Molecular pathology of hereditary cerebral hemorrhage with amyloidosis-Dutch type

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Chapter 1

Introduction

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Hereditary cerebral hemorrhage with amyloidosis-Dutch type (HCHWA-D) is an autosomal dominant hereditary disease caused by a missense mutation on chromosome 21 in the amyloid precursor protein (APP), resulting in a glutamine for glutamic acid substitution (NP_000475.1:p.Glu693Gln, known as APP E693Q) (1). HCHWA-D patients suffer predominantly from hemorrhagic strokes, infarcts, and vascular dementia (2). The so-called APP ‘’Dutch’’ mutation, originally described in families from small coastal villages in the Netherlands, is characterized by a severe Cerebral Amyloid Angiopathy (CAA) pathology.

The term CAA pathology is first used by Mandybur in 1975 (3) and is defined by the progressive accumulation of amyloid beta (Aβ) in the cerebrovasculature, resulting in acellular thickening of the vessel wall (4). CAA pathology is a risk factor for lobar intracerebral hemorrhages (ICH) (5) and for ischemic cerebral infarction (6). Because it disrupts the delicate cerebral vascular homeostasis, it can have both hemorrhagic and/or ischemic consequences (7).

HCHWA-D has been first described as the familial occurrence of ICH (8) but associated with the cerebrovascular pathology of Alzheimer’s disease (AD) only twenty-four years later (9). Shortly after, the Dutch mutation is identified as the first missense mutation associated with the AD phenotype (1), due to the shared pathological brain Aβ deposition. In AD Aβ is aggregating in parenchymal plaques but CAA is also found in 80 to 90% of AD cases from autopsy series (10–17). Therefore the vasculotropic Dutch-Aβ peptide has been extensively studied to unravel the etiology of AD cerebrovascular pathology (references in this chapter).

Aβ is a 4kDa peptide resulting from APP cleavage by processing enzymes (α-and β-secretases cleaving the N-terminal peptide and γ-secretases cutting the C-terminal). Although α-secretase cleavage results in a benign pathway, Aβ peptides produced by β-secretase cleavages can aggregate and form different Aβ species ranging from monomers to fibrils. The Dutch mutation is located near the α-secretase cleavage site of APP, and is thought to affect the APP processing (18). The Aβ peptide with the Dutch mutation is also known as Aβ E22Q, as the modification occurs in position 22 (when using Aβ peptide amino acid numbering). Depending on which cleavage site is used, different Aβ peptides are formed. Most studied isoforms are Aβ (1-40) (or Aβ40, 40 amino acids) and Aβ (1-42) (or Aβ42, 42 amino acids) but many N-terminal and C-terminal truncated peptides coexists in HCHWA-D (19), adding complexity to the aggregation process of the peptides.

Clinicopathology of HCHWA-D

White matter lesions (recognized as white matter hyperintensities [WMHs] in magnetic resonance imaging [MRI] scans) are the earliest radiological manifestations in pre-symptomatic mutation carriers (detectable in standard 1.5 Tesla [T] scan). Although more subtle, the grey matter is also affected by cortical thinning in relatively young mutation carriers (mean age 46 years) when compared at 3T MRI to a control group (20). Cortical microinfarcts detected at high resolution 7T MRI are also more prevalent in pre-symptomatic patients than in controls (21).WMHs are located in subcortical areas, and tend to be more severe in the occipital lobe (22). Other radiological manifestations such as microbleeds, intracerebral hemorrhages, superficial siderosis, convexity subarachnoid hemorrhages and microinfarcts, have a higher prevalence in symptomatic patients.

Strokes in HCHWA-D are mostly hemorrhagic but ischemic strokes can also occur. The hemorrhages mostly involve temporal and occipital lobes and occur predominantly in the deeper cortical layers and in subcortical white matter (2) but can be present in the cerebral cortex as well and tend to spare the frontal lobes (23). According to the latest clinical data, the first stroke (mean age onset 54 ±8 years, n=58) is fatal in only 14% of the cases (against two- third of patients 23 years ago; (2)) and the majority of hemorrhages (35%) are located in the occipital lobe followed by the parietal lobe (21%) (24). The mean number of strokes is 3 (range 0-10 strokes) and the mean survival after the first stroke is 10 years (range 0-28 years). Epilepsy occurs in about half of the patients who have suffered from one or more strokes (25). Cognitive decline can precede the onset of hemorrhagic strokes (22) although in a recent study, cognitives abnormalities are not detected in presymptomatic mutation carriers (n=12, (21)). Cognitive decline frequently occurs in a stepwise fashion between stroke episodes (26,27).

Neuropathological features of HCHWA-D

CAA pathology in HCHWA-D is widespread and invariably affects cerebral and cerebellar meningeal arteries and cerebrocortical arterioles with a higher severity occipitally (23). The amyloid angiopathy is believed to progress from the leptomeninges towards the neocortex and in most severe cases subcortical white matter and capillaries are involved (vessels anatomy in **Figure 1**). Subcortical white matter shows areas of demyelination, axonal loss, and gliosis (leukoencephalopathy). Tau pathology (one of the neuropathological hallmarks of AD) in HCHWA-D is rare and not associated with dementia (28).

Aβ protein deposition starts at the abluminal basement membrane of vascular smooth muscle cells (VSMCs; grade 1 CAA, **Figure 2A**). At later

stages, amyloid fibrils are observed between VSMCs and in heavily affected vessels, VSMCs are completely displaced by the amyloid (grade 2 CAA, **Figure 2B**). With CAA progression, additional radial layers of Aβ (one or two) around a layer of homogeneous Aβ develop in cerebrocortical arterioles at the level of cortical layers II–III of severe cases (absent in leptomeninges and cerebellum) (23,29). Vessels with radial Aβ are associated with degenerating neurites, reactive astrocytes and activated microglia [30, Maat schieman p227].

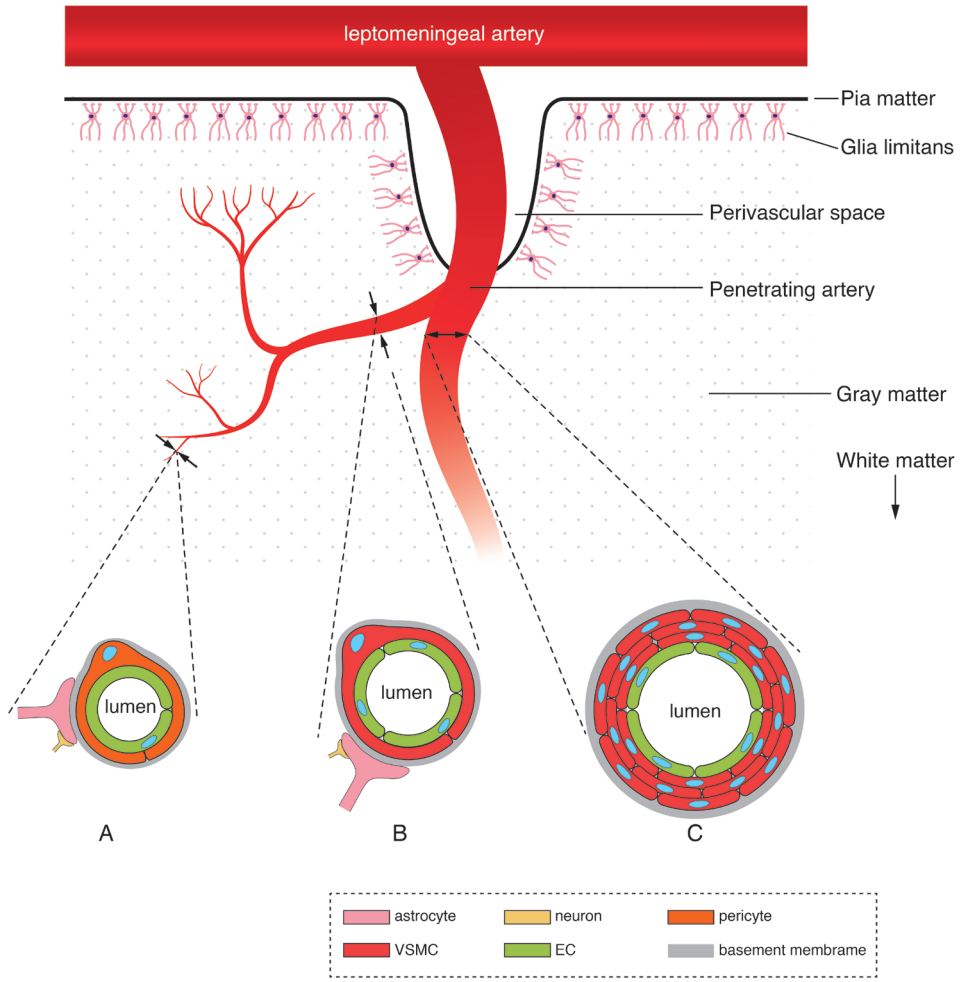

Figure 1: Illustration of the cortical brain vessels anatomy and details of the vascular components in (A) a capillary at the neurovascular unit (NVU), (B) an arteriole and (C) a penetrating artery.

Non-fibrillar Aβ clouds and fine diffuse plaques in the parenchyma tend to disappear with age and suggests a clearance of non-fibrillar parenchymal Aβ by glial cells in early stage of the disease (23,31). Indeed, although non-activated glial cells (astrocytes and microglia) are bearing cytoplasmic Aβ granules, activated glial cells in fibrillar deposits (parenchymal or perivascular associated with CAA) are devoid of Aβ granules. This suggests that glial response to fibrillar Aβ is not clearly linked with Aβ removal (32). Consequently, in contrast to parenchymal Aβ, CAA severity defined by CAA load and vessel wall thickening tends to intensify with age, even though it might differ considerably between patients of comparable age (28).

Further, disease progression in HCHWA-D is also associated with secondary microvascular degenerations or CAA-associated microvasculopathies such as vascular fibrosis (or hyalinization), microaneurysms, macrophage infiltration, "vessel-within-vessel" configurations (grade 3 CAA in **Figure 2C**), calcifications and vascular thrombi (33). CAA-associated microvasculopathies correlate with the number of cerebrovascular lesions (CAA-associated hemorrhages and/or infarcts; (34)) and with dementia diagnosis (28).

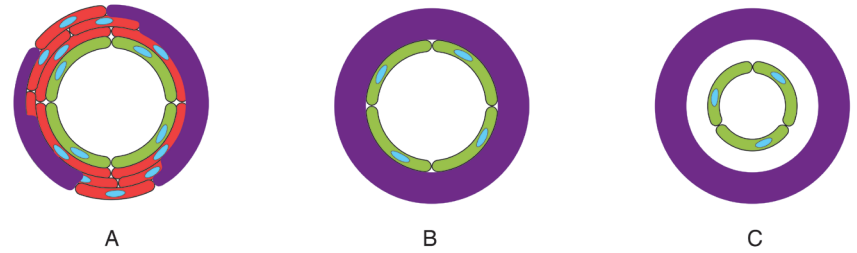

Figure 2: Illustration of CAA severity grading (based on Vonsattel & Greenberg hemorrhage risk scale 1 to 3,(106)). (A) Grade 1 CAA. Start of amyloid deposits (purple colour). (B) Grade 2 CAA. The media of this cortical vessel is fully replaced by amyloid and the wall is thickened. (C) Grade 3 CAA. Example of secondary microvasculopathies classified as grade 3, here a cracking of the vessel wall that creates a "vessel-within-vessel" appearance.

Aβ-associated proteins found in vascular deposits are investigated in HCHWA-D. Similarly to findings in AD, Amyloid P-component and Apolipoprotein E (ApoE) are identified in vascular and parenchymal Aβ (35–37). Particularly, APP and CystatinC immunoreactivity are strongly associated with CAA in HCHWA-D (38,39). Inflammatory proteins are not investigated in HCHWA-D brains except for the presence of complement proteins in amorphous plaques (40) and the association of molecular chaperone proteins with CAA (HspB8, Hsp20 and Hsp27), which could

mediate inflammatory reactions (41). The occurrence of other proteins could also vary depending on the type of material used (cryosections vs formalin-fixed and antibodies specificities). As such the presence of heparan sulfate proteoglycans found by van Horssen (42) but not by van Duinen (43), α1-antichymotrypsin found by Timmers (35), but not by Rozenmuller (40) and low-density lipoprotein receptor-related protein-1 (LRP-1) found by Wilhelmus (44), but not by Deane (45) are a matter of debate.

One characteristic feature in HCHWA-D is the presence extra-cellular matrix (ECM) parenchymal coarse deposits presenting a strong immunoreactivity for several ECM components (HSPG, laminin, collagen type 3 and 4), clustering around thick-walled Aβ vessels, but not associated with Aβ plaques. Collagen type 1 and 3 and fibronectin are associated with strongly Aβ-laden arterioles (43). Interestingly, lysyl oxidase (LOX) and tissue transglutaminase (tTG), which are enzymes cross-linking ECM-proteins, are associated with angiopathic vessels in HCHWA-D (46,47). Laminin, fibronectin, HSPG, and collagen are substrate for these enzymes whose reaction might participate in CAA formation.

Pathomechanisms of HCHWA-D

In vitro studies in human cerebrovascular cells have largely demonstrated a higher toxicity of the synthetic Aβ Dutch peptide compared to the wild type peptide (48–54). More precisely, with the Dutch mutation, a charged residue is substituted with an uncharged residue that results in higher oligomer stability favorizing the formation of these non-fibrillar toxic assemblies (55–58). Moreover, Dutch amyloid seeds, have prion-like effect on WT Aβ and are thus harmful and irreversible (59).

Amyloid deposits in HCHWA-D are a mixture of wild type and Dutch variant (60,61). Whereas CAA in general is mostly composed of Aβ40 and to a less extent of Aβ42, it is hypothesized that the Dutch mutated Aβ42 might seed and trigger the CAA formation. Indeed, both Dutch-mutated Aβ40 and wild type Aβ40 are present in isolated vessels from brain tissue, but only the Dutch-mutated Aβ42, and not the wild-type Aβ42 is detected (19). Moreover, histological studies with C-terminal specific antibodies have shown that Aβ42 preceeds Aβ40 deposition in cortical arterioles (23). In addition, electronic microscopy identified non-fibrillar Aβ42 as the first species deposited in the basement membrane of capillaries (62).

The vascular pathogenicity of the Dutch mutation is also influenced by an increase in the Aβ40:Aβ42 ratio (63), as demonstrated in transgenic mice overexpressing in neurons the human APP gene with the E693Q mutation (64). This mouse model, called APP Dutch model, develops an extensive CAA pathology (around 22-25 months) composed of Aβ40 predominantly with few diffuse Aβ42 parenchymal plaques similar to the neuropathology

of HCHWA-D. Increase in Aβ42 concentration by crossing with a PS45 transgenic line (familial AD-causing PS1 mutations) resulted in abundant parenchymal plaque formation at a young age, with limited CAA pathology (64).

So far, no risk factors have been linked with the clinical symptoms of HCHWA-D. In particular, the ApoE genotype (influence on CAA pathology described in the next section) and the polymorphism in the Presenilin (PS) 1 gene, both highly impacting Aβ transport and processing, have been investigated and did not show any significant association with the disease phenotype (65,66). Only gender may modulate the phenotypic expression of the mutation, indeed the mortality rate is respectively significantly higher for female but lower for individuals with a maternal transmission (67). Nevertheless the reason is unidentified and a recent study on a smaller cohort did not confirm the gender association with the mortality rate (24).

The Dutch mutation can also alter other mechanisms having influence on Aβ accumulation and clearance from interstitial cerebral fluid. It is suggested from *in vitro* studies that the mutation could enhance the resistance to proteolytic degradation (68,69) thereby reducing the Aβ turnover rate, while Aβ production rate seemed unaffected (70–73). Furthermore, altered affinity changes due to the Dutch mutation affects Aβ transport across the blood-brain-barrier (74). One explanation could be a lower affinity for LRP1 which could affect the LRP-mediated brain capillary clearance (45).

Pathomechanisms such as alteration in vessel wall integrity (VSMCs disappearance), activation of perivascular cell (astrogliosis and microglosis) and disturbances in peripheral drainage (basement membrane thickening), although more severe in HCHWA-D, are shared features of all CAA pathologies (75–78).

CAA pathology: sporadic CAA (sCAA) and AD with CAA

CAA pathology is frequent in normal ageing, may be asymptomatic in mild cases (79), but is an important cause of spontaneous lobar ICH (80). When taken at any level of severity, in population-based (>85 years) and community-based (median age 88.5) studies, neuropathological evidence of CAA are recorded in respectively 69.6% and 78.9% of autopsied cases (81,82). Earlier studies have related that CAA pathology is related to cognitive impairment and dementia in ageing (83). It is in addition recently proposed that besides being more prevalent among AD patients, CAA might induces an independent cognitive contribution to AD dementia (81,84).

CAA pathology in AD with CAA or in sCAA are intermingled disorders closely resembling at pathological investigation when solely regarding at Aβ vascular deposition (29). A distinction is made in subjects which rely both on the clinical diagnosis of dementia and on the definite neuropathologic

examination (tau pathology seen as neurofibrillary tangles) presence is a hallmark in AD). Both in AD with CAA and in sCAA, subjects can present an hemorrhagic phenotype which is related to CAA severity. Indeed, in AD with CAA, CAA pathology is predominantly mild to moderate but cases with the higher frequency of hemorrhages had also a more severe CAA (85). Likewise, in sCAA cases presenting lobar ICH, CAA pathology severity is, in general higher (86,87).

Besides ageing, which is the strongest known clinical risk factor for developing CAA pathology (88), certain genetic risk factor have been identified. As in AD, ApoE genotype is strongly associated with CAA pathology and has influence on the pathophysiology of CAA (89–91). ApoE ε2 and ApoE ε4 are related to more severe CAA but only ApoE ε4 is linked with capillary involvement (92,93). Carriers of ApoE ε2 risk are more at risk for CAA-related hemorrhages (87,91,94). Other non-ApoE gene polymorphisms have been compared in a meta-analysis and the strongest association with CAA pathology are found for the transforming growth factor β1 gene (TGFβ1), the translocase of outer mitochondrial membrane 40 gene (TOMM40) and the complement component receptor 1 gene (CR1) (95).

Interestingly, TGFβ1 expression modulates the CAA phenotype. In transgenic mice, both astrocytic or neuronal overexpression of TGFβ1 resulted in cerebral angiopathy due to an increase in vascular fibrosis (96,97). Moreover, co-overexpression of TGFβ1 and APP in mice resulted in a reduction in parenchymal Aβ plaque load with CAA increase (98). Multiple studies have shown a role for TGFβ1 in promoting APP and Aβ production by astrocytes *in vitro* (99–102) but also *in vivo* with increased endogenous APP and Aβ levels in TGFβ1-astrocytic mouse model (102). However, whether these animal models actually accumulate murine Aβ is likely mouse strain-dependant (103). In VSMCs, TGFβ1 associated to ApoE4 protein strongly increased the amount of cellular Aβ (104) and enhances Aβ internalization in a dose-dependent manner [30, Prior & Urmoneit p255].

Two different CAA grading methods, both based on Aβ staining, are primarily referred to in neuropathological studies. A first semi-quantitative approach is ranking CAA mostly based on its spreading from leptomeninges to intracortical area (105). A second approach focused on the vessel wall morphology of individual vessel, is assessing a scale ranging from 1 to 3 for hemorrhage risk (106), as illustrated in **Figure 2.** More recently, two similar approaches have been proposed for CAA pathologic assessment (16,107) in an attempt to find a consensus on a single method to assess CAA severity.

HCHWA-D: a model to study biomarkers & therapy for CAA pathology

Totally reliable and noninvasive diagnostic tests of CAA pathology as well as anti-CAA therapy do not exist. Therefore HCHWA-D, as an accepted monogenetic model of CAA pathology, is useful to develop biomarkers (either radiologic imaging or molecular signature) and to find new therapeutic targets.

Neuroimaging biomarkers of CAA pathology at MRI are developped in symptomatic (after first clinically assessed stroke) and pre-symptomatic HCHWA-D patients. In particular, the current diagnostic Boston criteria (based on the pattern of hemorrhagic lesions and superficial siderosis to asses probable CAA during life) have been evaluated and its sensitivity were improved by the inclusion of microbleed counts (108). Lately, two studies identified early imaging biomarker (before cognitive symptoms and ICH) for CAA pathology diagnosis by inclusion of presymptomatic carriers. In the first study, WMHs and microinfarcts which are ischaemic manifestations of CAA have been detected with high field (3T) and ultra-high field (7T) MRI (21). In the second study measuring regional cerebral blood flow (by Blood-Oxygen-Level Dependent functional MRI or BOLD fMRI), an altered vascular reactivity to visual stimulation in occipital lobe was detected in pre-symptomatic mutation carriers (109). More recently, a striped cortex appearance on 7T MRI (visualized as hypointense lines perpendicular to the pial surface) solely detected in 40% of symptomatic patients (n=15) has for that reason been described as a neuroimaging marker of advanced CAA pathology (110).

Fluid biomarkers, in particular Aβ, sAPP and Tau (total tau, and phosphorylated tau) protein levels in plasma and cerebrospinal fluid (CSF) are the most common studied biomarkers in amyloid beta related pathologies. In HCHWA-D, Aβ42 level in plasma are decreased (111) although no difference are perceived in sCAA (112). In CSF, pronounced decreased levels of Aβ40 and Aβ42 are measured in HCHWA-D pre-symptomatic mutation carriers (113) and less pronounced but consistent decreased levels are found in sCAA (114,115).

Lastly, other AD specific biomarkers have been tested in an HCHWA-D western Australian family. Pulpil flash response, which is linked to cholinergic deficit in AD, is reduced in mutation carriers and deserves further investigation (116). In the same study, mutation carriers tested with positron emission tomography imaging with Pittsburgh compound B (PiB-PET) showed a higher compound retention, although below the standard threshold for amyloid positivity in AD.

So far, the above mentioned biomarkers can estimate CAA pathology but none of them can precisely determine its severity, nor predict hemorrhagic

risk, nor assess with certainty the efficiency of a therapy. More specific biomarkers are highly needed in clinical trials of Aβ disease-modifying therapies (117). Although no therapy exist against CAA, besides focusing on amyloid removal therapies uniquely, alternative paths targeting aggravating factors of CAA pathology could help slowing down the CAA build up and delay the onset of symptoms.

Scope and outline of this thesis

The general aim of this thesis is to disentangle the molecular pathogenesis behind CAA formation in HCHWA-D. Since no proven therapeutic treatment exists to prevent or even delay the CAA pathology, understanding the underlying pathomechanisms in HCHWA-D is important and may lead to identification of potential therapeutic targets.

Chapter 2 review the literature on HCHWA-D pathogenesis, combining neuropathological and *in vitro* findings and focusing in particular on the role of ECM in HCHWA-D.

Former research in CAA field indicates the existence of factors able to influence Aβ to accumulate predominantly in vessels rather than in brain parenchyma, such as TGFβ. Identification of aggravating factors of CAA pathology that can interact with currently approved drugs is one area of investigation and therefore we explored in **Chapter 3** TGFβ pathway activation in HCHWA-D compared to sCAA.

In order to interpret imaging findings and better evaluate the disease progression **chapter 4 & 5** are dedicated to calcifications in HCHWA-D, a specific CAA-associated microvasculopathy. **Chapter 4** is a histopathological study assessing the histological correlate of a recently discovered MRI radiologic finding in HCHWA-D. **Chapter 5** is exploring the pathomechanisms leading to these abnormalities and tries to assess the relationship of these changes and the TGFβ findings from chapter 3.

Chapter 6 is an exploratory transcriptomic study to identify major deregulated pathways in HCHWA-D and broaden our comprehension of molecular pathogenesis.

References

1. Levy E, Carman MD, Fernandez-Madrid IJ, Power MD, Lieberburg I, Van Duinen SG, et al. Mutation of the Alzheimer's disease amyloid gene in hereditary cerebral hemorrhage, Dutch type. Science (80-). 1990 Jun 1;248(4959):1124–6.
2. Wattendorff AR, Frangione B, Luyendijk W. Hereditary cerebral hemorrhage with amyloidosis, Dutch type(HCHWA-D): clinicopathological studies. J Neurol Neurosurg psychiatry. 1995;58:699–705.
3. Mandybur TI. The incidence of cerebral amyloid angiopathy in Alzheimer's disease. Neurology. 1975 Feb;25(2):120–6.
4. Attems J, Jellinger K, Thal DR, Van Nostrand W. Review: Sporadic cerebral amyloid angiopathy. Neuropathol Appl Neurobiol. 2011 Feb;37(1):75–93.
5. Kimberly WT, Gilson A, Rost NS, Rosand J, Viswanathan A, Smith EE, et al. Silent ischemic infarcts are associated with hemorrhage burden in cerebral amyloid angiopathy. Neurology. 2009 Apr;72(14):1230–5.
6. Cadavid D, Mena H, Koeller K, Frommelt RA. Cerebral beta amyloid angiopathy is a risk factor for cerebral ischemic infarction. A case control study in human brain biopsies. J Neuropathol Exp Neurol. 2000 Sep;59(9):768–73.
7. Van Nostrand WE. The influence of the amyloid ß-protein and its precursor in modulating cerebral hemostasis. Biochim Biophys Acta - Mol Basis Dis. 2015;
8. Luyendijk W, Schoen JH. Intracerebral Hematomas. a Clinical Study of 40 Surgical Cases. Psychiatr Neurol Neurochir. 1964;67:445–68.
9. Luyendijk W, Bots GT, Vegter-van der Vlis M, Went LN, Frangione B. Hereditary cerebral haemorrhage caused by cortical amyloid angiopathy. J Neurol Sci. 1988 Jul;85(3):267–80.
10. Vinters H V, Gilbert JJ. Cerebral amyloid angiopathy: incidence and complications in the aging brain. II. The distribution of amyloid vascular changes. Stroke. 1983;14(6):924–8.
11. Vonsattel JPG, Myers RH, Tessa Hedley□Whyte E, Ropper AH, Bird ED, Richardson EP. Cerebral amyloid angiopathy without and with cerebral hemorrhages: A comparative histological study. Ann Neurol. 1991 Nov;30(5):637–49.
12. Esiri MM, Wilcock GK. Cerebral amyloid angiopathy in dementia and old age. J Neurol Neurosurg Psychiatry. 1986 Nov;49(11):1221–6.
13. Kalaria RN, Ballard C. Overlap between pathology of Alzheimer disease and vascular dementia. Alzheimer Dis Assoc Disord. 1999;13 Suppl 3:S115-23.
14. Jellinger KA. Alzheimer disease and cerebrovascular pathology: An update. J Neural Transm. 2002 May;109(5–6):813–36.
15. Love S, Miners S, Palmer J, Chalmers K, Kehoe P. Insights into the pathogenesis and pathogenicity of cerebral amyloid angiopathy. Front Biosci (Landmark Ed. 2009 Jan;14:4778–92.
16. Owsley C, McGwin G, Sloane ME, Stalvey BT, Wells J. Timed instrumental activities of daily living tasks: Relationship to visual function in older adults. Optom Vis Sci. 2001;78(5):350–9.
17. Arvanitakis Z, Leurgans SE, Wang Z, Wilson RS, Bennett DA, Schneider JA. Cerebral amyloid angiopathy pathology and cognitive domains in older persons. Ann Neurol. 2011 Feb;69(2):320–7.

18. De Strooper B, Annaert W. Proteolytic processing and cell biological functions of the amyloid precursor protein. J Cell Sci. 2000 Jun;113 (Pt 1:1857–70.
19. Nishitsuji K, Tomiyama T, Ishibashi K, Kametani F, Ozawa K, Okada R, et al. Cerebral Vascular Accumulation of Dutch- Type Ab42 , but Not Wild-Type Ab42 , in Hereditary Cerebral Hemorrhage With Amyloidosis , Dutch Type. J Neurosci Res. 2007;2923:2917–23.
20. Fotiadis P, van Rooden S, van der Grond J, Schultz A, Martinez-Ramirez S, Auriel E, et al. Cortical atrophy in patients with cerebral amyloid angiopathy: a case-control study. Lancet Neurol. 2016 Jul;15(8):811–9.
21. van Rooden S, van Opstal AM, Labadie G, Terwindt GM, Wermer MJH, Webb AG, et al. Early Magnetic Resonance Imaging and Cognitive Markers of Hereditary Cerebral Amyloid Angiopathy. Stroke. 2016 Dec;47(12):3041–4.
22. Bornebroek M, Haan J, Maat-Schieman ML, Van Duinen SG, Roos R a. Hereditary cerebral hemorrhage with amyloidosis-Dutch type (HCHWA-D): I--A review of clinical, radiologic and genetic aspects. Brain Pathol. 1996 Apr;6(2):111–4.
23. Maat-schieman M, Roos R, Duinen S Van, van Duinen S. Review Article Hereditary cerebral hemorrhage with amyloidosis- Dutch type. Neuropathology. 2005 Dec;25(February):288–97.
24. Van Etten ES, Gurol ME, Van Der Grond J, Haan J, Viswanathan A, Schwab KM, et al. Recurrent hemorrhage risk and mortality in hereditary and sporadic cerebral amyloid angiopathy. Neurology. 2016;87(14):1482–7.
25. Bornebroek M, Haan J, Roos RAC. Hereditary cerebral hemorrhage with amyloidosis - Dutch type (HCHWA-D): A review of the variety in phenotypic expression. Amyloid. 1999 Sep;6(3):215–24.
26. Bornebroek M, Haan J, Van Buchem MA, Lanser JBK, Simone De Vries-vd Weerd MAC, Zoeteweij M, et al. White matter lesions and cognitive deterioration in presymptomatic carriers of the amyloid precursor protein gene codon 693 mutation. Arch Neurol. 1996;53(1):43–8.
27. Haan J, Lanser JB, Zijderveld I, van der Does IG, Roos RA. Dementia in hereditary cerebral hemorrhage with amyloidosis-Dutch type. Arch Neurol. 1990 Sep;47(9):965–7.
28. Natté R, Maat-Schieman MLC, Haan J, Bornebroek M, Roos RAC, Van Duinen SG. Dementia in hereditary cerebral hemorrhage with amyloidosis-Dutch type is associated with cerebral amyloid angiopathy but is independent of plaques and neurofibrillary tangles. Ann Neurol. 2001 Dec;50(6):765–72.
29. Maat-Schieman MLC, Van Duinen SG, Bornebroek M, Haan J, Roos RAC. Hereditary cerebral hemorrhage with amyloidosis-Dutch type (HCHWA-D): II - A review of histopathological aspects. Brain Pathol. 1996 Apr;6(2):115–20.
30. Verbeek M, de Waal R, Vinters, HV E. Cerebral amyloid angiopathy in Alzheimer's disease and related disorders. Vinters MMV• RMW de W• H V., editor. Dordrecht, the Netherlands: Kluwer Academic Publishers; 2000.
31. Maat-Schieman MLC, Yamaguchi H, Van Duinen SG, Natté R, Roos RAC. Age-related plaque morphology and C-terminal heterogeneity of amyloid β in Dutch-type hereditary cerebral hemorrhage with amyloidosis. Acta Neuropathol. 2000 Apr;99(4):409–19.
32. Maat-Schieman MLC, Yamaguchi H, Hegeman-Kleinn IM, Welling-Graafland C, Natté R, Roos RAC, et al. Glial reactions and the clearance of amyloid β protein in the brains of patients with hereditary cerebral hemorrhage with amyloidosis-Dutch type. Acta Neuropathol. 2004 May;107(5):389–98.

33. Vinters H V., Natté R, Maat-Schieman MLC, Van Duinen SG, Hegeman-Kleinn I, Welling-Graafland C, et al. Secondary microvascular degeneration in amyloid angiopathy of patients with hereditary cerebral hemorrhage with amyloidosis, Dutch type (HCHWA-D). Acta Neuropathol. 1998 Mar;95(3):235–44.
34. Natté R, Vinters H V., Maat-Schieman MLC, Bornebroek M, Haan J, Roos RAC, et al. Microvasculopathy is associated with the number of cerebrovascular lesions in hereditary cerebral hemorrhage with amyloidosis, dutch type. Stroke. 1998 Aug 1;29(8):1588–94.
35. Timmers WF, Tagliavini F, Haan J, Frangione B. Parenchymal preamyloid and amyloid deposits in the brains of patients with hereditary cerebral hemorrhage with amyloidosis--Dutch type. Neurosci Lett. 1990 Oct;118(2):223–6.
36. Wisniewski T, Frangione B. Molecular biology of Alzheimer's amyloid—Dutch variant. Mol Neurobiol. 1992 Mar;6(1):75–86.
37. J Haan, C Van Broeckhoven, C M van Duijn, E Voorhoeve, F van Harskamp, J C van Swieten, M L Maat-Schieman, R A Roos EB. The apolipoprotein E epsilon 4 allele does not influence the clinical expression of the amyloid precursor protein gene codon 693 or 692 mutations. Ann Neurol. 1994;36:434–7.
38. Rozemuller AJ, Roos RA, Bots GT, Kamphorst W, Eikelenboom P, Van Nostrand WE. Distribution of beta/A4 protein and amyloid precursor protein in hereditary cerebral hemorrhage with amyloidosis-Dutch type and Alzheimer's disease. Am J Pathol. 1993;142(5):1449–57.
39. Haan J, Maat-Schieman ML, van Duinen SG, Jensson O, Thorsteinsson L, Roos R a. Co-localization of beta/A4 and cystatin C in cortical blood vessels in Dutch, but not in Icelandic hereditary cerebral hemorrhage with amyloidosis. Acta Neurol Scand. 1994 May;89(5):367–71.
40. Rozemuller JM, Bots GT, Roos R a, Eikelenboom P. Acute phase proteins but not activated microglial cells are present in parenchymal beta/A4 deposits in the brains of patients with hereditary cerebral hemorrhage with amyloidosis-Dutch type. Neurosci Lett. 1992 Jun 22;140(2):137–40.
41. Wilhelmus MMM, Boelens WC, Otte-Höller I, Kamps B, Kusters B, Maat-Schieman MLC, et al. Small heat shock protein HspB8: its distribution in Alzheimer's disease brains and its inhibition of amyloid-beta protein aggregation and cerebrovascular amyloid-beta toxicity. Acta Neuropathol. 2006 Feb;111(2):139–49.
42. van Horssen J, Otte-Holler I, David G, Maat-Schieman ML, van den Heuvel LP, Wesseling P, et al. Heparan sulfate proteoglycan expression in cerebrovascular amyloid deposits in Alzheimer's disease and hereditary cerebral hemorrhage with amyloidosis (Dutch) brains. Acta Neuropathol. 2001 Dec;102(6):604–14.
43. van Duinen SG, Maat-Schieman MLC, Bruijn JA, Haan J, Roos RAC, Wattendorff AR, et al. Cortical Tissue of Patients With Hereditary Cerebral-Hemorrhage With Amyloidosis (Dutch) Contains Various Extracellular-Matrix Deposits. Lab Investig. 1995 Aug;73(2):183–9.
44. Wilhelmus MMM, Otte-Höller I, van Triel JJJ, Veerhuis R, Maat-Schieman MLC, Bu G, et al. Lipoprotein receptor-related protein-1 mediates amyloid-beta-mediated cell death of cerebrovascular cells. Am J Pathol. 2007 Dec;171(6):1989–99.
45. Deane R, Wu Z, Sagare A, Davis J, Du Yan S, Hamm K, et al. LRP/amyloid β-peptide interaction mediates differential brain efflux of Aβ isoforms. Neuron. 2004 Aug 5;43(3):333–44.

46. De Jager M, van der Wildt B, Schul E, Bol JGJM, van Duinen SG, Drukarch B, et al. Tissue transglutaminase colocalizes with extracellular matrix proteins in cerebral amyloid angiopathy. Neurobiol Aging. 2013 Apr;34(4):1159–69.
47. Wilhelmus MMM, Bol JGJM, van Duinen SG, Drukarch B. Extracellular matrix modulator lysyl oxidase colocalizes with amyloid-beta pathology in Alzheimer's disease and hereditary cerebral hemorrhage with amyloidosis-Dutch type. Exp Gerontol. 2013 Feb;48(2):109–14.
48. Wisniewski T, Ghiso J, Frangione B. Peptides homologous to the amyloid protein of Alzheimer's disease containing a glutamine for glutamic acid substitution have accelerated amyloid fibril formation. Biochem Biophys Res Commun. 1991;179(3):1247–54.
49. Verbeek MM, De Waal RMW, Schipper JJ, Van Nostrand WE. Rapid Degeneration of Cultured Human Brain Pericytes by Amyloid β Protein. J Neurochem. 2002 Mar;68(3):1135–41.
50. Davis J, Van Nostrand WE. Enhanced pathologic properties of Dutch-type mutant amyloid β-protein. Proc Natl Acad Sci. 1996 Apr 2;93(7):2996–3000.
51. Davis-Salinas J, Saporito-Irwin SM, Cotman CW, Van Nostrand WE. Amyloid β-Protein Induces Its Own Production in Cultured Degenerating Cerebrovascular Smooth Muscle Cells. J Neurochem. 1995 Nov 23;65(2):931–4.
52. Eisenhauer PB, Johnson RJ, Wells JM, Long HJ, Simons ER, Davies TA, et al. Toxicity of various amyloid beta peptide species and activated platelets on cultured human blood-brain barrier endothelial cells: Increased toxicity of amyloid dutch type mutant. Neurobiol Aging. 2000;21:220.
53. Davis J, Cribbs DH, Cotman CW, Van Nostrand WE. Pathogenic amyloid β-protein induces apoptosis in cultured human cerebrovascular smooth muscle cells. Amyloid. 1999 Sep;6(3):157–64.
54. Melchor JP, McVoy L, Van Nostrand WE. Charge alterations of E22 enhance the pathogenic properties of the amyloid β-protein. J Neurochem. 2000 May;74(5):2209–12.
55. Miravalle L, Tokuda T, Chiarle R, Giaccone G, Bugiani O, Tagliavini F, et al. Substitutions at codon 22 of Alzheimer's abeta peptide induce diverse conformational changes and apoptotic effects in human cerebral endothelial cells. J Biol Chem. 2000 Sep 1;275(35):27110–6.
56. Sian a K, Frears ER, El-Agnaf OM, Patel BP, Manca MF, Siligardi G, et al. Oligomerization of beta-amyloid of the Alzheimer's and the Dutch-cerebral-haemorrhage types. Biochem J. 2000;349:299–308.
57. Kassler K, Horn AHC, Sticht H. Effect of pathogenic mutations on the structure and dynamics of Alzheimer's A beta 42-amyloid oligomers. J Mol Model. 2010 May;16(5):1011–20.
58. Ohshima Y, Taguchi K, Mizuta I, Tanaka M, Tomiyama T, Kametani F, et al. Mutations in the β-amyloid precursor protein in familial Alzheimer's disease increase Aβ oligomer production in cellular models. Heliyon. 2018;(October 2017):e00511.
59. Condello C, Lemmin T, Stöhr J, Nick M, Wu Y, Maxwell AM, et al. Structural heterogeneity and intersubject variability of Aβ in familial and sporadic Alzheimer's disease. Proc Natl Acad Sci. 2018;201714966.
60. van Duinen SG, Castano EM, Prelli F, Bots GT, Luyendijk W, Frangione B. Hereditary cerebral hemorrhage with amyloidosis in patients of Dutch origin is related to Alzheimer disease. Proc Natl Acad Sci. 1987 Aug;84(16):5991–4.

61. Prelli F, Levy E, van Duinen SG, Bots GTAM, Luyendijk W, Frangione B. Expression of a normal and variant Alzheimer's β-protein gene in amyloid of hereditary cerebral hemorrhage, Dutch type: DNA and protein diagnostic assays. Biochem Biophys Res Commun. 1990 Jul;170(1):301–7.
62. Natté R, Yamaguchi H, Maat-Schieman MLC, Prins FA, Neeskens P, Roos RAC, et al. Ultrastructural evidence of early non-fibrillar Aβ42 in the capillary basement membrane of patients with hereditary cerebral hemorrhage with amyloidosis, Dutch type. Acta Neuropathol. 1999 Dec;98(6):577–82.
63. Herzig MC, Van Nostrand WE, Jucker M. Mechanism of cerebral beta-amyloid angiopathy: murine and cellular models. Brain Pathol. 2006 Jan;16(1):40–54.
64. Herzig MC, Winkler DT, Burgermeister P, Pfeifer M, Kohler E, Schmidt SD, et al. Aβ is targeted to the vasculature in a mouse model of hereditary cerebral hemorrhage with amyloidosis. Nat Neurosci. 2004 Oct;7(9):954–60.
65. Bornebroek M, Haan J, Van Duinen SG, Maat-Schieman ML, Van Buchem M a, Bakker E, et al. Dutch hereditary cerebral amyloid angiopathy: structural lesions and apolipoprotein E genotype. Ann Neurol. 1997 May;41(5):695–8.
66. Bornebroek M, Haan J, Backhovens H, Deutz P, Van Buchem M a, van den Broeck M, et al. Presenilin-1 polymorphism and hereditary cerebral hemorrhage with amyloidosis, Dutch type. Ann Neurol. 1997 Jul;42(1):108–10.
67. Bornebroek M, Westendorp RG, Haan J, Bakker E, Timmers WF, Van Broeckhoven C, et al. Mortality from hereditary cerebral haemorrhage with amyloidosis--Dutch type. The impact of sex, parental transmission and year of birth. Brain. 1997 Dec;120 (Pt 1:2243–9.
68. Tsubuki S, Takaki Y, Saido TC. Dutch, Flemish, Italian, and Arctic mutations of APP and resistance of Aβ to physiologically relevant proteolytic degradation. Lancet. 2003 Jun 7;361(9373):1957–8.
69. Morelli L, Llovera RE, Mathov I, Lue L-F, Frangione B, Ghiso J, et al. Insulin-degrading enzyme in brain microvessels: proteolysis of amyloid {beta} vasculotropic variants and reduced activity in cerebral amyloid angiopathy. J Biol Chem. 2004 Dec 31;279(53):56004–13.
70. De Jonghe C, Zehr C, Yager D, Prada CM, Younkin S, Hendriks L, et al. Flemish and Dutch mutations in amyloid β precursor protein have different effects on amyloid β secretion. Neurobiol Dis. 1998 Oct;5(4):281–6.
71. Watson DJ, Selkoe DJ, Teplow DB. Effects of the amyloid precursor protein Glu693 →Gln 'Dutch' mutation on the production and stability of amyloid β-protein. 1999;709:703–9.
72. Nilsberth C, Westlind-Danielsson a, Eckman CB, Condron MM, Axelman K, Forsell C, et al. The "Arctic" APP mutation (E693G) causes Alzheimer's disease by enhanced Abeta protofibril formation. Nat Neurosci. 2001;4(9):887–93.
73. Stenh C, Nilsberth C, Hammarback J, Engvall B, Naslund J, Lannfelt L. The Arctic mutation interferes with processing of the amyloid precursor protein. Neuroreport. 2002 Oct;13(15):1857–60.
74. Monro OR, Mackic JB, Yamada S, Segal MB, Ghiso J, Maurer C, et al. Substitution at codon 22 reduces clearance of Alzheimer's amyloid-β peptide from the cerebrospinal fluid and prevents its transport from the central nervous system into blood. Neurobiol Aging. 2002;23(3):405–12.
75. 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 Apr;18(2):253–66.

76. Thal DR, Griffin WST, de Vos RAI, Ghebremedhin E. Cerebral amyloid angiopathy and its relationship to Alzheimer's disease. Acta Neuropathol. 2008 Jun;115(6):599–609.
77. Zlokovic B V. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. Nat Rev Neurosci. 2011 Dec;12(12):723–38.
78. Nicolakakis N, Hamel E. Neurovascular function in Alzheimer's disease patients and experimental models. J Cereb Blood Flow Metab. 2011 Jun;31(6):1354–70.
79. Greenberg SM. Cerebral amyloid angiopathy: prospects for clinical diagnosis and treatment. Neurology. 1998 Sep;51(3):690–4.
80. Viswanathan A, Greenberg SM. Cerebral amyloid angiopathy in the elderly. Ann Neurol. 2011 Dec;70(6):871–80.
81. Boyle PA, Leurgans S, Wilson RS, Bennett DA. Cerebral amyloid angiopathy and cognitive outcomes in community-based older persons. 2015;
82. Tanskanen M, Mäkelä M, Myllykangas L, Notkola IL, Polvikoski T, Sulkava R, et al. Prevalence and severity of cerebral amyloid angiopathy: A population-based study on very elderly Finns (Vantaa 85+). Neuropathol Appl Neurobiol. 2012;38(4):329–36.
83. Greenberg SM, Gurol ME, Rosand J, Smith EE. Amyloid angiopathy-related vascular cognitive impairment. Stroke. 2004 Nov;35(11 Suppl 1):2616–9.
84. Vemuri P, Lesnick TG, Przybelski S a., Knopman DS, Preboske GM, Kantarci K, et al. Vascular and amyloid pathologies are independent predictors of cognitive decline in normal elderly. Brain. 2015;761–71.
85. 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 Jun;46(6):1592–6.
86. Vinters H V. Emerging Concepts in Alzheimer's Disease. Annu Rev Pathol Mech Dis. 2015;10(1):291–319.
87. Charidimou A, Martinez-Ramirez S, Shoamanesh A, Oliveira-Filho J, Frosch M, Vashkevich A, et al. Cerebral amyloid angiopathy with and without hemorrhage: evidence for different disease phenotypes. Neurology. 2015;84(12):1206–12.
88. Kövari E, Herrmann FR, Hof PR, Bouras C. The relationship between cerebral amyloid angiopathy and cortical microinfarcts in brain ageing and Alzheimer's disease. Neuropathol Appl Neurobiol. 2013;39(5):498–509.
89. Greenberg SM, Rebeck GW, Vonsattel JP, Gomez-Isla T, Hyman BT. Apolipoprotein E epsilon 4 and cerebral hemorrhage associated with amyloid angiopathy. Ann Neurol. 1995 Aug;38(2):254–9.
90. Greenberg SM, Briggs ME, Hyman BT, Kokoris GJ, Takis C, Kanter DS, et al. Apolipoprotein E epsilon 4 is associated with the presence and earlier onset of hemorrhage in cerebral amyloid angiopathy. Stroke. 1996 Aug;27(8):1333–7.
91. Greenberg SM, Vonsattel JP, Segal AZ, Chiu RI, Clatworthy AE, Liao A, et al. Association of apolipoprotein E epsilon2 and vasculopathy in cerebral amyloid angiopathy. Neurology. 1998 Apr;50(4):961–5.
92. Love S, Chalmers K, Ince P, Esiri M, Attems J, Jellinger K, et al. Development, appraisal, validation and implementation of a consensus protocol for the assessment of cerebral amyloid angiopathy in post-mortem brain tissue. Am J Neurodegener Dis. 2014;3(1):19–32.
93. Yu L, Boyle P a., Nag S, Leurgans S, Buchman AS, Wilson RS, et al. APOE and cerebral amyloid angiopathy in community-dwelling older persons. Neurobiol Aging. 2015;1–8.

94. 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 Jun;41(6):716–21.
95. Rannikmäe K, Samarasekera N, Martînez-Gonzâlez NA, Al-Shahi Salman R, Sudlow CLM. Genetics of cerebral amyloid angiopathy: systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2013 Aug;84(8):901–8.
96. Wyss-Coray T, Masliah E, Mallory M, McConlogue L, Johnson-Wood K, Lin C, et al. Amyloidogenic role of cytokine TGF-β1 in transgenic mice and in Alzheimer's disease. Nature. 1997;389(6651):603–6.
97. Ueberham U, Ueberham E, Brückner MK, Seeger G, Gärtner U, Gruschka H, et al. Inducible neuronal expression of transgenic TGF-β1 in vivo: Dissection of short-term and long-term effects. Eur J Neurosci. 2005 Jul;22(1):50–64.
98. Wyss-Coray T, Lin C, Yan F, Yu GQ, Rohde M, Mcconlogue L, et al. TGF-β1 promotes microglial amyloid-β clearance and reduces plaque burden in transgenic mice. Nat Med. 2001 May;7(5):612–8.
99. Gray CW, Patel AJ. Regulation of beta-amyloid precursor protein isoform mRNAs by transforming growth factor-beta 1 and interleukin-1 beta in astrocytes. Brain Res Mol Brain Res. 1993 Aug;19(3):251–6.
100. Amara FM, Junaid A, Clough RR, Liang B. TGF-β1, regulation of Alzheimer amyloid precursor protein mRNA expression in a normal human astrocyte cell line: mRNA stabilization. Mol Brain Res. 1999 Jul;71(1):42–9.
101. Burton T, Liang B, Dibrov A, Amara F. Transforming growth factor-beta-induced transcription of the Alzheimer beta-amyloid precursor protein gene involves interaction between the CTCF-complex and Smads. Biochem Biophys Res Commun. 2002 Jul 19;295(3):713–23.
102. Lesné S, Docagne F, Gabriel C, Liot G, Lahiri DK, Buée L, et al. Transforming growth factor-β1 potentiates amyloid-β generation in astrocytes and in transgenic mice. J Biol Chem. 2003 May 16;278(20):18408–18.
103. Ueberham U, Zobiak B, Ueberham E, Brückner MK, Boriss H, Arendt T. Differentially expressed cortical genes contribute to perivascular deposition in transgenic mice with inducible neuron-specific expression of TGF-β1. Int J Dev Neurosci. 2006;24(2–3):177–86.
104. Mazur-Kolecka B, Frackowiak J, Le Vine H, Haske T, Evans L, Sukontasup T, et al. TGFβ1 enhances formation of cellular Aβ/apoE deposits in vascular myocytes. Neurobiol Aging. 2003;24(2):355–64.
105. 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 Jul;52(7):702–8.
106. Greenberg SM, Vonsattel JP. Diagnosis of cerebral amyloid angiopathy. Sensitivity and specificity of cortical biopsy. Stroke. 1997 Jul;28(7):1418–22.
107. Deramecourt V, Slade JY, Oakley AE, Perry RH, Ince PG, Maurage CA, et al. Staging and natural history of cerebrovascular pathology in dementia. Neurology. 2012;78(14):1043–50.
108. van Rooden S, van der Grond J, van den Boom R, Haan J, Linn J, Greenberg SM, et al. Descriptive analysis of the Boston criteria applied to a Dutch-type cerebral amyloid angiopathy population. Stroke. 2009 Sep;40(9):3022–7.

109. van Opstal AM, van Rooden S, van Harten T, Ghariq E, Labadie G, Fotiadis P, et al. Cerebrovascular function in presymptomatic and symptomatic individuals with hereditary cerebral amyloid angiopathy: a case-control study. Lancet Neurol. 2017;16(2):115–22.
110. Koemans EA, van Etten ES, van Opstal AM, Labadie G, Terwindt GM, Wermer MJH, et al. Innovative Magnetic Resonance Imaging Markers of Hereditary Cerebral Amyloid Angiopathy at 7 Tesla. Stroke. 2018 Apr;
111. Bornebroek M, De Jonghe C, Haan J, Kumar-Singh S, Younkin S, Roos R, et al. Hereditary cerebral hemorrhage with amyloidosis dutch type (AβPP 693): Decreased plasma amyloid-β 42 concentration. Neurobiol Dis. 2003 Dec;14(3):619–23.
112. Greenberg SM, Cho HS, O'Donnell HC, Rosand J, Segal AZ, Younkin LH, et al. Plasma beta-amyloid peptide, transforming growth factor-beta 1, and risk for cerebral amyloid angiopathy. Ann N Y Acad Sci. 2000 Apr;903:144–9.
113. Van Etten ES, Verbeek MM, Van Der Grond J, Zielman R, Van Rooden S, Van Zwet EW, et al. β-Amyloid in CSF: Biomarker for preclinical cerebral amyloid angiopathy. Neurology. 2017;88(2):169–76.
114. Verbeek MM, Kremer BPH, Rikkert MO, Van Domburg PHMF, Skehan ME, Greenberg SM. Cerebrospinal fluid amyloid beta(40) is decreased in cerebral amyloid angiopathy. Ann Neurol. 2009 Aug;66(2):245–9.
115. Renard D, Castelnovo G, Wacongne A, Le Floch A, Thouvenot E, Mas J, et al. Interest of CSF biomarker analysis in possible cerebral amyloid angiopathy cases defined by the modified Boston criteria. J Neurol. 2012 Nov;259(11):2429–33.
116. Frost S, Kanagasingam Y, Sohrabi H, Taddei K, Bateman R, Morris J, et al. Pupil Response Biomarkers Distinguish Amyloid Precursor Protein Mutation Carriers from Non-Carriers. Curr Alzheimer Res. 2013;10(8):790–6.
117. Sperling RA, Jack CRJ, Black SE, Frosch MP, Greenberg SM, Hyman BT, et al. Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: recommendations from the Alzheimer's Association Research Roundtable Workgroup. Alzheimers Dement. 2011 Jul;7(4):367–85.