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REVIEW

Cerebral amyloidosis: amyloid subunits, mutants and phenotypes

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Abstract Cerebral amyloid diseases are part of a complex group of chronic and progressive entities bracketed together under the common denomination of protein folding disorders and characterized by the intra- and extracellular accumulation of fibrillar aggregates. Of the more than 25 unrelated proteins known to produce amyloidosis in humans only about a third of them are associated with cerebral deposits translating in cognitive deficits, dementia, stroke, cerebellar and extrapyramidal signs, or a combination thereof. The familial forms reviewed herein, although infrequent, provide unique paradigms to examine the role of amyloid in the mechanism of disease pathogenesis and to dissect the link between vascular and parenchymal amyloid deposition and their differential contribution to neurodegeneration.

Keywords Amyloid proteins · Cerebral amyloid angiopathy · Amyloid plaques · Protein folding disorders

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Introduction

Cerebral amyloid diseases are considered to be part of an emerging complex group of chronic and progressive entities collectively known as "Disorders of Protein Folding" that include, among many others, Alzheimer's disease (AD), polyglutamine-repeat disorders, cataracts, amyotrophic lateral sclerosis, Parkinson's disease and other synucleinopathies, tauopathies, a variety of systemic amyloidosis, prion diseases, cerebellar ataxias and type-II diabetes [1–4]. In all these diseases, through mechanistic pathways poorly understood, soluble proteins normally found in biological fluids change their conformation and form either insoluble aggregates that accumulate intra- or extra-cellularly or fibrillar lesions usually associated with local release of inflammatory mediators, oxidative stress, complement activation, cell toxicity, apoptosis, or a combination thereof resulting in cell damage, organ dysfunction and eventually death.

Regardless of the organ targeted and the misfolded protein involved, all extracellular fibrillar deposits, generically referred to as amyloid, share common physical, structural, and tinctorial properties. In general, they are: (1) highly polymerized and poorly soluble assemblies, features that preclude their efficient physiologic in vivo removal by macrophages requiring the use of strong detergents, harsh acid conditions or concentrated

Table 1 Human amyloid subunits linked to disease

Biological function of the precursor protein	Protein precursor of the amyloid subunit	Chromosome	Amyloid subunit	Systemic (S) or organ-restricted (R)	Central nervous system	Sporadic (S) or hereditary (H)
Immune system associated proteins	Light chain λ	22	ALλ	S, R	Yes	S
	Light chain κ	2	ALκ	S, R	Yes	S
	Heavy chain γ	14	AHγ	S, R	No	S
	Heavy chain μ	14	AHμ	S, R	No	S
	Heavy chain α	14	AHα	S, R	No	S
	β2-Microglobulin	15	Aβ2M	S	No	S
Apolipoproteins	apoSAA	11	AA	S	No	S
	apoA-I	11	AApoA-I	S	No	H
	apoA-II	1	AApoA-II	S	No	H
	apoA-IV	11	AApoA-IV	S	No	H
Transport proteins	Transtyretin	18	ATTR	S	Yes	S, H
	Lactoferrin	3	ALac	R	No	H
Regulatory proteins	Gelsolin	9	AGel	S	Yes	H
	Semenogelin I	20	ASem	R	No	H
Coagulation factors	Fibrinogen, α chain	4	AFib	S	No	H
Hormones	Calcitonin	11	ACal	R	No	H
	Prolactin	6	APro	R	No	H
	Atrial natriuretic factor	1	AANF	R	No	H
	Amylin	12	AIAPP	R	No	H
	Insulin	11	AIns	R	No	H
Enzymes	Lysozyme	12	ALys	S	No	H
Enzymatic inhibitors	Cystatin C	20	ACys	S	Yes	H
Cell receptor	Oncostatin M receptor	5	AOMR	R	No	S, H
Cell adhesion proteins	Keratoepithelin	5	AKep	R	No	H
Cytoskeletal proteins	Tau	17	ATau	R	Yes	S, H
	Keratin	12,17	AKer	R	No	H
Infectious agents	Prion protein	20	APrP^{SC}	R	Yes	S, H
Proteins of unknown biological function	Lactadherin	15	AMed	R	No	Unknown
	ODAM	4	AOaap	R	No	H
	Aβ precursor protein	21	Aβ	R	Yes	S, H
	ABri precursor protein	13	ABri	S	Yes	H
	ADan precursor protein	13	ADan	S	Yes	H

chaotropes to partially extract them in vitro from the tissue deposits; (2) weakly antigenic, consistently failing to induce a high titer response or high affinity antibodies in different animal species; (3) structurally rich in β-pleated sheet conformations, a property accountable for the apple-green birefringence of the deposits when observed under polarized light after Congo red staining as well as for their yellow–green fluorescence after thioflavin S staining; and (4) fibrillar in shape when negatively stained and observed under the electron microscope [5–7].

Amyloid proteins

Amyloid fibrils are composed of self-assembled, low-molecular-weight peptides usually representing fragments of larger precursor molecules normally present in body fluids. In humans, more than 25 different proteins are known to self-assemble and form fibrillar amyloid structures. The respective precursors are totally unrelated proteins which under physiologic conditions exhibit a wide range of biological functions (Table 1). Despite these differences, all share the conformational, immunogenic, and

tinctorial properties described above and are typically constituted of molecules in the mass range of 4–30 kDa with frequent heterogeneity at the amino and/or carboxyl-terminal ends.

Cerebral amyloid diseases

The most frequent forms of amyloidoses are those localized to the central nervous system (CNS). Only about one-third of amyloid proteins known to be linked to disease in humans (Table 1) produce fibrillar deposits in the CNS which, in turn, translate in cognitive deficits, dementia, stroke, cerebellar and extrapyramidal signs, or a combination thereof. Classical lesions in the CNS, illustrated in Fig. 1, are usually found in the form of: (1) parenchymal pre-amyloid deposits, amorphous non-fibrillar structures negative under Congo red or thioflavin S staining, which are visualized by their diffuse immunoreactivity with specific antibodies, and are extractable by treatment with aqueous buffers in the presence of mild detergents; (2) parenchymal fibrillar amyloid lesions, usually in the form of compact plaques exhibiting extensive Congo red/thioflavin S staining, which are immunoreactive with specific antibodies and poorly soluble, requiring the use of either chaotropes (e.g., 6 M guanidine-HCl) or strong acids (e.g., formic acid) to be retrieved from the lesions; and (3) cerebral amyloid angiopathy (CAA), Congo red/thioflavin S positive fibrillar deposits affecting the media and adventitia of medium-sized and small cerebral arteries and arterioles as well as many cerebral capillaries. In general terms, stroke—either ischemic or hemorrhagic—is the most common clinical manifestation of amyloid deposition primarily restricted to cerebral vessel walls, whereas widespread distribution throughout brain parenchymal areas is concomitantly associated with dementia.

Aβ-related cerebral amyloidoses

Sporadic AD

Late-onset (sporadic) AD is the most common form of dementia in humans over the age of 65 and affects more than 50% of individuals 85 or older. It is a debilitating neurodegenerative disorder that directly affects millions of people and indirectly touches the lives of tens of millions of others who must deal with many years of cognitive decline of their loved ones. Currently, with an estimated 5.3 million Americans having AD and a health care cost of more than US$148 billion each year, the disease is one of the major public health concerns, not only in the US but in all developed countries. These figures are likely to increase dramatically in the next decades with the aging of the world population. Advances in medicine and medical technology, as well as improved social and environmental conditions, are expanding life expectancy with significant numbers living well into their 80s and 90s. Since the incidence and prevalence of AD and other dementias increase with age, the number of people with these conditions will also grow rapidly unless new therapeutic avenues are discovered precluding or at least delaying the disease onset.

Neuropathological hallmarks of AD (Fig. 1a–c), described more than 100 years ago, are the presence of intraneuronal neurofibrillary tangles (NFT)—deposits of hyperphosphorylated protein tau in the form of paired helical filaments—together with the existence of parenchymal extracellular deposits composed of both diffuse pre-amyloid lesions and mature amyloid plaques. Together with these features, fibrillar amyloid deposition is also commonly observed in medium-sized and small cerebral vessels. Although its significance was ignored for decades, the vascular dysfunction resulting from amyloid deposition at the cerebral vessel walls is considered today an active player in the mechanism of neurodegeneration and a major contributor to the disease pathogenesis [8–12]. Cerebrovascular and parenchymal lesions are composed of self-aggregates of Aβ protein generated by proteolytic cleavage of a larger precursor APP by the so-called β and γ secretases [7, 13, 14]. While a single protein, BACE1, is responsible for the β-secretase activity, γ-secretase is composed of four essential subunits: presenilin-1 (PS1) or presenilin-2 (PS2), together with nicastrin, APH-1, and PEN-2 [15, 16]. The γ-secretase complex cleaves at multiple sites within the transmembrane domain of APP, generating Aβ peptides ranging in length from 38 to 42 residues [17]. Nearly 90% of secreted Aβ ends at residue 40, whereas Aβ42 accounts for only <10%, and peptides ending at residues 38 are minor components [15]. Notably, the pattern and distribution of these species varies among the different topographical lesions. Parenchymal deposits consist of Aβ42 as the major component, whereas vascular Aβ—particularly in the large leptomeningeal vessels—is primarily composed of Aβ40 species organized in large concentric sheets and replacing the smooth muscle cell layer [18]. Amyloid associated with arterioles and small cortical arteries contains a mixture of Aβ40 and Aβ42, while deposits affecting the capillary network are mainly composed of Aβ42 [19]. The reasons for this selectivity as well as its importance for the pathogenesis of the disease remain unclear.

Familial AD

Early-onset familial forms of AD with clinical symptoms appearing before the age of 65 account for less than

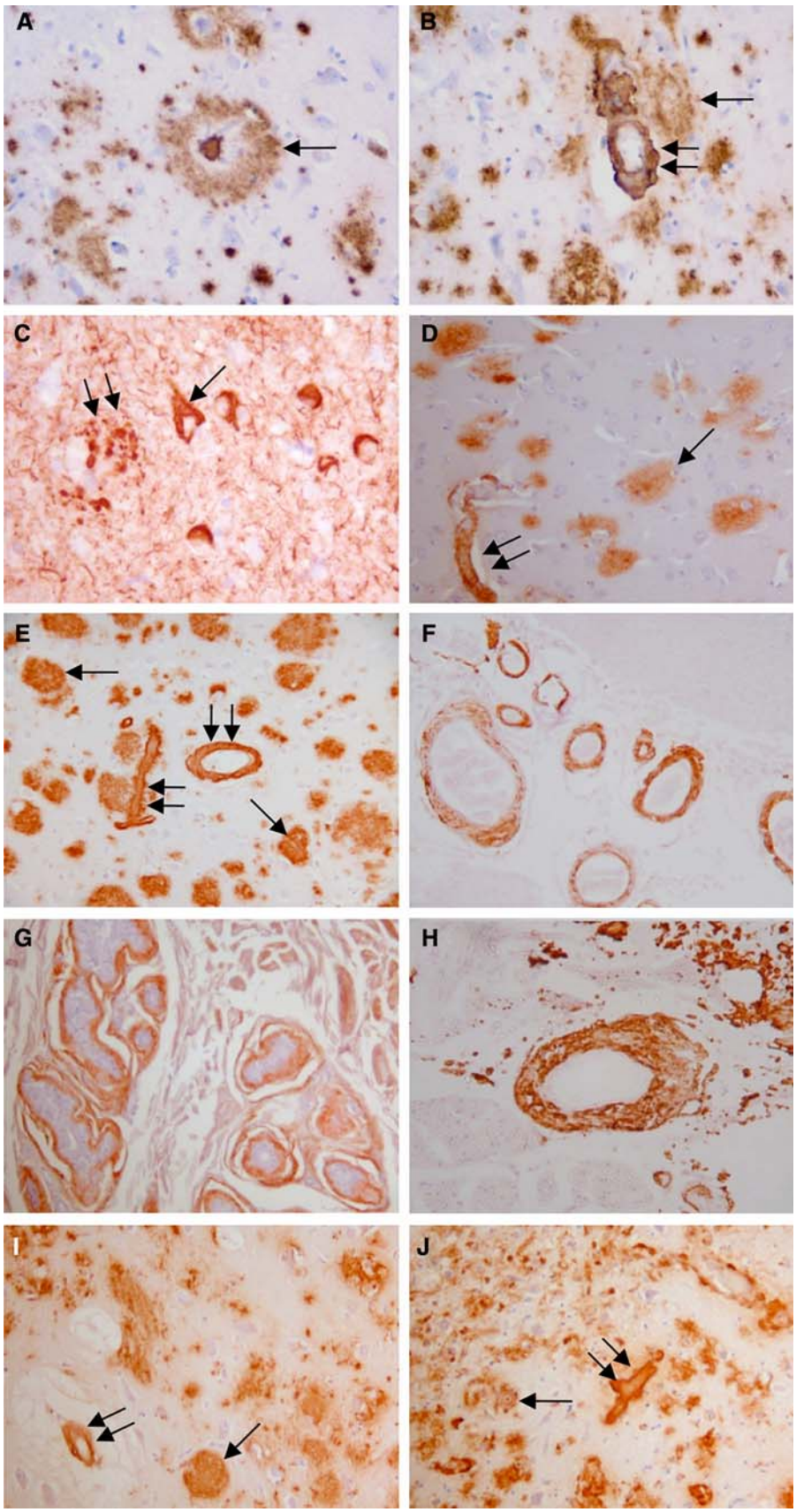

Fig. 1 Immunohistochemical analysis of amyloid deposits in cerebral amyloidosis. **a** Aβ-positive plaques (*arrow*) and **b** cerebral amyloid angiopathy (*double arrow*) in a case of Alzheimer's disease. **c** Neurofibrillary tangles (*arrow*), neuropil threads and plaque-associated abnormal neurites (*double arrow*) demonstrated with tau immunohistochemistry in Alzheimer's disease. **d** Aβ deposition in blood vessels (*double arrow*) and diffuse parenchymal plaques (*arrow*) in the cerebral cortex in HCHWA-D. **e** Deposition of Aβ-peptide in characteristic cotton wool plaques (*arrow*) together with severe CAA (*double arrow*) is a feature of familial Alzheimer's disease with ΔI83/ΔM84 *PS1* mutation. **f** Accumulation of mutated cystatin C in leptomeningeal blood vessels in a case of HCHWA-Icelandic type. **g** AGel deposition in skin blood vessels in familial amyloidosis of the Finnish type. **h** ATTR deposition in leptomeningeal blood vessels in the Hungarian form of meningovascular amyloidosis. **i** Widespread ABri deposition in large parenchymal plaques (*arrow*) and ABri CAA (*double arrow*) in familial British dementia. **j** Severe CAA (*double arrow*) and diffuse plaques (*arrow*) due to ADan deposition in familial Danish dementia

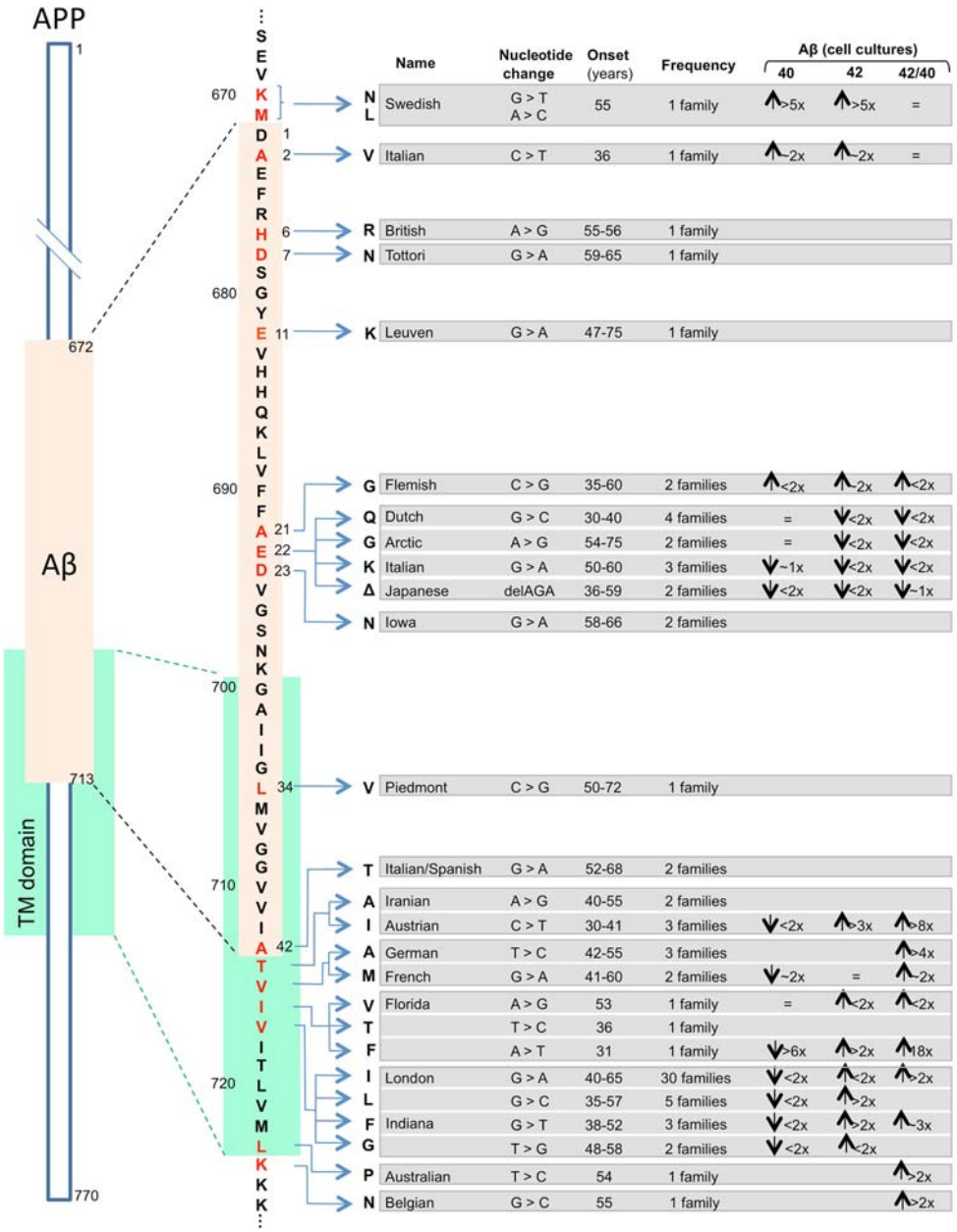

Fig. 2 Pathogenic mutations in exons 16 and 17 of APP. The diagram summarizes the location, nucleotide change, disease onset, and frequency of each of the known pathogenic mutations. Variations in Aβ40 and Aβ42 concentrations secreted by transfected cells in culture are also indicated

5–10% of the total cases. They are linked to mutations in three different genes codifying for APP, PS1, and PS2. In addition, specific allelic combinations of the *APOE* gene have been linked to AD as a risk factor for the disease [20]. The APOE ε4 genotype which occurs in 16% of the population [21] is the major susceptibility gene identified in the human genome for both rare early-onset and sporadic late-onset AD [22]. Nevertheless, in spite of this association, many ε4-positive individuals do not develop AD and many AD patients do not carry these genes suggesting that APOE ε4 gene may act as a molecular chaperone promoting fibrillogenesis and deposition of Aβ [23].

Of the genes directly related to the development of familial AD, *PSEN1* and *PSEN2* mutations affect the levels of Aβ42 production, whereas nucleotide changes within the APP molecule have a differential effect depending on the location of the mutated residue (Fig. 2). Amino acid substitutions flanking the Aβ region in close proximity to the β-secretase cleavage site modulate the rate of enzymatic processing of APP, resulting in increased production of Aβ42 and Aβ40 while maintaining the ratio Aβ42/Aβ40 unaffected and translating in a classic early-onset AD clinical phenotype [24, 25]. As illustrated in Fig. 2, the Swedish double mutation (K670N/M671L) [26] increases the production of Aβ40 and Aβ42 by >5-fold, a feature that

has been reproduced with transfected cells in culture [27, 28]. Similarly, the recently reported Italian mutation (A673V) [29] that manifests as early-onset AD only in homozygous individuals (see below) shows enhanced production of both Aβ species by ~2-fold maintaining the ratio Aβ42/Aβ40 unaltered, features also reproduced in cell cultures. In contrast, the numerous mutations occurring in close proximity to the γ-secretase cleavage sites are typically associated with increased production of Aβ42—and, in many instances, lower levels of Aβ40—in a similar manner to the effect caused by mutations in the presenilin genes [27, 30]. As a result, the ratio Aβ42/Aβ40 in all these mutants is several fold elevated, in some cases reaching ~18-fold values (see Fig. 2). Amino acid substitutions within residues 21–23 and 34 of the Aβ peptide are, with few exceptions [31], associated with prominent vascular compromise. As detailed below, many of these mutants are primarily associated with episodes of cerebral hemorrhage rather than dementia. For space considerations, we will limit this review to those Aβ variants located within the Aβ sequence. A complete list of all reported APP genetic variants as well as the pertinent references may be found at the Alzheimer Disease and Frontotemporal Dementia Mutation Database (http://www.molgen.ua.ac.be/ADMutations/) and have been reviewed in [25].

Aβ mutations within the 21–23 amino acid residue cluster

The Aβ region comprising residues 21–23 is considered a "hot spot" for mutations due to the high number of genetic variants reported in this area of the molecule. Mutations within this amino acid cluster, described below, typically show strong vascular compromise and primarily associate with CAA, hemorrhagic strokes and dementia.

AβE22Q mutation

The first described intra-Aβ mutation was found in a condition known as hereditary cerebral hemorrhage with amyloidosis, Dutch type (HCHWA-Dutch), an autosomal dominant disorder clinically defined by recurrent strokes, vascular dementia, and fatal cerebral bleeding in the fifth to sixth decades of life. The mutation in which Gln replaces a Glu residue at position 22 (AβE22Q) results from a single nucleotide transversion (G for C) at codon 693 [32]. Carriers of the mutation develop recurrent episodes of cerebral hemorrhages correlating with massive amyloid deposition in the walls of leptomeningeal and cortical arteries and arterioles (Fig. 1d), as well as in vessels in the brainstem and cerebellum [33], a phenotype recapitulated, albeit at old age, in transgenic mice carrying the mutation [34]. In addition to the vascular involvement, parenchymal amyloid deposits resembling the diffuse preamyloid lesions seen in AD are also observed in Dutch familial cases, while dense-core plaques and neurofibrillary tangles are rare or even completely absent [32]. The non-fibrillar diffuse plaques, variably associated with reactive astrocytes and activated microglia [35], seem to evolve into more fibrillar, dense lesions which are more abundant in older patients while younger patients have more fine diffuse plaques [36]. Nevertheless, the degree of dementia appears to be independent of plaque involvement and neurofibrillary degeneration, which is absent or limited, and contrastingly correlates with the severity of CAA [37].

Aβ1-40 is the predominant Aβ species of HCHWA-D vascular amyloid, with wild-type and Dutch-type mutated sequences present at a 1:1 molar ratio. In contrast, Aβ1-42 is only a minor component of the vascular deposits [34, 38, 39] and is uniquely associated with species bearing the mutation and not with those originated from the normal allele [40]. In cerebral cortex Aβ1-42 forms—either wild-type or carrying the E22Q substitution—were not detectable by western blotting, and the Aβ1-42:Aβ1-40 ratio, as determined by ELISA, was considerably lower than in AD cases [34].

In vitro cell culture studies demonstrate that E22Q has potent toxic effects on cerebrovascular endothelial and smooth muscle cells [41, 42], likely reflecting the in vivo hemorrhage-associated phenotype. The variant is a strong inducer of the Bax pro-apoptotic mitochondrial pathway leading to the release of cytochrome *c* to the cytosol, events accompanied by downstream nuclear fragmentation [43]. The effect of E22Q on endothelial cells goes beyond the induction of apoptosis. The variant is also a potent angiogenesis inhibitor, affecting the FGF-2 signaling pathway, downregulating phosphorylation of the FGF-2 receptor, and the Akt survival signaling [44]. All these events lead to the ultimate endothelial dysfunction and are likely to contribute—solely or partially—to the disturbances in membrane permeability and hemorrhagic manifestations present in the kindred.

E22Δ deletion mutation

Recently, a novel deletion mutation of the APP gene (E693Δ) was reported in Japan in patients showing Alzheimer's-type dementia and which results in a variant-Aβ lacking Glu at position 22 [45]. No neuropathological information is available to date on these cases but in vitro culture experiments indicate enhanced intracellular accumulation and markedly reduced secretion of this variant-Aβ in transfected cells. Notably, intracellular E22Δ was found to be predominantly composed of oligomeric forms which accumulate in endoplasmic reticulum, Golgi apparatus, early and late endosomes, lysosomes, and

autophagosomes [40], all of which have been proposed as intracellular sites of Aβ generation and/or degradation, suggesting an impairment of APP/Aβ trafficking associated with the mutation. Consistent with the nonfibrillogenic property of E22Δ, a very low amyloid signal was observed in the patient's brain on positron emission tomography using Pittsburgh compound-B, pointing out to synaptotoxic Aβ oligomers as the likely cause of dementia in this pedigree [45, 46].

Aggregation studies using synthetic homologues demonstrated that AβE22Δ is more resistant than wild-type Aβ to proteolytic degradation exhibiting a unique property of enhanced oligomerization in the absence of fibrillization. In line with the notion of oligomeric assemblies as the culprit of AD pathogenesis, E22Δ inhibits hippocampal long-term potentiation more powerfully than wild-type Aβ upon injection into rat cerebral ventricles.

AβE22K mutation

The substitution of G for A at codon 693 resulting in a Glu for Lys amino acid change at position 22, the same site of the Dutch mutation, was found in three apparently unrelated Italian families [41]. This genetic variant, although much less studied than the Dutch, is also linked to familial CAA with cerebral hemorrhage. The disease, associated with early onset and death between ages of 65 and 75, is clinically characterized by a 10- to 20-year progression of recurrent strokes and mild cognitive decline. The neuropathological findings also appear to resemble those in the Dutch kindred with extensive Aβ deposits in the walls of leptomeningeal and cortical vessels. The parenchymal compromise is limited to diffuse thioflavin S-negative deposits with absence of mature plaques and neurofibrillary tangles. Immunochemical studies with C-terminal specific antibodies indicate that, as it is most common in CAA pathology including that associated with the Dutch variant [36], Aβ40 species predominate in the vascular deposits and Aβ42 in the parenchyma.

The Italian variant exhibits in vitro a predominantly unordered secondary structure and a low fibrillization tendency resulting in the formation of atypical fibrils—short and straight, without the distinctive twisted pattern characteristic of most amyloid molecules and at an even lower rate than the Aβ40 wild-type counterpart [41]. These conformational properties correlate well with the predominantly thioflavin S-negative fluorescence of the parenchymal and vascular deposits observed in the Italian kindred, as well as with the lack of toxicity for vessel wall cells exhibited by synthetic homologues of the genetic variant. The lower capacity of Italian-Aβ to induce apoptosis in cerebrovascular endothelial cells in comparison to the Dutch variant may in turn reflect the later onset of the disease.

AβE22G mutation

A form of AD affecting a family of northern Sweden and spanning four generations is characterized by a different genetic substitution, A to G also at codon 693, known as the Arctic mutation, and which results in the substitution of Glu for Gly at position 22 of Aβ. The phenotypic manifestation of the disease is memory impairment at early onset—mean age 57 years—with progressive cognitive decline rather than stroke [47]. The clinical history is typical of AD but without the severe amyloid angiopathy that characterizes the other mutations within the Aβ sequence. The disease shows a slow insidious progression and decline in short-term memory as the first presenting symptoms with no signs of strokes or significant vascular involvement found in the cases that were subjected to neuroimaging studies. The parenchymal compromise is recapitulated in transgenic mice carrying the Arctic mutation which show an aggressive formation of plaque deposits in association with dystrophic neurites and in the absence of vascular involvement. However, the disease appears to be pleiotropic since one possibly related Swedish patient with the same mutation demonstrated moderate to severe CAA in cortical and leptomeningeal vessels as well as senile plaques and neurofibrillary tangles [48].

In vitro, E22G induces a dramatic increase in the rate and capacity to form protofibrils in comparison to the wild-type counterpart [47], significantly enhancing the peptide insolubility, a phenomenon likely correlating with the accelerated disease initiation and progression observed in vivo. E22G had a weaker apoptotic effect on cerebrovascular endothelial cells in comparison with the hemorrhage-associated E22Q correlating with the absence of stroke and hemorrhagic manifestations in the Arctic kindred [44]. Notably, carriers of the Arctic mutation show lower levels of both Aβ42 and Aβ40 than healthy family members, a feature observed even in very young mutation carriers—20–30 years before the expected onset of the disease—suggesting a long period of biochemical abnormality before the clinical onset. The decreased levels of Aβ peptides observed in the Arctic cases were also reproduced in transfected cell lines and have been claimed to reflect an altered APP processing induced by the mutation [47].

AβA21G mutation

The Flemish mutation is a C to G transversion at codon 692 of APP resulting in an Ala for Gly substitution at position 21 of Aβ and leading to a form of AD with prominent amyloid angiopathy. The presence of the mutation which correlates with early onset of the disease and death occurring at a mean age of 53, has been reported in two

kindreds, a four-generation Dutch family with 17 affected members [49] and a British family with five affected individuals. Whereas some of the cases presented with lobar intracerebral hemorrhage, other members in both pedigrees developed presenile dementia. Neuropathologically, affected brains demonstrate diffuse cortical atrophy and an abundance of vascular and parenchymal Aβ deposits, primarily ending at position 40, together with neurofibrillary tangles. Vascular amyloid, present in cortical and leptomeningeal vessel walls, accumulate in the basement membrane of small vessels and capillaries. Although diffuse plaques are present, there is a predominance of mature plaques, typically surrounded by tau-reactive dystrophic neurites and which exhibit atypically large cores that may account up to 48% of the entire plaque size. Remarkably, these plaques are mostly of perivascular or vasocentric nature appearing to radiate from the affected vessel, a feature which suggests that the AD pathology might be a secondary consequence to CAA.

In contrasting difference to other mutations occurring within the Aβ sequence, the Flemish variant peptides display increased in vitro solubility and a decreased rate of protofibrillar structures formation in comparison with the wild-type counterparts [50]. Although Flemish homologues exhibit a time-dependent increase in thioflavin-T binding correlating with the formation of β-sheet-containing assemblies, there is an overall poor fibrillization tendency [51]. Moreover, once formed, fibrils exhibit morphological differences with the wild-type structures. Electron microscopic studies revealed variations in the diameter of the filaments, and in the extent and density of the lateral filament associations as well as in the helicity of the fibrils compared to wild-type fibrils. These structural differences have been claimed to potentially alter the thermodynamic stability of the fibrils and their ability to be metabolized or degraded, features that could explain the aggressiveness of the disease in spite of the higher solubility of the synthetic homologues [52].

AβD23N mutation

The Iowa genetic variant consists of a G to A substitution at codon 694 of APP, resulting in the change of Asp for Asn at residue 23 of Aβ, and a loss of a negatively charged residue, as in the Dutch substitution, occurring at the immediate location of the molecule. The genetic variant was identified in an Iowa family of German descent [53, 54]. Patients of the Iowa kindred develop progressive, early onset AD-like memory impairment and personality changes with cerebral atrophy, leukoencephalopathy, and occipital lesions neuropathologically identified as calcified, amyloid-laden meningeal vessels. Although small hemorrhages could be identified by MRI and postmortem examination, there were no reported episodes of clinically manifest intracerebral hemorrhage. Of note, a second family from Spain, carrying an identical mutation, presents cerebral hemorrhage in the majority of the cases, suggesting that the mutation may or may not produce major hemorrhagic episodes under different biological conditions [55, 56]. The neuropathological features of the Iowa variant consist of a predominant vascular compromise coexisting with scattered pre-amyloid deposits, abundant neurofibrillary tangles and dystrophic neurites in the presence of remarkably few mature plaques [53]. A wide range of CAA-associated changes have been described in Iowa patients including luminal narrowing, wall thickening, and occluded small vessels, together with loss of smooth muscle cells, microbleeds, and presence of perivascular inflammatory cells [57].

An interesting feature of the Iowa amyloid deposits is the presence of post-translationally modified iso-Asp residues, not only at the position of the mutation, residue 23, but also in the Asp residues at positions 1 and 7 [58]. The deposits, both vascular and parenchymal, exhibit a predominant Aβ1-40 composition by immunohistochemistry while ELISA quantitation in brain homogenates revealed a 20-fold higher ratio of Aβ1-40 over Aβ1-42 [58]. Biochemical studies indicate that the brain deposits are highly heterogeneous at both N-, and C-termini and contained both mutated and non-mutated Aβ molecules [59], as also shown in Dutch deposits [39] and prion diseases [60], as well as in systemic forms of amyloidosis [61–65]. It is likely that the deposition of the respective mutated species exerts a seeding effect—or a conformational mimicry—enhancing the fibrillization and subsequent co-deposition of the wild-type counterparts, as previously proposed [66–68]. Synthetic homologues bearing the Iowa mutation, in a similar manner to the Dutch variant and in contrast to the Flemish, rapidly assemble in solution to form fibrils consistent with their high content in β-sheet secondary structure [51]. This conformational tendency for fibrillization appears to confer, in turn, enhanced toxicity for smooth muscle cells in vitro with a concomitant decrease in the cells α-actin expression [41, 69].

Intra-Aβ mutations located outside the cluster 21–23

Aβ amino acid substitutions outside positions 21–23, translate into clinical phenotypes of early-onset cognitive impairment associated or not with stroke and hemorrhage, depending on the specific location of the genetic variation. In some recently reported variants, the genetic defects were discovered by DNA sequencing on patients still alive, and therefore neuropathological information is unavailable at the moment.

AβL34V mutation

One of the most recently identified mutations that predominantly associates with CAA and recurrent cerebral hemorrhages is located within the Aβ sequence, but apart from the 21–23 cluster. The C to G transversion at codon 705 leads to a replacement of Leu at position 34 by a Val residue [70]. The mutation occurs in a three-generation family from the Piedmont region in Italy and presents with early onset, usually ranging between 50 and 72 years of age. The clinical features of the disease include recurrent hemorrhagic strokes, weakness and parasthesias together with confusional states. Cognitive impairment is infrequent as a presenting symptom but is observed after various episodes of intracerebral hemorrhages.

Neuropathological examination of the few available cases showed severe CAA with compromise of small and medium-size arteries as well as capillaries in all lobes of the brain, particularly the occipital and cerebellar regions. The vascular involvement includes vessel-within-the-vessel configurations, microhemorrhages, microaneurisms, microthrombi, and lymphocytic infiltration of the vessel walls. Diffuse and dense-cored plaques as well as neurofibrillary pathology were notably absent [54].

The limited studies currently available indicate that freshly solubilized L34V—similarly to wild-type Aβ—exhibits a predominantly unordered conformation but in difference to the non-mutated peptide its structure shifts to a mostly β-sheet profile by 24 h. This pro-amyloidogenic conformational change as well as the aggregation properties of the L34V resemble that of E22Q, although with more extended lag-phase and lower intensity, correlating with the comparable but less aggressive clinical phenotype of the Piedmont kindred [71]. In agreement with these structural data and the similar clinical manifestations, both variants elicit analogous caspase-mediated mitochondrial pathways in cerebral vessel wall cells, although within different time-frames and intensity [72]. These activated pathways are susceptible to pharmacologic modulation either through direct inhibition of mitochondrial cytochrome *c* release or by the action of pan and pathway-specific caspase inhibitors, giving clear indication of the independent or synergistic engagement of both extrinsic and intrinsic apoptotic mechanisms.

AβA42T mutation

A mutation at codon 713 of APP (G to A transition) resulting in an Ala for Thr substitution at position 42 of the Aβ molecule was reported in an Italian family of 54 members spanning four generations [73]. Notably, this mutation had been previously described in a single individual from France [74] but no clear-cut relationship with the disease pathogenesis could be demonstrated at that time. The mutation, of unknown penetrance since most healthy carriers are currently below the age of onset, is unique in view of the fact that, although located within the Aβ sequence, it is also adjacent to the γ-secretase cleavage site. The affected kindred presents an autosomal dominant form of dementia with clinical symptoms of AD, severe CAA, and multiple infarcts. Clinical manifestations include early age of onset—between 52 and 68 years—progressive cognitive decline, and stroke-like episodes including monoparesis and language disturbances. The same A42T mutation was found in a family in Spain [75], which presented with comparable clinical manifestations as in the Italian cases. Neuropathologic examination in both kindreds revealed the presence of the hallmark lesions of AD, senile plaques, CAA, neurofibrillary tangles and neuropil threads. CAA was particularly severe with the presence of 8- to 10-nm fibrils within and around the vessel walls. Leptomeningeal arteries and small parenchymal vessels in the cerebral hemisphere and cerebellum were severely affected by amyloid deposition. The normal architecture of the compromised vessels was disrupted by amyloid deposition presenting thickening and double barreling of the walls, loss of smooth muscle cells, and narrowing of the lumina.

AβD7N mutation

A missense mutation of G for A in the first nucleotide of codon 678, which translates in an Asp for Asn substitution at position 7 of Aβ, was found in a Japanese-Tottori pedigree. The clinical manifestations of the mutation were symptoms of progressive dementia that fulfilled the NINCDS–ADRDA criteria for AD [76]. Symptoms appeared at about 60 years of age, slowly worsening for more than a decade without signs of vascular involvement either clinically or neuroradiologically [31]. Both of the siblings studied were heterozygous for the mutation.

In vitro analyses demonstrated that the AβD7N substitution selectively accelerated the elongation phase of Aβ fibril formation. Unexpectedly, the process occurred without significant protofibril formation [77], thus different from wild-type Aβ40 and Aβ42 as well as other intra-Aβ mutations in which protofibril formation precedes the assembly of mature fibrillar conformations [47, 50].

AβH6R mutation

A genetic variation at codon 678, adjacent to the location of the Tottori mutation, causing an amino acid substitution of His at position 6 with Arg was reported in a family from the United Kingdom [78]. Neuropathological studies confirmed the signature lesions of AD with an age of onset at

55 years. In spite of these findings, the pathogenicity of the mutation still requires further assessment since the genetic variation was present in only one of two siblings affected by AD [78]. The AβH6R mutation—like the Tottori—does not affect Aβ production. Synthetic homologues of both genetic variants, as indicated above, show enhanced fibrillogenesis selectively promoting the elongation phase of fibril formation. Notably, in both cases, the levels of protofibrils are markedly inhibited suggesting that the two mutations might induce unique mechanisms causing structural Aβ changes without increasing the formation of metastable intermediates [77].

AβE11K mutation

A mutation at codon 682 of APP was found in a family in Leuven, Belgium, which translates in a substitution of Glu for Lys at residue 11 of Aβ, a highly conserved position of the molecule [79]. The clinical manifestation of the mutation is an AD-like phenotype but with a very early age of onset (47 years). No neuropathological data is available to the moment for these cases.

Notably, the amino acid substitution is located at one of the two adjacent β-sites for APP cleavage by BACE 1. Although the β-secretase predominant cleavage point is found upstream in the APP molecule and results in the generation of Aβ1-40/42 species, under certain conditions including specific sequence and structural constraints, the β-site originating Aβ11-40/42 fragments also becomes significant. Studies examining the selectivity of the β-secretase cleavage of APP showed that blocking the β'-site by introducing the AβE11K variant in conjunction with the artificial AβY10K mutation shifted BACE1 cleavage entirely to the β-site [80]. Whether any alterations in APP processing exist in patients bearing the AβE11K variant remains to be determined.

AβA2V mutation

The last intra-Aβ mutation reported to the moment consists of a C to T transition at position 673 that results in an Ala to Val substitution at residue 2 of Aβ and leads to AD only in the homozygous state. The genetic defect induces a very aggressive early-onset phenotype with established behavioral changes and cognitive deficits at the age of 36 which evolved toward severe dementia with spastic tetraparesis, and complete loss of autonomy in about 8 years. Notably, the disease affected two homozygous siblings while six relatives—aged between 21 and 88 years—who carried the mutation in the heterozygous state were not affected, as deduced by their neuropsychological assessment [29]. The A2V substitution appears to affect APP processing resulting in enhanced Aβ production with no alteration in the ratio of Aβ42 to Aβ40, similar to the K670N/M691L Swedish double mutation (Fig. 2).

In vitro studies of AβA2V fibrillogenesis showed that, as it happens with many other genetic variants, the presence of the mutation enhances the aggregation and fibrillogenic properties of the Aβ molecule [41, 47, 51]. Notably, the coexistence of the mutant peptide with equimolar concentrations of wild-type Aβ results in a clear inhibition of fibrillogenesis. It has been proposed that the interaction between both Aβ species interferes with the nucleation-dependent polymerization processes hindering amyloidogenesis and neurotoxicity. This negative effect on in vitro amyloid fibril formation induced by the coexistence of both subunits may correlate with the protective effect observed in the heterozygous carriers.

Non-Aβ Familial AD mutations

AD clinical phenotypes are also observed in patients with mutations in non-APP genes. Depending on the respective genes involved, some of these familial cases exhibit deposition of Aβ peptides (e.g., *PSEN* mutations) while others show deposition of unrelated amyloid molecules with clinical phenotypes of dementia and/or hemorrhagic stroke.

Presenilin mutations

PS mutations are associated, as described above, with the presence of familial forms of AD, accounting for $\sim$80% of the early-onset AD cases. Although more than 120 mutations in the *PSEN1* gene have been associated with autosomal dominant early-onset AD, only eight missense mutations have been found in the *PSEN2* gene [81–87]. The phenotype associated with each genetic variant depends on the gene, type of mutation, and transmembrane domain affected [88]. Most of PS mutations are characterized by accelerated Aβ production, an onset before the age of 60 years, and an almost complete penetrance [82]. Only a few *PSEN2* mutations exhibit incomplete penetrance and variable clinical expression, overlapping with late-onset AD [89, 90].

Of the many *PSEN1* and *PSEN2* mutations described, only a few are associated with the presence of CAA. Specifically, mutations located after codon 200 appear to result in a particularly severe vascular compromise. In cases with Δ9 and ΔI83/ΔM84 (Fig. 1e) deletions in the *PSEN1* gene, the clinical phenotype includes spastic paraparesis and cotton wool plaques together with extensive and severe CAA [91]. The predominance of cotton wool plaques is, however, not unique to these mutations as they have also been described in association with a number of other *PSEN1* genetic variants. CAA was also identified as a

prominent feature in a Volga-German family characterized by the change of Asn for Ile at position 141 in the *PSEN2* gene. The mutation was also associated with cerebral hemorrhage in at least one case in the family. For a complete detailed list of PS1 and PS2 mutants see http://www.molgen.ua.ac.be/ADMutations/.

Non-Aβ cerebral amyloidosis

Cystatin C-related cerebral amyloidosis

Hereditary cerebral hemorrhage with amyloidosis, Icelandic type (HCHWA-Icelandic), is an autosomal dominant disorder described in individuals from small rural communities of western Iceland [92]. The disease is associated with a T to A point mutation [93], translating into a Leu for Gln change at position 68 of cystatin C, a ubiquitously expressed inhibitor of cysteine proteases codified by a single gene on chromosome 20. The 110-residue-long amyloid subunit constituting the amyloid deposits in HCHWA-Icelandic not only bears the mutated amino acid residue but it is also degraded at the N-terminus, starting at position 11 of the normal cystatin C [94, 95]. The main clinical hallmark of the disease is cerebral hemorrhage with fatal outcome in the third to fourth decade of life in approximately 50% of the cases. Strokes are rare after the age of 50, and cognitive decline followed by dementia may occur in those cases that survive the hemorrhagic episodes. Neuropathologically, the mutation is associated with massive amyloid deposition within small arteries and arterioles of leptomeninges, cerebral cortex, basal ganglia, brainstem, and cerebellum (Fig. 1f). Although brain involvement is the main clinicopathological feature, silent amyloid deposits have also been described in peripheral tissues, such as skin, lymph nodes, spleen, salivary glands, and seminal vesicles.

The biochemical and structural properties of the variant form of cystatin C have been extensively studied. The mutated residue is located within the hydrophobic core of the protein and the amino acid substitution affects the stability of the molecule destabilizing alpha-helical structures and yielding a more unfolded molecule with higher tendency to form dimeric assemblies compared with the wild-type counterpart (reviewed in [96]). The crystal structure of the cystatin C variant revealed that dimerization occurs through three-dimensional domain swapping [97] and, in turn, through dimer association, results in the formation of larger amyloid-like structures with involvement of intermolecular β-sheet interactions [98]. The N-terminal truncation of the molecule found in vivo in the amyloid deposits of the Icelandic patients seems not to be crucial for the overall domain-swapped dimer formation; however, the absence of the N-terminal decapeptide appears to facilitate the subsequent association of the protein via β-sheet interactions through intermolecular contacts [99].

Gelsolin-related cerebral amyloidosis

Gelsolin-related amyloidosis, also known as familial amyloidosis Finnish type (FAF), is an autosomal dominant condition of systemic compromise characterized by ophthalmologic, dermatologic, and neurological symptoms with common cerebral amyloid deposition (reviewed in [100]). Although the majority of FAF patients have been reported in Finland with a marked geographic clustering of cases in the southeastern part of the country, the disease has worldwide distribution [101]. Two different mutations at codon 187 of gelsolin, an actin-binding protein, cosegregate with the disease. The first mutation, described in Finnish, Dutch, American, and Japanese families, results from a single G to A transition at position 654, the first nucleotide of codon 187 and translates in an Asp for Asn change [102–105]. A different amino acid substitution at the same nucleotide is present in patients of Danish and Czech origin suffering from the same disorder [101]. In these cases, a transition of G to T results in the presence of a Tyr instead of the normally occurring Asp.

Clinical manifestations result from the compromise of multiple organs and include peripheral neuropathy, facial palsy, dry and itchy skin, intermittent proteinuria, and cardiac symptoms. Patients have typical faces with droopy eyelids and protruding lips. Lattice corneal dystrophy, a lace-like deposition of amyloid within the stroma, is the earliest clinical finding of the syndrome. Amyloid deposition in the spinal and cerebral blood vessel walls, meninges, spinal nerve roots and sensory ganglia are critical features of this systemic amyloidosis contributing to the CNS symptoms. Amyloid deposition in basement membranes and vessels (Fig. 1g) is common to most of the organs, in addition to the CNS [101].

Biochemical analysis of the deposits revealed that the amyloid fibrils are formed by a 7-kDa internal degradation product of the gelsolin molecule. This amyloid subunit is located in a repetitive motif with actin-binding activity—highly conserved among species—and spanning from position 173 to residue 243 of the gelsolin molecule [105].

Transthyretin-related cerebral amyloidosis

Familial transthyretin (TTR)-related amyloidosis is a systemic disorder usually associated with peripheral neuropathy and involvement of visceral organs, with only exceptional cases presenting with CNS compromise. Three unrelated families have been reported carrying different point mutations in the chromosome 18-*TTR* gene and

showing abundant cerebral amyloid deposition in the presence of rare hemorrhagic episodes. The Hungarian kindred, consisting of 56 members spanning four generations, is associated with a single A for G missense mutation at codon 18 resulting in the presence of Gly instead of Asp [106, 107]. The onset of symptoms varies between 36 and 53 years, with death occurring between the ages of 50 and 60. The major clinical symptoms include short-term memory decline, hearing loss, cerebellar dysfunction with ataxia, and bilateral pyramidal dysfunction with progressive spasticity. Most patients show temporary disorientation, and migraine-like headache with vomiting, and tremor. Neuropathological studies revealed extensive amyloid deposition (Fig. 1h) in meningeal vessels as well as in subarachnoid, subpial, and subependymal cerebrospinal regions, and spinal ganglia. Although not associated to any clinical symptoms, small systemic deposits were also present in kidney, skin, ovaries, and peripheral nerves.

A different mutation, T for G at codon 30 resulting in the substitution of Val for Gly and also presenting with CNS compromise, was identified in a large Ohio family of German ancestry consisting of 59 members spanning four generations [108]. The main clinical symptoms are slowly progressive dementia, seizures, ataxia, hemiparesis, decreased vision, and mutism. The age of onset is between 46 and 56 years with the duration of disease varying between 3 and 26 years. The histopathological hallmark is the presence of amyloid deposits in the subependymal region, the leptomeninges, the choroid plexus, and in the wall of the subarachnoid blood vessels. Small and medium-sized vessels are the most severely affected by amyloid even though notably, the vascular compromise is absent once the vessels penetrate into the brain parenchyma. Although not a frequent finding, vascular amyloid has also been described affecting vessels of virtually all visceral organs, skin, and skeletal muscle [109].

More recently, a different mutation in the TTR gene was linked to lethal CAA and cerebral hemorrhage in a single case in Japan [110]. The point mutation associated with the disease takes place also at codon 30 and results in the substitution of Val for Met. This mutation is the most common genetic variation related to the TTR-associated form of systemic amyloidosis known as familial amyloidotic polyneuropathy (FAP) which typically presents with massive amyloid deposition in the peripheral nervous and vascular systems as well as in systemic organs, but with uncommon cerebral compromise. The case, belonging to a typical FAP pedigree, presented with renal dysfunction as the starting symptom followed by cardiac involvement and death by complications of the heart condition. Histopathologic studies at autopsy disclosed, in addition to the systemic compromise, massive intracerebral hemorrhages in the absence of neurofibrillary tangles and senile plaques. Cerebral amyloid formation was apparent not only in the choroid plexus and leptomeninges but also in dilated small arteries in the cerebral cortex. The case presents a striking difference with typical FAP phenotypes associated with the identical mutation, in which amyloid accumulation in cerebrocortical vessels is not only significantly lower than the systemic deposition, but it has never been associated with hemorrhagic complications.

Immunoglobulin-related cerebral amyloidosis

Cerebral immunoglobulin-light-chain deposition is found in different clinicopathologic entities including amyloidoma, leptomeningeal vascular amyloidosis, solitary intracerebral plasmacytoma, primary intracerebral lymphoma with plasmacytic differentiation, and multiple sclerosis with demyelination-associated amyloid deposition, as well as in a proposed new entity named Widespread Subcortical Vascular Amyloidosis with Leukoencephalopathy (WSVAL) [111]. Of all these rare diseases with brain-restricted AL-type deposition, the most frequent form is the presence of amyloidomas which typically occur in the absence of systemic amyloidosis. Since the first description of tumor-like amyloid formations within the brain [112], only 27 cases have been described so far [113]. In addition to these, a few case reports describe amyloidomas localized in the head and nervous system including at the skull base [114], within the trigeminal nerve [115] and involving spinal and peripheral nerves [116–118].

Amyloidomas may occur in all brain regions with predominance of frontal lobe localization and close contact with the ventricle system. In most of the patients, the lesions were found within the white matter; only one case presented the tumor-like mass in the cortical tissue, while around 30% of cases showed simultaneous cortical and subcortical compromise [113].

The cases studied at immunohistochemical or biochemical levels demonstrated a high prominence of λ-chain with only two cases showing simultaneous λ and κ deposition without a predominance of one of the subtypes [111, 113]. Recent studies using the state-of-the-art technology liquid chromatography-electrospray tandem mass spectrometry (LC/MS–MS) after laser-capture microdissection identified only λ-light chain as the component of the relative small number of amyloidomas studied [119].

Prion-related cerebral amyloidosis

A unique category in amyloid disorders is constituted by prion-related diseases, in which the etiology is thought to be related to the conversion, by a post-translational process, of the normal prion protein PrP^{C} into an infectious

and pathogenic form PrP^{SC}. The infectious etiological agent is devoid of nucleic acids and was called prion to denote its proteinaceous nature and distinguish it from viruses and viroids [120]. The infective protein PrP^{SC} differs from the normal counterpart only in the conformational folding, in which the higher β-sheet content of the disease-associated form translates in enhanced propensity to aggregation and resistance to proteolysis. This group of diseases includes, among others, Creutzfeldt–Jakob disease (CJD), kuru, Gerstmann–Sträussler–Scheinker disease (GSS), and fatal familial insomnia in humans as well as scrapie and bovine spongiform encephalopathy in animals.

Extensive cortical spongiform change, gliosis, and neuronal loss are common but not invariable features of these disorders. Amyloid angiopathy is infrequent although it is noticeably present in rare hereditary disease forms, which are characterized by a premature stop codon mutation of the *PRPN* gene. Detailed neuropathological data have been documented in a single pedigree caused by a T to G mutation occurring at codon 145 and resulting in an early stop codon (Y145STOP) and the production of a N- and C-terminally truncated PrP peptide 70 amino acids long. In this genetic variant, the main neuropathological finding is PrP-immunoreactive-CAA in leptomeningeal and parenchymal blood vessels together with prominent perivascular amyloid deposition and neurofibrillary tangle pathology [121]. A similar mutation, Y163STOP, in a different family also presents with a neuropathological phenotype characterized by vascular and parenchymal disease-associated PrP deposition and extensive NFT pathology [25]. Both the Y145STOP and Y163STOP mutations result in truncated C-termini with loss of the glycosylphosphatidylinositol (GPI) anchor, which is added post-translationally to the C-terminus of PrP and is required to attach it to the outer leaflet of the plasma membrane [122].

BRI2 gene-related dementias

This novel group of hereditary disorders, also known as chromosome 13 dementias, and composed of familial British and Danish dementias (FBD and FDD, respectively), presents with cognitive impairment as one of the main defining clinical phenotypes [123, 124]. Both diseases, share many features with AD including the presence of neurofibrillary tangles, parenchymal pre-amyloid and amyloid deposits, extensive CAA and a variety of co-localized amyloid-associated proteins and inflammatory components. These early-onset conditions, as described below, are linked to specific mutations at or near the stop codon of the chromosome 13 gene *BRI2* that cause generation of longer-than-normal protein products.

Interesting new findings have demonstrated a cross-talk between BRI2 and APP that could bring new lights into the molecular mechanisms underlying neurodegeneration. Although BRI2 has still an unknown function, it was recently shown to specifically interact with APP. As a result of this binding interaction, BRI2 masks the cleavage sites of β- and α-secretase on APP and the γ-secretase docking site on the APP C-terminal fragment C99. As a consequence, BRI2 modulates APP processing inhibiting Aβ formation and deposition properties, a feature observed in both cell culture and mouse models of AD [125–128].

Familial British dementia

This hereditary disorder originally reported in 1933, is the first described cerebral amyloidosis in the Western world [129] and affects an extensive pedigree of British origin which spans over nine generations [123]. The disease presents with early onset, typically around the fifth decade of life, being its earliest manifestations personality changes—with patients becoming irritable or depressed—followed by cerebellar ataxia and spastic paralysis more severe than that seen in atypical forms of AD or in GSS. Pseudo-bulbar palsy and dysarthria are universal and all patients progress to a chronic vegetative state becoming mute, unresponsive, quadriplegic, and incontinent. Neuropathologically, FBD cases exhibit severe and widespread amyloid angiopathy of the brain (Fig. 1i) and spinal cord and characteristic perivascular changes that include vessel-associated amyloid plaques and white matter changes resembling Binswanger's leukoencephalopathy. Notably, despite the extensive amyloid deposition in the vasculature, large intracerebral hemorrhage is a rare feature. Neuritic and non-neuritic amyloid plaques affect cerebellum, hippocampus, amygdala and, occasionally, cerebral cortex. Neurofibrillary degeneration is indistinguishable from that observed in AD cases. As it occurs in other forms of non-Aβ cerebral amyloidosis described above, FBD presents systemic thioflavin-S-positive deposits in many organs, including pancreas, adrenal gland, lung, myocardium, liver, spleen, and skeletal muscle [130]. Nevertheless, this systemic deposition appears to be asymptomatic since clinical phenotypes of all described cases are only related to the cerebral compromise.

The disease is associated with a T to A substitution at codon 267 of *BRI2* which results in the presence of an Arg residue in place of the stop codon normally occurring in the wild-type precursor molecule and a longer open-reading frame of 277 amino acids instead of 266 [131]. Furin-like processing of this longer precursor releases a C-terminal fragment 34 amino acids long, named ABri, which is found constituting the characteristic cerebral and systemic deposits in FBD [130, 131].

ABri synthetic homologues recapitulate in vitro the aggregation/fibrillization propensity observed in vivo in the tissue deposits by forming spontaneous β-sheet-rich structures and exhibiting fast aggregation kinetics. In fact, ABri molecules demonstrate an even higher tendency to form high-ordered oligomeric assemblies than Alzheimer's Aβ42. Consistent with the behavior of other amyloid forming proteins, ABri aggregation kinetics is favored by slightly acidic conditions which result in the formation of protofibrils as intermediate structures during fibril maturation [123].

Familial Danish dementia

Familial Danish dementia (FDD), also known as heredopathia ophthalmo-oto-encephalica, is an early onset autosomal dominant disorder originating in the Djürsland peninsula in Denmark and also associated with a genetic mutation in the *BRI2* gene [132]. A 10-nt duplication insertion mutation between codons 265 and 266 abolishes the normal stop codon and results, as in the case of FBD, in an extended precursor protein which possess 277 amino acids instead of the normal 266 [132, 133]. The C-terminal peptide ADan (which is 34 amino acid long), as the ABri counterpart, is cleaved from the mutated precursor protein, and readily forms the deposited amyloid fibrils. The disease, identified in a single family and spanning three generations, is clinically characterized by the development of cataracts, hearing loss and progressive cerebellar ataxia before the age of 40 with subsequent paranoid psychosis and dementia. Death occurs in most patients during their fifth or sixth decade. The disease is characterized by diffuse brain atrophy with a severe involvement of the cerebellum, cerebral cortex, and white matter. Neuropathological characteristics, similarly to those seen in FBD, include widespread amyloid angiopathy (Fig. 1j) in the blood vessels of the cerebrum, choroid plexus, cerebellum, spinal cord, and retina. Neurofibrillary pathology is severe in the limbic structures and is also present in neocortical areas where it is more pronounced than in FBD. Abnormal neurites, as seen in some other forms of CAA, mainly cluster around the vascular deposits and are absent around nonfibrillar diffuse parenchymal lesions [134].

An interesting feature observed in FDD cases is the deposition of variable amounts of Aβ in blood vessels and, to a lesser extent, in brain parenchyma in the form of pre-amyloid deposits, either in combination with ADan or in isolated lesions [135]. Biochemical analysis of extracted brain amyloid revealed that CAA deposited Aβ is an N-terminal truncated form of Aβ42, a surprising finding in view of the prevalence of Aβ ending at position 40 in vascular deposits observed in sporadic and familial AD, Down syndrome, and normal aging [66]. Detailed mass spectrometry analysis of extracted brain amyloids revealed that the deposited ADan species, similarly to the ABri counterparts, are post-translationally modified at the N-terminus [66, 130]. The glutamate to pyroglutamate modification, involving the loss of one molecule of water, is notably not present in the circulating ADan or ABri counterparts, indicative of in situ generation. Similar modifications have been described in Aβ deposits [136, 137] and appear to convey in vitro high insolubility and aggregation proclivity to the peptides, with significant changes in the oligomerization kinetics and enhanced toxicity [138]. It has been proposed that the presence of pGlu, even in minor concentrations, may act as potential seeding species for aggregate formation in vivo and even contribute to the formation of mixed aggregates such as those observed in FDD and composed of ADan and Aβ subunits [139].

Intracellular amyloid Tau

The original definition of amyloid [140] comprised only the extracellular deposition of fibrillar material exhibiting the typical tinctorial properties described above (e.g., birefringence after Congo red staining). It is now agreed that the definition needed to be expanded to incorporate intracellular aggregates sharing the classical amyloid properties. Although many different intranuclear or intracytoplasmatic protein inclusions have been described associated with specific diseases, the only intracellular components fulfilling the complete definition criteria of amyloid are the neurofibrillary tangles, exhibiting cross-β X-ray diffraction pattern and typical Congo red and thioflavin-S staining [141]. Other intraneuronal inclusion bodies, such as Lewy bodies in Parkinson's disease, intranuclear inclusions in Huntington disease, as well as inclusions of neuroserpins and ferritin in familial neurodegenerative disorders, are not considered amyloids [142].

The presence of NFTs, one of the histopathological trademarks of AD, was described by Alois Alzheimer himself in affected limbic and cerebral cortices via light microscopic evaluation following silver tissue impregnation by the Bielschowsky method. Tangles are composed by building blocks of aberrantly phosphorylated species of the microtubule associated protein tau which accumulate in the perinuclear cytoplasm of selected neurons in the form of paired, helically wound filaments (PHF). These filaments aggregate into masses inside nerve cell bodies, known as NFT, in neuronal processes as neuropil threads, and as dystrophic neurites typically associated with the amyloid plaques [143, 144], described above.

In addition to AD, NFT are also found in other neurodegenerative disorders grouped under the denomination of

tauopathies. Some examples of tauopathies, in addition to AD, are certain forms of frontotemporal lobar degeneration including Pick's disease, progressive supranuclear palsy, and corticobasal degeneration [145]. The demonstration that mutations in the tau gene are associated with frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) has provided convincing evidence that tau protein plays a key role in neurodegeneration. This also suggests that distinct sets of tau isoforms expressed in different neuronal populations could lead to different pathologies [146].

Nature of the pathogenic subunits

Aggregation/fibrillization of amyloid subunits seems to play a critical role in neurodegeneration. It is now considered that the transition from soluble monomeric species circulating under normal conditions to the oligomeric, protofibrillar and end-point fibrillar assemblies contributes significantly to disease pathogenesis. In particular, intermediate oligomeric and protofibrillar forms of Aβ seem to display the most potent effects in neuronal cells inducing synaptic disruption and neurotoxicity [147, 148], while in contrast, the abundance of mature amyloid plaques correlates poorly with AD severity [149, 150]. Oligomeric intermediate assemblies also exhibit potent apoptotic properties for cerebral microvascular endothelial cells, an effect exacerbated in genetic variants associated with CAA and intracerebral hemorrhage like AβE22Q [43, 44]. Although soluble Aβ oligomers have been observed in AD brains [151, 152], there is no consensus regarding the exact nature of these pathogenic assemblies, their order of appearance in the aggregation process or whether they are transient intermediate species evolving into higher order conformers. A large and confusing body of literature exists describing many types of Aβ assembly forms, including protofibrils, annular structures, paranuclei, Aβ-derived diffusible ligands (ADDLs), globulomers and amyloid fibrils [147, 153]. The basis for these discrepancies are the diverse experimental protocols comprising not only high variability among the source of Aβ synthetic homologues but also different solubilizing strategies combined or not with the use of alternative protocols to remove pre-existing β-sheet elements with potential seeding capability. An element contributing to these disparities is the broad definition of oligomers which, in general, are considered Aβ assemblies not-pelleted from the respective physiological or experimental fluids by high-speed centrifugation. As a result of this empiric definition, the structural assemblies encompassed in each category depend highly on the experimental conditions of each study.

Soluble prefibrillar oligomers have been implicated as primary causative agents not only in AD but also in many different degenerative diseases in which the additional accumulation of large fibrillar deposits is seen by some as either of an inert or a protective nature [153]. Parkinson-related α-synuclein—like Aβ—can form pore-like annular structures in vitro [154]. Mutations associated with early onset of the disease not only exhibit accelerated protofibrillar formation in vitro but in the case of A30P α-synuclein the presence of the mutation additionally slows the conversion of the protofibrillar intermediates into the insoluble amyloid fibrils [155–157]. Similar oligomeric assemblies have also been reported for components of the Huntington disease-related polyglutamine peptides [158] as well as for the amyloid subunits of the chromosome 13-associated dementias. In the latter case, the respective amyloid subunits have been shown to undergo supramolecular conformational changes in reconstituted membranes forming morphologically compatible ion-channel-like structures and eliciting single ion-channel currents [133, 159].

Conclusions and perspective

A clear understanding of the basic biochemistry of the key players in the molecular mechanisms of cerebral amyloidoses may ultimately provide a framework for developing drugs or other treatments to alleviate the severe pathology these molecules can cause in the elderly. Whether these treatments will eventually come as enzyme inhibitors, peptide aggregation blockers, trafficking modulators, immunization therapies, or a combination thereof, is not settled at this time. Science is still at a stage of development of the knowledge on the molecular basis of neurodegeneration. In spite of the many studies, significant breakthroughs in early diagnosis and therapeutics are pending, and relevant questions remain unanswered. Whether soluble oligomers bind to specific receptors, causing selective malfunctions in particular subsets of neurons, or whether the physical assembly of amyloidogenic proteins onto cellular membranes with ion-like channel formation cause the observed range of adverse signaling effects remain to be further elucidated. Also unknown is whether the amyloid assemblies formed under different conditions—exhibiting different sizes and structural conformations—or those originating from different amyloid subunits display unique toxic activities. The availability of familial forms of cerebral amyloidoses, either related to genetic variants of Aβ or to non-Aβ proteins, provides unique paradigms to examine the role of amyloid in the mechanism of disease pathogenesis and to dissect the link between vascular and parenchymal amyloid deposition and their differential contribution to

neurodegeneration. At the moment, it seems clear that different amyloid species have the capability to induce similar neuropathological changes leading to the same scenario: neuronal loss and dementia. Unrelated peptides likely adopt similar altered amyloidogenic configurations and trigger comparable downstream detrimental effects in neuronal cells.

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