

Cerebral Amyloid Angiopathy: A Systematic Review

Alessandro Biffi,^{a,b,c} Steven M. Greenberg^{b,c}

^aCenter for Human Genetic Research, Massachusetts General Hospital, Boston MA, USA

^bDepartment of Neurology, Massachusetts General Hospital, Boston MA, USA

^cProgram in Medical and Population Genetics, Broad Institute, Cambridge, MA, USA

Received September 2, 2010

Revised September 17, 2010

Accepted September 17, 2010

Correspondence

Alessandro Biffi, MD
Hemorrhagic Stroke Research
Group and Center for Human
Genetics Research,
Department of Neurology,
Massachusetts General Hospital,
185 Cambridge Street,
CPZN 6818, Boston,
MA 02114, USA
Tel +1-617-643-3304
Fax +1-617-643-3293
E-mail abiffi@partners.org

Cerebral amyloid angiopathy (CAA) is a disorder characterized by amyloid deposition in the walls of leptomeningeal and cortical arteries, arterioles, and less often capillaries and veins of the central nervous system. CAA occurs mostly as a sporadic condition in the elderly, its incidence associating with advancing age. All sporadic CAA cases are due to deposition of amyloid- β , originating from proteolytic cleavage of the Amyloid Precursor Protein. Hereditary forms of CAA are generally familial (and therefore rare in the general population), more severe and earlier in onset. CAA-related lobar intracerebral hemorrhage is the most well-studied clinical condition associated with brain amyloid deposition. Despite ever increasing understanding of CAA pathogenesis and availability of reliable clinical and diagnostic tools, preventive and therapeutic options remain very limited. Further research efforts are required in order to identify biological targets for novel CAA treatment strategies. We present a systematic review of existing evidence regarding the epidemiology, genetics, pathogenesis, diagnosis and clinical management of CAA.

J Clin Neurol 2011;7:1-9

Key Words cerebral amyloid angiopathy, cerebral hemorrhage, dementia.

Introduction

The term cerebral amyloid angiopathy (CAA) describes an heterogeneous group of biochemically and genetically diverse central nervous system (CNS) disorders. All these medical conditions share a characteristic morphological finding on pathological examination, i.e. amyloid fibrils deposited in the walls of small to medium-sized, blood vessels mostly arterial. In some instances amyloid deposits have been also observed in the capillaries of CNS parenchyma and of the leptomeninges. CAA mostly occurs in the sporadic form in the elderly, while rare familial forms occur in younger patients and are generally lead to more severe clinical manifestations. While more than 25 human proteins or have been found to form amyloid fibrils *in vivo*, only 7 have been described in CNS disorders,^{1,2} and all sporadic forms and most hereditary forms of CAA affecting the human brain are of the A β type (A β -CAA)(Table 1). In A β -CAA the action of β - and γ -secretases on the amyloid precursor protein (APP) lead to deposition of amyloid- β (A β) peptide, mirroring some aspect of Alzheimer's disease (AD) pathophysiology.³

In this review we will present a summary of existing evidence regarding the epidemiology, genetics and pathogenesis

of CAA, provide an overview of diagnostic tools available to clinical neurologists, as well as summarize current guidelines and recommendation for prevention and treatment of CAA-intracerebral hemorrhage (ICH)(See Appendix for literature Search criteria).

Historical Perspective

Vascular β -amyloid deposition in the central nervous system was first described by Gustav Oppenheim in 1909. Oppenheim found foci of necrosis in the brain parenchyma adjacent to hyalinized capillary walls in 6 of 14 brains of autopsied individuals with senile dementia and the pathological changes of AD.⁴ In 1938, Scholz published the first article focusing solely on cerebral vascular abnormalities now recognized as CAA.⁵ The observation that CAA is limited to the vascular media without adjacent parenchymal involvement was made in 1954 by Stefanos Pantelakis.⁶ He also described many of the hallmark pathological features of CAA: 1) preferential involvement of the small arteries and capillaries of the meninges, cerebral cortex, and cerebellar cortex; 2) topographical distribution favoring the posterior brain regions; 3) lack of staining of vessels in the white

Table 1. Sporadic and familial (hereditary) CAA forms

Amyloid peptide	Precursor protein	Chromosome	Disease	Notes	Hemorrhagic stroke
A β	APP	-	Sporadic CAA		+
A β	APP	-	CAA related to sporadic AD	No increase in lobar ICH risk	-
A β	APP	21	CAA related to familial AD	Associated to presenilin-1 and presenilin-2 mutations	-
A β	APP	21	CAA in Down syndrome	Lobar ICH is rarely observed	-
A β	APP	21	Hereditary Cerebral Hemorrhage with Amyloidosis: Dutch type	Described in 2 large families from the Netherlands Age at onset: 50 years Lobar hemorrhages, focal neurological deficits, dementia, and leukoencephalopathy	+
A β	APP	21	Hereditary Cerebral Hemorrhage with Amyloidosis: Italian type	Described in 3 Italian families Age at onset: 50 years Lobar hemorrhages and dementia	+
A β	APP	21	Hereditary Cerebral Hemorrhage with Amyloidosis: Flemish type	Described in a dutch family (discovered in Belgium, therefore called "Flemish") and a British family Age at onset: 45 years Progressive AD-like dementia, in some patients associated with a lobar hemorrhage	+/-
A β	APP	21	Hereditary Cerebral Hemorrhage with Amyloidosis: Iowa type	Described in a Iowa family and a Spanish family Age at onset: 50-66 years Memory impairment, expressive language dysfunction, personality changes, myoclonic jerks, short-stepped gait, no clinically manifest ICH (family from Iowa) or lobar hemorrhages (family from Spain)	+/-
A β	APP	21	Hereditary Cerebral Hemorrhage with Amyloidosis: Piedmont type	Described in one family from Piedmont (Italy) Age at onset: 50-70 years Recurrent lobar hemorrhages, cognitive decline	+
A β	APP	21	Hereditary Cerebral Hemorrhage with Amyloidosis: Arctic (Icelandic) type	Described in one family from northern Sweden Age at onset: ~60 years Progressive cognitive decline (no strokes)	-
ACys	Cystatin C	20	Hereditary Cerebral Hemorrhage with Amyloidosis: Icelandic type	Described in 9 sub-families in Iceland (one sporadic case in the US) Causes systemic amyloidosis Age at onset: 20-30 years Recurrent lobar hemorrhages	+
ATTR	Transthyretin	18	Meningovascular amyloidosis	Polyneuropathy is the main clinical symptom Rarer findings: ataxia, spasticity and dementia Systemic amyloidosis	In some families (rare)
AGel	Gelsolin	9	Familial Amyloidosis-Finnish Type	Progressive corneal lattice dystrophy, cranial and peripheral neuropathy, cutaneous amyloidosis Systemic amyloidosis	-
PrPSc	Prion Protein	20	Gerstmann-Sträussler-Scheinker syndrome	Described in one family Progressive cognitive decline	-
ABri	ABri precursor protein	13	Familial British Dementia	Described in 4 families Age at onset: 45-50 years Progressive dementia, cerebellar ataxia, spastic tetraparesis	-
ADan	ADan precursor protein	13	Familial Danish Dementia	Described in 1 family from Denmark Age at onset: 30 years Cataracts, deafness, progressive ataxia, dementia (previously known as "heredopatia ophtalmo-oto-encephalica")	-

AD: Alzheimer's disease, CAA: cerebral amyloid angiopathy, ICH: intracerebral hemorrhage.

matter; 4) association with increased age and dementia; 5) lack of association with hypertension and arteriosclerosis; 6) lack of association with amyloidosis of the other organs. Over the following 20 years multiple case reports and small series suggested an association between CAA and lobar ICH. Okazaki and colleagues published a seminal article in 1979, clarifying the relationship between CAA and lobar ICH.⁷ They identified 23 consecutive cases of moderate to severe CAA from autopsies at Mayo Clinic (Rochester, MN). A history of lobar, multiple hemorrhages was very common in these patients. Fibrinoid degeneration of the vessel walls with microaneurysm formation was sometimes seen, as well as a double-barreled vessel wall appearance caused by cracking of the arterial media. Based on these findings, the authors concluded that CAA was an under-recognized cause of lobar ICH in the elderly, thus providing the foundation for further exploration of CAA and CAA-related lobar ICH (CAA-ICH).

Sporadic Cerebral Amyloid Angiopathy

As previously mentioned (Table 1), sporadic CAA mostly occurs in the elderly because of A β deposition (A β -CAA). A β is a normally secreted, ~4 kDa, 40 or 42 amino acids in length, proteolytic product of the 677-770 amino acid type 1 integral membrane protein referred to as the A β precursor protein (A β PP, or more commonly APP) encoded by the APP gene on chromosome 21.⁸⁻¹¹ Generation of A β from APP requires two proteolytic events, a proteolytic cleavage at the amino terminus of the A β sequence referred to as β -secretase and a cleavage at the carboxyl terminus known as γ -secretase.

Epidemiology

CAA is a frequent pathological finding and a fairly common clinical entity in the elderly. As a detectable pathology (regardless of severity), cerebrovascular amyloid is present in approximately 10% to 40% of elderly brains and 80% or more in brains with concomitant AD.¹² Even when taking only relatively advanced amyloid pathology in consideration, CAA remains a frequent finding. CAA pathology graded as moderate or severe (see below for pathology grading scores) was estimated to be present in 2.3% of 65 to 74 year olds, 8.0% in 75 to 84 year olds, and 12.1% in those over 85 years in analyses of brains from the Harvard Brain Tissue Resource Center. Of note, these figures were corrected for over-representation of AD referrals.¹³ An even higher estimate of 21% for the prevalence of CAA graded as severe emerged from other analyses of autopsied individuals aged 85 to 86.¹⁴ The role of CAA in cerebrovascular epidemiology is of course mostly related to the increased risk for lobar ICH. Indeed, estimates for the proportion of spontaneous hemorrhages

in the elderly attributable to CAA range from 10% to 20% in autopsy series to 34% in clinical series.^{12,15}

Pathogenesis

The 40-amino-acid-long A β (A β 1-40) is more soluble than the longer A β 1-42 and the two molecules differ in the distribution in brain and vessel walls. A β 1-40 tends to be the major form in the amyloid in artery walls in CAA, whereas A β 1-42 is more prominent in the plaques in brain tissue.^{16,17} It is generally accepted that conformational transitions occurring in native soluble amyloid molecules increase their content in β -sheet structures, thus favoring the formation and deposition of more insoluble oligomeric structures. In turn, these deposits trigger a secondary cascade of events including, among others, release of inflammatory components, activation of the complement system, oxidative stress, alteration of the blood-brain barrier (BBB) permeability, and cell toxicity.^{18,19}

While both deposited and soluble A β molecules are identical in their primary structure, they exhibit completely different solubility and tinctorial properties. Soluble A β forms undergo a change in conformation (via mechanisms that remains largely unknown) resulting in a predominantly β -sheet structure, highly prone to oligomerization, fibrillization and deposition. The identification of soluble A β species in the systemic circulation, brain interstitial fluid and CSF, together with the ability of the BBB to regulate A β transport in both directions, originally suggested plasma A β to be a potential precursor of deposited amyloid.²⁰ However, lack of brain lesions in transgenic models exhibiting several fold increased in plasma soluble A β strongly argues against the sole contribution of circulating species to brain deposition.²¹

Since smooth muscle cells, pericytes and endothelial cells all express APP²² and isolated cerebral microvessels and meningeal blood vessels are able to produce A β ²³ the cerebral vasculature itself was therefore proposed as a possible source of cerebral A β . Nevertheless, the sole contribution of smooth-muscle cells to A β -CAA is made less likely by the existence of amyloid deposits in capillaries (which are devoid of smooth muscle) in CAA patients. In recent years, the hypothesis of a neuronal origin of A β and other amyloid proteins has therefore been gathering support.^{22,25-27} It has been proposed that amyloid produced by neurons is drained along the perivascular interstitial fluid pathways of the brain parenchyma and leptomeninges, depositing along the vessels under specific pathologic conditions.^{28,29}

Since no evidence of increased A β production has been found in sporadic CAA, imbalance between A β production and clearance is generally considered a key element in the formation of amyloid deposits. The amphiphilic nature of A β precludes its crossing through the BBB unless mediated by specialized carriers and/or receptor transport mechanisms. These mecha-

nisms control the uptake of circulating A β into the brain³⁰⁻³⁶ and regulate clearance.³⁷⁻⁴³ Among receptors involved, Receptor for Advance Glycation End-products actively participates in brain uptake of free A β at the vessel wall level.³⁰ Other receptors are more relevant for the transport of A β complexed with other molecules: LRP-1 mediates transcytosis of A β -ApoE complexes contributing to rapid CNS clearance,⁴¹ whereas megalin mediates in the cellular uptake and transport of A β -ApoJ.³⁶

The hypothesis of defective A β degradation, while less extensively studied as a possible mechanism for amyloid accumulation, should not be overlooked. Neprilysin, endothelin-converting enzyme, insulin-degrading enzyme, beta-amyloid-converting enzyme 1, plasmin and matrix metalloproteases are among the major enzymes known to participate in brain A β catabolic pathways.⁴⁴⁻⁴⁶ Reduced levels and/or activity of A β degrading enzymes favor A β accumulation, as documented in murine models, in which gene deletion of different proteases translate into increased levels of A β deposition.^{45,46}

Genetics of sporadic CAA

The ApoE ϵ 4 and ϵ 2 alleles are the only genetic risk factors robustly associated with risk of developing sporadic A β -CAA.⁴⁷ Interestingly ApoE ϵ 2, which exerts a protective effect on AD risk, increases risk of ICH in A β -CAA patients.^{48,49} ApoE interacts with soluble and aggregated A β *in vitro* and *in vivo* and is therefore likely to be involved in both parenchymal and vascular amyloidosis.⁵⁰⁻⁵³ Further studies tested the role of human ApoE alleles on the formation of parenchymal and vascular amyloid. The presence of the ϵ 4 allele led to substantial A β -CAA with only few parenchymal amyloid deposits. The ϵ 3 allele, however, resulted in almost no vascular and parenchymal amyloidosis.⁵⁴ In young mice, an increased ratio of A β 40 : 42 was observed in brain extracellular pools and a lower A β 40 : 42 ratio in CSF, suggesting that ApoE ϵ 4 causes altered clearance and transport of A β within different brain compartments. These findings highlight again the importance of a high A β 40 : 42 ratio for the formation of vascular amyloid. Other genetic risk factors for A β -CAA have been investigated, but their role remains unclear, thus requiring additional research efforts.

Neuropathology

Characteristic findings

In hematoxylin-eosin stained sections severe CAA can be recognized by acellular thickening of blood vessel walls, but this finding is non-specific for CAA since it occurs in a variety of other disorders, including hypertensive angiopathy.⁵⁵ In CAA, A β is deposited mainly as amyloid- β fibrils in close contact with smooth muscle cells.^{56,57} Non-fibrillar, monomeric and oligomeric A β was also demonstrated inside smooth muscle cells.⁵⁶

Depending on the severity of CAA, A β depositions have been shown primarily in the abluminal portion of the tunica media, often surrounding smooth muscle cells, and in the adventitia. With increasing severity, A β infiltrates all layers of the vessel wall, which shows loss of smooth muscle cells. Finally, the vascular architecture is severely disrupted and “double barreling”, microaneurysm formation, fibrinoid necrosis, and evidence of perivascular leakage may be seen.⁵⁸ Even in very high degrees of CAA-related changes, endothelial cells are well preserved and usually not affected. Perivascular hemorrhages are frequent around blood vessels affected with CAA.

Several authors also reported CAA-associated inflammation/vasculitis.^{59,60} Two subtypes of CAA-associated inflammation have been described so far: a non-vasculitic form called perivascular infiltration, which is characterized by perivascular infiltration of the parenchyma by multinucleated giant cells and a vasculitic form called transmural granulomatous angiitis, which is characterized by inflammation of the vessel wall with the occasional presence of granulomas. Both pathologic forms can co-occur, suggesting at least a partial overlap in biological mechanisms.

Topographical distribution

CAA distribution is characteristically patchy and segmental. In one given histological slide there may be foci showing vessels with varying degrees of amyloid depositions adjacent to foci showing vessels without any amyloid deposition. This phenomenon might lead to an under-diagnosis of CAA in postmortem examination, as even in severe cases a given histological slide might not contain amyloid-laden blood vessels. It has been shown by many authors that CAA is most frequent in the occipital lobe, followed by either frontal, temporal or parietal lobes, respectively. Furthermore, the occipital lobe is not only the site most frequently affected with CAA but also most severely so. CAA is more rarely seen in the basal ganglia, thalamus, and cerebellum, while both white matter and brainstem are usually spared.⁶¹⁻⁶³

Histological diagnosis

Histological diagnosis of CAA requires use of special staining for amyloid under light microscopy. Puchtler alkaline Congo red stain has been the standard method of amyloid staining for a long time, but since this stain is relatively unstable and has low sensitivity, a control staining with positive specimens is absolutely essential.⁶⁴ Daylon stain (also known as direct fast scarlet) is more sensitive: it is therefore of greater utility in detecting smaller amounts of amyloid deposition, but requires more careful observation because of a known tendency to overstain.⁶⁴ Fluorescent microscopy is also useful for the diagnosis of amyloidosis. Thioflavin-S is a sensitive stain for amyloid deposi-

tion, and it has been used from long time along with Congo-red staining.⁶⁵ Immunohistochemistry with fluorescent antibodies specific for precursor proteins is also a reliable diagnostic complement.

CAA severity grading

Two grading systems for CAA are commonly used in routine neuropathology. Olichney et al.⁶⁶ proposed the scale: 0, no A β positive blood vessels; 1, scattered A β positivity in either leptomeningeal or intracortical blood vessels; 2, strong, circumferential A β positivity in either some leptomeningeal or intracortical blood vessels; 3, widespread, strong, circumferential A β positivity in leptomeningeal and intracortical blood vessels; 4, same as 3 with additional dyschoric changes. Vonsattel et al.⁶⁷ graded CAA with respect to the severity of pathological changes in a given blood vessel: mild, amyloid is restricted to the tunica media without significant destruction of smooth muscle cells; moderate, the tunica media is replaced by amyloid and is thicker than normal; severe, extensive amyloid deposition with focal wall fragmentation or even double barreling of the vessel wall, microaneurysm formation, fibrinoid necrosis, and leakage of blood through the blood vessel wall.

Clinical features

CAA can be completely asymptomatic, especially since approximately 50% of individuals over 80 years of age display some pathology evidence of amyloid deposition as part of normal aging processes. However, amyloid deposition in cerebral blood vessels does favor development of several clinical conditions. Amyloid deposition can weaken cerebral blood vessels walls, causing rupture and therefore leading to both asymptomatic microbleeds and lobar ICH. Amyloid deposits can also obliterate the vessel lumen, leading to ischemia and related clinical manifestations (cerebral infarction, “incomplete infarction”, leukoaraiosis). Focal neurological deficits, disturbances of consciousness, progressive cognitive decline, dementia, and death can occur as a consequence of these vascular mechanisms (albeit additional biological processes are also likely to be implicated).¹⁵

CAA-related ICH (CAA-ICH) accounts for 5-20% of all spontaneous (non-traumatic) ICH in elderly subjects. CAA-ICH tends to be lobar in location, due to the involvement of superficial cortical and leptomeningeal vessels, and often manifests as recurrent or multiple simultaneous bleeding events, because of the widespread nature of the angiopathy. Hypertension is less commonly associated with lobar hemorrhages than with non-lobar ICH.¹⁵ Increasing evidence is emerging that CAA may be a risk factor for thrombolysis-related intracerebral hemorrhage. CAAH and thrombolysis-related intracerebral hemorrhage share some clinical features, such as predisposition to lo-

bar or superficial regions of the brain, multiple hemorrhages, increasing frequency with age, and an association with dementia.⁶⁸ *In vitro* work showed that accumulation of amyloid-beta peptide causes degeneration of cells in the walls of blood vessels, affects vasoactivity, and improves proteolytic mechanisms, such as fibrinolysis, anticoagulation, and degradation of the extracellular matrix.⁶⁸

Clinical diagnosis

While hemorrhagic stroke is the defining clinical characteristic raising concern for CAA, there are no pathognomonic clinical features of CAA-ICH. Headache, focal neurological deficits, seizures and altered level of consciousness occur in all ICH patients, based on hematoma size and location rather than pathophysiological mechanisms. Spontaneous bleeding due to CAA, as previously mentioned, can also be small and asymptomatic and is commonly referred to as a “microbleed”.^{69,70} Microbleeds are part of the integrated clinical and imaging assessment leading to CAA diagnosis during life (see below), and have also been shown to correlate with risk of cognitive decline, functional dependence and lobar ICH recurrence.⁷¹ A recent study, based on assessment of microbleeds and leukoaraiosis in CAA-ICH and hypertensive ICH patients, suggested that both pathophysiological mechanisms might be present simultaneously in up to 25% of ICH patients.⁷²

A definitive CAA diagnosis can only be formulated after histological investigation of affected brain tissue, obtained at autopsy or via brain biopsy. In practice evidence of CAA is very often found unexpectedly at post-mortem investigation. Non-invasive CAA diagnostic criteria have been therefore developed and refined in the past decade, in order to both improve and standardize diagnosis during life (Table 2).⁷³ Additional refinement of these criteria based on inclusion of superficial siderosis among imaging markers of CAA has been recently proposed.⁷⁴ Furthermore, positron emission tomography imaging with the beta-amyloid-binding compound Pittsburgh Compound B has been recently proposed as a potential noninvasive method for CAA detection in living subjects.⁷⁵ A recent report suggested that severity of Pittsburgh Compound B retention is associated with risk of recombinant tissue-type plasminogen activator-associated intraparenchymal hemorrhage.⁷⁶

Prevention and treatment

No evidence-based treatment or preventive strategy for CAA or CAA-ICH exists at this time. Corticosteroid treatment has been shown in some case reports and small series to ameliorate symptoms associated with CAA-related inflammation, possibly by reducing vasogenic edema.⁷⁷ Other immunosuppressant treatments have been reported to influence the course of inflammatory CAA, but available evidence is extremely limited.⁷⁸ How-

Table 2. Boston criteria for CAA diagnosis

1. Definite CAA
Full postmortem examination demonstrating:
<ul style="list-style-type: none"> • Lobar, cortical, or corticosubcortical hemorrhage • Severe CAA with vasculopathy* • Absence of other diagnostic lesion
2. Probable CAA with supporting pathology
Clinical data and pathologic tissue (evacuated hematoma or cortical biopsy) demonstrating:
<ul style="list-style-type: none"> • Lobar, cortical, or corticosubcortical hemorrhage • Some degree of CAA in specimen • Absence of other diagnostic lesion
3. Probable CAA
Clinical data and MRI or CT demonstrating:
<ul style="list-style-type: none"> • Multiple hemorrhages restricted to lobar, cortical, or corticosubcortical regions (cerebellar hemorrhage allowed) • Age ≥ 55 years • Absence of other cause of hemorrhage[†]
4. Possible CAA
Clinical data and MRI or CT demonstrating:
<ul style="list-style-type: none"> • Single lobar, cortical, or corticosubcortical hemorrhage • Age ≥ 55 years • Absence of other cause of hemorrhage[†]

INR >73.0 or other nonspecific laboratory abnormalities permitted for diagnosis of possible CAA.

*Von Sattel JP, Myers RH, Hedley-Whyte ET, Ropper AH, Bird ED, Richardson EP Jr. Cerebral amyloid angiopathy without and with cerebral hemorrhages: a comparative histological study. *Ann Neurol* 1991;30:637-649.⁶⁷ †Other causes of intracerebral hemorrhage include: excessive warfarin dosing (INR >3.0), antecedent head trauma or ischemic stroke, CNS tumor, vascular malformation, CNS vasculitis, blood dyscrasia, coagulopathy.

CAA: cerebral amyloid angiopathy.

ever, recently reported results from the PROGRESS trial suggests that blood pressure control is likely to reduce risk of CAA-ICH recurrence.⁷⁹ While CAA has been shown to represent a risk factor for thrombolysis-associated ICH and warfarin-related hemorrhagic stroke, no clear tools for risk prediction and stratification have yet been developed and validated. In particular, there is growing interest in the possible role of leukoaraiosis and microbleeds as surrogate markers for CAA severity, and therefore as possible tools for prediction of CAA-ICH.⁸⁰ Of note, a recent study found an association between aspirin use and CAA-ICH recurrence, providing preliminary evidence of a possible association between microbleed burden and re-bleeding risk due to antiplatelet treatment.⁸¹ Similarly, in light of recent evidence associating statin treatment with increased risk for ICH recurrence additional research is necessary in order to determine the risks and benefits of lipid-lowering treatment for CAA patients.⁸²

Hereditary Cerebral Amyloid Angiopathy

Overall, hereditary forms of CAA (Table 1) are generally more severe than sporadic forms and often characterized by earlier age of onset, more severe clinical course, and earlier age of neurologic devastation and/or death.⁸³⁻⁸⁹ Unlike sporadic CAA, he-

reditary forms are exceedingly rare and tend to present in selected families in the form of autosomal dominant disorders. Both sporadic and hereditary CAA often cause cognitive impairment, but lobar ICH is not a consistent feature of all hereditary CAA forms. Specifically, hereditary CAA can be further classified in A β and non-A β forms, based on the accumulating peptide (or fragment). While involvement of leptomeningeal or cerebral vessels has been described in all familial syndromes, lobar ICH rarely dominates the clinical picture of non-A β CAA, with the remarkable exception of the non-A β Icelandic type. As for familial A β forms (Fig. 1), although some alterations in APP processing have been associated with corresponding mutations (particularly the Flemish mutation), their primary characteristic appears to be a modification of biochemical and cell biological properties of the peptide itself, including conformation, aggregation and fibril generation. Of note, APOE seems to play less of a significant role in hereditary than sporadic CAA, possibly reflecting the overriding role of the autosomal dominant A β mutation in determining Amyloid accumulation and therefore disease risk and clinical course.

Conclusion

CAA presents in both sporadic and hereditary familial forms.

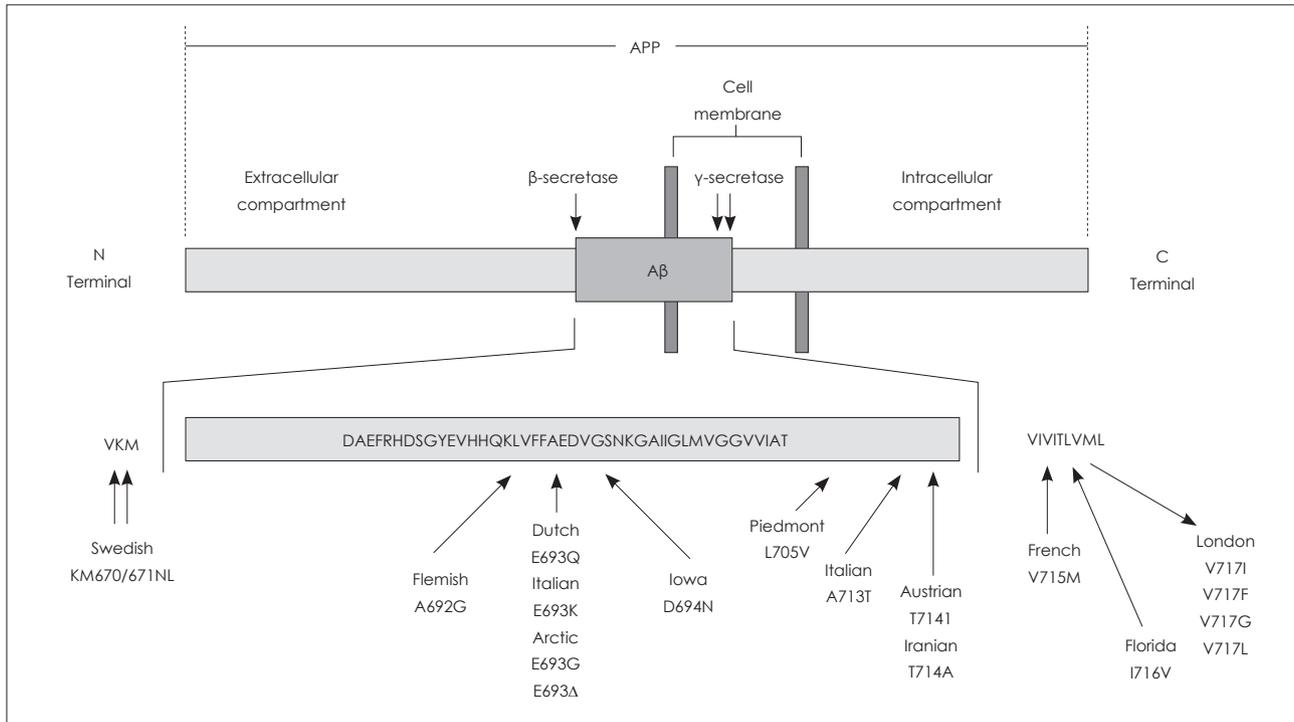


Fig. 1. Mutations in the APP gene and their relationship to the amino acid sequence of the A β peptide. APP: amyloid precursor protein.

While hereditary forms are rare in the population and tend to affect younger individuals, sporadic CAA is a common disease of the elderly, its incidence and severity increasing with age. The emphasis placed on CAA in medical practice and research is justified by its association with cognitive decline, dementia and, more importantly, spontaneous lobar ICH. In the past decade a vast body of knowledge has been gathered on CAA pathogenesis, and efficient clinical and imaging tools have been developed to allow reliable diagnosis in life. However, further research efforts are required in order to identify targets for therapeutic and preventive interventions, aimed at limiting mortality, disability and neurological compromise associated with this CAA and CAA-related ICH.

Conflicts of Interest

The authors have no financial conflicts of interest.

REFERENCES

- Revesz T, Ghiso J, Lashley T, Plant G, Rostagno A, Frangione B, et al. Cerebral amyloidopathies: a pathologic, biochemical, and genetic view. *J Neuropathol Exp Neurol* 2003;62:885-898.
- Frangione B, Révész T, Vidal R, Holton J, Lashley T, Houlden H, et al. Familial cerebral amyloid angiopathy related to stroke and dementia. *Amyloid* 2001;8 Suppl 1:36-42.
- Selkoe DJ. Alzheimer's disease: genes, proteins, and therapy. *Physiol Rev* 2001;81:741-766.
- Oppenheim G. Über "drusige Nekrosen" in der Grosshirnrinde. *Neurol Centralbl* 1909;28:410-413.
- Scholz WZ. Studien zur pathologie der hirnarterien und capillaren. *Gesamte Neurol Psychiatr* 1938;162:694-715.
- Pantelakis S. [A particular type of senile angiopathy of the central nervous system: congophilic angiopathy, topography and frequency]. *Monatsschr Psychiatr Neurol* 1954;128:219-256.
- Okazaki H, Reagan TJ, Campbell RJ. Clinicopathologic studies of primary cerebral amyloid angiopathy. *Mayo Clin Proc* 1979;54:22-31.
- Goldgaber D, Lerman MI, McBride OW, Saffiotti U, Gajdusek DC. Characterization and chromosomal localization of a cDNA encoding brain amyloid of Alzheimer's disease. *Science* 1987;235:877-880.
- Haass C, Schlossmacher MG, Hung AY, Vigo-Pelfrey C, Mellon A, Ostaszewski BL, et al. Amyloid beta-peptide is produced by cultured cells during normal metabolism. *Nature* 1992;359:322-325.
- Robakis NK, Ramakrishna N, Wolfe G, Wisniewski HM. Molecular cloning and characterization of a cDNA encoding the cerebrovascular and the neuritic plaque amyloid peptides. *Proc Natl Acad Sci USA* 1987;84:4190-4194.
- Busciglio J, Gabuzda DH, Matsudaira P, Yankner BA. Generation of beta-amyloid in the secretory pathway in neuronal and nonneuronal cells. *Proc Natl Acad Sci USA* 1993;90:2092-2096.
- Jellinger KA. Alzheimer disease and cerebrovascular pathology: an update. *J Neural Transm* 2002;109:813-836.
- Greenberg SM, Vonsattel JP. Diagnosis of cerebral amyloid angiopathy. Sensitivity and specificity of cortical biopsy. *Stroke* 1997;28:1418-1422.
- Neuropathology Group. Medical Research Council Cognitive Function and Aging Study. Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). *Lancet* 2001;357:169-175.
- Greenberg SM. *Stroke: Pathophysiology, Diagnosis and Management*. New York: Harcourt Inc., 2004;693-697.
- Ishii K, Tamaoka A, Mizusawa H, Shoji S, Ohtake T, Fraser PE, et al. Abeta1-40 but not Abeta1-42 levels in cortex correlate with apolipoprotein E epsilon4 allele dosage in sporadic Alzheimer's disease. *Brain Res* 1997;748:250-252.

17. Harper JD, Lieber CM, Lansbury PT Jr. Atomic force microscopic imaging of seeded fibril formation and fibril branching by the Alzheimer's disease amyloid-beta protein. *Chem Biol* 1997;4:951-959.
18. Ghiso J, Rostagno A, Tomidokoro Y, Lashley T, Bojsen-Møller M, Braendgaard H, et al. Genetic alterations of the BRI2 gene: familial British and Danish dementias. *Brain Pathol* 2006;16:71-79.
19. Rostagno A, Lal R, Ghiso J. Protein misfolding, aggregation, and fibril formation: common features of cerebral and non-cerebral amyloid diseases. In: Dawbarn D, Allen S. *The neurobiology of Alzheimer's disease*. Oxford: Oxford University Press, 2007;133-160.
20. Zlokovic BV. Vascular disorder in Alzheimer's disease: role in pathogenesis of dementia and therapeutic targets. *Adv Drug Deliv Rev* 2002;54:1553-1559.
21. Kawarabayashi T, Shoji M, Sato M, Sasaki A, Ho L, Eckman CB, et al. Accumulation of beta-amyloid fibrils in pancreas of transgenic mice. *Neurobiol Aging* 1996;17:215-222.
22. Burgermeister P, Calhoun ME, Winkler DT, Jucker M. Mechanisms of cerebrovascular amyloid deposition. Lessons from mouse models. *Ann N Y Acad Sci* 2000;903:307-316.
23. Kalaria RN, Premkumar DR, Pax AB, Cohen DL, Lieberburg I. Production and increased detection of amyloid beta protein and amyloidogenic fragments in brain microvessels, meningeal vessels and choroid plexus in Alzheimer's disease. *Brain Res Mol Brain Res* 1996;35:58-68.
24. Chesebro B, Trifilo M, Race R, Meade-White K, Teng C, LaCasse R, et al. Anchorless prion protein results in infectious amyloid disease without clinical scrapie. *Science* 2005;308:1435-1439.
25. Herzog MC, Winkler DT, Burgermeister P, Pfeifer M, Kohler E, Schmidt SD, et al. Abeta is targeted to the vasculature in a mouse model of hereditary cerebral hemorrhage with amyloidosis. *Nat Neurosci* 2004;7:954-960.
26. Van Dorpe J, Smeijers L, Dewachter I, Nuyens D, Spittaels K, Van Den Haute C, et al. Prominent cerebral amyloid angiopathy in transgenic mice overexpressing the london mutant of human APP in neurons. *Am J Pathol* 2000;157:1283-1298.
27. Vidal R, Barbeito AG, Miravalle L, Ghetti B. Cerebral amyloid angiopathy and parenchymal amyloid deposition in transgenic mice expressing the Danish mutant form of human BRI2. *Brain Pathol* 2009;19:58-68.
28. Weller RO, Massey A, Newman TA, Hutchings M, Kuo YM, Roher AE. Cerebral amyloid angiopathy: amyloid beta accumulates in putative interstitial fluid drainage pathways in Alzheimer's disease. *Am J Pathol* 1998;153:725-733.
29. Weller RO, Subash M, Preston SD, Mazanti I, Carare RO. Perivascular drainage of amyloid-beta peptides from the brain and its failure in cerebral amyloid angiopathy and Alzheimer's disease. *Brain Pathol* 2008;18:253-266.
30. Deane R, Du Yan S, Subramanian RK, LaRue B, Jovanovic S, Hogg E, et al. RAGE mediates amyloid-beta peptide transport across the blood-brain barrier and accumulation in brain. *Nat Med* 2003;9:907-913.
31. Ghilardi JR, Catton M, Stimson ER, Rogers S, Walker LC, Maggio JE, et al. Intra-arterial infusion of [125I] A beta 1-40 labels amyloid deposits in the aged primate brain in vivo. *Neuroreport* 1996;7:2607-2611.
32. Mackic JB, Weiss MH, Miao W, Kirkman E, Ghiso J, Calero M, et al. Cerebrovascular accumulation and increased blood-brain barrier permeability to circulating Alzheimer's amyloid beta peptide in aged squirrel monkey with cerebral amyloid angiopathy. *J Neurochem* 1998;70:210-215.
33. Maness LM, Banks WA, Podlisny MB, Selkoe DJ, Kastin AJ. Passage of human amyloid beta-protein 1-40 across the murine blood-brain barrier. *Life Sci* 1994;55:1643-1650.
34. Martel CL, Mackic JB, Matsubara E, Governale S, Miguel C, Miao W, et al. Isoform-specific effects of apolipoproteins E2, E3, and E4 on cerebral capillary sequestration and blood-brain barrier transport of circulating Alzheimer's amyloid beta. *J Neurochem* 1997;69:1995-2004.
35. Poduslo JF, Curran GL, Sanyal B, Selkoe DJ. Receptor-mediated transport of human amyloid beta-protein 1-40 and 1-42 at the blood-brain barrier. *Neurobiol Dis* 1999;6:190-199.
36. Zlokovic BV, Martel CL, Matsubara E, McComb JG, Zheng G, McCluskey RT, et al. Glycoprotein 330/megalin: probable role in receptor-mediated transport of apolipoprotein J alone and in a complex with Alzheimer disease amyloid beta at the blood-brain and blood-cerebrospinal fluid barriers. *Proc Natl Acad Sci U S A* 1996;93:4229-4234.
37. Bading JR, Yamada S, Mackic JB, Kirkman L, Miller C, Calero M, et al. Brain clearance of Alzheimer's amyloid-beta40 in the squirrel monkey: a SPECT study in a primate model of cerebral amyloid angiopathy. *J Drug Target* 2002;10:359-368.
38. DeMattos RB, Bales KR, Cummins DJ, Paul SM, Holtzman DM. Brain to plasma amyloid-beta efflux: a measure of brain amyloid burden in a mouse model of Alzheimer's disease. *Science* 2002;295:2264-2267.
39. Ghersi-Egea JF, Gorevic PD, Ghiso J, Frangione B, Patlak CS, Fenstermacher JD. Fate of cerebrospinal fluid-borne amyloid beta-peptide: rapid clearance into blood and appreciable accumulation by cerebral arteries. *J Neurochem* 1996;67:880-883.
40. Monro OR, Mackic JB, Yamada S, Segal MB, Ghiso J, Maurer C, et al. Substitution at codon 22 reduces clearance of Alzheimer's amyloid-beta peptide from the cerebrospinal fluid and prevents its transport from the central nervous system into blood. *Neurobiol Aging* 2002;23:405-412.
41. Shibata M, Yamada S, Kumar SR, Calero M, Bading J, Frangione B, et al. Clearance of Alzheimer's amyloid-ss(1-40) peptide from brain by LDL receptor-related protein-1 at the blood-brain barrier. *J Clin Invest* 2000;106:1489-1499.
42. Zlokovic BV, Yamada S, Holtzman D, Ghiso J, Frangione B. Clearance of amyloid beta-peptide from brain: transport or metabolism? *Nat Med* 2000;6:718-719.
43. Cirrito JR, Deane R, Fagan AM, Spinner ML, Parsadanian M, Finn MB, et al. P-glycoprotein deficiency at the blood-brain barrier increases amyloid-beta deposition in an Alzheimer disease mouse model. *J Clin Invest* 2005;115:3285-3290.
44. Miners JS, Baig S, Palmer J, Palmer LE, Kehoe PG, Love S. Abeta-degrading enzymes in Alzheimer's disease. *Brain Pathol* 2008;18:240-252.
45. Selkoe DJ. Clearing the brain's amyloid cobwebs. *Neuron* 2001;32:177-180.
46. Wang YJ, Zhou HD, Zhou XF. Clearance of amyloid-beta in Alzheimer's disease: progress, problems and perspectives. *Drug Discov Today* 2006;11:931-938.
47. Sudlow C, Martínez González NA, Kim J, Clark C. Does apolipoprotein E genotype influence the risk of ischemic stroke, intracerebral hemorrhage, or subarachnoid hemorrhage? Systematic review and meta-analysis of 31 studies among 5961 cases and 17,965 controls. *Stroke* 2006;37:364-370.
48. Nicoll JA, Burnett C, Love S, Graham DI, Dewar D, Ironside JW, et al. High frequency of apolipoprotein E epsilon 2 allele in hemorrhage due to cerebral amyloid angiopathy. *Ann Neurol* 1997;41:716-721.
49. Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. *JAMA* 1997;278:1349-1356.
50. Wisniewski T, Golabek A, Matsubara E, Ghiso J, Frangione B. Apolipoprotein E: binding to soluble Alzheimer's beta-amyloid. *Biochem Biophys Res Commun* 1993;192:359-365.
51. Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Englund J, Salvesen GS, et al. Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. *Proc Natl Acad Sci U S A* 1993;90:1977-1981.
52. Russo C, Angelini G, Dapino D, Piccini A, Piombo G, Schettini G, et al. Opposite roles of apolipoprotein E in normal brains and in Alzheimer's

- er's disease. *Proc Natl Acad Sci U S A* 1998;95:15598-15602.
53. Wisniewski T, Lalowski M, Golabek A, Vogel T, Frangione B. Is Alzheimer's disease an apolipoprotein E amyloidosis? *Lancet* 1995;345:956-958.
 54. Holtzman DM. Role of apoE/Abeta interactions in the pathogenesis of Alzheimer's disease and cerebral amyloid angiopathy. *J Mol Neurosci* 2001;17:147-155.
 55. Graham DI, Lantos PL. *Greenfield's Neuropathology*. London: Arnold, 2002;293-296.
 56. Frackowiak J, Zoltowska A, Wisniewski HM. Non-fibrillar beta-amyloid protein is associated with smooth muscle cells of vessel walls in Alzheimer disease. *J Neuropathol Exp Neurol* 1994;53:637-645.
 57. Wisniewski HM, Wegiel J, Vorbrodt AW, Mazur-Kolecka B, Frackowiak J. Role of perivascular cells and myocytes in vascular amyloidosis. *Ann N Y Acad Sci* 2000;903:6-18.
 58. Revesz T, Holton JL, Lashley T, Plant G, Rostagno A, Ghiso J, et al. Sporadic and familial cerebral amyloid angiopathies. *Brain Pathol* 2002;12:343-357.
 59. Eng JA, Frosch MP, Choi K, Rebeck GW, Greenberg SM. Clinical manifestations of cerebral amyloid angiopathy-related inflammation. *Ann Neurol* 2004;55:250-256.
 60. Scolding NJ, Joseph F, Kirby PA, Mazanti I, Gray F, Mikol J, et al. Abeta-related angiitis: primary angiitis of the central nervous system associated with cerebral amyloid angiopathy. *Brain* 2005;128:500-515.
 61. Attems J, Jellinger KA, Lintner F. Alzheimer's disease pathology influences severity and topographical distribution of cerebral amyloid angiopathy. *Acta Neuropathol* 2005;110:222-231.
 62. Pfeifer LA, White LR, Ross GW, Petrovitch H, Launer LJ. Cerebral amyloid angiopathy and cognitive function: the HAAS autopsy study. *Neurology* 2002;58:1629-1634.
 63. Ellis RJ, Olichney JM, Thal LJ, Mirra SS, Morris JC, Beekly D, et al. Cerebral amyloid angiopathy in the brains of patients with Alzheimer's disease: the CERAD experience, Part XV. *Neurology* 1996;46:1592-1596.
 64. Puchtler H, Waldrop FS, Meloan SN. A review of light, polarization and fluorescence microscopic methods for amyloid. *Appl Pathol* 1985;3:5-17.
 65. Stiller D, Katzenkamp D, Thoss K. [Staining mechanism of thioflavin T with special reference to the localization of amyloid]. *Acta Histochem* 1972;42:234-245.
 66. Olichney JM, Hansen LA, Hofstetter CR, Grundman M, Katzman R, Thal LJ. Cerebral infarction in Alzheimer's disease is associated with severe amyloid angiopathy and hypertension. *Arch Neurol* 1995;52:702-708.
 67. Vonsattel JP, Myers RH, Hedley-Whyte ET, Ropper AH, Bird ED, Richardson EP Jr. Cerebral amyloid angiopathy without and with cerebral hemorrhages: a comparative histological study. *Ann Neurol* 1991;30:637-649.
 68. McCarron MO, Nicoll JA. Cerebral amyloid angiopathy and thrombolysis-related intracerebral haemorrhage. *Lancet Neurol* 2004;3:484-492.
 69. Greenberg SM, Vernooij MW, Cordonnier C, Viswanathan A, Al-Shahi Salman R, Warach S, et al. Cerebral microbleeds: a guide to detection and interpretation. *Lancet Neurol* 2009;8:165-174.
 70. Greenberg SM, Nandigam RN, Delgado P, Betensky RA, Rosand J, Viswanathan A, et al. Microbleeds versus macrobleeds: evidence for distinct entities. *Stroke* 2009;40:2382-2386.
 71. Greenberg SM, Eng JA, Ning M, Smith EE, Rosand J. Hemorrhage burden predicts recurrent intracerebral hemorrhage after lobar hemorrhage. *Stroke* 2004;35:1415-1420.
 72. Smith EE, Nandigam KR, Chen YW, Jeng J, Salat D, Halpin A, et al. MRI markers of small vessel disease in lobar and deep hemispheric intracerebral hemorrhage. *Stroke* 2010;41:1933-1938.
 73. Knudsen KA, Rosand J, Karluk D, Greenberg SM. Clinical diagnosis of cerebral amyloid angiopathy: validation of the Boston criteria. *Neurology* 2001;56:537-539.
 74. Linn J, Halpin A, Demaerel P, Ruhland J, Giese AD, Dichgans M, et al. Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy. *Neurology* 2010;74:1346-1350.
 75. Johnson KA, Gregas M, Becker JA, Kinnecom C, Salat DH, Moran EK, et al. Imaging of amyloid burden and distribution in cerebral amyloid angiopathy. *Ann Neurol* 2007;62:229-234.
 76. Ly JV, Rowe CC, Villemagne VL, Zavala JA, Ma H, O'Keefe G, et al. Cerebral β -amyloid detected by Pittsburgh compound B positron emission topography predisposes to recombinant tissue plasminogen activator-related hemorrhage. *Ann Neurol* 2010;68:959-962.
 77. Kloppenborg RP, Richard E, Sprengers ME, Troost D, Eikelenboom P, Nederkoorn PJ. Steroid responsive encephalopathy in cerebral amyloid angiopathy: a case report and review of evidence for immunosuppressive treatment. *J Neuroinflammation* 2010;7:18.
 78. Luppe S, Betmouni S, Scolding N, Wilkins A. Cerebral amyloid angiopathy related vasculitis: successful treatment with azathioprine. *J Neurol* 2010;257:2103-2105.
 79. Arima H, Tzourio C, Anderson C, Woodward M, Boussier MG, MacMahon S, et al. Effects of perindopril-based lowering of blood pressure on intracerebral hemorrhage related to amyloid angiopathy: the PROGRESS trial. *Stroke* 2010;41:394-396.
 80. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol* 2010;9:689-701.
 81. Biffi A, Halpin A, Towfighi A, Gilson A, Busl K, Rost N, et al. Aspirin and recurrent intracerebral hemorrhage in cerebral amyloid angiopathy. *Neurology* 2010;75:693-698.
 82. Athyros VG, Tziomalos K, Karagiannis A, Wierzbicki AS, Mikhailidis DP. Aggressive statin treatment, very low serum cholesterol levels and haemorrhagic stroke: is there an association? *Curr Opin Cardiol* 2010;25:406-410.
 83. Palsdottir A, Snorraddottir AO, Thorsteinsson L. Hereditary cystatin C amyloid angiopathy: genetic, clinical, and pathological aspects. *Brain Pathol* 2006;16:55-59.
 84. Bornebroek M, De Jonghe C, Haan J, Kumar-Singh S, Younkin S, Roos R, et al. Hereditary cerebral hemorrhage with amyloidosis Dutch type (A β PP 693): decreased plasma amyloid-beta 42 concentration. *Neurobiol Dis* 2003;14:619-623.
 85. De Jonghe C, Zehr C, Yager D, Prada CM, Younkin S, Hendriks L, et al. Flemish and Dutch mutations in amyloid beta precursor protein have different effects on amyloid beta secretion. *Neurobiol Dis* 1998;5:281-286.
 86. Farzan M, Schnitzler CE, Vasilieva N, Leung D, Choe H. BACE2, a beta-secretase homolog, cleaves at the beta site and within the amyloid-beta region of the amyloid-beta precursor protein. *Proc Natl Acad Sci U S A* 2000;97:9712-9717.
 87. Haass C, Hung AY, Selkoe DJ, Teplow DB. Mutations associated with a locus for familial Alzheimer's disease result in alternative processing of amyloid beta-protein precursor. *J Biol Chem* 1994;269:17741-17748.
 88. Sten C, Nilsberth C, Hammarbäck J, Engvall B, Näslund J, Lannfelt L. The Arctic mutation interferes with processing of the amyloid precursor protein. *Neuroreport* 2002;13:1857-1860.
 89. Van Nostrand WE, Melchor JP, Cho HS, Greenberg SM, Rebeck GW. Pathogenic effects of D23N Iowa mutant amyloid beta-protein. *J Biol Chem* 2001;276:32860-32866.