guilt in those relatives who are genotype negative. Testing may also uncover non-paternity that itself may cause emotional turmoil [72–74]. The risks of genotyping are not merely psychological. While a 2008 federal law, the Genetic Information Nondiscrimination Act (GINA), prohibits health insurance and employers with > 15 employees from genetic discrimination, life, long-term care, and disability insurance policies can consider these results, and individuals undergoing testing should be aware of this. While hATTR patients will likely have their disease discoverable through other medical tests, such as echocardiography, first degree relatives should be counseled to consider obtaining life and disability insurance *prior* to genetic testing, so they legally have no symptoms nor knowledge of genotypic risk for hATTR. Asymptomatic minors, who cannot consent to genetic testing and may not appreciate the emotional or financial implications of knowing their carrier status, should delay genetic testing until adulthood.

Genotype-positive/phenotype-negative patients

Genotype-positive individuals who lack clinical signs or symptoms of hATTR should have regular follow-up with a provider knowledgeable about the disease. While imperfect, a monitoring plan should be devised based on the mutation, presentation, and the age of onset of affected family members. We recommend monitoring with symptom review, echocardiography, and laboratories (B-type natriuretic peptide and high sensitivity troponin) usually 10–15 years prior to proband symptom onset [77]. Those patients with V30M or T60A patients will benefit from regular neurology specialist follow-up and possibly an EMG. Data for use of disease-modifying therapy in genotype-positive/phenotype-negative individuals is lacking, but identification of subtle clinical hATTR in its early stages, when disease-modifying therapies are most effective, is imperative. More studies are needed to determine the clinical benefit and cost effectiveness of genetic testing, surveillance, and early treatment on the survival and quality of life in asymptomatic carriers.

Summary

With cardiac amyloid is an increasingly recognized cause of mortality and morbidity among US adults, a high clinical suspicion of ATTR-CA in at-risk patients is imperative. Between 10 and 20% of patients hospitalized or being treated for conditions like HFpEF or aortic stenosis may have undiagnosed amyloidosis, representing significant, unrealized opportunities for treatment and intervention in these patients. This is particularly true of persons of color who are likely being underdiagnosed and undertreated in many areas of America.

There are now multiple FDA-approved medical therapies that can either slow the progression of hATTR amyloid or improve quality of life. However, these therapies are most effective in those with early staged disease. The variable penetrance of TTR mutations, such as V122I, means that the diagnosis of even elderly patients with advanced disease can have important therapeutic implications for a patient's relatives, potentially delaying the onset of illness in those ultimately affected.

Author contribution Each author contributed significantly to justify authorship. Dr. Cowger, a senior writer, was involved with outline of paper concept, reference review, and manuscript editing. Dr. Arno was involved with writing paper, reference review, and manuscript editing.

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