2017

Progetto Ematologia Romagna

L'amiloidosi AL

Inquadramento dell'argomento

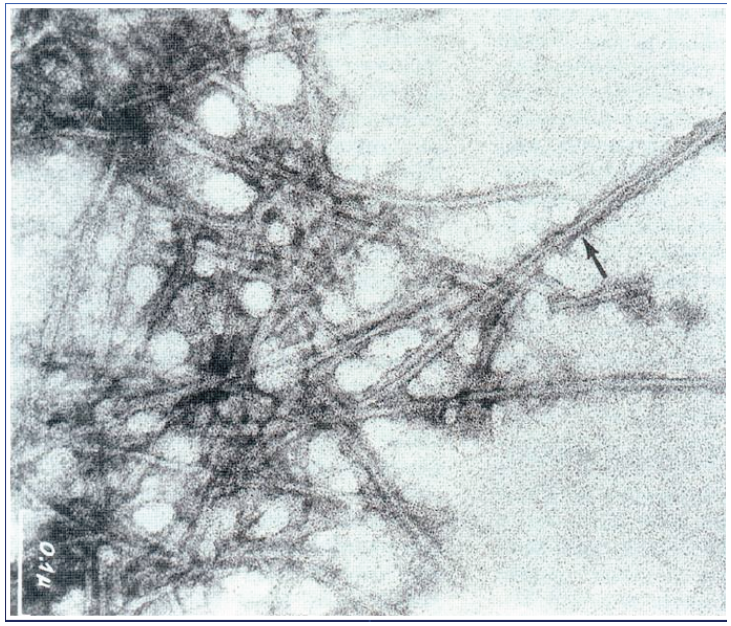
Patrizia Tosi
UO Ematologia Rimini

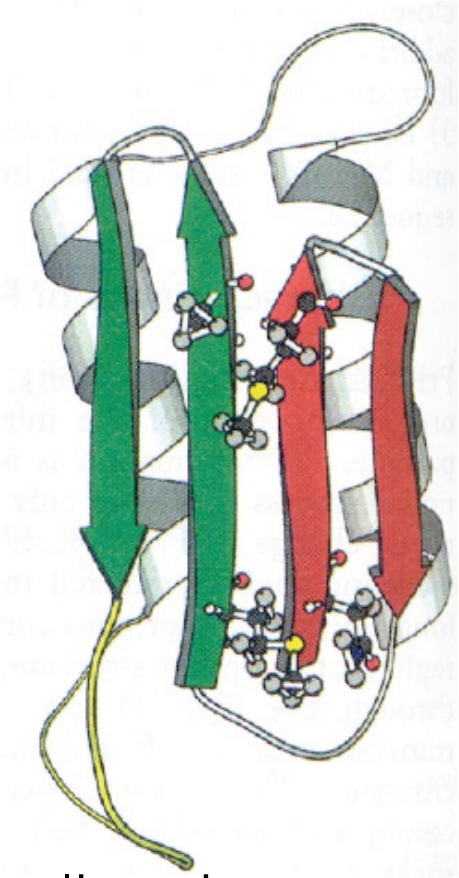
Definizione

Disordini del metabolismo proteico più frequentemente acquisiti

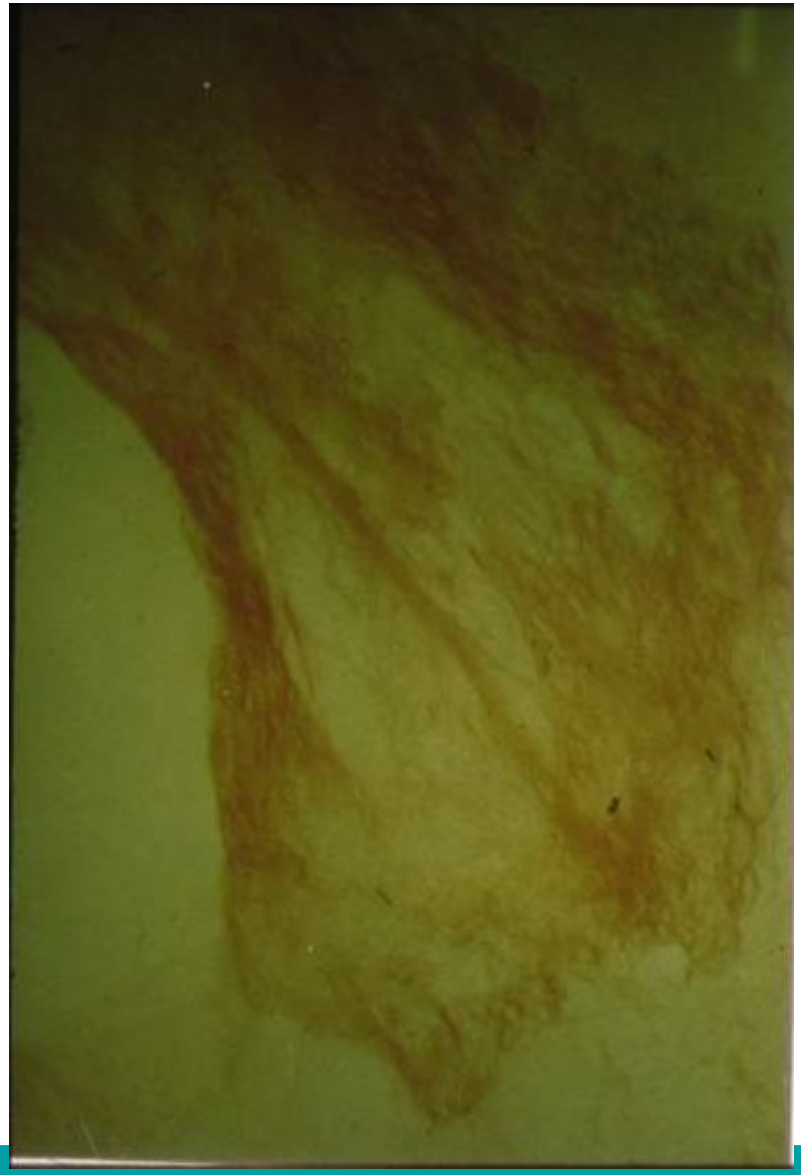
Deposizione extracellulare di materiale proteico autologo fibrillare (7.5-10nM) con la struttura a foglietto pieghettato di tipo beta

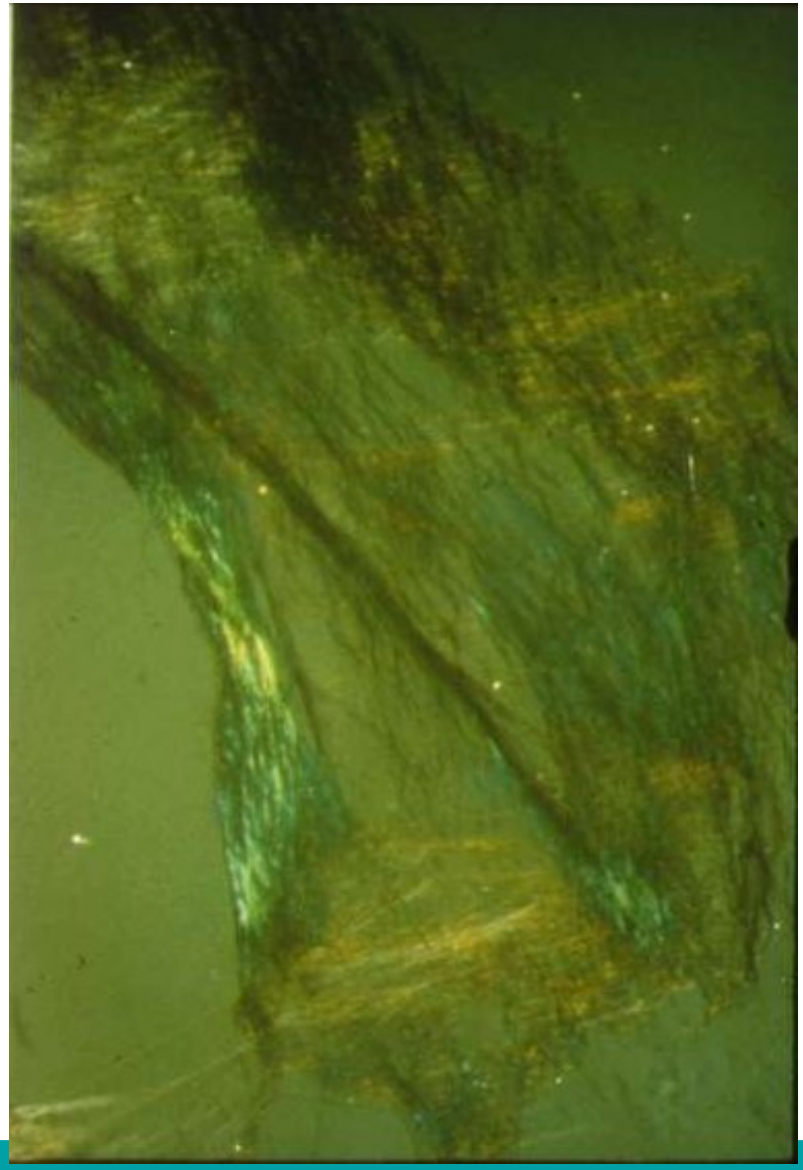
Il nome amiloide è stato attribuito da Virchow (1854) perché il materiale trattato con iodio e acido solforico assume lo stesso colore che assume l'amido trattato allo stesso modo



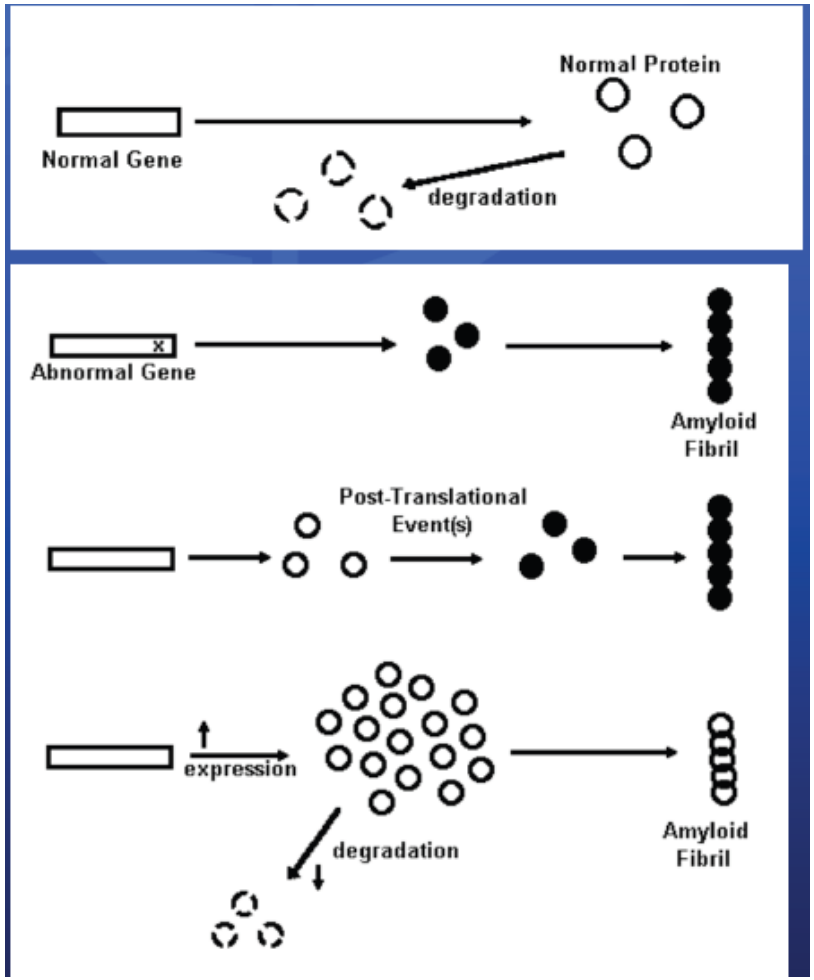


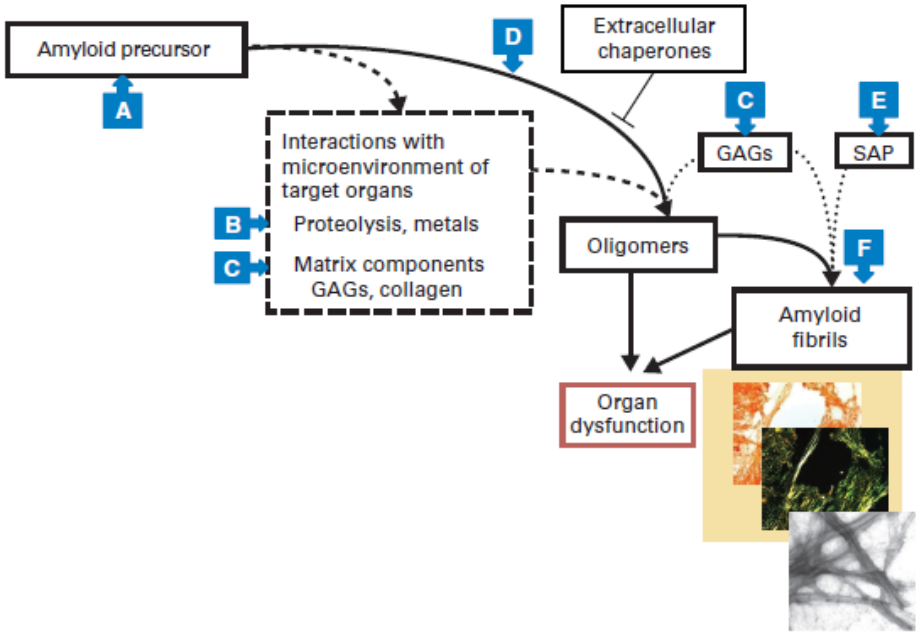
+ costituenti non fibrillari: glicosaminoglicani e componente P





Meccanismi di formazione dell'amiloide





NOMENCLATURE ARTICLE

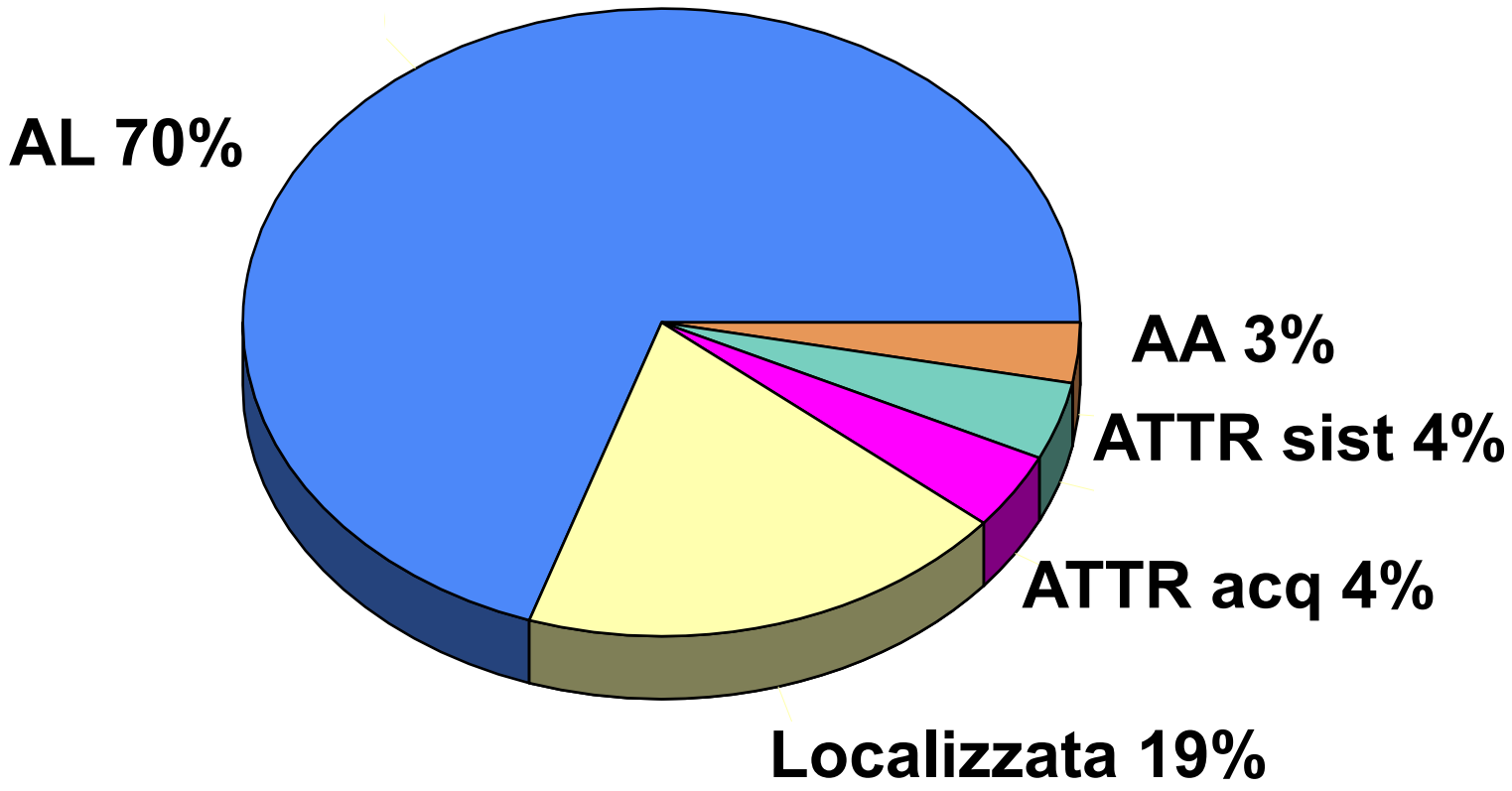
Amyloid fibril proteins and amyloidosis: chemical identification and clinical classification International Society of Amyloidosis 2016 Nomenclature Guidelines

Jean D. Sipe[1], Merrill D. Benson[2], Joel N. Buxbaum[3], Shu-ichi Ikeda[4], Giampaolo Merlini[5], Maria J. M. Saraiva[6], and Per Westermark[7]

Nomenclatura:
A+ substrato normale

Fibril protein	Precursor protein	Systemic and/ or localized	Acquired or hereditary	Target organs
AL	Immunoglobulin light chain	S, L	A, H	All organs, usually except CNS
AH	Immunoglobulin heavy chain	S, L	A	All organs except CNS
AA	(Apo) Serum amyloid A	S	A	All organs except CNS
ATTR	Transthyretin, wild type	S	A	Heart mainly in males, ligaments, tenosynovium
	Transthyretin, variants	S	H	PNS, ANS, heart, eye, leptomeninges
Aβ2M	β2-Microglobulin, wild type	S	A	Musculoskeletal system
	β2-Microglobulin, variant	S	H	ANS
AApoAI	Apolipoprotein A I, variants	S	H	Heart, liver, kidney, PNS, testis, larynx (C-terminal variants), skin (C-terminal variants)
AApoAII	Apolipoprotein A II, variants	S	H	Kidney
AApoAIV	Apolipoprotein A IV, wild type	S	A	Kidney medulla and systemic
AApoCII	Apolipoprotein C II, variants	S	H	Kidney
AApoCIII	Apolipoprotein C III, variants	S	H	Kidney
AGel	Gelsolin, variants	S	H	PNS, cornea
ALys	Lysozyme, variants	S	H	Kidney
ALECT2	Leukocyte chemotactic factor-2	S	A	Kidney, primarily
AFib	Fibrinogen α, variants	S	H	Kidney, primarily
ACys	Cystatin C, variants	S	H	PNS, skin
ABri	ABriPP, variants	S	H	CNS
ADan*	ADanPP, variants	L	H	CNS
Aβ	Aβ protein precursor, wild type	L	A	CNS
	Aβ protein precursor, variant	L	H	CNS
AαSyn	α-Synuclein	L	A	CNS
ATau	Tau	L	A	CNS
APrP	Prion protein, wild type	L	A	CJD, fatal insomnia
	Prion protein variants	L	H	CJD, GSS syndrome, fatal insomnia
	Prion protein variant	S	H	PNS
ACal	(Pro)calcitonin	L	A	C-cell thyroid tumors
AIAPP	Islet amyloid polypeptide**	L	A	Islets of Langerhans, insulinomas
AANF	Atrial natriuretic factor	L	A	Cardiac atria
APro	Prolactin	L	A	Pituitary prolactinomas, aging pituitary
AIns	Insulin	L	A	Iatrogenic, local injection
ASPC***	Lung surfactant protein	L	A	Lung
AGal7	Galectin 7	L	A	Skin
ACor	Corneodesmosin	L	A	Cornified epithelia, hair follicles
AMed	Lactadherin	L	A	Senile aortic, media
AKer	Kerato-epithelin	L	A	Cornea, hereditary
ALac	Lactoferrin	L	A	Cornea
AOAAP	Odontogenic ameloblast-associated protein	L	A	Odontogenic tumors
ASem1	Semenogelin 1	L	A	Vesicula seminalis
AEnf	Enfurvitide	L	A	Iatrogenic

Amiloidosi in 1315 pazienti (Mayo clinic 1982-1992)



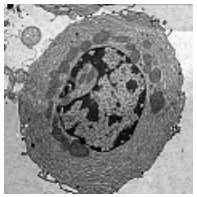
Amiloidosi AL

Associata a sd linfoproliferative con componente monoclonale

- **Mieloma (< = 20%)**
- **M. di Waldenstrom**
- **Linfomi**

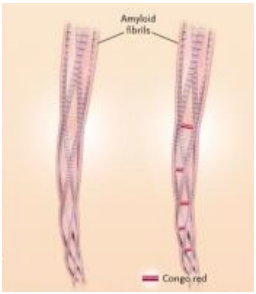
Sd linfoproliferativa clonale

Immunoglobulin light chain amyloidosis (AL)
Incidence 10 patients/million/year – 10% of MM patients

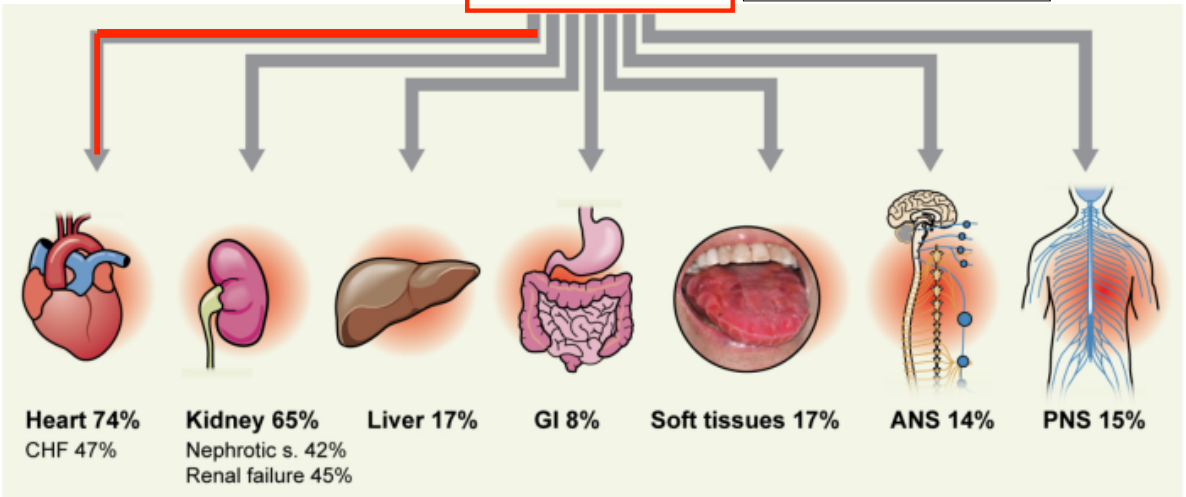


Small dangerous clone[1]
(BMPC 7%)
53% LC only 75% λ

Amyloid fibrils



Proteotoxicity | structural damage



[1]*Merlini & Stone, Blood. 2006*

IGLV1-44 IGVL6-57

Amyloidogenic light chains induce cardiomyocyte contractile dysfunction and apoptosis via a non-canonical p38α MAPK pathway

Jianru Shi[a], Jian Guan[a,b], Bingbing Jiang[a], Daniel A. Brenner[a], Federica del Monte[c], Jennifer E. Ward[d], Lawreen H. Connors[d], Douglas B. Sawyer[e], Marc J. Semigran[f], Thomas E. Macgillivray[g], David C. Seldin[b,d], Rodney Falk[h], and Ronglih Liao[a,b,1]

4188–4193 | PNAS | March 2, 2010 | vol. 107 | no. 9

Novel mitochondrial protein interactors of immunoglobulin light chains causing heart amyloidosis

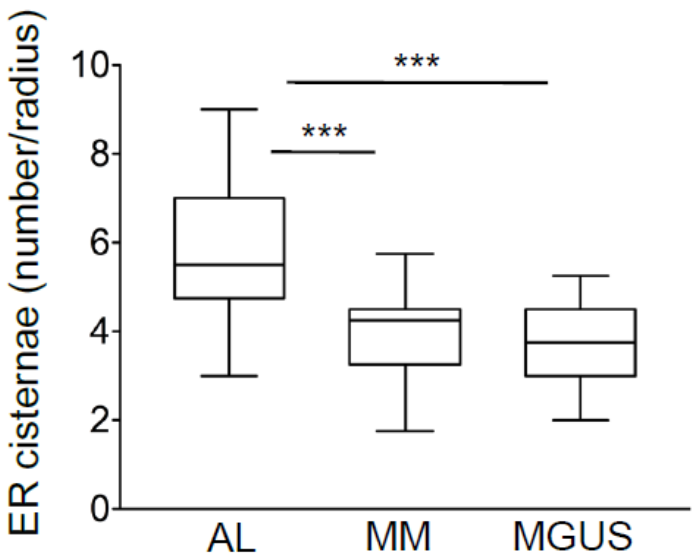
Francesca Lavatelli,[*,†,‡,§,1] Esther Imperlini,[¶,1] Stefania Orrù,[¶,‖] Paola Rognoni,[*,†,‡,§] Daniela Sarnataro,[¶,#] Giuseppina Palladini,[**,‡,§] Giuseppe Malpasso,[†,‡,§,††] Maria Eugenia Soriano,[‡‡] Andrea Di Fonzo,[*,†,‡,§] Veronica Valentini,[*,†,‡,§] Massimiliano Gnecchi,[†,‡,§,††,§§] Stefano Perlini,[‡,§,**] Francesco Salvatore,[¶,#,2] and Giampaolo Merlini[*,†,‡,¶¶,2]

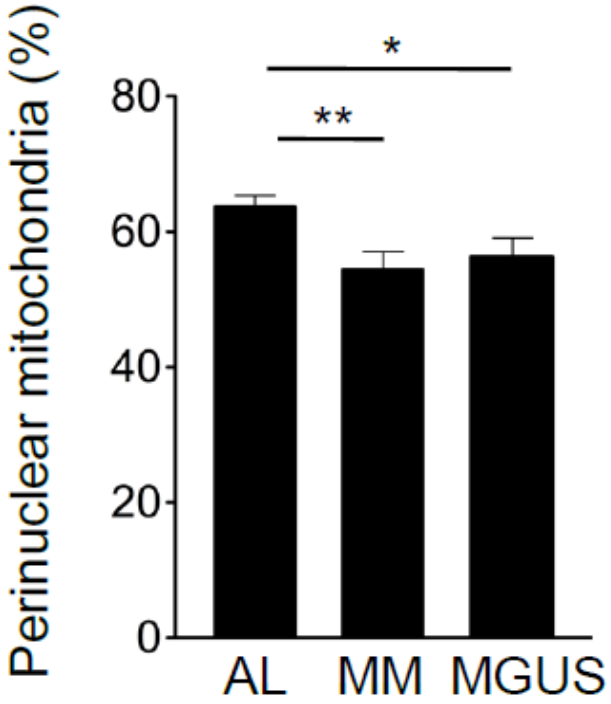
The FASEB Journal Vol.29, No.11 , pp:4614-4628, March, 2017

Meccanismi di tossicità delle LC amiloidogenetiche

The amyloidogenic light chain is a stressor that sensitizes plasma cells to proteasome inhibitor toxicity

Laura Oliva,[1] Ugo Orfanelli,[1] Massimo Resnati,[1] Andrea Raimondi,[2] Andrea Orsi,[3] Enrico Milan,[1] Giovanni Palladini,[4] Paolo Milani,[4] Fulvia Cerruti,[5] Paolo Cascio,[5] Simona Casarini,[4] Paola Rognoni,[4] Thierry Touvier,[6] Magda Marcatti,[7] Fabio Ciceri,[7,8] Silvia Mangiacavalli,[9] Alessandro Corso,[9] *Giampaolo Merlini,[4] *Simone Cenci [1,8]





Light Chain Amyloidosis: Patient Experience Survey from the Amyloidosis Research Consortium

Isabelle Lousada · Raymond L. Comenzo · Heather Landau · Spencer Guthrie · Giampaolo Merlini

Median age at diagnosis, years (range)	57 (20–83)
Type of amyloidosis, *n* (%), *n* = 484	
AL amyloidosis	347 (71.7)
AA amyloidosis	23 (4.8)
Hereditary transthyretin-related amyloidosis	35 (7.2)
Hereditary non–transthyretin-related amyloidosis	6 (1.2)
Other	25 (5.2)

Time from initial symptoms to diagnosis of amyloidosis, *n* (%), *n* = 459	
<6 months	171 (37.3)
6–12 months	118 (25.7)
12–18 months	44 (9.6)
18–24 months	34 (7.4)
2–3 years	44 (9.6)
>3 years	48 (10.5)

Light Chain Amyloidosis: Patient Experience Survey from the Amyloidosis Research Consortium

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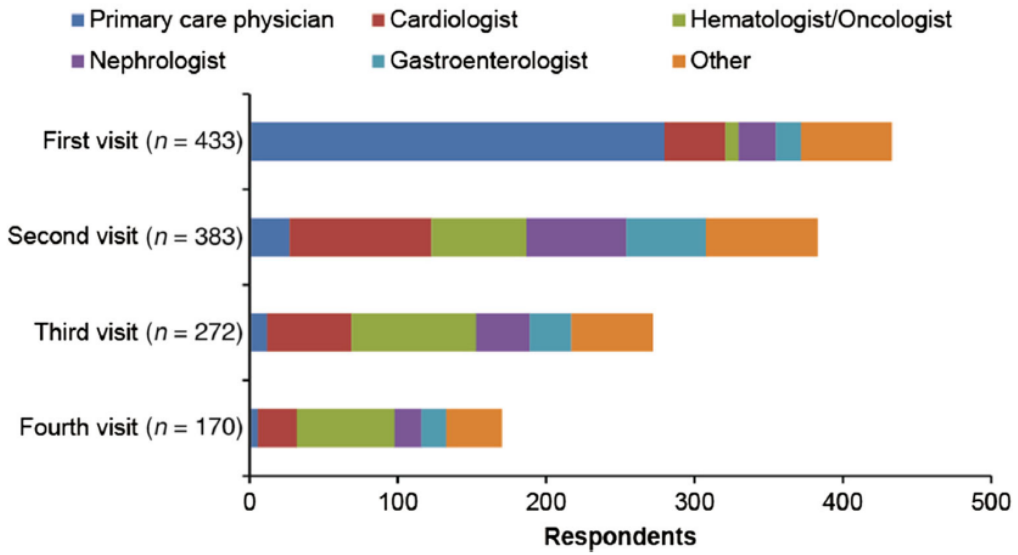
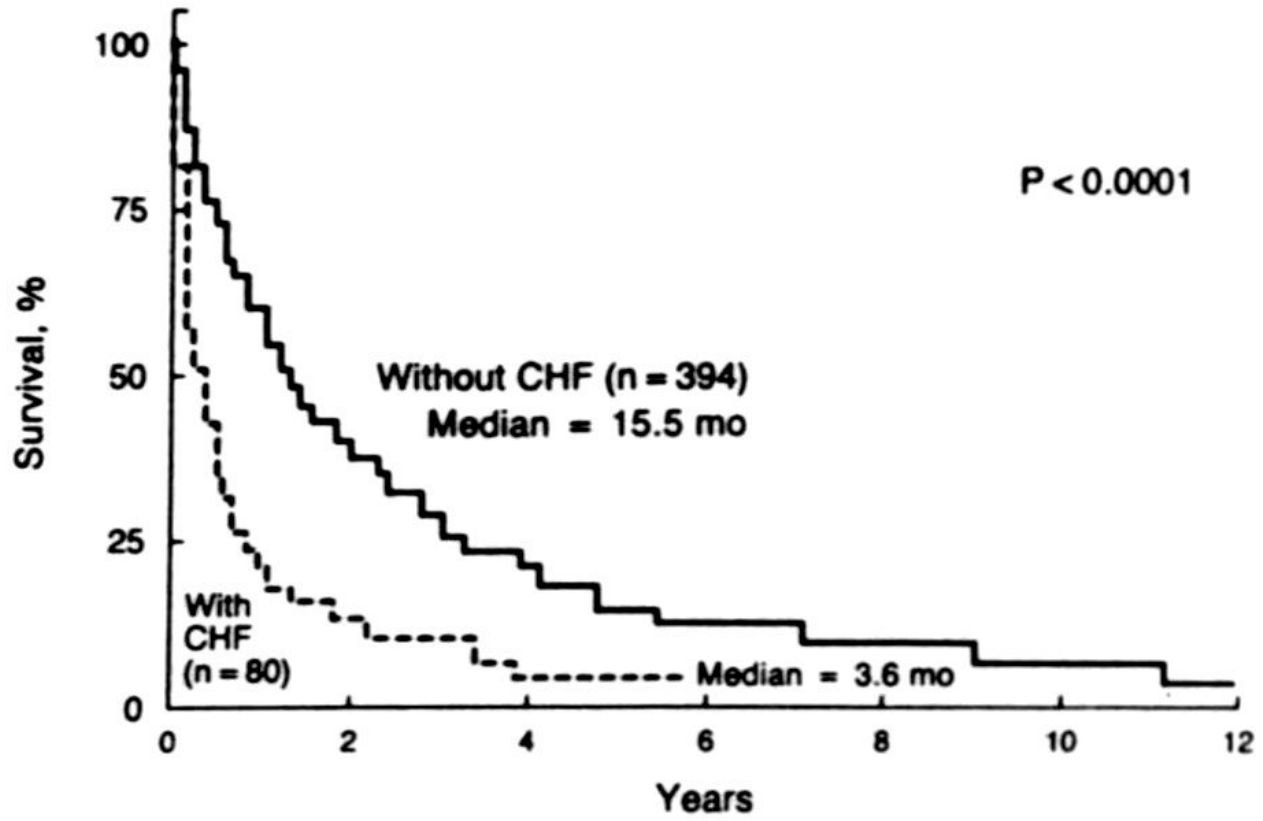
Different physicians visited before establishment of a diagnosis, *n* (%), *n* = 459

1	35 (7.6)
2	108 (23.5)
3	93 (20.3)
4	77 (16.8)
≥5	146 (31.8)

Specialty of diagnosing physician, *n* (%), *n* = 402

Hematologist/oncologist	137 (34.1)
Nephrologist	91 (22.6)
Cardiologist	75 (18.7)
Gastroenterologist	32 (8.0)
Neurologist	19 (4.7)
Primary care physician	16 (4.0)
Other[a]	32 (8.0)





Kyle RA et al, Sem Haematol 1995