Familial Amyloidosis: What is it? How is it inherited?

Amyloid Support Group Familial Amyloidosis Meeting
Chicago, Illinois
Saturday, October 29, 2011

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Boston Amyloid Treatment and Research Center

BOSTON UNIVERSITY School of Medicine

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When was TTR amyloid discovered?

- 1854 Virchow (Germany) Discovery of amyloid in tissue
- 1952 Andrade (Portugal) A peculiar form of peripheral neuropathy (Brain journal)

Dr. Andrade reported an amyloid disease prevalent in one area of northern Portugal. He showed that it was inherited and caused neuropathy in mid-life.

First Symposium, Groningen 1967

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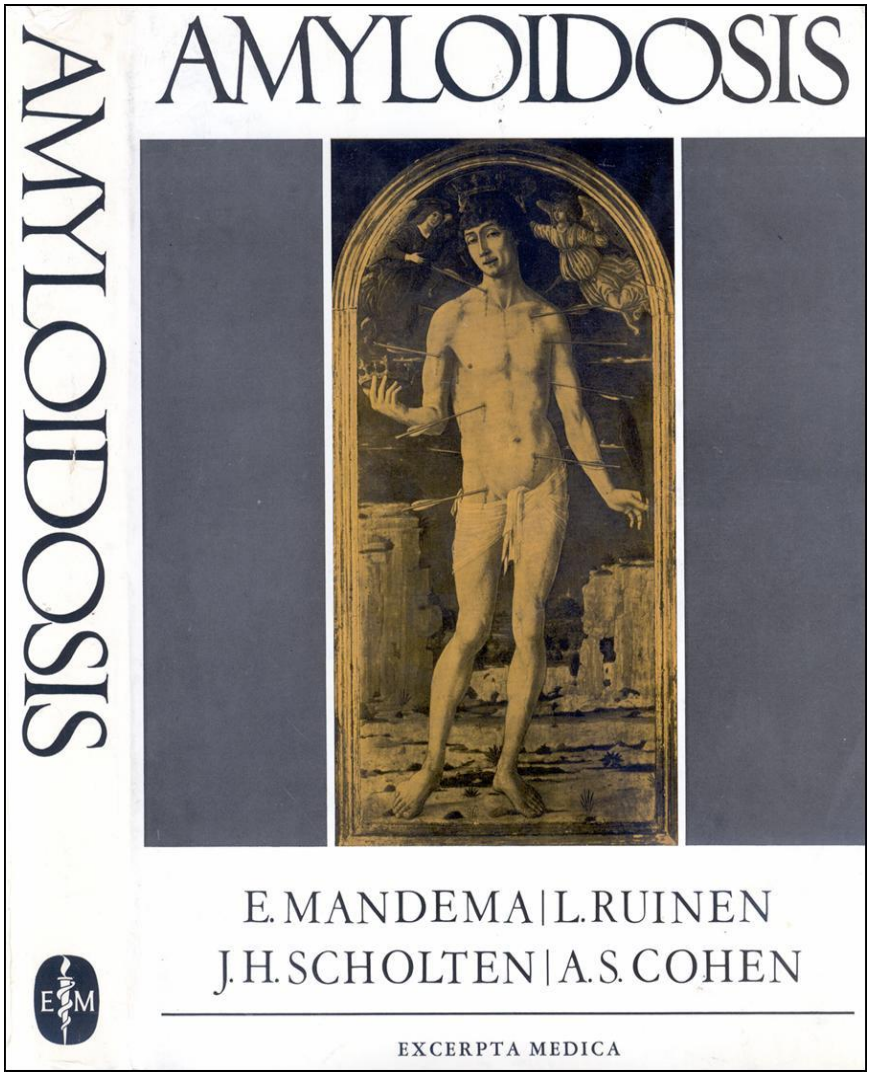
First Symposium Proceedings…



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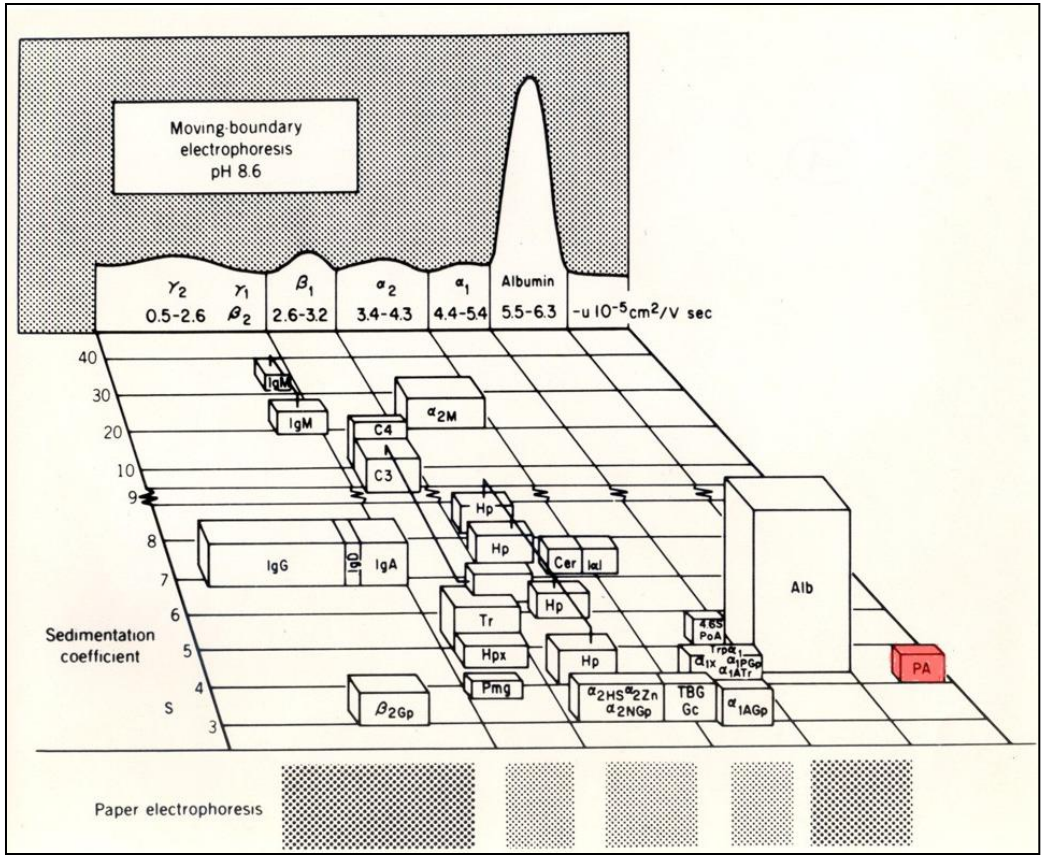
1967 1st Symposium on Amyloidosis

- 6 clinical reports: FAP; Secondary (AA); diagnostic tests; 3 reports on amyloid and aging
- Familial amyloidotic polyneuropathy, Dr. Andrade reported 696 cases in 173 families in northern Portugal (Povoa de Varzim)
  - proved the hereditary nature of the disease
  - showed degeneration of peripheral nerves by pathologic examination
  - "no mild cases"

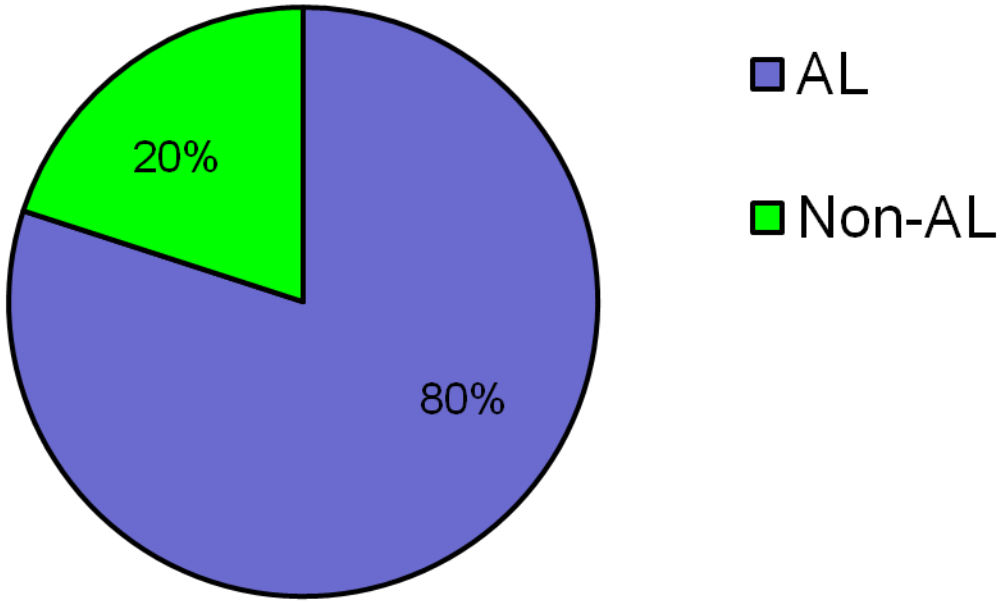
Further studies….

- 1978 — Amyloid deposits stained with antibody to prealbumin (TTR)
- 1981 — Amyloid fibrils proven to be prealbumin
- 1983 — First discovery of prealbumin gene mutation (Val-30-Met)
- 1986 — Prealbumin re-named trans thy retin
- 1983-present — More than 100 pathologic TTR mutations discovered

Prealbumin aka transthyretin



Systemic amyloidosis:



Systemic non-AL amyloidoses

- AA (or secondary) 2%
- Age-related (senile) systemic amyloidosis 2-3%
- Familial forms due to gene mutations
  - ATTR 10-12%
  - Apolipoprotein AI < 1%
  - Apolipoprotein AII < 1%
  - Fibrinogen A alpha < 1%
  - Lysozyme < 1%
  - Gelsolin < 1%

When were rare familial types discovered?

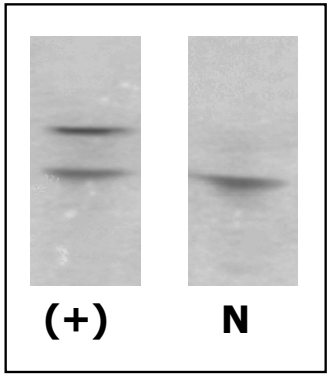
Type	Discovery	# mutant forms	Clinical feature *predominant
Apolipoprotein AI	Benson, 1988	15	kidney*, liver, heart, skin
Apolipoprotein AII	Benson, 2001	5 (all stop codons)	kidney
Fibrinogen A α	Benson, 1993	9	kidney*, nervous system
Lysozyme	Pepys, 1993	6	kidney*, GI, skin
Gelsolin	Maury, 1990	2	cranial neuropathy*, cornea, kidney

Making the correct diagnosis

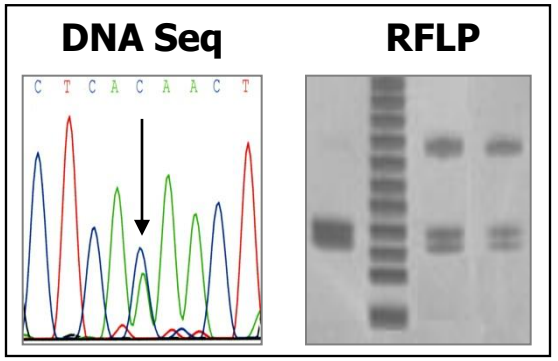
- Tissue biopsy positive for amyloid
- R/O AL and AA amyloidoses
- Confirm tissue type by immunohistochemistry with antibody to specific protein (or mass spec, if avail.)
- Confirm all inherited forms by genetic analysis of patient's DNA

Diagnostic testing

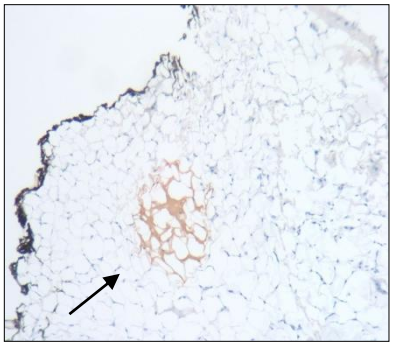
- Isoelectric focusing: <u>detection</u> of variant TTR protein in serum



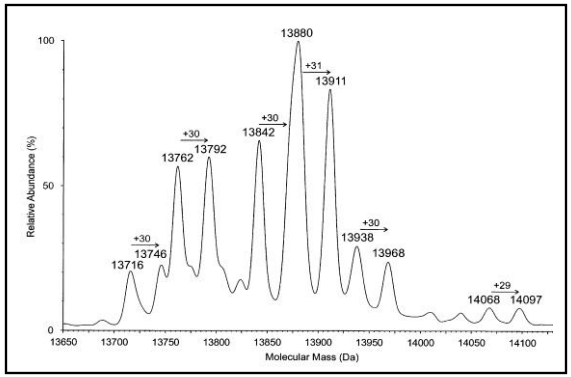
- Genetic analyses: <u>identification</u> of gene mutation



- Immunohisto-chemistry: <u>identification</u> of deposited protein in fat or tissue biopsies



- Mass spectrometry: <u>characterization</u> of TTR variant



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Senile systemic amyloidosis (SSA)

- Caused by wild-type TTR
- Heart predominant organ involved
- Older age; mostly men
- Also called age-related amyloidosis or senile cardiac amyloidosis

SSA diagnosis made by:

- Tissue biopsy positive for amyloid
- Amyloid deposits positive for TTR
- TTR genetic testing negative for a TTR mutation
- Clinical picture of older person, most likely with cardiomyopathy and without multisystem disease

THE AUSTIN DAILY TEXAN, 3/25/08

114-year-old Arbella Perkins Ewings, considered the oldest person in Texas, died Saturday at a Dallas retirement home.

At 114, one of Texas' supercentenarians dies

By: Andrew Kreighbaum

Posted: 3/25/08

Genes and lifestyle choices are known to prolong a person's life, but caretakers of the oldest Texan say faith kept her active for more than a century.

Arbella Perkins Ewings of Dallas was 114 years old when she died Saturday. She was one of a small subset of Americans called supercentenarians - people who have exceed the age of 110. Ewings had been living at home before she was moved into a nursing home to receive treatment for a broken hip.

Female supercentenarians are statistically dominant, outnumbering men in the group by as many as 10-to-1. Coles speculated that the XX chromosome structure in a woman's genome may act as a compensation measure. Men only have one X chromosome, and if it is defective he cannot compensate for it as a woman could.

The cause of death of most supercentenarians is TTR-amyloidosis, a failure of a thyroid hormone that controls metabolism and maintains body temperature.

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Familial (ATTR) amyloidosis:
most common familial form

Trans thy retin	is a transport protein for thyroid hormone and retinol binding protein
Cause:	Autosomal dominant inheritance of a mutant transthyretin gene (100+ variants, 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

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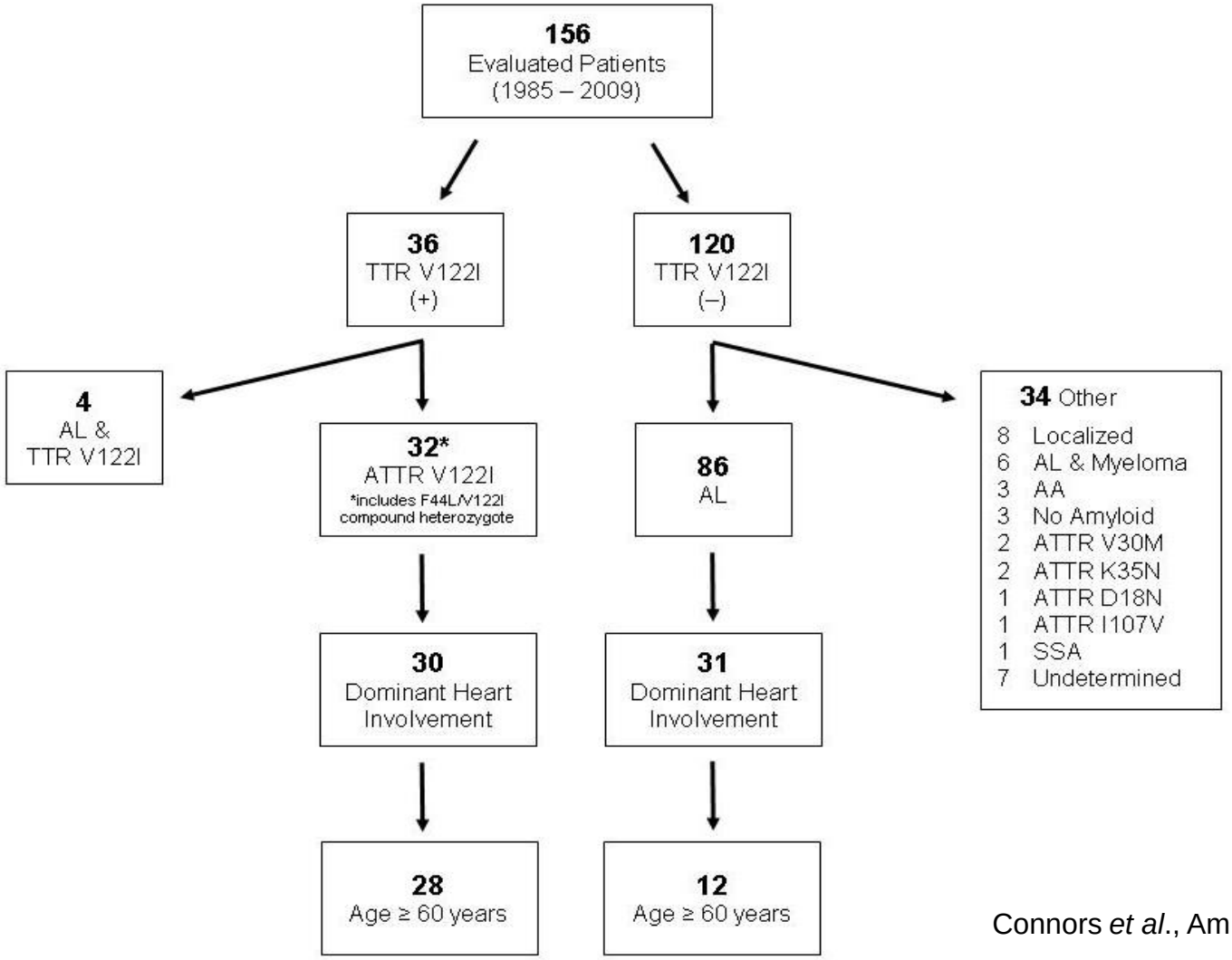
TTR mutation: V122I

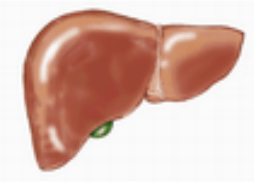
- variant TTR present in 4% of individuals of African ancestry
- associated with cardiomyopathy of late onset
- incidence of disease unknown

TTR-V122I in Black patients with amyloidosis



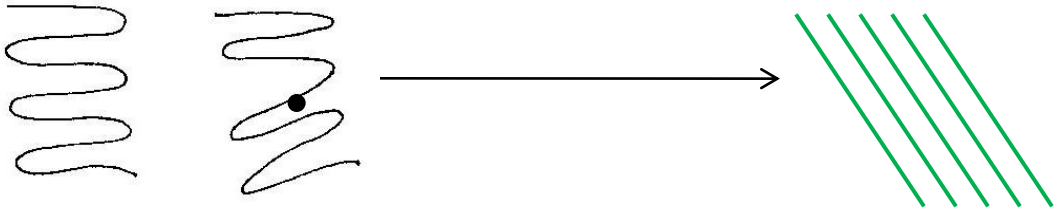
Connors *et al.*, Am Heart J, 2009

TTR amyloid pathogenesis…



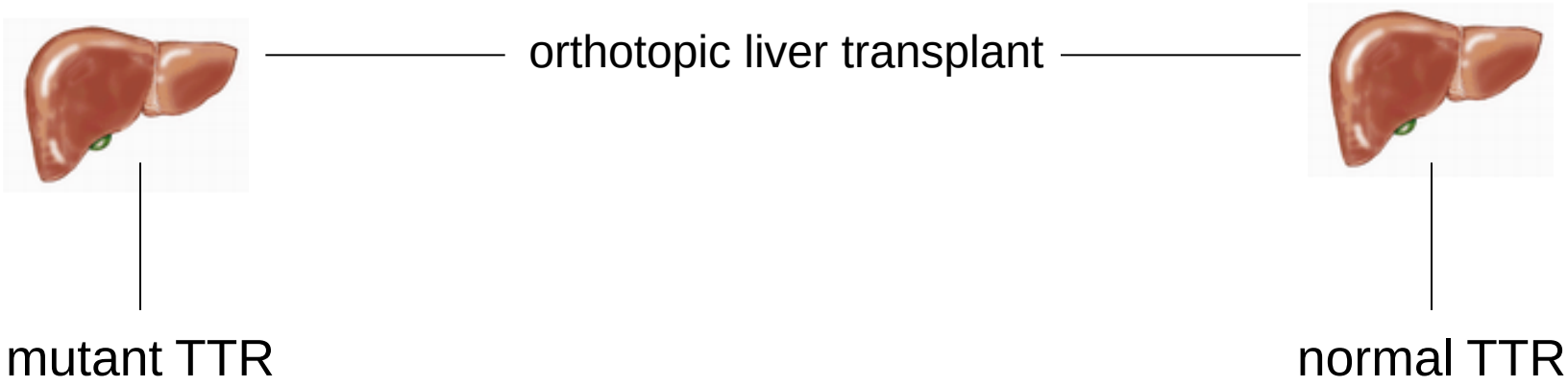
transthyretin

127 amino acids
(building blocks)



Normal TTR Mutant TTR amyloid deposits

Treatment of familial TTR amyloidosis



Aggressive treatment

Significant mortality and morbidity risk

Requires: Early disease status & availability of donor

Diagnosis and treatment of ATTR amyloidosis

Diagnosis:

IEF screening test will show variant protein in serum; DNA sequencing necessary for diagnosis of mutation.

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

Major treatment:

- liver transplantation
- diflunisal: multicenter international clinical trial in progress
- Tafamidis (Pfizer) multicenter international trial awaits FDA approval
- ALN-TTR-NT-001 (Alnylam) in clinical trial in Europe
- ISIS
- Other

ATTR 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

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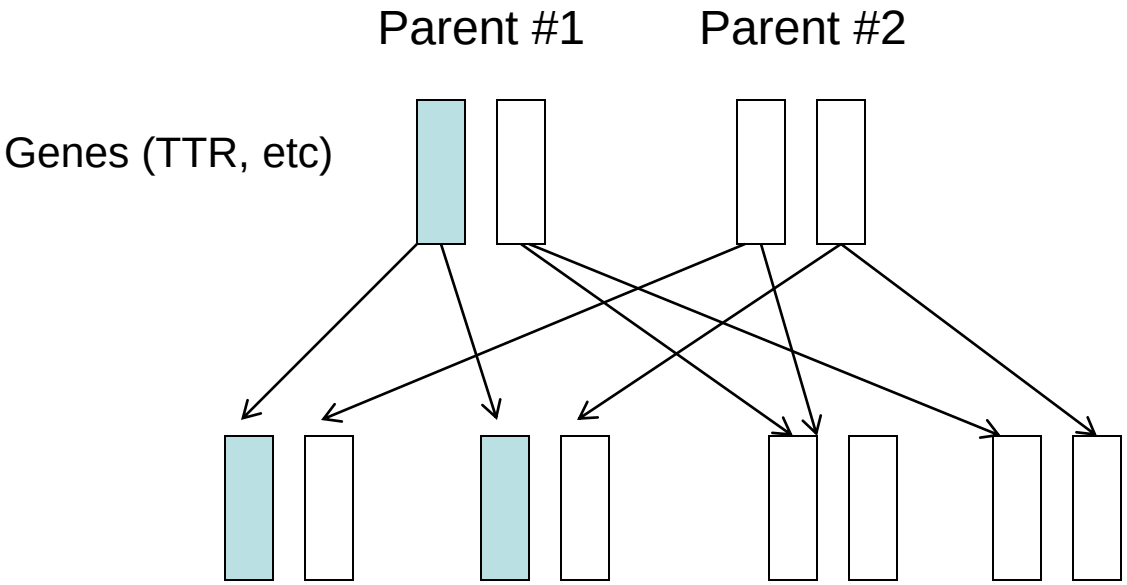
Treatment of rare types of familial amyloidosis

Type	Prognosis	Treatment
Apolipoprotein AI	Slow to progress	Made in liver (and GI); kidney or kidney/liver transplant
Apolipoprotein AII	Rare; early (30s); slow to progress	Renal transplant gives favorable results
Fibrinogen A α	After onset, rapid progression to azotemia	Made in liver; good prognosis with liver transplant
Lysozyme	Slow to progress	Made in PMNs and macrophages; No specific treatment; renal transplant leads to good outcome
Gelsolin	Slow to progress	No treatment; plastic surgery

Autosomal dominant inheritance…



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

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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Support

- Patients
- Gruss & Wildflower Foundations
- PO1 HL 068705
- RO1 DK 090696
- RO1 AG 031804

Clinical Team

- Amyloid: Skinner, Libbey, Cowan, O'Connell
- Hematology: Seldin, Sanchorawala, Sloan, Andrea, Lerner, Quillen
- Transplant & Clinical Trials: Finn, Shelton, Brauneis, Fennessey
- Apheresis Program: Quillen
- Pulmonary: Berk
- Cardiology: Ruberg, Meier-Ewert
- Renal: Dember, Stern, Havasi

Research Team

- Gerry Lab: Connors, Spencer, Chan, Prokaeva, Klimtchuk, Koch, Lu
- Amyloid Pathology: O'Hara, Soo Hoo, Kroll, Erdogan, Henderson, Andry
- Transgenics, siRNA, miRNA: Seldin, Ward, Hovey, Shibad, Weng
- MRI: Anderson, Hamilton, Ruberg
- Mass Spec: Costello, Theberge, Hong
- Vickery Trinkaus-Randall, Flora Ren
- Flora Sam
- Ronglih Liao, James Guan

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