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REVIEW ARTICLE

The ABC's of Alzheimer risk gene *ABCA7*

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Abstract

Alzheimer's disease (AD) is a growing problem worldwide. Since *ABCA7*'s identification as a risk gene, it has been extensively researched for its role in the disease. We review its recently characterized structure and what the mechanistic insights teach us about its function. We furthermore provide an overview of identified *ABCA7* mutations, their presence in different ancestries and protein domains and how they might cause AD. For *ABCA7* PTC variants and a VNTR expansion, haploinsufficiency is proposed as the most likely mode-of-action, although splice events could further influence disease risk. Overall, the need to better understand expression of canonical *ABCA7* and its isoforms in disease is indicated. Finally, ABCA7's potential functions in lipid metabolism, phagocytosis, amyloid deposition, and the interplay between these three, is described. To conclude, in this review, we provide a comprehensive overview and discussion about the current knowledge on ABCA7 in AD, and what research questions remain.

KEYWORDS
ABCA7, Alzheimer's disease, amyloid metabolism, lipid metabolism, missense mutation, phagocytosis, PTC mutation, RNA expression, VNTR repeat

Highlights

- Alzheimer's risk-increasing variants in *ABCA7* can be found in up to 7% of AD patients.
- We review the recently characterized protein structure of ABCA7.
- We present latest insights in genetics, expression patterns, and functions of ABCA7.

1 | INTRODUCTION

According to the World Health Organization (WHO), currently over 55 million people globally are suffering from dementia, with the number of dementia patients expected to triple by 2050.[1] Thus, there is an urgent need for therapeutics that can help prevent and slow down the different forms of this disorder. The most common form of dementia is Alzheimer's disease (AD), representing about 60%–70% of cases. Alzheimer's disease is clinically characterized by a progressive loss of memory and deterioration of cognitive functions, and pathologically characterized by neurodegeneration, extracellular amyloid β (Aβ) plaques, and intracellular neurofibrillary tangles.[2,3] These biological hallmarks are already present in the brain up to decades before the onset of symptoms during the so-called "preclinical phase."[3,4] This phase provides a unique window of opportunity for therapeutic treatment, acting on dysregulated pathways before too substantial neuronal loss has occurred. In order to do so, an understanding is needed of who is at risk for developing AD, when their expected age at onset (AAO) is

and which treatment they would benefit from most. In order to do so, genetics could be a great aid.

Alzheimer's disease is caused by a combination of environmental and genetic factors with the latter having a large contribution in both early-onset (EOAD, AAO < 65 years) and late-onset (LOAD, AAO > 65 years).[5] In the 1990's the first risk genes for the disease were identified including *APOE*, *APP*, *PSEN1*, and *PSEN2*, the latter three leading to an autosomal dominant form (reviewed in detail in Ref. 6).[6] However, most of our knowledge about AD genetics was gathered after the introduction of genome-wide association studies (GWAS), revealing common variants associated with a modest increased risk for AD.[7] A first GWAS on 3941 AD patients and 7848 controls revealed three novel risk genes,[8] while one of the latest GWAS uncovered a staggering 75 risk genes.[9] Targeted resequencing of these loci can further reveal causal variants underlying disease mechanisms and rare variants contributing to disease.[7] Identification of these new risk loci emphasized the involvement of additional pathways that are affected in AD pathology, besides the Aβ and tau pathways, such as lipid and cholesterol metabolism, synaptic dysfunction, immune response and inflammation, and endocytosis and lysosomal dysfunction.[9,10] ATP-binding cassette Subfamily A Member 7, *ABCA7*, was first identified as a risk gene for AD in a GWAS study in 2011.[11]

Since then, many other *ABCA7* variants that increase AD risk have been identified, including rare variants with larger effect sizes. In this review, we will elaborate on the knowledge gathered about ABCA7's structure, disease-associated variants, expression, splicing, and function, and how these can impact one's risk for AD.

RESEARCH IN CONTEXT

1. **Systematic review**: We reviewed the literature on ABCA7, mainly in the context of Alzheimer's disease (AD), using literature search engines (i.e., PubMed or Google Scholar), with a focus on established important findings and new findings from the past 5 years.
2. **Interpretation**: Genetic evidence underlines the importance of ABCA7 in AD, but how ABCA7 dysfunction contributes to AD is not yet fully explained. With the recent determination of its protein structure and emerging single-cell/nuclei RNA sequencing studies, refined opportunities arise to explore how genetic variation affects ABCA7's functions in lipid metabolism, phagocytosis, and/or amyloid β processing in AD. This review provides researchers with an important foundation for future work in this area.
3. **Future directions**: Future directions include investigation of (1) *ABCA7* variants in different ethnicities, (2) the role of *ABCA7* (isoform) expression at single-cell level, (3) disease penetrance modifiers and, (4) ABCA7 dysfunction in disease-relevant model systems.

2 | STRUCTURE

The *ABCA7* gene is located on chromosome 19p13.3 and has 47 exons. The canonical transcript is 6815 base pairs (bp) long and encodes for a protein of 2146 amino acids (aa) with a molecular weight of 220 kDa.[12] For a long time, the structure of ABCA7 was unknown and largely based on predictions inferred from its sequence similarities with *ABCA1* (54%) and *ABCA4* (59%).[12,13] However, recently its structure was determined by cryo-EM, which confirmed its structure with two transmembrane domains (TMDs), where the first two helices are separated from each other by an extracellular domain (ECD) and cytoplasmic nucleotide binding domains (NBDs) preceding regulatory domain (RDs) (Figure 1A and 1C).[13] Both TMD domains contain six membrane-spanning helices, as well as one broken helix going in and out of the membrane at the extracellular site. Helices of the TMD are connected by loops, some of which are structured and contain intracellular helices (IHCs) such as the loop between helix 2 and 3 of TMD1, and helix 8 and 9 of TMD2. Other intracellular helices can be found right before every TMD. Some parts of the structure could not be determined by cryo-EM, probably due to their highly mobile or flexible nature, including a flexible region within the RD1 (from arginine 1041 to arginine 1072). An overview of which amino acids belong to which domain, and the corresponding chromosomal positions, as well as an overview of important amino acids in each domain can be found in Table S1.

The ABCA7 protein is a lipid exporter using energy stemming from ATP hydrolysis to switch between its conformational states (Figure 1B). ABCA7 exports cholesterol but mostly phospholipids to acceptor molecules like apolipoprotein A1 (ApoA-I) using an "alternating access" mechanism.[14–18] In its open conformation, ABCA7 is open towards the lumen, allowing entry of bilayer lipids, with mainly TM helices 1, 2, 5, and 11 having a close association.[13] Le and colleagues further propose an intermediate "half-open" conformation during which lipid flipping from the inner to outer membrane may occur.[13] When ATP is bound, the NBDs will interact, leading to a closed TMD, with the exception of a small opening towards the ECD and extracellular space, the so-called "exit pocket." This pocket is mainly hydrophobic, with the exception of a few positively charged residues, can likely accommodate two acyl chains and may aid in the extrusion of lipids to the ECD. The ECD also contains a hydrophobic tunnel where lipids will reside until their transfer to an acceptor molecule. After ATP hydrolysis, ABCA7 will alternate its opening again and go back to the open conformation. Conformational transitions happen mainly with conserved rigid-body motions, although the TMD2-NBD2 pair is much more mobile, which is a unique feature of ABCA7. Overall TMD1 has more extensive contacts with the ECD domains, mainly ECD2, and is more closely associated with lipids present in the lumen.[13] NBDs are associated with the opposite RDs through structured linker-regions and bear Walker A and Walker B motifs, as well a signature ABC motif, features present in all ABC transporters.[13,19] The Walker

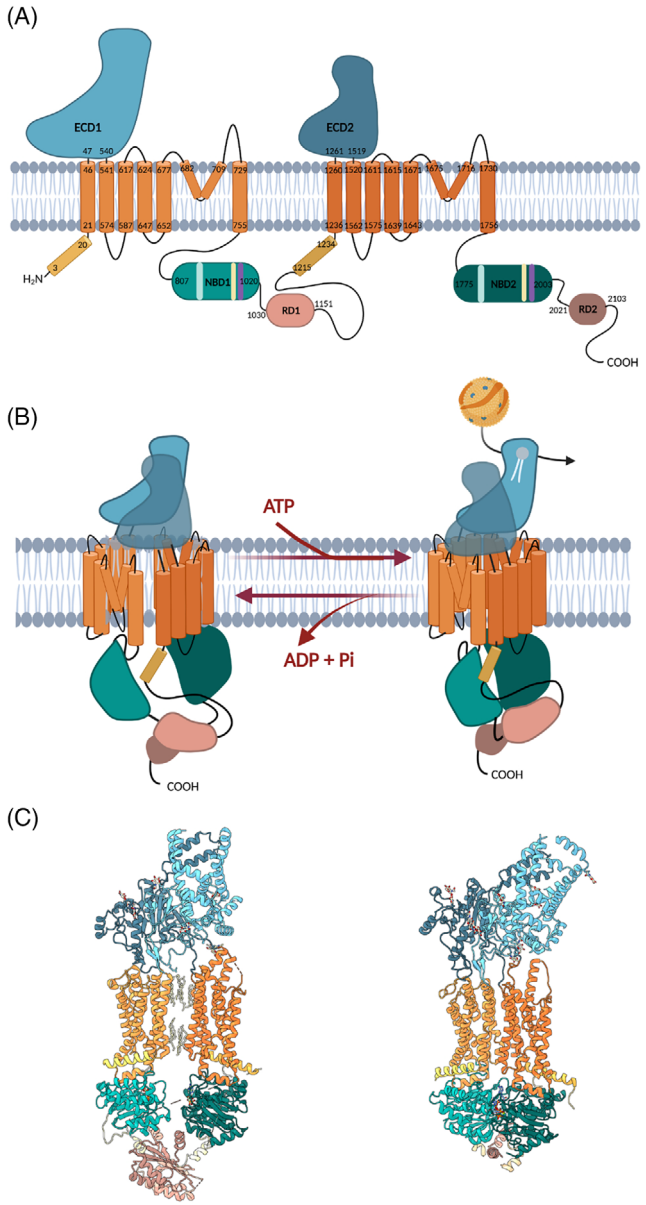

FIGURE 1 ABCA7 structure. (A) ABCA7 topological structure with amino acid range of the different domains shown, based on Le et al. (2022)[13] (PDB accession number: 8eeb). In the NBD domains (green) the Walker A motif (light blue), Walker B motif (light yellow) and signature motif (purple) are indicated. (B) ABCA7 3D structure in open and closed conformation, respectively, with intracellular helices (yellow), transmembrane domains (orange), extracellular domains (blue), nucleotide-binding domains (green), and regulatory domains (pink). (C) The same colors were used in the 3D ABCA7 structure in open (left) and closed (right) conformation based on PDB accession numbers 8edw and 8eop, respectively. Loops, linkers, and other structures that do not belong to one of these domains are colored beige. Sugars and bound ATP are shown in white and red

A motif is generally accepted to be GxxxxGK(T/S), with x representing any amino acid, and contains the P-loop, in which the lysine (K) residue is especially important for binding the phosphates of ATP.[20,21] In ABCA7, the Walker A motifs are GHNGAGKT and GVNGAGKT in NBD1 and NBD2, respectively. The Walker B motif has the sequence motif hhhhDE, with h representing hydrophobic amino acids, and plays an important role in the ATPase activity, especially the aspartate (D) and glutamate (E) residues, with the latter leading to reduced ATPase activity when mutated.[13,20,21] As depicted in Table S1, we considered sequences VVILDE in NBD1 and VVFLDE in NBD2 as the Walker B motifs. Finally, the signature ABC transporter (C) motif is less well defined but often the motif is proposed to be LSGGQ.[22] We defined it as LSGGM and YSGGN in NBD1 and NBD2, respectively, similarly to Vigneshwaran and colleagues[20], although Aikawa et al. define a longer sequence.[23] Other important residues in the protein include residues playing a role in lipid extrusion, whose positively charged side chains are oriented towards the lipids in the lumen such as R475 (ECD1), R478 (ECD1), R482 (ECD1), R544 (TMD1), R548 (TMD1), and K1407 (ECD2), and one residue which is oriented towards the exit pocket and changes orientation between the open and closed formation (R678). Not much is known about the function of the RDs, but in other ABCA transporters, they have been suggested to stabilize NBD interactions and interact with each other during the open conformation.[24–26] ABCA7 activity can be modulated by its environment with cholesterol having an inhibitory effect on ATP hydrolysis while activity was highest in phosphatidylethanolamine and phosphatidylserine nanodiscs.[13] Mutations in *ABCA7* have been found throughout the protein, in all the described domains.

3 | *ABCA7* AD-ASSOCIATED VARIANTS

3.1 | Common variants

During GWAS, common single nucleotide polymorphisms (SNPs) are investigated for their association with a trait, such as AD. SNPs showing genome-wide significant association with the trait of interest (also called sentinel SNPs) are most often not directly affecting disease risk, but rather indirectly, through the phenomenon of linkage disequilibrium (LD) with actual functional variants that are in close genomic proximity. *ABCA7* was first implicated in AD in GWAS studies, when a significant association was found between intronic SNP rs3764650 and AD in a European cohort.[11] Furthermore, in Europeans, associations have been found for SNPs rs4147929,[11,27,28] rs3752246,[29,30] rs3752231,[31,32] rs111278892,[33] and rs12151021[9,34–36] in GWAS studies, and rs78117248 in an *ABCA7* resequencing study[37] (Table S2). All these SNPs have low risk-increasing odds ratios (OR) of about 1.1–1.2[9,38] (Table 1).

Rs78117248 is in strong LD (D' > 0.94) with all GWAS SNPs as determined in LDlink in all European non-Finnish cohorts in GRCh38 (high coverage) (accessed on 20/11/2023 via https://ldlink.nih.gov/?tab=ldpair), although within the group of GWAS SNPs, there is variability in LD, ranging from very low LD (D' = 0.038) to full LD (D' = 1) (Table S3).[39] Especially rs111278892 and rs3752231 are in low LD with rs3752246 and rs4147929, suggesting that they might be tagging two separate functional variants. It is unlikely that rs78117248 is the functional variant at the *ABCA7* locus due to its intronic location and low predicted pathogenicity. For both rs3764650 and rs78117248,

TABLE 1 Overview of *ABCA7* AD-related SNPs.

Common SNPs	Genomic location (GRCh38)	cDNA	Predicted protein	Risk allele	Ethnicity	Risk allele frequency (%)	*p*-Value	OR
rs111278892	chr19:1039324 C > G	upstream ABCA7	/	G	European	0.16	4.59×10^{22}	1.10 (1.08-1.12)
rs3752229	chr19:1041353 A > G	c.−9A > G	/	G	Chinese[44]	0.37	1.83×10^{-5}	1.26 (1.13-1.40)
rs3752231	chr19:1043639 C > T	c.931-86C > T	/	T	European	0.25	5.30×10^{23}	1.09 (1.07-1.10)
rs3764648	chr19:1044754 T > C	c.1215+10T > C	/	T	Chinese[44]	0.34	3.98×10^{-5}	1.26 (1.13-1.40)
rs3764650	chr19:1046521 T > G	c.1622+115T > G	/	G	European	0.09	9.54×10^{-5}	1.10 (1.08-1.13)
					East-Asian[45]	0.36	0.01	1.43 (1.09-1.89)
					Mixed ancestry[a 46]	0.11	1.13×10^{-8}	1.01 (0.97-1.05)
rs142076058	chr19:1046907del	c.1732_1775del	p.Arg578Ala fs	44 bp deletion	African American[43]	0.059	1.41×10^{-5}	1.81 (1.38-2.37)
rs4147914	chr19:1049270 G > A	c.2385G > A	p.Leu795Leu	A	Chinese[44]	0.42	1.64×10^{-4}	1.22 (1.10-1.35)
rs12151021	chr19:1050875 A > G	c.2553-46A > G	/	A	European	0.32	1.59×10^{-37}	1.10 (1.09-1.12)
					Mixed ancestry[47]	0.32	3.90×10^{-33}	1.11 (1.09-1.13)
rs3752246	chr19:1056493 G > C	c.4580G > C	p.Gly1527Ala	G	European	0.17	3.53×10^{-27}	1.11 (1.09-1.12)
					Chinese[44]	0.36	3.66×10^{-6}	1.29 (1.16-1.44)
rs115550680	chr19:1050421 A > G	c.2553-500A > G	/	G	African American[42]	0.057	2.2×10^{-9}	1.79 (1.47-2.12)
rs78117248	chr19:1052854 A > G	c.3221-475A > G	/	G	European	0.023	8.47×10^{-9}	1.16 (1.11-1.20)
rs150594667	chr19:1056150 G > T	c.4323G > T	p.Ala1441Ala	T	Chinese[44]	0.013	1.77×10^{-4}	1.98 (1.39-2.84)
rs4147929	chr19:1063444 A > G	c.5713-100A > G	/	A	European	0.17	2.08×10^{-25}	1.10 (1.08-1.12)
					East-Asian[45]	0.36	0.006	1.45 (1.11-1.89)

Note: For each SNP, the genomic location in Hg38 is shown and the coding and protein nomenclature according to HGVS and which is the AD risk-increasing allele. Per ethnicity in which it is identified, the frequency of the alternative allele in gnomAD v4.0.0 is shown in European (non-Finnish), East-Asian (also for Chinese individuals), African/African American ancestries or overall (for mixed ancestry). *p*-Value and odds ratio (OR) for the risk-increasing allele is shown according to Bellenguez et al. (2022),[9] unless specified otherwise in Ethnicity column.

[a]This SNP was associated with all cause dementia.

carrying the risk allele was significantly associated with longer length of a variable number of tandem repeats (VNTR) polymorphism, located in intron 18 of the gene.[40] Length of this VNTR varies substantially between individuals, ranging between 300 bp to more than 10 kb. However, carrying at least one expanded VNTR, with a length of over 5.6 kb, was associated with a 4.5 higher risk for AD. This expansion was observed in about 7% of AD patients and, hence, is quite common. An increased VNTR length was additionally associated with lowered *ABCA7* expression, abnormal $A\beta_{42}$ CSF levels, and increased in-frame exon 19 skipping, which removes part of the first NBD domain.[40] The VNTR expansion was moreover associated with lower $A\beta_{40}$, $A\beta_{42}$, sAPPα, sAPPβ, and YKL-40 CSF levels.[41] This expanded VNTR might therefore (partially) explain the GWAS signals in Caucasians.

In African Americans, an ethnicity-specific GWAS SNP rs115550680 was detected which has an OR of 1.8[38,42] and is in full LD with a premature termination codon (PTC) variant caused by a 44 bp deletion (rs142076058).[43] The latter is common in African American cohorts (5.85% in gnomAD v4.0.0) but not in other ethnicities with only 0.0048% of non-Finnish Europeans carrying the variant. A recent study in a Chinese population discovered association with AD for known variant rs3752246 and novel risk SNPs rs3752229, rs4147914, rs3764648, and rs150594667.[44] All had an OR of around 1.2–1.3, with the exception of rs150594667 for which it was almost 2. The LD patterns of the different variants were similar. In East-Asian populations, also associations with AD have been detected for SNPs rs3764650 and rs4147929.[45] Finally, for both rs3764650 and rs12151021, significant association has been detected in a mixed ancestry study of all cause dementia[46] and AD, respectively.[47]

Differences in association signals between ethnicities could be due to discrepancies in genetic architecture such as LD structure and allele frequencies. Associations with *ABCA7* SNPs in Caucasian, African American, as well as East Asian cohorts does seem to suggest a contribution to AD pathophysiology in all three. So far, most associations have been found for Caucasian cohorts, and to lesser extent in East-Asian populations. It should be noted though that, in large (GWAS) studies, European ancestry is by far the most represented, with much bigger cohort sizes, even though both African Americans and Hispanic Americans have higher risks to develop AD.[48] Thus, the overrepresentation of associated GWAS SNPs in Caucasian cohorts likely does not have a biological foundation but is reflective of these discrepancies in research possibilities between populations. In fact, in African Americans, *ABCA7* has even been shown to have a stronger effect size in AD than *APOE*.[49] Expanding research beyond the European population is thus essential. To truly understand ABCA7 risk in AD it is also critical to further identify the underlying functional variants.

The abovementioned GWAS sentinel SNPs have also been studied for their association with AD endophenotypes, such as amyloid deposition, tau pathology, brain morphology, and various clinical symptoms, which has been extensively reviewed before.[38,50] Shortly, multiple genetic markers were associated with increased amyloid pathology, which has been replicated in several studies,[38,51-54] which could be indicative for a role of ABCA7 dysfunction in the amyloid pathway. Evidence for association with tau pathology has been more inconsistent.[38,51,54,55] Studies in different brain regions generally suggested association of risk alleles with either brain atrophy or altered functional connectivity.[38,56-59] Finally, for association with different measures of cognitive decline and memory, mixed results have been found as well.[38,56]

3.2 | Rare variants

Besides the common GWAS SNPs, the intronic rs78117248 SNP, the African American 44 bp deletion variant (rs142076058) and the expanded VNTR, numerous rare variants (minor allele frequency < 1%), which are generally enriched in AD patients, have been identified in *ABCA7* as well. These mutations can be split up into two groups: missense variants and PTC variants, the latter including nonsense, frameshift, and splice site mutations that cause the formation of an early stop codon. This enrichment of rare variants in AD patients was first noted in 2015 in multiple independent studies[37,60-62] but has since been replicated many times. A meta-analysis in 2019 found a significant enrichment of PTC and missense mutations in patients with an OR of 2.6 and 1.8, respectively,[38] while a gene-burden test in exome sequencing data of 32,558 Caucasian individuals suggested significant ORs of 1.7 and 1.4.[63] A similar approach on 148,508 individuals, of whom 22,080 had at least one parent with AD/dementia or AD diagnosis themselves, found a nominally significant enrichment of rare *ABCA7* variants in disease, although an OR was not reported.[64] Power in this cohort to find significance may have been decreased by the proxy approach in which not all 22,080 AD-classified individuals actually developed AD, carried risk variants or may have had parents with other types of dementia. Nevertheless, all these studies strongly imply that rare variants in *ABCA7* are risk-increasing for AD with higher effects than the common genetic risk factors.

3.3 | *ABCA7* PTC variants

Several studies have identified an enrichment of *ABCA7* PTC variants in AD mutations with ORs ranging between 1.4 and 5.[38] The lowest OR was found in a study on an African American cohort, and this number was likely largely influenced by the 44 bp deletion (rs142076058, p.R578fs), which is common in African Americans (found in up to 21.7% of AD patients) but has a weaker risk-increasing effect.[65] In a large burden analysis and case-control meta-analysis, OR in Caucasians is determined to be 1.7 and 2.6, respectively, with frequencies in AD patients ranging between 0.39% and 4.4%.[38,63] It should be noted that many of these studies might even underestimate this number as one of the more ubiquitous rare PTC variants (in non-Finnish Europeans [NFE] in gnomAD v.4.0.0 a frequency of 0.31%), a splice region mutation c.5570+5G > C (rs200538373), is often not included. This mutation is not located at the canonical splice donor or acceptor site, but can still dysregulate splicing and cause the usage of an alternative splice donor, causing an out-of-frame partial intron 41 retention.[60,66] Moreover, it is possible that other intronic variants may also affect splicing

TABLE 2 PTC and predicted damaging missense variants in healthy individuals of different ancestries.

Parameter	Non-Finnish European	Finnish European	African American	East Asian	South Asian	Admixed American	Ashkenazi Jewish	Middle Eastern
Total population size	590,031	32,026	37,545	22,448	45,546	30,019	14,804	3031
Minimum sequenced individuals	5190	276	15,156	3472	316	984	4832	912
PTC variants	0.74%	0.40%	6.64%	0.52%	0.57%	0.98%	0.92%	0.95%
Damaging missense variants	1.57%	1.25%	2.24%	0.89%	2.84%	1.29%	2.97%	5.87%
APOE ε4 variant	15.06%	19.19%	22.05%	9.78%	10.06%	10.69%	12.03%	6.81%

Note: Table showing *ABCA7* variants population frequency detected in healthy controls of different ancestry in gnomAD v4.0.0, as well as the lowest number of sequenced individuals for a SNP. PTC variants were selected as frameshift, stop gained (or nonsense), splice acceptor, and splice donor variants, with those flagged as low confidence or dubious quality removed. Predicted missense variants that were enriched in AD patients in Holstege et al. (2022)[63] with REVEL > 0.25 were studied for their frequency in gnomAD v4.0.0. Carrier frequency of the *APOE ε4* variant in gnomAD v4.0.0 is shown in each population as well.

and thus could be counted as PTC variants, and are not included in these numbers either, as was seen for some deep intronic variants in *ABCA4*.[67]

When studying the frequency of PTC variants (n = 542) in predominantly cognitively healthy individuals of different ancestry in the gnomAD browser (accessed November 2023), many of the above-mentioned findings can be confirmed (Table 2).[68] In African/African Americans, the frequency of PTC variants is by far the largest, largely driven by the p.R578fs variant. In people of South or East Asian descent, and those with Finnish ancestry, PTC variants are least common.

The same variants (n = 542) were also studied for their presence in the different protein domains of ABCA7 (Figure 2, Figure S1). Most PTC mutations were observed in the ECD1 (n = 115), followed by regions with no known functional or structural domains (n = 90), ECD2 (n = 88), NBD1 (n = 62), NBD2 (n = 60), TMD1 (n = 49), TMD2 (n = 47), RD1 (n = 21), and RD2 (n = 14). When considering the size of the protein domains by normalizing mutation counts by dividing it by the number of amino acids in the protein domain, the highest relative count was observed in ECD2, and the lowest in both regulatory domains (Figure S1A). When further considering frequency of the PTC variants in the NFE cohort in gnomAD v4.0.0., we find that PTC mutation frequency, normalized against domain size, is highest in both ECD domains (Figure 2). However, PTC mutations likely lead to nonsense-mediated decay of the mutant transcript, or -if truncated proteins are formed- loss of protein domains. This is mainly determined by the position of the stop codon rather than the mutation itself, which may be in a different protein domain downstream of the mutation. Therefore, functional inferences about differences in PTC mutation frequencies between protein domains should be made with caution.

About 77.3% of Belgian PTC carriers had a familial history of AD, which was higher than the 50% familial history in the general AD cohort.[69] The relatively high OR of AD conferred by *ABCA7* PTC mutations compared to common risk variants may contribute to this observation of familial clustering. Moreover, segregation with the disease in a Belgian cohort was noted for the p.E709fs mutation.[37] In the general Caucasian cohort, carriers had an average age at onset (AAO) of 67 years.[63,69] However, a large variability in age was observed, even within carriers of the same mutation.[66,69] Together with the observation of mutations in healthy controls, this emphasizes that likely other genetic or environmental factors exist that can modify penetrance and disease severity in carriers. According to one study, *APOE* genotype did not significantly change AAO, but the study probably lacked statistical power due to the low frequency of *ABCA7* PTC variants. Further research into other modifiers is of great interest because it could shed further light on molecular mechanisms protecting against development of AD pathology.

PTC mutation carriers generally present with a classical amnestic AD phenotype and neuropathological assessment of typical AD, albeit with a strong vascular phenotype.[66,70,71] However, a study at the Mayo Clinic suggested that PTC mutation carriers have more phenotypic variability and aggressive clinical features, due to the high familial history, earlier AAO and high rates of depression.[72] Cerebral amyloid angiopathy is quite often observed in mutation carriers.[71] In a whole-exome rare-variant association study with AD-related traits, PTC mutation carriers had nominally significant abnormal $A\beta_{42}$, P-tau_{181}, and T-tau CSF levels when compared to non-carrier AD patients, suggesting a role of ABCA7 dysfunction in increased amyloid deposition and NFT.[73] A significant increase in T-tau levels in PTC carriers were further supported in a recent study on CSF levels in *ABCA7* mutation carriers.[41]

3.4 | *ABCA7* missense variants

Missense variants have been less widely studied than PTC variants due to their likely variable nature. Indeed, while many (predicted) damaging *ABCA7* missense variants have been observed in AD patients, one protective variant (p.G215S) has been reported, and others are predicted to be neutral.[38,66,74,75] Predicted pathogenic variants increase AD risk with OR varying between 1.4 and 1.8 in Caucasian cohorts.[38,63] Damaging missense variants were enriched in East-Asian AD patients as well, but studies about their presence and effects in other ethnicities are lacking.[44] In the Caucasian population, about 5.58% of EOAD

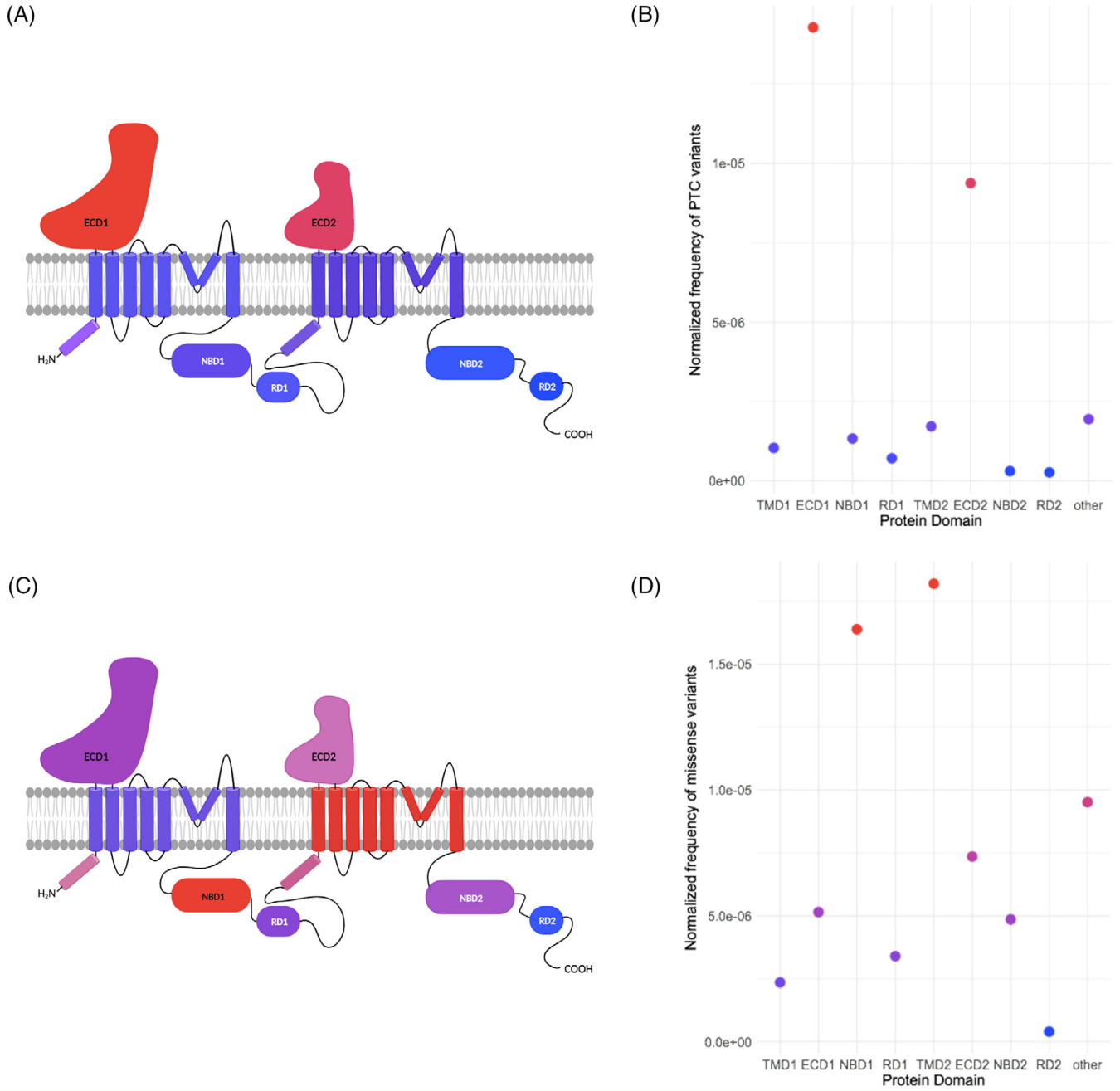

FIGURE 2 PTC and missense variants across the ABCA7 protein domains. The PTC (A and B) and missense (C and D) variant normalized frequency when adjusted for protein domain size and variant frequency in non-Finnish Europeans, across the different protein domains as shown on the ABCA7 structure (A, C) and in a graph (B, D). The normalized frequency is going from high (red) to low (blue). TMD = transmembrane domain, ECD = extracellular domain, NBD = nucleotide binding domain, RD = regulatory domain

and 4.68% of LOAD patients carry a missense mutation with a REVEL score over 0.25. Missense mutation carriers had an average AAO of 67.9 years in Caucasians.[63] Of AD patients with a missense variant, 55.8% had a familial history of the disease,[74] which is less than for PTC mutation carriers. Not much information is available about clinical phenotypes or biomarker levels of missense carriers, but co-segregation with the disease has been found for variants p.G1820S (CADD score: 32, REVEL: 0.91) and p.R880Q (CADD score: 28.7, REVEL: 0.72) in European families,[74,76] and nominally significant linkage of 13 rare missense mutations in 20 Caribbean Hispanic families.[77] It should be noted that (deep) intronic variants are often not included in these studies but may also have an effect by affecting regulatory motifs.

At the population level, individuals with Middle Eastern ancestry have the highest frequency of expected damaging *ABCA7* missense variants, followed by individuals of Ashkenazi Jewish, South Asian, and African American ancestry (Table 2). Interestingly, South Asian individuals had an average low frequency of PTC variants but high frequency of missense variants. As the included missense variants were selected

based on variants observed in a study in Caucasians, South-East Asian ancestry-specific mutations (as well as those specific for other non-European ancestries) may have been overlooked, which could have impacted the reported frequencies.

Predicted damaging variants derived from Holstege and colleagues ($n = 302$)[63] were also studied on their presence in the different protein domains of ABCA7 (Figure 2, Figure S1). From high to low, missense variants were detected in loop regions, not belonging to any of the domains ('other', $n = 74$), followed by ECD1 ($n = 48$), NBD1 ($n = 46$), NBD2 ($n = 37$), TMD2 ($n = 32$), ECD2 ($n = 25$), TMD1 ($n = 21$), RD1 ($n = 13$), and RD2 ($n = 6$). When normalized for domain size (and for variant frequency), both ECD domains had low counts and frequencies of missense variants and RD2 even had the lowest frequency of all. This could mean that these domains are functionally and/or structurally very important and less tolerant to variation, although currently not much is known about their function. In the regions between the domains, without known structural or functional importance, many variants can be found (Figure S1B), although it lowers to a third place when taking into account the frequency (Figure 2). Although variants here could impact ABCA7 function or structure, the effect of the mutations is not quite as straightforward, and the higher number of predicted damaging missense mutations does suggest that it might be more tolerant to variation. The NBD domains play a role in binding ATP and ATPase activity, but especially NBD1 had a higher number and frequency of missense variants, suggesting that perhaps not all residues in the NBD domain are critical for its function. Only two predicted damaging variants can be found in the known important motifs in the domain: one in the Walker B motif of NBD1 (1051510:C > G) (although none of the variants change the important aspartate and glutamate amino acids), and one in the signature C motif in NBD2 (rs148635111). It is also interesting to note that NBD1 seems much more susceptible to variation than NBD2. When taking into account variant frequency, TMD2 has the highest presence of possibly damaging missense mutations, while TMD1 scores rather low. TMD2 has been suggested to be more mobile compared to TMD1, while the transmembrane helices of TMD1 also have more contact with luminal lipids, which may explain this discrepancy.[13] Finally, in contrast to what we saw for PTC mutations, missense variants do not seem enriched in the ECDs. These domains have important residues forming the hydrophobic exit pocket, for interaction with extracellular (lipo)proteins, as well as some positively charged residues (mainly in ECD1) that interact with lipids in the lumen, which might explain the lower tolerance for variation. Of the important residues only one (rs147783767) is affected in the list of 302 predicted damaging variants, which might impact lipid interaction as hypothesized before.[13] Especially amino acid changes that alter the charge and hydrophobicity of such a residue may severely affect ABCA7 function.

3.5 | Other diseases

Besides Alzheimer's disease, *ABCA7* variants have been detected in other neurodegenerative diseases as well, such as frontotemporal dementia (FTD) and Parkinson's disease (PD). In a northern Chinese Han population, the A allele and GG genotype of common rs4147929 and rs3752246 SNPs, respectively, were associated with PD.[78] Rare PTC and missense mutations too were identified in clinical PD cohorts, most which had been observed in AD as well, such as the p.E709fs variant.[72,79] These variants were strongly, but not significantly enriched in the PD cohort, compared to healthy controls. In a clinical and biomarker-validated FTD cohort, one homozygous p.E709fs mutation carrier was identified with semantic variant primary progressive aphasia (svPPA), while another svPPA patient carried both an *ABCA7* partial deletion and a GRN variant.[80,81] In another clinical FTD cohort, two likely damaging *ABCA7* variants, also found in AD patients before, were identified.[82] Finally, in a cohort of mixed *post mortem* confirmed non-AD pathologies (including vascular dementia, dementia with Lewy bodies, pathological aging, and progressive supranuclear palsy patients), a significant enrichment of *ABCA7* PTC variants, similar to that in AD cohorts (which were present in the AD cohort as well) was found.[83] All together, these findings emphasize the clinical and neuropathological heterogeneity in mutation carriers, and suggest that, through its pleiotropic functions, dysregulated ABCA7 could contribute to both AD and non-AD neuropathological lesions. For example, dysfunction of phagocytosis due to mutations may not only affect amyloid-β clearance in AD, but also α-synuclein clearance in PD. Moreover, it could also pinpoint that there could be overlap in the genetic architecture of different neurodegenerative diseases.

4 | SUSPECTED MODE-OF-ACTION OF MUTATIONS

PTC variants, missense variants and a VNTR repeat expansion in *ABCA7* have all been associated with increased AD risk. But how can these mutations cause the disease? PTC mutations cause the formation of an early stop codon, which is recognized by the cellular surveillance machinery of nonsense-mediated decay (NMD), resulting in the degradation of the transcript carrying the variant. As PTC mutations are often heterozygous, this would mean a 50% reduction in expression. Studies on either protein or RNA expression have shown highly variable levels of *ABCA7*, both in mutation carriers and non-carriers, complicating analysis, but generally levels were decreased in carriers.[37,84,85] Thus, haploinsufficiency is most often proposed as a probable mode of action; the reduced expression being insufficient for ABCA7 to carry out its physiological function. A transcript analysis in PTC carriers revealed two mechanisms that could possibly alter expression levels (Figure 3). First of all, incomplete degradation of mutant bearing transcripts, hence NMD escape, was observed, ranging from 5% to almost no degradation.[66] There are a few potential consequences to this observation. It is possible that a functional protein is still formed, either due to PTC readthrough, most likely for nonsense mutations, or due to a functional truncated protein. However, most observed PTC mutations remove important domains and peptides, making the latter improbable. Alternatively, the formed protein could have gain of function (GOF) effects, resulting in disease. How-

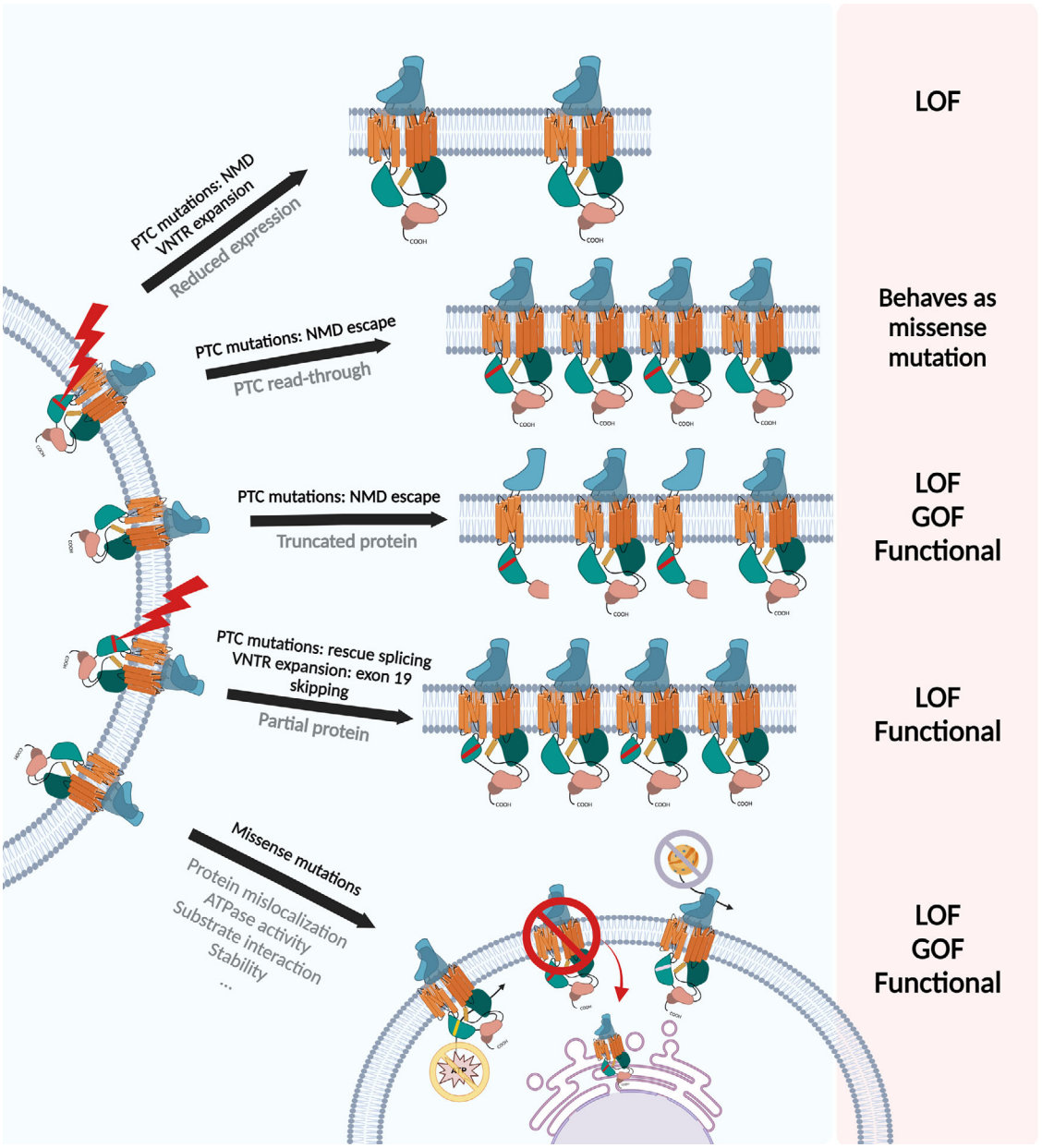

FIGURE 3 Possible mode-of-action of different *ABCA7* mutations. Possible effect of premature termination codon (PTC), missense and VNTR expansion mutations (shown as the red region in the NBD1 domain) on the protein, from top to bottom: (1) protein is not formed because of the VNTR expansion or nonsense-mediated decay (NMD) of PTC mutations, leading to reduced expression; (2) due to a PTC read-through (usually with nonsense mutations), the full protein is formed; (3) there is NMD escape leading to a truncated protein; (4) rescue splicing of PTC mutations or exon 19 skipping due to the VNTR causes the formation of mostly the full protein with some parts missing (e.g., part of NBD1 domain in example); (5) missense mutations could have multiple different effects such as decrease in ATPase activity (in yellow), protein mislocalization (in red), or affecting substrate interaction (in purple). These events could either lead to a functional protein, a loss-of-function (LOF) or a gain-of-function (GOF)

ever, in that case often accumulation of PTC mutations can be found in a specific region of the protein, while in *ABCA7* PTC mutations occur frequently in different domains throughout the protein (Figure 3). A dominant negative effect is most often observed in multimeric protein complexes, and thus also a rather unlikely mechanism for *ABCA7*. Finally, if protein does get formed, it could still have the same loss-of-function (LOF) effect if it is unstable or non-functional. A second mechanism that could explain variation in expression levels was the presence of "rescue" splice events that were able to salvage the effect of the PTC mutation by in-frame exon skipping of the exon carrying the mutation or usage of an alternative splice site that renders the transcript in-frame again.[66] Rescue splicing would lead to the formation of the protein, with either the part of the protein that was skipped missing, or with a few extra amino acids. Whether these proteins are functional depends on the variant and its rescue event and needs to be explored. Both NMD escape and rescue splicing can alter *ABCA7*

expression and could, thus, also influence disease severity in carriers. Further investigation into its role as a possible modifier is warranted.

A longer VNTR too has been linked to reduced *ABCA7* expression, further suggesting haploinsufficiency as a potential mechanism[40] (Figure 3). While the exact mechanism linking VNTR expansion to reduced expression remains to be explored, a possible explanation could be the instability of the protein due to the expanded repeat, chromatin changes or effect of transcription factor binding motifs in the VNTR.[40] Furthermore, alternative splicing events were detected surrounding the VNTR. In-frame exon 19 skipping in particular correlated with a longer VNTR length.[40] This splice event removes about 17% of the first NBD domain (but does not affect any of its motifs), which likely results in an unfunctional protein, which could further contribute to a loss-of-function effect.

Finally, for the missense variants, different mechanisms might be at play for different mutations. They could have an impact on protein activity, substrate interactions, structure, stability, folding, or subcellular localization (Figure 3). One study examined subcellular localization of 10 in silico predicted pathogenic variants (p.L620P, p.G826R, p.A845V, p.R880Q, p.R989H, p.G1731S, p.G1820S, p.R1932C, p.P1952R, and p.F2100S) with amino acid conservation with ABCA1 and ABCA4, three predicted benign variants (p.E188G, p.R1349Q, and p.G1527A), and the p.G215S protective variant in HeLa cells.[74] For all the predicted damaging variants reduced colocalization with a plasma membrane marker was observed, while the majority of them (all but p.G826R, p.R880Q, and p.R989H) had increased colocalization with an endoplasmic reticulum (ER) marker. Thus, these data suggest that, for at least a subset of variants, mislocalization is a likely risk increasing mechanism. Moreover, mutations in certain important residues in the ECD and TMD1 with connection to the lipid pocket were found to reduce ATPase activity.[13] It is hypothesized that these variants may hinder lipid extrusion, which in its turn could affect NBD dimerization and, thus, causing this observed reduction in activity. Further research into the different mechanisms behind the variants and their effect on RNA expression, protein expression, and protein functionality is needed to fully grasp how they increase AD risk.

5 | *ABCA7* EXPRESSION

5.1 | *ABCA7* expression across tissues

ABCA7 is ubiquitously expressed in humans as is shown in the GTEx and HPA database (accessed in October 2023).[86,87] Highest expression can be found in the pituitary gland, bone marrow, whole blood, spleen, thymus, and lung, while in the brain expression is high in the cerebellum and choroid plexus and average in cerebral cortex. Hence, among the highest expressed regions are several lymphoid tissues and brain regions. In the Agora Knowledge Portal, dorsolateral prefrontal cortex (DLPFC) was suggested as region with highest expression, even higher than in cerebellum (accessed via https://agora.adknowledgeportal.org/ in October 2023). Of note, the Agora Knowledge Portal holds data on *post mortem* AD patients, whereas tissues investigated in GTEx and HPA are not selected for a specific disease, which might contribute to these differences. In other brain regions, *ABCA7* mRNA is expressed at lower levels. One study investigated ABCA7 protein expression using mass spectrometry on nine brain regions in three individuals, and detected highest protein expression in the amygdala, superior temporal gyrus, and parietal lobe,[88] although results would need to be replicated in a larger cohort. Importantly, it should be noted that, in all these tissues, *ABCA7* expression is rather low compared to other genes, which complicates investigation of the role of ABCA7 in AD. For comparison, *ABCA7* expression is shown in relation to a selection of other AD-associated genes and a housekeeping gene (*GAPDH*) in four different brain regions (Figure S2).

5.2 | *ABCA7* expression across cell types

A first study about *ABCA7* expression in different brain cell types was performed in primary human cells and found the highest expression in microglia and neurons.[89] However, since the emergence of single-cell and single-nuclei sequencing, studying cell type specific expression has become much more straightforward. A small study in 466 cells derived from the temporal lobe tissue showed by far highest expression of *ABCA7* in astrocytes (accessed via celltypes.org/brain in September 2023).[90] In two studies *ABCA7* was found to be highest expressed in excitatory neurons, followed by inhibitory neurons, and then microglia and astrocytes (accessed via Human Protein Atlas [HPA] in September 2023).[87,91] In another study a similar pattern was seen, with the exception that *ABCA7* expression was strongest in astrocytes (accessed via Allen Brain Atlas in September 2023).[9] In mice, expression was actually lowest in astrocytes, and highest in oligodendrocytes and neurons, followed by microglia, endothelial cells, and oligodendrocytes, further emphasizing the importance of research on human material (accessed via https://www.brainrnaseq.org/ in September 2023). Further studies are needed to form a consensus. Understanding the cell types in which *ABCA7* is expressed can help us understand its function and dysfunction in disease. Moreover, getting insight into whether cell type expression is similar on protein level is warranted.

5.3 | Patients versus controls

Several studies have investigated whether *ABCA7* expression in brain is altered between AD patients and controls (Table 3). In the Agora AMP-AD knowledge portal (accessed in October 2023), nine different regions were investigated, revealing significant differential expression in only one. In the dorsolateral prefrontal cortex (Brodmann Area 10 [BA10]), *ABCA7* had a higher expression in AD patients. A change in the same direction was detected in an analysis performed by Liu and colleagues,[92] based on data from the Harvard Brain Tissue Resource Center (HBTRC).[93] They also reported increased expression in the visual cortex compared to controls. Fold changes of differential expression were small, ranging between 1.08 and 1.10. Often studies present contradicting results. While one meta-analysis did not find

TABLE 3 Differential RNA expression of *ABCA7* between AD patients and controls.

Parameter		AMP-AD[a]	Liu et al.[b]	Patel et al.[c]	Ciryam et al.[d]	AddNeuroMed[b]	Martínez-Iglesias et al.[e]
No. of samples	AD patients	478	129	746	765	145	7
	Controls	300	101	755	699	104	9
Frontal lobe	Anterior cingulate cortex	=	NA	=	+	NA	NA
	Dorsolateral prefrontal cortex	+	+			NA	NA
	Frontal pole	=	NA			NA	NA
	Inferior frontal gyrus	=	NA			NA	NA
Posterior cingulate cortex		=	NA	NA		NA	NA
Temporal lobe	Superior temoral gyrus	=	NA	=		NA	NA
	Parahippocampal gyrus	=	NA			NA	NA
	Temporal cortex	=	NA			NA	NA
Cerebellum		=	=	=		NA	NA
Parietal lobe		=	NA	=		NA	NA
Occipital lobe	Visual cortex	NA	+	NA		NA	NA
Blood		NA	NA	NA	NA	+	–

Note: Differential RNA expression of ABCA7 between AD patients and controls in different cohorts and brain regions. "+" indicates expression is increased in AD patients (blue),). NA (not applicable) when region was not studied. " = " indicate that no significant differences were found.
[a]Agora AMP-AD database (sccessed via https://agora.adknowledgeportal.org/ in October 2023).
[b]Liu et al. (2020).[92]
[c]Patel et al. (2019).[94]
[d]Ciryam et al. (2016).[95]
[e]Martínez-Iglesias et al. (2023).[96]

changes in expression in the frontal lobe, temporal, cerebellum, or parietal lobe (Table 3),[94] another reported higher expression in AD patients across the brain.[95] Two studies investigated expression differences in blood, again with contrasting results, with one reporting higher expression in blood in patients[92] and another a reduction[96] (Table 3). Finally, one study investigated ABCA7 protein expression in hippocampus and parietal cortex in individuals with different levels of Braak pathology.[85] In people with moderate to advanced AD pathology (Braak stage II-V), ABCA7 expression was reduced compared to people with low (Braak stage I) or no pathology. Moreover, results showed that individuals with lower ABCA7 expression developed AD neuropathology at a younger age, while those with higher expression were older at onset.

Overall, based on these findings, it is hard to draw any conclusions about how *ABCA7* expression might impact or change because of the disease. Discrepancies between studies can have different causes. Due to low *ABCA7* expression in many brain regions, spurious findings may happen, which can further be impacted by differences in assays, disease stage of included participants, average AAO, and various other factors. Insight into changes in *ABCA7* level during disease duration is warranted. Moreover, cell composition in the studied brain region, could also impact results, as all these studies were done with bulk sequencing and different cell types may have variable expression effect sizes or directions.[97] Differential expression patterns may also differ between RNA and protein.

Furthermore, risk alleles of identified GWAS risk SNPs were also studied for their association with RNA expression (Table 4). While expression differences were often consistent in different brain regions within carriers of a certain risk allele, they did differ across studied SNPs, even within one region. While hypothalamus, cerebellum, putamen, and spinal cord were consistently associated with increased expression in variant carriers, mixed directions were seen in the amygdala, nucleus accumbens, caudate, and substantia nigra. In two of the more AD-relevant brain regions such as hippocampus and anterior cingulate cortex, variants were always associated with reduced expression. Furthermore, Lyssenko and colleagues noted that the GWAS SNPs toward the 5′ end of the gene tend to lower expression levels in variant carriers, while those toward the 3′ end show the opposite effect.[98]

The 5′ end near the promotor of the gene is known to generally carry more cis-acting regulatory elements than the 3′ end and thus, they speculate that these variants tend to disrupt the promotor. Additionally, they speculate that those toward the 3′ end may compromise ABCA7 activity, resulting in accumulation of ABCA7 substrate and, through a feedback loop, an up-regulation of *ABCA7* transcription.[98] Those mechanisms would partially explain the observed differential expression patterns.

To conclude, based on these findings, it is too early to say whether increased *ABCA7* expression may cause AD, *ABCA7* is upregulated as a consequence of the disease or a reduction is the culprit. The

TABLE 4 Differential *ABCA7* RNA expression in risk allele carriers of GWAS SNPs.

SNP	Risk allele	Risk allele frequency	OR	Anterior cingulate cortex*	Amygdala	Hypothalamus	Hippocampus	Cerebellum	Nucleus accumbens	Caudate	Putamen	Substantia Nigra	Spinal cord
rs11670349	T	0.15	1.09 (1.07–1.11)	–	–	=	–	=	–	=	=	=	=
rs11670373	T	0.15	1.09 (1.07–1.11)	–	–	=	–	=	–	=	=	=	=
rs72973561	T	0.19	1.06 (1.04–1.08)	–	–	=	–	=	=	=	=	=	=
rs111278892	G	0.16	1.10 (1.08–1.12)	–	–	=	–	=	–	=	=	=	=
rs3795065	C	0.34	1.08 (1.06–1.09)	=	=	=	=	+	+	+	+	+	+
rs3764645	A	0.52	1.07 (1.06–1.09)	=	=	=	=	+	=	=	+	=	+
rs3752231	T	0.25	1.09 (1.07–1.10)	–	–	=	=	=	=	=	=	=	=
rs72973584	T	0.12	1.10 (1.08–1.13)	–	–	=	–	=	–	–	=	–	=
rs3764650	G	0.09	1.10 (1.08–1.13)	-	=	=	=	=	=	=	=	=	=
rs12151021	A	0.32	1.10 (1.09–1.12)	=	=	+	=	+	+	=	=	=	+
rs9282562	C	0.11	1.12 (1.10–1.15)	–	–	=	–	=	–	–	=	=	=
rs3752241	C	0.83	1.08 (1.06–1.10)	=	=	=	=	=	=	+	=	=	=
rs3752246	G	0.17	1.11 (1.09–1.12)	=	+	+	=	+	+	+	+	=	+
rs4147929	A	0.17	1.10 (1.08–1.12)	=	+	+	=	+	+	+	+	=	+

Note: Differential ABCA7 RNA expression in risk allele carriers of GWAS SNPs in different brain regions. "+" indicates expression is increased in AD patients (blue), "-" signifies reduction (red). "=" mean no significant differences were detected. Results were based on Lyssenko et al. (2022)[98] with the exception of rs3764650* in the anterior cingulate cortex, from Vasquez et al. (2013).[99] Risk allele frequency was determined in non-Finnish Europeans in gnomAD v4.0.0, and odds ratio (OR) was determined in the meta-analysis of Bellenguez et al. (2022).[9]

enrichment of PTC mutations in patients, as well as findings in different in vitro and in vivo studies detailed in the following section, do seem to suggest the latter two as the more probable mechanism.

5.4 | *ABCA7* isoform expression

In 2003, the first alternative *ABCA7* isoform was described, "type II," a splice variant with 41 exons.[15] Due to faulty splicing, intron 6 retention is caused resulting in a PTC, and then a novel in-frame start codon, a few base pairs upstream of exon 7. These isoforms were found to display differences in tissue expression and subcellular localization. Type II was identified to be more highly expressed in lymphoid tissues. Type II was detected to be located primarily at the ER and be incapable of ApoA1-mediated lipid release, while type I resides at the plasma membrane. These differences suggest possible isoform-specific biological functions.[15] Nowadays, 17 additional isoforms are listed in GENCODE and the GTEx portal (accessed September 2023).[86,100] Expression patterns of these isoforms have not yet been investigated, nor has it been demonstrated if they form into (functional) proteins and what their biological relevance is. However, many of them, including type II, are predicted to be expressed at higher levels than the canonical isoform, across tissue and brain regions. Furthermore, the identification of undescribed alternative splice events in relation to PTC mutations, so called rescue splicing, or the expanded VNTR, suggests that we are currently only seeing the tip of the iceberg. Uncovering the full splice complexity of *ABCA7* could tell us more about its function and its impact on disease. Indeed, two TWAS (transcriptome-wide association studies) already uncovered differences in splicing between AD and control individuals in dorsolateral prefrontal cortex[101] and temporal lobe.[102]

6 | ABCA7 FUNCTION

ABCA7 has been suggested to play a role in multiple pathways. Through its homology with *ABCA1*, and transporter function, it has been suggested as a lipid transporter that can regulate lipid metabolism, while through homology with the *Ced-7*, a *C. elegans* gene involved in engulfment of cell corpses during programmed cell death, it has been linked to phagocytosis.[103] Through these functions ABCA7 has been linked to amyloid processing and deposition too. We will shortly go over these suggested functions and studies supporting it.

6.1 | Lipid metabolism

The brain is a very lipid-rich organ, with lipids playing crucial roles in development and functioning.[104] The lipid composition in the two layers of the plasma membrane is vastly different with an enrichment of in phosphatidylserine, phosphatidylethanolamine, and phosphatidylinositol on the inner leaflet and phosphatidylcholine and sphingomyelin on the outer leaflet. These lipids can furthermore assemble in lipid rafts, which have crucial functions in signal transduction and cell adhesion.[105] Dysregulation of lipids can thus have detrimental effects, and has been identified in early stages of AD.[105,106] Similarly to ABCA1, ABCA7 plays a role in export of cholesterol and phospholipids to acceptor molecules such as ApoA-I.[14-18] ABCA7 was also suggested to regulate efflux of cholesterol across the blood-brain barrier (BBB) and to the cerebrospinal fluid, through transfer to acceptor molecules, although further studies are needed to confirm these findings.[107,108] Moreover, ABCA7 has been suggested to play a role in lipid flipping and can, therefore, change the local membrane lipid environment (Figure 4).[13,109] The lipid environment in turn has been suggested to affect ABCA7 function as well, as cholesterol depletion led to upregulation of ABCA7, likely through the sterol regulatory element-binding protein 2 (SREBP2) pathway and the membrane environment modulated ABCA7 activity in a species-dependent manner.[13,110] ABCA7 can impact lipids as is shown in *Abca7* knock-out (KO) mice with an the altered brain phospholipid profile[111] and lowered cholesterol and HDL serum in female mice.[112] Moreover, in the thymus and antigen presenting cells in KO mice, lipid rafts were also found to be altered.[113] In *Abca7* heterozygous knockout mice, a change in fatty acids profiles was noted.[114] However, in contrast with these findings, in *Abca7* deficient primary macrophages no changes in cholesterol and phospholipid efflux were observed.[112]

While most of these findings were established in vitro and in vivo, an effect of ABCA7 on lipid profiles was also noted in humans. Using liquid chromatography coupled-mass spectrometry (LC-MS/MS) in plasma an altered lipid profile was detected in AD patients and *ABCA7* GWAS SNP (rs3752246 or rs4147929) carriers had a differential association with more than half of the detected diacylglycerol and phosphatidylinositol lipids.[106] In a single-nuclei study in *ABCA7* PTC mutation carriers, altered gene expression was found in genes involving lipid metabolism, mitochondrial function, DNA damage and NF-kB signaling in excitatory neurons when compared to healthy controls.[91] Changes in lipid profile were further confirmed when MS was performed on prefrontal cortex and iPSC-derived neurons with an upregulation of triacyl glycerides and changes in phospholipid species, especially phosphatidylcholine.[91] In contrast, Picataggi and colleagues in vitro detected less phosphatidylcholine in ABCA7-mediated HDL than ABCA1-HDL.[107] Von Maydell and colleagues suggested that lipid dysregulation in PTC mutation carriers could be the upstream mechanism resulting in the other detected dysregulated pathways.[91] They hypothesized that different phospholipid sensing and synthesis could cause accumulation of triglycerides intracellularly. Neurons have limited storage capacity in lipid droplets compared to glial cells, causing fatty acid oxidation and mitochondrial stress, which in turn could cause the formation of ROS (reactive oxygen species) that lead to DNA damage and inflammation.[91] In a study in flies, ROS were stated to cause increased lipid synthesis in neurons.[115] To avoid neurotoxicity, lipids were then transferred via APOD or APOE to glial cells where they were sequestered in lipid droplets. Fly ABCA1 and ABCA7 orthologues were found to be crucial for lipid droplet formation, and when the process was disrupted, neurodegeneration was observed.[115] One group formulated the altered lipidostasis hypothesis that states that ABCA7

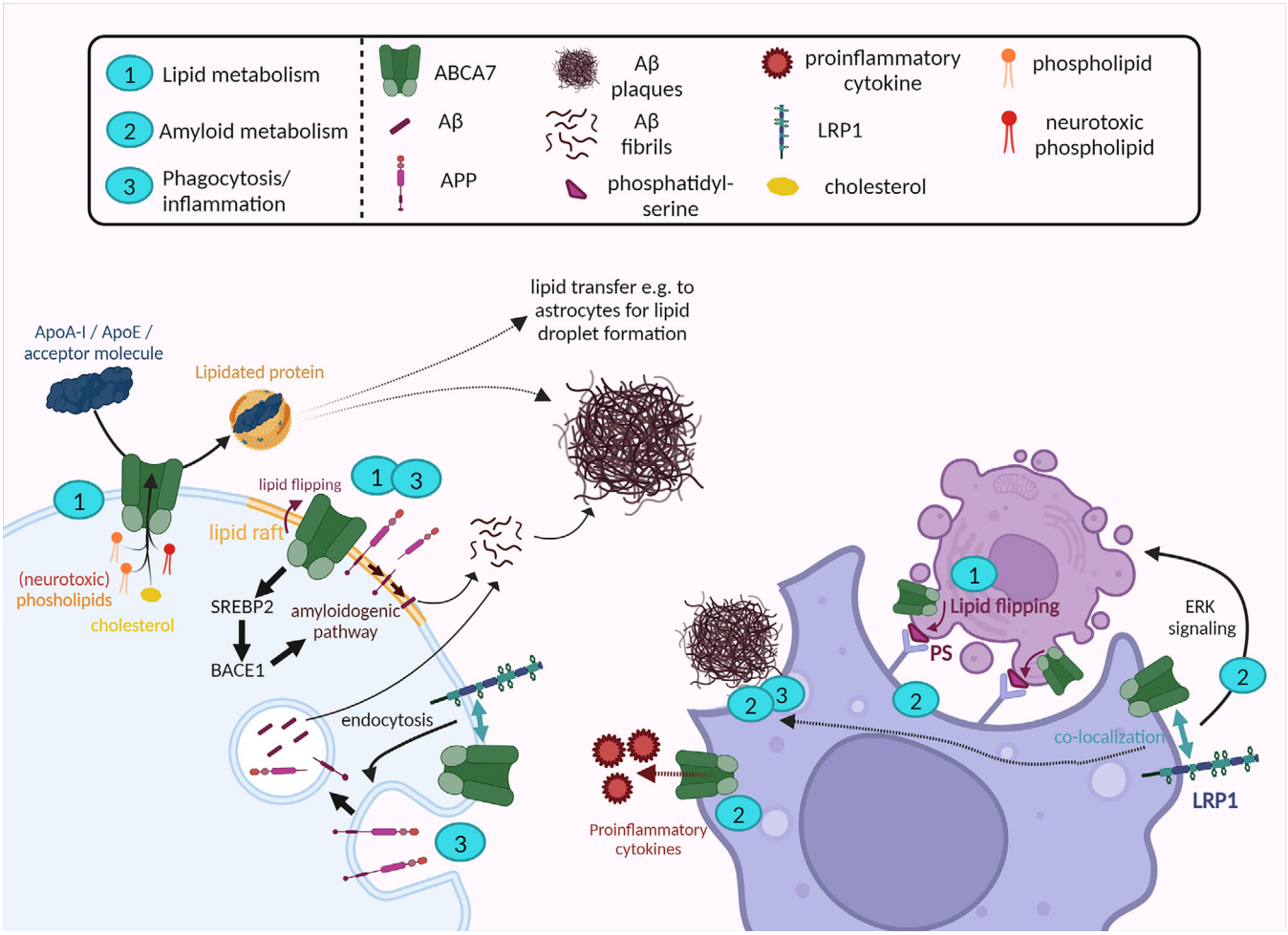

FIGURE 4 Potential ABCA7 functions. ABCA7 has mainly been linked to roles in lipid metabolism (1), phagocytosis (2), and amyloid metabolism (3). The suggested functions in several cell types but mainly neurons (blue) or phagocytosing cells such as microglia (purple) are shown and described from left to right. ABCA7 plays a role in lipidating acceptor molecules such as ApoA or ApoE with cholesterol or (neurotoxic) phospholipids. These molecules can help with lipid transfer, for example, to astrocytes for lipid droplet formation, or with Aβ clearance. ABCA7 can also affect Aβ processing by stimulating the amyloidogenic pathway through the SREBP2 pathway and BACE1 expression, or by changing membrane microenvironment and lipid rafts with lipid flipping. It can furthermore affect APP endocytosis through interactions with LRP1. In microglia, it may affect expression of proinflammatory cytokines and phagocytosis of Aβ peptides and apoptotic cells by stimulating ERK signaling after co-localization with LRP1. It furthermore can affect apoptotic cell clearance by increasing phosphatidylserine at the outer leaflet with lipid flipping

might be responsible for the efflux of a neurotoxic lipid.[85] When this currently unknown lipid is not sufficiently exported, either due to increases in lipid concentration or ABCA7 disruptions by mutations for example, this can lead to disease.[85]

6.2 | Phagocytosis

Phagocytosis by microglia plays an important role in the immune system of the brain and neuroinflammation. The role of the immune system in AD is a double-edged sword and still under debate, as excessive inflammation is detrimental in the disease while an oppression of clearance of apoptotic cells and amyloid-β (Aβ) is damaging as well.[116] In mouse fibroblasts *Abca7* depletion impaired phagocytosis.[110] In mouse macrophages, the same finding was observed in vivo and in vitro when *Abca7* was depleted, but not with *Abca1*, suggesting that ABCA1 does not play a role in phagocytosis.[117] In vitro, LRP1 stimulation by apoptotic cells both led to localization with ABCA7, and an increase in extracellular ERK signaling, known to play a role in phagocytosis (Figure 4).[118] *Abca7* deficiency decreased trafficking of both ABCA7 and LRP1 to the membrane, abolishing ERK signaling.[118] In *Abca7* haplodeficient mice, partial ABCA7 deficiency compromised microglial proinflammatory responses by impairing CD14 expression in the brain upon acute neurotoxic lipopolysaccharide stimulation (Figure 4).[114] These mice also had altered endosomal morphology in microglia. Lipid metabolism and phagocytosis are furthermore not two completely separate pathways. Statins that reduced cellular lipids caused an upregulation of *ABCA7*, followed by increased phagocy-

tosis in vitro.[119] Moreover, ABCA7 can influence composition and asymmetric distribution of the lipid bilayer, such as increased lipid flipping of phosphatidylserine from the cytoplasmic to the extracellular leaflet, creating an "eat-me" signal in apoptotic cells (Figure 4).[13,109] An enrichment of phosphatidylserine on the extracellular surface has been linked to phagocytosis and assembly of phagocytosis-associated protein at the membrane.[120,121] Impairment of ABCA7, thus, could evolve in reduced phagocytosis of apoptotic cells, increasing inflammation. Moreover, a role in phagocytosis has also been implicated due to the observed effect of ABCA7 deficiency on amyloid deposition in the brain.

6.3 | Contribution to amyloid deposition

In AD mouse models, *Abca7* KO reduced uptake of both $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ was observed in microglia and macrophages,[122] and increased amyloid plaques in the brain.[123] One study showed no differences in soluble $A\beta$ in micro dialysis studies, suggesting that ABCA7 mainly affects clearance of aggregated $A\beta$.[111] In *Abca7*$^{+/-}$ mice, disturbed endosomal-lysosomal trafficking was observed, accompanied by abnormal accumulation of $A\beta$.[114] In two papers, ABCA7 was also suggested to play a role in $A\beta$ efflux at the BBB, which needs to be further investigated.[108,124] Besides amyloid clearance, ABCA7 has proposed functions in APP processing and $A\beta$ production. While α-secretase functions in non-raft regions in the plasma membrane, β- and γ-secretase, which produce neurotoxic $A\beta$ peptides, are localized in the cholesterol-rich lipid rafts.[125] Changes in lipid raft composition due to ABCA7 dysfunction, can thus affect APP processing (Figure 4). Furthermore, in AD mice models with *Abca7* KO, higher levels of SREBP2 were found and in primary mouse neurons increase in *BACE1* expression along with $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ levels.[111] These findings suggest that $A\beta$ production could be dysregulated due to changes in the SREBP2/BACE1 pathway (Figure 4). ABCA7 can also regulate APP endocytosis, and LRP1 signaling to the membrane, which both further influences APP processing (Figure 4).[126,127] Finally, *ABCA7* PTC carriers have been found to have high amounts of cerebral amyloid angiopathy, characterized by accumulation of amyloid in blood vessels and increases in CSF amyloid biomarkers.[71,73]

APOE is the main cholesterol transporter in the brain, transporting cholesterol to lipid droplets and the BBB, but it can influence amyloid burden too (Figure 4) (42,43). Lipidated ApoE stimulates $A\beta$ clearance, which is less efficient in the ApoE4 variant than ApoE3 or ApoE2.[128] Interaction between ABCA7 and APOE has been suggested, both genetically due to its synergistic effects on memory or AD risk,[45,56] and on a molecular level where ABCA7 can impact lipidation of APOE.[129] *APOE4* is strongest risk factor for (sporadic) AD in populations of European ancestry, occurring in up to 15% of non-Finnish Europeans (Table 2).[130] In African-Americans the frequency is even higher, although its effect size has been estimated to be smaller, with *ABCA7* suggested to be a bigger risk gene (Table 2).[49,130] In an East-Asian population APOE4-related AD risk is higher, but the risk allele was less prevalent (Table 2).[131] Other populations have been studied less extensively.

6.4 | Similarities and differences between AD risk genes ABCA7 and ABCA1

PTC mutations in *ABCA1* had long been identified as causal for Tangier disease or a familial HDL deficiency,[132] but recently a common SNP was found to be associated with AD in a GWAS analysis.[9] Rare PTC and missense variants in *ABCA1* were associated with AD too in a large burden analysis.[63] The identified common SNP rs1800978 had a smaller effect size compared to *ABCA7* GWAS SNP rs12151021, but the rare variants had a bigger effect size but lower frequency than those in *ABCA7* in a cohort of European ancestry (Table S4).[9,63] Besides a high sequence homology, there is also some functional overlap between the two proteins. ABCA1 is a lipid exporter as well, lipidating acceptor molecules such as ApoA-I and ApoE, and its deficiency too has been implicated to cause increased amyloid pathology.[133] However, differences in preferred substrates and efficiencies have been noted with ABCA1 mainly being suggested as a cholesterol exporter to lipid-poor particles, and ABCA7 having a greater affinity for phospholipids.[16,17,107] Cholesterol depletion in model systems, led to an upregulation of *ABCA7* but downregulation of *ABCA1*, possibly due to differential transcriptional regulation through the SREBP and liver X receptor (LXR) receptor pathways respectively.[110,134] ABCA1 plays a role in the transport of cholesterol through the blood brain barrier (BBB), while for ABCA7 only few studies have suggested a possible role on cholesterol or $A\beta$ efflux, indirectly through acceptor molecules, at the BBB.[108,124] Finally, although *ABCA1* deletions in mice and deficiency in humans have been associated with increased neuroinflammation, likely through effects of cholesterol efflux, a direction function and possible role in phagocytosis by microglia and macrophages, such has been identified for ABCA7, has not been noted.[135] Different roles of the two proteins are further emphasized by differences in most prominent expressing cell types and (brain) tissues (Table S4). While *ABCA7* expression has mainly been implicated in neurons and microglia, and in lesser extent astrocytes, *ABCA1* expression has been detected mainly in astrocytes, oligodendrocyte precursor cells (OPCs), and endothelial cells, with astrocytes being the most important cell type for cholesterol synthesis in the brain.[9,87,89–91] In the brain, a high expression is found in the anterior cingulate cortex (ACC), basal ganglia, thalamus, and midbrain, as opposed to cerebellum or choroid plexus.[86,87] While in AD patients an overexpression of *ABCA7* was noted in the DLPFC alone in the Agora Knowledge Portal (accessed via https://agora.adknowledgeportal.org/ in February 2024), while *ABCA1* is significantly overexpressed with a log2-fold change between 0.17 and 0.58 in the ACC, inferior frontal gyrus, posterior cingulate cortex, parahippocampal gyrus, superior temporal gyrus, and temporal cortex.

Thus, despite similarities in structure and lipid function, differences in expression, substrates, phagocytotic function, and ABCA7's lack to

compensate for the effect of Tangier's disease, emphasizes important differences between the two.

7 | SUMMARY AND FUTURE DIRECTIONS

Since its first association with AD in GWAS studies, additional common GWAS SNPs, a common VNTR expansion, rare PTC variants and rare damaging missense variants have been discovered in *ABCA7*. These variants have been mainly studied in Europeans, and to lesser extent, African American cohorts, while the presented frequencies of these mutations in individuals from other ancestries emphasize that *ABCA7* is a risk factor in other ancestries too; thus, further ancestry-wide investigation is warranted. This is especially true for the VNTR expansion which has so far only been characterized in a Belgian cohort.[38] The recent protein structure determination of ABCA7 reveals protein characteristics and domains.[13] We described a lower frequency of missense variants in the RD domains, and TMD1 suggesting that these domains are less tolerant to variation. While for missense mutations different mode-of-actions could be at play, with mislocalization to the ER discovered for a group of them, for PTC variants and VNTR expansion, haploinsufficiency is the most likely cause of disease. On the role of *ABCA7* expression in brain generally, and in AD specifically, many conflicting studies exist. Thus, we cannot exclude that increased *ABCA7* expression is harmful in disease, as supported by increased expression in few brain regions in AD and GWAS risk SNPs. It is also possible that during disease ABCA7 is upregulated as a response to neuropathological lesions, and mutation carriers get sick due to lack of functional protein. However, the presence of the PTC mutations, in combination with in vitro and in vivo studies, and backed up by other GWAS risk SNPs, do support the hypothesis that reduction in ABCA7 is the pathological mechanism. Further studies into expression of *ABCA7* RNA and protein in AD are needed to answer this question. Expression in PTC mutation carriers can further be modified by NMD escape and rescue splicing, possibly partially explaining the wide variability in disease severity and penetrance observed in PTC carriers. Studying the effect on protein expression, and presence of truncated proteins, would further improve our understanding of disease mechanisms in PTC carriers. Moreover, characterization of other modifiers that can influence risk for the two other mutation groups as well is warranted if we want to provide disease prognosis. Furthermore, the identification of splice events in PTC carriers (rescue splicing) and VNTR expansion carriers (exon 19 skipping), suggest that *ABCA7* splicing complexity is higher than our current understanding of it and should be investigated in more detail. Especially the presence of isoforms and isoform-specific functions are a priority.

ABCA7 has been proposed to have functions in lipid metabolism, phagocytosis, and the amyloid pathway, but is still not fully comprehended. Although research generally supports the function in lipid metabolism, additional research into the exact substrates of ABCA7 is needed, especially in human iPSC cells and brain tissue. It should also be studied how ABCA7 deficiency alters lipid profiles in these and the exact consequences and roles in AD. An effect of ABCA7 deficiency on phagocytosis has also been shown, for example, through ERK signaling or CD14-mediated pathways. Lipid metabolism and phagocytosis functions of ABCA7 are not fully independent of each other and can both further influence amyloid deposition or APP processing. In order to understand which treatments could be beneficial in mutation carriers, a better understanding of the functions, possible therapeutical targets, and role in AD of ABCA7 is necessary. Possible directions could be PTC readthrough drugs for nonsense mutations, anti-sense oligonucleotide treatment to stabilize beneficial and functional (rescue) isoforms or destabilize deleterious ones, expression-altering therapies, or immune-modulating drugs.

Finally, the functions of ABCA7, consequences of mutations and differences in (isoform) expression could be cell type specific and difficult to fully comprehend using bulk analysis. With the emergence of single-cell approaches, these difficulties can be overcome and hopefully help expand our understanding of ABCA7 up to the point where we can accurately diagnose, predict, and treat the disease in mutation carriers.

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CONFLICT OF INTEREST STATEMENT

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SUPPORTING INFORMATION

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