HEREDITARY TRANSTHYRETIN AMYLOIDOSIS: OPPORTUNITIES & CHALLENGES

by

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TABLE OF CONTENTS

List of Figures and Tables

Abbreviations

AN	Autonomic neuropathy
ATTRwt	wild-type transthyretin amyloidosis
CAA	Cerebral amyloid angiopathy
CIDP	Chronic inflammatory demyelinating polyneuropathy
CM	Cardiomyopathy
CNS	Central nervous system
CTS	Carpal tunnel syndrome
hATTR	Hereditary transthyretin amyloidosis
hATTR-CM	Hereditary transthyretin amyloidosis with cardiomyopathy
hATTR-PN	Hereditary transthyretin amyloidosis with polyneuropathy
Echo	Echocardiogram
HF	Heart failure
HGVS	Human Genome Variation Society
IHC	Immunohistochemistry
AL amyloidosis	Immunoglobulin light chain amyloidosis
MGUS	Monoclonal gammopathy of uncertain significance
MRI	Magnetic resonance imaging
NCV	Nerve conduction velocity
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PN	Peripheral neuropathy
PST	Presymptomatic testing
RBP	Retinol binding protein
THAOS	Transthyretin Amyloidosis Outcome Survey
USA	United States of America
VA	Vitreous amyloidosis

Abstract

Hereditary transthyretin amyloidosis (hATTR) is a progressive, autosomal dominant, multisystem disease with incomplete and age-related penetrance. The disease presents many challenges for diagnosis, as well as presymptomatic and symptomatic management, due to its clinical heterogeneity. With the recent approval of three therapeutics by the Food and Drug Administration (FDA), the medical community has become increasingly aware of hATTR. Despite this increase in awareness, hATTR is still underdiagnosed. With the aim of raising awareness of this condition among a variety of healthcare providers, clinical information was extracted from over 400 original research articles in order to create an updated variant tabulation. With now over 130 pathogenic *TTR* variants, and a total of greater than 150 variants, an updated variant tabulation is necessary. Clinical manifestations and ages of onset were of particular interest and variants with the most severe phenotype are described in further detail. Finally, an analysis of genetic counseling issues is conducted, utilizing updated knowledge of the condition to provide a thorough examination of genetic counseling challenges specific to hATTR amyloidosis.

I. Introduction

A. Amyloid and Amyloidoses

Amyloidoses are a heterogeneous group of disorders characterized by localized or systemic tissue deposition of insoluble protein fibrils, known as amyloid (Benson et al., 2018). The term amyloid refers to a diverse group of abnormally folded proteins that share common biochemical, biophysical, and staining properties, most notably due to having an extensive β-sheet-rich structure (Eanes & Glenner, 1968). The β-sheet structure is made up of β-strands held together by hydrogen bonds (Balbach et al., 2002). An excessive β-sheet structure is responsible for amyloid's insoluble property and tendency to organize into fibrils (Serpell, 2014). The mature amyloid fibril is an unbranched fiber that is made up of 4-6 protofilaments (Serpell et al., 2000; Serpell, 2014). Each protofilament is a narrow structure of varying length, made up of protofibrils that are shorter β-sheet structures (Serpell, 2014). After Congo red or thioflavin S tissue staining, amyloid fibrils emit a characteristic yellow-green birefringent glow under polarized light (Glenner at al., 1974). Importantly, amyloid is not inherently pathogenic as functional amyloid has been described in bacteria and eukarya, including fungi and animals (Chiti and Dobson, 2006; Fowler et al., 2007; Greenwald and Riek, 2010). However, all types of amyloid associated with amyloidoses are pathogenic.

Amyloid deposits consist of amyloid fibrils as well as additional components which can vary with the amyloid type. Serum amyloid P-component and heparan sulfate proteoglycan are closely associated with most amyloid fibril types (Benson et al., 2018). Research has historically been focused on the amyloid fibril, but interest in the roles of SAP, HSPG, and other compounds have increased in recent years. Attention has revolved around the fibril and its precursor protein

because it determines properties of the amyloid deposit, the primary sites of tissue deposition, and its resulting disease pathogenesis (Benson et al., 2018).

There are at least 37 known human proteins with a predisposition to misfold and form these pathogenic amyloid fibrils (Chiti & Dobson, 2017). Of these, fourteen are associated with a hereditary form of amyloidosis (Benson et al., 2018). Transthyretin amyloidosis has both sporadic and hereditary forms. Hereditary transthyretin amyloidosis (hATTR; MIM# 105210) is responsible for the majority of hereditary amyloidosis cases and is caused by mutations in the *TTR* gene. The other thirteen proteins responsible for hereditary amyloidoses are immunoglobulin light chain (AL), β2-microglobulin, apolipoprotein A I, apolipoprotein A II, apolipoprotein C II, apolipoprotein C III, gelsolin, lysozyme, fibrinogen alpha, cystatin C, ABriPP, ADanPP, and Aβ protein precursor, and prion protein (Benson et al., 2018).

B. Transthyretin and Amyloidosis

Transthyretin, previously named prealbumin or thyroxine-binding prealbumin, is a highly conserved homotetrameric protein (Vieira & Saraiva, 2014). Its connection to amyloidosis was established when transthyretin was identified as the amyloid-fibril protein associated with "familial amyloidotic polyneuropathy," now known to be one of the major clinical subtypes of hATTR (Costa, Figueira, & Bravo, 1978). Decades later, a similar discovery was made for the sporadic form, now known as wildtype transthyretin amyloidosis (ATTRwt) (Westermark, Sletten, Johansson, & Cornwell. 1990).

The wild-type gene product of *TTR* (MIM# 176300) is a 127-amino-acid mature protein after cleavage of a 20-amino-acid signal peptide (Kanda, Goodman, Canfield & Morgan, 1974). In its functional form, four monomers of TTR assemble noncovalently to form a mirror-image-

symmetric homotetramer (Fig. 1) capable of binding its two ligands, thyroxine, and retinol binding protein (RBP) bound to vitamin A (Kanai, Raz, & Goodman, 1968; Oppenheimer, 1968; Blake, Geisow, Oatley, Rérat, & Rérat, 1978). The majority of TTR is synthesized in the liver (90%) and assembled as a tetramer in the endoplasmic reticulum of hepatocytes before secretion into serum (Quintas, Vaz, Cardoso, Saraiva, & Brito, 2001). The remainder is synthesized in extrahepatic sites, most notably in the choroid plexus and retinal pigment epithelium (Felding & Fex, 1982; Aleshire, Bradley, Richardson, & Parl, 1983; Soprano, Herbert, Soprano, Schon, & Goodman, 1985; Cavallaro, Martone, Dwork, Schon, & Herbert, 1990; Schreiber et al., 1990; Kawaji et al., 2005). The choroid plexus is considered the main TTR source for cerebral spinal fluid (CSF) (Aleshire et al., 1983; Schreiber et al., 1990).

Although the molecular mechanism of TTR amyloidogenesis is still under investigation (Fig. 2), monomers have been identified as the structural units that comprise the fibrils (Redondo, Damas, & Saraiva, 2000). The disassociation of the TTR tetramer into monomers has been identified as the rate-limiting step of fibril formation (Colon & Kelly, 1992; Hammarstrom et al., 2003). The TTR monomers then partially misfold into an intermediate state that can self-assemble into amyloid fibrils (Lai, Colón, & Kelly, 1996). Many *TTR* mutations, almost all missense, result in altered proteins (Table 1) that decrease the stability of the homotetramer to varying degrees (Benson & Kincaid, 2007). In lab assays, variants with greater thermodynamic instability were found to produce the largest amount of monomers and aggregates under conditions deemed close to physiological (Quintas et al., 2001). Interestingly, in vivo, the TTR variants with the lowest homotetrameric stability are not secreted efficiently from the liver and, thus, have less ability to promote amyloid deposition in certain tissues (Sekijima et al., 2005).

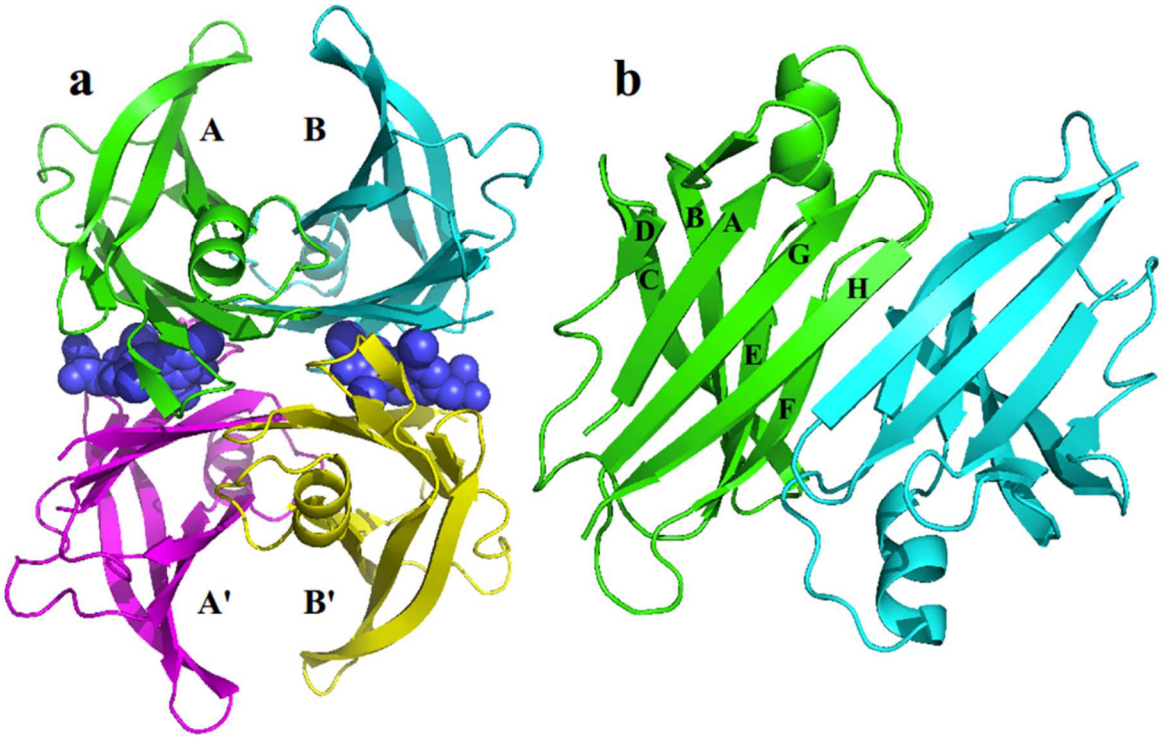

Figure 1: Structure of TTR-T4 Complex. T4 molecules are displayed in the binding cavities as spheres and TTR monomers as ribbons. (a) The two monomers present in the asymmetric unit of the crystal structures used are labelled as A and B, symmetry related monomers as A' and B'. (b) View of the A-A' monomer-monomer interface. Source: Saldaño et al., 2017.

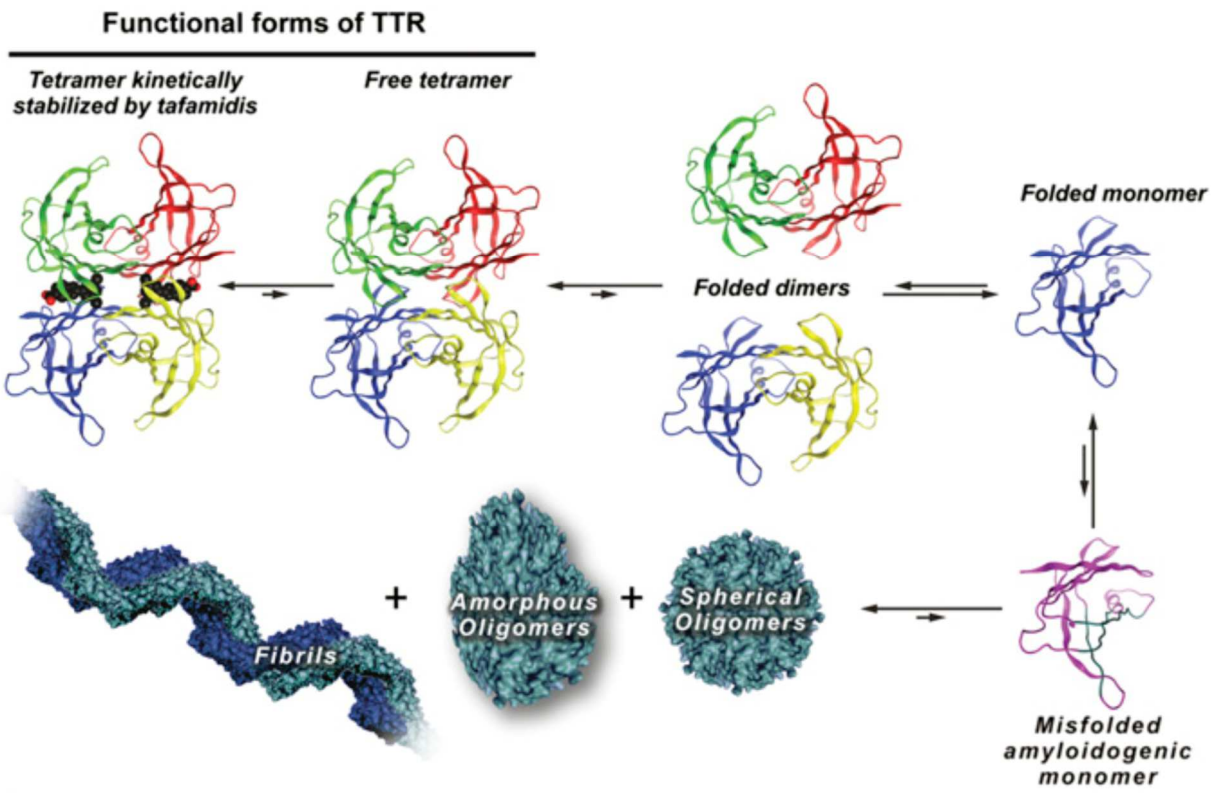

Figure 2: TTR Structures Associated with Pathology. The TTR amyloid cascade. Amyloid formation by TTR requires rate-limiting tetramer dissociation to a pair of folded dimers, which then quickly dissociate into folded monomers. Partial unfolding of the monomers yields the aggregation-prone amyloidogenic intermediate. The amyloidogenic intermediate of TTR (lower right) retains much of its native structure (shown in purple), probably with some β-strand dissociation (shown in turquoise). The amyloidogenic intermediate can misassemble to form a variety of aggregate morphologies, including spherical oligomers, amorphous aggregates, and fibrils. Source: Bulawa et al., 2012.

Table 1: *TTR* Amyloidogenic Variant Tabulation

Abbreviations: *, Subclinical; Am, American; AN, Autonomic neuropathy; CTS, Carpal tunnel syndrome; CM, Cardiomyopathy; Cu, Cutaneous; E, Eye involvement; K, Kidney involvement; LM, Leptomeningeal amyloidosis; MCV, meningocerebrovascular amyloidosis; CAA, cerebral amyloid angiopathy; My, Myopathy; N, neurologic, unspecified; PN, peripheral neuropathy; yrs, years; LTx, Liver transplantation; HTx, Heart transplant; §, Regions with highest disease prevalence; HL, hearing loss; HM, homozygote; HTZ; heterozygote

Variant	Exon	Ages of Onset (Decade)	Reported Phenotypes	Ethnicity/Ancestry (Geography)	Special Features
Cys10Arg	2	6-7th	AN, CM, E, PN	Hungarian-Am	Asymptomatic females in 7th & 8th decades
Leu12Met	2	5th	AN, CM, PN	South Korean	
Leu12Pro	2	3-5th	AN, CM, E, K, LM, PN	English, Portuguese, Nigerian	All patients with LM; Poor LTx outcomes reported; Grand mal seizures as only symptom in 2 patients; HL reported
Leu12Val	2	4-5th	AN, CM, CTS, PN	Bolivian, "Caucasian" (Germany)	
Asp18Asn	2	6th	CM, PN	African-Am, Liberian, Chinese	All patients with CM
Asp18Gly	2	3-6th	AN, Cu, E, LM, MCV	Chinese, Hungarian, Japanese	All patients with CNS involvement; Variability in disease duration (4-22 yrs)
Asp18Glu	2	5-6th	AN, CM, CTS, E, K, PN	Am, Columbian, English-Scottish, South Korean	
Ala19Asp	2	6th	AN, CM, PN	Brazilian, Swedish-German (Brazil), (Germany)	Only info: 6th decade of life at dx
Val20Ile	2	5-7th	AN, CM, CTS, PN	German, Irish-Am	All patients with CM, requiring HTx
Arg21Gln	2	N/A	CM, PN	(France)	
Ser23Asn	2	5th	CM, PN	German-Italian, Peruvian, Portuguese, Spanish-Italian Ecuadorian	
Pro24Ser	2	6-8th	AN, CM, CTS, My, PN	Am, Japanese	
Ala25Ser	2	6th	AN, CM*, PN	Am	Rapidly progressive sensorimotor PN

Ala25Thr	2	5th	LM, PN	Japanese	Predominant LM involvement
Val28Met	2	6th	AN, PN	Portuguese	
Val28Ser	2	5th	AN, CM, E, PN	Chinese	Double nucleotide substitution
Val30Ala	2	3-6th	AN, CM, K*, PN	Chinese, German-Am, Indian	
Val30Leu	2	5-6th	AN, CM, K, PN	Japanese, Swedish	Rapid disease progression; Poor LTx outcomes
Val30Gly	2	5-6th	E, LM, My, PN	German-Am, (USA)	All patients with E and LM
Val30Met	2	2-9th	AN, CM, CTS, E, K, LM, PN	(Cyprus, Japan, Majora, Portugal, Sweden) §	Anticipation noted; Disease features vary by region
Val32Ala	2	6-7th	AN, CM, PN	"Caucasian," Chinese, Jewish-Iranian	Ambulation affected within 2-3 years of disease onset
Val32Gly	2	4th	PN	French, (France)	
Phe33Cys	2	4th	CM, E, K, PN	Polish-Am	Vitreous opacities 16 yrs prior to other symptoms
Phe33Ile	2	3-4th	AN, E, K*, PN	Am, Israeli-Ashkenazi Jewish, Indian	Vitreous opacities may be first and only symptom
Phe33Leu	2	5-7th	AN, CM, CTS, K, PN	Ashkenazi Jewish, Chinese, Hungarian, Polish, Polish-Am, Polish-Lithuanian, Swedish, Taiwanese	
Phe33Val	2	3-6th	AN, CM, CTS, E, K, PN	British, Chinese, Japanese, Macedonian	
Arg34Gly	2	6th	CTS, E, PN	Chinese, Kosovar	All with E; Ocular involvement included vitreous opacities, vitreous hemorrhage, and glaucoma
Arg34Ser	2	N/A	CM, PN	Polish-Italian (United States)	
Arg34Thr	2	4-6th	AN, CM, PN	Italian, Chinese	
Lys35Asn	2	4-6th	AN, CM, E, K, PN	Chinese, Korean, South Korean, French	All presented with sensory neuropathy
Lys35Thr	2	5-7th	AN, CM, CTS, E, PN	Ashkenazi Jewish-Am, Chinese	Discordant female monozygotic twins reported

Ala36Asp	2	N/A	AN, PN	Japanese	
Ala36Pro	2	3-5th	AN, CM, CTS, E, K, LM, MCV, PN	Chinese, Greek-Am, Italian, Polish-Ashkenazi Jewish, South Korean	Most patients with AN, E, and PN; Poor LTx Outcomes
Asp38Ala	2	5-8th	AN, CM, CTS, PN, Pu	Am, Japanese, Korean, South Korean	Diffuse pulmonary involvement
Asp38Val	2	6-7th	AN, CM, PN	Ghanaian, Polish, South Korean	
Asp39Val	2	4-5th	AN, CM, PN	Chinese Malaysian, German	
Thr40Asn	2	7th	AN, CM, CTS, PN	Russian, (Germany)	
Trp41Leu	2	4-5th	AN, E, PN	Russian, Russian-Romanian	All presented with vitreous opacities
Glu42Gly	2	4-5th	AN, CM, E, PN	Chinese, Japanese, Italian, Italian-Am	
Glu42Asp	2	7th	AN, CM	French	
Pro43Ser	2	9th	CM	Japanese	
Phe44Leu	2	8th	CM, PN	"Caucasian," Nigerian	Compound heterozygote
Phe44Tyr	2	N/A	AN, CM, PN	French	
Phe44Ser	2	4-5th	AN, E, PN	Irish-Am, Japanese, Lithuanian-German	
Ala45Ser	2	7th	CM, CTS, PN	Swedish	Development of CM after LTx reported
Ala45Thr	2	6th	AN, CM	Irish-Italian, (Italy), (USA)	
Ala45Asp	2	5th	AN, CM, My, PN	Japanese, American	
Ala45Gly	2	8th	CM, CTS, PN*	Dutch, (Sweden)	
Gly47Arg	2	2-4th	AN, CM, CTS, E, LM, PN	Am, Chinese, Italian, Japanese, Korean	
Gly47Ala	2	3-6th	AN, CM, CTS, K, PN	French, Italian, Mexican	
Gly47Glu	2	3-7th	AN, CM, K, PN	Am, Chinese, Dutch, English, Finnish, Italian, (Germany), Turkish	Poor LTx outcomes reported; Mild PN
Gly47Val	2	8th	AN, CM, PN	Japanese, Sri Lankan, Tamil Malaysian	
Thr49Ala	3	4-6th	AN, CM, CTS, E, K, PN	French, Han Chinese, Italian, Japanese	Major causes of mortality were dysautonomia and cachexia, followed by CM
Thr49Ile	3	7th	AN, CM, PN	French, Japanese, Spanish	

Thr49Pro	3	6th	LM, PN	Irish	
Thr49Ser	3	2-4th	AN, CM, PN	Indian, Turkish	Anticipation >10 yrs
Ser50Arg	3	2-6th	AN, CM, CTS, Cu, E, K, PN	French, French Italian, Japanese, Mexican, Portuguese, Spanish, Vietnamese	
Ser50Ile	3	5-6th	AN, CM, My, PN	Japanese	
Glu51Gly	3	N/A	CM	American	
Glu51_Ser52dup	3	4th	AN, CM, CTS, K, M, PN	African-Am	
Ser52Pro	3	3-6th	AN, CM, K*, PN	Bulgarian, Mexican, (UK)	Development of CM after LTx reported
Gly53Arg	3	5-6th	CAA, LM	American	Hydrocephalus as presenting symptom
Gly53Glu	3	3-6th	AN, CM, K, LM, PN	Brazilian, French, Indian, Italian, Swedish, Turkish	All patients with CM
Gly53Ala	3	2nd	AN, CM*, E, K, LM, PN	British	Severe headaches since 18 yrs, other symptoms developed at 40 yrs
Glu54Leu	3	5th-8th	AN, CM, CTS, PN	Belgian, Swedish	Double nucleotide substitution
Glu54Lys	3	2-4th	AN, CM, E, K, PN	Costa Rican, Italian, Japanese, Malay Malaysian, Turkish	All died before age 40 yrs
Glu54Gly	3	3-4th	AN, CM, E, K, PN	Am, British, Korean, South Korean, Turkish	
Glu54Asp	3	N/A	CM	(Germany)	
Glu54Gln	3	4-6th	AN, CM, CTS, PN	Italian, Romanian	
Leu55Gln	3	5th	AN, CM, CTS, E, PN	Spanish-Am, Swedish	Development of CM after LTx reported
Leu55Arg	3	4-6th	AN, CM, CTS, E, LM, PN	Chinese, Han Chinese, (Germany)	
Leu55Pro	3	2-4th	AN, CM, E, PN	Chinese, German Dutch Am, Japanese, Korean, Taiwanese	Anticipation >10 yrs
His56Arg	3	N/A	CM	American	
Gly57Arg	3	N/A	CM, CTS, PN	Swedish, (Italy)	
Leu58Arg	3	4th	AN, CM, CTS, E, LM*, PN	Japanese	
Leu58His	3	5th	CM, CTS, PN	Am, German-Am, German	Majority develop CTS first; CTS may be first and only symptom
Thr59Arg	3	6th	AN*, CM	Japanese	

Thr59Lys	3	4-7th	AN, CM, PN	Chinese, Egyptian, Italian	All patients presented with heart failure; Sudden cardiac death in 1 patient
Thr60Ala	3	6-8th	AN, CM, CTS, K, LM, My, PN	English, Irish, Scottish	Compound HTZ reported
Glu61Lys	3	6-8th	AN, CM, CTS, PN	Japanese, Polish	
Glu61Gly	3	6th	CM, CTS, PN	English Dutch	Hematuria due to TTR-positive bladder polyp
Glu61Ala	3	7th	CM, CTS	(USA)	
Glu62Lys	3	6-8th	CM, CTS, PN	(Italy, France, Czech Republic)	
Phe64Ile	3	8th	AN, CM, K, PN	Caucasian (Italy)	
Phe64Leu	3	7-8th	AN, CM, CTS, E, PN	Italian-Am, Italian, Sicilian	HZ reported with earlier onset in 6th decade; Only women identified as asymptomatic later in life; Pure motor neuropathy reported
Phe64Ser	3	3rd	AN, CM, CTS, E, LM, PN	African-Am, Italian Canadian	LM prominent in Italian Canadian family, AN prominent in African-Am patient
Phe64Val	3	4th	AN, CM, PN	"Caucasian," German	
Gly67Arg	3	5-6th	AN, E	Bangladeshi, “Caucasian”	All patients with E
Gly67Glu	3	4-6th	AN, CM, E, K*, PN	Chinese, Macanese	
Ile68Leu	3	7-8th	AN, CM, CTS, PN	German, Italian	Higher male prevalence; Rapid progression; Compound HTZ and HM reported
Tyr69His	3	4-7th	AN, CM, CTS, E, LM, PN	Italian-Am, Scottish, Swedish	
Tyr69Ile	3	7th	AN, CM, CTS	Japanese	Double nucleotide substitution
Lys70Asn	3	3-7th	CTS, E, K, PN	German-Am	Tongue and forearm fasciculations reported
Lys70Glu	3	5-8th	CTS, E, PN	Finnish	

Val71Ala	3	3-6th	AN, CM, CTS, E, K, PN	Australian, Bengali, Brazilian, Dutch, English, French, Majorcan, Polish, Spanish	
Ile73Val	3	5-7th	AN, CM, K*, PN	Bangladeshi, Indian, Polish, Taiwanese	
Ser77Phe	3	6-8th	AN, CM, PN	Bulgarian, French	Poor 9 -year LTx survival (24%)
Ser77Tyr	3	6-7th	AN, CM, CTS, E, K, My, PN	Am, English, French, German-Am, Jewish-Yemenite, Israeli-Yemenite, Spanish	Conjunctival lymphangiectasia is a biomarker of severe disease
Tyr78Phe	3	6-8th	AN, CM, CTS, Cu, E, K, PN	Italian	Significant clinical heterogeneity
Ala81Thr	3	7-8th	CM, CTS	(USA), (Western Europe)	
Ala81Val	3	7th	AN, CM, CTS, E, PN	Polish, Russian-Polish, (England)	
Gly83Arg	3	4-5th	CM, E, PN	Chinese	Prominent eye involvement
Ile84Asn	3	6-7th	CM, CTS, E	Italian-Am, Japanese	
Ile84Ser	3	5-6th	CM, CTS, E, PN	Swiss-Am, Hungarian	
Ile84Thr	3	6th	CM, PN	Am, German	
His88Arg	3	6-8th	CM, CTS, PN, K	Hungarian, Swedish	
Glu89Gln	3	6-7th	AN, CM, CTS, PN	Bulgarian, Sicilian-Italian, Turkish	
Glu89Lys	3	2-6th	AN, CM, CTS, E, PN	Am, Canadian, Korean, Polish, Swiss	Rapid disease progression, requiring HTx; Development of PN after HTx and were listed for, or received, LTx
His90Asp	3	N/A	CM, CTS, PN	British, (UK)	
Ala91Ser	3	7th	AN, CM, CTS, PN	French, (France)	
Gln92Lys	3	7th	CM, K*	Japanese	
Val93Met	4	5th	AN, CM, PN	Malian	Misdiagnosed as ALS; Pure motor neuropathy; Symptoms stable for five years; Tongue fasciculations reported
Val94Ala	4	7th	AN, CM, PN	“Caucasian”, German Greek	

Ala97Ser	4	5-9th	AN, CM, K*, PN	Chinese, Chinese Malaysian, Korean, Taiwanese	Possible onset of disease in one patient at age 23; Spinal stenosis reported
Ala97Gly	4	6th	CM, PN	Japanese	
Arg103Ser	4	N/A	CM	American	
Ile107Val	4	5-8th	AN, CM, CTS, My, PN	Brazilian, French, German, German-Am, Japanese, Kazakhstani	
Ile107Phe	4	7th	AN, CM, K, PN	British, Italian, (Germany)	Spinal stenosis reported
Ile107Met	4	6th	AN, E, PN	Chinese, German	
Ala109Ser	4	7th	AN, PN	Japanese	
Leu111Met	4	4-5th	AN, CM, CTS, K, PN	Danish	Prominent heart involvement; Good LTx and combined LTx-HTx outcomes
Ser112Ile	4	N/A	CM, PN, K	Italian	
Pro113Thr	4	N/A	CM, CTS, E	French	
Tyr114Cys	4	4-7th	AN, CAA, CM, E, LM, My, PN	Am, Argentinian, Chinese, Japanese	
Tyr114His	4	6-7th	CM, CTS, Cu, PN	Japanese	Mild disease course; Predominant CTS involvement; Nodular cutaneous amyloidosis; Spinal stenosis reported
Tyr114Ser	4	7th	CM, CTS, PN	Japanese	Mild PN
Tyr116Ser	4	6-8th	AN, CM, E, CTS, PN	French, Han Chinese	
Tyr116His	4	7th	N	Mexican	
Ala120Ser	4	7th	AN, CM, CTS, My, PN	Afro-Caribbean, Am, Italian	
Val121Ala	4	8th	CM, K	(Japan)	
Val122del	4	6th	AN, LM, PN	Ecuadorian-Am, (Spain)	
Val122Ile	4	6-9th	AN, CM, CTS, K, My, PN	African, African-Am, Brazilian, Italian, Jamaican (Britain), Japanese, Mexican, Portuguese	HZ and compound HTZ reported with earlier age of onset in 5th and 6th decades; Hearing Loss
Val122Ala	4	7th	CM	British, Chinese	
Asn124Ser	4	7th	CM, K	Italian	Prominent kidney involvement

Amyloidogenic *TTR* mutations act by a toxic gain-of-function mechanism (Sekijima, 2015). In contrast, simple gain-of-function mutations that increase binding affinity for thyroxine cause the condition euthyroid hyperthyroxinemia (MIM# 145680; Moses, Lawlor, Haddow, & Jackson, 1982). Simple loss-of-function mutations, which might be expected to cause symptoms of thyroxine or vitamin A deficiency, have not been reported.

Wild-type TTR is also capable of forming amyloid fibrils that deposit in tissues and disrupt their function. Wild-type transthyretin amyloidosis (ATTRwt), originally referred to as senile cardiac amyloidosis, typically becomes clinically evident in the 8th decade of life (González-López et al., 2017). Historically, this acquired form was associated with isolated cardiac involvement, but later recognition of systemic symptoms prompted the use of the term senile systemic amyloidosis (Pitkänen, Westermark, & Cornwell, 1984). Previously studied ATTRwt cohorts suggested a large male predominance of up to 98%, but a more recent study suggested the prevalence of ATTRwt among women may be underestimated due to a later age of onset and less severe or atypical presentations (Connors et al., 2016; González-López et al., 2017).

ATTRwt is now being diagnosed more often than hATTR and is likely a relatively common disease in elderly populations, especially among individuals with cardiac disease (Treibel et al., 2016; Mohamed-Salem et al., 2018). Autopsy studies first raised suspicion that ATTRwt may be quite common but undiagnosed, with 25% of individuals over the age of 80 having histological evidence of TTR amyloid deposits in the heart (Cornwell, Murdoch, Kyle, Westermark, & Pitkänen, 1983; Tanskanen et al., 2008). Although awareness of ATTRwt has increased, the misconception that ATTRwt is rare persists and the condition is still likely underdiagnosed (Rubin & Maurer, 2020). The aggregation of wild-type TTR suggests the protein

has intrinsic amyloidogenic properties, perhaps augmented by the aging process (Teng et al., 2001).

C. Hereditary Transthyretin Amyloidosis

Hereditary transthyretin amyloidosis (hATTR) is a progressive, multisystem disease that most commonly affects the peripheral nerves, often leading to both somatic and autonomic impairment, and/or the heart, and can cause life-threatening cardiac disease (Adams, Koike, Slama, & Coelho, 2019). In addition, amyloid deposition can also occur in many other tissues, leading to additional clinical manifestations, as detailed in section I.E., and summarized in Figure 3 and Table 1. This autosomal dominant condition is characterized by incomplete penetrance and variable expressivity (Adams et al., 2019). With rare exceptions, hATTR has adult onset with the decade of onset varying enormously, somewhat dependent on the particular *TTR* variant (Table 1).

First described by Andrade (1952) in Portugal as a "peculiar form of peripheral neuropathy," the familial nature and presence of amyloid in sural nerve biopsies was noted in this initial report. The analysis of clinical symptoms in this Portuguese population highlighted the predominance of autonomic and sensorimotor neuropathy, as well as ocular and cardiac involvement. Over the next few decades, the same condition was identified in Japan and Sweden (Araki, 1984; Andersson, 1976). This guided the mistaken belief that this disorder was restricted to certain geographical regions, leading to these areas – even now – being referred to as "endemic regions." However, our knowledge of this condition expanded greatly after the elucidation of the genetic etiology and discovery of the first pathogenic variant of *TTR*,

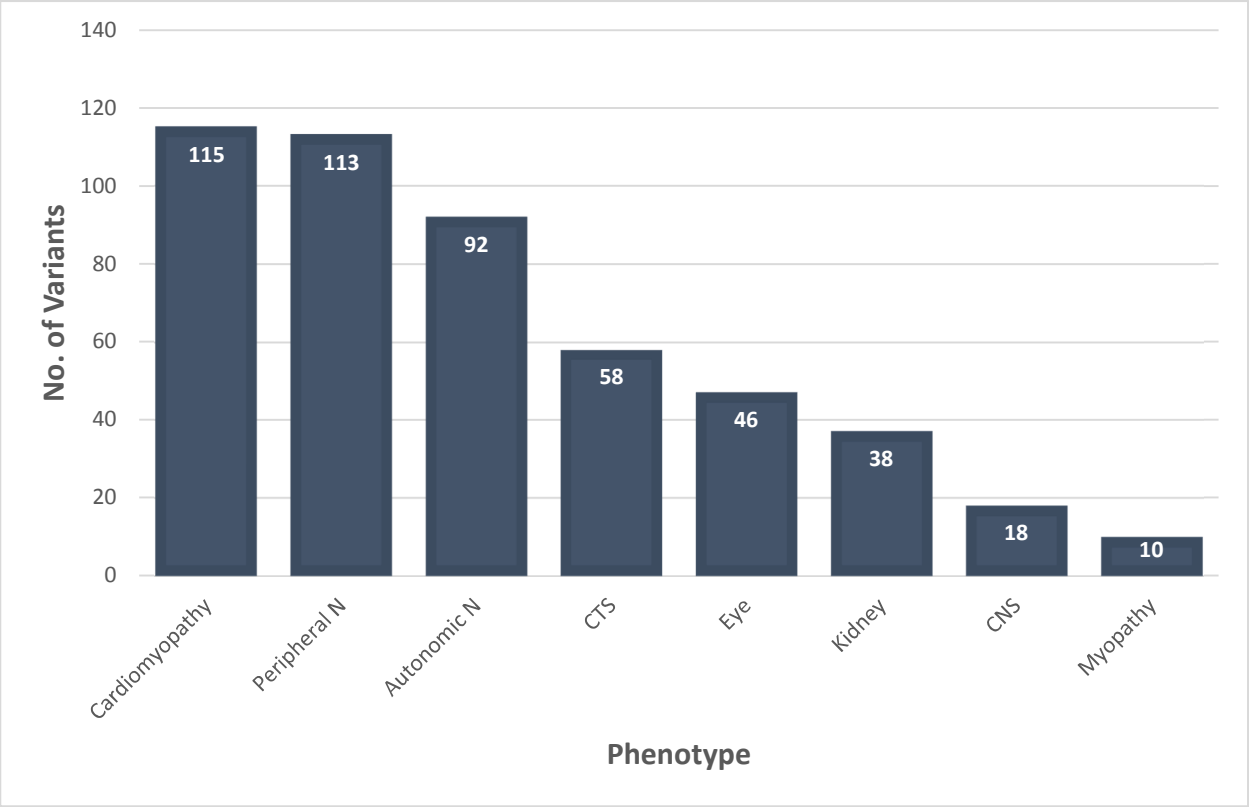

Figure 3: Number of Variants Associated with Each Phenotype. Of the 134 amyloidogenic variants, 115 are associated with cardiomyopathy, 113 with peripheral neuropathy, 92 with autonomic neuropathy, 58 with carpal tunnel syndrome (CTS), 46 with ocular involvement (eye), 38 with kidney involvement, 18 with central nervous system (CNS) involvement, and 10 with myopathy.

Val30Met (Dwulet & Benson, 1984); based on newer nomenclature that includes the signal sequence (see section I.D.), it is also known as p.Val50Met (den Dunnen & Antonarakis, 2000).

With the availability of genetic testing, the number of reported *TTR* variants has increased greatly since the 1980's. As of 2021, there are over 150 known *TTR* variants, of which over 130 are amyloidogenic (Table 1); others are non-amyloidogenic, but some can modify the phenotype of a pathogenic variant (Table 2). The clinical phenotype of hATTR is still expanding (e.g., Pinto et al., 2020). The complexity and variability of the clinical phenotype are further discussed in section I.E., below.

Hereditary transthyretin amyloidosis has now been diagnosed worldwide, with more than 29 countries represented in the literature (Adams et al., 2019). Nonetheless, the prevalence of hATTR is not uniform, but rather varies greatly by geographical region. Northern Portugal, northern Sweden, two regions of Japan, Cyprus, and Majorca have the highest prevalence, 1 to 10 per 10,000 (Adams et al., 2019). Haplotype studies focused on Val30Met suggest multiple founders, with a common founder for Japanese and Portuguese patients and a separate founder for Swedish patients (Zaros et al., 2008; Ohmori, 2004). In so-called non-endemic areas, where disease prevalence is lower, haplotypes vary significantly, suggesting additional heterogeneous origins (Ueda, Yamashita, Misumi, Masuda, & Ando, 2018). Worldwide, the number of persons affected with hATTR is estimated to be ~50,000 (Hawkins et al., 2015; Schmidt et al., 2018).

Although Val30Met is the most common variant in Europe, and the most studied, it is commonly misstated to be the most common variant worldwide (Maurer et al., 2016). In fact, the Val122Ile variant has a prevalence of 3.43 per 100 among African Americans (Jacobson et al., 2015), making it the most common *TTR* variant not only in the United States, but also worldwide (Maurer et al., 2016). In the United States of America (USA), Val122Ile is followed by

Table 2: Non-amyloidogenic *TTR* Variant Table

Variant	Exon	Reported Phenotype	Other Biologic or Special Features	Ethnicity/Ancestry, (Geography)
Gly6Ser	2	Non-amyloidogenic	Associated with hyperthyroxinemia	Scottish, Danish, Norwegian,
		Vitreous Amyloidosis	Homozygous	American
Met13Ile	2	Non-amyloidogenic		German
Asp74His	3	Non-amyloidogenic		German
His90Asn	3	Non-amyloidogenic		German, Portuguese
Asp99Asn	4	Non-amyloidogenic		Danish
Gly101Ser	4	Non-amyloidogenic		Japanese
Pro102Arg	4	Non-amyloidogenic		German
Arg104Cys	4	Non-amyloidogenic		American
Arg104His	4	Non-amyloidogenic	Protective effect	Japanese, Chinese
Ala108Ala	4	Non-amyloidogenic		Portuguese
Ala108Val	4	Non-amyloidogenic	Protective effect	Portuguese
Ala109Thr	4	Non-amyloidogenic	Associated with hyperthyroxinemia	Portuguese
Ala109Val	4	Non-amyloidogenic	Associated with hyperthyroxinemia	American
Leu110Pro	4	Intellectual Disability, VUS for hATTR		Thai
Tyr116Val	4	Non-amyloidogenic	Double nucleotide substitution	French-Canadian
Thr119Met	4	Non-amyloidogenic	Protective	French, Portuguese
Thr119Thr	4	Non-amyloidogenic		Brazilian
Pro125Ser	4	Non-amyloidogenic		Italian
Lys126Arg	4	Non-amyloidogenic		European

Thr60Ala, and then Val30Met (Maurer et al., 2016). The distribution of TTR variants in the USA is summarized in Figure 4 (Zhen et al., 2015).

The diagnosis of hATTR is currently based on the identification of a pathogenic *TTR* variant in the presence of amyloid deposits in one or more tissues (Adams et al., 2016). If a patient tests positive for a *TTR* mutation but lacks clinical manifestations and evidence of amyloid deposition (e.g., if tested because a family member has hATTR), they are considered asymptomatic carriers. Once TTR amyloid is detected, the patient is diagnosed with hATTR. Amyloid is detected, by Congo-red staining and microscopic exam under polarized light, by its yellow-green birefringence. The fibril type is then identified by immunoassay with anti-TTR antibodies or mass spectrometry-based methods (Gilbertson et al., 2015). Tissues utilized for biopsy include skin, sural nerve, kidney, labial salivary gland, gastrointestinal mucosa, abdominal fat pad and the rectum, with fat pad and rectal biopsies most often performed (Adams et al., 2016).

Histological confirmation of amyloid by biopsy is considered the gold standard for diagnosis (Gertz et al., 2020). However, the patchiness of amyloid deposits results in suboptimal sensitivity; hence, a negative biopsy is not sufficient to rule out amyloidosis (Adams et al., 2016). Noninvasive detection of cardiac TTR amyloidosis is possible by nuclear scintigraphy scan with technetium radiotracers (Fig. 5), a serendipitous finding that some have used for diagnostic purposes (Gillmore et al., 2016). Because technetium binds to amyloid made of either TTR or immunoglobulin light chains, serological testing for the latter must also be done to rule out another form of amyloidosis associated with monoclonal gammopathy. If the scan reveals grade 2 or 3 myocardial uptake of technetium in the absence of a monoclonal protein, then myocardial TTR-associated amyloidosis can be diagnosed noninvasively (Gillmore et al., 2016).

Figure 4: Geographic Distribution of Mutations in 252 US Patients. Geographic distributions of mutations in 252 US patients with transthyretin (TTR)- and non-TTR-related amyloidosis (ATTR). Values inside each symbol indicate the number of patients with a particular mutation in that state. Source: Zhen et al., 2015.

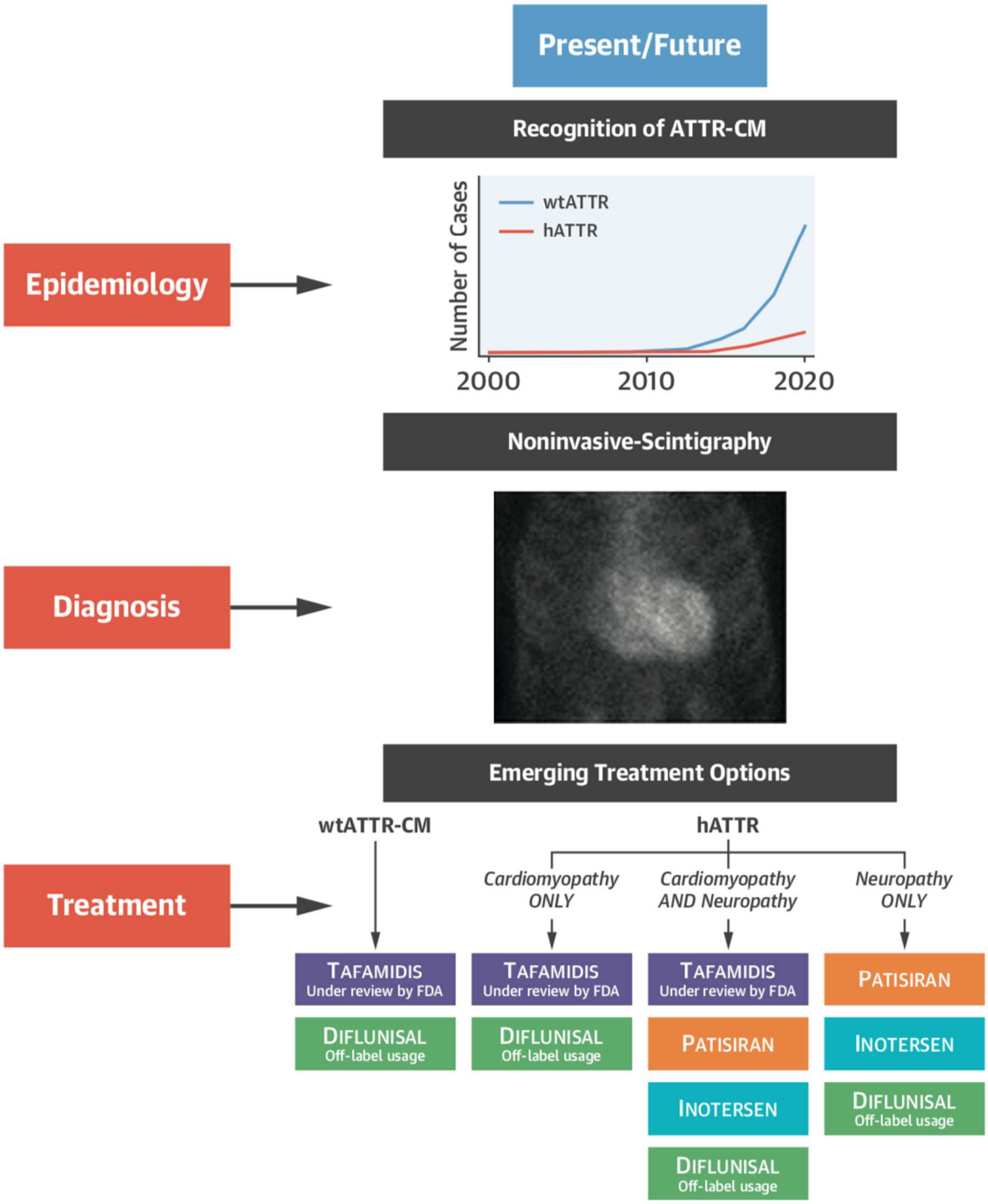

Figure 5: Transthyretin Cardiac Amyloidosis. The present and future of transthyretin amyloid cardiomyopathy (ATTR-CM) with respect to epidemiology, diagnostic approach, and treatment. Source: Ruberg et al., 2019.

Prior to 2018, liver transplantation was the only treatment option available for hATTR patients. While this therapeutic strategy eliminates the major source of mutant TTR production, it has many limitations, including limited efficacy in certain *TTR* genotypes (Kapoor, Rossor, Laura, & Reilly, 2019). In addition, the continued production of variant TTR in the choroid plexus and retinal pigment epithelium provides an ongoing supply of amyloidogenic proteins to structures of the brain and eye (Haraoka et al., 2002; Maia et al., 2015; Salvi et al., 2015). Moreover, deposition of wild-type TTR amyloid fibrils in hATTR patients, most notably in the myocardium, can increase rapidly after liver transplantation and lead to severe cardiac amyloidosis (Yazaki et al., 2007; Okamoto et al., 2011).

The therapeutic landscape for hATTR changed dramatically in 2018 and 2019, with FDA approval of three disease-modifying therapeutic agents, each with a different mechanism of action: Onpattro® (patisiran), a small interfering RNA, Tegsedi® (inotersen), an antisense oligonucleotide, and Vyndaqel® (tafamidis), a tetramer stabilizer (Figs. 5 and 6) (Planté-Bordeneuve, 2018; Müller et al., 2020). Patisiran, inotersen, and tafamidis slow the progression of the disease by RISC-mediated cleavage of the *TTR* mRNA, RNase H1-mediated degradation of *TTR* mRNA, and stabilization of the TTR homotetramer, respectively (Mathew & Wang, 2019). Both patisiran and inotersen are approved for hATTR amyloidosis with polyneuropathy, and tafamidis for hATTR and ATTRwt amyloidosis with cardiomyopathy (Müller et al., 2020). Additionally, diflunisal, a well-known nonsteroidal anti-inflammatory drug, has shown promise in clinical trials as a tetramer stabilizer for patients with hATTR amyloidosis (Berk et al., 2013; Lorhmann et al., 2020). Although it has not been approved by the FDA for this use, it can be prescribed off-label for hATTR amyloidosis patients (Kapoor et al., 2019). None of these treatments has demonstrated the ability to reverse amyloid fibril deposition (Adams et al., 2019).

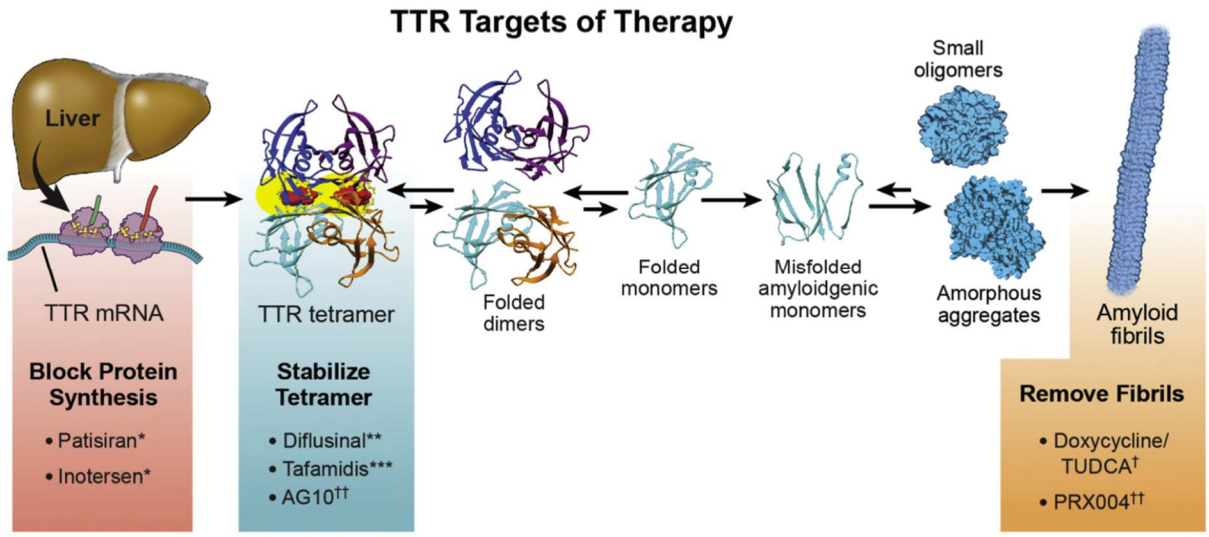

Figure 6: TTR Targets of Therapy. Therapeutic strategies for ATTR-CM are illustrated with agents either presently approved, under review, or in development. *TTR silencers patisiran and inotersen are not presently approved for ATTR-CM but rather for hATTR polyneuropathy (with or without cardiomyopathy). **Diflunisal may be used off-label in selected patients with ATTR-CM but only with careful monitoring. ***The agent tafamidis is undergoing U.S. Food and Drug Administration review for an ATTR-CM indication. †Combination of doxycycline and tauroursodeoxycholic acid (TUDCA) can be used in conjunction with other strategies and is being evaluated in a clinical trial. ††AG10, a TTR stabilizer, and PRX004, a monoclonal antibody that binds and potentially removes ATTR deposits, are both in development. Source: Ruberg et al., 2019.

Therefore, early diagnosis of hATTR is essential to both preserve the quality of life and extend the life expectancy of hATTR patients (Nativi-Nicolau et al., 2021).

Due to the new therapeutic options, awareness of hATTR has increased in recent years. As a testament to this increased awareness, as well as the phenotypic heterogeneity of the condition, in the last five years clinical awareness of hATTR-CA specifically, has moved beyond the typical specialties of neurology, cardiology, and gastroenterology to additional medical specialties, including urology, rheumatology, geriatrics and anesthesiology (Dang et al., 2020). However, hATTR is still considered underdiagnosed, perhaps in part because the literature is scattered and fragmented. The most recent *TTR* variant tabulation, with 113 amyloidogenic variants (Nuvolone, Obici, & Merlini, 2012) was adapted from a 2007 report of 89 amyloidogenic variants (Benson & Kincaid, 2007). However, with over 130 pathogenic *TTR* variants now known, an updated tabulation is necessary, along with an effort to understand phenotypes of this growing library of variants. This information is needed not only by the medical community, but also by the growing ranks of genetic counselors who will educate and advise patients, their family members, and those who learn of their *TTR* carrier status as a secondary finding.

D. Variant Nomenclature

Protein-coding changes in the TTR protein were originally described based on sequence of the mature protein, after cleavage of the 20-amino-acid signal peptide, known as legacy nomenclature. However, more recently the Human Genome Variation Society (HGVS), recommends amino-acid numbering beginning at the translation-initiation codon, regardless of subsequent processing of the gene product (den Dunnen & Antonarakis, 2000), known as

standard nomenclature. For instance, the first *TTR* variant described, Val30Met, would be referred to as Val50Met after accounting for the signal peptide sequence. Nonetheless, many members of the global community of hATTR researchers continue to report *TTR* variants using the older, legacy nomenclature. Furthermore, many authors are not specifying which nomenclature they are using in a particular publication.

Awareness of these differences in variant nomenclature is of the utmost importance for interpretation of *TTR* sequence data. Potential ambiguity may arise resulting in variant misclassification by genetic testing laboratories or in misunderstanding by physicians and genetic counselors. For instance, there are pathogenic variants at two different amino-acid positions 20 residues apart that share the same amino acid in the wild-type TTR sequence. In these situations, it could be difficult to discern if a protein variant, such as Ala45Thr, was referring to the legacy nomenclature with a protein substitution at position 45 in the mature protein, or to the newer HGVS-recommended nomenclature, which would refer to position 25 in the mature protein, which is also Ala in the wildtype. Without explicitly stating the nomenclature being utilized, this particular variant could be easily misinterpreted without additional information. Not surprisingly, none of the pathogenic *TTR* variants is located in the signal sequence (Table 1; Appendix 1).

Throughout this report, unless otherwise specified, the legacy nomenclature will be used. However, to avoid ambiguity, both the standard and legacy nomenclatures will be given when necessary.

E. hATTR Amyloidosis Phenotypes: Clinical and Pathological Features

1. Overview

The clinical heterogeneity of hATTR is not only vast but also expanding as new manifestations are recognized. Understanding the complex relationships between *TTR* genotype and clinical phenotypes(s) requires an appreciation of the scope of clinical and pathological features. The disease has often been classified in the literature as early- and late-onset, referring to an age of onset before or after 50 years, respectively. The term "early" is also used to refer to the stage of the disease along the time course of its progression. For clarity, in this document, the terms early and late will be used exclusively to refer to age of onset, while the terms beginning and advanced will be used to describe the approximate stage of disease. Below, I outline common and uncommon clinical manifestations, offer additional insight into pathological features, and highlight the prevalence of the manifestations according to the Transthyretin Amyloidosis Outcome Survey (THAOS) (Coelho, Maurer, & Suhr, 2013). Launched in 2008, THAOS (ClinicalTrials.gov identifier NCT00628745; see Web Resources) is a longitudinal, observational study conducted on a global, multi-center scale aimed at better understanding the natural history of ATTR amyloidosis, both hereditary and wild-type forms. THAOS has a target enrollment of 8000 participants, which gives it the depth and sensitivity to reveal phenotypes not widely recognized in the past, e.g., sensory neuropathy among patients with Val122Ile-associated hATTR (Coelho et al., 2013). Although the study is not scheduled to complete data collection until 2023, multiple publications have reported on its interim findings (e.g., Schumacher et al., 2015). Much of the data available, through THAOS and other sources, is dominated by the Val30Met variant because it is the most studied, and the most common variant in Europe.

2. Peripheral and Autonomic Neuropathy

Neuropathy is probably the best-characterized phenotype associated with hATTR. Specifically, progressive sensory, motor, and autonomic neuropathy are common among hATTR patients (Adams et al., 2019). The THAOS registry found 86.1% and 50.1% of enrolled hATTR patients experienced sensory neuropathy and autonomic neuropathy, respectively (Coelho et al., 2013). Neuropathic symptoms are progressive, with slower progression typically documented in early-onset disease, and more rapid progression in late-onset disease (Adams et al., 2019).

Clinical features of hATTR-associated peripheral neuropathy are best discussed in terms of early- and late-onset disease, which differ somewhat in pattern of affected axons. While both early-and late-onset disease follow a classic pattern of symmetrical features and distal-to-proximal spread, the initial presentation in early-onset is typically one of length-dependent small-fiber neuropathy due to axonal degeneration in the lower extremities (Said, Ropert, & Faux, 1984; Sobue et al., 1990; Takahashi, Yi, Kimura, & Araki, 1991; Koike et al., 2004; Conceição & De Carvalho, 2007). Patients experience sensory disturbances first in the feet, including hypesthesia and paresthesia. The small-fiber neuropathy progresses proximally with the hands becoming affected around the time that the sensory disturbances have reached the level of the knees, resulting in a glove-and stocking-distribution (Ando et al., 2013). Motor neuropathy typically follows within a few years after the development of sensory symptoms, also beginning in the distal lower extremities before progressing proximally. Common symptoms of motor neuropathy include foot drop and wrist drop, with difficulty walking and using hands and fingers.

In contrast, late-onset disease typically presents with all-fiber neuropathy, followed by rapid progression. Patients experience both sensory and motor disturbances at initial stages of the disease (Ikeda et al., 1987; Misu et al., 1999; Koike et al., 2002). Additionally, these symptoms

can present in distal regions of all limbs, as opposed to only the lower limbs as seen in patient with early-onset disease (Adams et al., 2019). Atypical presentations include gait disturbances, upper-limb-only polyneuropathy in ~15%, and a pure motor neuropathy in less than 1%, further complicating the diagnosis (Lozeron et al., 2013; Mariani et al., 2015; Théaudin et al., 2019). Advanced stages of the disease in all patients with progressive peripheral neuropathy are marked by complete sensory loss, significant muscle atrophy, and paralysis.

Nerve biopsies, most commonly of the sural nerve, were used for many decades to diagnose hATTR-peripheral neuropathy, but the method has less-than-optimal sensitivity and is falling out of favor (Adams et al., 2020). Due to the patchy distribution of amyloid deposition and inherent limitations of biopsies, it is not uncommon for nerve biopsies to have absent or scarce amyloid detected (Koike et al., 2004). When peripheral nerve amyloid is present on biopsy or at autopsy, the deposits are localized to the endoneurium (Koike et al., 2004), an important clue to pathogenesis.

In a follow-up study, endothelial cell abnormalities in sural nerve biopsies of hATTR patients were found to disrupt the blood-nerve barrier; this was not found in samples from patients with a similar axonal neuropathy of a different etiology (Koike et al., 2016). Another group identified endoneurial edema, by magnetic resonance neurography, in asymptomatic *TTR* mutation carriers, lending further support to the proposed timeline of blood-nerve-barrier disruption occurring before amyloid deposition (Kollmer et al., 2015). The exact mechanism underlying endothelial disruption is also a topic of debate, with studies implicating a number of factors including potential effects of TTR protofilaments, wild-type or mutant TTR tetramers, inflammatory cytokines, or RBP (Gonçalves, Teixeira-Coelho, & Saraiva, 2014; Nunes et al., 2013; Du et al., 2017; Koike & Katsuno, 2019).

Due to the wide range of clinical presentations, misdiagnoses of hATTR-associated peripheral neuropathy are common. Although hATTR is not typically a disease of demyelination, chronic inflammatory demyelinating polyneuropathy (CIDP) is one of the most common misdiagnoses (Cortese et al., 2017; Lozeron et al., 2018). CIDP is a common misdiagnosis in late-onset cases of hATTR, especially at advanced stages, due to overlapping clinical features and electrophysiologic data (Mathis, Magy, Diallo, Boukhris, & Vallat, 2012; Conceição et al., 2016; Lozeron et al., 2018). Due to the high rate of misdiagnosis, studies have attempted to identify diagnostic tests that distinguish ATTR-related neuropathy from other neuropathies. Reduced ulnar nerve sensory nerve conduction velocity, insensitivity to cold, and mechanical hyperalgesia helped differentiate hATTR-peripheral neuropathy from other neuropathies, including diabetic neuropathy, chemotherapy-induced neuropathy, and CIDP, 82%, 82.7%, and 62% of the time, respectively (Escolano-Lozano, Barreiros, Birklein, & Geber, 2018).

As with peripheral neuropathy, it is helpful to discuss autonomic neuropathy in terms of its early- and late-onset disease presentations. Specifically, in Val30Met patients, autonomic dysfunction is common at onset in approximately ~90% of early-onset cases, as opposed to only ~10-11.7% of late-onset cases (Coutinho, DeSilva, Lima, & Barbosa, 1980; Koike et al., 2002; González-Duarte, Barroso, Mundayat, & Shapiro, 2019). As mentioned previously, small-fiber neuropathy is more common in early-onset and is therefore associated with the higher prevalence of autonomic dysfunction in these patients. These clinical differences have also been noted to correlate well with pathological findings in autopsy studies. For instance, amyloid deposits and neuronal loss were overall more prevalent in the dorsal root and sympathetic ganglia among early-onset cases than late-onset cases in Val30Met Japanese patients (Koike et al., 2004). In both groups, deposition in the ventral root was either absent or minimal (Koike et al., 2004).

While the prevalence, onset in the disease course, and severity typically vary between early- and late-onset cases, the symptoms themselves are similar. Autonomic neuropathy can affect the cardiovascular, gastrointestinal, genitourinary, and ocular systems. Specifically, symptoms include orthostatic hypotension, alternating constipation and diarrhea, nausea, vomiting, delayed gastric emptying, anhidrosis, sexual dysfunction, urinary retention, incontinence, sweating abnormalities, dry eyes, and impaired pupillomotor functions (González-Duarte et al., 2019). Specifically, dry eye, sexual dysfunction, and orthostatic hypotension have been observed as early autonomic symptoms (Ando et al., 2013; González-Duarte et al., 2019).

The severity of the autonomic neuropathy also progresses over time, leading to life-threatening complications. Most notably, arrythmias and severe orthostatic hypotension, especially when complicated by cardiac amyloidosis, can result in sudden death (Delahaye et al., 2001). Additionally, urosepsis, secondary to urinary retention, has been documented as a cause of death (Conceição et al., 2016). Finally, gastrointestinal disturbances not only have a clear impact on quality of life but are also predictors of reduced survival (Suhr, Danielsson, Holmgren, & Steen, 1994).

While dry eyes and gastrointestinal system impairment are commonly attributed to autonomic neuropathy, their etiologies may be multifactorial consequences of hATTR. For instance, gastric retention has been attributed to autonomic dysfunction despite poor correlation between positive autonomic testing and gastrointestinal symptoms (Wixner et al., 2012). Dry eyes have also been postulated to be associated with amyloid deposition in the lacrimal gland, in addition to autonomic neuropathy (Nagai, Yunoki, & Hayashi, 2020). Ocular and gastrointestinal clinical features are discussed further in sections E.6. and E.9. below.

There is no established standardized approach to evaluate hATTR patients for autonomic dysfunction. Among the available testing methods are assessment of heart rate variability, tilt-table testing to quantify orthostatic hypotension, and sudomotor function by electrochemical skin conductance studies (Niklasson, Olofsson, & Bjerle, 1989; Castro, Miranda, Castro, de Carvalho, & Conceição, 2016). Symptom-based scales, such as Norfolk (QOL-DN), Rasch-built Overall Disability Scale (R-ODS), and Composite Autonomic Symptom Score 31 (COMPASS-31), are also utilized (Adams et al., 2019).

3. Cardiac amyloidosis

Cardiac involvement is a common manifestation of hATTR. The THAOS registry reported 42.1% of enrolled patients exhibited symptoms of cardiac disease (Coelho et al., 2013). Cardiac involvement is characterized by progressive infiltrative cardiomyopathy (Ando et al., 2013). There is a large range of clinical presentation from asymptomatic individuals despite the presence of TTR amyloid in the heart to congestive heart failure requiring transplant (Rapezzi et al., 2010)

The cardiac manifestations include diastolic abnormalities due to restrictive cardiomyopathy, conduction abnormalities, arrhythmias, and valvular regurgitation. A preserved ejection fraction is common in beginning stages of disease (Ando et al., 2013). These patients have histopathological evidence of prominent amyloid deposition throughout the myocardium (Koike et al., 2004). Characteristics of the restrictive cardiomyopathy include increased biventricular wall thickness (>12 mm), ventricular stiffness, and ventricular diastolic dysfunction, due to TTR amyloid deposition between myocytes (Siddiqi & Ruberg, 2018). In advanced stages of disease, restrictive filling patterns can be found (Ando et al., 2013). The signs

and symptoms in these patients often mimic hypertensive and/or hypertrophic cardiomyopathy, leading to misdiagnosis (Shah et al., 2016).

In early-onset hATTR cases, arrhythmias, notably atrial fibrillation and atrial flutter, and conduction blocks, notably bundle branch block but also atrioventricular and sinoatrial block, are common causes of referral for cardiology evaluation (Ikeda et al., 1987; Koike et al., 2002). Autopsy studies of early-onset cases have revealed more prominent amyloid deposition in the atria, with subendocardial regions more affected than the myocardium, correlating with the more commonly noted clinical manifestations and subsequent need for a pacemaker (Koike et al., 2004).

The clinical spectrum of cardiac amyloidosis varies greatly among hATTR patients, contributing to underdiagnosis. However, diagnosis has improved in recent years due to increased awareness among cardiologists, establishment of reliable biomarkers, and advancements in imaging modalities. Markedly elevated levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and troponin T levels, out of proportion to the degree of heart failure, are suggestive of cardiac amyloidosis (Takashio et al., 2018; Maurer et al., 2019). Abnormalities on echocardiogram or cardiac magnetic resonance imaging (MRI) can raise suspicion of cardiac amyloidosis but are not sufficient for diagnosis (Falk, 2005; Maceira et al., 2005). The fortuitous finding decades ago that ^{99m}technetium-labeled bone scan radiotracers can localize in cardiac amyloid, has only recently led to approval of this method for diagnosis of TTR cardiac amyloidosis if monoclonal gammopathy is ruled out (Ali, Turner, Rosenbush, & Fordham, 1981; Gillmore et al., 2016). Rarely, cardiac amyloidosis can be difficult to distinguish from coronary artery disease if amyloid has deposited in the epicardial vessels (Falk & Dubrey, 2010).

4. The several forms of CNS-associated amyloidosis

Leptomeningeal amyloidosis is characterized by amyloid deposition in the leptomeninges (the arachnoid and pia mater), as well as in the vessels in the subarachnoid space, causing central nervous system (CNS) dysfunction. Symptoms are variable, including progressive dementia, headache, ataxia, seizures, spasticity, sensorineural hearing loss, and stroke-like episodes (Gertz, 2017). Leptomeningeal amyloidosis is caused by the production of TTR by the choroid plexus, rather than by the liver (Mitsuhashi et al., 2005). Ocular and leptomeningeal amyloidosis are commonly seen together (Ando et al., 2013).

Contrast enhancement on brain MRI can be suggestive of leptomeningeal amyloid deposits (Smirniotopoulos, Murphy, Rushing, Rees, & Schroeder, 2007; Czeyda-Pommershein et al., 2015), especially when seen along the Sylvian and other cortical fissures, surface of the brainstem, cerebellum, and spinal cord (Nakamura et al., 2005; Dowell, Fleck, Vakili, & Benson, 2007). However, MRI enhancement is a nonspecific finding, and should therefore be interpreted in light of other factors, such as history of recurrent neurological episodes, increased CSF protein levels, other systemic involvement, or notable family history, in order to raise suspicion of amyloidosis (Beckius & Shah, 2018).

Cerebral amyloid angiopathy (CAA) involves progressive amyloid deposition in the blood vessel walls of the brain, with pathological changes to the vasculature leading to diverse clinical manifestations (Vinters, 1987). Major clinical manifestations of CAA include cerebral hemorrhage, ischemic lesions, and dementia (Revesz et al., 2003). Unlike with the leptomeninges, the TTR amyloid present in CAA is thought to be mainly produced in the liver, not the choroid plexus (Yamashita et al., 2008). Nonetheless, CAA and leptomeningeal

amyloidosis commonly occur in the same patient (Ando et al., 2013). The term meningocerebrovascular amyloidosis has been used in the literature to describe patients with CAA and leptomeningeal amyloidosis without ocular involvement (Garzuly, Vidal, Wisniewski, Brittig, & Budka, 1996; Vidal et al., 1996).

It is important to briefly note that the amyloid deposits associated with Alzheimer's disease differ in important ways from those causing CNS involvement in hATTR. Most important, the amyloid fibrils are derived from two different proteins, and they deposit in different structures. Alzheimer's disease-associated amyloid is composed of Aβ peptides that deposit in extracellular plaques within the brain parenchyma (Tiwari, Atluri, Kaushik, Yndart, & Nair, 2019). In contrast, CNS involvement in hATTR is due to TTR-amyloid fibrils that deposit in blood vessels of the leptomeninges and with greater disease duration, can involve meningocortical vessels and superficial parenchyma (Ushiyama, Ikeda, & Yanagisawa, 1991; Maia et al., 2015).

5. Ocular Amyloidosis

Vitreous amyloidosis (VA) is considered the most common ocular manifestation among hATTR patients (Reynolds et al., 2017). The clinical manifestations of vitreous amyloidosis include pseudopodia lentis, glass wool vitreous opacites (floaters), and retinal perivascular amyloid deposits (Venkatesh et al., 2017). Deposition of amyloid in the vitreous of the eye is believed to be secondary to retinal pigment epithelium production of TTR. This idea is supported by the progression of ocular involvement in hATTR patients even after liver transplantation (Haraoka et al., 2002). The vitreous matrix shares structural and biochemical similarities to the basement membrane of cells due to an abundance of collagen (Misumi et al., 2009). Because

TTR amyloid has demonstrated a tendency to deposit in the basement membrane of cells, authors suggest it harbors a similar affinity for the vitreous matrix (Missmahl & Gafni, 1964; Venkatesh et al., 2017).

Additional ocular manifestations include abnormal conjunctival vessels, keratoconjunctivitis sicca, chronic open-angle glaucoma, anterior capsular opacity, and an irregular, scalloped pupil (Martins et al., 2015). A scalloped inner border of the pupil (Fig. 7), due to amyloid deposition in the ciliary nerve that controls pupillary constriction, is considered pathognomonic for hATTR (Lessell, Wolf, Benson, & Cohen, 1975). The progression of these symptoms, particularly with regard to vitreous opacities and/or glaucoma, lead to decreased visual acuity (Ando et al., 2013). Treatment by vitrectomy can restore normal or near-normal visual acuity (Doft et al., 1987; Koga et al., 2003; Beirão, Matos, Beirão, Costa, & Torres, 2011).

The frequency and type of ocular involvement varies greatly between *TTR* variants, and even among those patients with the same variant. For instance, vitreous amyloidosis is seen in all individuals that carry Ala36Pro, none of the carriers of Thr60Ala, and in variable minorities of Val30Met patients, depending on geographical region, ranging from 0.78-24% (Tsukahara & Matsuo, 1977; Coutinho et al., 1980; Kito, Itoga, Kamiya, Kishida, & Yamamura, 1980; Beirão et al., 2011; Reynolds et al., 2017). Ocular involvement can occur as the first manifestation of the disease, later in the disease course, and in some cases, as the only manifestation (Kawaji et al., 2004; Yazaki et al., 2002).

6. Nephropathy

Renal manifestations of hATTR include proteinuria and potentially, end stage renal disease (Ando et al., 2013). Although many *TTR* variants are not associated with nephropathy,

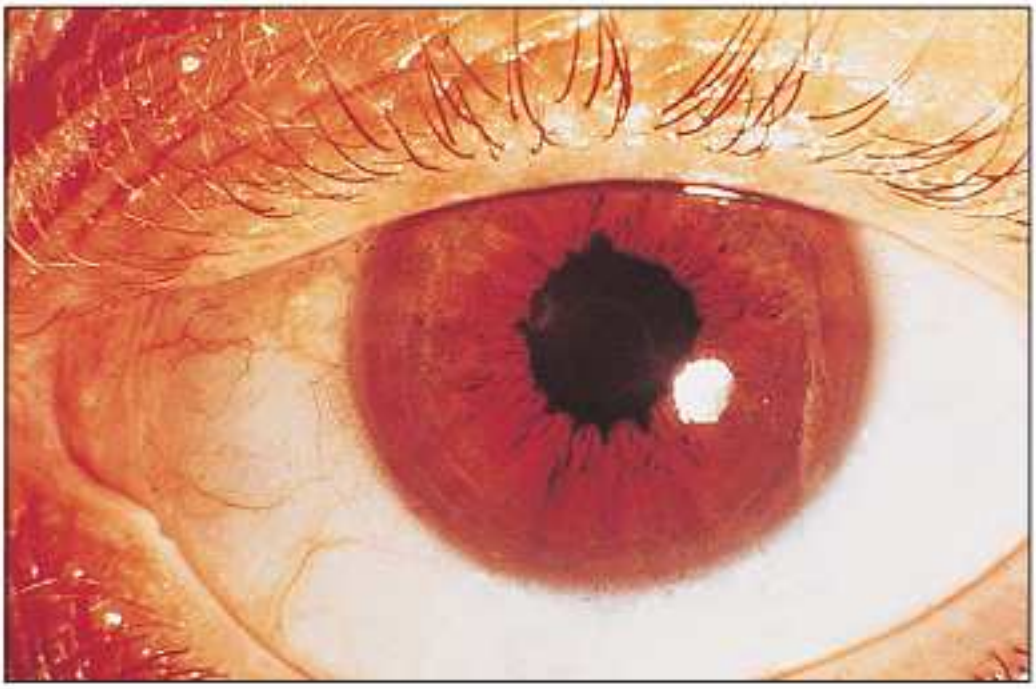

Figure 7: Scalloped Pupil. Photograph shows a scalloped pupil, pathognomonic for hATTR, indicated by the irregular border of the pupil. Source: Lessell et al., 1975.

Val30Met and Val122Ile, two of the most common mutations worldwide, are among the approximately two dozen that are (Lobato & Rocha, 2012; Table 1). Nephropathy is therefore a potential feature in the majority of European and African American patients with hATTR. Specifically, severe nephropathy is common among early-onset cases of Val30Met hATTR, especially those of Portuguese descent, but rare in late-onset cases (Lobato, 2003). The literature has limited information regarding details of the renal involvement in non-Val30Met variants, so the current understanding of hATTR-associated nephropathy is especially Val30Met-centered.

Initial studies conducted in the 1970's and 80's identified clinically evident renal involvement in 19-50% of the Swedish and Japanese Val30Met patients studied (Andersson, 1976; Steen, Wahlin, Bjerle, & Holm, 1982; Ikeda et al., 1987). Later studies demonstrated significant amyloid deposition in kidney biopsies of all Val30Met patients with proteinuria, and even in some without clinical evidence of nephropathy (Lobato et al., 1998; Lobato et al., 2003; Snanoudji et al., 2004; Oguchi, Takei, & Ikeda, 2006). The renal pathology revealed a correlation between renal dysfunction and amyloid deposition in structures of the cortex (e.g., glomeruli), but not amyloid in medullary structures (Lobato et al., 1998).

Notably, Val30Met individuals who do develop proteinuria, do so at the beginning of the disease course of hATTR, presenting a crucial opportunity for diagnosis. In one study, 72.2% of Val30Met patients (n = 18) developed proteinuria before neuropathy, by a median time interval of almost five years (Moreira et al., 2017). Detection of microalbuminuria has strong predictive value: half of Val30Met patients with microalbuminuria developed overt nephropathy within two years, and renal failure within five (Lobato et al., 2003). Therefore, it is recommended that kidney evaluation for hATTR patients include assessment of microalbuminuria, proteinuria, and estimated glomerular filtration rate (Rocha et al., 2011).

7. Myopathy

Although uncommon, myopathy causing proximal or diffuse muscle weakness and atrophy has been reported in small numbers of hATTR patients across numerous genotypes (Prayson, 1998; Yamashita et al., 2005; Misumi et al., 2014; Carr et al., 2015; Patel, Tagoe, Bieri, Weidenheim, & Tauras, 2018; Pinto et al., 2020). Unlike distal muscle weakness and atrophy, proximal and diffuse muscle involvement cannot be easily explained as a secondary consequence of polyneuropathy. This myopathic phenotype has gained recent attention and has even been suggested to be an underrecognized in hATTR (Pinto et al., 2020). Notably, all patients who developed myopathy did so after the onset of sensory or autonomic neuropathy, with one patient developing myopathy three years after undergoing a liver transplantation as treatment for polyneuropathy. In the three other reported cases of hATTR with myopathy who underwent liver transplantation, none showed progression of myopathy after transplant (Yamashita et al., 2005).

Studies have identified varying muscle pathology findings, apparently depending on the *TTR* genotype. For instance, Yamashita et al. (2005) identified amyloid deposits around blood vessels and in the perimysium and endomysium of the muscle biopsies from Ser50Ile and Tyr114Cys patients, leading authors to suggest an intramuscular ischemic mechanism. Pinto et al. (2020) reported similar findings of amyloid deposits in the perimysium and endomysium. In addition, Pinto et al. (2020) identified necrotic and regenerating fibers, which are more common characteristics of other amyloid myopathies. In the same study, authors also observed rimmed vacuoles, non-rimmed vacuoles, pathological myofiber size variability, and denervation or reinnervation.

8. Focal Connective Tissue Deposition

Although more commonly and consistently associated with the wildtype form of the disease (ATTRwt), carpal tunnel syndrome, spinal canal stenosis and ruptured bicep tendons have also been identified as manifestations in the beginning stages of hATTR. These are typically considered idiopathic at the time of diagnosis, until disease progression leads to additional manifestations that raise clinical suspicion.

Carpal tunnel syndrome, defined as symptomatic compression of the median nerve as it passes through the carpal tunnel at the wrist, is the most common nerve-entrapment syndrome (Olney, 2001). The estimated prevalence of carpal tunnel syndrome in the general adult population ranges from 2.7-4.9% (Atroshi, 1999; Bickel, 2010). The recognition that many ATTR patients have a history of carpal tunnel syndrome, followed by studies that identified TTR amyloid in ligamentous tissue removed during carpal-tunnel release surgery, have led to the acceptance of carpal tunnel syndrome, particularly when bilateral, as an early, red flag symptom for ATTR amyloidosis (Gioeva et al., 2013; Sperry et al., 2018; Aus dem Siepen, 2019). Nonetheless, there is still considerable diagnostic delay; the mean time between carpal tunnel-release surgery and diagnosis of ATTR was ~5.5 years (Aus dem Siepen et al., 2019).

Additional wrist structures showing deposition of amyloid include the flexor retinaculum (roof of the carpal tunnel), synovia, flexor tendon sheath, and vessel walls of capillaries, small arteries, and veins (Stein, Störkel, Linke, & Goebel, 1987). Not all hATTR patients experience clinical improvement after carpal tunnel-release surgery, raising the question of other contributors to symptoms. Koike et al. (2009) compared electrophysiological data from the ulnar and median nerves of Val30Met patients with CTS with those of age-matched patients with idiopathic CTS. Their findings suggested that polyneuropathy, rather than solely entrapment

injury may also play a role in hATTR patient's CTS symptoms. (Koike et al., 2009). While no relationship has been found between ATTR-associated carpal tunnel syndrome and survival, it may be associated with future development of cardiac amyloidosis, which can be life-threatening (Aus dem Siepen et al., 2019).

Spinal stenosis, defined as symptomatic narrowing of spinal foramina and/or the spinal canal, is a relatively common cause of pain, as well as sensory and motor deficits (Katz & Harris, 2008). One cause of spinal stenosis, especially in the lumbar region, is thickening of the ligamentum flavum (Katz & Harris, 2008). Two studies have documented the presence of amyloid in 96% and 100% of ligamentum flavum samples removed during decompression surgery for lumbar spinal stenosis (Westermark, Westermark, Suhr, & Berg, 2014; Yanagisawa et al, 2015). Of the ligamentum flavum samples that underwent proteomic analysis, wild-type TTR amyloid was identified in ~33% (Westermark et al., 2014) and ~45% (Yanagisawa et al., 2015). Additionally, Aus dem Siepen et al. (2019) conducted a retrospective analysis of the records of 136 patients with hATTR who were evaluated from 2005 to 2016 at the Heidelberg Amyloidosis Center. The study identified a history of spinal stenosis in 5% of the hATTR cohort (Aus dem Siepen et al., 2019).

Non-traumatic, spontaneous bicep tendon ruptures have also been implicated as an early symptom heralding ATTR amyloidosis. The estimated prevalence in the general population of a spontaneous bicep rupture between the ages of 56 to 74 is <0.001% (Safran & Graham, 2002). In contrast, one study identified a history of bicep tendon rupture in 33.3% (37/111) of ATTRwt patients (95% CI, 24.7-42.9%) (Geller, Singh, Alexander, Mirto, & Falk, 2017). This would suggest a 10^4-fold increase in tendon-rupture risk, but it is also possible that this cohort was not a

representative sample. The same study identified a median time of five years between tendon rupture and diagnosis of ATTR amyloidosis.

9. Other manifestations

Although more common in other types of amyloidosis, such as AL amyloidosis, pulmonary amyloidosis has been identified in hATTR patients as well (Yazaki et al., 2000; Ussavarungsi et al., 2017). Prior to the identification of the first *TTR* variant, a ~90-year retrospective review of medical records at Johns Hopkins University documented pulmonary amyloidosis in three patients with "familial amyloidosis with polyneuropathy" (Smith, Hutchins, Moore, & Humphrey, 1979). Later, a 13-year record review at Mayo Clinic revealed pulmonary amyloidosis in one patient with "familial amyloidosis" (Utz, Swenson, & Gertz, 1996). Among genotyped cases, diffuse pulmonary amyloidosis was noted at autopsy in two hATTR patients with the Ala38Asp variant who suffered from severe pulmonary congestion (Yazaki et al., 2000). Ussavarungsi et al. (2017) conducted a retrospective review of medical records at Mayo Clinic in Rochester spanning January 1, 1997, and September 30, 2014. Of the 76 patients with autopsy-proven pulmonary amyloidosis, three were identified with hATTR, though the variants were not explicitly identified. In these three patients, all had alveolar septal involvement with deaths unrelated to the documented pulmonary deposition.

Despite limited documentation, cutaneous deposition of amyloid may be relatively common in hATTR. The utility of skin biopsies for diagnosis lends support to the idea that the skin is commonly involved, albeit subclinically until advanced stages of the disease (Rubinow & Cohen, 1981; Rocha et al., 2005). Cutaneous manifestations tend to occur later in the disease course and therefore may not be involved in the diagnosis (Rocha et al., 2005). Preorbital

purpura, although more commonly associated with light-chain amyloidosis, is pathognomonic for amyloidosis and has been documented in hATTR patients specifically (Colucci et al., 2014; Lanou et al., 2016). Dermal amyloid deposition has been noted in the blood vessel walls, dermis, arrector pili, and sweat glands (Rubinow & Cohen, 1981; Mochizuki, Kamakura, Masaki, & Hirata, 2001; Harkany et al., 2002; Magy et al., 2003). Visible skin involvement includes atrophic scars, petechia, eyelid ecchymoses, cutaneous tubercula, shiny skin, and bullous lesions (Rubinow & Cohen, 1981; Mochizuki, Kamakura, Masaki, & Hirata, 2001; Magy et al., 2003; Dekmezian, Tschen, & Cho-Vega, 2004).

II. Methods

A. Assembly of an up-to-date comprehensive *TTR* variant list

Variants of interest included both amyloidogenic and non-amyloidogenic *TTR* alleles. The initial collection of *TTR* variants for this discussion began with the transthyretin section of an online database, Mutations in Hereditary Amyloidosis (see Web Resources; Rowczenio et al., 2014). This database cites peer-reviewed publications, as well as conferences and personal communications, as sources of information. According to the research network section of Orphanet (see Web Resources), this registry had been established through a European Commission-funded project named "EURAMY: systemic amyloidoses in Europe," based at University of Uppsala in Sweden. The funded project appears to have ended and the EURAMY website (euramy.org) is no longer accessible. Nonetheless, the online TTR variant registry does have relatively recent entries (2019) and lists as the responsible persons, Dr. Dorota Rowczenio (Head of Genetic Services, National Amyloidosis Centre, University College London Medical School) and Dr. Ashutosh Wechalekar (Senior Lecturer, University College London).

Variants listed in the registry were utilized to search for related publications in the peer-reviewed literature. Information included in the registry, such as the coding sequence changes, patient ancestries, and reported phenotype(s), was all checked using independent sources; most were verified but discrepancies were revealed, and additional information discovered. In other words, the registry was a very good starting place, but was incomplete, at times unreliable, and its current activity level is uncertain.

Additional variants that were not included in the registry were collected in various ways. The variant list was supplemented by the identification of variants in studies that sought to characterize the genetic landscape of TTR in a specific geographical region, as well as by

searching for “novel” or “new” *TTR* variants in PubMed. The most recent report of a novel *TTR* variant was published this year (Aono et al., 2021). A total of 153 variants were curated, of which a majority are pathogenic, with 18 considered non-amyloidogenic.

B. Extraction of phenotype data

Qualitative data were gathered in order to describe the clinical manifestations associated with each pathogenic *TTR* variant. Both PubMed and Google Scholar search engines were used to identify published literature regarding specific variants. In addition to the variant, “transthyretin” and “amyloidosis” were added to each search-term string. The same search terms were used in both databases to cross-reference the literature results and to find any additional sources. All told, phenotype information was extracted from over 300 original research articles. Clinical manifestations and ages of onset were of particular interest, as were variants with the most severe phenotypes, which were described in further detail. The information collected was used to populate a “Variant List” spreadsheet, which was condensed to essential items for Table 1 (pathogenic variants) and Table 2 (non-amyloidogenic variants).

The primary data sources included case reports, case series, and original research studies on various aspects of hATTR disease diagnosis, progression, and management, e.g., outcomes following liver transplantation. The data available for each variant varied dramatically, which ultimately informed multiple aspects of the table. For some variants, multiple reports that provided partially overlapping clinical data were consulted to aggregate data on members of the same family. Clinical manifestations of family members of the proband were only included if those members had been genotyped or had been diagnosed with amyloidosis while living or by autopsy.

Because of the possibility that genetic ancestry could affect phenotypic manifestations, ethnicity and/or ancestry information was collected. If no demographic information was available, the country in which the study took place was noted.

C. Challenges faced during data collection

Due to the use of various notation styles, multiple searches were conducted for each variant. For instance, for the variant Gly6Ser (p.Gly26Ser), the search terms included Gly6Ser, Ser 6, Serine 6, Glycine 6 Serine, substitution of serine for glycine at position 6, and G6S. It was also necessary to search in parallel for a given amino-acid position using the modified nomenclature, because some recent articles utilize the HGVS-recommended codon-numbering scheme exclusively.

Keeping track of specific families to connect phenotype and genotype data published at different times was sometimes difficult – as is often the case in human genetic disease literature. First, many important descriptions of a family's phenotype were published before the identification of the *TTR* variant. These older papers were typically referenced in newer papers that reported identification of the *TTR* variant in the family. Second, the ways in which variants were described varied considerably; some were only referred to as "novel" or as a "variant associated" with a certain phenotype. Lastly, transthyretin was originally referred to as prealbumin, or thyroxine-binding prealbumin, further complicating searches targeting older literature. Connors, Lim, Prokaeva, Roskens, and Costello (2003), who published a *TTR* variant tabulation with ~100 alleles, was particularly helpful to identify pertinent older publications with clinical information.

Clinical descriptions in the published literature are presented without use of a controlled vocabulary and may be influenced by the priorities of authors' clinical or research specialties, as well as regional norms for terminology. This can lead to ambiguity or missing information. Notably, for some *TTR* variants, no age-of-onset information was available. Some clinical descriptions included symptoms without specifying what diagnostic workup had been done, leaving uncertainty about the hATTR-associated phenotypes in those patients.

The level of detail about patient ethnicity provided was highly variable. More fundamentally, the term "ethnicity" was often used without definition, making it difficult to know whether it reflects genetic ancestry.

Finally, important insights about hATTR-related challenges facing patients and clinicians emerged from attending an Amyloidosis Support Group annual meeting in early 2020. For instance, clinicians reported have difficulty classifying whether a newly reported symptom is hATTR-related or not, such as sore knees or Achilles' tendon. Patients expressed feelings of anxiety when there is uncertain if new symptoms are unrelated to hATTR and possibly age-related, or an indication of disease progression. Additionally, patients expressed frustration with the lack of awareness regarding hATTR amyloidosis before and after their diagnosis. Specific examples include patients being told their symptoms of polyneuropathy were "in their head" before the diagnosis and that their symptoms were not severe enough to begin treatment, after the diagnosis. Lastly, of the five families present, only two had seen genetic counselors regarding hATTR amyloidosis.

III. Results

A. Overview

A total of 153 *TTR* variants were curated and discussed below. Of the 153 variants, a majority were amyloidogenic with only 19 variants (12.4%) considered non-amyloidogenic. Of the amyloidogenic variants, 132 (98%) were missense; one *TTR* duplication and one deletion were also documented. The 19 non-amyloidogenic variants consisted of 17 missense and 2 synonymous variants. There was a total of 52, 59, and 23 amyloidogenic variants in exons 2, 3, and 4, respectively. There was a total of 2, 2, and 15 non-amyloidogenic variants in exons 2, 3, and 4, respectively.

B. Most common variant: Val122Ile (p.Val142Ile)

The Val122Ile variant was first described by Gorevic et al. in 1989, in a patient previously misdiagnosed with ATTRwt. Today, it is recognized as the most common variant worldwide (Coelho et al., 2013; Maurer et al., 2016). Specifically, Jacobson et al. (2015) reported an allele frequency of 0.0173 among African Americans, with ~3.43% of African Americans under age 65 carrying at least one copy of the variant. However, while the frequency of Val122Ile carriers is well established, the disease prevalence is not. Val122Ile has incomplete and age-related penetrance, like many other hATTR variants. Recent studies have estimated penetrance in the range of 7-20% (Quarta et al., 2015; Agbor-Etang, Okafor, Farber-Eger, & Wells, 2020), while older studies suggested a higher penetrance. There are also notable sex differences when it comes to Val122Ile carriers and the development of clinically evident hATTR. Batra et al. (2021) studied 73 individuals with Val122Ile-hATTR-CM and found that women were on average seven years older at diagnosis (76 versus 69 years; $P < .001$) but had

similar 3-year mortality rates to men (34% versus 43%, P = .64). Although Val122Ile has a higher prevalence in the African American population and West African countries, it has also been identified in other populations. For instance, the Val122Ile has also been identified in Brazilian, Mexican, Italian, Japanese, and Portuguese populations (Ammirati et al., 2012; Yoshinaga et al., 2017; Devarapalli et al., 2019; Sirdesai et al., 2019; Ono et al., 2019).

Age of onset for Val122Ile heterozygous individuals typically occurs after the age of 60, with a majority presenting in their 8th decade of life (Reddi et al. 2014). Disease onset has been documented as late as the 9th decade of life (Sirdesai et al., 2019). In homozygotes, symptom onset typically occurs about a decade earlier, with a majority presenting in their 7th decade of life (Reddi et al., 2014). In the cohort studied by Reddi et al. (2014), two compound heterozygotes, with Thr60Ala and Ile68Leu, had an even earlier documented onset in the 6th decade of life (Reddi et al., 2014).

Val122Ile-hATTR is clinically characterized by late-onset cardiomyopathy, with 96.6% of individuals in the THAOS registry having cardiac involvement (Coelho et al., 2013). Although historically associated with isolated cardiac involvement, additional system involvement has only recently been appreciated. For instance, the THAOS registry also revealed a striking 56.3% of Val122Ile-hATTR patients with sensory neuropathy (Coelho et al., 2013). Other possible manifestations include motor neuropathy, autonomic neuropathy, carpal tunnel syndrome, kidney involvement, and myopathy (Coelho et al., 2013). No Val122Ile heterozygotes have been documented in the literature with ocular involvement (Reynolds et al., 2017). Atypical presentations have included upper-extremity neuropathy, gastrointestinal amyloid deposition leading to bowel rupture, and axonal polyneuropathy, all without cardiac involvement, in Mexican, Irish, and Italian patients, respectively (Stancanelli et al., 2017; Devarapalli et al.,

2019; Sirdesai et al., 2019). The more recent discovery of Val122Ile in patients with atypical presentation and without known African ancestry suggests the possible underestimation of this variant in populations other than African Americans (Stancanelli et al., 2017).

Life expectancy has been estimated in multiple studies, with a median survival after diagnosis ranging from 25.6 to 31 months, or ~2.1 to 2.6 years for Val122Ile-hATTR-CM patients (Connors et al., 2009; Ruberg et al., 2012; Dungu et al., 2016; Lane et al., 2019). A staging system utilizing NT-proBNP and eGFR to categorize the severity of cardiac involvement was utilized and found a median survival of 54.4, 28.8, and 17.7 months at Stage I, II, and III, respectively, among Val122Ile-hATTR patients (Gillmore et al., 2018). Lane et al. (2019) compared survival from diagnosis of hATTR with cardiomyopathy (hATTR-CM) between patients with Val122Ile and non-Val122Ile variants and found a significantly shorter survival among Val122Ile patients of 31 versus 69 months, or ~2.6 versus 5.75 years.

C. Variants that may be predictive of high severity

The most severe phenotypes, described as either (i) early-onset with time until death or transplant of ≤5 years or (ii) late-onset with time until death or transplant of ≤3 years, are summarized and described below. Variants were included if at least half of the reported cases fit the previous description. The caveat, of course, is that the literature may not reflect the lower end of the severity range of phenotypes associated with these variants; indeed, cases are more likely to be reported because they are severe. These missense variants are presented in order of the position of the affected amino acid. Val122Ile fits this description as well, as discussed above.

Ala25Ser (p.Ala45Ser): The substitution of serine for alanine at position 25 has only been described in one American family (Yazaki et al., 2002). It was identified in a 52-year-old female

whose symptoms began at the age of 50. The disease course was rapid with progressive sensorimotor neuropathy and autonomic dysfunction in the form of recurrent diarrhea. Within two years, the patient required wheelchair assistance. The patient received a liver transplant at age 52 but died suddenly one month after the operation (Yazaki et al., 2003). The older sister of the patient was found to be positive for the same variant and had numbness in her toes that was originally attributed to frostbite. Within four months, the sister experienced dysesthesia in her lower extremities and despite lacking symptoms of cardiac involvement, had an EKG and ^{99m}Tc-scan suggestive of cardiac amyloidosis.

Val30Leu (p.Val50Leu): The Val30Leu variant has been described in Japanese and Swedish populations. The age of onset ranged from 40 to 53 with multiple patients presenting with a rapid disease course requiring a transplant within 2-3 years of onset. Notably, treatment with a liver transplant as opposed to a combined heart-liver transplant resulted in poor patient outcomes for the two patients documented to have undergone the procedure. Yazaki et al. (2007) investigated the amyloid fibrils before and after liver transplantation in these patients, both of whom died one year after transplant. The study revealed a 1:1 ratio of wild-type to variant transthyretin in the myocardium before liver transplantation, and a 9:1 ratio afterwards. These data indicated that wild-type deposition after a liver transplantation can preferentially occur in the myocardium, leading to fatal cardiac dysfunction.

Leu55Pro (p.Leu75Pro): The Leu55Pro variant has been described in German-Dutch American, Taiwanese, Chinese, Japanese, and Korean populations and is associated with early-onset disease, with multiple cases of adolescent onset documented (Jacobson, McFarlin, Kane, & Buxbaum, 1992; Yamamoto et al., 1994; Chou, Lee, Chang, Buxbaum, & Jacobson, 1997; Kon et al., 2015; Lee et al., 2019). Ages of onset range from 14 to 35, with a rapidly progressive

disease course. Clinical manifestations are generally homogeneous, with most individuals developing autonomic neuropathy, cardiomyopathy, peripheral neuropathy and ocular involvement. Anticipation was noted in families, with younger generations presenting at earlier ages. In light of the multiple adolescent cases, Lee et al. (2019) suggests hATTR to be suspected even in pediatric populations when symmetric length-dependent neuropathy is present, especially with a family history of cardiomyopathy or neuropathy.

Glu89Lys (p.Glu109Lys): The Glu89Lys variant has been described in an American individual and in Canada, as well as Korean and Swiss populations (Nakamura, Hamidi Asl, & Benson, 2000; Niederhauser et al., 2011; Reynolds et al., 2017; Choi et al., 2018). It is characterized by rapidly progressive cardiomyopathy that requires a transplant soon after symptom onset, carpal tunnel syndrome, autonomic neuropathy, and polyneuropathy, with only one individual having ocular involvement. Notably, multiple patients presented with cardiomyopathy first, later developing polyneuropathy and other symptoms. Early-onset (<50) was noted in every patient, with a wide range of onset from 19-47 years, with the majority developing symptoms in their fifth decade of life. Individuals who received a heart transplant had marked progression of polyneuropathy and later either received, or were listed for, a liver transplant.

D. Age of Onset may be associated with amino-acid position of the pathogenic variant

Among the 122 amyloidogenic variants with information regarding age of onset, 30 are associated with early-onset, 37 with mixed age of onset, and 55 with late-onset (Figure 8). The number of variants and the percentage of variants per exon associated with each age-of-onset group is shown in Figures 9 and 10, respectively.

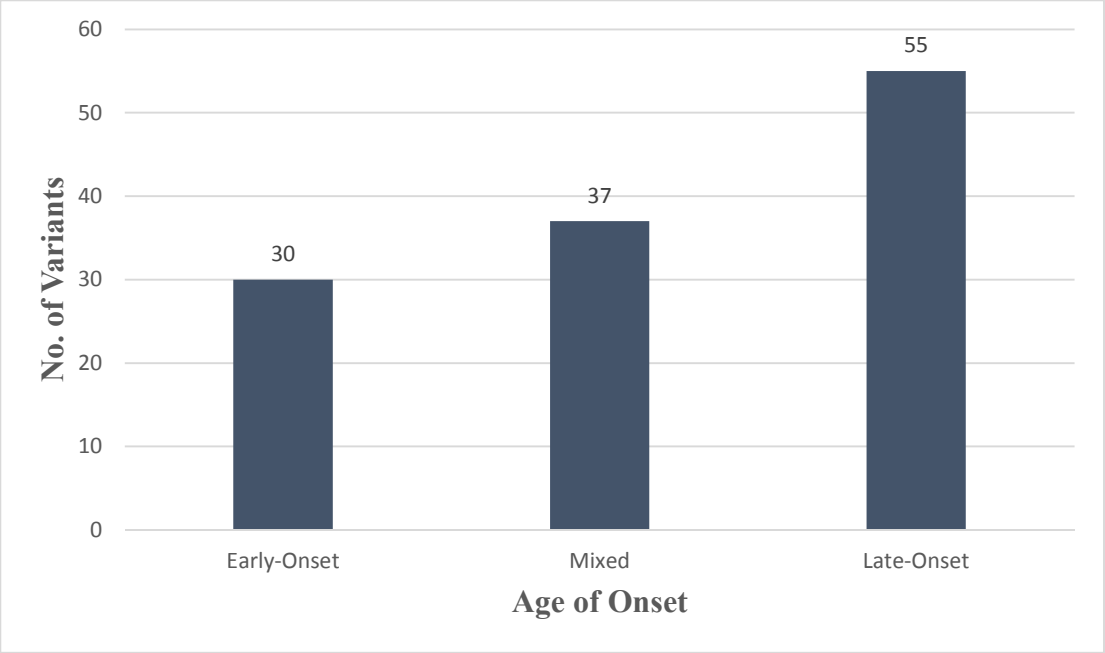

Figure 8: Number of Variants with Associated Ages of Onset. Most variants were associated with late-onset disease, followed by a mixed age of onset, with the fewest number of variants associated with early-onset disease.

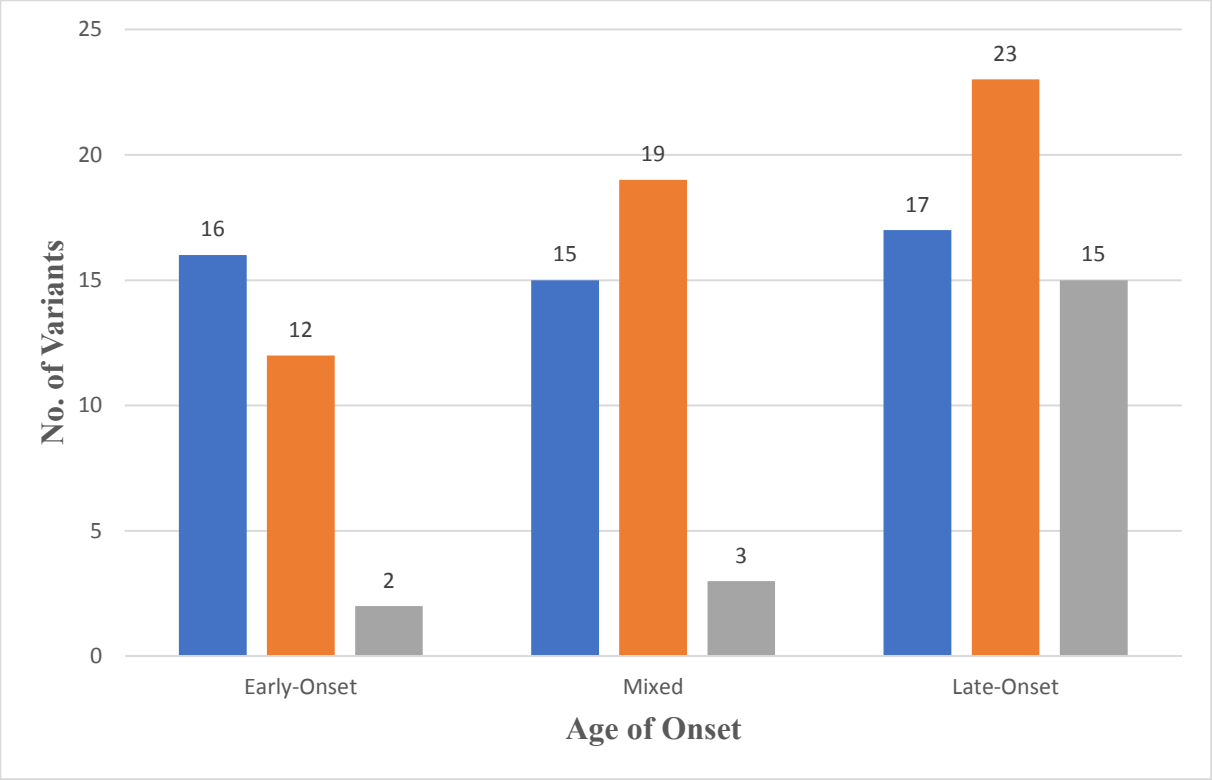

Figure 9: Number of Variants with Associated Ages of Onset per Exon. Color legend: Blue, Exon 2; Orange, Exon 3; Gray, Exon 4.

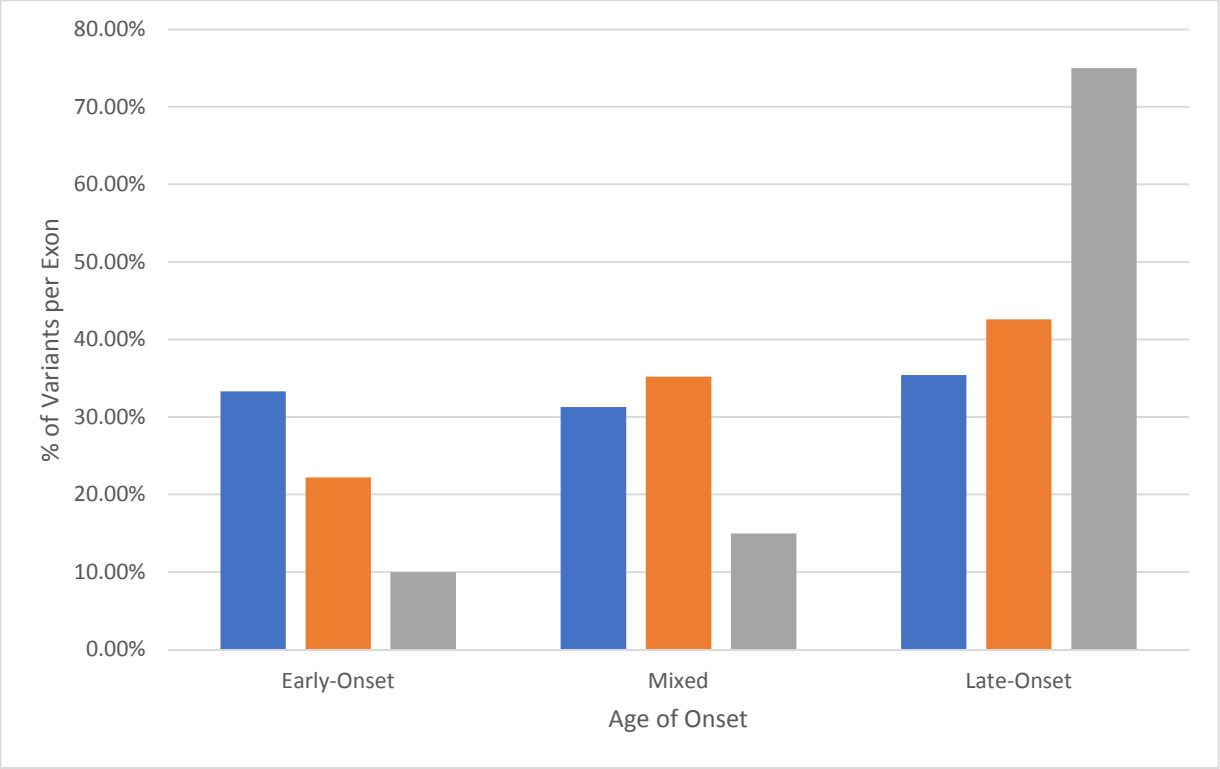

Figure 10: Percent of Variants per Exon with Associated Age of Onset. Color legend: Blue, Exon 2; Orange, Exon 3; Gray, Exon 4. Of the 48 variants with age of onset information located in exon 2, 33.3% were associated with early-onset, 31.3% were associated with mixed age of onset, and 35.4% were associated with late-onset. Of the 54 variants with age of onset information located in exon 3, 22.2% were associated with early-onset, 35.2% were associated with mixed age of onset, and 42.6% were associated with late-onset. Of the 20 variants with age of onset information located in exon 4, 10% were associated with early-onset, 15% with mixed age of onset, and 75% with late-onset.

Eight variants had disease onset documented in the second decade of life. There were no reports of onset in the first decade of life. These variants were clustered at the end of exon two and exon three, specifically amino acid positions 30 to 89. The earliest age of onset was documented at the age of 14 in a patient with the Leu55Pro variant (Bekircan-Kurt, Güneş, Yılmaz, Erdem-Özdamar, & Tan, 2015). Symptoms were severe enough to impact reproductive potential in multiple individuals. Rather dramatic anticipation was noted in families with Gly47Arg, Thr49Ser, Leu55Pro, and Glu89Lys variants, with disease onset decreasing from the fifth and fourth decades, to the second decade over just two generations. Interestingly, of the three documented cases in which authors suggested a de novo mutation in the proband, two of them had Gly47Arg and Leu55Pro. These individuals presented at 32 and 31 years, respectively, over a decade older than those who had documented inheritance from a parent.

In thirty variants, all documented patients had disease onset before the age of 50. This group includes five of the variants discussed earlier with onset in the 2nd decade. These thirty variants ranged from exon 2 to 4, with 16 (53.3%) in the second exon, 12 (40%) in the third exon, and 2 (6.7%) in the fourth exon.

In thirty-seven variants, ages of onset in patients ranged from early- to late-onset of disease. This group includes three of the variants discussed earlier with onset in the 2nd decade. These thirty-seven variants ranged from exon 2 to 4, with 15 (40.5%) in the second exon, 19 (51.4%) in the third exon, and 3 (8.1%) in the fourth exon.

In fifty-five variants, all documented patients had disease onset after the age of 50. These fifty-five variants ranged from exon 2 to 4, with 17 (30.9%) in the second exon, 23 (41.8%) in the third exon, and 15 (27.3%) in the fourth exon.

Onset in the 9th decade of life was documented in four variants, Val30Met, Pro43Ser, Val122Ile, and Ala97Ser. The first two variants are in the second exon, with the final two located in exon four of the *TTR* gene.

E. Clinical Manifestations: relationships among tissues involved and exons affected

1. Amyloidogenic

Among 134 amyloidogenic variants, 115 were associated with cardiomyopathy, 113 were associated with peripheral neuropathy, 92 with autonomic neuropathy, 58 with carpal tunnel syndrome, 47 with ocular involvement, 38 with kidney involvement, 18 with central nervous system involvement, and 10 with myopathy (Fig. 3). The number of variants in exons 2, 3, and 4 associated with each phenotype is shown in Figure 11, with the percentage of variants per exon associated with each phenotype are shown in Figure 12.

Peripheral neuropathy, commonly sensorimotor, but also sensory without motor involvement, and rarely motor without sensory involvement, was identified as a feature in 113 variants. Therefore, 84.3% of pathogenic *TTR* variants caused peripheral neuropathy. Peripheral neuropathy was commonly associated with autonomic neuropathy in 86 of the 113 variants. Autonomic neuropathy was identified as a clinical manifestation in 92 variants. Autonomic neuropathy was present without peripheral neuropathy in six variants, but autonomic neuropathy was never seen in isolation.

Cardiomyopathy was identified as a clinical manifestation associated with 115 variants, two more variants than peripheral neuropathy. Of the 115 variants causing CM, 55 were also associated with carpal tunnel syndrome. Carpal tunnel syndrome was identified in 58 total variants, leaving only three variants with carpal tunnel syndrome without cardiomyopathy.

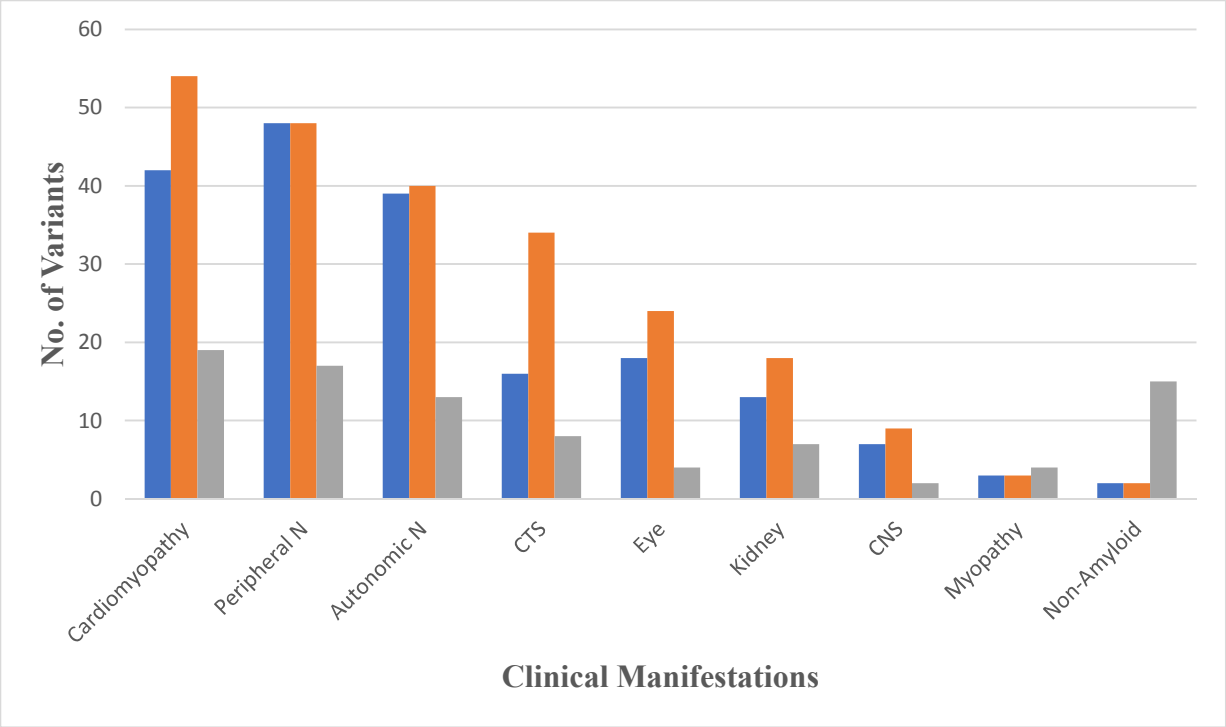

Figure 11: Number of Variants per Exon Associated with Each Phenotype. Color legend: Blue, Exon 2; Orange, Exon 3; Gray, Exon 4.

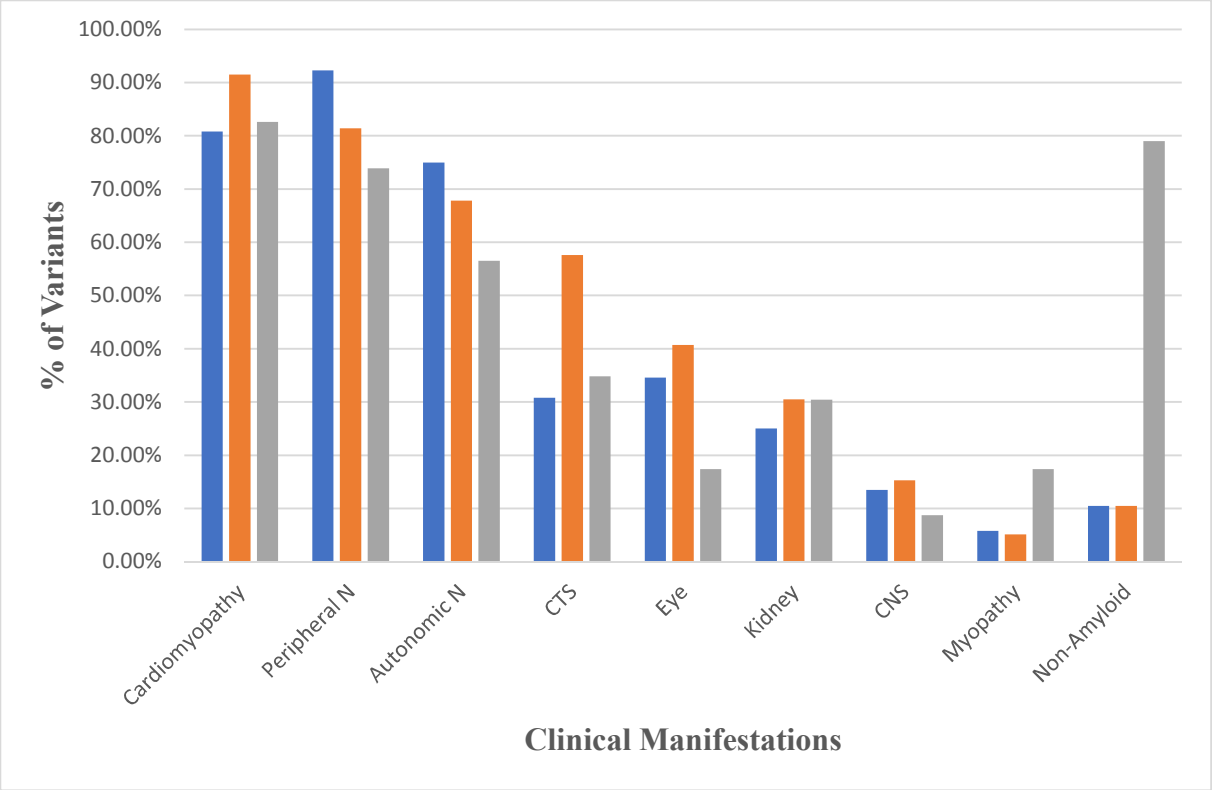

Figure 12: Percentage of Variants per Exon Associated with Each Phenotype. Color legend: Blue, Exon 2; Orange, Exon 3; Gray, Exon 4. Of the 52 amyloidogenic variants in exon 2, 80.8% were associated with CM, 92.3% were associated with PN, 75.0% were associated with AN, 30.80% with CTS, 34.60% with eye involvement, 25.0% with kidney involvement, 13.5% with CNS involvement, and 5.8% with myopathy. Of the 59 amyloidogenic variants in exon 3, 91.5% were associated with CM, 81.4% with PN, 67.8% with AN, 57.6% with CTS, 40.7% with eye involvement, 30.5% with kidney involvement, 15.3% with CNS involvement, and 5.1% with myopathy. Of the 23 variants in exon 4, 82.6% were associated with CM, 73.9% with PN, 56.5% with AN, 34.8% with CTS, 17.4% with eye involvement, 30.4% with kidney involvement, 8.7% with CNS involvement, and 17.4% with myopathy. Of the 19 non-amyloidogenic variants, 10.5% are located in exon 2, 10.5% in exon 3, and 79% in exon 4.

Therefore, approximately 47.80% of variants with CM also have CTS as a possible clinical manifestation, whereas approximately 94.8% of variants with CTS have CM listed as a possible clinical manifestation.

Ocular involvement has been identified in patients with 46 variants, or 34.3% of 134 pathogenic variants. Ocular involvement is associated with leptomeningeal involvement in 12 (26.0%) of 46 variants. In contrast, leptomeningeal amyloidosis has been identified in 18 variants, with ocular involvement in 12 (66.7%). Therefore, leptomeningeal involvement is likely to be associated with ocular involvement, but ocular involvement is less likely to be associated with leptomeningeal amyloidosis.

Kidney involvement, identified as either amyloid deposits by biopsy, autopsy, or imaging, proteinuria, reduced estimated glomerular filtration rate, or chronic renal failure, was identified in patients with 38 variants. Subclinical involvement was noted in 7 out of 38 variants, meaning amyloid was identified but no clinical manifestations of kidney disease were observed in those individuals.

Myopathy is a potentially underdiagnosed phenotype that has been so far identified in patients with 10 variants. Of these, the range of ages of onset is notably more specific than other phenotypes from 4^{th} to 8^{th} decades of life. All variants with myopathy have peripheral neuropathy as a potential manifestation, and a majority have autonomic neuropathy, cardiomyopathy and carpal tunnel syndrome listed as well. It is also seen with ocular involvement, renal involvement, and leptomeningeal amyloidosis.

Only nine variants were associated with isolated, i.e., single tissue involvement. Of the nine, one variant presented with only peripheral neuropathy, and eight with isolated cardiac involvement. It is important to note that this may be due to lack of additional clinical information

available, rather than actual single system involvement. No other phenotypes were noted in isolation. All phenotypes were associated with variants from each of the exons, though the percentage of variants associated with a phenotype did vary slightly by exon.

2. Non-Amyloidogenic

Nineteen variants are considered non-amyloidogenic, with 15 (78.9%) located in the fourth exon. The remaining four non-amyloidogenic variants (21.1%) are split evenly between exons 2 and 3. Three variants have also been noted to confer protection in documented compound heterozygotes, i.e., combinations of a pathogenic variant and a non-amyloidogenic variant. Protection has been observed with variants Arg104His, Ala108Val, and Thr119Met. Three non-amyloidogenic variants have been associated with euthyroid hyperthyroxinemia due to an increased binding affinity for thyroxine. These include Gly6Ser, Ala109Thr, and Ala109Val.

IV. Discussion

A. Special considerations regarding hATTR in the United States

The United States has hATTR patient demographics unique from those of the rest of the world. Maurer et al. (2016), utilizing THAOS data, found that patients in the United States are more often older (70 vs. 46 years), male (85.4% vs. 50.6%), and African American (25.4% vs. 0.5%) than in other regions of the world. A total of 390 individuals with ATTR amyloidosis were enrolled, of which 189 had ATTRwt. Of the 201 patients with hATTR from the United States, 34 mutations were identified, with the two most common variants being Val122Ile (n=91, 45.3%) and Thr60Ala (n=41, 20.4%) (Maurer et al., 2016). From the literature review conducted, 44 variants have now been identified either in the United States or in patients described as American (Table 1). Therefore, Ruberg et al. (2012) recommends a high suspicion of cardiac amyloidosis in older African American patients with heart failure with preserved ejection fraction and a general consideration of the possibility of hATTR in any African American patients with heart failure.

The American Heart Association acknowledged that reductions in cardiovascular disease in the USA have not be shared equally across all racial groups (Carnethon et al., 2017). Specifically, the reduction in incidence and mortality has not been as substantial in the African Americans population where the burden of cardiovascular disease is still high (Carnethon et al., 2017). Authors cite cardiovascular health differences as the primary health disparity between African Americans and white Americans, with African Americans having higher risk factors such as hypertension, diabetes, and obesity (Carnethon et al., 2017). One review article suggested that hypertension accounts for 50% of the racial differences in mortality between Black and white individuals in the United States (Musemwa & Gadegbeku, 2017). However,

Dungu et al. (2016) comment that cardiomyopathy in Black Val122Ile-hATTR patients is often misattributed to hypertension.

The common misdiagnoses among hATTR-CM patients are further exacerbated when individuals also have comorbidities, such as hypertension. Moreover, this is further complicated by racial health disparities of these specific co-morbidities in the African American community. Therefore, there is a number of factors that should be elucidated further in order to confirm whether or not Val122Ile-hATTR-CM has an inherently more aggressive course and if current health disparities are exacerbating the underdiagnosis and misdiagnosis of Black Val122Ile - hATTR-CM patients.

B. Genetic Counseling Perspective & Considerations

Genetic counselors are uniquely equipped to care for patients before, during, and after the genetic testing process and are therefore crucial members of hATTR patients' care team. Clinical genetic counseling involves a client-centered communication approach that aims to promote patient knowledge, adaptation, and adjustment to the medical or psychosocial implications of relevant genetic information (Resta et al., 2006). Specific roles of a genetic counselor often include assessing a patient's genetic risk, discussing and recommending the appropriate genetic testing strategy, communicating results, and providing support to not only the patient, but often family members as well.

The clinical information gathered and discussed in this thesis has numerous implications for genetic counseling of hATTR patients. Personal and family histories are crucial in the development of a differential and subsequent genetic testing strategies. Despite its autosomal dominant inheritance, a patient may not have a known family history of amyloidosis. This could be due to de novo mutations, incomplete penetrance, late-disease onset, or due to other family

members, especially from older generations, not receiving a diagnosis despite having clinical manifestations suggestive of hATTR (Hellman et al., 2008; Maurer et al., 2017). Therefore, suspicion should be raised for hATTR when a personal or family history involves progressive peripheral neuropathy or autonomic neuropathy, with heart, eye, or kidney abnormalities; or cardiac disease with peripheral nerve, eye, or kidney abnormalities (Ando et al., 2013; Adams et al., 2016). In cases of clinical onset in the second decade of life, there are important implications for pediatric genetic counseling, including recurrence risk. Lee et al. (2019) recommends suspicion of hATTR be raised in a pediatric setting when symmetric length-dependent neuropathy is identified with a family history of cardiomyopathy, autonomic, and/or peripheral neuropathy, highlighting the importance of a thorough family history once again.

Presymptomatic testing (PST) refers to genetic testing of an asymptomatic individual for a disease-causing mutation. The term "predictive testing" is often used interchangeably with PST, but also has a broader colloquial use that includes all genetic testing for individuals without symptoms, such as screens of healthy individuals. Therefore, PST is the most accurate term in the context of hATTR and will be used exclusively. Attitudes towards PST for hATTR have become increasingly positive in light of effective therapies that have optimal efficacy at early stages of disease (Schmidt et al., 2016). Areas with a high prevalence of hATTR have implemented genetic counseling protocols that reflect the needs of that geographical region, whereas areas with lower disease prevalence typically have a less structured approach (Schmidt et al., 2016). For instance, Portugal has an established PST protocol that reflects the early-onset, highly penetrant and rapid progressive nature of the hATTR (Paneque et al., 2019). In contrast, in other countries, such as the United States, communication about the condition, the testing and return of test results is managed by a physician and/or a genetic counselor. However, it is

important to note that both early- and late-onset hATTR populations commonly experience psychological issues surrounding PST (Graceffa et al., 2009; Paneque et al., 2009). Clinical guidelines for PST set forth by a European expert panel in 2013 emphasized the involvement of appropriately trained professionals in the PST process, such as medical geneticists or genetic counselors (Skirton, Goldsmith, Jackson, & Tibben, 2013). Additionally, recommendations specific to PST for hATTR emphasize non-directive communication (Obici et al., 2016). Obici et al. (2016) also highlighted the need for post-test follow up regardless of result and a discussion of potential insurance issues. Follow-up studies will be needed to reassess the counseling strategies of non-directive vs. directive communication now that disease-modifying therapies are available.

While genetic testing in a minor with symptoms suggestive of hATTR is not controversial, presymptomatic testing (PST) for adult-onset conditions in minors is not recommended (Borry, Stultiens, Nys, Cassiman, & Dierickx, 2006). Depending on the condition, a suitable alternative to PST in minors may involve disease-specific clinical surveillance. However, I can envision two specific situations in which presymptomatic testing may be warranted in a minor. First, when an older sibling is diagnosed with hATTR in their second decade of life, PST would be reasonable in order to best care for the patient. Second, PST in a minor should also be considered when family members had disease onset in their third decade of life. Anticipation is a documented phenomenon in hATTR, with successive generations presenting at younger ages, especially if the mother was the transmitting parent (Lemos et al., 2014). Additional justification for PST is the fact that available therapeutics have demonstrated greater efficacy when started at the beginning of the disease course. Hence, I suggest that consideration should be given to testing asymptomatic minors for this typically adult-onset

condition that can manifest in the second decade of life. This decision will ultimately be determined by the parent's desires, as well as the child's assent.

In adults, PST for hATTR also has important considerations. Currently, it is recommended that at-risk individuals undergo testing 10 years before the earliest age of onset in the family (Conceição et al., 2019). However, if after appropriate genetic counseling patients wish to have testing done earlier, their right to know should be respected.

The clinical information summarized in this thesis also has implications for post-test counseling. Although genetic counselors are not involved in providing or prescribing treatment, they often outline next steps that the patient can expect with regard to their medical care as impacted by their genetic test result. With a symptomatic individual, a discussion can include whether their manifestations have been reported in the literature in patients with the same variant, as well as the additional clinical manifestations that are associated with the variant. This can facilitate an explanation as to why the patient is being referred to additional specialists despite a lack of relevant symptoms, such as an ophthalmology referral despite an absence of visual disturbances. If a presymptomatic individual is found to have a *TTR* variant, a discussion of the condition's incomplete penetrance, in addition to the associated clinical manifestations, is especially important. Ideally, the clinical surveillance strategy and the incomplete penetrance of the condition would have been discussed during pre-test counseling. Penetrance estimates should be referenced if they are available for the specific variant, although these estimates may not reflect the true penetrance due to the manner in which this information is collected and reported. In both asymptomatic and symptomatic individuals, the clinical heterogeneity of the condition within variants, and even within families, should be emphasized.

Numerous studies on genetic counseling outcomes have suggested the process leads to increased patient knowledge, perceived personal control, positive health behaviors, and risk perception accuracy as well as a decrease in patient anxiety and decisional conflict (Madlensky et al., 2017). Positive outcomes such as these require up-to-date knowledge of the relevant conditions.

V. Appendix

Abbreviations: *, Subclinical; Am, American; AN, Autonomic neuropathy; CTS, Carpal tunnel syndrome; CM, Cardiomyopathy; Cu, Cutaneous; E, Eye involvement; K, Kidney involvement; LM, Leptomeningeal amyloidosis; MCV, meningocerebrovascular amyloidosis; CAA, cerebral amyloid angiopathy; My, Myopathy; N, neuropathy, unspecified; PN, peripheral neuropathy; yrs, years; LTx, Liver transplantation; HTx, Heart transplant; §, Regions with highest disease prevalence; HL, hearing loss; HM, homozygote; HTZ; heterozygote

Variant	HGVS Nomenclature	Ages of Onset (Decade)	mRNA Sequence Variant	Codon Change	Exon	Reported Phenotypes	Ethnicity/Ancestry (Geography)	Special Features
Cys10Arg	p.Cys30arg	6-7th	c.88T>C	TGT>CGT	2	AN, CM, E, PN	Hungarian-Am	Asymptomatic females in 7th & 8th decades
Leu12Met	p.Leu32Met	5th	c.94C>A	CTG>ATG	2	AN, CM, PN	South Korean	
Leu12Pro	p.Leu32Pro	3-5th	c.95T>C	CTG>CCG	2	AN, CM, E, K, LM, PN	English, Portuguese, Nigerian	All patients with LM; Poor LTx outcomes reported; Grand mal seizures as only symptom in 2 patients; HL reported
Leu12Val	p.Leu32Val	4-5th	c.94C>G	CTG>GTG	2	AN, CM CTS, PN	Bolivian, "Caucasian" (Germany)	
Asp18Asn	p.Asp38Asn	6th	c.112G>A	GAT>AAT	2	CM, PN	African-Am, Liberian, Chinese	All patients with CM
Asp18Gly	p.Asp38Gly	3-6th	c.113A>G	GAT>GGT	2	AN, Cu, E, LM, MCV	Chinese, Hungarian, Japanese	All patients with CNS involvement; Variability in disease duration (4-22 yrs)
Asp18Glu	p.Asp38Glu	5-6th	c.114T>A/G	GAT>GAA/G	2	AN, CM, CTS, E, K, PN	Am, Columbian, English-Scottish, South Korean	

Ala19Asp	p.Ala39Asp	6th	c.116C>A	GCT>GAT	2	AN, CM, PN	Brazilian, Swedish-German (Brazil), (Germany)	Only info: 6th decade of life at dx
Val20Ile	p.Val40Ile	5-7th	c.118G>A	GTC>ATC	2	AN, CM, CTS, PN	German, Irish-Am	All patients with CM, requiring HTx
Arg21Gln	p.Arg41Gln	N/A	c.122G>A	CGA>CAA	2	CM, PN	(France)	
Ser23Asn	p.Ser43Asn	5th	c.128G>A	AGT>AAT	2	CM, PN	German-Italian, Peruvian, Portuguese, Spanish-Italian Ecuadorian	
Pro24Ser	p.Pro44Ser	6-8th	c.130C>T	CCT>TCT	2	AN, CM, CTS, My, PN	Am, Japanese	
Ala25Ser	p.Ala45Ser	6th	c.133G>T	GCC>TCC	2	AN, CM*, PN	Am	Rapidly progressive sensorimotor PN
Ala25Thr	p.Ala45Thr	5th	c.133G>A	GCC>ACC	2	LM, PN	Japanese	Predominant LM involvement
Val28Met	p.Val48Met	6th	c.142G>A	GTG>ATG	2	AN, PN	Portuguese	
Val28Ser	p.Val48Ser	5th	c.142_143GT>TC	GTG>TCG	2	AN, CM, E, PN	Chinese	Double nucleotide substitution
Val30Ala	p.Val50Ala	3-6th	c.149T>C	GTG>GCG	2	AN, CM, K*, PN	Chinese, German-Am, Indian	
Val30Leu	p.Val50Leu	5-6th	c.148G>C	GTG>CTG	2	AN, CM, K, PN	Japanese, Swedish	Rapid disease progression; Poor LTx outcomes
Val30Gly	p.Val50Gly	5-6th	c.149T>G	GTG>GGG	2	E, LM, My, PN	German-Am, (USA)	All patients with E and LM
Val30Met	p.Val50Met	2-9th	c.148G>A	GTG>ATG	2	AN, CM, CTS, E, K, LM, PN	(Cyprus, Japan, Majora, Portugal, Sweden)§	Anticipation noted; Disease features vary by region
Val32Ala	p.Val52Ala	6-7th	c.155T>C	GTG>GCG	2	AN, CM, PN	"Caucasian," Chinese, Jewish-Iranian	Ambulation affected within 2-3 years of disease onset
Val32Gly	p.Val52Gly	4th	c.155T>C	GTG>GGG	2	PN	French, (France)	

Phe33Cys	p.Phe53Cys	4th	c.158T>G	TTC>TGC	2	CM, E, K, PN	Polish-Am	Vitreous opacities 16 yrs prior to other symptoms
Phe33Ile	p.Phe53Ile	3-4th	c.157T>A	TTC>ATC	2	AN, E, K*, PN	Am, Israeli-Ashkenazi Jewish, Indian	Vitreous opacities may be first and only symptom
Phe33Leu	p.Phe53Leu	5-7th	c.157T>A	TTC>CTC	2	AN, CM, CTS, K, PN	Ashkenazi Jewish, Chinese, Hungarian, Polish, Polish-Am, Polish-Lithuanian, Swedish, Taiwanese	
Phe33Val	p.Phe53Val	3-6th	c.157T>G	TTC>GTC	2	AN, CM, CTS, E, K, PN	British, Chinese, Japanese, Macedonian	
Arg34Gly	p.Arg54Gly	6th	c.160A>G	AGA>GGA	2	CTS, E, PN	Chinese, Kosovar	All with E; Ocular involvement included vitreous opacities, vitreous hemorrhage, and glaucoma
Arg34Ser	p.Arg54Ser	N/A	c.162A>C	AGA>AGC	2	CM, PN	Polish-Italian (United States)	
Arg34Thr	p.Arg54Thr	4-6th	c.161G>C	AGA>ACA	2	AN, CM, PN	Italian, Chinese	
Lys35Asn	p.Lys55Asn	4-6th	c.165G>T/C	AAG>AAT/C	2	AN, CM, E, K, PN	Chinese, Korean, South Korean, French	All presented with sensory neuropathy
Lys35Thr	p.Lys55Thr	5-7th	c.164A>C	AAG>ACG	2	AN, CM, CTS, E, PN	Ashkenazi Jewish-Am, Chinese	Discordant female monozygotic twins reported
Ala36Asp	p.Ala56Asp	N/A	c.167C>A	GCT>GAT	2	AN, PN	Japanese	
Ala36Pro	p.Ala56Pro	3-5th	c. 166G> C	GCT>CCT	2	AN, CM, CTS, E, K, LM, MCV, PN	Chinese, Greek-Am, Italian, Polish-Ashkenazi Jewish, South Korean	Most patients with AN, E, and PN; Poor LTx Outcomes
Asp38Ala	p.Asp58Ala	5-8th	c.173A>C	GAT>GCT	2	AN, CM, CTS, PN, Pu	Am, Japanese, Korean, South Korean	Diffuse pulmonary involvement

Asp38Val	p.Asp58Val	6-7th	c.173A>T	GAT>GTT	2	AN, CM, PN	Ghanaian, Polish, South Korean	
Asp39Val	p.Asp59Val	4-5th	c.176A>T	GAC>GTC	2	AN, CM, PN	Chinese Malaysian, German	
Thr40Asn	p.Thr60Asn	7th	c.179C>A	ACC>AAC	2	AN, CM, CTS, PN	Russian, (Germany)	
Trp41Leu	p.Trp61Leu	4-5th	c.182G>T	TGG>TTG	2	AN, E, PN	Russian, Russian-Romanian	All presented with vitreous opacities
Glu42Gly	p.Glu62Gly	4-5th	c.185A>G	GAG>GGG	2	AN, CM, E, PN	Chinese, Japanese, Italian, Italian-Am	
Glu42Asp	p.Glu62Asp	7th	c.186G>T	GAG>GAT	2	AN, CM	French	
Pro43Ser	p.Pro63Ser	9th	c.187C>T	CCA>TCA	2	CM	Japanese	
Phe44Leu	p.Phe64Leu	8th	c.190T>C	TTT>CTT	2	CM, PN	"Caucasian," Nigerian	Compound heterozygote
Phe44Tyr	p.Phe64Tyr	N/A	c.191T>A	TTT>TAT	2	AN, CM, PN	French	
Phe44Ser	p.Phe64Ser	4-5th	c.191T>C	TTT>TCT	2	AN, E, PN	Irish-Am, Japanese, Lithuanian-German	
Ala45Ser	p.Ala65Ser	7th	c.193G>T	GCC>TCC	2	CM, CTS, PN	Swedish	Development of CM after LTx reported
Ala45Thr	p.Ala65Thr	6th	c.193G>A	GCC>ACC	2	AN, CM	Irish-Italian, (Italy), (USA)	
Ala45Asp	p.Ala65Asp	5th	c.194C>A	GCC>GAC	2	AN, CM, My, PN	Japanese, American	
Ala45Gly	p.Ala65Gly	8th	c.194C>G	GCC>GGC	2	CM, CTS, PN*	Dutch, (Sweden)	
Gly47Arg	p.Gly67Arg	2-4th	c.199G>A/C	GGG>A/CGG	2	AN, CM, CTS, E, LM, PN	Am, Chinese, Italian, Japanese, Korean	
Gly47Ala	p.Gly67Ala	3-6th	c.200G>C	GGG>GCG	2	AN, CM, CTS, K, PN	French, Italian, Mexican	
Gly47Glu	p.Gly67Glu	3-7th	c.200G>A	GGG>GAG	2	AN, CM, K, PN	Am, Chinese, Dutch, English, Finnish, Italian, (Germany), Turkish	Poor LTx outcomes reported; Mild PN

Gly47Val	p.Gly67Val	8th	c.200G>T	GGG>GTG	2	AN, CM, PN	Japanese, Sri Lankan, Tamil Malaysian	
Thr49Ala	p.Thr69Ala	4-6th	c.205A>G	ACC>GCC	3	AN, CM, CTS, E, K, PN	French, Han Chinese, Italian, Japanese	Major causes of mortality were dysautonomia and cachexia, followed by CM
Thr49Ile	p.Thr69Ile	7th	c.206C>T	ACC>ATC	3	AN, CM, PN	French, Japanese, Spanish	
Thr49Pro	p.Thr69Pro	6th	c.205A>C	ACC>CCC	3	LM, PN	Irish	
Thr49Ser	p.Thr69Ser	2-4th	c.206C>G	ACC>AGC	3	AN, CM, PN	Indian, Turkish	Anticipation >10 yrs
Ser50Arg	p.Ser70Arg	2-6th	c.208A>C; c.210T>A/G	AGT>CGT; AGA/G	3	AN, CM, CTS, Cu, E, K, PN	French, French-Italian, Japanese, Mexican, Portuguese, Spanish, Vietnamese	
Ser50Ile	p.Ser70Ile	5-6th	c.209G>T	AGT>ATT	3	AN, CM, My, PN	Japanese	
Glu51Gly	p.Glu71Gly	N/A	c.212A>G	GAG>GGG	3	CM	American	
Glu51_Ser52dup	p.Glu71_Ser72dup	4th	c.212_217dupAGTCTG	Duplication	3	AN, CM, CTS, K, M, PN	African-Am	
Ser52Pro	p.Ser72Pro	3-6th	c.214T>C	CTC>CCT	3	AN, CM, K*, PN	Bulgarian, Mexican, (UK)	Development of CM after LTx reported
Gly53Arg	p.Gly73Arg	5-6th	c.217G>A	GGA>AGA	3	CAA, LM	American	Hydrocephalus as presenting symptom
Gly53Glu	p.Gly73Glu	3-6th	c.218G>A	GGA>GAA	3	AN, CM, K, LM, PN	Brazilian, French, Indian, Italian, Swedish, Turkish	All patients with CM
Gly53Ala	p.Gly73Ala	2nd	c.218G>C	GGA>GCA	3	AN, CM*, E, K, LM, PN	British	Severe headaches since 18 yrs, other symptoms developed at 40 yrs
Glu54Leu	p.Glu74Leu	5th-8th	c.220_221GA>TT	GAG>TTG	3	AN, CM, CTS, PN	Belgian, Swedish	Double nucleotide substitution

Glu54Lys	p.Glu74Lys	2-4th	c.220G>A	GAG>AAG	3	AN, CM, E, K, PN	Costa Rican, Italian, Japanese, Malay Malaysian, Turkish	All died before age 40 yrs
Glu54Gly	p.Glu74Gly	3-4th	c.221A>G	GAG>GGG	3	AN, CM, E, K, PN	Am, British, Korean, South Korean, Turkish	
Glu54Asp	p.Glu74Asp	N/A	c.222G>C	GAG>GAC	3	CM	(Germany)	
Glu54Gln	p.Glu74Gln	4-6th	c.220G>C	GAG>CAG	3	AN, CM, CTS, PN	Italian, Romanian	
Leu55Gln	p.Leu75Gln	5th	c.224T>A	CTG>CAG	3	AN, CM, CTS, E, PN	Spanish-Am, Swedish	Development of CM after LTx reported
Leu55Arg	p.Leu75Arg	4-6th	c.224T>G	CTG>CGG	3	AN, CM, CTS, E, LM,PN	Chinese, Han Chinese, (Germany)	
Leu55Pro	p.Leu75Pro	2-4th	c.224T>C	CTG>CCG	3	AN, CM, E, PN	Chinese, German-Dutch Am, Japanese, Korean, Taiwanese	Anticipation >10 yrs
His56Arg	p.His76Arg	N/A	c.227A>G	CAT>CGT	3	CM	American	
Gly57Arg	p.Gly77Arg	N/A	c.229G>A	GGG>AGG	3	CM, CTS, PN	Swedish, (Italy)	
Leu58Arg	p.Leu78Arg	4th	c.233T>G	CTC>CGC	3	AN, CM, CTS, E, LM*, PN	Japanese	
Leu58His	p.Leu78His	5th	c.233T>A	CTC>CAC	3	CM, CTS, PN	Am, German-Am, German	Majority develop CTS first; CTS may be first and only symptom
Thr59Arg	p.Thr79Arg	6th	c.236C>G	ACA>AGA	3	AN*, CM	Japanese	
Thr59Lys	p.Thr79Lys	4-7th	c.236C>A	ACA>AAA	3	AN, CM, PN	Chinese, Egyptian, Italian	All patients presented with heart failure; Sudden cardiac death in 1 patient
Thr60Ala	p.Thr80Ala	6-8th	c.238A>G	ACT>GCT	3	AN, CM, CTS, K, LM, My, PN	English, Irish, Scottish	Compound HTZ reported

Glu61Lys	p.Glu81Lys	6-8th	c.241G>A	GAG>AAG	3	AN, CM, CTS, PN	Japanese, Polish	
Glu61Gly	p.Glu81Gly	6th	c.242A>G	GAG>GGG	3	CM, CTS, PN	English-Dutch	Hematuria due to TTR-positive bladder polyp
Glu61Ala	p.Glu81Ala	7th	c.242A>C	GAG>GCG	3	CM, CTS	(USA)	
Glu62Lys	p.Glu82Lys	6-8th	c.243G>A	GAG>AAG	3	CM, CTS, PN	(Italy, France, Czech Republic)	
Phe64Ile	p.Phe84Ile	8th	c.250T>A	TTT>ATT	3	AN, CM, K, PN	Caucasian (Italy)	
Phe64Leu	p.Phe84Leu	7-8th	c.250T>C	TTT>CTT	3	AN, CM, CTS, E, PN	Italian-Am, Italian, Sicilian	HZ reported with earlier onset in 6th decade; Only women identified as asymptomatic later in life; Pure motor neuropathy reported
Phe64Ser	p.Phe84Ser	3rd	c.251T>C	TTT>TCT	3	AN, CM, CTS, E, LM, PN	African-Am, Italian Canadian	LM prominent in Italian Canadian family, AN prominent in African-Am patient
Phe64Val	p.Phe84Val	4th	c.250T>G	TTT>GTT	3	AN, CM, PN	"Caucasian," German	
Gly67Arg	p.Gly87Arg	5-6th	c.259G>C	GGG>CGG	3	AN, E	Bangladeshi, “Caucasian”	All patients with E
Gly67Glu	p.Gly87Glu	4-6th	c.260G>A	GGG>GAG	3	AN, CM, E, K*, PN	Chinese, Macanese	
Ile68Leu	p.Ile88Leu	7-8th	c.262A>C/TTA	ATA>C/TTA	3	AN, CM, CTS, PN	German, Italian	Higher male prevalence; Rapid progression; Compound HTZ and HM reported
Tyr69His	p.Tyr89His	4-7th	c.265T>C	TAC>CAC	3	AN, CM, CTS, E, LM, PN	Italian-Am, Scottish, Swedish	
Tyr69Ile	p.Tyr89Ile	7th	c.265_266TA>AT	TAC>ATC	3	AN, CM, CTS	Japanese	Double nucleotide substitution

Lys70Asn	p.Lys90Asn	3-7th	c.270A>C	AAA>AAC	3	CTS, E, K, PN	German-Am	Tongue and forearm fasciculations reported
Lys70Glu	p.Lys90Glu	5-8th	c.268A>C	AAA>CAA	3	CTS, E, PN	Finnish	
Val71Ala	p.Val91Ala	3-6th	c.272T>C	GTG>GCG	3	AN, CM, CTS, E, K, PN	Australian, Bengali, Brazilian, Dutch, English, French, Majorcan, Polish, Spanish	
Ile73Val	p.Ile93Val	5-7th	c.277A>G	ATA>GTA	3	AN, CM, K*, PN	Bangladeshi, Indian, Polish, Taiwanese	
Ser77Phe	p.Ser97Phe	6-8th	c.290C>T	TCT>TTT	3	AN, CM, PN	Bulgarian, French	Poor 9 -year LTx survival (24%)
Ser77Tyr	p.Ser97Tyr	6-7th	c.290C>A	TCT>TAT	3	AN, CM, CTS, E, K, My, PN	Am, English, French, German-Am, Jewish-Yemenite, Israeli-Yemenite, Spanish	Conjunctival lymphangiectasia is a biomarker of severe disease
Tyr78Phe	p.Tyr98Phe	6-8th	c.293A>T	TAC>TTC	3	AN, CM, CTS, Cu, E, K, PN	Italian	Significant clinical heterogeneity
Ala81Thr	p.Ala101Thr	7-8th	c.301G>A	GCA>ACA	3	CM, CTS	(USA), (Western Europe)	
Ala81Val	p.Ala101Val	7th	c.302C>T	GCA>GTA	3	AN, CM, CTS, E, PN	Polish, Russian-Polish, (England)	
Gly83Arg	p.Gly103Arg	4-5th	c.307G>C	GGC>CGC	3	CM, E, PN	Chinese	Prominent eye involvement
Ile84Asn	p.Ile104Asn	6-7th	c.311T>A	ATC>AAC	3	CM, CTS, E	Italian-Am, Japanese	
Ile84Ser	p.Ile104Ser	5-6th	c.311T>G	ATC>AGC	3	CM, CTS, E, PN	Swiss-Am, Hungarian	
Ile84Thr	p.Ile104Thr	6th	c. 311T>C	ATC>ACC	3	CM, PN	Am, German	
His88Arg	p.His108Arg	6-8th	c.323A>G	CAT>CAG	3	CM, CTS, PN, K	Hungarian, Swedish	
Glu89Gln	p.Glu109Gln	6-7th	c.325G>C	GAG>CAG	3	AN, CM, CTS, PN	Bulgarian, Sicilian-Italian, Turkish	

Glu89Lys	p.Glu109Lys	2-6th	c.325G>A	GAG>AAG	3	AN, CM, CTS, E, PN	Am, Canadian, Korean, Polish, Swiss	Rapid disease progression, requiring HTx; Development of PN after HTx and were listed for, or received, LTx
His90Asp	p.His110Asp	N/A	c.328C>G	CAT>GAT	3	CM, CTS, PN	British, (UK)	
Ala91Ser	p.Ala111Ser	7th	c.331G>T	GCA>TCA	3	AN, CM, CTS, PN	French, (France)	
Gln92Lys	p.Gln112Lys	7th	c.334G>A	GAG>AAG	3	CM, K*	Japanese	
Val93Met	p.Val113Met	5th	c.337G>A	GTG>ATG	4	AN, CM, PN	Malian	Misdiagnosed as ALS; Pure motor neuropathy; Symptoms stable for five years; Tongue fasciculations reported
Val94Ala	p.Val114Ala	7th	c.341T>C	GTA>GCA	4	AN, CM, PN	“Caucasian”, German-Greek	
Ala97Ser	p.Ala117Ser	5-9th	c.349G>T	GCC>TCC	4	AN, CM, K*, PN	Chinese, Chinese Malaysian, Korean, Taiwanese	Possible onset of disease in one patient at age 23; Spinal stenosis reported
Ala97Gly	p.Ala117Gly	6th	c.350C>G	GCC>GGC	4	CM, PN	Japanese	
Arg103Ser	p.Arg123Ser	N/A	c.367C>A	CGC>AGC	4	CM	American	
Ile107Val	p.Ile127Val	5-8th	c.379A>G	ATT>GTT	4	AN, CM, CTS, My, PN	Brazilian, French, German, German-Am, Japanese, Kazakhstani	
Ile107Phe	p.Ile127Phe	7th	c.379A>T	ATT>TTT	4	AN, CM, K, PN	British, Italian, (Germany)	Spinal stenosis reported
Ile107Met	p.Ile127Met	6th	c.381T>G	ATT>ATG	4	AN, E, PN	Chinese, German	
Ala109Ser	p.Ala129Ser	7th	c.385G>T	GCC>TCC	4	AN, PN	Japanese	
Leu111Met	p.Leu131Met	4-5th	c.391C>A	CTG>ATG	4	AN, CM, CTS, K, PN	Danish	Prominent heart involvement; Good LTx and combined LTx-HTx outcomes

Ser112Ile	p.Ser132Ile	N/A	c.395G>T	AGC>ATC	4	CM, PN, K	Italian	
Pro113Thr	p.Pro123Thr	N/A	c.397C>A	CCC>ACC	4	CM, CTS, E	French	
Tyr114Cys	p.Tyr134Cys	4-7th	c.401A>G	TAC>TGC	4	AN, CAA, CM, E, LM, My, PN	Am, Argentinian, Chinese, Japanese	
Tyr114His	p.Tyr134His	6-7th	c.400T>C	TAC>CAC	4	CM, CTS, Cu, PN	Japanese	Mild disease course; Predominant CTS involvement; Nodular cutaneous amyloidosis; Spinal stenosis reported
Tyr114Ser	p.Tyr134Ser	7th	c.401A>C	TAC>TCC	4	CM, CTS, PN	Japanese	Mild PN
Tyr116Ser	p.Tyr136Ser	6-8th	c.407A>C	TAT>TCT	4	AN, CM, E, CTS, PN	French, Han Chinese	
Tyr116His	p.Tyr136His	7th	c.406T>C	TAT>CAT	4	N	Mexican	
Ala120Ser	p.Ala140Ser	7th	c.418G>T	GCT>TCT	4	AN, CM, CTS, My, PN	Afro-Caribbean, Am, Italian	
Val121Ala	p.Val141Ala	8th	c.422T>C	GTC>GCC	4	CM, K	(Japan)	
Val122del	p.Val142del	6th	c.424_426	Del GTC	4	AN, LM, PN	Ecuadorian-Am, (Spain)	
Val122Ile	p.Val142Ile	6-9th	c.424G>A	GTC>ATC	4	AN, CM, CTS, K, My, PN	African, African-Am, Brazilian, Italian, Jamaican (Britain), Japanese, Mexican, Portuguese	HZ and compound HTZ reported with earlier age of onset in 5th and 6th decades; Hearing Loss
Val122Ala	p.Val142Ala	7th	c.425T>C	GTC>GCC	4	CM	British, Chinese	
Asn124Ser	p.Asn154Ser	7th	c.431A>G	AAT>AGT	4	CM, K	Italian	Prominent kidney involvement

VI. Web Resources

Mutations in Transthyretin Gene (*TTR*)
http://amyloidosismutations.com/mut-attr.php

Orphanet
https://www.orpha.net/consor/cgi-bin/ResearchTrials_Networks.php?lng=EN&data_id=79754

Transthyretin Amyloidosis Outcome Survey (THAOS)
https://www.clinicaltrials.gov/ct2/show/NCT00628745

VII. Bibliography

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