Review

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Not So Rare After All: Rethinking Hereditary Transthyretin Amyloidosis

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Abstract

Background: Transthyretin amyloidosis (ATTR) is a rare, often underdiagnosed and undertreated, autosomal dominantly inherited, progressive disease that affects multiple systems of the body. It results from the extracellular accumulation of misfolded transthyretin (TTR) protein as insoluble amyloid fibrils, predominantly causing cardiomyopathy, polyneuropathy or mixed phenotypes. It can occur in a hereditary form (ATTRv) and in a wild-type form (ATTRwt), with over 150 different pathogenic mutations having been identified worldwide. The clinical presentation is highly variable, leading to a diagnostic delay of 2–5 years. Transthyretin (TTR) amyloidosis is an inherited disease for which recent advances in pathogenesis, diagnosis and treatment have revolutionized its management. Objectives: The aims of this review are to provide an update on the epidemiology and genotype-phenotype correlation, on current diagnostic techniques and on emerging and individualized treatments for this rare hereditary disease. Particular attention will be given to the early diagnosis Methods: A systematic literature search was conducted across major databases to identify studies addressing clinical characteristics, diagnostic modalities, and treatment outcomes in hereditary and wild-type ATTR amyloidosis. Registry data from THAOS and other multinational cohorts were analyzed to evaluate phenotypic variability across genotypes and geographic regions. Results: Clinical presentation of TTR related amyloidosis (h-Amyloid) can range from early onset to late onset with late onset having worse neurological and cardiac involvement at time of diagnosis. The Val30Met mutation is the most common TTR mutation worldwide, however patients with non-V30M mutations can have very different presentations of h-amyloidosis. Identifying "red flag" symptoms in a patient with suspicious clinical presentation can initiate correct diagnostic pathway. Non-invasive imaging, especially bone scintigraphy, has greatly facilitated the diagnosis of patients with Transthyretin related cardiac amyloidosis (ATTR-CM). First generation h-amyloid treatments or TTR stabilizers such as tafamidis have been shown to significantly improve survival in patients with h-amyloidosis. The second generation treatments such as RNA silencers (patisiran, vutrisiran, inotersen, eplontersen) have been shown to halt the disease progression. Present data from small to moderate-sized patient cohorts demonstrate that TTR-targeting therapy is associated with reduction of cardiovascular events and improvement in survival compared with current standard of care. Early recognition of key clinical features and application of a diverse diagnostic strategy, in conjunction with timely initiation of disease-modifying therapy, are critical to optimal management of patients with hereditary transthyretin (ATTR) amyloidosis. Conclusions: The therapeutic options have evolved and improved in recent years, and with current diagnostic tools, the opportunity to alter the natural history of a disease that was once invariably fatal is better than ever. Because the disease is systemic, a thorough, multidisciplinary approach to patient management is ideal.

Keywords: transthyretin amyloidosis; ATTR cardiomyopathy; hereditary amyloidosis; tafamidis; gene silencers; early diagnosis; disease-modifying therapy

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1. Introduction and Background

1.1. Definition and Pathophysiology

Hereditary transthyretin amyloidosis (ATTRv) is a fatal, autosomal dominant inherited disease caused by pathogenic variants in both TTR gene alleles. These variants make the TTR protein misfolded and destabilize the native tetrameric form, leading to the formation of extracellular amyloid fibrils deposits in various tissues [1]. The peripheral nervous system is the most commonly affected organ, followed by heart, eyes, kidneys, and gastrointestinal tract. Over 140 different pathogenic mutations have been identified in the TTR gene to date, and the Val30Met (p.Val50Met) variant is the most common worldwide [2]. The clinical manifestation of this disease is remarkable in its clinical heterogeneity, ranging from a predominantly neurological presentation to predominantly cardiac or mixed presentations.

Both heterogeneous transthyretin (TTR) variants and wild-type TTR can form amyloid deposits in specific tissues by dissociating into monomers, misfolding and aggregating into amyloid fibrils, causing tissue damage, serious illness and death. Small molecules that stabilize the TTR tetramer and transthyretin lowering therapies by gene silencing are the available disease-modifying therapies [3,4].

1.2. Historical Perspective and Current Relevance

ATTRv was first described by Corino de Andrade in 1952 in Portuguese families. For decades, ATTRv was considered to be an extremely rare disease affecting endemic foci of patients in Portugal, Sweden and Japan [5]. The clinical diagnosis of ATTRv was based on suspicion supported by relevant family history and on relatively specific but not pathognomonic clinical and electrocardiographic features. However, the diagnostic approach to this disease has completely changed in the last decade. New non-invasive imaging techniques have revealed that the prevalence of the disease is significantly higher than previously thought, and it is likely that many cases of ATTRwt have been misdiagnosed or delayed in diagnosis for long time. The availability of disease-modifying therapies for ATTRwt has significantly changed the approach to this disease and early diagnosis has become a priority to prevent organ damage which is irreversible once established [6].

1.3. Scope of the Review

Comparison of three aspects of patients with hereditary transthyretin amyloidosis (ATTRv) and wild- type transthyretin amyloidosis (ATTRwt) including clinical profile of patients with hereditary transthyretin amyloidosis, the role of genetic testing for patients of all ages, and the contrary evidence that these patients are not as rare as thought. Recent and large patient registries and multicenter data are reviewed to provide a current overview of the information that is known and some of the ignorance and gaps that need to be addressed and clarified.

2. Article Selection Methodology

A systematic literature review was performed to select the most relevant papers concerning hereditary transthyretin amyloidosis (ATTRv) published in the last six years (2020–2026). The literature search involved different databases and registries using the following search terms: hereditary transthyretin amyloidosis, ATTRv, transthyretin gene mutations, genetic testing, epidemiology and/or prevalence of. Additional articles comparing the clinical features and/or outcomes of hereditary transthyretin amyloidosis (ATTRv) and wild-type transthyretin amyloidosis (ATTRwt) and the usefulness of genetic testing in different ages were included in this literature review. For the systematic literature review, 77 articles were included. The following criteria were used to select the relevant papers for this systematic literature review: original work, systematic reviews, registry articles; studies published on peer-reviewed journals from January 2020 to April 2026. Articles not meeting the following exclusion criteria were also included: less than three patients in case reports; light-chain amyloidosis; articles without original data (clinical and/or genetic

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findings). To select relevant papers to review multicenter data, different registries were searched, mainly THAOS (Transthyretin Amyloidosis Outcomes Survey), HEAR (Healthcare European Amyloidosis Registry), and recently created REACT-SP (Transthyretin Cardiac Amyloidosis Registry of São Paulo) and national and regional registries from endemic and non-endemic regions around the world. Using this approach more than 45 relevant publications were identified and used as the foundation for this detailed review of key clinical features, prevalence and management strategies for patients with clinical symptoms of transthyretin amyloidosis (ATTRv).

3. Clinical Profile: ATTRv Versus ATTRwt

3.1. Demographic Differences

Patients with hereditary transthyretin amyloidosis (h-ATTR) differ demographically from those with wild-type transthyretin amyloidosis (wt-ATTR). The Brazilian REACT-SP registry includes 644 patients with h-ATTR, the majority of them presenting to medical attention at a very young age and having a long delay in time to diagnosis. In contrast, patients with wt-ATTR do not have onset of symptoms at a young age ($p<0.001$). The THAOS registry has also shown that patients with symptomatic h- ATTR have a mean age of onset which varies by genotype and is 56.6 years [2].

Using data from the HEAR registry, the clinical features of patients with hereditary transthyretin-mediated amyloidosis (ATTRv Val122Ile) were compared with those of wild-type patients (ATTRwt) [8]. Hereditary patients were significantly younger at diagnosis (78±9 years vs 83±7 years, $p<0.001$), had significantly more severe cardiac involvement, and should therefore not be considered as being “too old” for a diagnosis of ATTRv [9].

3.2. Phenotypic Presentations

The clinical distinction between sporadic (ATTRv) and hereditary (ATTRwt) transthyretin amyloidosis (TTR-A) is often limited to the evaluation of phenotypic differences. In the REACT-SP cohort, cardiac involvement was significantly different between the two groups (43.9% in ATTRv versus 89.9% in ATTRwt, $p<0.001$), whereas neurological phenotype was more common in ATTRv (56.8% versus 31.7%, $p<0.001$) [10]. Notably, a mixed phenotype (cardiac and neurological involvement) was observed in about 25.6% of the patients enrolled. From a 40-year experience of a single Italian referral center for amyloidosis, three main different phenotypes of TTR-A have been identified: cardiac, neurological and mixed. The clinical and instrumental features of the three different phenotypes are described and discussed in the 325 patients with different pathogenic TTR mutations [11].

Lessons learned from the Portuguese epidemic of hereditary transthyretin (TTR) cardiac amyloidosis (ATTRv-CM) with the Val30Met mutation highlight the preponderance of cardiac involvement, affecting more than one-fifth of affected individuals, which is independently predicted by male gender and prior liver transplantation [12]. Patients with the V30M mutation are significantly younger than those with wild-type TTR (ATTRwt) and more frequently present with conduction abnormalities and less commonly with atrial fibrillation. Understanding these differences can guide targeted screening and management of patients with hereditary TTR cardiac amyloidosis [13].

3.3. Cardiac and Neurological Manifestations

Cardiac features of US variants of transthyretin (TTR) differ from those with wild-type transthyretin (ATTRwt). The val122Ile variant is considered to be a cardiac disease; however, 90% of V122I patients also have neuropathy [14]. Patients with V122I had the highest levels of proBNP and interventricular septum thickness (5,939±962 pg/mL and 1.70±0.29 cm, respectively), followed by late-onset V30M and L58H. Carpal tunnel syndrome was found in 58% to 97% of the patients.

In addition to organ specific manifestations, neurological manifestations of hereditary amyloidosis have genotype specific features. The THAOS study compared late-onset versus early-

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onset Val30Met amyloidosis and found more severe neurological impairment in late-onset patients at the time of the study. The median derived Neuropathy Impairment Score in the Lower Limbs (DNS_IL) was 25.0 for late-onset patients versus 8.0 for early-onset patients. In many cases, neurological findings predominated over cardiac findings in late-onset patients [9]. The variability of the electrophysiological features of patients with diagnosed and symptomatic transthyretin (TTR) hereditary (voltage dependent muscle protein) neuropathy at time of presentation may pose diagnostic difficulties, particularly in early stages of the disease [15].

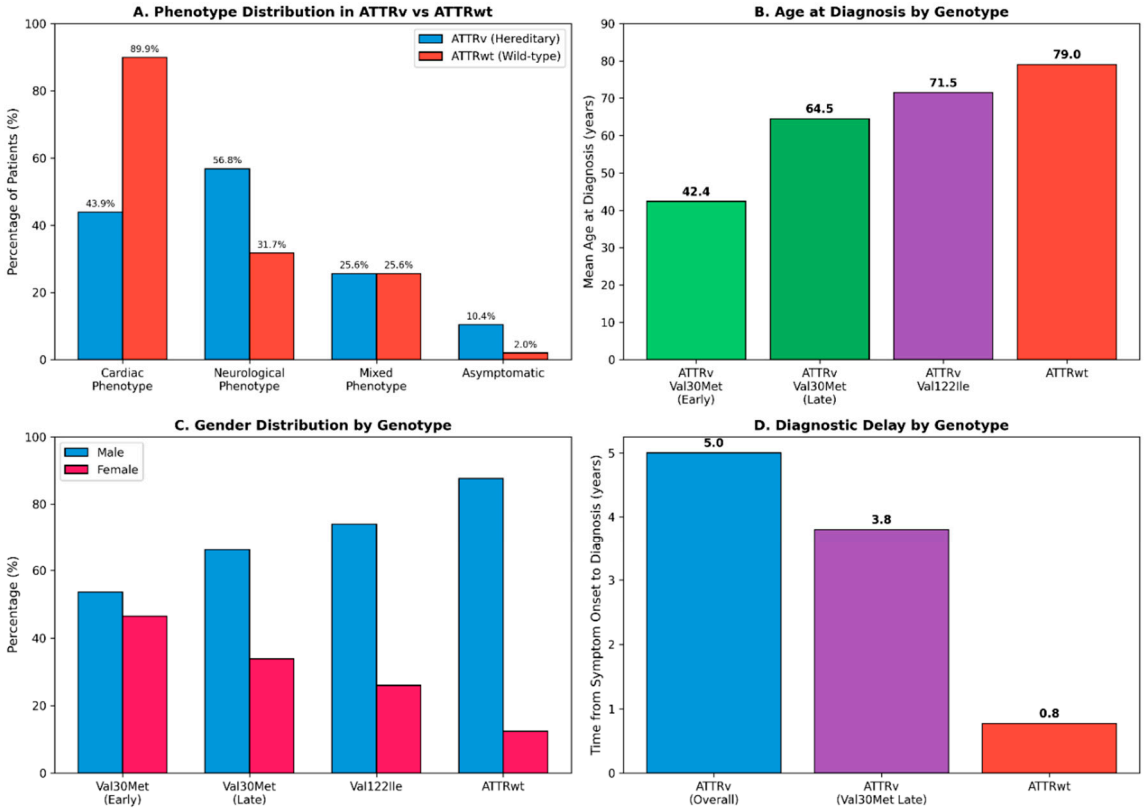

Figure 1. Clinical characteristics comparison between hereditary (ATTRv) and wild-type (ATTRwt) transthyretin amyloidosis. (A) Phenotype distribution in ATTRv and ATTRwt amyloidosis. The majority of patients with hereditary amyloidosis (black bars) show neurological involvement, whereas patients with wild-type amyloidosis (white bars) show predominantly cardiac involvement (left panel). Early-onset Val30Met patients (black bars) have the earliest onset of symptoms, whereas later onset of symptoms is observed in other genotypes (grey bars) and in wild-type amyloidosis (white bars) (centre panel). The majority of patients are males, and the gender imbalance is more pronounced in later onset (dotted line) and in wild-type amyloidosis (white bars) (right panel). Delay to diagnosis is longer in hereditary than in wild-type amyloidosis (D, black bars = ATTRv, white bars = ATTRwt). Data derived from REACT-SP, THAOS, and HEAR registries.

4. Epidemiology and Global Distribution

4.1. Endemic Versus Non-Endemic Areas

ATTRv was initially considered endemic to Portugal, Sweden, Japan and the Balearic Islands (Spain). The Balearic Islands, mainly Mallorca and Menorca, contain one of the major global foci of the Val30Met (V30M) variant of transthyretin [16]. The prevalence of this variant is 1 in 2,900 in Mallorca and 1 in 4,700 in Menorca. Out of a screening of 1,478 individuals, 319 tests were positive for ATTRv, with 96.4% of the positive tests being V30M. Most (93%) of these individuals with the V30M mutation were also found to have the G6S mutation on the same chromosome, indicating a unique, island-specific founder effect. The experience gained in the screening of this relatively small

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island population over a 23-year period has provided a unique database regarding the prevalence of the disease.

The TTR-related amyloidosis (TRA) is another endemic disease with a specific genetic pattern in Bulgaria. The data from a 7-year long selective screening program show that 340 carriers of TTR mutations have been identified, of them the majority (78.53%) are Glu89Gln-mutated [17]. Thirty-nine of the 65 screened subjects with previously unknown mutated TTR have developed from asymptomatic to symptomatic and adequate treatment was provided. The largest nationwide study of patients with clinical and pathological diagnosis of autosomal dominant transthyretin-related amyloidosis (ATTRv) in Spain includes 4,526 patients. Of them 393 are carriers of pathogenic variants of TTR. Two new high-prevalence areas of the disease in Spain are Cádiz, Castellón, Ciudad Real, Huelva, Valencia and Zamora [18].

4.2. Prevalence Data and Underdiagnosis

ATTRv is more common than previously realised. Following a comprehensive genomic screen of 134,753 individuals for pathogenic TTR variants, pathogenic or likely pathogenic variants were identified in 0.12% of individuals screened. The Val122Ile variant was the most common variant identified accounting for 0.08% of individuals screened. Notably, only 2 of the 157 individuals identified with variants of TTR had been diagnosed with amyloidosis [19].

In individuals ≥60 years of age with a P/LP TTR variant, 14% had established heart disease with increased ventricular septal thickness (>1.2 cm). Only one individual had been diagnosed with amyloidosis [20].

The population prevalence of the p.Asp119Asn variant in Japan is about 1 in 130 Japanese adults, substantially higher than that of destabilizing TTR variants in Europeans. The variant independently predicted heart failure and was associated with double the cardiovascular mortality. Ancestry-tailored genetic screening for heart failure could be recommended for Japanese migrants. Here we report the first case of the p.Asp119Asn variant in an Austrian patient. The estimated prevalence in the Austrian population is about 1:200,000, but the real number of affected individuals might be higher since all patients with this variant have been diagnosed in the referral center for hereditary transthyretin-related amyloidosis in Austria [21].

4.3. Specific Mutation Distributions

The Val122Ile (V142I) mutation is less commonly studied than Val100Ile, but is present at higher than expected frequency in some populations of African ancestry. The frequency of the variant allow for the expectation that approximately 3-4% of the African American population may be carriers of this variant, and hereditary ATTR-CM is most commonly caused by this variant in the US [22]. A recent phenome-wide association study confirmed the association of V122I with hATTR amyloidosis-associated polyneuropathy and showed that the cumulative incidence of the common hATTR amyloidosis manifestations approached 37.4%. Importantly, this study revealed the underdiagnosis of hATTR amyloidosis despite well characterized high carrier frequencies.

Original data from Spain are also presented for the Val142Ile variant, which is known not to be restricted to African populations [23]. Of 75 probands studied from Spain, 89.3% described themselves as of European ethnicity, whereas only 8% were of African ethnicity. The most common reason for diagnosis were cardiac symptoms (85.3%), followed by neurological (46.7%). Frequencies obtained from databases varied between 0.0% and 0.12%.

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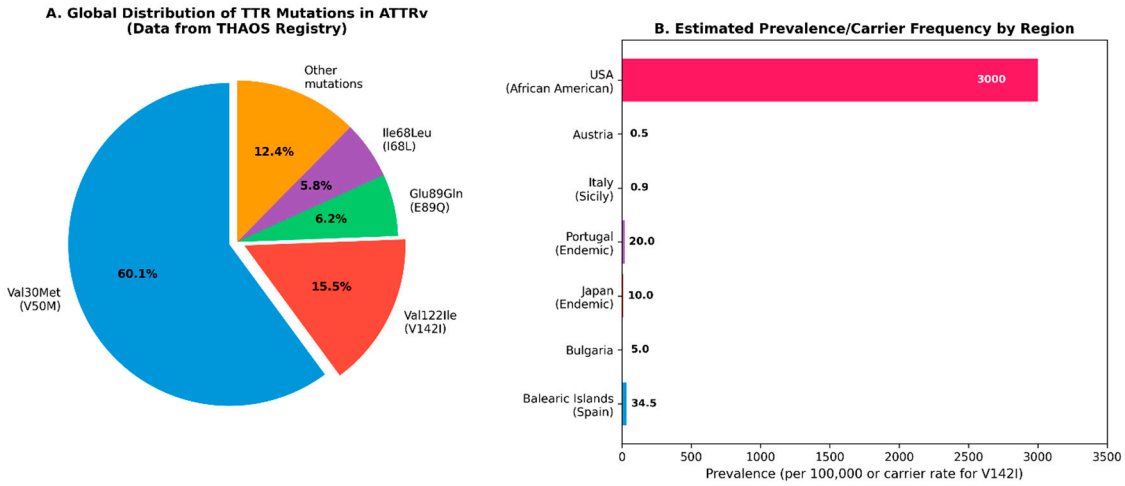

Figure 2. Global distribution of TTR mutations and prevalence estimates. (A) Distribution of major TTR mutations in hereditary transthyretin amyloidosis worldwide (THAOS registry). The most common mutation in the world remains Val30Met. (B) Estimated prevalence and carrier frequency by geographic region. Variability between populations is considerable. The exceptionally high carrier frequency for Val142Ile in the African American population is noteworthy. Data from national registries, and from genomic screening studies.

5. Importance of Genetic Testing at Any Age

5.1. Underdiagnosis in Elderly Patients

The common clinical presentation of genetic forms of ATTR-CM is that of an elderly patient who is diagnosed to have wild-type disease. However, this is not always the case. In a recent study of 52 Italian patients who were older than 70 years with cardiac ATTR, 19% (10 patients) were found to have a genetic form of the disease with 4 different pathogenic mutations. Identification of family members with the same mutation was found in 9 of 16 first-degree relatives. One patient with suspected amyloidosis has been confirmed and is receiving appropriate therapy [24]. Most importantly, this study demonstrates to other practitioners that in the elderly patient with suspected cardiac amyloidosis, wild-type is not always the answer.

Preferably wild-type ATTR-CM is diagnosed after the age of 65 years. From the HEAR registry it emerges that 4.7% of the patients with diagnosed ATTRwt-CM were diagnosed at or before the age of 65 years (ATTRwt-Yy). The majority of these patients had multiple extracardiac manifestations and showed a particular phenotype with pronounced osteoarticular disease [25]. The finding of patients with ATTRwt who are diagnosed at younger ages underlines the possibility of the underestimation of undetected hereditary forms of this cardiomyopathy and highlights the relevance of a genetic diagnosis, independent of the age of diagnosis.

5.2. Family Screening and Cascade Testing

Extended family members can be screened for genetic testing, which can lead to a chain of tests to identify presymptomatic carriers of TTR-related disease. In Bulgaria, following the asymptomatic family members for TTR-related disease led to the observation of disease transmission in 39 of the monitored 65 individuals [17]. Family members should be offered genetic counselling and screening for TTR-related disease as asymptomatic prior to the onset of clinical symptoms of the disease. The TTR genotype is not predictive of this capacity [26].

The early diagnosis of patients with transthyretin (TTR) related cardiovascular disease is useful for the management of carriers, since the patients who are asymptomatic have the same good prognosis of healthy individuals, whereas those who develop clinical symptoms of TTR-related cardiovascular disease (ATTRv) have a very poor outcome [11]. We studied a cohort of 78 Italian

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carriers of TTR-related amyloidosis and during a median follow-up of 51 months 11.5% of the studied individuals developed symptoms of ATTRv. We performed a combination of clinical evaluation, heart ultrasound, 12-lead ECG, cardiac gated M-Mode echocardiography, Tissue-Doppler Imaging and heart rate variability (HRV) tests in a group of 57 healthy carriers of amyloidogenic mutations and a complete neurological assessment, including nerve conduction studies. Some patients with normal nerve conduction studies were found to have subclinical forms of the disease. The determination of nerve conduction studies cannot be useful for screening carriers of mutations associated with amyloidosis [27].

5.3. Screening in High-Risk Populations

Screening for hereditary transthyretin (TTR)–related amyloidosis (hATTR) in high-risk populations has revealed higher-than-expected detection rates. The TRAM study screened 5,141 patients with suspected polyneuropathy and/or cardiomyopathy of unknown origin for hereditary ATTR, and 1.1% (58 of 5,141) of patients were found to have a pathogenic TTR mutation [6]. Thus, systematic genetic testing for hATTR should be routinely performed in patients with unexplained polyneuropathy and/or cardiomyopathy. In the DISCOVERY study, 8% of the 2143 US patients with suspected cardiac amyloidosis (Ct Amyloid) were found to have a pathogenic TTR mutation. The most common mutation in the Black/African American population was Val122Ile [28].

Among a pilot cohort of African Americans with clinically diagnosed bilateral CTS, the frequency of the V122I mutation was found to be higher than that reported in the general population (3–4%), at 12.5% (2 of 16 patients). Targeted screening for early diagnosis should be implemented for individuals with bilateral CTS [29].

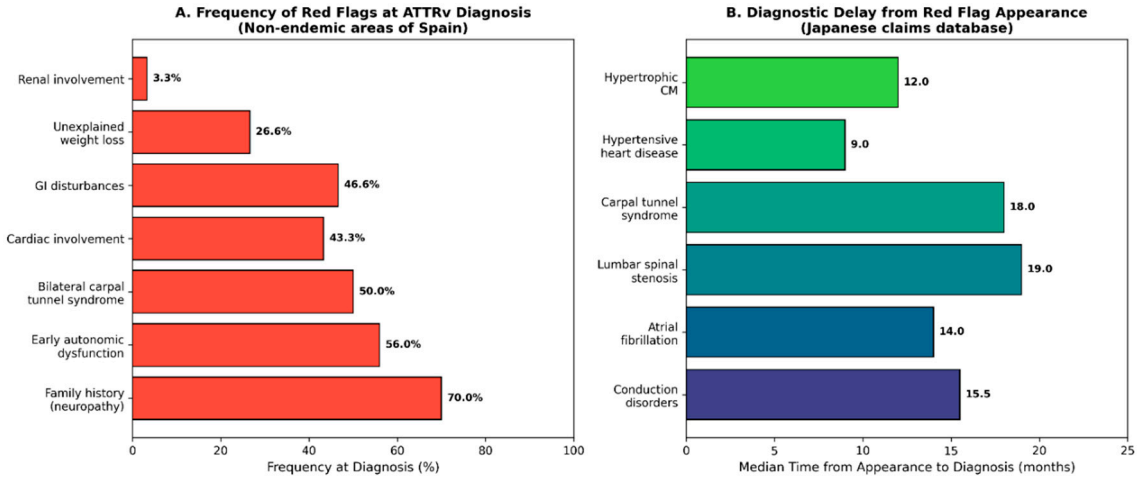

Figure 3. | Red flags for ATTRv diagnosis and diagnostic delays. Figure shows data from patients with adulthood onset of ATV from non-endemic areas of Spain (A) and from a Japanese claims database (B). Delay in diagnosis, especially for those extracardiac manifestations that cause patients to seek help from orthopedic surgeons or neurosurgeons because of lumbar spinal stenosis or carpal tunnel syndrome, among other complaints. Awareness of these red flags among all physicians is necessary.

6. Evidence That ATTRv Is Not as Rare as Commonly Thought

6.1. Screening Studies and Detection Rates

Several screening studies have demonstrated that hereditary transthyretin (TTR) cardiac amyloidosis (ATTRv) is more common than previously recognised. In Kumamoto, Japan, the incidence of ATTR-CM in the elderly (>65 years) was found to be approximately 1 per 10,000 person-years [30]. However, only 7% of patients in regional hospitals had genetic testing performed, in

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contrast to 82% of patients in specialist centres. The Greek RETTRACE study found that 8.5% (4 of 47) of patients with confirmed ATTR-CM had mutations (some rare) including Val114Ala and Ala101Thr [31].

Screening of patients ≥ 60 years of age in a large cohort found increased odds of heart disease in patients with P/LP TTR variants. The 7 P/LP variants identified in this study account for all cases of hereditary ATTR and, although the study population is predominantly of European-ancestry, hereditary ATTR is clearly not negligible [19]. The CATCH study screening elderly individuals from the general population found the prevalence of wild-type ATTR-CA to be 0.34–0.46%. Importantly, no TTR gene mutations were found in these patients, and thus systematic hereditary screening is not warranted [32].

6.2. New Endemic Foci Identified

New endemic foci have been recently reported in different parts of the world even in continents in which the disease was considered rare. Here, we propose that Croatia should be considered as a new endemic area for the rare p.Asp38Glu Transthyretin mutation, with the Croatian Transthyretin Cardiac Amyloidosis Registry (CroATTR) identifying 12 asymptomatic carriers of this mutation residing in a small geographic area in southeastern Croatia [33]. This is the largest global report of patients with this rare mutation. A new endemic variant of Hepatitis E, the Glu89Lys variant, with founder effect, has recently been identified in a specific area of Spain. It shows complete penetrance and early onset [34].

The Ala97Ser (p.Ala117Ser) mutation has a significant founder effect in South Mainland China and is the largest cohort reported so far [35]. All patients developed late onset symptoms with a mean onset age of 56.5±7.2 years, predominantly with neurological presentation. The Gly103Arg variant is unique to the Chinese population and predominantly found in southern China [36].

6.3. Population-Based Genomic Studies

Population-based genomic studies have provided some of the strongest evidence to date that a variant form of Familial Amyloid Cardiomyopathy variant (ATTRv) is more common than previously believed. In the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) a Val122Ile mutation was found in 0.8% of participants, with particularly increased prevalence in participants >50% African ancestry (3.4%). Dominican participants had the highest prevalence among the different Hispanic/Latino populations studied [37].

Prevalence of TTR variants was observed in approximately 0.75% (95/7,949) of Japanese participants in Biobank Japan. The most prevalent region was Kanto (0.78%), followed by Kansai (1.08%) and others. Notably, p.Asp119Asn conferred a 39% increased risk of heart failure and >2-fold increased risk of cardiovascular mortality. Ancestry-specific screening for TTR variants in East Asians is warranted [20].

Table 1. Prevalence of ATTRv in various screening studies and populations, demonstrating that hereditary forms are more common than historically recognized across diverse populations.

Population/Study	Sample Size	ATTRv Prevalence/Detection	Most Common Mutation
TRAM Study (Germany/Austria/Switzerland)	5,141	1.1%	Various (21 variants)

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DISCOVERY (US cardiac amyloidosis suspects)	1,001	7.4%	Val122Ile
African American bilateral CTS	16	12.5%	Val122Ile
Italian elderly cardiac ATTR (>70y)	52	19%	Val30Met, Ile68Leu, Val142Ile, Phe84Leu
Greek LVH population	294	8.5% of ATTR-CM	Various
Hispanic/Latino (HCHS/SOL)	12,687	0.8% carriers	Val122Ile
Japanese (Biobank Japan)	7,949	0.75% carriers	Asp119Asn

7. Diagnostic Approaches and Therapeutic Advances

7.1. Modern Diagnostic Algorithm

The diagnosis of transthyretin cardiac amyloidosis (ATTR-CM) has undergone a revolution with the introduction of non-invasive approaches. A diagnostic pathway is a screening test (negative for monoclonal protein) followed by a bone scintigraphy with 99mTc-DPD or similar probe [38]. Patients with increased cardiac uptake and a restrictive pattern at Echocardiography can be given a non-invasive diagnosis of ATTR-CM. Importantly, the diagnostic process should also provide information regarding the genetic form of transthyretin amyloidosis in the index patient, whether it is a hereditary form with a specific point mutation or a wild-type form. This information is important to screen family members and perhaps guide treatment decisions [39].

Cardiac magnetic resonance imaging with T1 mapping has high diagnostic accuracy for the diagnosis of heart failure, with high sensitivity and positive predictive value at all ages, with high specificity in elderly patients (92.9%, 95.8%, 95%, respectively). The use of native T1 and extracellular volume fraction (Ecv) for T1 mapping enables a definitive diagnosis in 81% of cases, thereby potentially avoiding the need for gadolinium-based contrast media. Early detection of heart failure will enable clinicians to make timely decisions and intervene earlier in the disease process [40].

7.2. Disease-Modifying Therapies

Treatment strategies for the management of patients have evolved and now include a number of disease-modifying therapies, with evidence emerging that the TTR Stabilizers, such as tafamidis, can produce a survival benefit in both wild-type and hereditary ATTR-CM [41]. Importantly, the real-world experience with tafamidis in patients with hereditary ATTR-CM have shown that patients treated with the TTR Stabilizer have a lower risk of the composite endpoints of major adverse cardiovascular events (MACE); the hazard ratio was 0.81 (95% CI: 0.72-0.92, p=0.001) [42]. Targeting amyloid production at the level of TTR mRNA through gene-silencing therapies, patisiran, vutrisiran, inotersen, and eplontersen have also received strong evidence supporting their use [43].

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The Italian multicenter PatisiranItaly study included 181 patients with symptom manifestation of polyneuropathy (ATTRv). The results showed that ~70% of patients (mild and severe, with different genotypes) experienced stabilization of neuropathy progression [4]. All study patients reported no adverse effects and the drug was well-tolerated. The newly approved gene silencers, including vutrisiran, are expected to produce similar results but with more convenient administration to patients. Analyses of available data also show that patients undergoing the liver transplant (OLT) could benefit from the disease-modifying therapy for hereditary transthyretin amyloidosis. Data obtained from post-OLT patients with this genetic disease support this hypothesis [44].

7.3. Prognosis and Survival

Treatment with disease-modifying therapies has dramatically changed the outlook for patients with hereditary transthyretin-mediated amyloidosis (ATTRv). In a large Spanish cohort of 177 patients with a mean (±SD) age of 63±10 years, those treated with disease-specific therapies including tafamidis, patisiran, inotersen or liver transplant had improved survival ($p < 0.001$) [45]. Five-year event-free survival from symptom onset was 80.2% and from diagnosis 66.9%. Patients with NYHA class II–IV, left ventricular ejection fraction ≤50%, NT-proBNP ≥160 ng/dL or neurological involvement had a poor prognosis.

Patients with Val122Ile hereditary transthyretin cardiac amyloidosis (hATTR-CM) treated with tafamidis had reduced mortality and heart failure hospitalisation when compared to untreated individuals. The tafamidis-treated group had a longer median survival time (616 days versus 595 days, p=0.005) and longer time to heart failure hospitalisation (464 days versus 233 days, p=0.035). Early diagnosis and treatment should be considered as potential benefits for hATTR-CM patients [46].

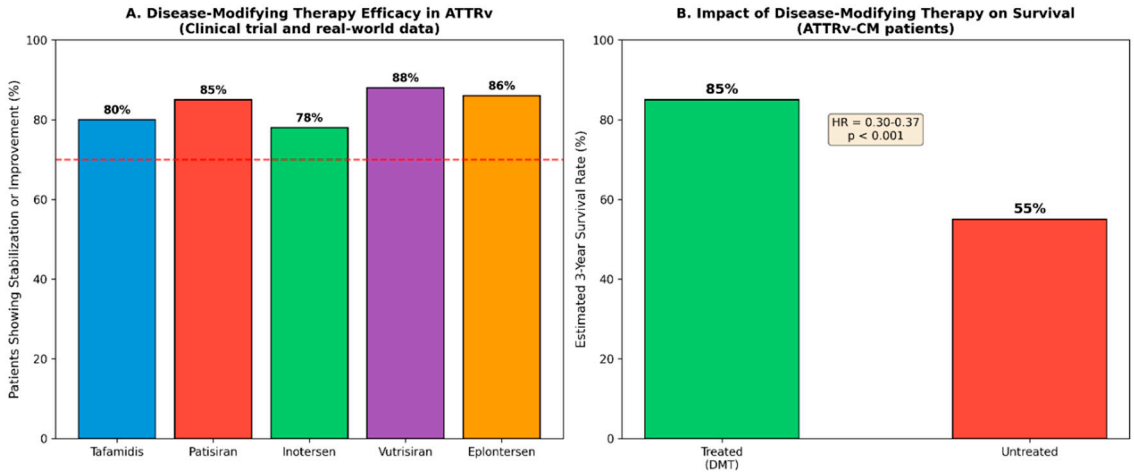

Figure 4. Treatment outcomes in hereditary transthyretin amyloidosis. (A) Disease-modifying therapy efficacy across different agents showing high rates of stabilization or improvement. (B) Impact of disease-modifying therapy on survival in ATTRv cardiomyopathy patients, demonstrating substantial survival benefit with treatment. Data derived from clinical trials and real-world registry analyses.

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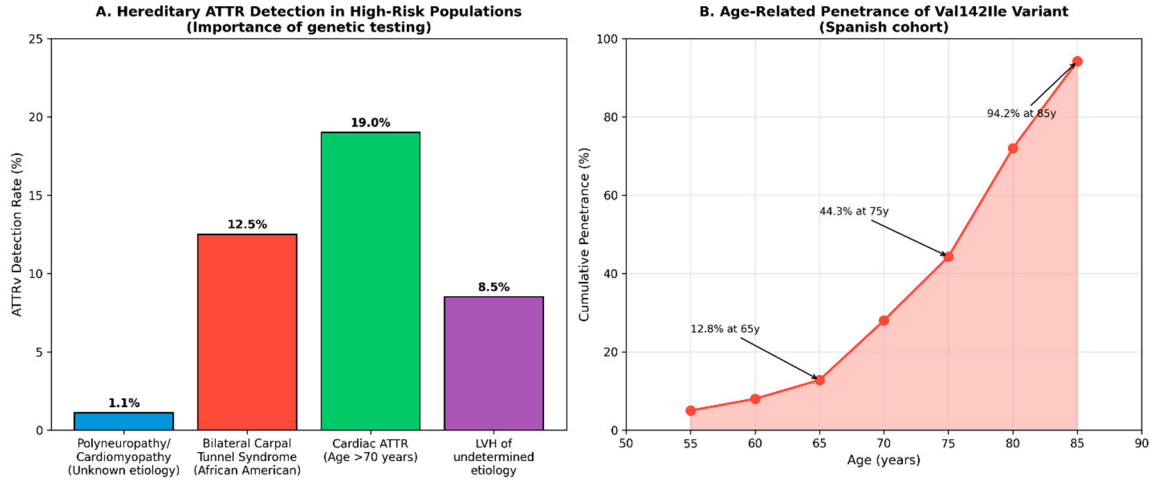

Figure 5. Importance of genetic testing across ages and populations. (A) ATTRv detection rates in various high-risk populations, demonstrating that genetic testing reveals substantial hereditary disease even in elderly cardiac amyloidosis patients. (B) Age-related penetrance of Val142Ile variant in Spanish cohort, showing progressive increase with age that supports screening at any age to identify at-risk individuals before symptom onset. Data from multiple screening studies and registry analyses.

Conclusions

Background & objectives: Hereditary transthyretin amyloidosis (hATTR) is characterized by clinical variability that remains poorly understood. This systematic review and meta-analysis updates current knowledge and insights on the hATTR and on wild-type transthyretin amyloidosis (wtATTR). Methods: The literature search was conducted on PubMed, Embase, Web of Science, Scopus, and DOAJ from 2020 to 2026. Results: Patients with hATTR have a distinct clinical profile that is characterized by younger onset, predominant neurological presentation, longer diagnostic delay and genetic variability that predicts phenotype and prognosis. These features should be recognized by clinicians during the diagnostic process of transthyretin amyloidosis. Genetic testing should not be delayed regardless of the age of the patient, and approximately 20% of patients with suspected cardiac wtATTR are actually aged over 70 years with underlying mutations. Conclusion: hATTR is substantially more common than previously considered. Successive screening studies in different populations and geographic locations have revealed unexpectedly high prevalence and new endemic foci of hATTR around the world.

The advent of disease-modifying therapies for hereditary transthyretin cardiomyopathy/polyneuropathy (ATTRv) has transformed the prognosis for patients with this treatable systemic disease. Early diagnosis and treatment of patients with “red flags” such as bilateral carpal tunnel syndrome, unexplained polyneuropathy, conduction disease, and heart failure with reduced or preserved ejection fraction is crucial. ATTRv should be in the differential for any patient of any age and ethnicity presenting with autonomic dysfunction. A high index of suspicion is needed among a variety of specialists including cardiologists, neurologists, gastroenterologists, and orthopedic surgeons to prevent delayed diagnosis.

Abbreviation	Full Term
ATTRv	Hereditary transthyretin amyloidosis
TTR	Transthyretin
ATTRwt	Wild-type transthyretin amyloidosis
wt-ATTR	Wild-type transthyretin amyloidosis
h-ATTR	Hereditary transthyretin amyloidosis

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Abbreviation	Full Term
REACT-SP	Transthyretin Cardiac Amyloidosis Registry of São Paulo
THAOS	Transthyretin Amyloidosis Outcomes Survey
HEAR	Healthcare European Amyloidosis Registry
TTR-A	Transthyretin amyloidosis
V30M / Val30Met / p.Val50Met	Valine 30 Methionine mutation
V122I / Val122Ile / p.Val142Ile	Valine 122 Isoleucine mutation
L58H	Leucine 58 Histidine mutation
proBNP	Pro-B-type natriuretic peptide
DNS_IL	Derived Neuropathy Impairment Score in the Lower Limbs
TRA	TTR-related amyloidosis
Glu89Gln	Glutamic acid 89 Glutamine mutation
ATTR-CM	Transthyretin amyloid cardiomyopathy
P/LP	Pathogenic/Likely pathogenic variants
p.Asp119Asn	Aspartic acid 119 Asparagine mutation
V142I	Valine 142 Isoleucine mutation
p.Asp38Glu	Aspartic acid 38 Glutamic acid mutation
Glu89Lys	Glutamic acid 89 Lysine mutation
p.Ala117Ser / Ala97Ser	Alanine 117 Serine mutation
Gly103Arg	Glycine 103 Arginine mutation
HCHS/SOL	Hispanic Community Health Study/Study of Latinos
CTS	Carpal tunnel syndrome
TRAM Study	Epidemiological analysis for hereditary Transthyretin-Related AMyloidosis study
DISCOVERY	Study of cardiac amyloidosis suspects
99mTc-DPD	Technetium-99m pyrophosphate scintigraphy
CMR / CMag	Cardiac magnetic resonance imaging
T1	T1 mapping
ECV	Extracellular volume fraction
MACE	Major adverse cardiovascular events
OLT	Orthotopic liver transplant
NYHA	New York Heart Association (classification)
NT-proBNP	N-terminal pro-B-type natriuretic peptide
hATTR-CM	Hereditary transthyretin cardiac amyloidosis
CroATTR	Croatian Transthyretin Cardiac Amyloidosis Registry
RETTRACE	Greek RETTRACE study
CATCH	Study screening elderly individuals from general population
LVH	Left ventricular hypertrophy
ECG	Electrocardiography/Electrocardiogram

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