Familial amyloidotic polyneuropathy

Hereditary transthyretin amyloidoses (ATTR)

E. Hund, Heidelberg

Familial transthyretin amyloidosis

Etiology: genetically determined variants of physiological serum proteins

	Variant protein	*Abbreviation*
→	transthyretin (ca. 70%)	ATTR
others:	Apolipoprotein-A1 u. A2	AApoA1/A2
	Fibrinogen-Aα	AFib
	Gelsolin	AGel
	Lysozym	ALys
	Cystatin C	ACys
	Aβ-precursor protein	Aβ

Familial transthyretin amyloidosis (ATTR)

History of TTR amyloidosis:

1949 Ostertag: „Familiäre Amyloidoseerkrankung“

1952 Andrade: „Peculiar form of peripheral neuropathy: Familial atypical generalized amyloidosis“

Familial amyloid polyneuropathy (FAP), „Mal dos pésinhos“

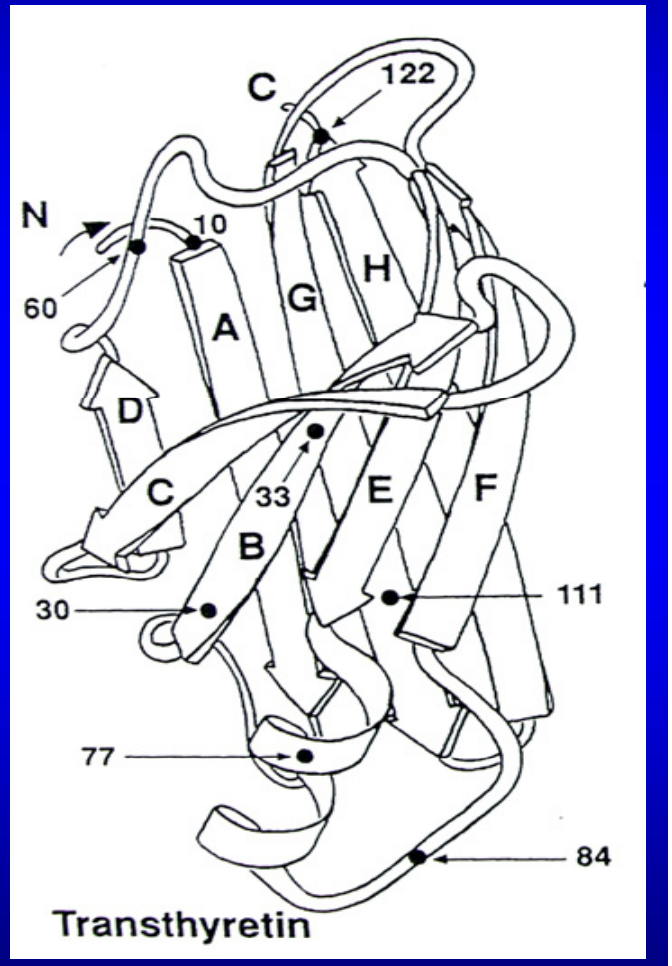
1978 Prealbumin (TTR) identified as the main component

1983 TTR-Met30 as the first identified mutation

Familial transthyretin amyloidosis (ATTR)

TTR: structure and genetic variants

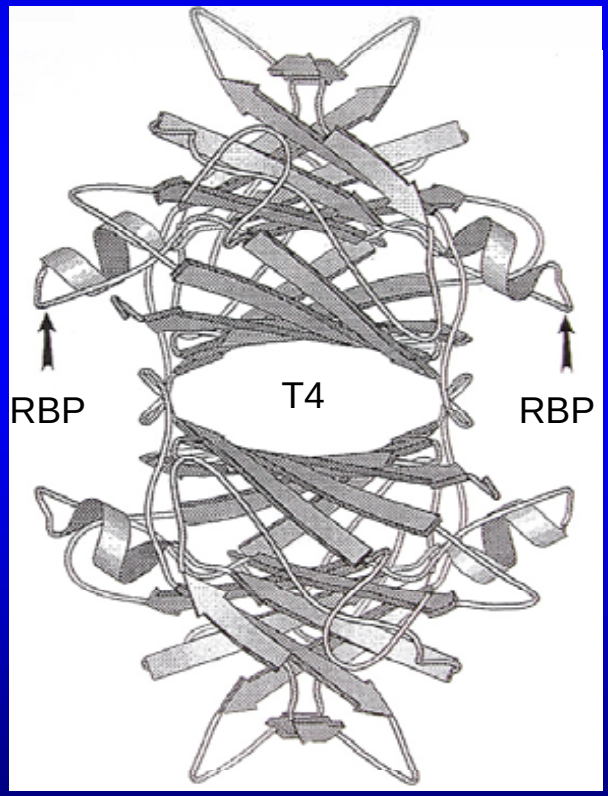
- *most frequent cause of ATTR*
  - over 100 mutations known,
  - mainly point mutations,
  - autosomal dominant inheritance
- *8 antiparallel β-chains*: native protein is weakly amyloidogenic (→ SCA, SSA)
- stable tetramer binds T4 and RBP

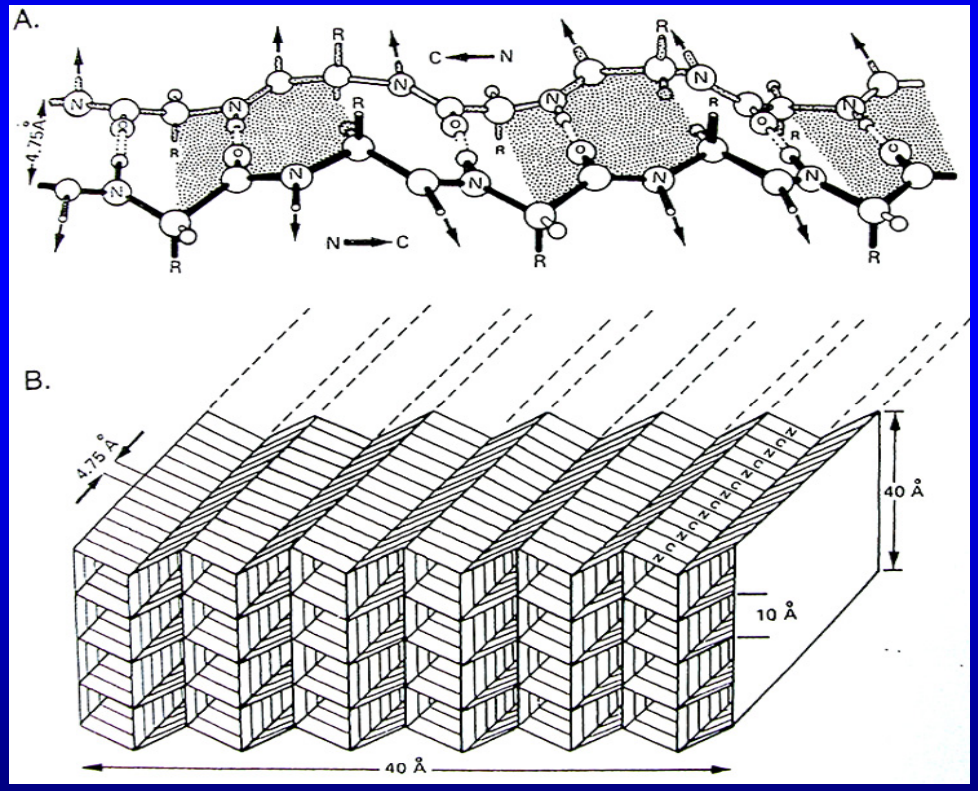


Main synthesis: liver (incretory)
Additional synthesis: retina, choroid plexus

Familial transthyretin amyloidosis (ATTR)

Conformational change into fibrillary protein matrix





Helix → (instable monomer) → β-sheet

Familial transthyretin amyloidosis (ATTR)

Clinical manifestations: organ involvement

FAP ⟷ FAC

- Peripheral nerve: polyneuropathy, CTS
- Heart: Cardiomyopathy (cardiac insufficiency, rhythm disturb.)
- Gut: diarrhea, often alternating with constipation
- Eye: various

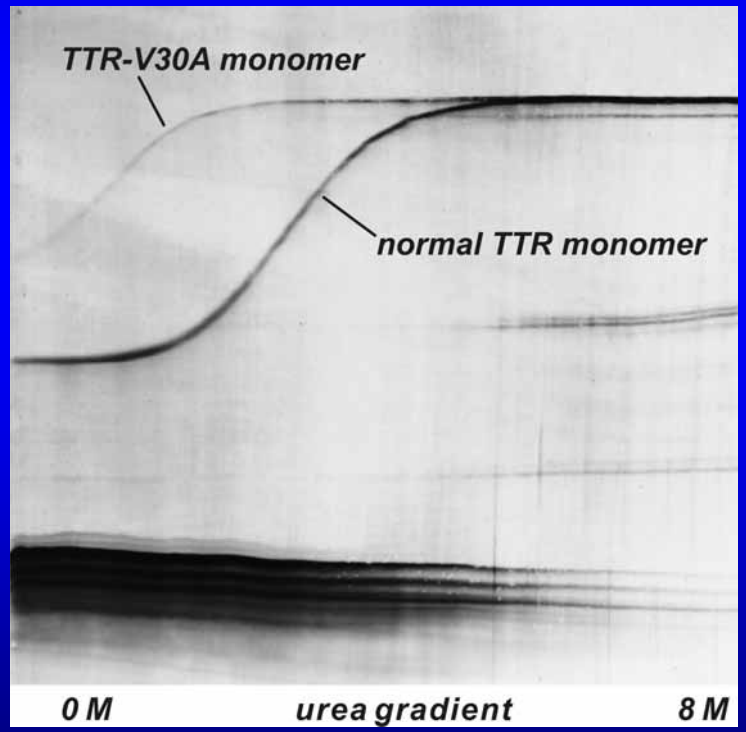
Only heart

Important: Kidney involvement only 10 %, liver never involved!!

Familial transthyretin amyloidosis (ATTR)

Diagnostics:

- biopsy with:
  - Congo red staining
  - immune histochemistry
- TTR electrophoresis
- molecular genetics



Familial transthyretin amyloidosis (ATTR)

Clinical particularities: two different age peaks

Peak age in Met30 mutations:

early onset (Portugal):	30-40 (33,5) yrs
late onset (Sweden):	50-60 (56,7) yrs !

In single cases as late as 78 yrs!

Familial transthyretin amyloidosis (ATTR)

Clinical particularities : isolated cases

- generally high proportion of „spontaneous“ cases:
  In French pts 65% with negative family history!

- low penetrance in Swedish patients:

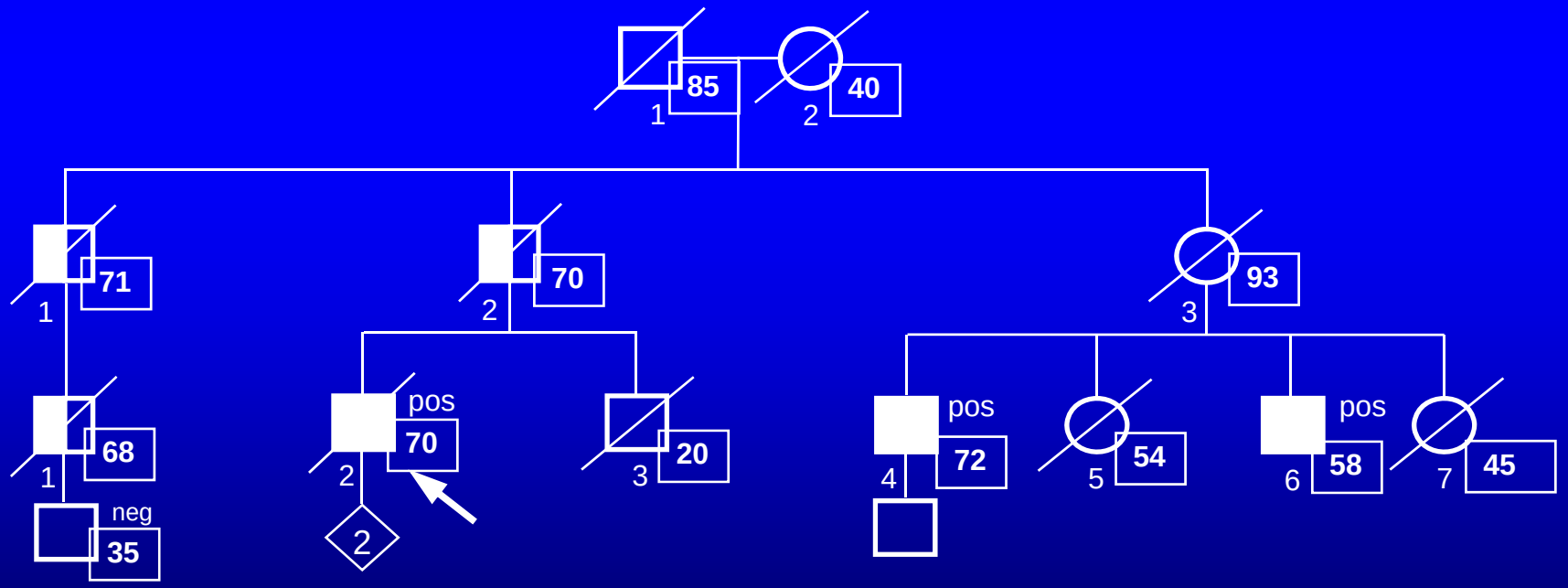
  by age 60 yrs: 22 %

  by age 90 yrs: 69 %

Therefore: numerous isolated cases!

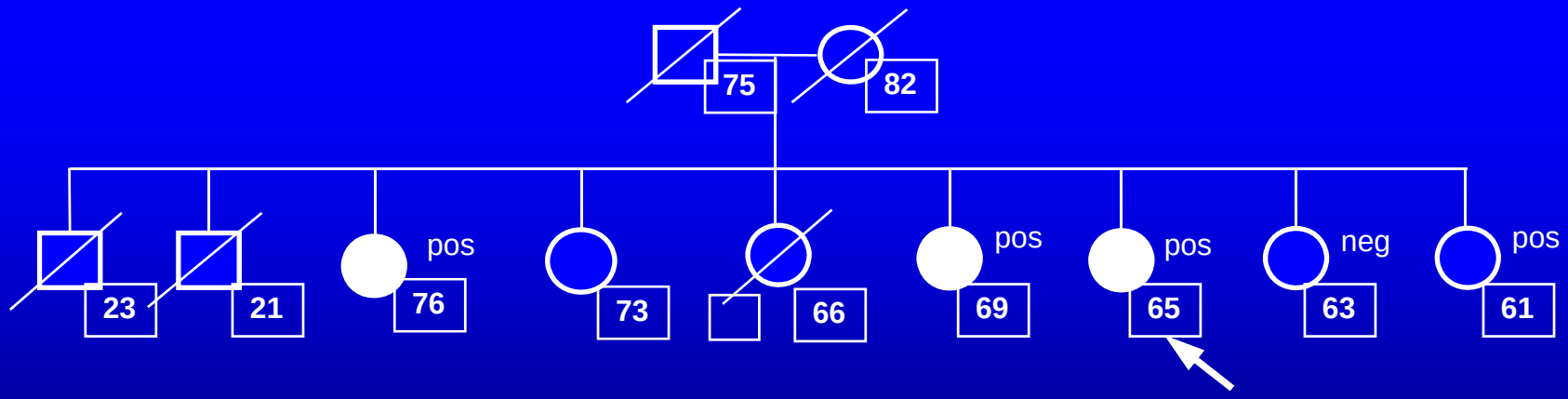
Familial transthyretin amyloidosis (ATTR)

Clinics: Tree of a TTR-Val107 family



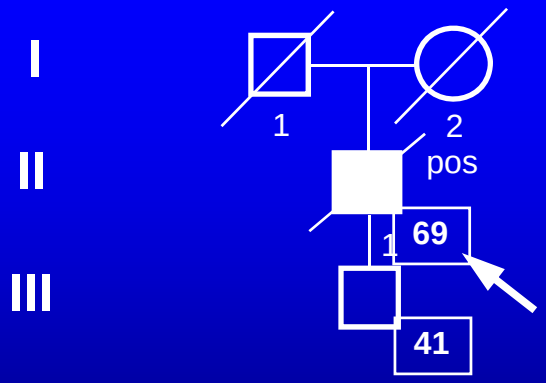
Familial transthyretin amyloidosis (ATTR)

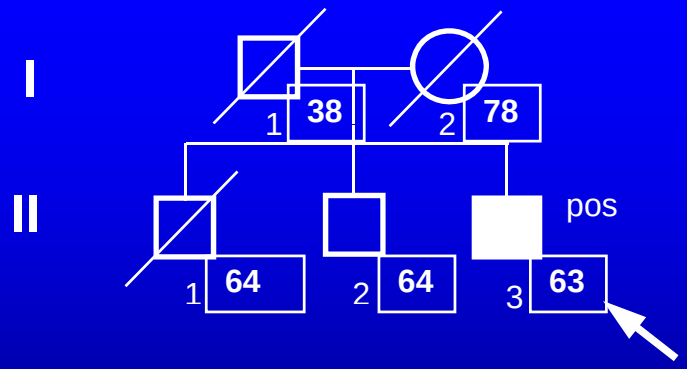
Clinics: Tree of a TTR-Val107 family



Familial transthyretin amyloidosis (ATTR)

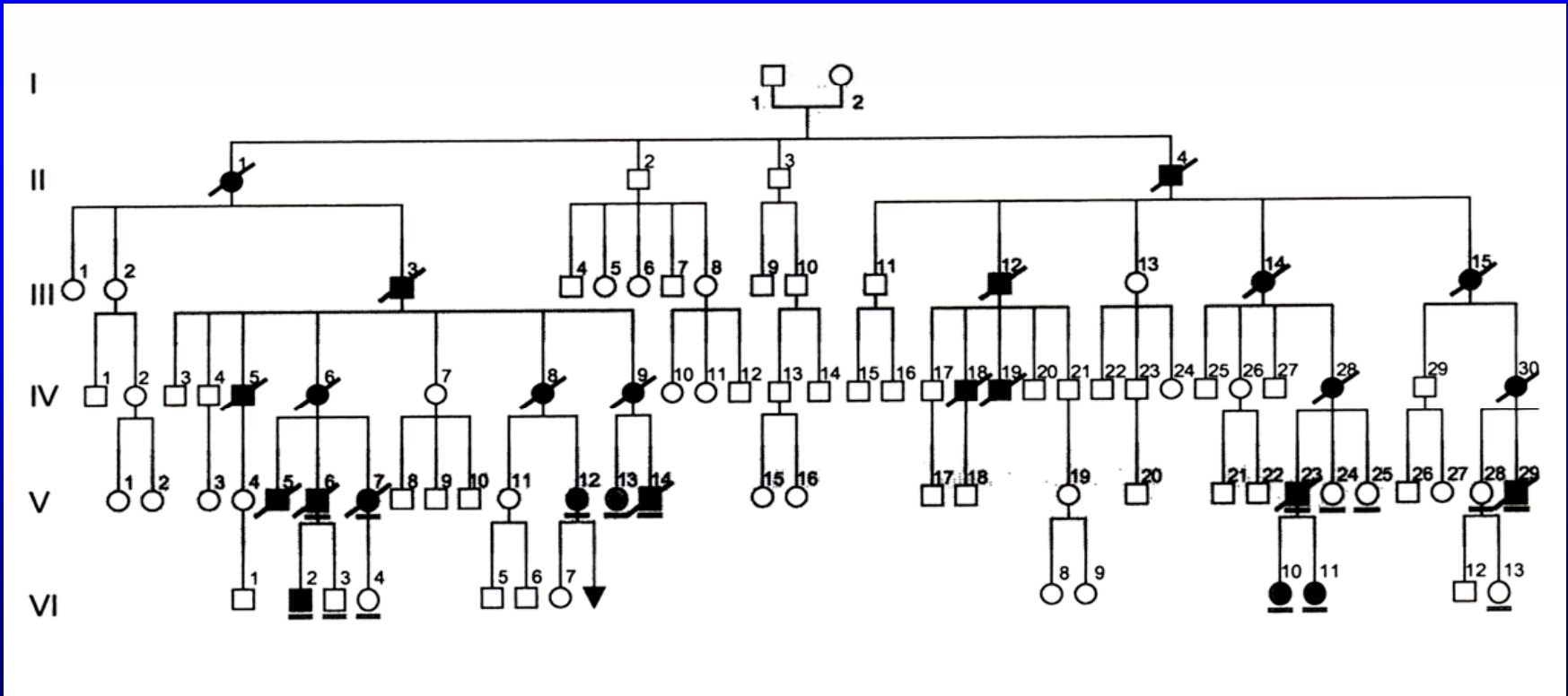
Clinics: Trees of singular TTR-Val107 probands





Familial transthyretin amyloidosis (ATTR)

Tree of a large family with the TTR-Met30 mutation

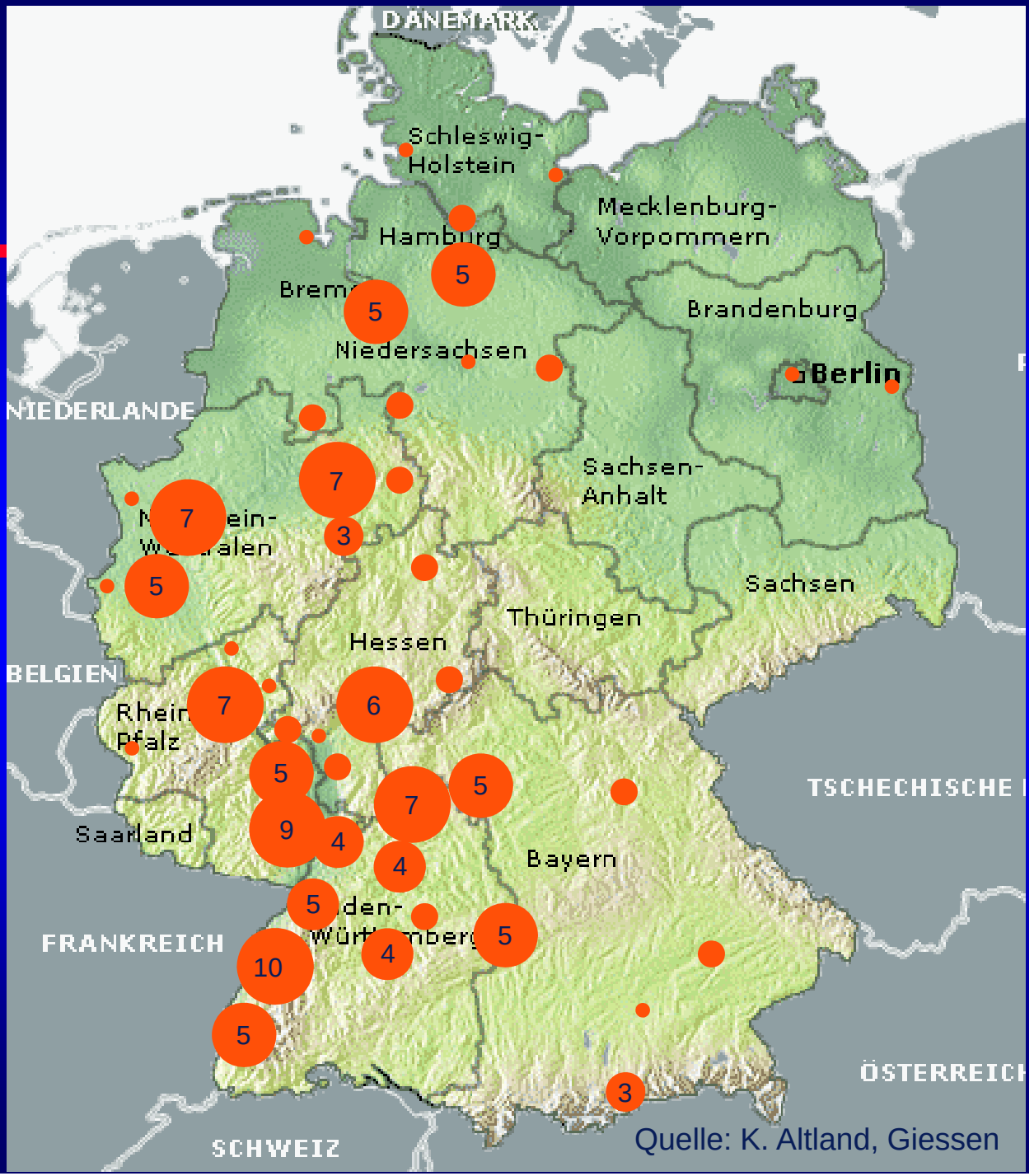


Quelle:
Prof. Willig

TTR mutations

Geographical distribution in GER

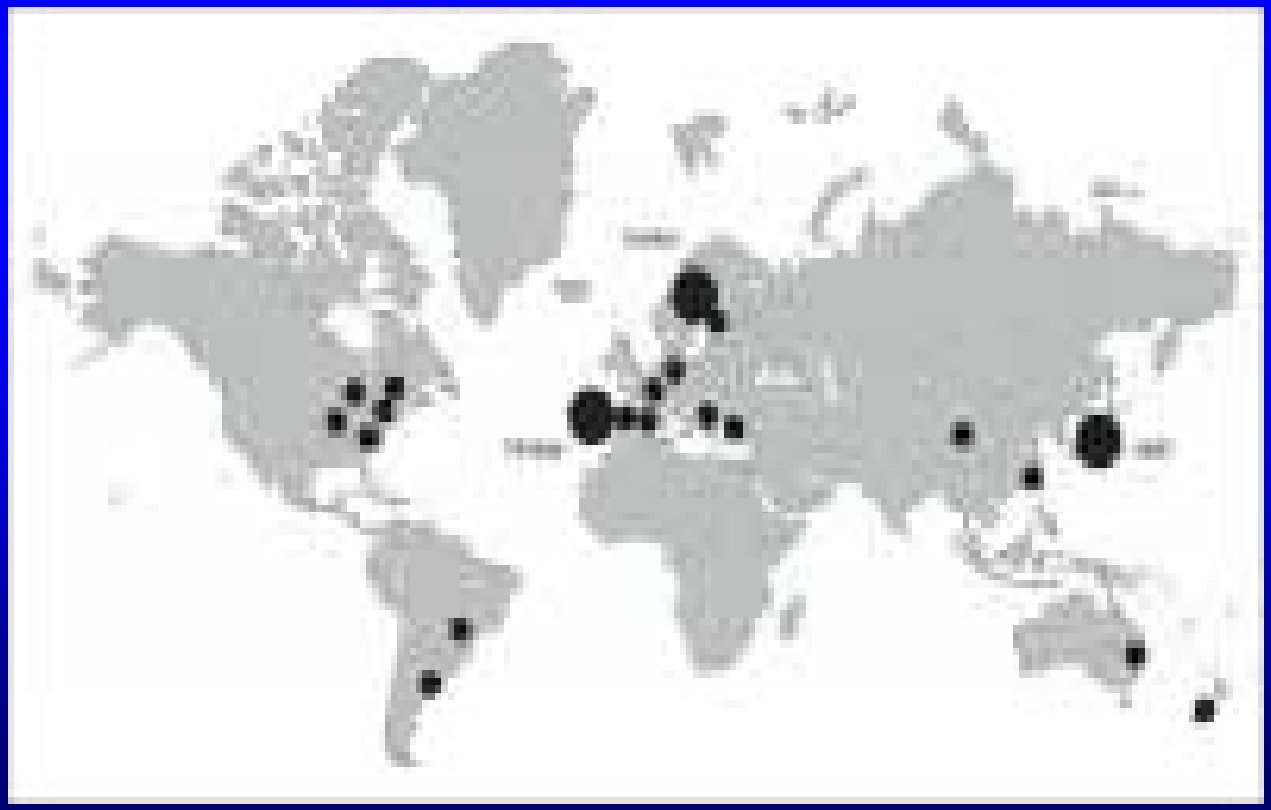
- 1 proband
- 2 probands
- 3 probands
- 4 probands
- 5 probands
- 6 and more



Quelle: K. Altland, Giessen

Familial transthyretin amyloidosis (ATTR)

Geographical distribution of hitherto identified cases:



Familial transthyretin amyloidosis (ATTR)

Prognosis:

Survival time:	5-15 yrs (P), 10-15 yrs (S)
Cause of death:	Cachexia or cardiac crisis

Familial transthyretin amyloidosis (ATTR)

Therapy:

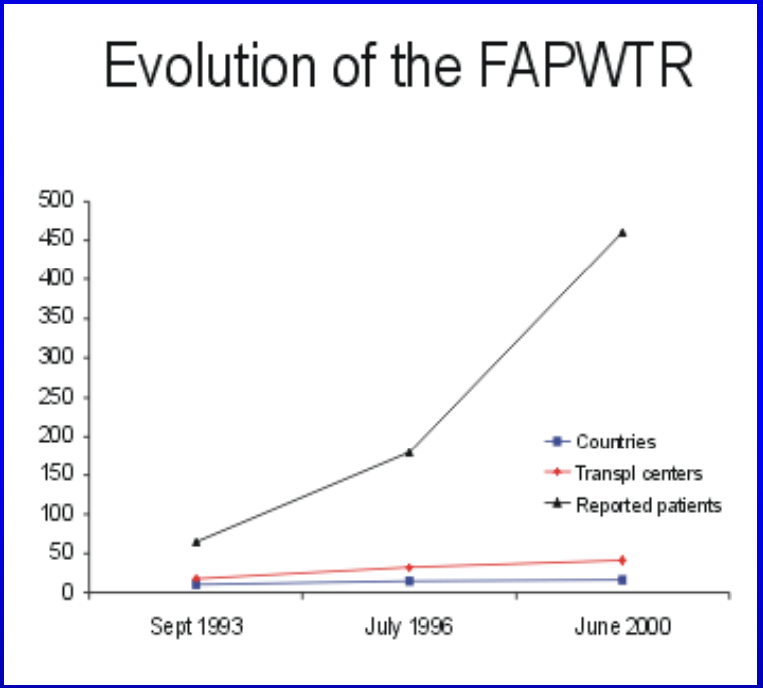
Liver transplantation (OLT)

Rationale:

Elimination of the main production site of variant TTR

Actually 110 OLTs/yr

By now over 1500 OLTs worldwide



Source: World Transplant Registry (www.fapwtr.org)

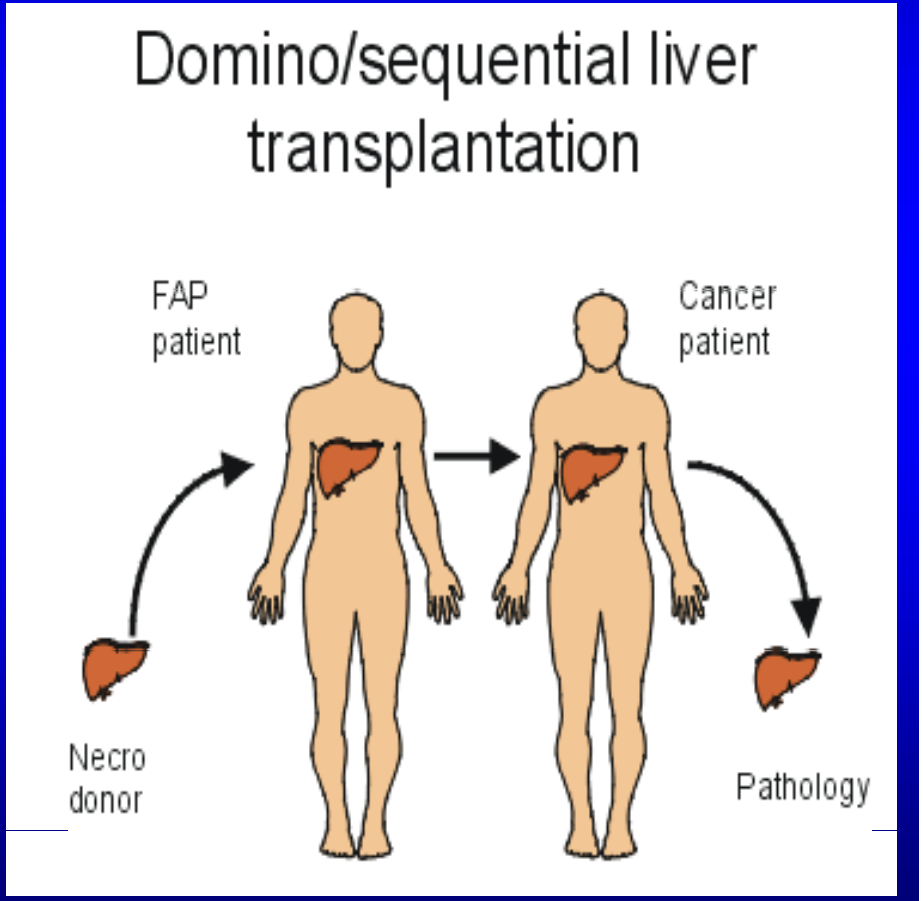
Familial transthyretin amyloidosis (ATTR)

Therapy:

liver transplantation (OLT)

Technique:
Domino-Tx,
today app. 80 DLTs/yr

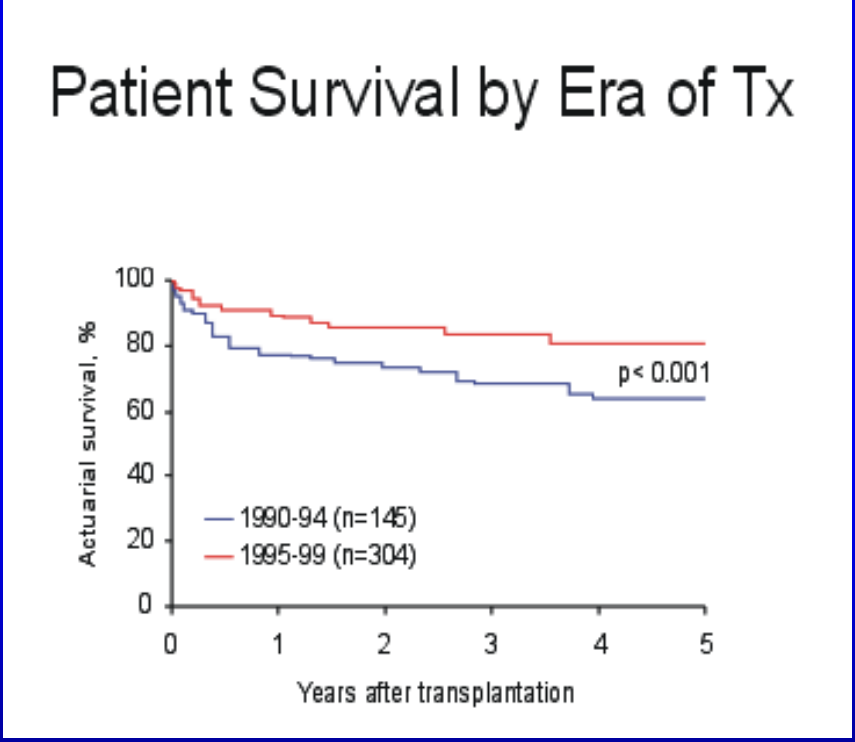
Risk:
TTR amyloidosis in the recipient
after 20 - 30 yrs possible



Familial transthyretin amyloidosis (ATTR)

Therapy: liver transplantation

Outcome:
5-year survival time with today's OP techniques and strategies excellent

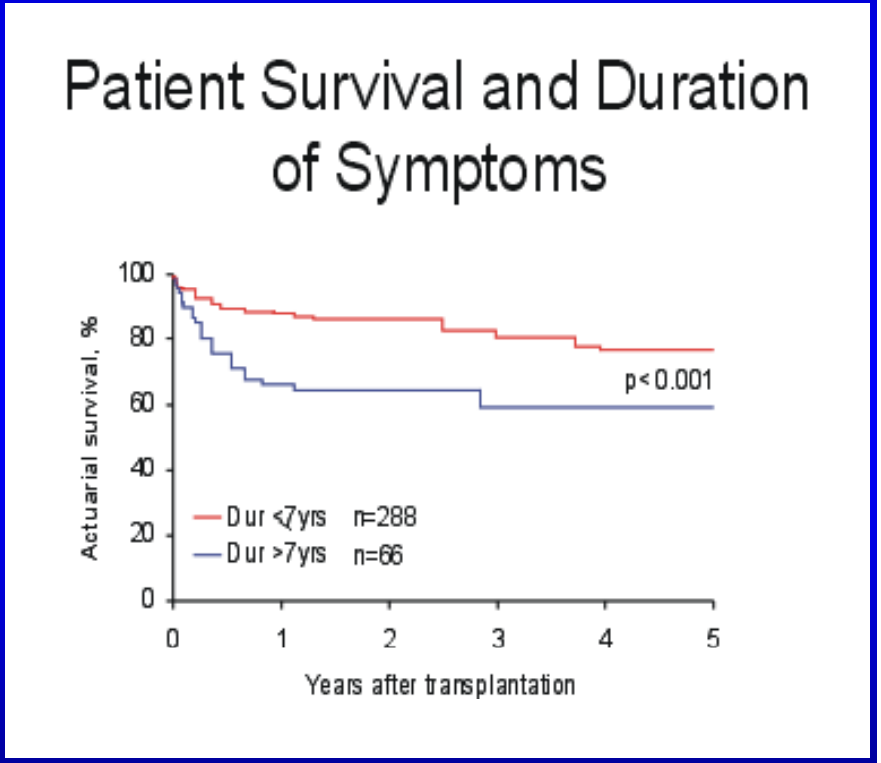


Source: World Transplant Registry (www.fapwtr.org)

Familial transthyretin amyloidosis (ATTR)

Therapy: liver transplantation

Outcome:
dependent of
- duration of symptoms
- i.e. with late operation prognosis is worse

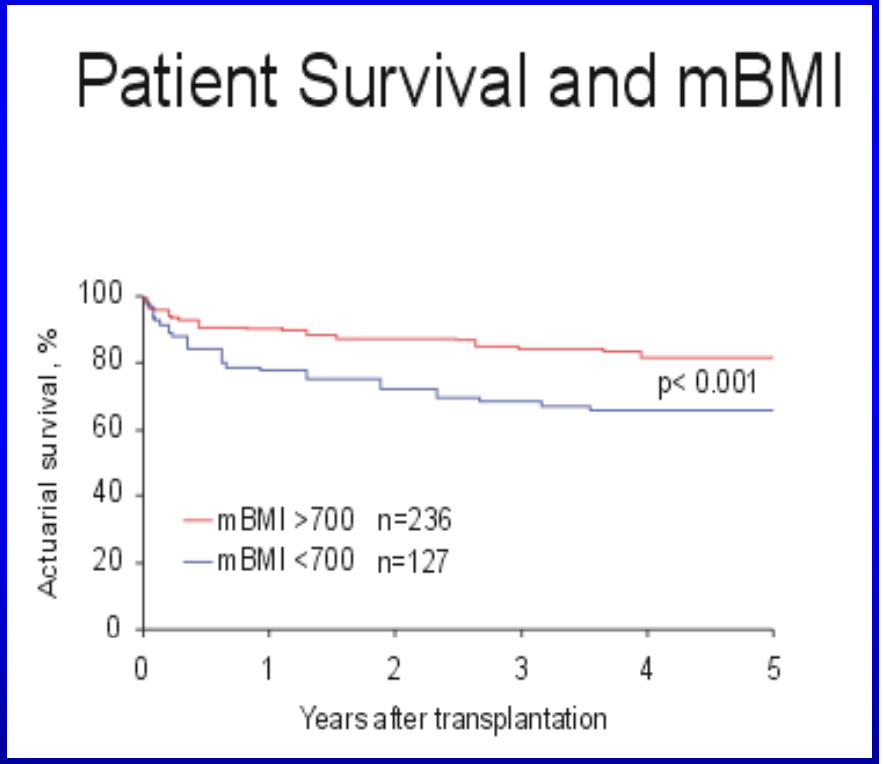


Source : World Transplant Registry (www.fapwtr.org)

Familial transthyretin amyloidosis (ATTR)

<u>Therapy</u>: liver transplantation

Outcome:
dependent of
- Body mass index
- i.e. with late operation prognosis is worse



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Conclusions

1) Hereditary TTR amyloidoses are systemic disorders with
   - rapidly progressing, invalidazing motor-sens.-autonome PNP
   - cardiac involvement limits outcome
   - isolated cardiac amyloidosis is typical of several mutations

2) TTR amyloidoses are characterized by two different age peaks (early vs. late onset / Portuguese vs. Swedish type)

3) Familiy history is frequently negative

4) Early liver Tx is the only available therapy