Familial Amyloidosis
Yesterday, today, and tomorrow

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Familial Amyloidosis Support Group Meeting
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Yesterday, today, tomorrow…

- Yesterday
  - History and nomenclature
  - Making the correct diagnosis
  - What families could expect

Discovery and identification of amyloidosis

1854 Discovery

Virchow VR.
Ueber einem Gehirn and Rueckenmark des Menschen auf gefundene Substanz mit chemischen reaction der Cellulose.
Virchows Arch Pathol Anat 1854;6:135-8.

1922 Identification by Congo Red staining

Bennhold H.
Eine spezifische Amyloidfärbung mit Kongorot.
Munch Med Wochenschr 1922;97:1537-8.

Discovery of systemic amyloidosis types…

1959	Amyloid fibril ultrastructure identified
1971	Primary amyloid: immunoglobulin light chain
1972	Secondary amyloid: subunit of the acute phase SAA protein
1981	Familial amyloid: transthyretin (gene mutations)
	Rare forms of familial amyloidosis

Classification of systemic amyloidosis

AL: Immunoglobulin light chain, kappa or lambda

ATTR: Transthyretin, ~100 variant forms cause amyloidosis

Rare familial:

AApo AI Apolipoprotein AI,

AApo AII Apolipoprotein AII,

AFib Fibrinogen,

ALys Lysozyme,

AGel Gelsolin

AA: Portion of serum amyloid A protein (SAA)

Distribution of common systemic types of amyloidosis…

AL :	80% of all amyloidoses
ATTR :	10% of all amyloidoses
Rare familial:	1% of all amyloidoses
AA :	2% of all amyloidoses

Familial (ATTR) amyloidosis

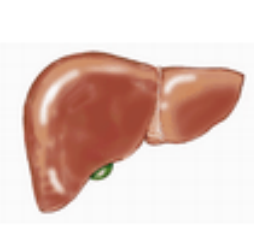
Trans thy retin is a transport protein for thyroid hormone and retinol binding protein

Cause: Autosomal dominant inheritance of a mutant transthyretin gene (100+ known, most cause amyloidosis)

Onset age: 20's-old age; same within family; onset for women is a little later than for men

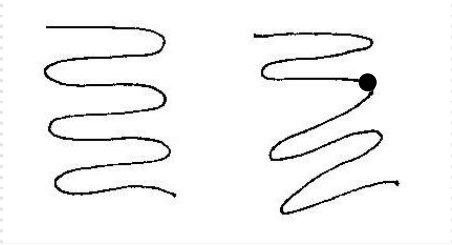
Survival: 7-15 years from diagnosis

TTR amyloid pathogenesis…



transthyretin

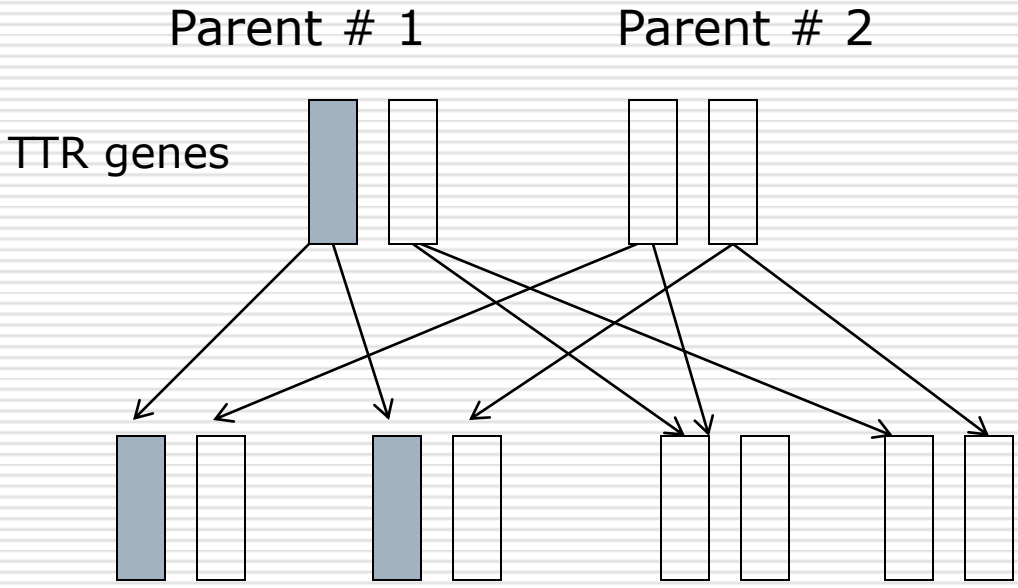
127 amino acids
(building blocks)



Normal TTR Mutant TTR

amyloid deposits

Autosomal dominant inheritance…



Each child has a 50-50 chance of inheriting the mutant gene

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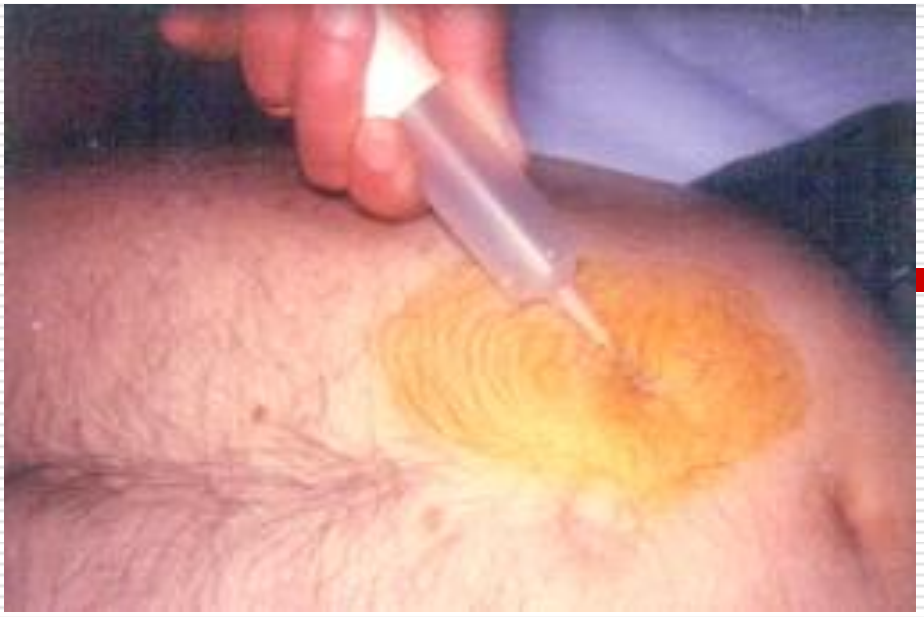
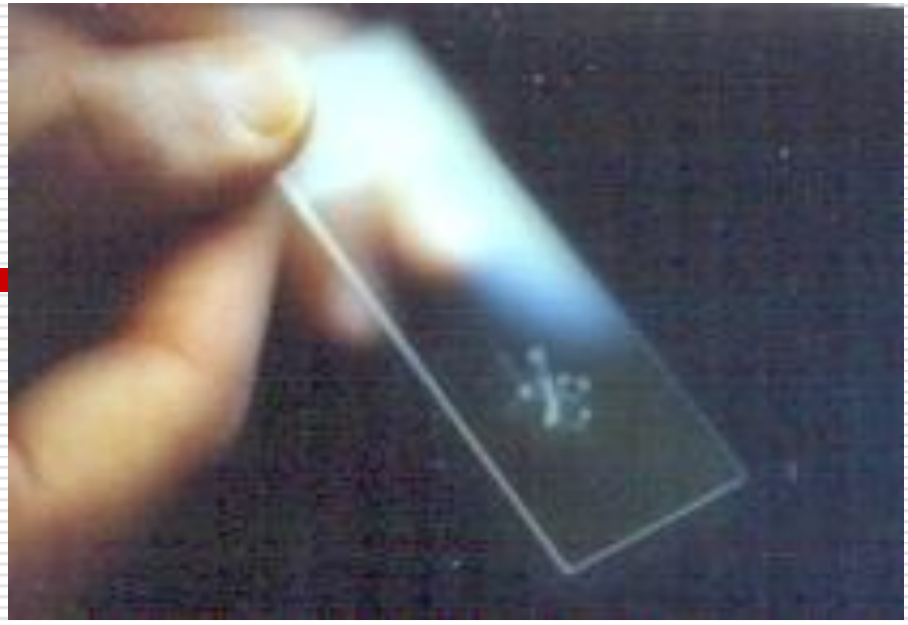
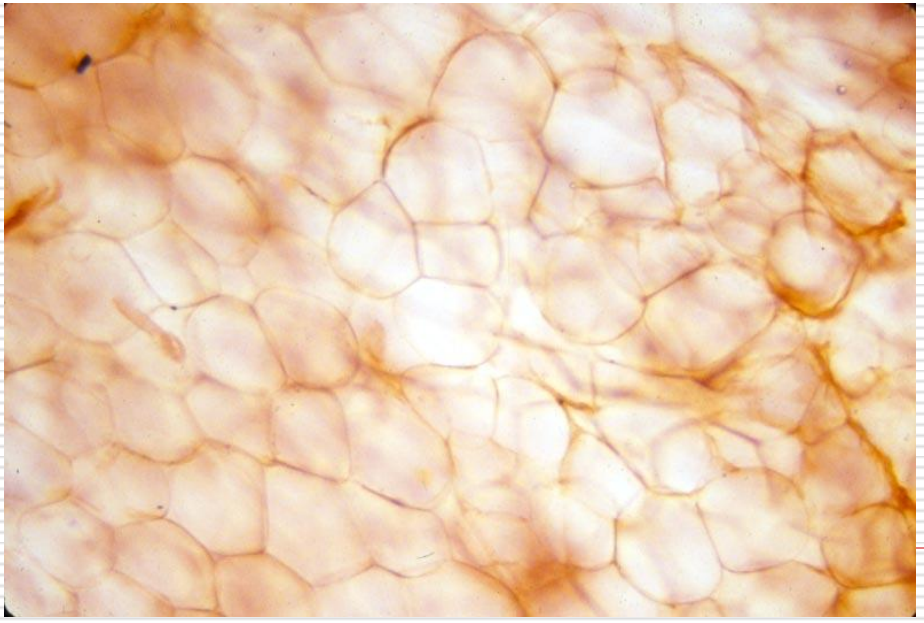
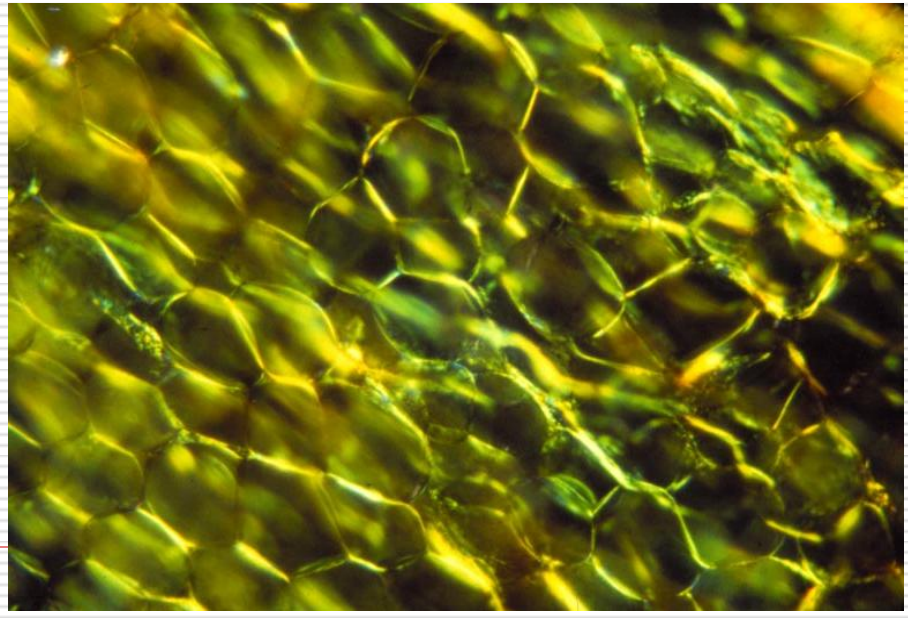
Making the correct diagnosis

- Tissue biopsy positive for amyloid
- Look for variant protein and/or gene mutation

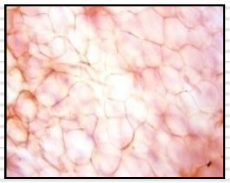


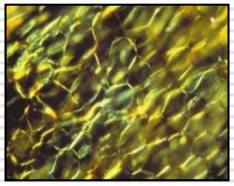






Diagnosing the amyloid type…

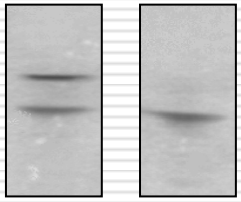




Fat or Tissue Biopsy (+)

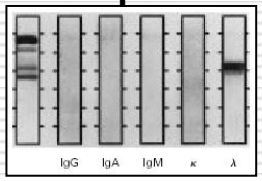
Clinical Features
ATTR: neuropathy, cardiomyopathy, vitreous opacities
AL: proteinuria, macroglossia, neuropathy, hepatomegaly
Family History: yes or no

Isoelectric Focusing

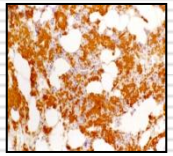


(+) **(-)**

Immunofixation Electrophoresis



Bone Marrow Biopsy



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Other Amyloid Diseases

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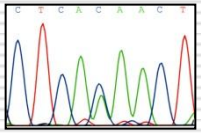
Light Chain Amyloidosis

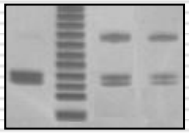
Mass spec for sequence variations and post-translational modifications

Molecular Genetics

DNA



RFLP



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Other Amyloid Diseases

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TTR Amyloidosis

•Yesterday, today, tomorrow…

- Yesterday
  - History and nomenclature
  - Making the correct diagnosis
  - Disease in patients; impact on families

Case 1

- 33 year old man of came for evaluation in 1976. Had onset of severe neuropathy at age 26 and diagnosis of Charcot-Marie Tooth disease, similar to his mother.
- Sensory loss in legs, arms, chest
- Motor loss with weakness of lower legs; urinary incontinence
- Autonomic neuropathy with orthostasis (BP 80/60 on standing); severe diarrhea and a 30 lb wt loss

Case 1 (con't)

- Died at age 36 of progressive disease; bed sores, sepsis, malnutrition, renal failure (due to antibiotics).
- Studies on his amyloid protein found familial amyloid to be TTR.

(The prealbumin nature of the amyloid deposits in FAP-Swedish variety, BBRC 99: 1326, 1981)

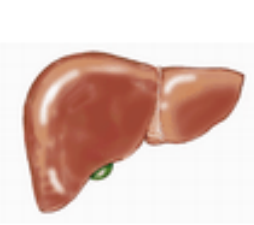
Case 1, sister

- 4 years younger than her brother, mother of 2 young children; she and husband were farmers
- At age 32 (time of brother's death) could not wear shoes because feet hurt; had to stop helping with the farm work
- Four years later, when testing available, she was tested for the mutant gene

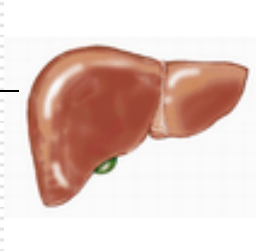
Yesterday, today, tomorrow

- Diagnostic techniques in place commercially and at specialized centers, but even so, often diagnosis is late
- Major treatment available for some individuals since 1992
- Family impact

Treatment of familial TTR amyloidosis



orthotopic liver transplant



mutant TTR

normal TTR

Aggressive treatment
Mortality and morbidity risk

Requires: Early disease status
Availability of donor

Yesterday, today, tomorrow…

- Medical knowledge to support early diagnoses and even better, presymptomatic diagnoses.
- Treatment options, some even before disease begins
- Family impact hopefully minimal

ATTR tomorrow…

Diagnosis: IEF screening test and DNA sequencing for at-risk family members

- ✓ Important to look for TTR mutation in all Black individuals with cardiomyopathy

Major treatment will have options that will be available worldwide:

1. liver transplantation
2. diflunisal: multicenter international clinical trial in progress
3. FoldRx1006A: multicenter international trial in review
4. more options needed, ALN-TTR

Supportive treatment

1. For heart:

   diuretics; low salt diet; rhythm control, if necessary

2. For peripheral neuropathy:

   medications; active exercises; ankle braces; foot care

3. For autonomic neuropathy: BP and GI

   midodrine for low BP, elastic stockings

   low fat diet, meds for diarrhea, food supplements, etc

4. Genetic counseling: new GINA information

Genetic Information Nondiscrimination Act (GINA)

- 2000 President signed order to protect federal employees from genetic discrimination in employment
- 2008 Congress finally passed GINA
- May 21, 2009 health insurance protection
- November 21, 2009 employment protection

In making decisions about your health insurance or employment, GINA prohibits:

- Using genetic test results on you
- Using genetic tests from a family member,
- Using manifestations of a genetic disease in the family
- Using the participation of you or family in genetic research

Also GINA prohibits….

- Insurers from using genetic information to set health insurance eligibility or premiums
- Insurers from requiring an individual to take a genetic test
- Using genetic information for hiring, firing, or promotions in employment decisions

GINA con't

- Legislation varies by state in protections provided
- Allows individuals experiencing discrimination to file a civil suit (damages capped at $300,000. plus back pay)

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