Familial Amyloidoses Other Than TTR

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Familial Amyloidosis Other Than TTR

1. TTR most common

2. Non-TTR more challenging
   a. Diagnosis – DNA testing
   b. Treatment – Organ involvement

3. Research – Limited financial support.

Table 1. Other systemic forms of amyloidosis.

Type of Amyloid	First Clinical Description	First Characterized Biochemically	Where First Discovered
ApoAI	1969[1]	1988[2]	United States
Fibrinogen Aα-Chain	1975[27]	1993[22]	United States
Lysozyme	1982[39]	1993[37]	United Kingdom
ApoAII	1973[44]	2001[46]	United States
Gelsolin	1969[52]	1990[53,54]	Finland
Cystatin-C	1972[61]	1986[62]	Iceland
LECT2	2008[64]	2008[64]	United States

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TRANSTHYRETIN AMYLOIDOSIS

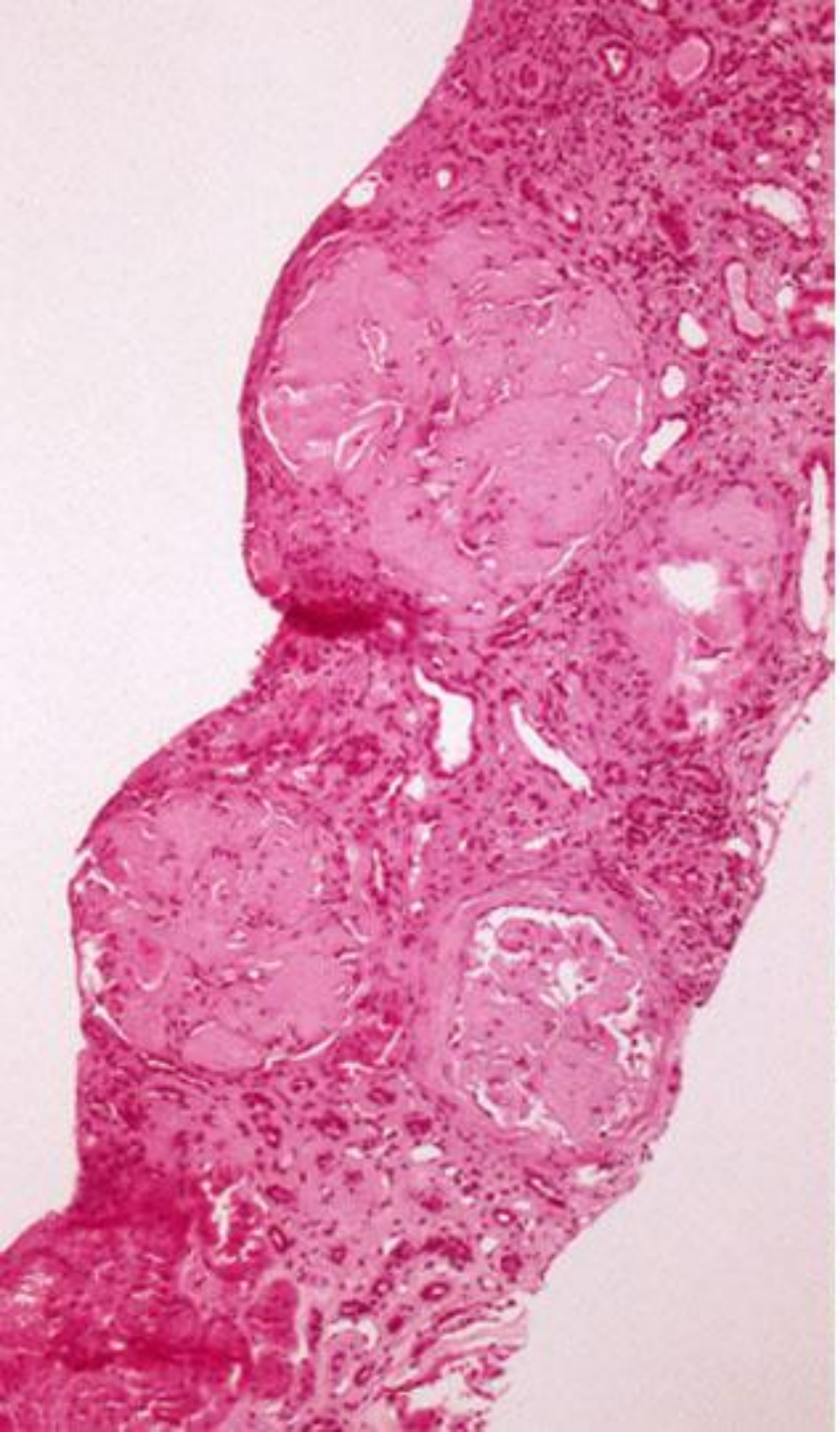
MUTATION	CODON CHANGE	CLINICAL FEATURES*	GEOGRAPHIC KINDREDS
Cys10Arg	TGT - CGT	Heart, Eye, PN	USA (PA)
Leu12Pro	CTG - CCG	LM	UK
Met13Lys	ATG - AAG		France
Asp18Glu	GAT - GAA	PN	South America, USA
Asp18Gly	- GGT	LM	Hungary
Asp18Asn	- AAT	Heart	USA
Val20Ile	GTC - ATC	Heart, CTS	Germany, USA
Ser23Asn	AGT - AAT	Heart	USA
Pro24Ser	CCT - TCT	Heart, CTS, PN	USA
Ala25Ser	GCC - TCC	Heart, CTS, PN	USA
Ala25Thr	- ACC	LM, PN	Japan
Val28Met	GTG - ATG	PN, AN	Portugal
Val30Met	- ATG	PN, AN, Eye, LM	Portugal, Japan, Sweden, USA (FAP I)
Val30Ala	- GCG	Heart, AN	USA
Val30Leu	- CTG	PN, Heart	Japan, Sweden
Val30Gly	- GGG	LM, Eye	USA
Val32Ala	- GCG	PN, AN, Heart	Singapore (Chinese)
Val32Gly	- GGG	PN,AN	France
Phe33Ile	TTC - ATC	PN, Eye	Israel
Phe33Leu	- CTC	PN, Heart	USA
Phe33Val	- GTC	PN, Eye	UK, Japan, China
Phe33Cys	- TGC	CTS, Heart, Eye, Kidney	USA
Arg34Ser	AGA - AGC/T	PN, Heart	USA
Arg34Thr	- ACA	PN, Heart	Italy
Arg34Gly	- GGA	Eye	UK (Kosovo)
Lys35Asn	AAG - AAC	PN, AN, Heart	France
Lys35Thr	- ACG	Eye	USA
Ala36Pro	GCT - CCT	Eye, CTS	USA
Asp38Ala	GAT - GCT	PN, Heart	Japan
Asp38Val	- GTT	PN, Heart	Guiana
Asp39Val	GAC - GTC	Heart	Germany
Trp41Leu	TGG - TTG	Eye, PN	USA
Glu42Gly	GAG - GGG	PN, AN, Heart	Japan, USA, Russia
Glu42Asp	- GAT	Heart	France
Phe44Ser	TTT - TCT	PN, AN, Heart	USA
Phe44Tyr	- TAT	PN, AN	France
Ala45Thr	GCC - ACC	Heart	USA
Ala45Asp	- GAC	Heart, PN	USA
Ala45Ser	- TCC	Heart	Sweden
Ala45Val	- GTC		France
Gly47Arg	GGG - CGG/AGG	PN, AN	Japan
Gly47Ala	- GCG	Heart, AN	Italy, France
Gly47Val	- GTG	CTS, PN, AN, Heart	Sri Lanka
Gly47Glu	- GAG	Heart, PN, AN	Turkey, USA, Germany
Thr49Ala	ACC - GCC	Heart, CTS	France, Italy
Thr49Ile	- ATC	PN, Heart	Japan, Spain
Thr49Pro	- CCC	Heart, PN	USA
Thr49Ser	- AGC	PN	India
Ser50Arg	AGT - AGG	AN, PN	Japan, France/Italy, USA
Ser50Ile	- ATT	Heart, PN, AN	Japan
Glu51Gly	GAG - GGG	Heart	USA
Ser52Pro	TCT - CCT	PN, AN, Heart, Kidney	UK
Gly53Glu	GGA - GAA	LM, Heart	Basque, Sweden
Gly53Ala	- GCA	PN, An, Heart, Eye, LM	UK
Gly53Arg	- AGA	LM	USA
Glu54Gly	GAG - GGG	PN, AN, Eye	UK
Glu54Leu	- TTG	Heart	Belgium
Glu54Lys	- AAG	PN, AN, Heart, Eye	Japan
Leu55Arg	CTG - CGG	LM	Germany
Leu55Gln	- CAG	Eye, PN	USA, Sweden
Leu55Pro	- CCG	Heart, AN, Eye	USA, Taiwan
His56Arg	CAT - CGT	Heart	USA
Gly57Arg	GGG - AGG	Heart, PN	Sweden
Leu58His	CTC - CAC	CTS, Heart	USA (MD) (FAP II)
Leu58Arg	- CGC	CTS, AN, Eye	Japan
Thr59Arg	ACA - AGA	Heart, AN	Japan
Thr59Lys	- AAA	Heart, PN, AN	Italy, USA (Chinese)
Thr60Ala	ACT - GCT	Heart, CTS	USA (Appalachian)
Glu61Lys	GAG - AAG	PN	Japan
Glu61Gly	- GGG	Heart, PN	USA
Glu62Lys	- AAG	PN	Italy
Phe64Leu	TTT - CTT/TTG	PN, CTS, Heart	USA, Italy
Phe64Ile	- ATT		
Phe64Ser	- TCT	LM, PN, Eye	Canada, UK
Gly67Arg	GGG-AGG	Eye, PN	USA
Ile68Leu	ATA - TTA	Heart	Germany
Tyr69His	TAC - CAC	Eye, LM	Canada, USA, Sweden
Tyr69Ile	- ATC**	Heart, CTS, AN	Japan
Lys70Asn	AAA - AAC	Eye, CTS, PN	USA
Val71Ala	GTG - GCG	PN, Eye, CTS	France, Spain
Ile73Val	ATA - GTA	PN, AN	Bangladesh
Tyr75Ile	ACC - ATC	Heart	France
Ser77Tyr	TCT - TAT	Kidney	USA (IL, TX), France
Ser77Phe	- TTT	PN, AN, Heart	France
Tyr78Phe	TAC - TTC	PN, CTS, Skin	France
Ala81Thr	GCA - ACA	Heart	USA
Ala81Val	- GTA	Heart	Russia, Poland
Ile84Ser	ATC - AGC	Heart, CTS, Eye	USA (IN), Hungary (FAP II)
Ile84Asn	- AAC	Heart, Eye	USA
Ile84Thr	- ACC	Heart, PN	Germany, UK
His88Arg	CAT - CGT	Heart	Sweden
Glu89Gln	GAG - CAG	PN, Heart	Italy
Glu89Lys	- AAG	PN, Heart	USA
His90Asp	CAT - GAT	Heart	UK
Ala91Ser	GCA - TCA	PN, CTS, Heart	France
Glu92Lys	GAG - AAG	Heart	Japan
Val93Met	GTG - ATG	PN	UK
Val94Ala	GTA - GCA	Heart, PN, AN, Kidney	Germany, USA
Ala97Gly	GCC - GGC	Heart, PN	Japan
Ala97Ser	- TCC	PN, Heart	Taiwan, USA
Arg103Ser	CGC - AGC	Heart	USA
Ile107Val	ATT - GTT	Heart, CTS, PN	USA
Ile107Met	- ATG	PN, Heart	Germany
Ile107Phe	- TTT	PN, AN	UK
Ala109Ser	GCC - TCC	PN, AN	Japan
Leu111Met	CTG - ATG	Heart	Denmark
Ser112Ile	AGC - ATC	PN, Heart	Italy
Tyr114Cys	TAC - TGC	PN, AN, Eye, LM	Japan, USA
Tyr114His	- CAC	CTS, Skin	Japan
Tyr116Ser	TAT - TCT	PN, CTS, AN	France
Ala120Ser	GCT - TCT	Heart	Afro- Caribbean
Ala120Thr	- ACT	PN, CTS	Japan
Val122Ile	GTC - ATC	Heart	USA
ΔVal122	- ΔΔΔ	Heart, PN	USA (Ecuador), Spain
Val122Ala	- GCC	Heart, Eye, PN	USA

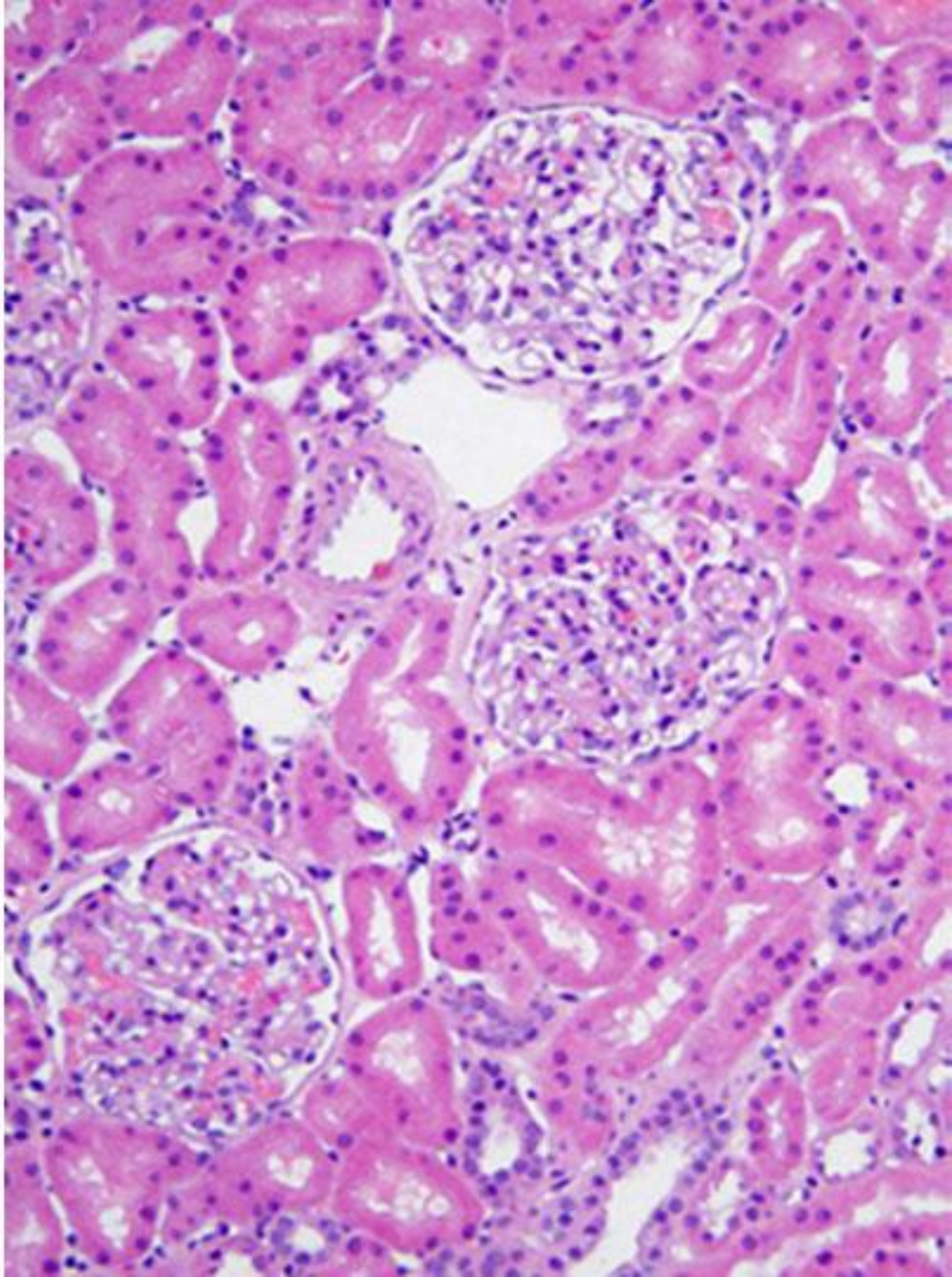
* = CLINICAL FEATURES: AN = Autonomic Neuropathy; CTS = Carpal Tunnel Syndrome; Eye = Vitreous Deposits; LM = Leptomeningeal; PN = Peripheral Neuropathy; ** = Double Nucleotide Substitution

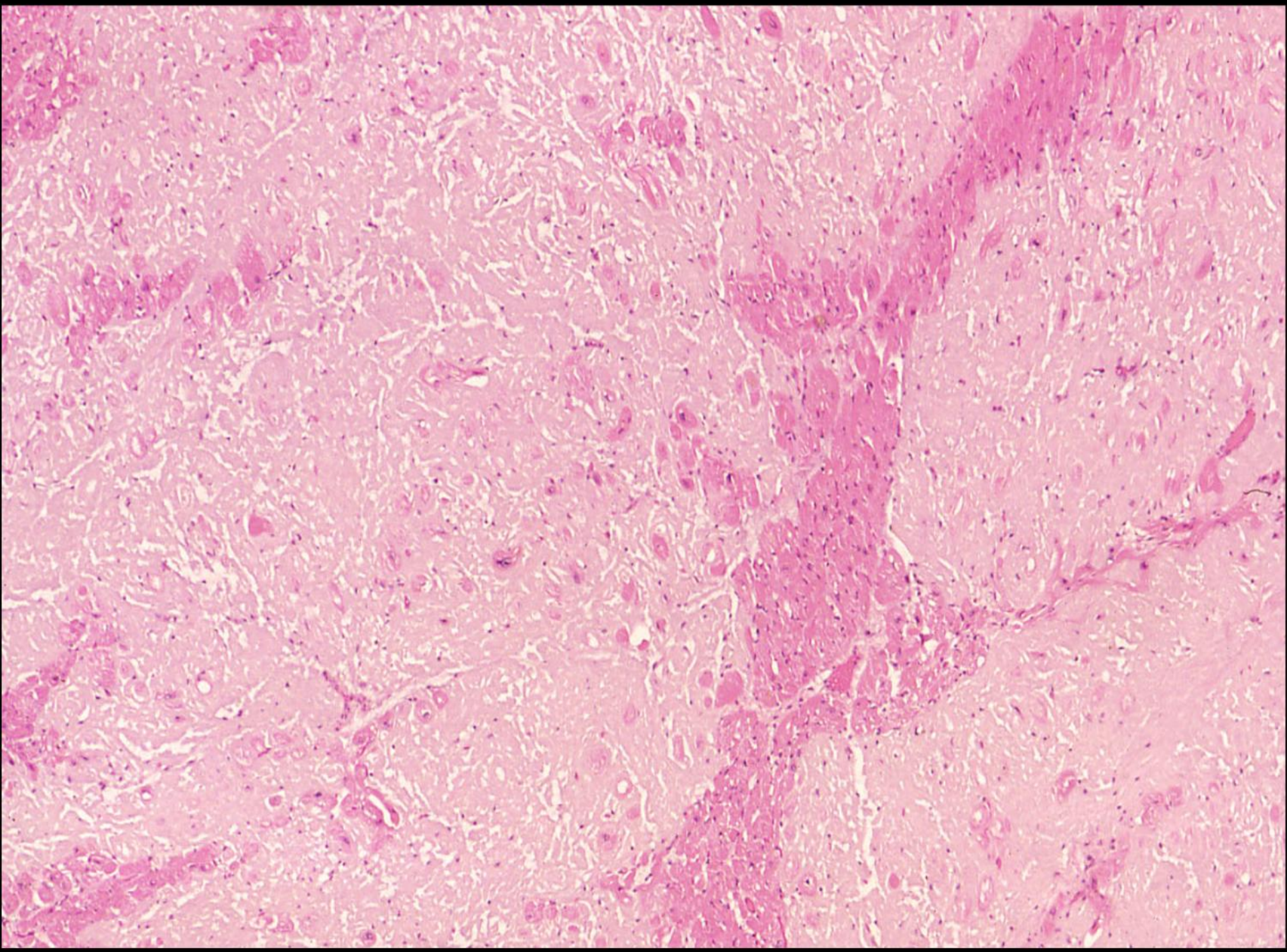
Mutant proteins other than transthyretin associated with autosomal dominant systemic amyloidosis.

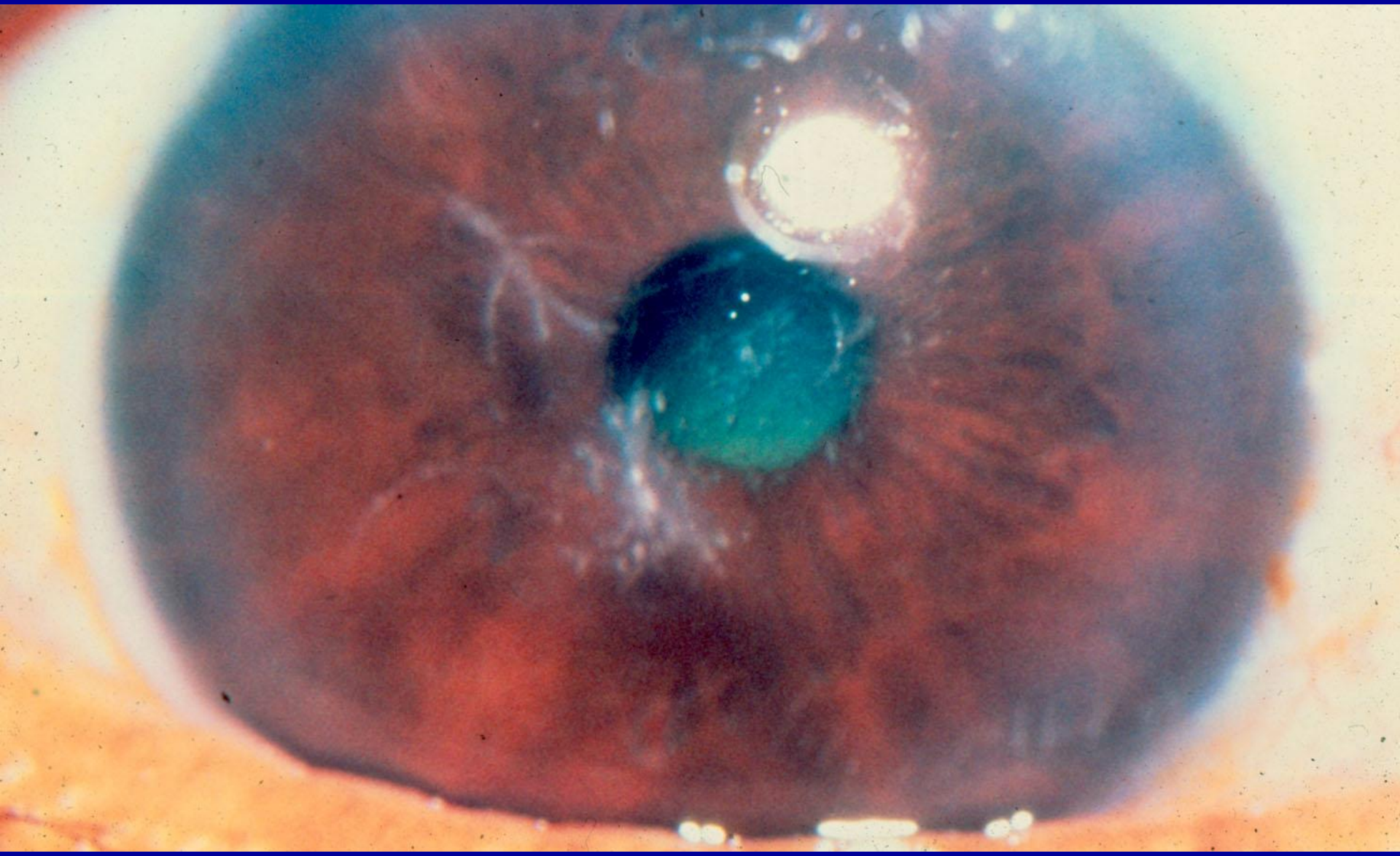
Protein	cDNA Change**	Amino Acid Change***	Codon Change	Clinical Features
Transthyretin	Greater than 100 mutations[†]			
Apolipoprotein AI	148G→C	Gly26Arg	GGC26CGC	PN[a], Nephropathy
	172G→A	Glu34Lys	GAA34AAA	Nephropathy
	251T→G	Leu60Arg	CTG60CGG	Nephropathy
	220T→C	Trp50Arg	TGG50CGG	Nephropathy
	del250-284insGTCAC	del60-71insVal/Thr	del60-71ins GTCAC	Hepatic
	263T→C	Leu64Pro	CTC64CCC	Nephropathy
	del280-288	del70-72	del70-72	Nephropathy
	284T→A	Phe71Tyr	TTC71TAC	Hepatic, Nephropathy
	294insA(fs)[b]	Asn74Lys(fs)[b]	AAC74AAAC(fs)[b]	Nephropathy
	296T→C	Leu75Pro	CTG75CCG	Hepatic
	341T→C	Leu90Pro	CTG90CCG	Cardiomyopathy, Cutaneous, Laryngeal
	532insGC(fs)[b]	Ala154(fs)[b]	GCC154GGC(fs)[b]	Nephropathy
	535ΔC	His155Met(fsx46)	CAT155ATG(fs)[b]	Nephropathy
	581T→C	Leu170Pro	CTG170CCG	Laryngeal
	590G→C	Arg173Pro	CGC173CCC	Cardiomyopathy, Cutaneous, Laryngeal
	593T→C	Leu174Ser	TTG174TCG	Cardiomyopathy
	595G→C	Ala175Pro	GCX175CCX[xxx]	Laryngeal
	604T→A	Leu178His	TTG178CAT	Cardiomyopathy, Laryngeal
Fibrinogen Aα	1718G→T	Arg554Leu	CGT554CTT	Nephropathy
	1634A→T	Glu526Val	GAG526GTG	Nephropathy
	1629delG	Glu524Glu(fs)[b]	GAG524GA_	Nephropathy
	1622delT	Val522Ala(fs)[b]	GTC522G_C	Nephropathy
	1676A→T	Glu540Val	GAA540GTA	Nephropathy
	del1636-1650insCA1649-1650			Nephropathy
	1712C→A	Pro552His	CCT552CAT	Nephropathy
	1670C→A	Thr538Lys	ACA538AAA	Nephropathy, Neuropathy
	1632delT	Thr525fs	ACT525AC_	Nephropathy
Lysozyme	221T→C	Ile56Thr	ATA56ACA	Nephropathy, Petechiae
	253G→C	Asp67His	GAT67CAT	Nephropathy
	244T→C	Trp64Arg	TGG64CGG	Nephropathy
	223T→A	Phe57Ile	TTT57ATT	Nephropathy
	413T→A	Trp112Arg	TGG112AGG	Nephropathy, GI
Apolipoprotein AII	301T→G	Stop78Gly	TGA78GGA	Nephropathy
	302G→C	Stop78Ser	TGA78TCA	Nephropathy
	301T→C	Stop78Arg	TGA78CGA	Nephropathy
	301T→A	Stop78Arg	TGA78AGA	Nephropathy
	302G→T	Stop78Leu	TGA78TTA	Nephropathy
Gelsolin	640G→A	Asp187Asn	GAC187AAC	PN[a], Lattice corneal dystrophy
	640G→T	Asp187Tyr	GAC187TAC	PN[a]
Cystatin C	280T→A	Leu68Gln	CTG68CAG	Cerebral hemorrhage

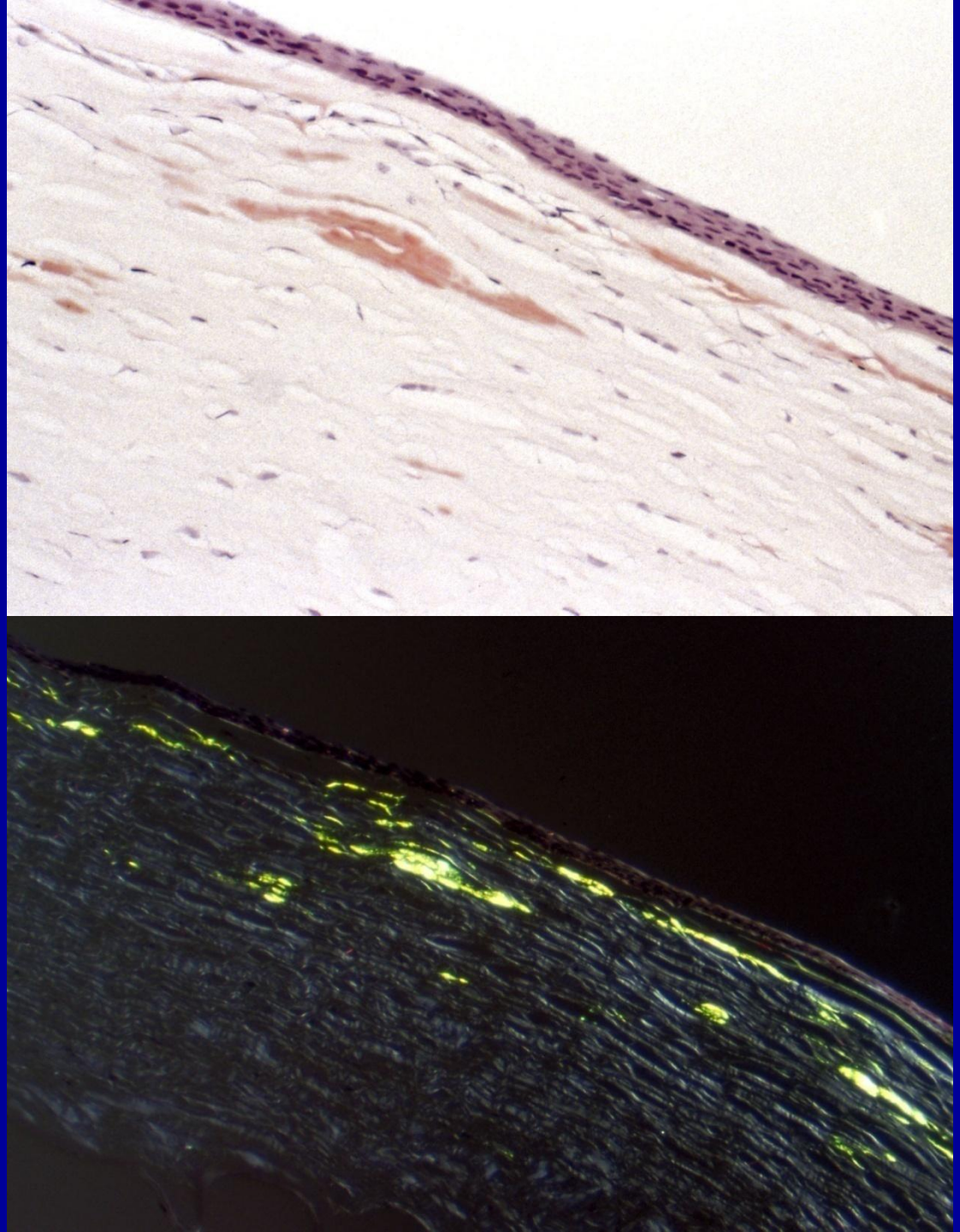
[a] PN = Peripheral Neuropathy
[b] fs = frame shift
[xx] Deduced
[†] List of most TTR mutations ( )
** cDNA numbering is from initiation codon (ATG)
*** Amino acids numbered for N-terminus of mature protein











Familial Amyloidosis Other Than TTR

Treatment –

- Apo AI – Liver transplant
  Affected organ transplant – kidney, heart
- Fibrinogen Aα – Liver transplant (probably curative)
  Affected organ transplant – kidney
- Lysozyme –
  Affected organ transplant – liver, kidney
- Apo AII –
  Affected organ transplant – kidney
- Gelsolin –
  Affected organ transplant – cornea
- Cystatin C –
  Avoid fever

LECT2

- What we know…
- 1. Mainly kidney pathology
- 2. Systemic disease – Liver (hepatic) amyloid deposition
- 3. Predominantly affects Hispanics (Mexicans)
- 4. DNA (gene) analysis –
- a. No mutation in LECT2 gene
- b. To date, all gene sequences have shown homozygosity for the Val 58 polymorphism

LECT 2

- What we do not know …

1. Frequency of LECT2 amyloidosis in different populations.

2. Is there a mutation in a gene, other than LECT2, that determines development of amyloidosis? (e.g. as seen in some forms of hereditary Alzheimer disease).

3. If there is a gene mutation, what percent of people with the mutation get the disease?

LECT2

- Importance of making the diagnosis…

1. Avoid treating the patient as AL (primary) amyloidosis (no chemotherapy).
2. Counseling – LECT2 amyloidosis appears to be a slowly progressive disease.
3. LECT2 patients are probably candidates for organ transplantation (kidney, liver).