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NOMENCLATURE ARTICLE

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

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Abstract

The Nomenclature Committee of the International Society of Amyloidosis (ISA) met during the XVth Symposium of the Society, 3 July–7 July 2016, Uppsala, Sweden, to assess and formulate recommendations for nomenclature for amyloid fibril proteins and the clinical classification of the amyloidoses. An amyloid fibril must exhibit affinity for Congo red and with green, yellow or orange birefringence when the Congo red-stained deposits are viewed with polarized light. While congophilia and birefringence remain the gold standard for demonstration of amyloid deposits, new staining and imaging techniques are proving useful. To be included in the nomenclature list, in addition to congophilia and birefringence, the chemical identity of the protein must be unambiguously characterized by protein sequence analysis when possible. In general, it is insufficient to identify a mutation in the gene of a candidate amyloid protein without confirming the variant changes in the amyloid fibril protein. Each distinct form of amyloidosis is uniquely characterized by the chemical identity of the amyloid fibril protein that deposits in the extracellular spaces of tissues and organs and gives rise to the disease syndrome. The fibril proteins are designated as protein A followed by a suffix that is an abbreviation of the parent or precursor protein name. To date, there are 36 known extracellular fibril proteins in humans, 2 of which are iatrogenic in nature and 9 of which have also been identified in animals. Two newly recognized fibril proteins, AApoCII derived from apolipoprotein CII and AApoCIII derived from apolipoprotein CIII, have been added. AApoCII amyloidosis and AApoCIII amyloidosis are hereditary systemic amyloidoses. Intracellular protein inclusions displaying some of the properties of amyloid, “intracellular amyloid” have been reported. Two proteins which were previously characterized as intracellular inclusions, tau and α -synuclein, are now recognized to form extracellular deposits upon cell death and thus have been included in Table 1 as ATau and A α Syn.

Abbreviations: ANS, Autonomic nervous system; CJD, Creutzfeldt Jakob disease; CNS, central nervous system; GSS, Gerstmann–Sträussler–Scheinker; ISA, International Society of Amyloidosis; PNS, peripheral nervous system; wt, wild type

The chemical diversity of amyloid and amyloidosis has been evident since the mid-1970s [1] and the number of known human amyloid proteins has steadily increased to 36 at present (Table 1). For more than 40 years, the Nomenclature Committee of the International Society of Amyloidosis (ISA) has published systematic nomenclature guidelines for amyloid fibril proteins and amyloidosis. Recently, the ISA

Keywords

Amyloid fibril, amyloid protein, amyloidosis, inclusion body, nomenclature

History

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Nomenclature Committee met during the XVth Symposium of the Society, 3 July–7 July 2016, Uppsala, Sweden, to assess the number of known amyloid fibril proteins and to review recommendations for clinical classification of amyloidosis syndromes.

Definition of an amyloid fibril protein

An amyloid fibril protein is a protein that is deposited as insoluble fibrils, mainly in the extracellular spaces of organs

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

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
A β 2M	β 2-Microglobulin, wild type	S	A	Musculoskeletal system
	β 2-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
A β	A β protein precursor, wild type	L	A	CNS
	A β protein precursor, variant	L	H	CNS
A α Syn	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

^aProteins are listed, when possible, according to relationship. Thus, apolipoproteins are grouped together, as are polypeptide hormones.

*ADan is the product of the same gene as ABri.

**Also called amylin.

***Not proven by amino acid sequence analysis.

and tissues as a result of sequential changes in protein folding that result in a condition known as amyloidosis.

An amyloid fibril protein occurs in tissue deposits as rigid, non-branching fibrils approximately 10 nm in diameter. The fibrils bind the dye Congo red and exhibit green, yellow or orange birefringence when the stained deposits are viewed by polarization microscopy. When isolated from tissues and analyzed by X-ray diffraction, the fibrils exhibit a characteristic cross β diffraction pattern.

Although Congo red staining properties constitute the gold standard for amyloid identification, interpretation is not always simple. New optically active, conformation sensitive

ligands have been introduced that may turn out to be very helpful [2].

To carry out chemical identification of an amyloid fibril protein, immunohistochemistry, Western blotting, mass spectrometry, after or without combination with laser capture, amino acid sequencing, and immune-electron microscopy are useful techniques. Imaging techniques have recently been suggested to give sufficient information for the diagnosis of some specific amyloid disorders [3] but experience is still limited. To be included in the official ISA Amyloid Fibril Protein Nomenclature List (Tables 1 and 2), an amyloid fibril protein must have been unambiguously characterized by

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

Fibril protein	Precursor protein	Systemic and/or localized	Affected organs or syndrome	Species
AL	Immunoglobulin light chain	S, L	Plasmacytoma	Cat, Horse
AA	(Apo) Serum amyloid A	S	Chronic inflammation or infections	Mouse, Cat, Cow, Dog, Duck, Guinea pig, etc.
AApoAI	Apolipoprotein AI	S	Age-related	Dog
AApoAII	Apolipoprotein AII	S	Age-related	Mouse
ATTR	Transthyretin, variant	S	Age-related	Vervet monkey
AFib	Fibrinogen A α	S	Spleen, liver	Stone marten
A β	A β precursor protein	L	Age-related	Dog, Sheep, Wolverine
AIAPP	Islet amyloid polypeptide	L	Islets of Langerhans, insulinoma	Apes, Cat, Raccoon
AIns	Insulin	L	Islets of Langerhans	Octodon degus
ACas	A-S2C casein	L	Mammary gland	Cow

protein sequence analysis when possible and described in a peer reviewed journal.

Two newly recognized fibril proteins, AApoCII derived from apolipoprotein CII [4] and AApoCIII derived from apolipoprotein CIII [5], have been added to Table 1. AApoCII amyloidosis and AApoCIII amyloidosis are rare hereditary systemic amyloidoses.

Amyloid fibril protein nomenclature

The amyloid fibril protein is designated protein A and followed by a suffix that is an abbreviated form of the parent or precursor protein name. For example, when amyloid fibrils are derived from immunoglobulin light chains, the amyloid fibril protein is AL and the disease is AL amyloidosis. Amyloid transthyretin is ATTR and the disease is ATTR amyloidosis. Thus AL or ATTR are not diseases; AL and ATTR are the disease causing proteins.

Traditionally, amyloid fibril protein variants have been named according to the substitution or deletion in the mature protein that is involved in the disease, e.g. ATTRV30M or ALysI56T and this principle should continue to be followed. The Sequence Variant Description Working Group (SVD-WG) convened by the Human Genome Variation Society recommends that observations be reported using an appropriate reference sequence, i.e. when genomic DNA is sequenced, a genomic DNA sequence is the preferred reference and (by inference) when a protein sequence is reported, an amino acid sequence is the preferred reference. The working group further recommends the use of the recently introduced Locus Reference Genomic sequence (LRG) (<http://www.lrg-sequence.org/>; the LRG collaboration maintains and creates LRGs [6]).

While the SVD-WG prefers the three letter amino acid designation to avoid confusion, the group finds the single letter amino acid code acceptable; we recommend use of the single letter amino acid code and the sequence numbering of the mature protein when reporting studies on amyloid proteins [7].

Amyloidosis nomenclature

The diseases known as the amyloidoses result from the systemic or localized deposition of amyloid fibrils in the

extracellular spaces of organs and tissues. To date, 36 distinct proteins have been identified as amyloid fibril proteins in human (Table 1). Amyloid deposition is seldom benign and, when clinical symptoms appear, they are frequently life-threatening.

A nomenclature should be stable but cannot be stationary. A surprising new example is the prion protein. A novel systemic form of amyloidosis with polyneuropathy associated has been described in which truncated prion protein is amyloid-forming [8]. This has been added to Table 1.

Many of the fibril forming proteins give rise to distinct amyloidosis syndromes named after that protein (Table 1), e.g. AL amyloidosis (localized or systemic), AA amyloidosis, wild type (wt) ATTR amyloidosis or hereditary ATTRV30M (*p.TTRV50M*) amyloidosis. The designations ATTRwt and ATTRm amyloidosis may be used for WT and hereditary ATTR amyloidosis, respectively. This chemically based nomenclature has been adopted by the World Health Organization [9] and consistently recommended by the ISA Nomenclature Committee (reviewed in reference [10]). It is of utmost importance to use the chemically based nomenclature, e.g. ATTRV30M amyloidosis or AL amyloidosis, in the diagnosis and treatment of amyloidosis, as the treatment plans for chemically distinct forms of amyloidosis differ markedly. It is to be emphasized that AL amyloidosis and ATTR amyloidosis are difficult to distinguish clinically and chemical identification of the amyloid fibril protein in each patient is required.

Amyloid fibril proteins in conditions other than amyloidosis

Some amyloid fibril proteins such as A β , ATau, A α -Syn and AIAPP play a pathologic role in neurodegenerative or endocrine diseases that are not clinically classified as amyloidosis.

Amyloid-like fibril aggregates of both mutant and wt forms of the tumor suppressor p53 have been detected in tumor tissues and are thought to be associated with cancer with a worsened prognosis (reviewed in reference [11]). Thus far these aggregates have not been shown to display amyloid fibril deposition *in vivo* and p53 has not been included in the current nomenclature.

Fibrillar fragments of prostatic acidic phosphatase (PAP) have been termed Semen-derived Enhancer of Virus Infection

Table 3. Intracellular inclusions with known biochemical composition, with or without amyloid properties.

Inclusion name	Site	Protein nature	Examples of associated disease
Lewy bodies	Neurons intracytoplasmic	α -synuclein*,**	Parkinson's disease
Huntington bodies	Neurons intranuclear	PolyQ expanded huntingtin	Huntington's disease
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's disease, fronto-temporal dementia, aging, other cerebral conditions
A α Syn	Neurons intracytoplasmic	α -synuclein**	Parkinson's disease, other cerebral conditions

*Simplified. Additional components may exist.

**Also included in Table 1 since deposits may appear extracellularly.

(SEVI). PAP fragments, are believed to play an active role in human immunodeficiency virus infections [12] and have been shown to form *in vivo* [13], although their role in transmission has been recently questioned [14].

There is a report that TTR aggregation plays a role in the pathogenesis of pre-eclampsia and that the native form prevents the onset of disease in a preclinical mouse model [15].

Intracellular amyloid protein inclusions

Intracellular protein inclusions such as neurofibrillary tangles have been described that have fibrillar structure, a cross β -sheet X-ray diffraction pattern and bind Congo red with green birefringence. The tangles had been considered to be “intracellular amyloid” and, up until now, were not included in the formal list of characterized amyloid fibril proteins. Lewy bodies in the brains of Parkinson's disease patients with dementia consist of fine amyloid-like fibrils, which sometimes, stain with Congo red and exhibit birefringence. Recently it has been recognized that ATau, associated with neurofibrillary tangles, and A α -Syn associated with Parkinson's disease accumulate, in extracellular deposits upon cell death. Therefore, these two proteins are now included in Table 1.

Other inclusions associated with neurodegenerative conditions have some, but not all, of the properties of amyloid fibrils. Some of the intracellular inclusions that have been biochemically characterized, at least partly, are included in Table 3.

Functional amyloid

Another nomenclature-related consideration has emerged with the use of the concept “functional” or non-pathologic amyloid. Structurally robust, protease resistant β -sheet fibrillar assemblies occur widely in nature, particularly in invertebrates, e.g. insects, spiders and also bacterial biofilms. In addition, it has been suggested that some human structures, such as the p-mel framework in melanosomes and the some polypeptide hormones when stored in secretory vesicles, have an amyloid fibril structure (reviewed in [16]). These more broadly applied circumstances have made it increasingly important to use clear definitions when using the words “amyloid” and “amyloidosis”.

Biophysical amyloid

The designation “amyloid”, first used in botany, was applied by Virchow, originally to corpora amylacea in the brain and later for the tissue deposits of systemic amyloidosis.

Subsequently, the concept of amyloid was expanded to denote diverse localized tissue deposits (e.g. in Alzheimer's disease or type 2 diabetes) with similar homogeneous appearance in light microscopy and with the same tinctorial and physical properties. The concept has further been broadened to include amyloid fibril formation in clinical conditions other than amyloidosis, e.g. formation of p53 amyloid-like fibrils in cancer (commented on above).

The concept of amyloid has been broadened into the extent that it is regularly used by biochemists and biophysicists for naturally occurring and synthetic protein fibrils with some amyloid properties. In order to avoid confusion, the ISA Nomenclature Committee has recommended the use of “amyloid-like” for synthetic fibrils [17].

Specific committee recommendations

- (1) Livers from patients with hereditary ATTR amyloidosis have been used for transplantation to non-ATTR patients with liver failure and subsequently ATTR amyloidosis has been observed in some recipients [18]. The term “Iatrogenic ATTR” has been used to describe these clinical situations. The Nomenclature Committee considers that authors may use the term Iatrogenic ATTR amyloidosis to describe ATTR amyloidosis as they wish and consider appropriate.
- (2) In 1999, the ISA Nomenclature Committee recommended that the mouse *Saa2* locus be renamed to mouse *Saa1*, based on the correspondence of its chromosomal mapping to that of human SAA1 [19]. The National Center for Biotechnology Information (NCBI) database retains the original *Saa2* designation for the locus now designated as mouse *Saa1*. Investigators will need to keep this in mind when using the NCBI databases. It is recommended that the 1999 ISA nomenclature for mouse genes and gene products continue to be used consistently.
- (3) The terms “hereditary amyloidosis” and “familial amyloidosis” refer to different entities. The term “hereditary amyloidosis” should be used when there is a mutation in the fibril protein gene itself, e.g. ATTR, ALys or AFib. The term “familial amyloidosis” should be used when the syndrome occurs in a familial setting due to mutations in genes expressing non-amyloid proteins, e.g. AA amyloidosis.
- (4) Synonyms and terminology used in the past when the chemical diversity of amyloid fibril proteins was

unrecognized remain in use today, but are not particularly useful and may be confusing. For example, synonyms for hereditary ATTR amyloidosis include Familial Amyloid Polyneuropathy Type I (Portuguese-Swedish-Japanese Type), Familial Amyloid Polyneuropathy Type II (Indiana/Swiss or Maryland/German Type), Leptomenigeal Amyloidosis, Familial Amyloid Cardiomyopathy, Familial Oculoleptomenigeal Amyloidosis (FOLMA). It is strongly recommended that the use of these terms be discontinued and that the syndrome be designated by the name of the protein. While the term familial amyloid polyneuropathy (FAP) is widely used in the neurology literature and may be included as appropriate, it is recommended that it be accompanied by ATTR.

- (5) The designation senile systemic amyloidosis (SSA) was coined when it became clear that this is a systemic disease with a specific amyloid protein and not only a cardiac disease that occurs particularly in old age [20]. It was later shown that the fibril protein in SSA is derived from WT TTR [21] and that the disease can occur at younger age. It is therefore the committee's recommendation to use "wild-type ATTR (ATTRwt) amyloidosis" instead of SSA. In a transition period both SSA and ATTRwt amyloidosis can be used simultaneously in order to avoid confusion.
- (6) The clinical classification of AL amyloidosis as primary amyloidosis or amyloidosis secondary to myeloma and AA amyloidosis as secondary amyloidosis is ambiguous and outdated and it has long been recommended that these designations not to be used [22].
- (7) The committee recommends that amyloid β precursor protein (A β PP) be used for the precursor of A β instead of amyloid precursor protein (APP).

Declaration of interest

The authors report no conflicts of interest.

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