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NOMENCLATURE ARTICLE

Amyloid nomenclature 2018: recommendations by the International Society of Amyloidosis (ISA) nomenclature committee

Merrill D. Benson[a], Joel N. Buxbaum[b], David S. Eisenberg[c], Giampaolo Merlini[d], Maria J. M. Saraiva[e], Yoshiki Sekijima[f], Jean D. Sipe[g] and Per Westermark[h]

[a]Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, IN, USA; [b]Department of Molecular Medicine, The Scripps Research Institute, La Jolla, CA, USA; [c]Department of Chemistry and Biochemistry, University of California, Los Angeles, California, USA; [d]Amyloid Research and Treatment Center, University of Pavia and IRCCS Policlinico San Matteo, Pavia, Italy; [e]Amyloid Unit, Institute of Molecular and Cellular Biology, University of Porto, Porto, Portugal; [f]Department of Medicine (Neurology and Rheumatology), Shinshu University School of Medicine, Matsumoto, Japan; [g]Department of Biochemistry (Retired), Boston University School of Medicine, Boston, MA, USA; [h]Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden

ABSTRACT

The nomenclature committee of the International Society of Amyloidosis (ISA) meets every second year to discuss and formulate recommendations. The conclusions from the discussion at the XVI International Symposium on Amyloidosis in Kumamoto, Japan, 25–29 March 2018 and afterwards are summarized in this Nomenclature Article. From having recommended the use of the designation "amyloid fibril" for *in vivo* material only, ISA's nomenclature committee now accepts its use more broadly following the international scientific literature. However, it is important always to stress the origin of the β-fibrils in order to avoid misunderstanding. Given the more broad use of the word "amyloid" several classes of amyloid fibrils may be distinguished. For the medical *in vivo* situation, and to be included in the amyloid nomenclature list, "amyloid" still means mainly extracellular tissue deposits of protein fibrils, recognized by specific properties, such as green-yellow birefringence after staining with Congo red. It should also be underlined that *in vivo* amyloid fibrils, in addition to the main protein contain associated compounds, particularly serum amyloid P-component (SAP) and proteoglycans, mainly heparan sulfate proteoglycan. With this definition there are presently 36 human amyloid proteins of which 14 appear only associated with systemic amyloidosis and 19 as localized forms. Three proteins can occur both as localized and systemic amyloidosis. Strictly intracellular aggregates are not included in this list.

Abbreviations: AL: amyloid light chain; ATTR: amyloid transthyretin; ISA: International Society of Amyloidosis; LRG: locus reference genomic

KEYWORDS
Amyloid; amyloidosis; misfolding; aggregation; nomenclature

Introduction

Since the second International Symposium on Amyloidosis in Helsinki, Finland in 1974 a nomenclature committee has met, officially recognized diseases related to the deposition of new amyloid proteins, discussed nomenclature problems and given recommendations. Since our journal started, these recommendations have been published in Amyloid.

The Nomenclature Committee of ISA met at the XVI International Symposium on Amyloidosis in Kumamoto, Japan, 25–29 March 2018 and current problems were discussed. Two new members were welcomed: David Eisenberg, USA and Yoshiki Sekijima, Japan. The basic nomenclature, most recently defined in 2016 [1], was confirmed.

Amyloid

The word "amyloid" is an enigmatic one that needs to be precisely defined. It means literally starch-like (amylon (Greek), amylum (Latin) is starch) and was originally used in botany but adopted by Rudolf Virchow 1854 to be used for the material we today call AA amyloidosis. Subsequently, when more defining histologic staining methods were developed, particularly Congo red combined with polarization microscopy, it was discovered that a number of similar mainly extracellular deposits could be identified in different tissues and each was usually associated with a specific disease. In order to differentiate these heterogeneous groups of deposits from the typical ones identified by Virchow, different names were given, e.g. para-amyloid. Para-amyloid was also a problematic name; it was

CONTACT Per Westermark Per.Westermark@igp.uu.se Department of Immunology, Genetics and Pathology, Uppsala University, SE 75185 Uppsala, Sweden

sometimes used for amyloid associated with myeloma (AL amyloid) or pancreatic islet amyloid in diabetes (AIAPP amyloid according to our present nomenclature). The nomenclature was purely descriptive since the biochemical nature was unknown. In 1959 Cohen and Calkins showed that the light microscopically hyaline-appearing amyloid in reality is composed of fibrils around 10 nm in width of indeterminate length. The next critical analytic step was the finding by Glenner and coworkers that the protein fibrils are aligned as "cross β-sheets" [2]. All this basic knowledge came from the medical field. Subsequently and most importantly it was demonstrated that a number of different polypeptides aggregate into *in vivo* amyloid deposits and that fibrils in any given patient's tissues were generally formed from a single protein precursor.

In human and veterinary medical practice amyloid is a pathological deposited proteinaceous material, recognized by certain properties and appearance. However, as is described below, the word amyloid is now used much more broadly.

Amyloidosis

Amyloidosis is a disease associated with deposits of amyloid fibrils found in humans and in many other vertebrate species. The designation amyloidosis is nowadays mainly used for systemic disease in which the aggregated proteins definitely are pathogenic. The situation is more complicated with localized forms. For example, although tumor-like AL amyloid ("amyloidoma") should be accepted as amyloidosis, the question of disease causation of amyloid is still uncertain in conditions such as Alzheimer's disease and type 2 diabetes. Although protein aggregation and amyloid formation are typical in both these diseases and most likely involved in their pathogenesis, they are still not primarily defined as amyloidoses but this may change in the future.

Amyloid fibril

The fibril constitutes the main component of amyloid deposits. It also determines many main properties of the material and of the amyloid diseases, including persistence and seeding behavior. The amyloid fibril is a polymeric structure in which protein backbones arranged in β secondary structure are hydrogen-bonded, forming long protofilaments. Two or more identical protofilaments interact via their sidechains to form the characteristic fibrils which are around 10 nm in diameter. This principal structure of the fibril can be mimicked *in vitro* with the use of well-defined peptides, also from peptides not appearing as *in vivo* amyloid. The hydrogen bonding of the peptide backbone as well as participation of sidechains have been analyzed in detail [3,4].

Although it is clear that there is no amyloid without fibrils, there are also other components present in the deposits. Some of them are more or less ubiquitous, particularly serum amyloid P-component (SAP) and heparan sulfate proteoglycan (HSPG). These are closely associated with the fibrils. There are in addition several other components present in the deposits such as several apolipoproteins. While the association of proteoglycans and SAP with amyloid has been studied in detail much less is known about the other components. The importance of the associated components for development of *in vivo* amyloid and for its persistence is still unclear.

Understanding the nature of the fibrils inspired George Glenner, the discoverer of the β-structure of amyloid fibrils, to suggest a new name for the diseases: β-fibrilloses [5]. However, and perhaps unfortunately, this nomenclature never took root. Even if the fibrils are the main component of *in vivo* amyloid they do not necessarily explain all of its properties. SAP may be of central importance for the resistance to degradation of amyloid fibrils [6] and bound HSPG, which explains the acidic character of amyloid and some specific staining properties, may interact with and influence cells at deposits.

The problem of nomenclature is that at present the medical and biophysical scientific communities are using different definitions of "amyloid". The designation amyloid came from the medical field but has been adopted by biochemists and biophysicists and is now generally used for all cross β-sheet fibrils. This use is fully established in the biochemical-biophysical field. The ISA Nomenclature Committee had earlier recommended the use of "amyloid-like" for such fibrils but given the situation we accept "amyloid fibrils" also for other β-sheet fibrils. However, for clarity the origin must always be described. The word "amyloid", without further explanation should be restricted to *in vivo* or *ex vivo* deposits.

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 some polypeptide hormones when stored in secretory vesicles, have an amyloid fibril structure (reviewed in [7]). These more broadly applied circumstances have made it increasingly important to use clear definitions when using the words "amyloid" and "amyloidosis".

Amyloid fibril classes

As described above, "amyloid" is used for several different natural and synthetic materials. The situation is becoming even more complicated now that cell biologists are beginning to use the term "amyloid-like" for a different type of fiber, those that form from the low-complexity domains of hydrogels [8]. There may be a need of creating terms for at least five classes of related fibrils:

1. *In vivo* and *ex vivo* disease-related fibrils
2. *In vivo* and *ex vivo* functional fibrils

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, Lung, Ligaments, Tenosynovium
	Transthyretin, variants	S	H	PNS, ANS, heart, eye, leptomen.
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
ACatK****	Cathepsin K	L	A	Tumor associated

[a]Proteins 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.
****Full amino acid sequence to be established.

3. Recombinant fibrils of disease-related proteins and of functional "amyloid" proteins
4. Fibrils from synthetic or non-disease-related peptides
5. Fibrils from hydrogels that give the cross-β diffraction pattern.

Currently, we recommend that use of "amyloid" (without further explanation such as "amyloid state" or "functional amyloid") and "amyloidosis" be restricted to pathological deposits in human and animal medical field. "Amyloid fibrils", "amyloid state" etc. can be used more broadly but have to be defined. However, this is a provisional recommendation and the subject will be discussed further.

Amyloid fibril protein nomenclature in medical practice

Given the relatively diverse use of "amyloid fibril" a clear definition of "amyloid" and "amyloidosis" is necessary in medical practice. In human and veterinary medicine "amyloid" means mainly extracellular deposits of a fibrillary protein with particular properties, which make them recognizable by different methods including affinity of Congo red and yellow-green birefringence after such staining. A number of proteins (presently 36 in human and 10 in other vertebrates) have been identified (Tables 1 and 2) and more are to be expected.

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	Many mammalian and avian species: Mouse, Cat, Cow, Dog, Duck, Guinea pig, etc.
AApoAI	Apolipoprotein AI	S	Age-related	Dog
AApoAII	Apolipoprotein AII	S	Age-related	Mouse
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
ACas	A-S2C casein	L	Mammary gland	Cow

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 ntracytoplasmic	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 disease, fronto-temporal dementia, aging, other cerebral conditions
AαSyn	Neurons Intracytoplasmic	α-synuclein**	Parkinson disease, other cerebral conditions

*Simplified. Additional components may exist.
**Also included in Table 1 since deposits may appear extracellularly.

Name of amyloid proteins and associated diseases

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. This designation should also be used for the associated amyloid disease. 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. Importantly, AL or ATTR are not diseases; AL and ATTR are the disease causing proteins.

Amyloid protein variants

As stated in the previous Nomenclature Guidelines [1] "amyloid fibril protein variants are named according to the substitution or deletion in the mature amyloid protein, e.g. ATTRV30M or ALysI56T and this principle should continue to be followed. The Sequence Variant Description Working Group (SVDWG) 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."

Amyloid disease 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. Since the previous Nomenclature Meeting in Uppsala 2016 one new protein has been identified as amyloid fibril components in human, cathepsin K, found localized to an angiomyolipoma [9]. Since the full amino acid sequence was not available it was not established whether the protein was wild-type or variant. For further description of the amyloid conditions please see previous publication [1]. For current proteins, see Table 1. New protein variants, particularly TTR are continuously reported and these can be found in [10].

The name "hereditary" is recommended rather than "familial". Thus, diseases depending on a mutation in the TTR gene should be called "hereditary ATTR (ATTRv; v for variant) amyloidoses". By fulfilling a patients" wish we now recommend ATTRv instead of ATTRm. The designations "familial amyloid polyneuropathy" and "familial amyloid cardiomyopathy" should be regarded as outdated and as exact as possible name should be used. An example is "ATTRV30M amyloidosis". Descriptions of major clinical presentation can be added, for example "with cardiomyopathy".

Amyloid proteins in animals

The number of known amyloid proteins in animals is 10, of which only one is not seen in human (Table 2). No hereditary forms are known.

Intracellular inclusions

Intracellular inclusions with or without amyloid staining properties are given in Table 3.

Specific recommendations

1. Amyloid fibrils are not uniform and several "classes" can be recognized. When the word "amyloid" is used a more precise definition is therefore necessary.
2. AL, ATTR, etc. are amyloid protein names. Corresponding diseases are AL amyloidosis, ATTR amyloidosis and so on.
3. Diseases depending on amyloid protein gene mutations are "hereditary" and should not be called "familial". The designations "familial amyloid polyneuropathy, FAP", or "familial amyloid cardiomyopathy, FAC" should be not used.
4. A variant amyloid fibril protein is best defined by exact description of the mutation. The variant should be defined by one-letter-code and be numbered from the mature protein, e.g. ATTRV122I or ATTRV30M. Instead of the exact mutation the designation ATTRv (variant) can be used and is preferred to ATTRm (mutant).
5. Please see also recommendations in the previous Nomenclature Article [1].

Disclosure statement

No potential conflict of interest was reported by the authors.

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