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Rare *ABCA7* mutations in Alzheimer's disease and cerebral amyloid angiopathy pathology

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ABSTRACT

Rare mutations in the ATP binding cassette subfamily A member 7 (*ABCA7*) gene are known risk factors for Alzheimer's disease (AD). Genetic sequencing in 1372 Belgian patients previously revealed rare *ABCA7* mutations in 102 carriers, 58 with a premature termination codon mutation (PTC) and 44 with a missense mutation. Among carriers, 14 received post-mortem examination. Here, we reviewed and report the demographics, clinicopathological phenotypes, and diagnoses of identified *ABCA7* mutation carriers. Carriers mostly developed late-onset AD (71 ± 9 years) and had a high familial load (67 % with positive family history). Patients presented with classic amnestic AD based on neuropsychological assessment, imaging and CSF biomarkers. However, vascular involvement was observed in a considerable part of patients, leading to diagnosis of vascular dementia (9 %) and cerebral amyloid angiopathy (CAA) (6 %). In line with this, neuropathology of the 14 examined carriers uncovered extensive levels of CAA and AD hallmarks. Carriers of an *ABCA7* missense mutations displayed a less aggressive phenotype, with comparable onset but longer disease duration compared to carriers of a PTC mutation. Furthermore, non-amnestic features including language, dysexecutive and behavioural symptoms, were more frequently seen in PTC patients (18 % vs 9 %), as was the case for concomitant vascular disease (22 % vs 10 %). Taken together, the clinical phenotype of rare *ABCA7* mutation carriers spans the AD-CAA spectrum. Patients present with a classical AD phenotype although clinical heterogeneity is observed among carriers. The presence of a cerebrovascular component (CAA) may, in part, explain this heterogeneity.

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1. Introduction

The *ABCA7* gene was first discovered as a late-onset Alzheimer's disease (AD) risk gene through genome-wide association studies (Hollingworth et al., 2011; Lambert et al., 2013). Now *ABCA7* is regarded as the second most important risk gene for AD. Its functional role was investigated in lipid metabolism and regulation of phagocytosis (Duchateau et al., 2024). Specifically, ABCA7 plays a role in lipid transport and homeostasis, particularly in immune cells. It is also implicated in the regulation of amyloid-beta peptide processing and clearance.(Santos-García et al., 2025).

Particularly, rare premature termination codon (PTC) mutations were found to be enriched in AD patients (odds ratio between 1.4 and 5) (Duchateau et al., 2024) and have displayed inheritance patterns resembling autosomal dominant AD (Cuyvers et al., 2015; Steinberg et al., 2015; Vardarajan et al., 2015). These mutations predict a loss of functional protein, though their exact mode of action is still being investigated (Allen et al., 2017; Duchateau et al., 2024). Genetic screening of the *ABCA7* gene in a large Belgian AD cohort identified an increased frequency of PTC mutations in patients compared to controls (Bossaerts et al., 2022, 2021; Cuyvers et al., 2015). The disease mechanisms and clinical relevance of rare *ABCA7* missense mutations is however less understood (Duchateau et al., 2024). Conflicting results have been published, but recent studies demonstrated that also predicted pathogenic missense variants can increase AD risk (De Roeck et al., 2019; Holstege et al., 2022). Secondly, co-segregation of an *ABCA7* missense mutation with an autosomal dominant inheritance pattern was found in a German family (p.R880Q) (May et al., 2018) and a Belgian family (p.G1820S) (Bossaerts et al., 2022). Third, several established disease-causing missense mutations in *ABCA1* and *ABCA4,* leading to Tangier or Stargardt disease, involve amino acid residues that are conserved and equally mutated in *ABCA7* (Bossaerts et al., 2022). Finally, in previous work, we demonstrated that rare *ABCA7* missense variants can cause protein mislocalization, and subsequent loss of protein function (Bossaerts et al., 2022).

Few studies investigated the clinical phenotype of PTC carriers and mostly reported AD diagnosis with early amnestic symptoms (Van den Bossche et al., 2016). Recently, a large genotype-phenotype correlation study examined the clinical and neuropathological phenotype of individuals ($n = 100$) with various diagnoses that carry six of the most common rare *ABCA7* PTC mutations (Campbell et al., 2022). In addition to memory deficits and AD diagnosis, 10 % had a non-memory presenting symptom and 20 % received another diagnosis than AD. Neuropathologically AD was seen in all but one patient, but co-pathology was frequently present and mostly vascular (Campbell et al., 2022). Other (co-)pathologies encountered were Parkinsonian syndromes (Allen et al., 2017; Campbell et al., 2022; Nuytemans et al., 2016). To our knowledge, no reports were published on the genotype-phenotype correlation of *ABCA7* missense carriers.

In previous work, we sequenced the *ABCA7*'s coding sequence in a Belgian cohort of 1376 unrelated AD patients to investigate the frequency of rare PTC and missense variants (Bossaerts et al., 2022, 2021; Cuyvers et al., 2015). Pathogenicity and segregation patterns of specific mutations – and possible modifiers thereof – are still poorly understood. To implement genetic screening of *ABCA7* in a clinical and diagnostic setting, further elucidation of prevalence, penetrance and clinicopathological characteristics of mutation carriers is indispensable. Here, we provide an in-depth comprehensive evaluation of the clinicopathological phenotype of 102 rare *ABCA7* carriers.

2. Materials and methods

2.1. Belgian AD cohort

2.1.1. Clinical characteristics of AD cohort

The AD patients carrying an *ABCA7* mutation studied here are part of a large, prospective, and longitudinal dementia research cohort, recruited and followed up since 1995 by neurologists of different university and general hospitals nationwide, collaborating in the framework of the Belgian Neurology (BELNEU) Consortium. The Belgian AD source cohort from whom the *ABCA7* carriers were identified was previously described (Bossaerts et al., 2021), and comprises 1376 AD patients. Index patients were evaluated using a standard protocol, which included a detailed clinical and familial history, neurological examination, neuropsychological testing, biochemical and neurochemical analyses, and neuroimaging. Diagnosis of mild cognitive impairment (MCI) or dementia due to possible, probable, definite AD diagnosis was made according to the National Institute on Aging – Alzheimer's Association (NIA-AA) diagnostic criteria (Albert et al., 2011; Jack et al., 2018; Jack Jr. et al., 2024; McKhann et al., 2011). In case of significant cerebrovascular disease, clinical diagnosis of possible or probable vascular dementia (VaD) was used according the National Institute of Neurological Disorders and Stroke and the Association International pour la Recherche et l'Enseignement en Neurosciences criteria (Román et al., 1993). Possible, probable or definite CAA diagnosis was based on the Boston criteria (Charidimou et al., 2022; Linn et al., 2010).

Given the prospective, longitudinal nature of our dementia research cohort, brain autopsy with subsequent neuropathological examination of consented patients who died, was performed systematically. Following formaldehyde fixation, specific brain regions were paraffin embedded according to a standard protocol of the IBB Neurobiobank (Sieben et al., 2018). Histochemical and advanced immunohistochemical analyses were performed as previously described (Vermeiren et al., 2014). Consensus criteria were used to establish the neuropathological diagnosis (Montine et al., 2012).

Written informed consent for participation in the clinical and genetic studies, and for brain autopsy, was obtained from participants and/or from their legal guardians. The study protocol and the informed consent forms were approved by the ethics committee of the University Hospital of Antwerp and the University of Antwerp, Belgium.

2.1.2. Genetic screening of the Belgium AD cohort

Sequencing data of *ABCA7* exons and splice sites of the Belgian AD cohort was available from previous screening efforts to investigate the frequency of rare *ABCA7* PTC and missense mutations (Bossaerts et al., 2022, 2021; Cuyvers et al., 2015). Screening was performed either through whole exome sequencing or multigene panel parallel sequencing (Bossaerts et al., 2022, 2021). All patients in the AD cohort were also screened for known pathogenic mutations in Mendelian genes linked with AD. The genes that were tested were *APP, PSEN1, PSEN2,* and the primary AD risk factor *APOE4*.

2.2. Cohort of ABCA7 PTC and missense mutation carriers

Mutation analysis of *ABCA7* in 1376 Belgian AD patients identification of 67 PTC (Bossaerts et al., 2021) and 96 missense (Bossaerts et al., 2022) mutation carriers. All participants were of Flemish-Belgian origin. Of note, the phenotypical characteristics of 16 PTC mutation carriers, have previously been reported by Van den Bossche, including four out of the 14 patients for whom neuropathology was available (Van den Bossche et al., 2016).

All available medical records of *ABCA7* carriers were reviewed by the same physician of the research team. We focused on likely pathogenic mutations (i.e., PTC mutations, and patient-only missense mutations with functional evidence of mislocalisation). Clinicopathological follow-up identified a small number of carriers with a non-AD diagnosis (such as LBD, VAD, normal cognitive decline). Those were excluded from the study.

Individuals for whom insufficient medical records were available, were also excluded. This inclusion process resulted in a final selection of 102 rare *ABCA7* mutation carriers (58 PTC and 44 missense carriers), which were evaluated further for their clinical characteristics by

retrospective chart review. An overview of the inclusion process is depicted in Fig. 1.

2.2.1. Clinical analysis

All data records, medical records, neuroimaging studies, and autopsy reports were reviewed retrospectively, and each patient's demographic, clinical and pathological characteristics were summarized in a standardized way. Availability of clinical data was summarized in Table 1. Age at onset (AAO) was defined as onset of the first symptoms as reported through history from the patient or the informant, or when unavailable, age at referral to the memory clinic. Disease duration (DD) was measured from symptom onset until the age at death. A positive familial history of neurodegenerative disease was assigned when medical records of the affected family members were available. If medical records of affected relative were unavailable, hearsay positive familial history was used. Ancillary investigations were performed and interpreted at the referring neurological center. Results of brain imaging studies were reported either based on visual appraisal of the images by the clinician or based on written interpretations by the radiologist or treating neurologist if the former were not available. T2*-weighted MRI images were performed in a subset of patients and were specifically analyzed for hemosiderin detection, exposing (small) hemorrhages and cortical superficial siderosis characteristic of CAA. CSF samples were obtained by lumbar puncture at the L3/L4 or L4/L5 interspace and collected in polypropylene tubes, after which they were immediately frozen in liquid nitrogen and subsequently stored at −80°C until analysis as previously described (Engelborghs et al., 2017; Willemse et al., 2019). To ensure comparable results of CSF AD-biomarkers, the BIODEM Lab reanalyzed CSF biomarkers of 54 carriers. The concentrations of core AD CSF biomarkers amyloid-β (Aβ)1–42 ($A\beta_{1-42}$), total tau (t-tau), and phosphorylated Tau(181) (P-tau) and amyloid-β1–40 ($A\beta_{1-40}$) were determined by automated analysis (EUROIMMUN Analyzer I-2P; Medizinische Labordiagnostika AG, Lübeck, Germany) using commercially available single-analyte ELISA kits(EUROIMMUN $A\beta_{42}$, EUROIMMUN $A\beta_{40}$, EUROIMMUN t-tau, and EUROIMMUN p-tau, respectively; Medizinische Labordiagnostika AG, Lübeck, Germany) according to manufacturer's instructions. Normal values for the core AD CSF biomarkers were t-tau (< 501 pg/mL), p-tau (<57 pg/mL), $A\beta_{1-42}$ (> 824 pg/mL), $A\beta_{1-42}/A\beta_{1-40}$ ratio (> 0,12). In five cases, CSF was unavailable for reanalysis, but biomarkers were deemed neurochemically characteristic for AD according to the medical records (Table 1).

2.2.2. Neuropathology of ABCA7 patients

Available neuropathology data of 14 *ABCA7* mutation carriers were reviewed and autopsied brains were reexamined. AD neuropathologic change score was evaluated and staged according to the NIA-AA 2012 criteria (Montine et al., 2012). We used the previously published methodology for CAA assessment (Love et al., 2014). This protocol allows scoring parenchymal and meningeal CAA individually on a 0–3 scale and capillary CAA as present/absent in designated Brodmann areas from the frontal, temporal, parietal, and occipital lobes. In one carrier (P27), reexamining brain tissue was impossible, but earlier assessment of meningeal CAA was performed through the Vonsattel score (Vonsattel et al., 1991).

2.3. Belgian control AD patients

To enable comparison of CAA severity between *ABCA7* carriers and non-carrier AD patients, we constructed a comparative control cohort of individuals with clinically diagnosed AD who did not carry an *ABCA7 variant* or another known pathogenic mutation in an AD-related gene (from here on referred to as the AD control cohort). Control patients were randomly selected from a larger cohort of 1024 unrelated AD patients (mean age at onset 75.4 ± 8.5 years; range 37–102 years; 64 % female). Patients were matched to *ABCA7* carriers based on sex, *APOE* genotype, and year of diagnosis. In total, 79 non-carrier individuals were included, of whom neuropathological data were available for 13 patients. All included participants were of Flemish-Belgian.

For *ABCA7* carriers, all available medical records were reviewed in detail by the same physician of the research team to ensure consistency in data extraction. Because the historical electronic patient files of the control cohort were no longer accessible, CAA-related imaging characteristics for non-carriers had to be reconstructed from narrative clinical summaries and neuroradiology or neurology reports, rather than from full source records or raw imaging data.

Neuropathological data were available for 13 non-carrier patients. Information was extracted from existing pathology reports, in contrast to the *ABCA7* cohort in which neuropathological examinations were systematically re-performed. For nine individuals (9/13), staging information such as a Braak neurofibrillary tangle stage and/or an ABC (Montine) score (NIA–AA 2012 framework) could be retrieved. For seven patients, the extent of CAA could be estimated from descriptive pathology narratives; however, the level of detail varied, and formal grading according to the Love et al. criteria was not available for any of the patients.

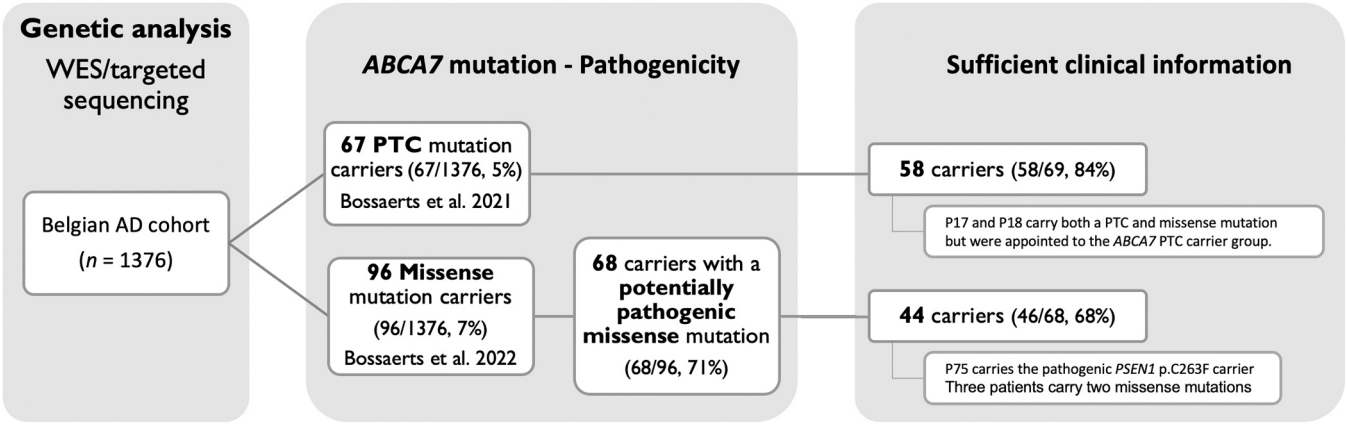

Fig. 1. Flowchart of inclusion and screening process leading to the *ABCA7* carrier cohort used for phenotype-genotype correlation. The final cohort to be extensively described was established following the method depicted in this flowchart. Potentially pathogenic missense mutations were those with functional evidence and/or present in patients only. The final cohort consisted of 102 *ABCA7* patients. Overall, five patients carried a double rare *ABCA7* mutation. Two individuals carried both a PTC and missense mutation and were added to the PTC mutation group. Three other individuals carried a double potentially pathogenic missense mutation. One carrier, P75, carried the known pathogenic *PSEN1* p.C263F mutation next to a rare potentially pathogenic missense mutation. Abbreviations: WES = whole exome sequencing.

Table 1
Baseline demographic and clinical characteristics of *ABCA7* carriers with availability of clinical and neuropathological data.

		Total (*n*=102)	*ABCA7* PTC carriers (*n*=58)	*ABCA7* Missense carriers (*n*=44)	*p*-value
Sex, *n* (%)	Male	39 *(38)*	20 *(35)*	19 *(43)*	0.415
***APOE*, *n* (%)**	ε4 +	65 *(64)*	33 *(57)*	32 *(73)*	0.215
Length of follow-up (y)	Mean (SD)	5 (4)	4 (3)	5 (4)	0.290
	Median (range)	4 (1–19)	3 (1–15)	4 (1–19)	
Year of Onset (calendar year)	Mean (SD)	2004 (7)	2004 (7)	2004 (6)	0.656
	Median (range)	2004 (1989–2017)	2004 (1989–2016)	2005 (1995–2017)	
Familial History, *n (%)*	S	23 *(33)*	9 *(23)*	14 *(45)*	0.073
	FH	47 *(67)*	30 *(77)*	17 *(55)*	
Clinical subtype, *n (%)*	EOAD (≤65)	31 *(30)*	20 *(35)*	11 *(25)*	0.386
	LOAD (>65)	71 *(70)*	38 *(65)*	33 *(75)*	
Clinical presentation, *n (%)*		82 *(80)*	49 *(85)*	33 *(75)*	0.315
Neuropsychological examination, *n (%)*		95 *(93)*	54 *(93)*	41 *(93)*	1.000
Structural imaging, *n (%)*	CT and/or MRI	101 *(99)*	57 *(98)*	44 *(100)*	1.000
	MRI°	12 *(12)*	5 *(9)*	7 *(16)*	0.354
Functional imaging, *n (%)*	SPECT and/or FDG-PET	84 *(82)*	46 *(79)*	38 *(86)*	0.437
CSF AD-biomarkers, *n (%)* [#]	CSF reanalysis	54 *(53)*	29 *(50)*	25 *(55)*	0.551
	Available AD biomarkers	58 *(57)*	33 *(57)*	25 *(57)*	1.000
Neuropathology, *n (%)*		14 *(14)*	10 *(17)*[a]	4 *(9)*[b]	0.264

Abbreviations: EOAD = early-onset Alzheimer's Disease; FH = (hearsay) familial history; FDG-PET = fluorodeoxyglucose positron emission tomography; LOAD = late-onset Alzheimer's Disease; MRI° = MRI T2* sequences; S = sporadic; SD = standard deviation; SPECT = Single Photon Emission Computed Tomography; y = years.
Percentage (%) within group of patients for whom we have information. The two patients carrying both a PTC and missense mutation were appointed to the *ABCA7* PTC carrier group.
*$P < 0.05$.
[#] In 54 cases CSF was available for (re)analysis of the AD-biomarkers at the BIODEM Lab. In five cases CSF analysis for AD-biomarkers was performed at the referring hospital, but CSF was unavailable for reanalysis.
[a] Four PTC carriers have been described in our prior work (Van den Bossche et al., 2016). Reexamination with special attention to presence and degree of CAA was performed.
[b] The neuropathology of four missense carriers was summarized in earlier work (Bossaerts et al., 2022).

2.4. Statistics

Kolmogorov-Smirnov tests were performed to explore data distribution. Differences in means of continuous variables between groups were calculated with independent two-sample T tests for normally distributed variables, and Mann Whitney U for non-normally distributed variables. Fisher's tests were used for categorical nominal variables, while Mann-Whitney *U* test was used for categorical ordinal variables. All tests were two-tailed, and the level of significance was set at P = 0.05. We used SPSS version 12 for all analyses.

3. Results

In the present study we investigated the clinicopathological phenotype of 102 patients carrying a predicted risk-increasing *ABCA7* variant. The PTC group included 56 heterozygous PTC mutation carriers and two individuals carrying both a PTC and a missense mutation, resulting in a total of 58 PTC mutation carriers. Both individuals were included in the PTC carrier group. Next, we identified 40 heterozygous missense mutation carriers and three compound heterozygous missense carriers (P69, P85, P89). One additional patient (P75) carried an *ABCA7* missense mutation, together with the known pathogenic *PSEN1* p.C263F mutation.

Baseline genetic, demographic, and clinical characteristics of the two groups are displayed in Table 1 & 2. Carriers received a diagnosis of MCI due to AD (*n*=6), dementia due to probable (*n*=68), possible AD (*n*=14), or definite AD (*n*=14). An overview of the clinical characteristics and AD CSF biomarker data is given in supplementary table S1–3.

3.1. Rare ABCA7 PTC mutation carriers

In total, 58 patients carried 14 different rare *ABCA7* PTC mutations (frameshift *n*=6, nonsense *n*=4, splice mutations *n*=5) (supplementary table S4). For the two individuals carrying both a PTC and a missense mutation (P17 and P18), P17 carried the two variants in trans, whereas phasing for P18 could not be determined.

3.1.1. Clinical characteristics

For the study, baseline diagnosis was made following the clinical diagnostic work-up closest to inclusion in the study cohort, so that all clinical, neuropsychological, imaging and biomarker data could be considered, to maximize the diagnostic accuracy.

Neuropathological examination proved definite AD diagnosis in ten carriers (10/58, 17 %). Probable AD (49/58, 84 %) was the dominant clinical diagnosis. Possible AD was proposed for five individuals (5/58, 9 %). Initial diagnosis of MCI was observed in 15/58 patients (26 %). Conversion to dementia was observed in three quarters (11/15, 73 %), after a mean follow up term of 4 ± 2 years (range 1–8). Notably, P52 presented without any subjective or objectifiable cognitive decline. He displayed multiple spontaneous lobar intracerebral hemorrhages (ICHs), corresponding with probable CAA diagnosis. Postmortem examination confirmed AD neuropathological changes (A3B3C2–3) with severe levels of CAA (stage 3 meningeal and parenchymal). Overall, five individuals displayed neuroimaging signs of probable (*n*=4) or possible (*n*=1) CAA (5/58, 9 %). In three individuals clinically suspect of vascular involvement, advanced levels of meningeal/parenchymal CAA were confirmed next to AD pathology. In the seven other patients with available neuropathology, pronounced CAA co-pathology was found (Table 4), although clinically there was no suggestion for vascular disease.

Six PTC patients (6/58, 10 %) were diagnosed with VaD (probable (*n*=3) and possible (*n*=3)), in addition to AD diagnosis (Table 3). Large artery disease was suspected in P10, P13 and P31. However, in P10 initial diagnosis was later corrected through neuropathological examination, revealing severe AD pathology and CAA co-pathology (Table 4). Watershed infarcts found in P13 were compatible with the proven carotid artery stenosis. In the remaining three patients with VaD diagnosis (P30, P35 and P51) neuroimaging was compatible with cerebral small vessel disease (CSVD), showing strategic lesions at thalamic or basal ganglia level.

An acute pyramidal syndrome clinically suspicious for stroke was observed in five individuals (5/58, 9 %). Neuroimaging confirmed an ischemic cerebrovascular accident with hemorrhagic transformation in

Table 2
Demographical and clinical characteristics of *ABCA7* carriers.

		Total (*n*=102)	PTC carriers (*n*=58)	Missense carriers (*n*=44)	*p*-value
AAO, y	Mean (SD)	71 (9)	70 (10)	72 (9)	0.129
	Median (range)	72 (48–92)	72 (48–90)	74 (51–92)	
AAD, y	Mean (SD)	79 (9)	78 (9)	82 (8)	**0.009***
	Median (range)	81 (54–95)	80 (54–95)	85 (61–94)	
DD, y	Mean (SD)	8 (4)	7 (4)	9 (4)	0.077
	Median (range)	8 (0–19)	7 (0–18)	8 (2–19)	
Clinical presentation, *n* (%)	Amnestic	67 *(82)*	37 *(76)*	30 *(91)*	0.089
	Language	7 *(9)*	7 *(14)*	0 *(0)*	**0.038***
	Dysexecutive	9 *(11)*	5 *(10)*	4 *(12)*	1.000
	Behavioral	7 *(9)*	3 *(6)*	4 *(12)*	0.431
EPS, *n* (%)		32 *(34)*	18 *(33)*	14 *(35)*	1.000
Depression, *n* (%)		32 *(31)*	16 *(28)*	16 *(36)*	0.393
VAD, *n* (%)	Probable/possible VAD	9 *(9)*	6 *(10)*	3 *(7)*	0.536
	Probable/possible CAA	6 *(6)*	5 *(9)*	1 *(2)*	0.232
	ICH	4 *(4)*	4 *(7)*	0 *(0)*	0.132
	MBs	2 *(18)*	1 *(25)*	1 *(14)*	1.000
	cSS	2 *(18)*	1 *(25)*	1 *(14)*	1.000
	WML – absent	24 *(25)*	17 *(30)*	7 *(17)*	0.620
	WML +	29 *(30)*	15 *(26)*	14 *(34)*	
	WML + +	28 *(29)*	13 *(23)*	15 *(37)*	
	WML + ++	17 *(17)*	12 *(20)*	5 *(12)*	
CSF $A\beta_{1-40}$ (pg/mL)	Mean (SD)	5854 (2342)	5678 (1880)	6067 (2831)	0.869
	Median (range)	5505 (2396–12555)	5590 (2515–9765)	5486 (2396–12555)	
CSF $A\beta_{1-42}$ (pg/mL)	Mean (SD)	503 (254)	534 (291)	465 (200)	0.316
	Median (range)	461 (168–1874)	511 (197–1874)	421 (168–1006)	
CSF p-tau (pg/mL)	Mean (SD)	126 (50)	130 (50)	122 (51)	0.437
	Median (range)	124 (34–207)	124 (34–207)	115 (45–191)	
CSF T-tau (pg/mL)	Mean (SD)	788 (324)	814 (323)	757 (329)	0.561
	Median (range)	690 (273–1496)	711 (317–1496)	665 (273–1341)	

Patients carrying both a PTC and missense mutation were included in the PTC mutation group and excluded in the missense mutation group.
Percentage *(%)* within group of patients for whom we have information. *$P < 0.05$.
Abbreviations: AAO = age at onset; AAD = age at death; CSF = cerebrospinal fluid; cSS = cortical superficial siderosis; DD = disease duration; EPS = extrapyramidal symptoms; ICH = intracerebral hemorrhage; MBs = microbleeds; SD = standard deviation; VAD = vascular dementia, WML = white matter lesions

P17, and an ICH in three different patients. Neuropathologically again confirmed pronounced levels of CAA and presence of arteriosclerosis in two individuals.

Extrapyramidal signs occurred in 15 out of 54 patients (27 %), emerging in the more advanced phases of the disease (Supplementary Table S5). In six cases (6/15, 40 %), it was provoked by use of antipsychotics, and in three cases (3/15, 27 %) vascular parkinsonism was suspected. A history of Parkinsonism was mentioned in three patients prior to the onset of memory impairment. P47 developed severe extrapyramidal signs later in disease course, which led to a possible diagnosis of Parkinson's disease.

Epileptic seizure(s) were suspected in a few patients ($n = 9$, 16 %), all during late-stage AD. Three patients sustained a tonic-clonic seizure, evoked by a spontaneous ICH in P17.

3.1.2. *Technical investigation findings (supplementary table S2)*

Structural imaging was available in all but one carrier (57/58, 98 %) (CT $n = 45$ and/or MRI $n = 26$). Variable degrees of cortico-subcortical atrophy in accordance with disease progression was observed. As illustrated in Fig. 2A, focal atrophy typically involved bilateral mesial temporal lobes (19/57, 33 %). Signs of CSVD were commonly found. As such, white matter hyperintensities or hypodensities were found in various degrees (37/57, 65 %). Moderate levels of WML are displayed in Fig. 2C. In a minority of patients (5/58, 9 %), MRI T2* sequences were available. Four patients (4/58, 7 %) suffered from lobar ICH(s) confirming probable CAA diagnosis (Table 2). In P6 and P56 neuroimaging biomarkers of CAA (lobar microbleeds (MBs) and/or cortical superficial siderosis (cSS)) were found, as shown in Fig. 2B (2/5, 40 %).

SPECT imaging (41/58, 71 %) or brain fluorodeoxyglucose (FDG)-PET-CT (7/58, 12 %) was performed in most carriers. Hypoperfusion or hypometabolism in the parietal and/or temporal regions was detected in many of the cases (38/46, 83 %) (supplementary fig. S1A). Signs of vascular involvement were seen, such as crossed cerebellar diaschisis (3/46, 7 %) and diminished perfusion of the left medial cerebral artery territory (2/46, 5 %).

Core AD CSF biomarkers were available in more than half of the carriers (33/58, 57 %), showing a characteristic AD profile (i.e. a rise in t-tau and p-tau in combination with a lowered $A\beta_{1-42}$ and $A\beta_{1-42}/A\beta_{1-40}$ ratio) in 31/33 (94 %). In P30 and P51, biomarker analyses were not compatible with AD, while neuroimaging showed signs of cerebral chronic microvascular disease. However, further progressive cognitive decline with predominant amnestic deficits, was present despite preventive measures for cardio- and cerebrovascular disease.

3.1.3. *Neuropathology (Table 4, Fig. 3A-F)*

Neuropathological examination was performed in 10 carriers, showing high to moderate levels of AD changes. Macroscopic examination detected diffuse cortical atrophy in various degrees in five carriers, while diffuse neuronal loss of cortices was seen in four carriers. Hippocampal atrophy was observed in four individuals, but neuronal loss was noted in all but one. Microscopic examination revealed pronounced severe levels of Aβ pathology in all, with high amounts of senile plaques in six patients. Distribution of senile plaques were mainly present in the hippocampus and cortex. Tau pathology was pronounced in two carriers but was less severe in the remaining individuals. Distribution of neurofibrillary tangles, dystrophic neurites and neuritic threads was found in all examined cortices, more so in the allocortex. Occasional TDP-43 positive inclusions were observed in two patients.

Most remarkable was the presence of excessive CAA levels in all carriers. Particularly in the leptomeninges CAA was widespread and circumferential as can be seen in Fig. 3C-F. Although CAA was also pronounced in the parenchymal blood vessels, they were attained less. Capillary CAA was noted in all but one individual. The age of carriers did not seem to affect the severity or distribution of CAA. Fig. 3E-F shows two major ICH with compression of the surrounding tissue in P2. Microscopic examination of P47 showed occipital cortical necrosis and

Table 3
Overview of Belgian *ABCA7* patients with diagnosis of vascular disease.

	Clinical diagnosis	Neuropsychological examination	Neuroimaging		CSF	Neuropathology
			MRI/CT	FDG-PET/SPECT		
P2	Prob AD Prob **CAA**		Multiple **lobar ICHs, SAB**			AD + **CAA**
P6	Prob ADPos **CAA**	Amnestic and **fronto-subcortical deficits:** prominent attention impairment, severe word fluency and word finding deficits, perseveration	T (L+R) atrophy. CML + +, **hemosiderin deposit**		AD+	
P10	**Prob VaD**	AD profile with **frontal signs** of inadequate behavior	T (R>L) atrophy. **Large iCVA R PO**	PT (R>L)		AD + **CAA**
P13	Prob AD**Prob VaD**[a]	AD profile with **fronto-subcortical deficits** (global aphasia, dysexecutive symptoms)	Prominent HC (L+R) atrophy. **Watershed iCVA**, **WML, CML**+++			
P17	Prob AD Prob **CAA**	Classical AD profile	Cortico-subcortical atrophy. **Lobar ICHs.** iCVA → hCVA	FP (L+R), T (R); **CCD**		
P30	Pos AD **Prob VaD**	Classical AD	T (R>L) atrophy. PV + BG WML, **CML**+++	PCC + **Th (L)**	AD-	
P31	Pos AD**Pos VaD**	**Asymmetrical**: prominent language deficit next to multiple other cognitive deficits	**T (L) atrophy**	**MCA (L)**		
P35	Prob AD **Pos VaD**	**Asymmetrical profile**: amnestic and concentration deficits, mental inflexibility, bradyphrenia	Global atrophyPV WML, CML, **iCVA BG (L+R)**	P + F (L), PT (L>R); **CCD**	AD+	
P51	Pos AD **Pos VaD**	Classical AD profile, **slow disease progression**	Global atrophy	PT (L>R), **F + BG (L)**	**PS**	
P52	**Prob CAA**	**No cognitive deficits**	Cortico-subcortical atrophy. Multiple **lobar ICHs.** PV WML, **CML**+++		AD+	AD + **CAA**
P56	Prob AD**Prob CAA**	Prominent amnestic deficits with **fronto-subcortical deficits:** executive and concentration	HC (L+R) atrophy **Lobar ICH, MBs, cSS**	PO + precuneus + PCC (L+R)	AD+	
P59	**Prob VaD**	**Fronto-subcortical deficits**: prominent bradyphrenia, mental rigidity and perseverations	T (L+R) atrophyPV WML, **CML**+++	Suggestive for AD		AD + **CAA**
P60	Prob AD **Prob CAA**	Classical AD profile though with **frontal deficits**: severe verbal disinhibition	Global and HC (L+R) atrophy**cSS** O (R); **MBs** O (L); PV WML, **CML**+++	P (L>R) + precuneus (L+R)	AD+	
P81	Prob AD **Prob VaD**	Classical AD profile with very **slow disease progression**	HC (L+R) atrophy. PV (R>L) WML, **CML**+++ ; **iCVA F+O (L)**		AD+	
P91	Pos AD **Pos VAD**	Classical AD profile with very **slow disease progression and subcortical deficits:** parkinsonian symptoms with bradyphrenia and -kinesis, hypomimia)	T (L+R) atrophy. PV WML+	FP + T + O (L+R), BG (L>R), **Th (L)**	**PS**	AD + **CAA**

Summarized clinical information available of 22 *ABCA7* patients in which vascular (co-)pathology was suspected at a clinical stage of diagnosis. In **bold** signs suggestive of vascular disease were highlighted. The results of neuropsychological examination, imaging, core Alzheimer's disease CSF biomarkers and neuropathological examination are displayed. Interpretation of CSF core Alzheimer's disease biomarker analysis is represented with (AD+) (results suggestive for AD pathology), presymptomatic (PS) (lowered $A\beta_{1-42}$ and $A\beta_{1-42}/A\beta_{1-40}$ ratio with normal ranges of p-tau and t-tau), and (AD-) (results not suggestive for AD pathology).
Abbreviations: AD = Alzheimer's disease; BG = basal ganglia; CAA = cerebral amyloid angiopathy; CAS = carotid artery stenosis; CCD = crossed cerebellar diaschisis; CML = chronic microvascular lesions (+ limited, ++ moderate, ++ extensive); cSS = cortical superficial siderosis; F = frontal; FP = frontoparietal; L = left; HC = hippocampal; ICH = intracerebral hemorrhage; iCVA = ischemic cerebrovascular accident; hCVA = hemorrhagic cerebrovascular accident; MB = microbleed; MCA = middle cerebral artery; O = occipital; P = parietal; PCC = posterior cingulate cortex; PO = parieto-occipital; pos = possible; prob = probable; PS = presymptomatic; PV = periventricular; PVSs = perivascular spaces; R = right; SAB = subarachnoidal bleeding; SPECT = single photon emission computed tomography; T = temporal; Th = thalamus; TO = temporo-occipital; VaD = vascular dementia; vasc comp = with vascular component; w = with; WML = white matter lesions
[a] Patient with known carotid artery stenosis, corresponding to watershed infarcts.

meningeal bleeding. A small hypothalamic bleeding was noticed P29, suggestive for underlying arteriosclerosis. This was seen in more patients (7/10, 70 %). Lastly, cortical hypoxia and focal necrosis were seen in P14.

3.2. Rare ABCA7 Missense mutation carriers

Overall, we included 46 patients carrying 38 different missense mutations (Supplementary Table S6). P17 and P18, who carried both a PTC and a missense mutation, were included and discussed in the PTC mutation group.

Among the three compound heterozygous missense carriers, P85 carried the variants in trans, whereas P69 and P89 carried the variants in cis. The remaining missense carriers were heterozygous for a single missense variant. In individual P75, the known pathogenic *PSEN1* p. C263F mutation (Perrone et al., 2020) was detected, as well as a single *ABCA7* missense variant.

3.2.1. Demographics

Demographic data of *ABCA7* missense carriers can be found in Tables 1–2.

3.2.2. Clinical characteristics

Clinical diagnoses included probable AD (32/44, 72 %) and possible AD (8/44, 18 %). Dementia was preceded by MCI due to AD (15/44, 34 %) with conversion to dementia ($n = 13$) after a mean DD of 3 ± 1 year (range 1–6) in 13/15 cases (87 %). Three individuals had a diagnosis of VaD next to AD (3/44, 7 %), two with probable and one with possible VaD. In all individuals CSVD was suspected, due to advanced periventricular WML (P59 and P81) or reduced thalamic and basal ganglia hypoperfusion (P91). Neuropathological examination confirmed CAA co-pathology next to AD pathology (A3B3C2 & A2B2C1) in P59 and P91. In addition, large ischemic sequalae were visible on neuroimaging of P81, suggestive for another vascular component (large artery disease/cardio-embolic) next to CSVD. Neuroimaging was compatible with probable CAA in P60. Additionally, P69 and P77 did not show clinical signs of vascular disease, but CAA co-pathology was revealed at neuropathological examination (Tables 3–4).

P67 first complained of a hypokinetic extrapyramidal tremor in the right hand and difficulties of fine motor skills, with an ambiguous

Table 4
Neuropathology of *ABCA7* mutation carriers in Belgian AD patients.

ID	*ABCA7* mutation		*APOE*	Gender	AAO	AAD	DD	Neuropathology		Love[28]			Other
	cDNA	Protein	genotype		(y)	(y)	(y)	Montine[25]	Braak stage	Meningeal CAA	Parenchymal CAA	Capillary CAA	
2	c.67-1G>A	p.0	33	f	64	67	3	A3B2C2	III	2	2	1	
10	c.2126_2132del	p.E709fs*86	33	f	90	92	2	A3B2C2	IV	2	1	1	
12	c.2126_2132del	p.E709fs*86	44	f	50	54	4	A3B2C3	IV	3	2	1*	
14	c.2126_2132del	p.E709fs*86	34	f	73	78	5	A3B3C2	V-VI	3	1	1	TDP-43 positive inclusions
16	c.2126_2132del	p.E709fs*86	34	f	64	74	10	A3B3C3	V	3	3	1	
21	c.3641G>A	p.W1214*	34	m	86	88	2	A3B2C3	IV	3	2	1*	
27	c.4008G>A	p.W1336*	33	f	48	55	7	A3B3C3	V	2°		2	TDP-43 positive inclusions
37	c.4208delT	p.L1403fs*12	33	f	61	70	9	A3B3C3	VI	3	2	1	
38	c.4416 +2T>Gc.4168T>C	p.0p.F1390L	34	f	59	73	14	A3B3C3	VI	3	3	1	
52	c.5570 +5G>C	p.0	34	m	NA	75	NA	A3B3C2	III	3	3	1	
59	c.499G<A	p.E167K	44	f	79	89	10	A3B3C2	V	2	2	1	
69	c.1766C>Gc.2476G>A	p.A589G p.G826R	34	m	64	75	11	A3B3C3	VI	3	3	1	
77	c.2632G>A	p.A878T	33	m	51	61	10	A3B3C3	V	3	3	1	TDP-43 positive inclusions Lewy bodies
91	c.5191G>A	p.G1731S	23	m	77	86	10	A2B2C1	III-IV	1–2	1	1	

Overview of neuropathological data of *ABCA7* patients. Scoring for meningeal and parenchymal CAA: 0 = no CAA, 1 = scant beta amyloid deposition, 2 = some circumferential beta amyloid, 3 = widespread circumferential beta amyloid. Scoring for capillary CAA: 1 = present (type 1), 1* = occasionally present, 2 = absent.
°Assessment of meningeal CAA was performed through the Vonsattel score (Vonsattel et al., 1991)
Abbreviations: AAD=age at death; f=female, m = male; NA = not assessed; y = year

reaction to levodopa. Complaints of cognitive decline started one year after tremor began. No other signs of parkinsonism were noticed, while the tremor stabilized. Overall extrapyramidal signs were present in 11/40 patients (28 %) but mostly developed three or six years after disease onset (supplementary table S5). P77 was clinically diagnosed dementia with Lewy Bodies, but neuropathological examination proved different, showing severe AD and CAA pathology. In three cases (3/11, 27 %) vascular parkinsonism was suspected. Concomitant use of antipsychotics was presumed to elicit parkinsonism in four participants (4/11, 18 %).

P77 suffered from a single tonic-clonic seizure six years after disease onset, while P74 described a one-time insult of general myoclonic jerks for 30 min.

3.2.3. *Technical investigation findings (Supplementary Table S2)*

Records of structural imaging were available for all carriers (CT $n = 34$ or MRI $n = 23$). When atrophy was localized, typically the bilateral (mesio)temporal region was involved (17/44, 39 %) (Fig. 2D). Characteristic signs of CAA were picked up by MRI-T2*, available for 7/44 (14 %) individuals (Fig. 2E and Table 2). WML varied from confluent cortico-subcortical and/or periventricular white to small punctuations (34/44, 77 %), as shown in Fig. 2F.

SPECT (n=34) or FDG-PET (n=4) in 38/44 patients (86 %) mainly reflected a relative functional loss in the parietal regions (30/38, 79 %) with extension to the temporal regions (22/38, 58 %) (supplementary fig. S1B). In addition, crossed cerebellar diaschisis was noted in 3/38 patients (8 %). P68 showed brain amyloid deposits on amyloid PET.

CSF biomarkers were available in 25/44 carriers (57 %), most of whom presented with a typical AD phenotype (20/25, 80 %). Two carriers had high levels of $A\beta_{1–42}$, but Aβ-ratio was diminished in combination with elevated tau-levels and thus presumed to be high $A\beta_{1–42}$ producers. Three out of 25 individuals (16 %) had neurochemical AD CSF biomarker profiles that were compatible with early AD (a low $A\beta_{1–42}$ level and a low $A\beta_{1–42}$/ $A\beta_{1–40}$ ratio in combination with normal tau-values). Further cognitive decline to AD dementia was neuropsychologically confirmed in P73 and P91.

3.2.4. *Neuropathology (Table 4, Fig. 3G-I)*

We here describe the neuropathological phenotype of four patients carrying a different missense variant. Except for P91, all missense patients showed signs of at least moderate AD neuropathological changes and advanced degrees of CAA. Atrophy was most pronounced in the neocortex. Particularly the hippocampus and medial temporal lobe were attained by neuronal loss, often accompanied by microspongiosis of cortical layer II. In P91 the atrophy was most severe, particularly the medial temporal lobe was affected, but also subcortical involvement of the various nuclei of the brainstem and substantia nigra of the mesencephalon were included.

Amyloid depositions were most severe in the allocortex in all carriers. In P91, amyloid pathology was less clear and mostly restricted to the allocortex. The remainder of patients displayed diffuse amyloid depositions and diffuse and classical senile plaques in the allo-and isocortex.

The neurofibrillary pathology again was most pronounced in the allocortex and isocortex in all patients. Contrary to amyloid deposition, P91 displayed most importantly extensive neurofibrillary alterations, most pronounced in the limbic system, but extended to the nuclei of the pontomesencephalic reticular formation. Next to neurofibrillary tangles and dystrophic neurites, we also encountered hippocampal astrocytic tangles, astrocytes, and gliosis in P91. In P77 tau-pathology was also seen in the thalamus and basal ganglia.

In addition, occasional TDP-43 positive inclusions were seen in P77. Multiple Lewy bodies were observed in the brainstem of P91, although diagnosis of Diffuse Lewy Body Disease was not reached.

We encountered pronounced levels of CAA in patients. Both meningeal and parenchymal blood vessels seemed evenly affected

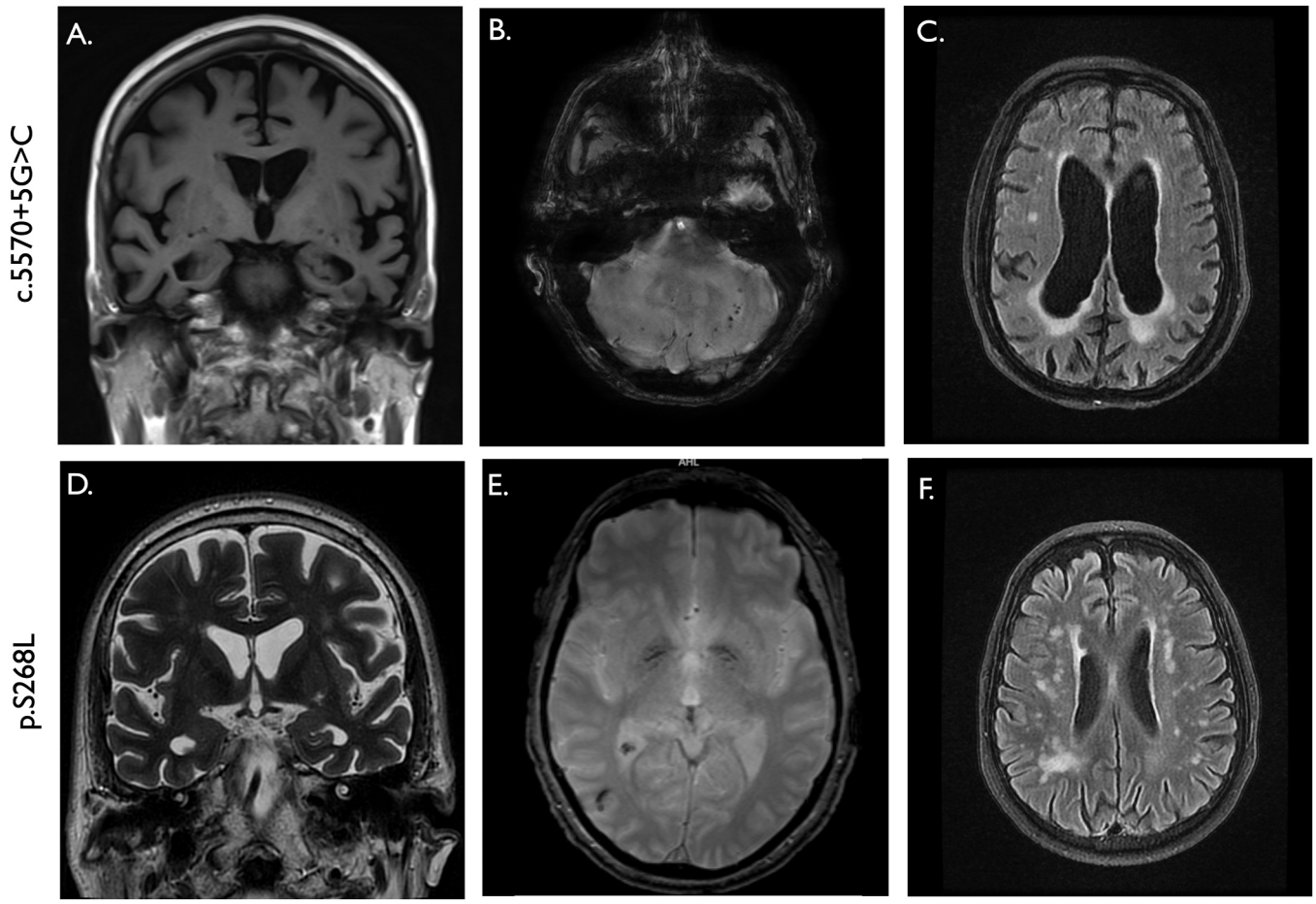

Fig. 2. Neuroimaging in *ABCA7* PTC mutation PTC carrier P56 and missense carrier P60 with signs of CAA. P56 is carrier of the c.5570 +5G>C PTC mutation (images A-C), and P60 is carrier of the p.S268L mutation (images D-F). **(A)** Coronal MRI FLAIR image showing global cortical atrophy and pronounced bilateral hippocampal atrophy. There are a few periventricular T2 lesions compatible with chronic microvascular damage.**(B)** Axonal T2*-weighted MRI image where numerous cortico-subcortical MBs in both the occipital lobes are visible, presumably because of CAA.**(C)** Axonal MRI FLAIR image showing moderate chronic microvascular lesions in the deep white matter.**(D)** Coronal T2 weighted MRI image showing global cortical atrophy and bilateral hippocampal atrophy.**(E)** Axonal T2*-weighted MRI image where, linear susceptibility artefact in the right occipital lobe conferring to a small occipital ICH.**(F)** Axonal MRI FLAIR image showing moderate chronic microvascular lesions in the deep white matter.Abbreviations: FLAIR = Fluid attenuated inversion recovery.

varying from scant to widespread circumferential Aβ. All missense carriers had capillary CAA. Age did not seem to influence AD or CAA neuropathology.

3.3. Genotype-phenotype correlations

3.3.1. ABCA7 PTC vs missense mutations (Table 2, Fig. 4)

Onset ages were comparable in both groups, but the age of survival was significantly shorter in PTC carriers with a difference of four years ($p = 0.009$). Memory problems were by far the most common clinical presentation in both groups. Yet, in PTC carriers a non-amnestic presentation was observed more often ($p = 0.089$), particularly language difficulties were frequently found ($p = 0.038$). Clinical signs and symptoms were equally divided in both groups. The most common perceived symptoms were identical in both groups and typical for AD (marked in bold in supplementary table S5).

Very rare PTC mutations seemed to present with a more aggressive phenotype (supplementary fig. S3 and table S9). Although not significant, disease started earlier in this group, at a mean age of 66 years ($p = 0.680$) and patients also died earlier at 74 on average ($p = 0.522$). Also, patients were more likely to have a positive family history ($p = 0.690$) and presented with a non-amnestic phenotype.

VAD was diagnosed more frequently in PTC carriers, although insignificant ($p = 0.490$). PTC carriers more frequently received a probable/possible CAA diagnosis, despite superior availability of T2*-sequences in missense patients (Table 1). In addition, PTC patients tended to be more susceptible developing ICHs. Nonetheless, on a neuropathological level moderate-to-severe CAA was detected in both groups and capillary CAA was present in all but one PTC carrier. Lastly, significantly less neuritic plaques were seen in missense patients ($p = 0.020$), conferring to an AD stadium that was less evolved than in PTC patients.

3.3.2. Effect of APOE ε4 (supplementary tables S7-S8 and figures S4-S7)

We investigated the possible modifying effect of *APOE* ε4 on both missense and PTC patients. No significant effect on demographics, clinical presentation or vascular disease were found. *APOE* genotype did not significantly impact AD neuropathological hallmarks (ABC-score). However, PTC patients carrying an *ε4* allele had higher levels of meningeal CAA (supplementary Fig. S7D). Further, *APOE* did not influence CAA (Love score).

In addition, we evaluated the effect of *APOE* on the demographic data of PTC patients carrying the same mutation (c.5570 +5G>C, p.E709fs, p.W1336*), but no significant effect was observed (Fig. 4).

3.3.3. Effect of sex (supplementary tables S9-S10)

We assessed whether sex modified the clinical expression of *ABCA7* mutations. Detailed results are provided in Supplementary

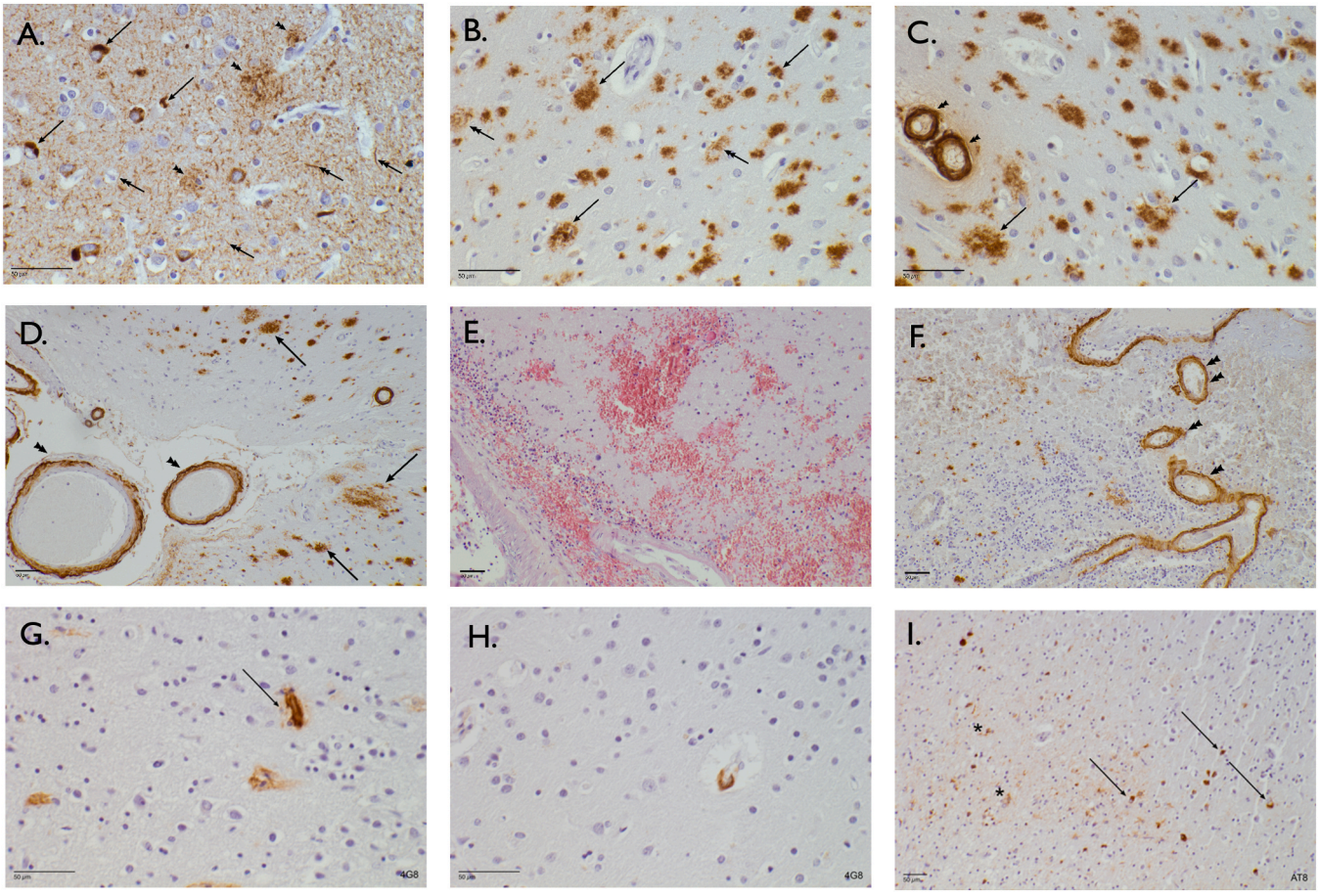

Fig. 3. Neuropathology of *ABCA7* mutation carriers. (A-F) PTC carrier P2, (G-I) missense carrier P60.(A) Hippocampus. AT8 stain. Moderate amount of NFTs (arrow) and DN (double arrowhead), but many NT (double arrow). **(B)** Hippocampus. 4G8 stain showing many SP (classic(arrow) and diffuse(double arrow)).**(C)** Frontal cortex. 4G8 stain. There are many SP (arrow), and CAA(double arrowhead) is also present. **(D)** 4G8 stain. Parietal cortex with many SP (arrow) and severe CAA (double arrowhead).**(E)** Hematoxylin Eosin stain. Cortical hemorrhage. **(F)** 4G8 stain. Cortical hemorrhage with abundant CAA (double arrowhead). **(G)** Hippocampus. 4 G stain. Presence of diffuse plaques and capillary CAA (arrow). **(H)** Area Striata. 4 G stain. Capillary CAA. **(I)** Hippocampus. AT8 stain. Presence of NFTs (arrow) and DNs(*).Abbreviations: DN=dystrophic neurites, NFT = neurofibrillary tangles, SP = senile plaques.

Tables S9–S10.

Significant sex differences were observed only among *ABCA7* PTC mutation carriers: male carriers had a shorter disease duration (6 vs. 9 years in females, $p = 0.003$), and a history of depression was reported exclusively in female carriers (24 %, 8 individuals; $p = 0.019$).

For *ABCA7* missense mutation carriers, no significant sex differences were identified.

3.3.4. *Comparison with matched sporadic AD control patients (supplementary tables S11-S13)*

To contextualize the clinical phenotype associated with *ABCA7* mutations, we compared carriers with a matched cohort of AD patients without *ABCA7* PTC or missense mutations (= AD control cohort). As intended by the matching procedure, both groups were comparable in terms of sex distribution and *APOE ε4* carriership (Supplementary Table S9).

In total, 79 sporadic AD controls had sufficient clinical and neuropathological information (vs n = 102 *ABCA7* carriers). Availability of structural imaging was higher among *ABCA7* carriers. Additionally, the year of disease onset differed significantly between groups, with *ABCA7* carriers more frequently diagnosed in more recent years (2004 vs. 2000; $p = 0.003$), which may have contributed to the lower availability of MRI-T2* imaging in the AD control cohort (4 vs. 12), although this difference was not statistically significant ($p = 0.292$).

Firstly, *ABCA7* carriers had a significantly younger age at onset (mean 71 vs. 75 years, $p = 0.012$). Consequently, carriers exhibited a higher proportion of EOAD cases (30 % vs. 15 %; $p < 0.001$) (Supplementary Table S11).

Clinical features suggestive of CAA were more common among *ABCA7* patients. Six carriers (6 %) met criteria for probable or possible CAA, compared with none of the AD controls ($p = 0.083$). Lobar intracerebral hemorrhage, cerebral microbleeds, and cortical superficial siderosis were observed exclusively in *ABCA7* carriers, although these differences did not reach statistical significance due to small numbers. WML burden differed significantly: carriers had higher WML scores overall ($p = 0.022$).

Neuropathological findings were in line with these observations. *ABCA7* carriers displayed a significantly higher severity of meningeal CAA compared to the AD control patients ($p = 0.039$). Parenchymal CAA did not differ significantly ($p = 0.193$), though the distribution suggested somewhat lower levels among the AD control patients (Fig. S8; Supplementary Table S13).

4. Discussion

ABCA7 has emerged as a significant risk factor for AD, with both common and rare variants contributing to AD risk. In an extensive collection of Belgian *ABCA7* carriers, we provide an in-depth genotype-phenotype characterization of the clinicopathological features of *ABCA7* patients. Here, we present a detailed phenotypic characterization of 102

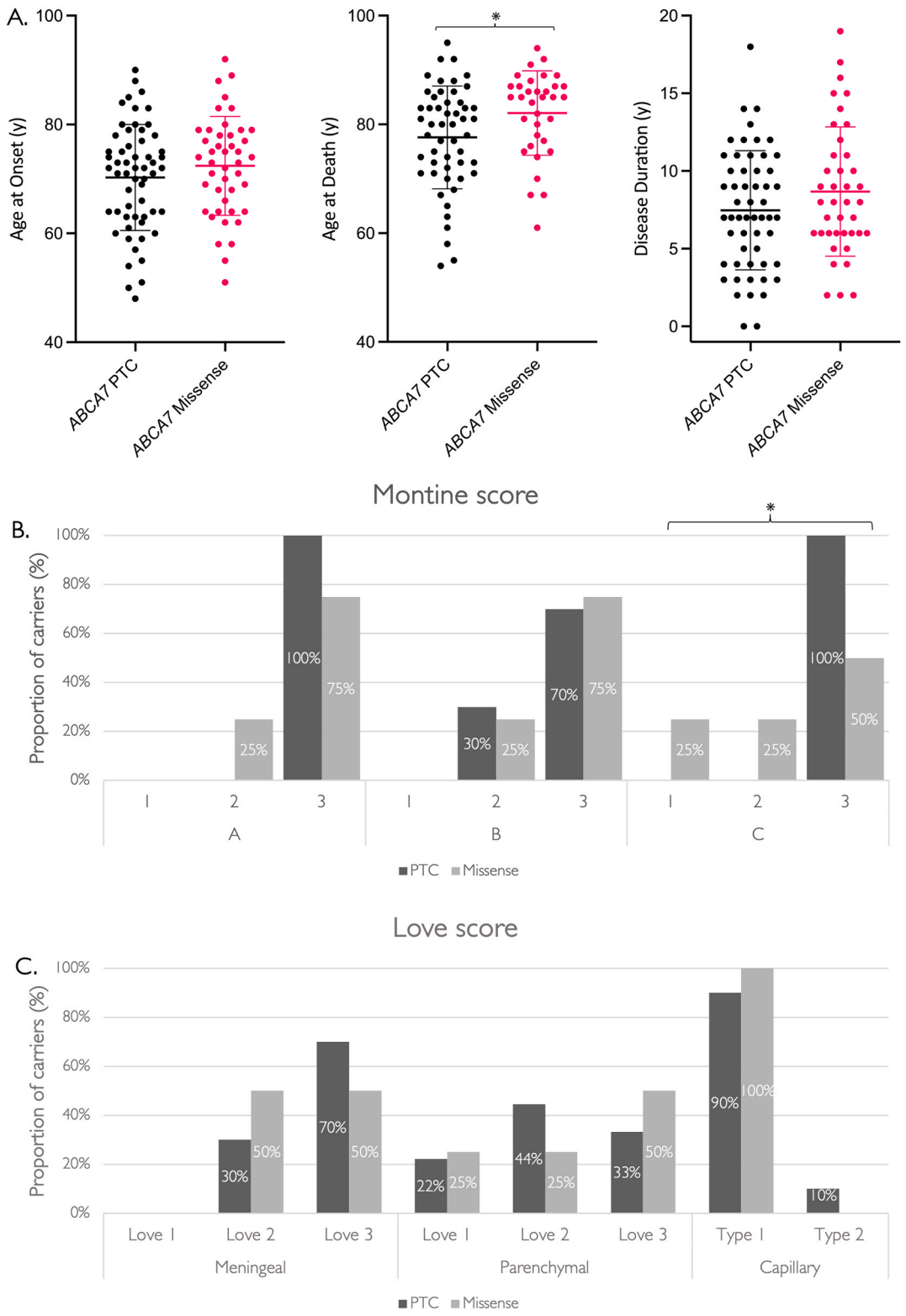

Fig. 4. Genotype–phenotype correlations in *ABCA7* carriers. In these graphs, AD patients are divided in groups based on their gene mutation, i.e., *ABCA7* PTC mutation carriers and *ABCA7* missense carriers. Scoring for meningeal and parenchymal CAA: 0 = no CAA, 1 = scant beta amyloid deposition, 2 = some circumferential beta amyloid, 3 = widespread circumferential beta amyloid. Scoring for capillary CAA: 1 = present (type 1), 1* = occasionally present, 2 = absent. **(A)** Demographical data. Box plots show the comparison of AAO, AAD and DD in PTC and missense carriers. Data are presented as median ± interquartile range. P values correspond to the values assessed Mann-Whitney U: AAO: p = 0.295; AAD: p = 0.017; DD: p = 0.284. **(B)** Montine scores. Distribution of AD neuropathological changes according ABC score in *ABCA7* mutation carriers among *ABCA7* mutation type(PTC vs missense). This bar graph shows the proportion of *ABCA7* carriers with AD neuropathological changes for each patient group. The bars are subdivided for the proportion of the mutation carriers. P values correspond to the values assessed by Mann-Whitney U: A: p = 0.114; B: p = 0.857; C: p = 0.020*. **(C)** CAA levels. Distribution of global meningeal and parenchymal CAA, as well as capillary CAA in *ABCA7* carriers. This bar graph shows the proportion of *ABCA7* carriers with CAA for each patient group. P values correspond to the values assessed by Mann-Whitney U: Meningeal: p = 0.497; Parenchymal: p = 0.867; Capillary: p = 0.527.Abbreviations: AAD = age at death.

Belgian AD patients carrying predicted risk-increasing 58 PTC and 44 missense mutations. In 14 out of 102 (14 %) patients, brain autopsy and detailed neuropathological examinations were performed.

Our findings indicate that *ABCA7* carriers present with a specific phenotypic profile with extensive accumulation of Aβ in both parenchymal plaques and cerebral arteries. Neuropathological examination revealed substantially higher levels of CAA in *ABCA7* carriers compared to non-carriers (AD control cohort), with a significant difference observed for meningeal CAA. While AD and CAA are two separate clinical entities, they are molecularly tightly linked (Greenberg et al., 2020). CAA often co-occurs with AD pathology, yet only approximately 50 % of AD patients show moderate-to-severe degrees of CAA (Charidimou et al., 2017; Jäkel et al., 2022).

ABCA7 carriers demonstrated a higher prevalence of probable or possible CAA compared to the AD controls (6 % vs. 0 %, $p = 0.021$), while CAA-related features such as ICH, MBs, and cSS were absent in the older control group. WML burden also differed significantly between groups, with *ABCA7* carriers more frequently exhibiting moderate to severe WMLs ($p = 0.022$), potentially reflecting increased vascular vulnerability. The observed rates of ICH and MBs among *ABCA7* carriers were comparable to those reported in previous AD cohorts (7 % for ICH and 24 % for MBs) (Kalaria and Sepulveda-Falla, 2021; Sepehry et al., 2016), while the prevalence of cSS appeared notably higher than earlier estimates (~5 %) (Zhou et al., 2019). Still, we suspect that CAA may be underdiagnosed in our cohorts due to the limited availability of T2*-weighted MRI sequences, which are critical for detecting hemosiderin-based CAA markers. Consequently, the true *in vivo* burden of CAA in *ABCA7* carriers may be higher than currently estimated.

Carriers of rare *ABCA7* mutations developed dementia at a significantly younger age of onset compared to the matched AD control group (71 ± 9 years vs 75 ± 11 years. This earlier onset becomes apparent when considered in the context of the broader Belgian AD population, which showed a mean age at onset of 75.4 ± 8.5 years. While *ABCA7* carriers displayed a wide range of onset ages (48–92 years), the AD control group showed an even broader distribution (44–101 years).

We investigated potential phenotypic differences in *ABCA7* missense carriers compared to the more established PTC mutations. Age at onset was not significantly different in missense carriers (72 ± 9 years) compared to PTC carriers (70 ± 10 years). We did observe a higher proportion of missense carriers with positive familial history (55 %) compared to our Belgian cohort of AD patients (50 %) (Bossaerts et al., 2021). Although most of our results were insignificant, PTC patients appeared to present with a more aggressive phenotype visible in demographics, positive familial history, clinical presentation and involvement of vascular disease. Yet, AAD was significantly earlier in PTC patients compared to missense carriers (78 ± 9 years vs 82 ± 8 years). Also, PTC carriers were more likely to present with language problems.

Of note, to overcome the possibility of including benign and protective missense variants, we carefully selected missense mutations that were present in patients only or were supported by functional evidence. Nevertheless, their precise contribution to AD and effect on the clinical phenotype is presently unknown (Bossaerts et al., 2022; De Roeck et al., 2019). This underscores the need for functional *in-vitro* characterization of the different types of *ABCA7* mutations and assessment of their individual contribution to AD risk. Continued identification of *ABCA7* rare variant carriers is necessary to increase sample size and power of future studies.

Another factor that could also have contributed to the observed clinical heterogeneity is the contribution of *ABCA7* to non-AD neuropathological lesions (Duchateau et al., 2024). In a third of the *ABCA7* carriers, we encountered extrapyramidal signs which mostly developed in a later disease stage as is to be expected (Tosto et al., 2015). However, in 23 % of patients with extrapyramidal signs a vascular mechanism was suspected. As mentioned, Belgian PTC mutation carriers were prone to present with language difficulties, suggestive for primary progressive aphasia. In our neuropathologically investigated cases, we noted signs of alpha-synucleinopathy in one missense carrier, and TDP-43 pathology in a PTC mutation carrier.

ABCA7 mutations have been reported in other non-AD neurodegenerative diseases, though their prevalence and contribution to non-AD pathologies is unclear (Allen et al., 2017; Campbell et al., 2022; Nuytemans et al., 2016). It has previously been suggested that *ABCA7* could play a role in Parkinson's disease (Campbell et al., 2022; Nuytemans et al., 2016; Van den Bossche et al., 2016; Yang et al., 2022). Additionally, CAA patients often display parkinsonian signs such as slower gait speed (Greenberg et al., 2020). Furthermore, *ABCA7* variants have also been observed in frontotemporal dementia patients. A case report of Wagner et al. reported a patient carrying the p.E709fs PTC mutation presenting with semantic variant primary progressive aphasia (Wagner et al., 2021). Another patient with partial deletion in *ABCA7* combined with a *GRN* p.Asp33Glu variant of uncertain significance similarly presented with frontotemporal dementia and semantic variant primary progressive aphasia (Antonell et al., 2020). *ABCA7* missense variants have also been reported in a clinical frontotemporal dementia cohort (Ciani et al., 2019).

Finally, we explored the modifying impact of *APOE* and whether it could explain the disease heterogeneity of ABCA7 carriers and be at the basis of the AD-CAA phenotypic spectrum. PTC patients carrying an ε4 allele, showed significantly higher degrees of meningeal CAA. Parenchymal and capillary CAA were not significantly different between ε4-carriers and non- ε4 carriers. Contrary to what could be expected, *APOE ε4* carriers presented at a later onset age and were less likely to have a positive familial history. The *APOE* genotype has been associated with an increased risk of AD and CAA (ε4), as well as hemorrhagic CAA (ε2) (Greenberg et al., 2020).

Evidence for a functional interaction between *APOE* and *ABCA7* remains mixed. Several studies reported no direct effect of *APOE* on *ABCA7*-related mechanisms or phenotypes (Bossaerts et al., 2021; Garliyev et al., 2024; Steinberg et al., 2015). Several lines of genetic evidence however suggest that *APOE* genotype may modulate the impact of *ABCA7* variation. Wang et al. (2022) observed increased AD risk in *APOE* ε4 carriers harboring specific *ABCA7* variants (rs3764650G and rs4147929A) (Wang et al., 2022), and Chang et al. (2019) reported an interaction effect of *APOE* with *ABCA7* (rs3764650) on memory performance(Chang et al., 2019). In addition, a recent study in individuals of African ancestry showed that an *ABCA7* frameshift deletion (rs142076058) substantially lowered the AAO among *APOE* ε3/ε4 carriers(Akgun et al., 2025). Together, these findings indicate that APOE may exert allele-specific modifying effects on ABCA7-related disease processes, although the underlying mechanisms remain to be clarified.

Although *APOE* ε4 carriers significantly showed higher levels of meningeal CAA, both meningeal and parenchymal CAA levels were overall extensive. Therefore, we hypothesize that *ABCA7* mutations could have contributed to these high levels of CAA. Increasing evidence is showing an involvement of ABC transporters in CAA, as they are known to facilitate Aβ clearance and increase APP processing (Banerjee et al., 2017; Miller, 2015). In a CAA mouse model, upregulation of *ABCA7* was found in early stages of CAA corresponding to a dysregulation of immune response and lipid processing networks associated with CAA (Taylor et al., 2020). Association studies of *ABCA7* and CAA show somewhat conflicting results. Mäkelä et al. described a strong correlation with the *ABCA7* locus (Mäkelä et al., 2018), while Blumenau found a nominal association between the *ABCA7* p.G1527A missense mutation and CSVD (Blumenau et al., 2020). In contrast, SNP rs3764650 (G) has been described as a risk factor for AD, but was found to have no direct influence on CAA (Beecham et al., 2014) or even have a protective factor in regard to CAA-CSVD (Bonaterra-Pastra et al., 2023). Furthermore, on a clinical level, Campbell reported important vascular involvement (not further specified) at neuropathological examination in *ABCA7* PTC carriers (Campbell et al., 2022). Our study suggests that *ABCA7* might indeed contribute to the high CAA levels seen in the

Belgian carriers.

In light of the novel amyloid-β immunotherapies designed to slow down AD progression, it may be relevant to also consider *ABCA7* in the genetic risk stratification, in addition to *APOE4* to help predict CAA levels and mitigate CAA-linked adverse side effects (Banerjee et al., 2017; Love et al., 2014; Sveikata et al., 2022).

4.1. Limitations

Although our sample size was modest, we extended the initial cohort of 22 PTC carriers to 58 carriers. In addition, to our knowledge, this is the first cohort of *ABCA7* missense carriers ever phenotypically characterized. Secondly, we only included patients with detailed clinical information available given by professionals specialized in cognitive neurology. Since patients have been included over a long period of time, not all carriers received the same clinical measurements and investigations. Stored biosamples including brain and CSF were reanalyzed for the largest part to ensure correct diagnosis and permit new findings. Neuroimaging scans were sometimes unavailable for reevaluation. Consequently, we were obliged to base our results on the reports of the radiologist or treating neurologist, which might have caused significant inter-observer variability. Lastly, for the AD control cohort, availability of historical medical records and neuroimaging data was more limited, which may have affected the level of detail in clinical and radiological characterization.

5. Conclusions

In summary, we provided an in-depth, comprehensive evaluation of the clinical phenotype associated to both *ABCA7* PTC and missense mutation carriers. We report a potential link between *ABCA7* and AD neuropathology with advanced CAA co-pathology. Antemortem, an important vascular component was found in 15 % of *ABCA7* mutation carriers, presumably corresponding with CSVD-CAA. However, we assume this might be an underestimation. Patients present with a classical AD phenotype but with pronounced clinical heterogeneity. The presence of a cerebrovascular component through CAA might partly explain this heterogeneity. Genotype-phenotype correlation revealed a more aggressive disease course in PTC carriers compared to missense carriers. The findings of our study indicate that further research into the relationship of *ABCA7* and CAA is warranted.

Submission declaration and verification

We declare that the present work has not been published previously (except in the form of an abstract) and is not under consideration for publication elsewhere. We also declare that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

CRediT authorship contribution statement

Kristel Sleegers: Writing – review & editing. **Sebastiaan Engelborghs:** Writing – review & editing, Visualization, Resources. **Elisabeth Hendrickx Van de Craen:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **De Deyn Peter P:** Resources. **Patrick Cras:** Writing – review & editing, Resources. **Tobi Van den Bossche:** Conceptualization. **Maria Bjerke:** Investigation, Data curation. **Christine Van Broeckhoven:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition. **Liene Bossaerts:** Validation, Methodology, Investigation, Formal analysis, Conceptualization. **Julie van der Zee:** Writing – review & editing, Supervision, Project administration. **Anne Sieben:** Resources, Data curation. **Rik Vandenberghe:** Resources. **Bernard Hanseeuw:** Resources. **Bruno Bergmans:** Resources.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work the author(s) used AI-based language tools (ChatGPT by OpenAI and Microsoft Copilot) in order to make some language refinements. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.

Ethical assurances

All research participants or their legal representatives signed informed consent for participation in clinical and genetic research. The local medical ethics committees approved the clinical study protocols and informed consent forms at the collaborating sampling sites. The genetic study protocols and informed consent forms were approved by the ethics committee of the Antwerp University Hospital and the University of Antwerp, Belgium.

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Declaration of Competing Interest

None of the authors have conflicts of interest to disclose.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neurobiolaging.2025.12.010.

References

Akgun, B., Gulyayev, A.V., Coker, M., Hamilton-Nelson, K.L., Olalusi, O., Adams, L.D., Akinwande, K., Whitehead, P.G., Diala, S., Ogunronbi, M., Laux, R.A., Akpalu, A., Starks, T.D., Sarfo, F.S., Chavez, J., Lwere, K., Beecham, G.W., Akinyemi, J.O., Obiako, R., Pericak-Vance, M.A., 2025. ABCA7 deletion lowers age at onset of Alzheimer's disease and interacts with APOE ε4 synergistically in African-ancestry populations. Alzheimers Dement. 21 (8), e70583. https://doi.org/10.1002/alz.70583.

Albert, M.S., DeKosky, S.T., Dickson, D., Dubois, B., Feldman, H.H., Fox, N.C., Gamst, A., Holtzman, D.M., Jagust, W.J., Petersen, R.C., Snyder, P.J., Carrillo, M.C., Thies, B., Phelps, C.H., 2011. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 7 (3), 270–279. https://doi.org/10.1016/j.jalz.2011.03.008.

Allen, M., Lincoln, S.J., Corda, M., Watzlawik, J.O., Carrasquillo, M.M., Reddy, J.S., Burgess, J.D., Nguyen, T., Malphrus, K., Petersen, R.C., Graff-Radford, N.R., Dickson, D.W., Ertekin-Taner, N., 2017. ABCA7 loss-of-function variants, expression, and neurologic disease risk. Neurol. Genet. 3 (1), e126. https://doi.org/10.1212/NXG.0000000000000126.

Antonell, A., Ramos-Campoy, O., Balasa, M., Borrego-Écija, S., Montagut, N., Falgàs, N., Tort-Merino, A., Olives, J., Fernández-Villullas, G., Bosch, B., Sanchez-Valle, R., Lladó, A., 2020. An ABCA7 partial deletion and a GRN variant in a semantic variant of primary progressive aphasia patient. Alzheimers Dement. 16 (3), e042483. https://doi.org/10.1002/alz.042483.

Banerjee, G., Carare, R., Cordonnier, C., Greenberg, S.M., Schneider, J.A., Smith, E.E., van Buchem, M.A., van der Grond, J., Verbeek, M.M., Werring, D.J., 2017. The increasing impact of cerebral amyloid angiopathy: essential new insights for clinical practice. J. Neurol. Neurosurg. Psychiatry 88 (11), 982–994. https://doi.org/10.1136/jnnp-2016-314697.

Beecham, G.W., Hamilton, K., Naj, A.C., Martin, E.R., Huentelman, M., Myers, A.J., Corneveaux, J.J., Hardy, J., Vonsattel, J.P., Younkin, S.G., Bennett, D.A., De Jager, P. L., Larson, E.B., Crane, P.K., Kamboh, M.I., Kofler, J.K., Mash, D.C., Duque, L., Gilbert, J.R., Montine, T.J., 2014. Genome-wide association meta-analysis of neuropathologic features of Alzheimer's disease and related dementias. PLoS Genet. 10 (9), e1004606. https://doi.org/10.1371/journal.pgen.1004606.

Blumenau, S., Foddis, M., Müller, S., Holtgrewe, M., Bentele, K., Berchtold, D., Beule, D., Dirnagl, U., Sassi, C., 2020. Investigating APOE, APP-Aβ metabolism genes and Alzheimer's disease GWAS hits in brain small vessel ischemic disease. Sci. Rep. 10 (1), 7103. https://doi.org/10.1038/s41598-020-63183-5.

Bonaterra-Pastra, A., Benítez, S., Pancorbo, O., Rodríguez-Luna, D., Vert, C., Rovira, A., Freijo, M.M., Tur, S., Martínez-Zabaleta, M., Cardona Portela, P., Vera, R., Lebrato-Hernández, L., Arenillas, J.F., Pérez-Sánchez, S., Domínguez-Mayoral, A., Fàbregas, J.M., Mauri, G., Montaner, J., Sánchez-Quesada, J.L., Hernández-Guillamón, M., 2023. Association of candidate genetic variants and circulating levels of ApoE/ApoJ with common neuroimaging features of cerebral amyloid angiopathy. Front. Aging Neurosci. 15, 1134399. https://doi.org/10.3389/fnagi.2023.1134399.

Bossaerts, L., Hendrickx Van de Craen, E., Cacace, R., Asselbergh, B., Van Broeckhoven, C., 2022. Rare missense mutations in ABCA7 might increase Alzheimer's disease risk by plasma membrane exclusion. Acta Neuropathol. Commun. 10 (1), 43. https://doi.org/10.1186/s40478-022-01346-3.

Bossaerts, L., Hens, E., Hanseeuw, B., Vandenberghe, R., Cras, P., De Deyn, P.P., Engelborghs, S., Van Broeckhoven, C., 2021. Premature termination codon mutations in ABCA7 contribute to Alzheimer's disease risk in Belgian patients. e307 Neurobiol. Aging 106 (307), e301–307. https://doi.org/10.1016/j.neurobiolaging.2021.04.023.

Campbell, A.S., Ho, C.C.G., Atık, M., Allen, M., Lincoln, S., Malphrus, K., Nguyen, T., Oatman, S.R., Corda, M., Conway, O., Strickland, S., Petersen, R.C., Dickson, D.W., Graff-Radford, N.R., Ertekin-Taner, N., 2022. Clinical deep phenotyping of ABCA7 mutation carriers. Neurol. Genet. 8 (2), e655. https://doi.org/10.1212/NXG.0000000000000655.

Chang, Y.T., Hsu, S.W., Huang, S.H., Huang, C.W., Chang, W.N., Lien, C.Y., Lee, J.J., Lee, C.C., Chang, C.C., 2019. ABCA7 polymorphisms correlate with memory impairment and default mode network in patients with APOE ε4-associated Alzheimer's disease. Alzheimers Res. Ther. 11 (1), 103. https://doi.org/10.1186/s13195-019-0563-3.

Charidimou, A., Boulouis, G., Frosch, M.P., Baron, J.-C., Pasi, M., Albucher, J.F., Banerjee, G., Barbato, C., Bonneville, F., Brandner, S., Calviere, L., Caparros, F., Casolla, B., Cordonnier, C., Delisle, M.-B., Deramecourt, V., Dichgans, M., Gokcal, E., Herms, J., Greenberg, S.M., 2022. The Boston criteria version 2.0 for cerebral amyloid angiopathy: a multicentre, retrospective, MRI-neuropathology diagnostic accuracy study. Lancet Neurol. 21 (8), 714–725. https://doi.org/10.1016/S1474-4422(22)00208-3.

Charidimou, A., Boulouis, G., Gurol, M.E., Ayata, C., Bacskai, B.J., Frosch, M.P., Viswanathan, A., Greenberg, S.M., 2017. Emerging concepts in sporadic cerebral amyloid angiopathy. Brain 140 (7), 1829–1850. https://doi.org/10.1093/brain/awx047.

Ciani, M., Bonvicini, C., Scassellati, C., Carrara, M., Maj, C., Fostinelli, S., Binetti, G., Ghidoni, R., Benussi, L., 2019. The missing heritability of sporadic frontotemporal dementia: new insights from rare variants in neurodegenerative candidate genes. Int. J. Mol. Sci. 20 (16), 3903. https://doi.org/10.3390/ijms20163903.

Cuyvers, E., De Roeck, A., Van den Bossche, T., Van Cauwenberghe, C., Bettens, K., Vermeulen, S., Mattheijssens, M., Peeters, K., Engelborghs, S., Vandenbulcke, M., Vandenberghe, R., De Deyn, P.P., Van Broeckhoven, C., Sleegers, K., 2015. Mutations in ABCA7 in a Belgian cohort of Alzheimer's disease patients: a targeted resequencing study. Lancet Neurol. 14 (8), 814–822. https://doi.org/10.1016/S1474-4422(15)00133-7.

De Roeck, A., Van Broeckhoven, C., Sleegers, K., 2019. The role of ABCA7 in Alzheimer's disease: evidence from genomics, transcriptomics and methylomics. Acta Neuropathol. 138 (2), 201–220. https://doi.org/10.1007/s00401-019-01994-1.

Duchateau, L., Wawrzyniak, N., Sleegers, K., 2024. The ABCs of Alzheimer risk gene ABCA7. Alzheimers Dement. 20 (5), 3629–3648. https://doi.org/10.1002/alz.13805.

Engelborghs, S., Niemantsverdriet, E., Struyfs, H., Blennow, K., Brouns, R., Comabella, M., Dujmovic, I., van der Flier, W., Frölich, L., Galimberti, D., Gnanapavan, S., Hemmer, B., Hoff, E., Hort, J., Iacobaeus, E., Ingelsson, M., de Jong, F.J., Jonsson, M., Khalil, M., Teunissen, C.E., 2017. Consensus guidelines for lumbar puncture in patients with neurological diseases. Alzheimers Dement. 8, 111–126. https://doi.org/10.1016/j.dadm.2017.04.007.

Garliyev, V., Lyssenko, C.A., Wiener, J.P., Praticò, D., Lyssenko, N.N., 2024. Very low levels of ABCA7 in the cerebrum and Alzheimer's disease onset between the ages of 60 and 80 independently of APOE. J. Neuropathol. Exp. Neurol. 83 (10), 808–821. https://doi.org/10.1093/jnen/nlae060.

Greenberg, S.M., Bacskai, B.J., Hernandez-Guillamon, M., Pruzin, J., Sperling, R., van Veluw, S.J., 2020. Cerebral amyloid angiopathy and Alzheimer disease - one peptide, two pathways. Nat. Rev. Neurol. 16 (1), 30–42. https://doi.org/10.1038/s41582-019-0281-2.

Hollingworth, P., Harold, D., Sims, R., Gerrish, A., Lambert, J.C., Carrasquillo, M.M., Abraham, R., Hamshere, M.L., Pahwa, J.S., Moskvina, V., Dowzell, K., Jones, N., Stretton, A., Thomas, C., Richards, A., Ivanov, D., Widdowson, C., Chapman, J., Lovestone, S., Williams, J., 2011. Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease. Nat. Genet 43 (5), 429–435. https://doi.org/10.1038/ng.803.

Holstege, H., Hulsman, M., Charbonnier, C., Grenier-Boley, B., Quenez, O., Grozeva, D., van Rooij, J.G.J., Sims, R., Ahmad, S., Amin, N., Norsworthy, P.J., Dols-Icardo, O., Hummerich, H., Kawalia, A., Amouyel, P., Beecham, G.W., Berr, C., Bis, J.C., Boland, A., Lambert, J.-C., 2022. Exome sequencing identifies rare damaging variants in ATP8B4 and ABCA1 as risk factors for Alzheimer's disease. Nat. Genet. 54 (12), 1786–1794. https://doi.org/10.1038/s41588-022-01208-7.

Jack Jr., C.R., Bennett, D.A., Blennow, K., Carrillo, M.C., Dunn, B., Haeberlein, S.B., Holtzman, D.M., Jagust, W., Jessen, F., Karlawish, J., Liu, E., Molinuevo, J.L., Montine, T., Phelps, C., Rankin, K.P., Rowe, C.C., Scheltens, P., Siemers, E., Snyder, H.M., Sperling, R., 2018. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement. 14 (4), 535–562. https://doi.org/10.1016/j.jalz.2018.02.018.

Jäkel, L., De Kort, A.M., Klijn, C.J.M., Schreuder, F., Verbeek, M.M., 2022. Prevalence of cerebral amyloid angiopathy: a systematic review and meta-analysis. Alzheimers Dement. 18 (1), 10–28. https://doi.org/10.1002/alz.12366.

Kalaria, R.N., Sepulveda-Falla, D., 2021. Cerebral small vessel disease in sporadic and familial alzheimer disease. Am. J. Pathol. 191 (11), 1888–1905. https://doi.org/10.1016/j.ajpath.2021.07.004.

Lambert, J.C., Ibrahim-Verbaas, C.A., Harold, D., Naj, A.C., Sims, R., Bellenguez, C., DeStefano, A.L., Bis, J.C., Beecham, G.W., Grenier-Boley, B., Russo, G., Thornton-Wells, T.A., Jones, N., Smith, A.V., Chouraki, V., Thomas, C., Ikram, M.A., Zelenika, D., Vardarajan, B.N., Amouyel, P., 2013. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nat. Genet. 45 (12), 1452–1458. https://doi.org/10.1038/ng.2802.

Linn, J., Halpin, A., Demaerel, P., Ruhland, J., Giese, A.D., Dichgans, M., van Buchem, M. A., Bruckmann, H., Greenberg, S.M., 2010. Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy. Neurology 74 (17), 1346–1350. https://doi.org/10.1212/WNL.0b013e3181dad605.

Love, S., Chalmers, K., Ince, P., Esiri, M., Attems, J., Jellinger, K., Yamada, M., McCarron, M., Minett, T., Matthews, F., Greenberg, S., Mann, D., Kehoe, P.G., 2014. 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. 3 (1), 19–32.

Mäkelä, M., Kaivola, K., Valori, M., Paetau, A., Polvikoski, T., Singleton, A.B., Traynor, B. J., Stone, D.J., Peuralinna, T., Tienari, P.J., Tanskanen, M., Myllykangas, L., 2018. Alzheimer risk loci and associated neuropathology in a population-based study (Vantaa 85+). Neurol. Genet. 4 (1), e211. https://doi.org/10.1212/NXG.0000000000000211.

May, P., Pichler, S., Hartl, D., Bobbili, D.R., Mayhaus, M., Spaniol, C., Kurz, A., Balling, R., Schneider, J.G., Riemenschneider, M., 2018. Rare ABCA7 variants in 2 German families with Alzheimer disease. Neurol. Genet. 4 (2), e224. https://doi.org/10.1212/NXG.0000000000000224.

McKhann, G.M., Knopman, D.S., Chertkow, H., Hyman, B.T., Jack Jr., C.R., Kawas, C.H., Klunk, W.E., Koroshetz, W.J., Manly, J.J., Mayeux, R., Mohs, R.C., Morris, J.C., Rossor, M.N., Scheltens, P., Carrillo, M.C., Thies, B., Weintraub, S., Phelps, C.H., 2011. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 7 (3), 263–269. https://doi.org/10.1016/j.jalz.2011.03.005.

Miller, D.S., 2015. Regulation of ABC transporters at the blood-brain barrier. Clin. Pharm. Ther. 97 (4), 395–403. https://doi.org/10.1002/cpt.64.

Montine, T.J., Phelps, C.H., Beach, T.G., Bigio, E.H., Cairns, N.J., Dickson, D.W., Duyckaerts, C., Frosch, M.P., Masliah, E., Mirra, S.S., Nelson, P.T., Schneider, J.A., Thal, D.R., Trojanowski, J.Q., Vinters, H.V., Hyman, B.T., 2012. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. Acta Neuropathol. 123 (1), 1–11. https://doi.org/10.1007/s00401-011-0910-3.

Nuytemans, K., Maldonado, L., Ali, A., John-Williams, K., Beecham, G.W., Martin, E., Scott, W.K., Vance, J.M., 2016. Overlap between Parkinson disease and Alzheimer disease in ABCA7 functional variants. Neurol. Genet. 2 (1), e44. https://doi.org/10.1212/NXG.0000000000000044.

Perrone, F., Bjerke, M., Hens, E., Sieben, A., Timmers, M., De Roeck, A., Vandenberghe, R., Sleegers, K., Martin, J.-J., De Deyn, P.P., Engelborghs, S., van der Zee, J., Van Broeckhoven, C., Cacace, R., Goeman, J., Crols, R., Dermaut, B., Ivanoiu, A., Hanseeuw, B., ,… on behalf of the Belgian Neurology Consortium, 2020. Amyloid-β1–43 cerebrospinal fluid levels and the interpretation of APP, PSEN1 and PSEN2 mutations. Alzheimers Res. Ther. 12 (1), 108. https://doi.org/10.1186/s13195-020-00676-5.

Román, G.C., Tatemichi, T.K., Erkinjuntti, T., Cummings, J.L., Masdeu, J.C., Garcia, J.H., Amaducci, L., Orgogozo, J.M., Brun, A., Hofman, A., 1993. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology 43 (2), 250–260. https://doi.org/10.1212/WNL.43.2.250.

Santos-García, I., Bascuñana, P., Brackhan, M., Villa, M., Eiriz, I., Brüning, T., Pahnke, J., 2025. The ABC transporter A7 modulates neuroinflammation via NLRP3 inflammasome in Alzheimer's disease mice. Alzheimers Res. Ther. 17 (1), 30. https://doi.org/10.1186/s13195-025-01673-2.

Sepehry, A.A., Lang, D., Hsiung, G.-Y., Rauscher, A., 2016. Prevalence of brain microbleeds in alzheimer disease: a systematic review and meta-analysis on the

influence of neuroimaging techniques. AJNR Am. J. Neuroradiol. 37 (2), 215–222. https://doi.org/10.3174/ajnr.A4525.

Sieben, A., Van Mossevelde, S., Wauters, E., Engelborghs, S., van der Zee, J., Van Langenhove, T., Santens, P., Praet, M., Boon, P., Miatton, M., Van Hoecke, S., Vandenbulcke, M., Vandenberghe, R., Cras, P., Cruts, M., De Deyn, P.P., Van Broeckhoven, C., Martin, J.J., 2018. Extended FTLD pedigree segregating a Belgian GRN-null mutation: neuropathological heterogeneity in one family. Alzheimers Res Ther. 10 (1), 7. https://doi.org/10.1186/s13195-017-0334-y.

Steinberg, S., Stefansson, H., Jonsson, T., Johannsdottir, H., Ingason, A., Helgason, H., Sulem, P., Magnusson, O.T., Gudjonsson, S.A., Unnsteinsdottir, U., Kong, A., Helisalmi, S., Soininen, H., Lah, J.J., Aarsland, D., Fladby, T., Ulstein, I.D., Djurovic, S., Sando, S.B., Stefansson, K., 2015. Loss-of-function variants in ABCA7 confer risk of Alzheimer's disease. Nat. Genet. 47 (5), 445–447. https://doi.org/10.1038/ng.3246.

Sveikata, L., Charidimou, A., Viswanathan, A., 2022. Vessels sing their ARIAs: the role of vascular amyloid in the age of aducanumab. Stroke 53 (1), 298–302. https://doi.org/10.1161/STROKEAHA.121.036873.

Taylor, X., Cisternas, P., You, Y., Xiang, S., Marambio, Y., Zhang, J., Vidal, R., Lasagna-Reeves, C.A., 2020. A1 reactive astrocytes and a loss of TREM2 are associated with an early stage of pathology in a mouse model of cerebral amyloid angiopathy. J. Neuroinflamm. 17 (1), 223. https://doi.org/10.1186/s12974-020-01900-7.

Tosto, G., Monsell, S.E., Hawes, S.E., Mayeux, R., 2015. Pattern of extrapyramidal signs in Alzheimer's disease. J. Neurol. 262 (11), 2548–2556. https://doi.org/10.1007/s00415-015-7886-1.

Van den Bossche, T., Sleegers, K., Cuyvers, E., Engelborghs, S., Sieben, A., De Roeck, A., Van Cauwenberghe, C., Vermeulen, S., Van den Broeck, M., Laureys, A., Peeters, K., Mattheijssens, M., Vandenbulcke, M., Vandenberghe, R., Martin, J.J., De Deyn, P.P., Cras, P., Van Broeckhoven, C., 2016. Phenotypic characteristics of Alzheimer patients carrying an ABCA7 mutation. Neurology 86 (23), 2126–2133. https://doi.org/10.1212/WNL.0000000000002628.

Vardarajan, B.N., Ghani, M., Kahn, A., Sheikh, S., Sato, C., Barral, S., Lee, J.H., Cheng, R., Reitz, C., Lantigua, R., Reyes-Dumeyer, D., Medrano, M., Jimenez-Velazquez, I.Z., Rogaeva, E., St George-Hyslop, P., Mayeux, R., 2015. Rare coding mutations identified by sequencing of Alzheimer disease genome-wide association studies loci. Ann. Neurol. 78 (3), 487–498. https://doi.org/10.1002/ana.24466.

Vermeiren, Y., Van Dam, D., Aerts, T., Engelborghs, S., De Deyn, P.P., 2014. Brain region-specific monoaminergic correlates of neuropsychiatric symptoms in Alzheimer's disease. J. Alzheimers Dis. 41 (3), 819–833. https://doi.org/10.3233/jad-140309.

Vonsattel, J.P., Myers, R.H., Hedley-Whyte, E.T., Ropper, A.H., Bird, E.D., Richardson, E. P., Jr, 1991. Cerebral amyloid angiopathy without and with cerebral hemorrhages: a comparative histological study. Ann. Neurol. 30 (5), 637–649. https://doi.org/10.1002/ana.410300503.

Wagner, M., Lorenz, G., Volk, A.E., Brunet, T., Edbauer, D., Berutti, R., Zhao, C., Anderl-Straub, S., Bertram, L., Danek, A., Deschauer, M., Dill, V., Fassbender, K., Fliessbach, K., Götze, K.S., Jahn, H., Kornhuber, J., Landwehrmeyer, B., Lauer, M., , … The German Frontotemporal Dementia Consortium, 2021. Clinico-genetic findings in 509 frontotemporal dementia patients. Mol. Psychiatry 26 (10), 5824–5832. https://doi.org/10.1038/s41380-021-01271-2.

Wang, L., Jiao, Y., Zhao, A., Xu, X., Ye, G., Zhang, Y., Wang, Y., Deng, Y., Xu, W., Liu, J., 2022. Analysis of genetic association between ABCA7 polymorphism and Alzheimer's disease risk in the southern Chinese population. Front. Aging Neurosci. 14, 819499. https://doi.org/10.3389/fnagi.2022.819499.

Willemse, E.A.J., Vermeiren, Y., Garcia-Ayllon, M.S., Bridel, C., De Deyn, P.P., Engelborghs, S., van der Flier, W.M., Jansen, E.E.W., Lopez-Font, I.B., Mendes, V., Manadas, B., de Roeck, N., Saez-Valero, J., Struys, E.A., Vanmechelen, E., Andreasson, U., Teunissen, C.E., 2019. Pre-analytical stability of novel cerebrospinal fluid biomarkers. Clin. Chim. Acta 497, 204–211. https://doi.org/10.1016/j.cca.2019.07.024.

Yang, Z., Xue, L., Li, C., Li, M., Xie, A., 2022. Association between ABCA7 gene polymorphisms and Parkinson's disease susceptibility in a northern Chinese Han population. Neurosci. Lett. 784, 136734. https://doi.org/10.1016/j.neulet.2022.136734.

Zhou, C., Liu, K., Yan, S., Jin, Y., 2019. Association between cortical superficial siderosis and dementia in patients with cognitive impairment: a meta-analysis. Front. Neurol. 10, *8*. https://doi.org/10.3389/fneur.2019.00008.