Familial Amyloidosis: Historical Perspective

Amyloid Support Group Familial Amyloidosis Meeting
Chicago, Illinois
Saturday, October 26, 2013

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BOSTON UNIVERSITY School of Medicine

Amyloidosis Center

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When was TTR amyloid discovered?

- 1854 Virchow (Germany) Discovery of amyloid in tissue (Virchow's Arch. Pathol. Anat. Physiol. (6: 268)

- 1952 Andrade (Portugal) A peculiar form of peripheral neuropathy (Brain 75:408)

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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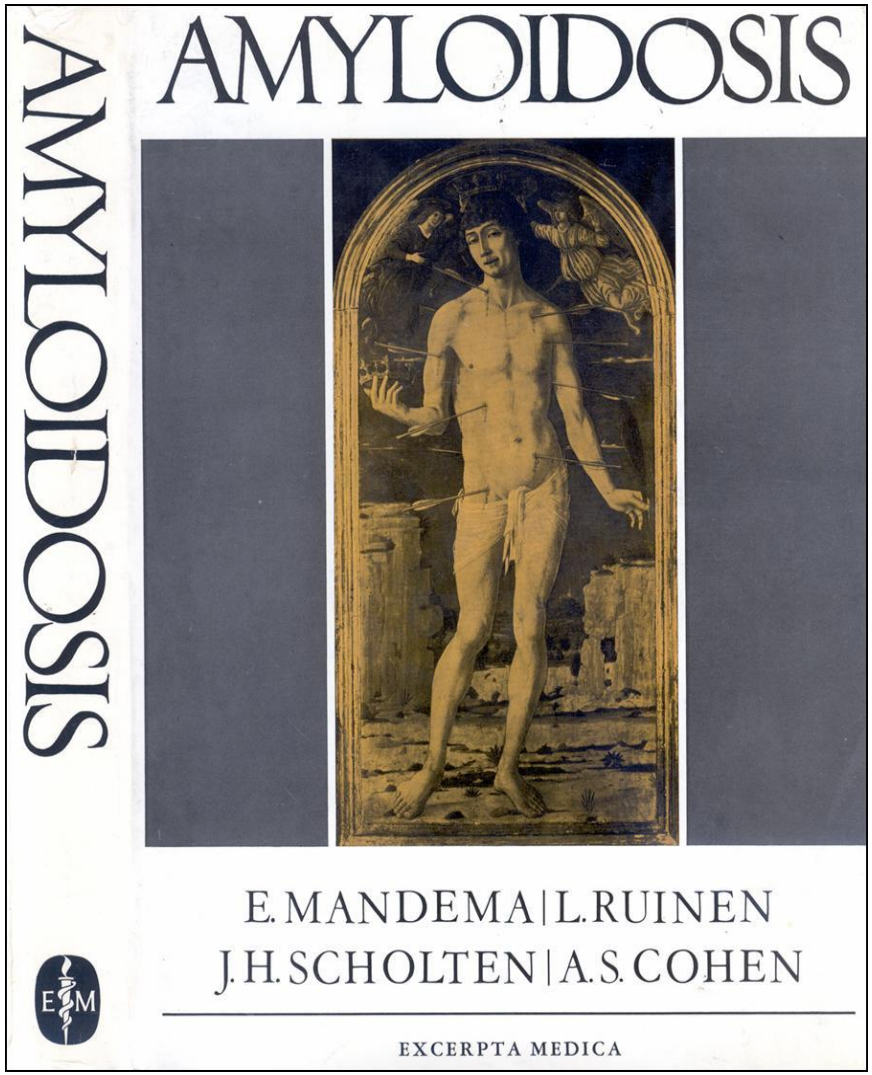
First Symposium Proceedings…



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1967 1st Symposium on Amyloidosis

- Six clinical reports:
  - one on familial amyloidosis associated with neuropathy, FAP
  - one on amyloid associated with rheumatoid arthritis
  - one on diagnostic tests
  - 3 reports on amyloid and aging

1967 1st Symposium on Amyloidosis

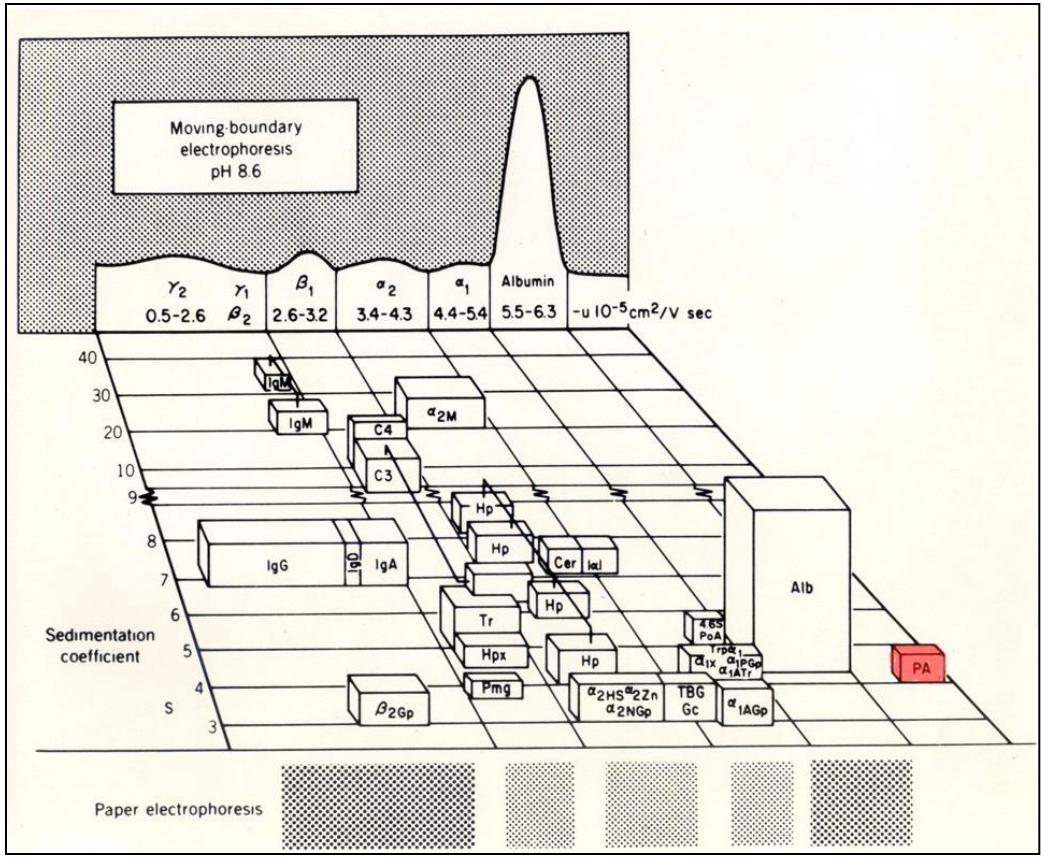
There were only 6 clinical reports. The most comprehensive was Dr. Andrade's report on 696 cases of amyloidotic polyneuropathy in 173 families in northern Portugal (Povoa de Varzim)

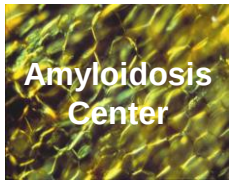
- all had biopsy proven amyloidosis
- hereditary nature of the disease
- showed degeneration of peripheral nerves by pathologic examination
- "no mild cases"

Further studies….

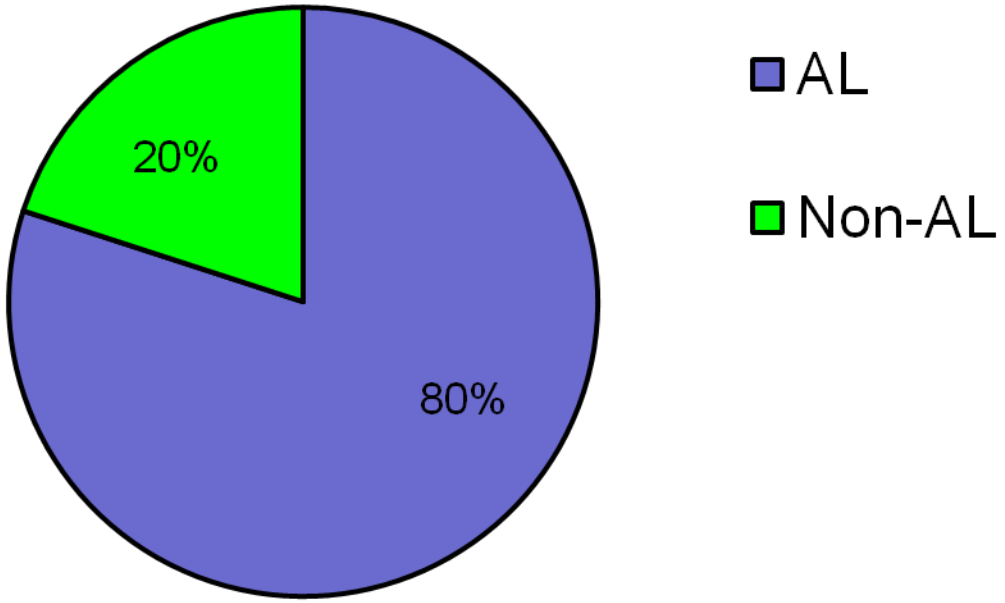
- 1978 — Amyloid deposits stained with antibody to prealbumin (TTR)
- 1981 — Amyloid fibrils proven to be prealbumin
- 1983 — First discovery of prealbumin gene mutation (Val-30-Met)
- 1986 — Prealbumin re-named trans thy retin
- 1983-present — More than 100 pathologic TTR mutations discovered

Prealbumin, aka transthyretin





Systemic amyloidosis:



Systemic non-AL amyloidoses (20%)

- 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 was SSA discovered?

- 1980 Sletten and colleagues noted the protein type was related to transthyretin (Scand. J Immunol. 12:503)
- 1983 Cornwell and colleagues reported on the clinical features of age-related cardiac amyloidosis (Am. J. Med. 75:618)

When were rare familial types discovered?

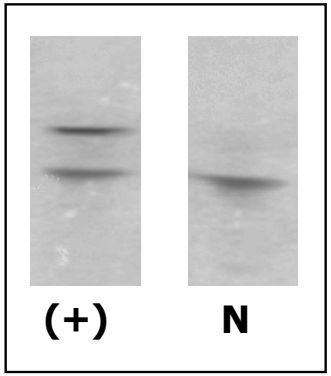
Type	Discovery	# mutant forms	Clinical feature *predominant
Apolipoprotein AI	Benson, 1988	15	kidney*, liver, heart, skin
Apolipoprotein AII	Benson, 2001	5 (all stop codons)	kidney
Fibrinogen A α	Benson, 1993	9	kidney*, nervous system
Lysozyme	Pepys, 1993	6	kidney*, GI, skin
Gelsolin	Maury, 1990	2	cranial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

Making the correct diagnosis

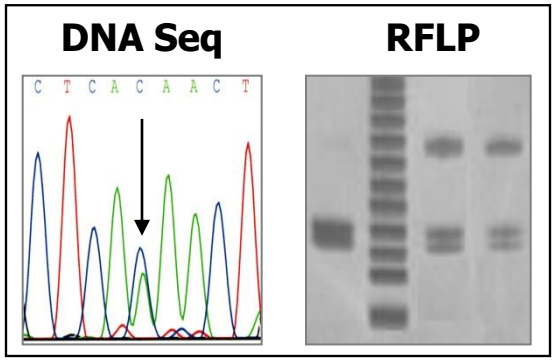
- Tissue biopsy positive for amyloid
- R/O AL and AA amyloidoses
- Confirm tissue type by immunohistochemistry with antibody to specific protein (or mass spec, if avail.)
- Confirm all inherited forms by genetic analysis of patient's DNA

Diagnostic testing

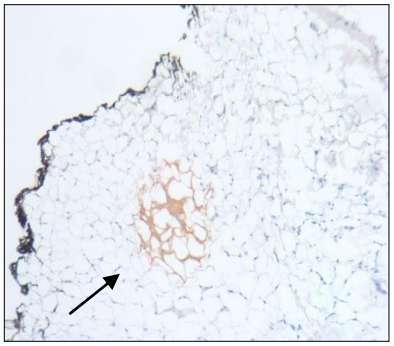
- Isoelectric focusing: <u>detection</u> of variant TTR protein in serum



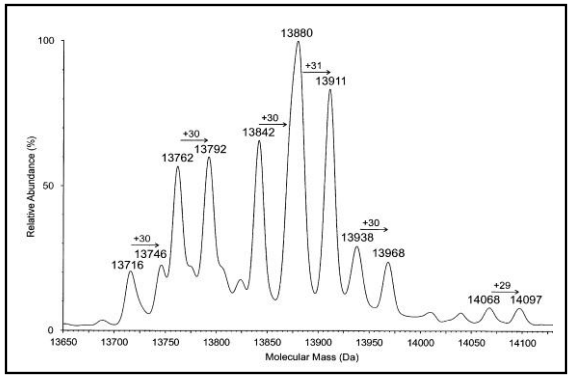
- Genetic analyses: <u>identification</u> of gene mutation



- 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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Age-related systemic amyloidosis (SSA)

- Caused by wild-type TTR
- Heart predominant organ involved
- Older age; mostly men
- Also called senile systemic 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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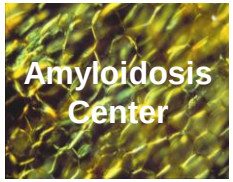

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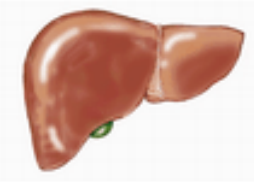
TTR mutation: V122I

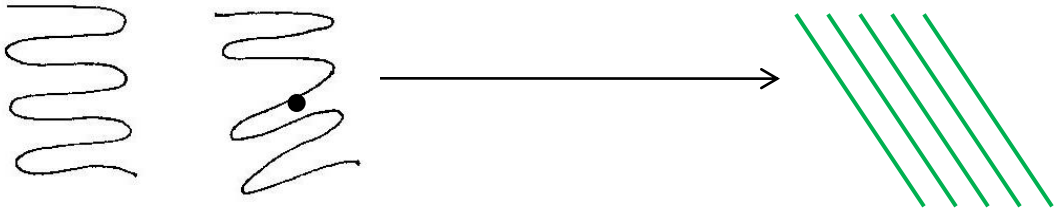
- variant TTR present in 4% of individuals of African ancestry
- associated with cardiomyopathy of late onset
- incidence of disease unknown

TTR amyloid pathogenesis…



transthyretin

127 amino acids
(building blocks)



Normal TTR Mutant TTR amyloid deposits

Diagnosis and treatment of familial 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 review
- Tafamidis (Pfizer): international trial awaits FDA approval
- ALN-TTR-NT-001 (Alnylam):clinical trial underway in Europe
- ISIS

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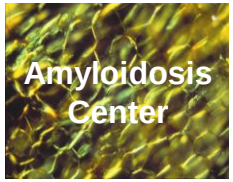

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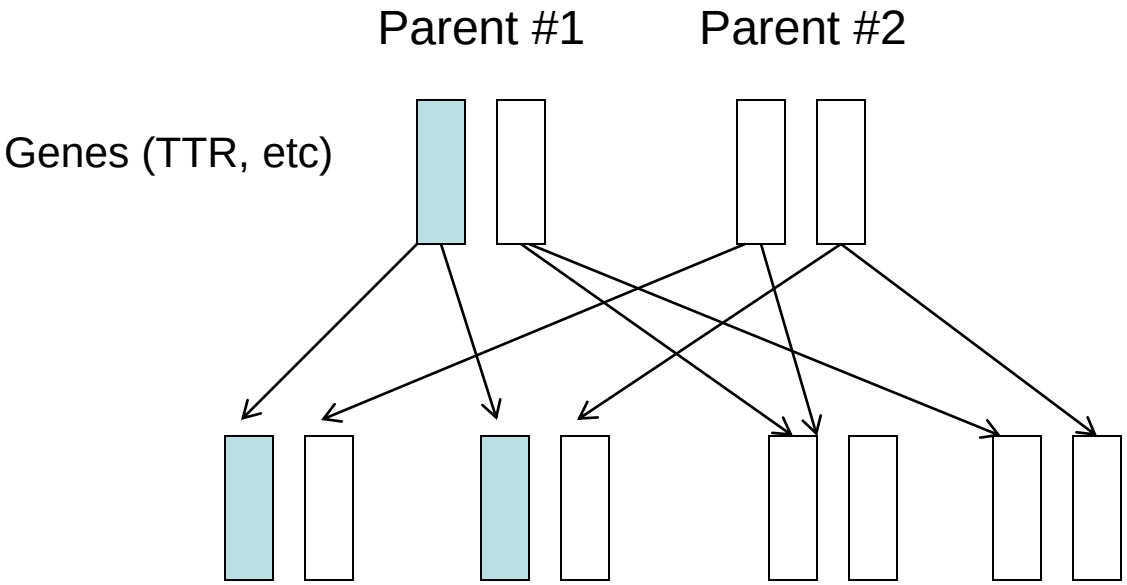
ATTR supportive treatment

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

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

- Center donors
- Gruss & Wildflower Foundations
- RO1 AG 031804

Clinical Research Team

- Amyloid: Berk, Fu, Libbey,
- Hematology: Seldin, Sanchorawala, Sloan, Renteria, Quillen
- Transplant & Clinical Trials: Sanchorawala,Finn, Shelton, Brauneis, Fennessey
- Apheresis Program: Quillen
- Pulmonary: Berk
- Cardiology: Ruberg, Meier-Ewert
- Renal: Stern, Havasi
- Neurology: Weisman

Laboratory Research Team

- Gerry Lab: Connors, Seldin, Spencer, Chan, Prokaeva, Klimtchuk, Greene, Koch, Sikora
- Amyloid Pathology: O'Hara, Cui, Lee, Henderson, Andry
- Transgenics, siRNA, miRNA: Seldin, Ward, Shibad, Weng
- MRI: Anderson, Hamilton, Ruberg
- Mass Spec: Costello, Zaia, Lu
- Imaging: Trinkaus-Randall, Ren
- Cardiac biomarkers: Connors, Sam
- Cardiac biology: Liao, Guan, Shen

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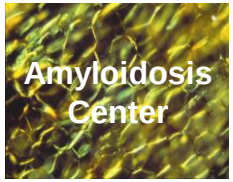

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Dr. Dyck working magic on Dr. Berk

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