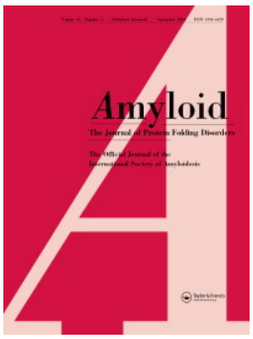

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NOMENCLATURE

Amyloid nomenclature 2024: update, novel proteins, and recommendations by the International Society of Amyloidosis (ISA) Nomenclature Committee

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ABSTRACT

The ISA Nomenclature Committee met at the XIX International Symposium of Amyloidosis in Rochester, MN, 27 May 2024. The in-person event was followed by many electronic discussions, resulting in the current updated recommendations. The general nomenclature principles are unchanged. The total number of human amyloid fibril proteins is now 42 of which 19 are associated with systemic deposition, while 4 occur with either localised or systemic deposits. Most systemic amyloidoses are caused by the presence of protein variants which promote misfolding. However, in the cases of AA and ATTR the deposits most commonly consist of wild-type proteins and/or their fragments. One peptide drug, previously reported to create local iatrogenic amyloid deposits at its injection site, has been shown to induce rare instances of systemic deposition. The number of described animal amyloid fibril proteins is now 16, 2 of which are unknown in humans. Recognition of the importance of intracellular protein aggregates, which may have amyloid or amyloid-like properties, in many neurodegenerative diseases is rapidly increasing and their significance is discussed.

KEYWORDS

Fibril; amyloid protein; nomenclature; intracellular aggregate; functional amyloid; iatrogenic amyloid

Introduction

A nomenclature group was established in 1979 at the 3rd International Symposium on Amyloidosis, in Póvoa de Varzim, Portugal. By that time, it had become clear that there were several human proteins that could form typical amyloid deposits. The discovered amyloid proteins were few but since different names were used by diferent investigators, a common nomenclature was deemed to be important. Since then the Nomenclature Committee has met during all the International Symposia on Amyloidosis. Since the International Society of Amyloidosis was formed, the Nomenclature Committee has served as one of its standing committees. Most recently, the Nomenclature Committee met on the 27 May 2024 at the XIX International Symposium of Amyloidosis in Rochester, Minnesota. At that meeting, the new member of the committee, Professor Ellen McPhail participated for the first time. She is replacing Professor Angela Dispenzieri, who we thank for all her work and input. The present updated Nomenclature classification and summary replaces the one published in 2022 [1].

Amyloid fibril

The basic structure of amyloid is the fibril. An amyloid fibril is built up by twisted protofilaments. An amyloid protofilament is a stack of protein layers in β-sheet structure, which when twisted about identical stacks, forms an amyloid fibril. Amyloid fibrils may be formed from 1, 2, 3, 4, or many such protofilaments. Protofilaments are bound to each other in a parallel fashion *via* their sidechains.

Amyloid protofilaments and fibrils can be generated *in vitro* from protein purified from *ex vivo* deposits but also from synthetic or recombinant peptides. Such fibrils exhibit the characteristic fibrillary ultrastructure, X-ray crystallographic diffraction patterns, and the binding of dyes such as thioflavin T and Congo red. Typical birefringence after staining with the latter dye is also seen. Recently it has become clear from several CryoEM studies that fibrils generated *in vivo* may differ from those derived from the same precursor obtained in the test tube. The variations probably reflect different mechanisms of amyloid formation *in vitro* and *in vivo*, perhaps related to the conformation or proteolytic stability of the *in vitro*

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fibrils compared with those purified from diseased tissue [2].

In 2018 the Nomenclature Committee agreed on a general definition of the name 'amyloid' which had been used differently by varying groups of researchers. Initially it was used to describe pathologic deposits of specific fibrillar protein aggregates with distinct microscopic properties, particularly affinity for the dye Congo red with typical birefringence. However, it is now clear that such staining can vary considerably in strength and appearance. Thus, in medicine amyloid was regarded as abnormal, an opinion which became untenable with the discovery of 'functional amyloids' (see below). Chemists often used the word amyloid for β-sheet protein fibrils of any kind, including synthetic or naturally appearing fibrils. The committee agrees that the term 'amyloid fibril' should be used for any cross β-sheet fibril [3]. It is recommended that when the word 'amyloid' is used, its nature and origin should be clear.

Functional amyloid

When it was found that nature has used beta pleated sheet aggregates for many functions, it was necessary to include these structures in the nomenclature and the term 'functional amyloid' was introduced. It should be underlined that with 'functional amyloid' in this paper, we mean amyloid structures exerting normal function, not to be confused with 'gain of function', an expression often used for new pathological properties acquired by protein aggregates. Diverse examples of functional amyloid can be found in many living organisms, including bacteria and fungi but also in vertebrates (reviewed in [4]). In humans, the most well-known examples are as a storage form for some but not all peptide hormones, the major basic protein of eosinophilic granulocytes and the melanosome protein PMEL-17. The exact molecular organisation is probably different from that of pathological amyloid fibrils, for example, these structures do not bind Congo red in the form the dye is used in clinical pathology.

Amyloid fibril classes

Early observations assumed that all amyloid fibrils were of similar or identical architecture despite being derived from a variety of precursor proteins. Modern biophysical studies have clearly shown that differences occur. Moreover, it has been found that fibrils formed *in vitro* from a recombinant protein (usually in short time frames) can differ profoundly from the *in vivo* fibrils formed from the same precursor (frequently over a long period of time). With the widened definition of 'amyloid' it is necessary to consider different amyloid fibril classes:

1. *In vivo* and *ex vivo* disease-related fibrils
2. *In vivo* and *ex vivo* functional fibrils
3. Recombinant fibrils of disease-related proteins and of functional amyloid proteins
4. Fibrils of synthetic or non-disease related peptides
5. Fibrils from condensates and hydrogels that give the cross-β diffraction pattern

Amyloid and amyloidosis in medical practice

Pathological amyloid

While the term amyloid is applied to a normal and physiologically important structure, the same term is also applied to the substance in human and animal pathology where the basic structure of the deposit is the β-sheet fibril. However, a number of additional constituents may be present in the deposit. The most well-known additional components include the pentraxin serum amyloid P-component (SAP or AP), bound to the fibrils in a calcium-dependent fashion and proteoglycans, mainly heparan sulphate proteoglycan (HSPG), which are always present in the extracellularly deposited amyloid. Although the importance of the accessory components for the development and persistence of the amyloid is unclear, SAP has been demonstrated to protect fibrils from degradation and lack of HSPG inhibits development of different amyloid forms in several animal models. There may be additional components.

Amyloidosis is a disease characterised by deposition of amyloid. When amyloid is distributed systemically, i.e. at a distance from the site of precursor synthesis (see below) the condition is always called amyloidosis. Amyloid can also appear locally but only some of these types are characterised as amyloidosis, the best example being localised AL amyloidosis. Many other conditions where local amyloid deposits (or their oligomeric precursors) are important components in the pathogenesis such as Alzheimer's disease, Parkinson's disease or type 2 diabetes, are usually not named amyloidoses. The reason for this varies but is often due to complex pathogenesis where protein aggregation is an important but not the sole component.

Amyloid proteins and their nomenclature

The principles of the nomenclature have been discussed in earlier versions of Nomenclature Committee reports, and for history, please see [3]. The structural proteins in or derived from amyloid fibrils are named after their precursors in abbreviated form preceded by the letter A for amyloid. Thus, immunoglobulin light chain amyloid protein is named AL and transthyretin amyloid protein ATTR, see Table 1. The protein can be specified further, e.g. ATTRv for variant, ATTRV30M for a specific amino acid substitution or ATTRwt for the wild-type form. For amyloid protein variants, the Nomenclature Committee recommends using the numbering based on the sequence of the mature amyloid protein, i.e. without leader sequence or propeptides (e.g. ATTRV30M). The recommendations the Human Genome Variation Society (HGVS) have been adopted [5]. It should be noted that HGVS recommend the use of variant instead of mutation. HGSV also recommends the use of amino acid three letter code in order to minimise the risk mistakes but also one letter code is accepted.

Table 1. Amyloid fibril proteins and their precursors in human[a].

Fibril protein	Precursor protein	Systemic or localised	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, H	All organs except CNS
ATTR	Transthyretin, wild type	S*	A	Heart mainly in males, lung, ligaments, tenosynovium
	Transthyretin, variants	S	H	PNS, ANS, heart, eye, kidneys, leptomeninges
Aβ2M	β2-microglobulin, wild type	S	A	Musculoskeletal system
	β2-microglobulin, variants	S	H	ANS, tongue, heart
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, heart, gastrointestinal
AApoAIV	Apolipoprotein A IV, variant	S	H	Heart, kidney
AApoCII	Apolipoprotein C II, variants	S	H	Kidney
AApoCIII	Apolipoprotein C III, variants	S	H	Kidney
AGel	Gelsolin, variants	S	H	Kidney 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, variants	L	H	CNS
AαSyn	α-Synuclein	L	A	CNS
	α-Synuclein, variant	L	H	CNS
ATau	Tau	L	A	CNS
	Tau, variant	L	H	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
ATMEM106B	Transmembrane 106B (TMEM106B)	L	A	Frontotemporal lobar degeneration diseases
ACal	(Pro)calcitonin	L	A	C-cell thyroid tumours
		S	A	Kidney
AIAPP	Islet amyloid polypeptide***	L	A	Islets of Langerhans, insulinomas
AANP	Atrial natriuretic peptide	L	A	Cardiac atria
APro	Prolactin	L	A	Pituitary prolactinomas, ageing pituitary
ASom	(Pro)somatostatin	L	A	Somatostatinomas
AGluc	Glucagon	L	A	Glucagonomas
APTH	Parathyroid hormone	L	A	Parathyroid tumours, Ageing parathyroid glands
AIns	Insulin	L	A	Iatrogenic, local injection
AEnf	Enfuvirtide	L	A	Iatrogenic, local injection
AGLP1	Glucagon-like peptide 1 analog	L	A	Iatrogenic, local injection
AIL1RAP	Interleukin-1 receptor antagonist protein	S, L	A	Iatrogenic, local injection
ASPC****	Lung surfactant protein	L	A	Lung
ACor	Corneodesmosin	L	A	Cornified epithelia, hair follicles
AMed	Lactadherin (MFG-E8)	L	A	Ageing aorta, media, elastic arteries
AKer	Kerato-epithelin	L	A	Cornea, hereditary
ALac	Lactoferrin	L	A	Cornea
AOAAP	Odontogenic ameloblast-associated protein	L	A	Odontogenic tumours
ASem1	Semenogelin 1	L	A	Vesicula seminalis
ACatK*****,******	Cathepsin K	L	A	Tumor associated
AEFEMP1*****	EGF-containing fibulin-like extracellular matrix protein 1 (EFEMP1	L	A	Veins Ageing associated-

[a]Proteins are listed, when possible, according to relationship. Thus, apolipoproteins are grouped together, as are polypeptide hormones.
*The question whether ATTR can appear as a strict localised form is not fully answered.
**ADan is the product of the same gene as ABri.
***Also called amylin.
****Not proven by amino acid sequence analysis.
*****Full amino acid sequence to be established.
******May be associated with cystatin C.

When describing precursor proteins, we recommend that both classical nomenclature (for example, in the case of TTR, numbering without the leader sequence has been used for a long time.) and standard protein nomenclature (counted from the start codon) are used side by side to avoid confusion, e.g. V30M (p.V50M) in the case of TTR. Since the TTR protein translated by silent variants is wild-type, and therefore, if ATTR amyloid is present, the patient is classified as having ATTRwt amyloidosis. Common silent variants include p.S120 = (S100 =)/c.360 C>T, p.T139 = (T119 =)/c.417G>A, and p.Y89 = (Y69 =)/c.267 C>T. Variants in the untranslated regions also do not affect the TTR amino acid sequence, and the TTR protein is wild-type. Therefore, If ATTR amyloid is positive, the patient is

classified as having ATTRwt amyloidosis. A common untranslated region variant is c.*3*11del.

We emphasise that the abbreviations are for the amyloid proteins, not the diseases. For the latter, the amyloid protein name followed by 'amyloidosis' should be used. Correct designations are, for example ATTR amyloidosis or AL amyloidosis. Clinically useful specifications may be allowed, such as ATTR cardiomyopathy or AL neuropathy.

For the sake of uniformity, we recommend using the variant state after the name, such as ATTRwt, or ATTRv. Please note that v should be used for variant, not m (mutant) [5] or h (hereditary), the latter since it may be mistaken for 'human'.

The numbering of amino acid residues in recombinant proteins should match, wherever possible, the numbering of residues in the fibril or fibril precursor protein

Localised vs. systemic amyloidosis

We define localised amyloid according to the expression site of the precursor protein. Thus, AMed amyloid, found primarily in the aorta, is classified as localised since it is deposited close to smooth muscle cells in arteries where the precursor protein lactadherin is expressed. Consequently, deposits can be found in vessels of several organs, e.g. the brain and the kidneys although the form of amyloidosis is characterised as local. AEFEMP1 amyloidosis, preferentially affecting gastrointestinal veins may be a similar example with its parent protein EGF-containing fibulin-like extracellular matrix protein 1 most likely originating from cells close to the deposits. There are examples where this distinction is yet not fully clear.

ATTR amyloidosis: always systemic or not?

ATTR amyloidosis, both of variant and of wild-type, are classified as systemic but deposits of ATTR amyloid are very commonly found in ligamentous tissues in various sites in the body without evidence of systemic disease. Such deposits, particularly carpal tunnel syndrome and lumbar spinal stenosis may be an early sign of systemic disease and are also included among the so-called red flags for ATTR amyloidosis, and may precede clinically apparent systemic disease by several years. A large prospective study reported that the relative risk of amyloidosis was ~3-fold higher (adjusted hazard ratio, 2.86; 95% CI, 1.71 to 4.77) in individuals with CTS compared with those without CTS, translating into a small increase of the absolute risk [6]. Screening for cardiac amyloidosis 5 to 15 years after surgery for bilateral carpal tunnel syndrome found approximately 5% of patients with early-stage transthyretin cardiac amyloidosis [7]. However, it is not yet possible to rule out the existence of truly localised ATTR amyloidosis limited to ligaments or similar structures. Obviously, more knowledge is required here.

Amyloid signature proteins

As stated above, amyloid deposits not only contain the main amyloid fibril proteins but may also have components that appear to be present in most deposits. The most well studied are serum amyloid P-component (SAP) and heparan sulphate proteoglycans (HSPG), both of which seem to be important both for the stability of the fibrils and, at least for HSPG, in their genesis. Apolipoprotein E may belong to this group of components. There are other proteins regularly found attached to the fibril by as yet undetermined mechanisms. They include among others, apolipoprotein A-IV with other components under continuing investigation. The presence of these proteins has been used in mass spectrometry as additional proof that the tissue extracted material contains amyloid. Therefore, these components have been designated as 'amyloid signature proteins' [8].

Recommendations regarding specific words or expressions

Amyloid plaque. Plaque refers to a flat object and has been used for long time for the distinct deposits of Aβ fibrils in the cerebral cortex. They are certainly not flat, rather globoid. It seems difficult to stop the use of this name in neuroscience but unfortunately its usage has tended to spread to other forms of amyloid as well, including systemic amyloidoses. This should be avoided.

Amyloid precursor protein (APP). APP is generally used in the Alzheimer literature but is an imprecise name since there are many amyloid precursor proteins. The correct name, in the context of Alzheimer's disease, should be Aβ protein precursor (AβPP).

Apple-green birefringence. Interestingly, the colour appearing in the polarisation microscope after staining with Congo red has been a matter of intense discussions for decades. In real world pathology samples, the colour varies much and there is usually a mixture of green, red, orange and yellow. The committee recommends the use of a more correct description such as the neutral designation 'characteristic birefringence'.

Both ATTR and AL cardiomyopathy are part of systemic diseases, always with deposits in several organs. When the expression AL or ATTR cardiomyopathy is used, it is important to always emphasise that the condition is systemic.

Novel amyloid fibril proteins and revision of the protein tables

No new proteins have been added to the 2022 list of human amyloid fibril proteins [1] and only small changes have been inserted (Table 1). A hereditary form of systemic AApoAIV amyloidosis depending on a mis sense mutation (p.D33N) has been described [9]. The number of identified amyloid fibril proteins is now 42 of which 14 appear only as systemic deposits, 23 are seen exclusively in local amyloid while 5 can appear as both types (Table 1). More knowledge regarding iatrogenic amyloid forms has been obtained, and particularly AIns following repeated local subcutaneous injections has turned out to be quite common and creates diagnostic problems, requiring more information. It is probable that in the future additional iatrogenic amyloids will be identified. It is obvious that clinical awareness of this possibility is important.

Changes in the human amyloid fibril protein nomenclature (Table 1)

Anakinra, an Interleukin-1 receptor antagonist protein analog was added to the 2022 list of human amyloid fibril proteins as an iatrogenic local amyloid form, appearing at injection sites of the drug [1]. Since then, two patients have been reported with systemic amyloidosis following long treatment with the same drug [10,11]. Analysis of the deposits showed that they consisted of Anakinra fibrils and the pathogenesis was dependent on a persistently high plasma concentration of the drug. Consequently, AIL1RAP has been added as a systemic amyloidosis protein.

Double amyloids

During the last years a many of reports on combined amyloid have appeared. It has long been known that two biochemically different amyloid forms can appear together, actually being described before any type of amyloid had been characterised [12]. The most common systemic amyloid combination includes AA in many countries but ATTRwt in the western world, particularly after the introduction of scintigraphy with bone tracers that has exponentially increased the diagnosis of ATTRwt amyloidosis. It is of interest that an M-protein is present in 23-39% of patients with ATTRwt amyloidosis and in 49% with ATTR V122I [13,14]. The reason of the association is not clear, but it may confound the differential diagnosis. Whether or not two clinical amyloid forms interact, e.g. by cross seeding as being demonstrated *in vitro* and in some animal models or contain complex fibrils composed of more than one protein is not known. Most prevalent combinations are those with one systemic and one localised type, e.g. localised AL amyloidosis and ATTRwt deposits in the lung.

Animal amyloid fibril proteins

For the 2022 Nomenclature Report only 11 animal amyloid forms had been biochemically characterised [1]. Four more types have been described and have been added to Table 2.

Apolipoprotein CIII

Systemic amyloidosis derived from apolipoprotein CIII was described from several lions (Panthera leo), living in an animal park in Japan [15]. Genetic sequence analysis showed only wild-type.

Apolipoprotein AIV

Systemic apolipoprotein AIV amyloidosis was found in an aged cotton-top tamarin (Saguinus oedipus), living in a Japanese zoo [16]. The animal had severe renal involvement but deposits were reported from many organs. Full amino acid sequence was not obtained.

Fibrinogen α chain

Fibrinogen α chain (AFib) amyloidosis is one of the most common human hereditary forms with a renal phenotype. A recent study has shown that AFib amyloidosis is common in ageing Japanese squirrels (Sciurus lis) as a systemic, non-hereditary form [17]. The deposition pattern in kidneys seems to be similar to that seen in human and the squirrel may offer a relevant animal model or the human disease.

Amyloid derived from α-S-1-casein

Mammary tumours in dogs may contain intersitital amyloid deposits. Murakami et al. showed that in four studied dog tumours, the amyloid fibrils consisted of truncated α-S-1-casein [18]. Bovine α-S-2-casein amyloid was included in earlier versions of the Table but α-S1-casein is derived from another gene and amyloid of this nature has now been added to Table 2.

The ability to form amyloid fibrils is found to be a generic property of proteins used in nature for different functions. It is expected that pathological amyloid will be found in most animals if studied well enough. An example is the finding of amyloid deposits apparently derived from apolipoprotein E in geckos [19].

Table 2. Amyloid fibril proteins and their precursors in animals.

Fibril protein	Precursor protein	Systemic and/or localised	Affected organs or syndrome	Species
AL	Immunoglobulin Light Chain	S, L	Plasmacytoma	Cat, Horse
AA	(Apo) Serum Amyloid A	S	Chronic Inflammation or Infections	Many mammalian and avian species: Mouse, Cat, Cow, Dog, Duck, Guinea pig, etc.
AApoCIII	Apolipoprotein CIII	S	Age-related	Lion
AApoAI	Apolipoprotein AI	S	Age-related	Dog
AApoAII	Apolipoprotein AII	S	Age-related	Mouse
AApoAIV	Apolipoprotein AIV	S	Age-related	Cotton-top tamarin
ATTR	Transthyretin	S	Age-related	Vervet monkey
AFib	Fibrinogen Aα	S	Spleen, Liver	Stone marten
Aβ	Aβ precursor protein	L	Age-related	Dog, Sheep, Wolverine
AIAPP	Islet Amyloid Polypeptide	L	Islets of Langerhans, Insulinoma	Apes, Cat, Racoon
AIns	Insulin	L	Islets of Langerhans	Octodon degus
ACas1	α-S!-casein	L	Mammary gland	Dog
ACas2	α-S2C casein	L	Mammary gland	Cow
AEFEMP1	EGF-containing fibulin-like extracellular matrix protein 1	S		Tsushima leopard cat
ATau	Tau	L	CNS	Primates, Felids, Bovids
APRP	Prion protein	L	CNS	Bovids, Deer, Mink. Felids, Primates, Camel, etc

Potential amyloid fibril proteins under investigation (Table 3)

Three additional putative non-human amyloid fibril proteins have been discussed [20–22] but the reports were found to have some limitations, hence these proteins were included as proteins under investigation. Four more proteins including rat polysaccharide-binding protein, galectin 7, desmin, and p53 remain on this list since no more information regarding the amyloid nature of these proteins has been published but the Committee welcomes suggestions (with accompanying published papers).

Pathological intracellular protein aggregates

Over the last decade, investigation of cellular inclusions, particularly some that arise in response to stress (e.g. P-bodies, stress granules), have suggested that these structures, which are not contained by discrete cellular membranes, result from liquid liquid phase separation, the ultimate consequence of which may be, in some cases, fibril formation. Many of the components are RNA binding proteins which are intrinsically disordered or contain low complexity, prion-like domains. Variants of some of these molecules have been associated with hereditary neurodegenerative or musculoskeletal disorders and show inclusions in the affected cells, which are generally not Congophilic (Table 4). However, when the suspect protein precursors are synthesised *in vitro* and incubated under fibril-forming conditions, the aggregates have the properties of amyloid fibrils. That seems to be the case for the amyotrophic lateral sclerosis (ALS)-associated proteins C9orf72 dipeptide repeat protein (C9orf72), cytotoxic granule associated RNA binding protein TIA1 (TIA1), heterogeneous nuclear ribonucleoprotein A1 (HNRNPA1), RNA-binding protein FUS (FUS), superoxide dismutase (SOD1), TAR DNA-binding protein 43 (TARDBP), TATA-binding protein-associated factor 2N (TAF15), and Ubiquilin-2 (UBQLN2).

Similar phenomena have been seen in other clinical contexts. Sequence variants in heterogeneous nuclear ribonucleoprotein A2 (HNRNPA2B1) have been reported in multisystem proteinopathy. Expanded repeats in huntingtin are associated with inclusions in Huntington's disease.

Table 3. Examples of proteins under investigation.

Protein	Species	Protein nature	Associated disease	Type of aggregate
Lipopolysaccharide-binding	Rattus norvegicus protein	Acute phase protein	Mammary tumours	Extracellular amyloid
Galectin 7	Homo sapiens	Galectin	Forms of localised dermal amyloid	Extracellular amyloid
Desmin	Homo sapiens	Intermediate filament	Myopathies	Intracellular, not fully characterised
p53	Homo sapiens aggregates	Intracellular fully characterised	Malignant tumours	Intracellular, not
α-synuclein	Equus ferus caballus	Intracellular pre-synaptic	Parkinson-like disease	Aggregates not fully characterized
Ameloblastin	Canis lupus familiaris Felis catus	Enamel protein	Odontogenic tumours	Extracellular amyloid

Table 4. Intracellular inclusions with known biochemical composition (with one exception), with or without amyloid properties.

Inclusion name	Site	Protein nature	Examples of associated disease or state
Lewy bodies	Neurons intracytoplasmic	α-synuclein*,**	Parkinson's disease, dementia with Lewy bodies
Huntington bodies	Neurons intranuclear	PolyQ expanded huntingtin	Huntington's disease
Not specified	Oligodendroglia intracytoplasmic	α-synuclein	Muscular atrophy
Not specified	Neurons intranuclear	PolyQ expanded androgen receptor	Spinobulbar muscular atrophy
Not specified	Neurons intranuclear	PolyQ expanded annexins	Spinocerebellar ataxia 1, 2, 3, 7
Not specified	Glia cells intracytoplasmic	PolyQ expanded α1A calcium channel	Spinocerebellar ataxia 6
Not specified	Neurons intranuclear	PolyQ expanded TATA-binding protein	Spinocerebellar ataxia 17
Not specified	Neurons intranuclear	PolyQ expanded atrophin 1	Dentatorubral-pallidoluysian atrophy
Hirano bodies	Neurons	Actin	Neurodegenerative disorders
Collins bodies	Neurons	Neuroserpin	Forms of familial presenile dementia
Not specified	Neurons, many different cells	Ferritin	Form of familial neurodegenerative disorder
Neurofibrillary tangles	Neurons intracytoplasmic	Tau**	Alzheimer disease, fronto-temporal dementia, ageing, other cerebral conditions
Pick bodies	Neurons intracytoplasmic	Tau	Pick's disease
AαSyn	Neurons intracytoplasmic	α-synuclein**	Parkinson disease, other cerebral conditions
Russell bodies	Plasma cells	Monoclonal immunoglobulin	Several conditions, incl. multiple myeloma
Dutcher bodies			
Mott cell inclusions			
Biondi rings	Choroid plexus epithelial cells	Unknown	Ageing
Crystal-like inclusions	Plasma cells, proximal tubule cells, histiocytes	Monoclonal light Ig chains, usually kappa, rarely lambda	Monoclonal kappa light chain diseases
Not specified	Tumor cells	p53	Tumor cells
Not specified	Neurons, muscle	TDP-43	ALS/FTD***

*Simplified. Additional components may exist.
**Also included in Table 1 since deposits may appear extracellularly.
***ALS Amyotrophic lateral sclerosis, FTD Frontotemporal dementia.

Polyadenylate-binding protein 2 (PABPN1) mutant proteins form nuclear aggregates in oculopharyngeal muscular dystrophy, while protein TFG (TFG) variants are associated with Charcot-Marie-Tooth disease type 2 and hereditary motor and sensory neuropathy with proximal dominant involvement.

For the most part, the inclusions (except for the neurofibrillary tangles composed of aggregated Tau) are non-Congophilic. Is this biophysically significant or methodologic? Are the aggregates on the fibril forming pathway and not recognised because of the insensitivity of Congo red binding or ultrastructural identification of amyloid fibrils? Alternatively, is it possible that despite being potentially amyloidogenic the biological effects are not dependent on fibril formation per se? Thus, in our current state of knowledge, the distinction among intracellular protein aggregates based on the presence of mature fibrils may have little pathologic relevance.

One major unsolved pathogenetic question is the specific organ targeting of amyloid proteins. Selective cell vulnerability to intra-cellular aggregates is likely to reflect the relationship between two major factors, the metastability of its proteome, the relative proportion of cellular proteins that are relatively unstable, and the activity of its proteostasis network, an issue thus far best studied in the nervous system. In ALS spinal motor neurons reveal an expression pattern consistent with protein instability, particularly in the pre-synaptic terminal, and a diminution in proteasomal degradative activity relative to ALS insensitive neurons [23,24]. In Alzheimer's disease, the comparison of gene expression between brain regions with differential vulnerability showed that those that were more resilient exhibited a specific signature of proteostasis factor expression, particularly that of molecular chaperones thought to affect folding and post-translational modifications of β-amyloid and tau [25]. Since the efficiency of the proteostatic machinery varies among species, individuals, tissues, and with age [26], it may, at least in part, account for the selective toxicity and timing of the appearance of amyloid species in the neurodegenerative/intracellular amyloidoses. With respect to the systemic amyloidoses, there are data describing interactions of amyloidogenic light chains [27–29] and transthyretin [30,31] with their relevant target cells. A more detailed understanding of the molecular mechanisms of selective targeting and vulnerability could lead to more effective treatments, and possibly rescue, of end-organ damage.

Comment on intracellular protein aggregates

As discussed above there are many intracellular inclusions, not all with known composition, of which several show at least some typical amyloid fibril properties (Table 4).

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