Genetics of Hereditary Amyloidosis

Anita Rauch

General characteristics of Hereditary Amyloidoses

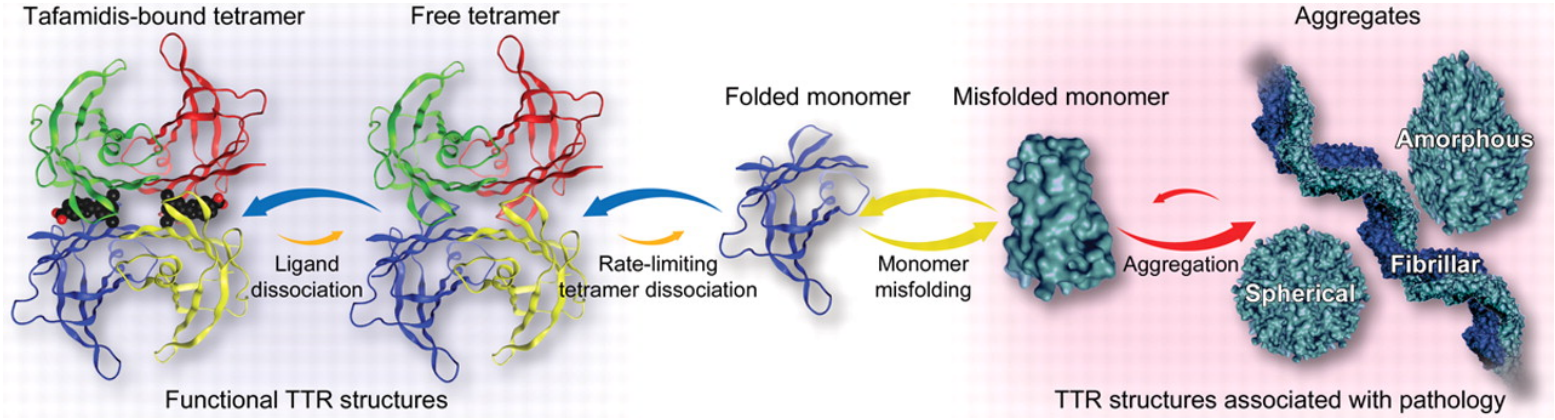
- Autosomal dominant inheritance
- Variable expressivity and penetrance
- Genotype-Phenotype correlation
- Specific, amyloidogenic mutations
- Endemic hotspot mutations

Phenotypic grouping of hereditary amyloidoses

Neuropathic (Polyneuropathy)	Non-Neuropathic (Nephropathy)	Cerebral (Dementia)
• Transthyretin • Apolipoprotein A-I • Gelsolin	• Fibrinogen A α • Lysozyme • Pyrin • Apolipoprotein A-II	• Presenilin 1 • Presenilin 2 • Amyloid precursor protein • Cystatin C • BRI

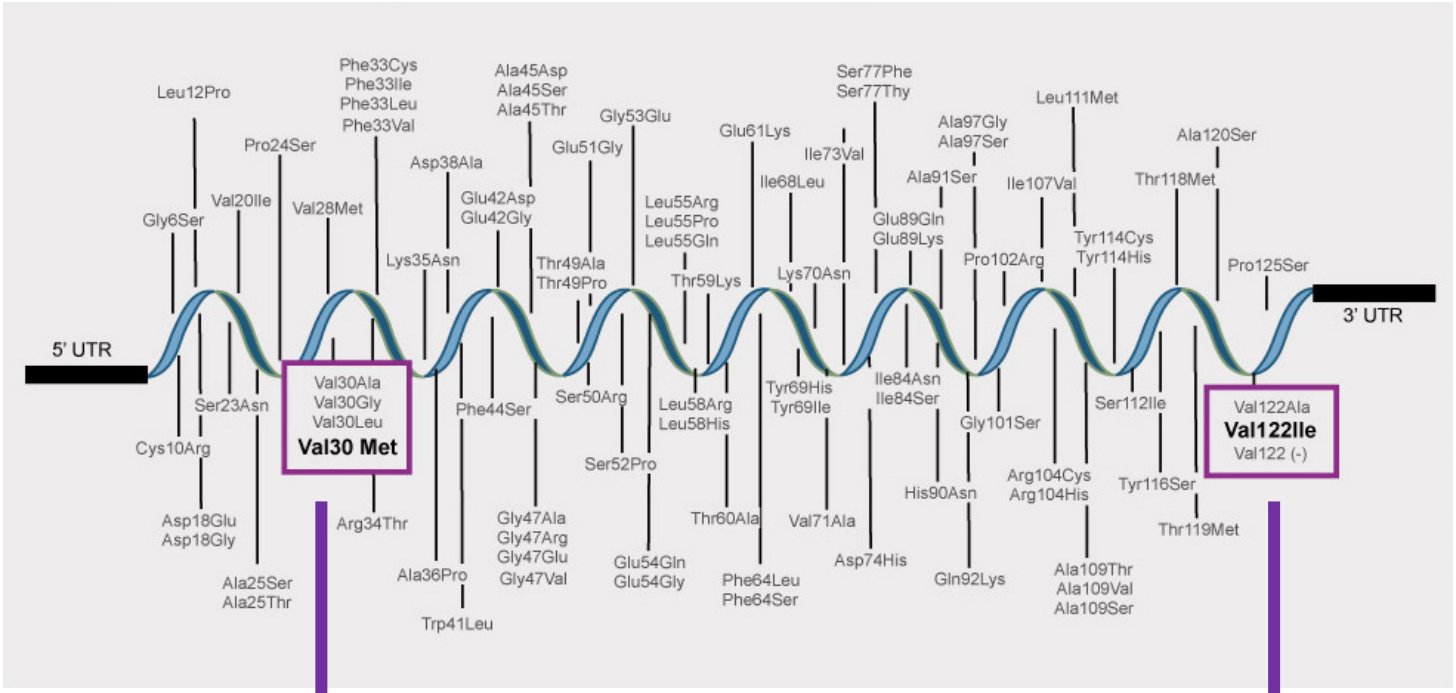
Most common type: Hereditary transthyretin amyloidosis

- TTR protein is produced primarily in the liver and is normally a carrier for retinol binding protein
- peripheral sensory neuropathy, autonomic neuropathy, and/or cardiomyopathy



Coelho T et al. Neurology 2012;79:785-792

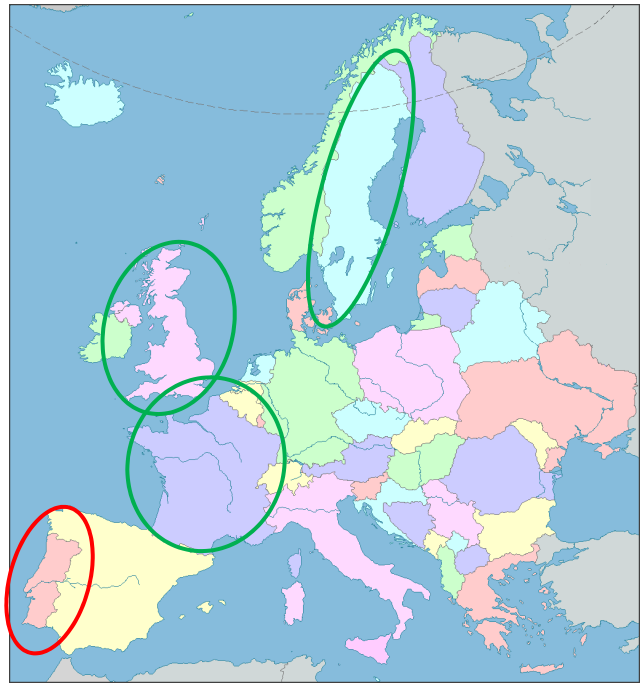
TTR (Transthyretin): more than 100 known mutations



Sensori-motor peripheral neuropathy
Rarely cardiac involvement

Senile cardiac amyloidosis
3-4% of African Americans are carriers

Population endemic clinical variability: Mean age of onset in Val30Met carriers



Portugues: 33.5 y
Swedish, French, or British much later

Japan: 62.7 y
Ogawa / Arao: 40.1 y

Genetic and environmental Modifiers

Variant c.416C>T (Thr119Met) has a protective effect on amyloidogenesis in individuals who have the Val30Met mutation

Familial euthyroid hyperthyroxinemia is caused by benign allelic variants in *TTR*, including Gly6Ser, Ala109Thr, Ala109Val, and Thr119Met

Hereditary gelsolin amyloidosis

- "Finnish type" G654A or T
- G654A also reported in Portugal, Japan and Iran
- G654T reported in Denmark, Czech Rep. and France
- Actin-modulating protein enhancing cell migration
- Mutation→ unable to bind calcium ions → proteolysis → fibrils
- Typically corneal lattice dystrophy during early middle-age
- Rare cases homozygous mutations: rapid decline and renal failure

Proteinuria and progressive renal failure

- Fribrinogen Aalpha-chain amyloidosis
  - 9 mutations, E526V most common
- Apolipoprotein AI amyloidosis
  - 13 variants
  - Possible neurological, cardiac, hepatic dysfunction
- Apolipoprotein AII amyloidosis
  - 4 mutations, earlier mean manifestation
- Lysozyme amyloidosis
  - 7 mutations, very slowly progressive

Hereditary Early-onset Alzheimer Disease

- 30-70 %***PSEN1*** (Presenilin 1)
  - ~150 Mutationen
- 10-15 % ***APP*** (Amyloid beta (A4) Precursor Protein)
  - >30 Mutationen
- 5 % ***PSEN2*** (Presenilin 2)
  - ~25 Mutationen

“Next generation” genetic diagnostics

→ Fast and efficient sequencing of gene panels