Transthyretin (ATTR) Amyloidosis:

tricks and treats

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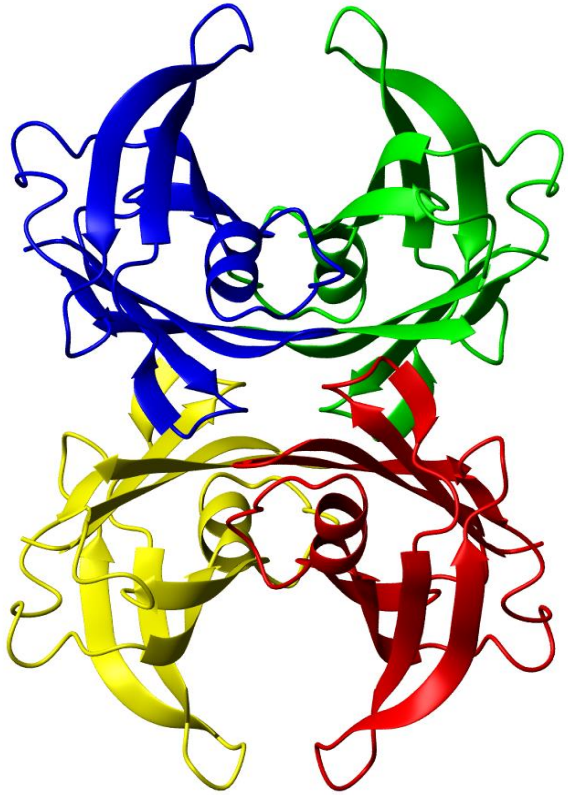
Inherited Amyloidoses

Subunit	Type	Source	Comment
Transthyretin	ATTR	Liver	PN/ANS, heart, GI, rarely kidney
Apolipoprotein AI/AII	AApoAI/AII	Liver/GI	Kidney, heart, PN (AI)
Fibrinogen Aα chain	AFib	Liver	Kidney
Lysozyme	ALys	GI tract	Kidney, liver, spleen
Gelsolin	AGel		Cranial neuropathy/lattice dystrophy

- Autosomal dominant genetics
- Slow clinical progression
- Solid organ transplantation

Transthyretin (TTR)



- 127 amino acid chain
- Primarily produced by liver (eye, brain)
- > 120 TTR mutations (amino acid substitutions)
- Untreated, people live 7-15 YRS after presentation
- Affects ~10-15,000 world-wide

Mutant (ATTRm) vs Wild-type (ATTRwt)

	ATTRm	ATTRwt
TTR Protein	Abnorm	Norm
Onset Age (YRS)	30-75	>60
Female	40%	<5%
Carpal Tunnel	+++	++++
Auto Neuropathy	+++	
Periph Neuropathy	++++	+
GI Motility	+++	
Cardiomyopathy	+++	+++++
Survival (YRS)	7-15	<5

Nomenclature for ATTRm

30

VALINE

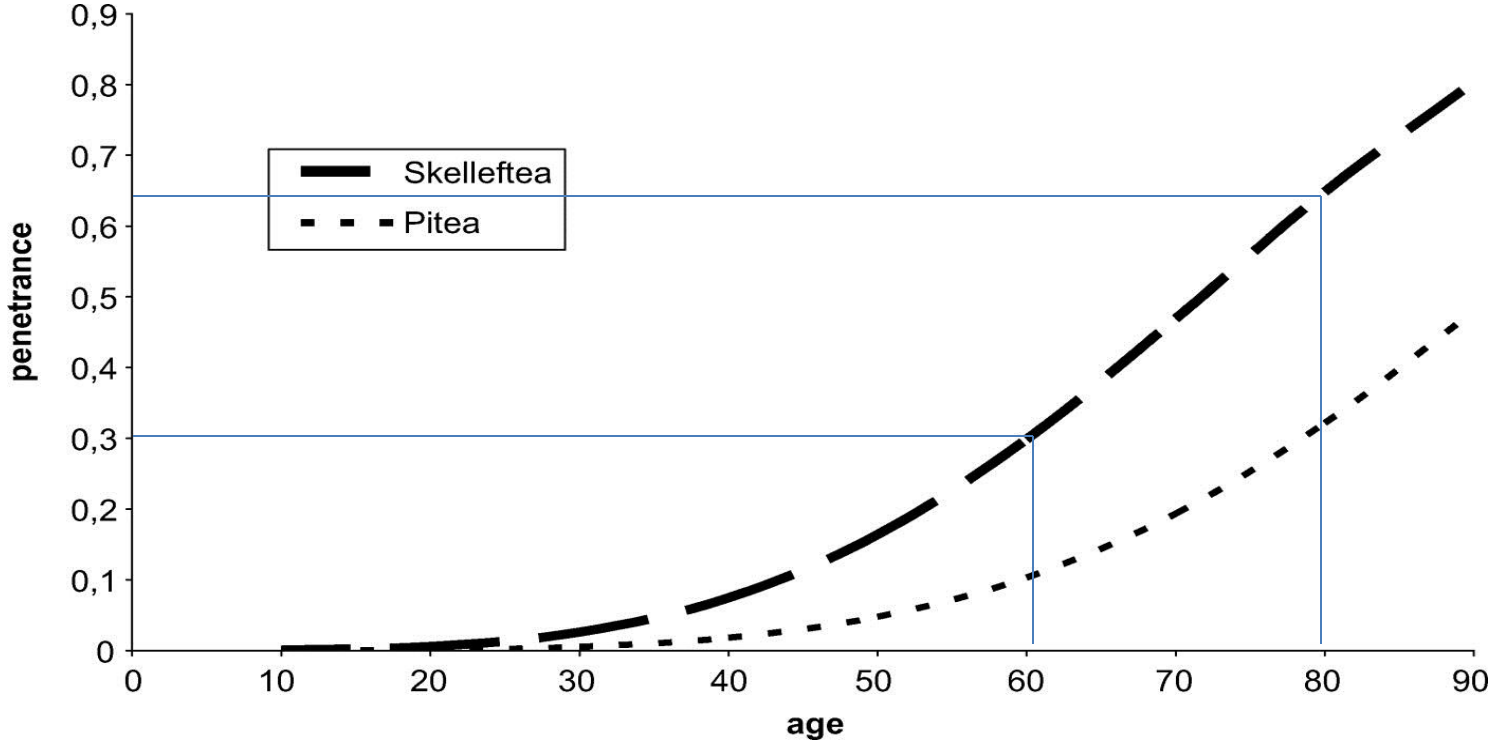
30

METHIONINE

Abbreviation: **V30M ATTR**

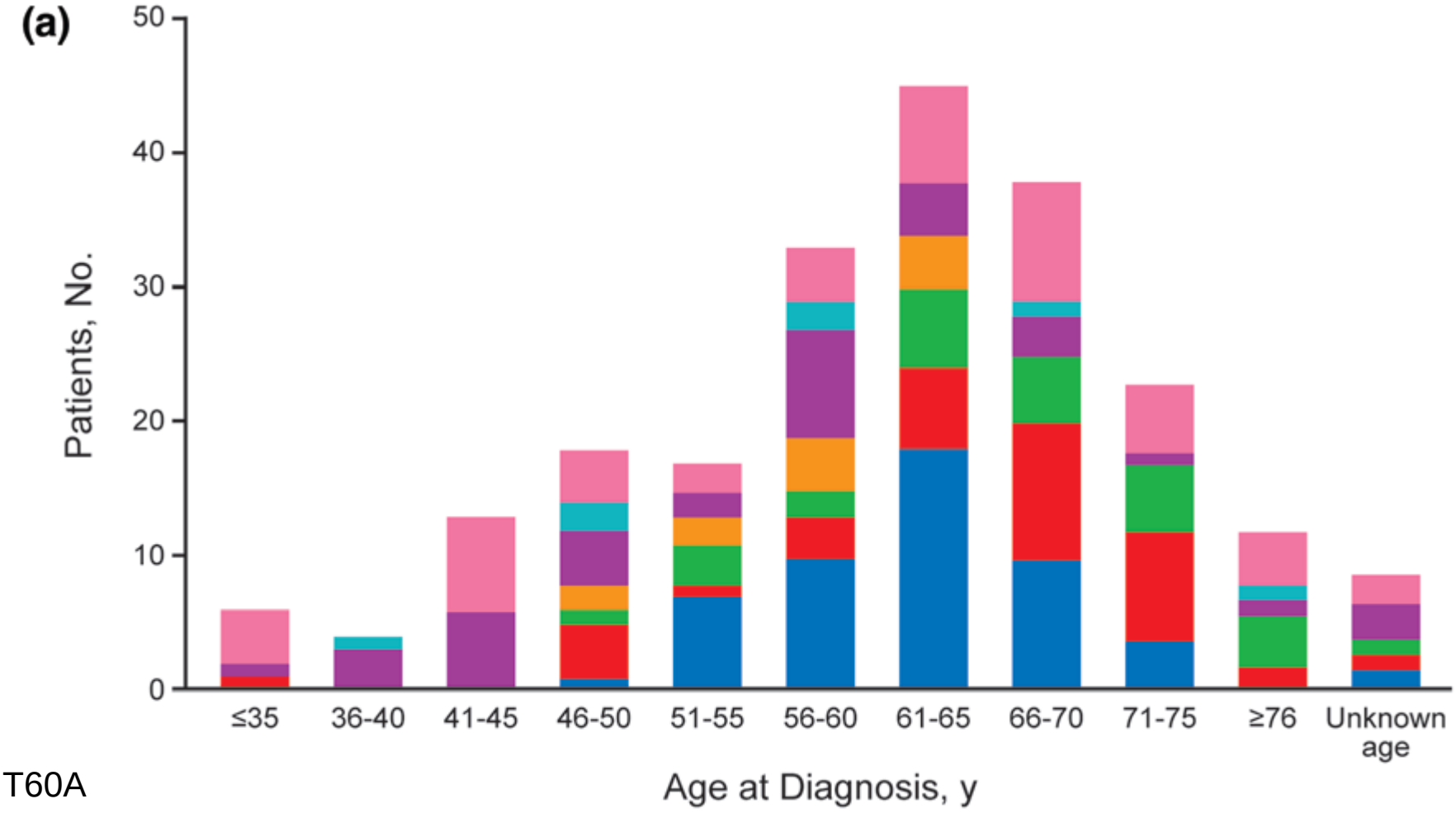
Penetrance: Will I get the disease?

77 Swedish families
235 affected
1353 family members



Hellman et al. Amyloid 15(3):181-6, 2008

Age of Onset in ATTRm



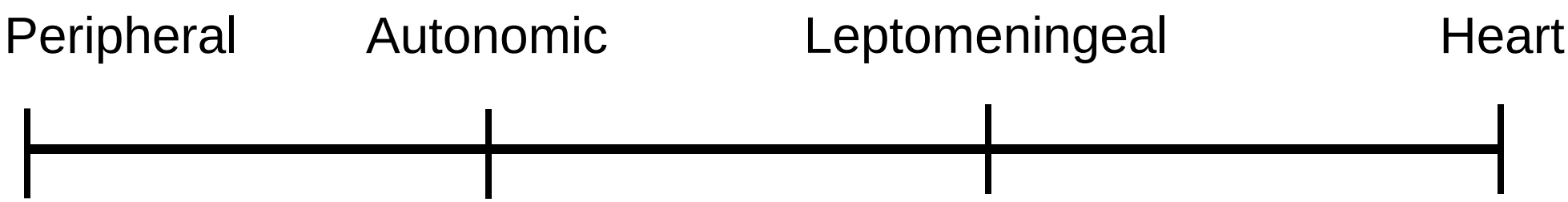
B = T60A
R = V30M
G = V122I

Zhen DB et al. Clin Genet 2015; 88:396

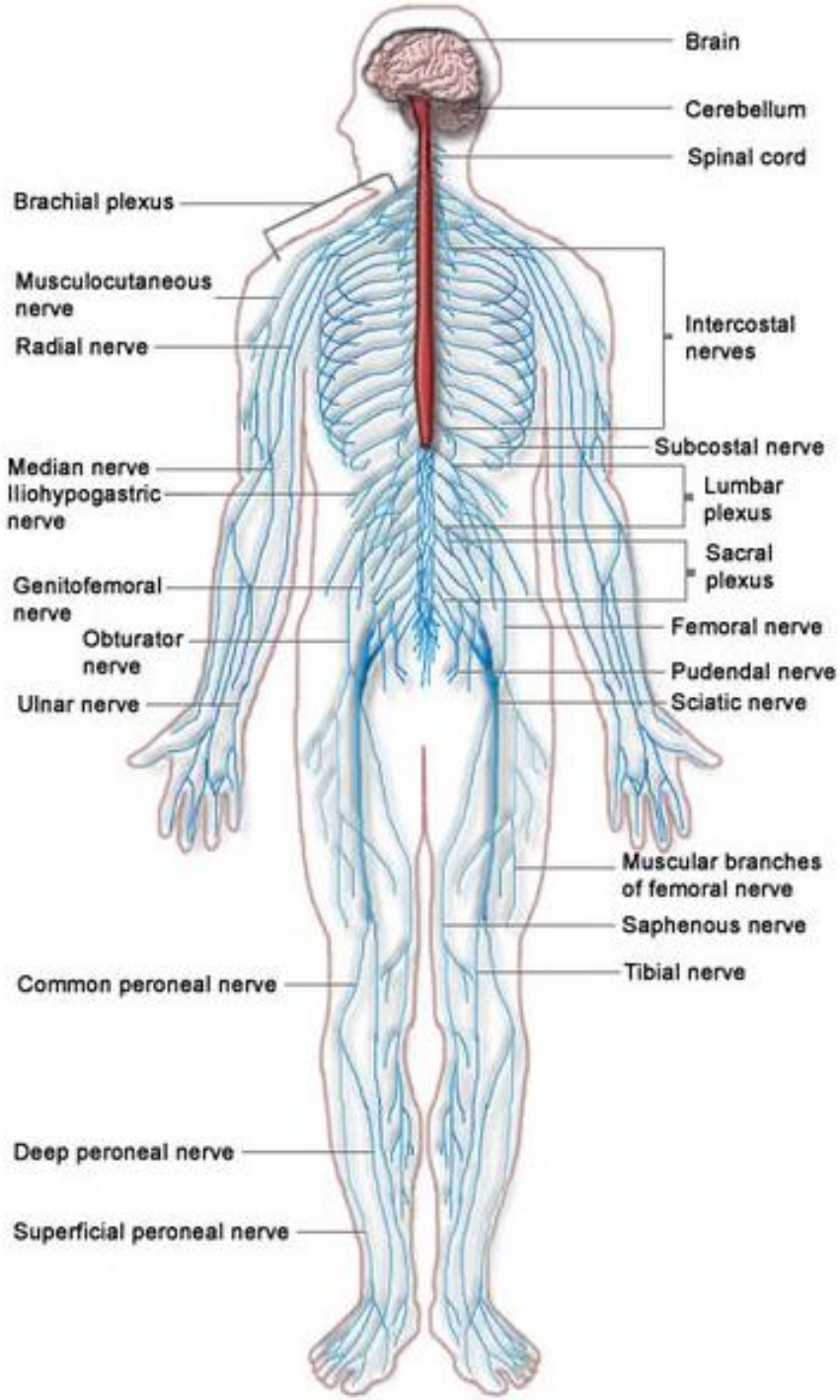
Most prevalent ATTRm in the USA

• V30M	Peripheral neuropathy
• T60A	Heart/Peripheral neuropathy
• V122I	Heart/Peripheral neuropathy
• L58H	Soft tissue/PN/Heart
• S77Y	Heart/PN/Soft tissue
• I84S	Heart/PN
• T49P	PN/Heart/Soft tissue

ATTRm Spectrum of Disease

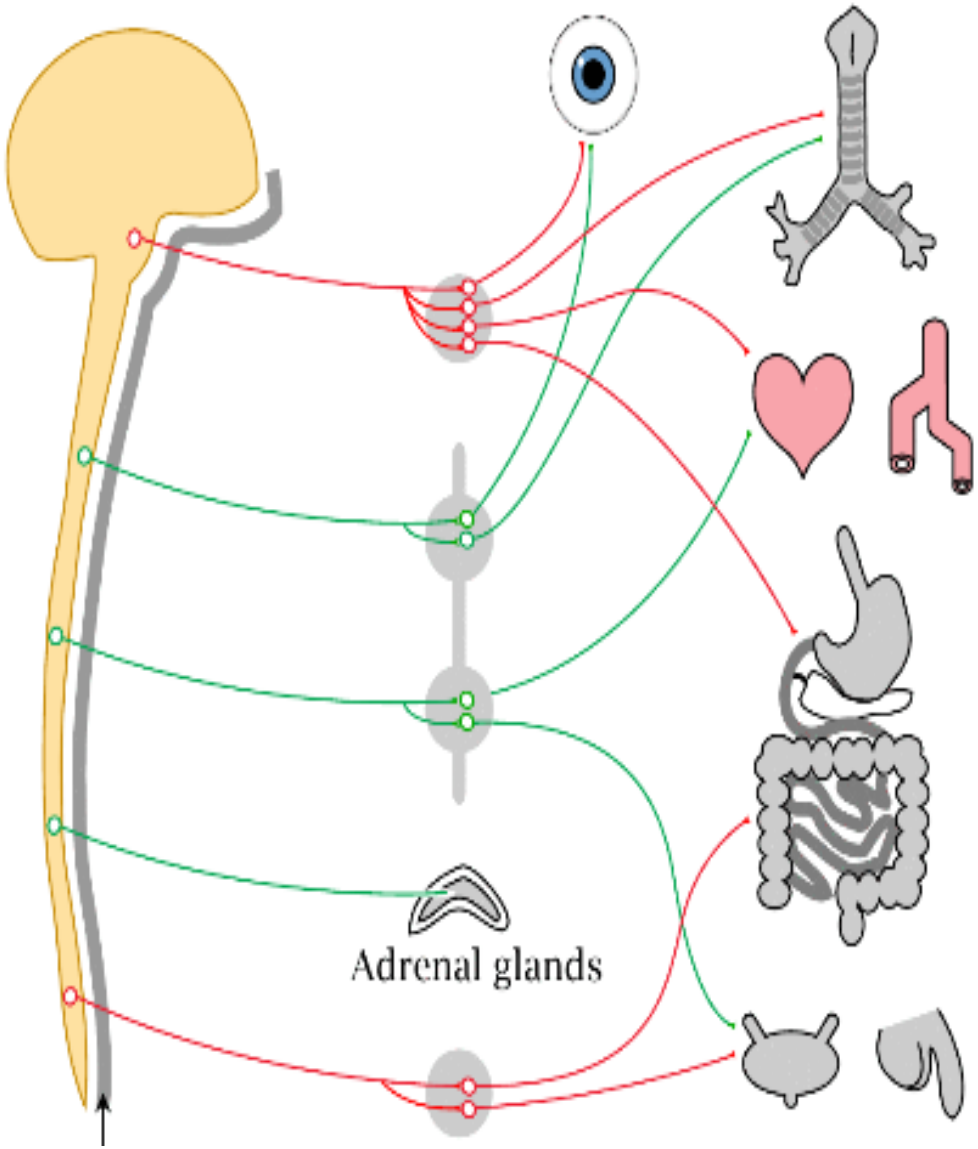


Peripheral	Autonomic	Leptomeningeal	Heart
Val30Met	Thr49Pro	Leu12Pro	Val122Ile
Leu58His	Glu42Gly	Asp18Gly	Thr60Ala
Thr60Ala	Thr60Ala	Leu55Arg	Ser77Tyr
Phe64Leu	Phe44Ser	Phe64Ser	Ile84Ser
Ala97Ser	Ser50Arg	Tyr114Cys	Val30Ala
			His90Asp



Peripheral Nervous System

- Ascending numbness,etc.
- Cold insensitivity
- Muscle weakness
- Stork walk (steppage gait)
- Inability to rise from seat
- Muscle atrophy



Autonomic Nervous System

- Dry eyes, mouth
- Altered sweating
- Blunted heart rate
- (near) blackouts
- Diarrhea/constipation
- Bladder dysfunction
- Erectile dysfunction

ATTRm: How many are we?

World wide	~10-15,000
United States	1:million to 1:100,000
	300 to 3,000 Dx
<u>African-Americans</u> (3.9%)	~1.4 million gene (+)
>65 year old (3-4%)	90,000-135,000 gene (+)
ATTR cardiomyopathy (7%)	<10,000

ATTRwt: How many are we?

Sweden

85 consec autopsies >80 yo	25% hearts (+) ATTR
LV involvement	16%
Significant amyloid	~8%

Finland

	256 autopsies
TTR amyloid	25%
Mod/Severe amyloid	5.5%

US 2010 Census

Men >80 years	4.08 million
ATTR cardiomyopathy	~ 250,000 men (6.5%)

Amyloid Treatment Strategies

- prevent protein misfolding
- suppress amyloidogenic protein production
- destabilizing amyloid deposits