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ABCA7, a Genetic Risk Factor Associated with Alzheimer's Disease Risk in African Americans

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Abstract

African American/Black adults are twice as likely to have Alzheimer's disease (AD) compared to non-Hispanic White adults. Genetics partially contributes to this disparity in AD risk, among other factors, as there are several genetic variants associated with AD that are more prevalent in individuals of African or European ancestry. The phospholipid-transporting ATPase ABCA7 (*ABCA7*) gene has stronger associations with AD risk in individuals with African ancestry than in individuals with European ancestry. In fact, *ABCA7* has been shown to have a stronger effect size than the apolipoprotein E (*APOE*) $\epsilon 4$ allele in African American/Black adults. ABCA7 is a transmembrane protein involved in lipid homeostasis and phagocytosis. ABCA7 dysfunction is associated with increased amyloid-beta production, reduced amyloid-beta clearance, impaired microglial response to inflammation, and endoplasmic reticulum stress. This review explores the impact of ABCA7 mutations that increase AD risk in African American/Black adults on ABCA7 structure and function and their contributions to AD pathogenesis. The combination of biochemical/biophysical and 'omics-based studies of these variants needed to elucidate their downstream impact and molecular contributions to AD pathogenesis is highlighted.

Keywords

African Americans; Alzheimer's disease; Blacks; health status disparities; human ABCA7 protein; proteomics; single nucleotide polymorphism; subfamily A of ATP binding cassette transporter

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INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease that leads to memory loss, cognitive decline, and activated immune response due to the increased presence of amyloid- (A) plaques and tau tangles in the brain [1]. In the United States, 6.2 million people are diagnosed with AD [2]; however, AD affects different racial/ethnic minorities disproportionately. AD occurs twice as frequently in African American/Black and one and a half times as frequently in Hispanic than non-Hispanic White adults [2–4], while it occurs less frequently in Asian American adults [5, 6]. Increased prevalence of AD in African American/Black adults could be related to differences in socioeconomic, comorbidities, and molecular factors between African American/Black and non-Hispanic White adults. For example, socioeconomic factors including education level and quality of education, local area/neighborhood, socioeconomic status, healthcare access, environmental factors, and willingness to seek care and treatment are not equitable between racial/ethnic subgroups [4, 7–10]. Comorbidities that increase AD risk such as hypertension and type 2 diabetes mellitus are also more prevalent in African American/Black adults than non-Hispanic White adults [5, 11–13].

Frequency and conferred risk of AD susceptibility genetic variants are also known to differ across racial/ethnic groups. It is important to note that existing genetic studies of AD have used both self-reported race/ethnicity and ancestry to distinguish racial/ethnic groups, which classify individuals based on distinct qualities. Racial groups are based on physical characteristics and skin color, which in turn influence many aspects of an individual's life, while ethnicity groups individuals by a shared culture or language, though these terms are often used together or interchangeably [14–16]. Ancestry, on the other hand, is the genetic origin of a population, which does not reflect the socioeconomic impact encompassed under self-reported race/ethnicity [15, 17] and does not always correlate well with self-reported race/ethnicity [18]. In this review, we will use self-reported racial/ethnic groups, though previous studies of ancestry will be referenced to comprehensively review relevant literature. In non-Hispanic White adults, the genetic factor that causes the greatest risk for AD is the apolipoprotein E (*APOE*) ϵ 4 allele. *APOE* ϵ 4 causes 20–50% higher AD risk in non-Hispanic White adults [19]. This risk does not replicate in African American/Black adults [20, 21]. On the other hand, mutations in the phospholipid-transporting ATPase *ABCA7* (*ABCA7*) gene have stronger associations with AD risk in African American/Black adults than non-Hispanic White adults [22–24]. The effect size of *ABCA7* single nucleotide polymorphism (SNP) rs115550680 is comparable to that of *APOE* [19, 23]. Furthermore, mutations specific to or more frequent in African American/Black adults in *ABCA7* have been discovered [3, 25].

ABCA7 is a transmembrane protein responsible for moving lipids across the cell membrane using energy from adenosine triphosphate (ATP) and it is involved in three major cellular processes: cholesterol metabolism, phospholipid regulation, and phagocytosis [26–29]. *ABCA7* has implications in AD pathogenesis and is involved in $A\beta$ clearance and amyloid- β protein precursor ($A\beta$ PP) transport [23, 25, 30]. Mutations in the *ABCA7* gene may disrupt one or more of the protein's functions and therefore contribute to the development of AD

neuropathology. However, not all mutations are equal and the specific changes to *ABCA7* function due to these AD risk mutations remain unknown. These changes are particularly important to understand due to the strong effects of *ABCA7*-conferred AD risk for African American/Black adults. Several recent reviews have discussed *ABCA7*'s involvement in AD [25, 29, 31, 32], though only one [33] has previously examined this relationship in the context of African American/Black adults, which focused primarily on cognitive impacts of *ABCA7* variants. This review, on the other hand, will specifically explore *ABCA7* genetic variants which increase AD risk in African American/Black adults and their contributions to AD pathogenesis via impacts on *ABCA7* structure and function that influence downstream cell processes. Though we focus on *ABCA7* variants found in African American/Black adults throughout this review, we note here that much of the research presented about mechanistic roles of *ABCA7* in AD is in other racial/ethnic groups, as such investigations in African American/Black adults are severely lacking.

ABCA7 AD GENETIC RISK VARIANTS IN AFRICAN AMERICANS

Mutations in *ABCA7* have been associated with increased AD risk in various racial/ethnic groups, including European [34–36], Latin American [37], non-Hispanic White [23, 38], and African American/Black groups [19, 23, 25, 39, 40] (Table 1). Some of these mutations increase AD risk in multiple racial/ethnic groups, such as rs3764650, while others are specific to a given group, such as rs3764647 and rs115550680. Additionally, several of the risk mutations identified across groups have different effect sizes and/or frequencies. As a whole, *ABCA7* risk variants have a greater impact on odds of AD diagnosis in African American/Black adults compared to other racial/ethnic groups [41]. *ABCA7* variants have been found to increase AD risk 1.8-fold in individuals with African ancestry and 1.1–1.2-fold in individuals with European ancestry [23]. Interestingly, one *ABCA7* variant (rs72973581) was predicted to be a potential protective factor against developing AD in a cohort of elderly adults from British and North American ancestry [42]. Further studies are needed to elucidate how this variant can impact *ABCA7* function.

ABCA7 mutations affecting African American/Black adults can be classified into common mutations with smaller effect sizes and rarer mutations with larger effect sizes. The more common mutations occur in ~10–25% of individuals with normal cognition and ~15–30% of individuals with AD and increase AD risk by up to 50% (Table 1). Most are missense mutations resulting in a single amino acid substitution in the *ABCA7* protein. This includes rs3764650, located in intron 13 of the *ABCA7* gene, which increases AD risk by 10–20% in African American/Black adults [39], though it has a larger effect size in non-Hispanic White [23, 38] and Colombian adults [37]. This variant only showed a trend of association with AD in a study of >500 African American/Black adults with normal cognition or who had AD, though it was in linkage disequilibrium with rs3764647, which did have a significant association with AD [40]. Higher percentages of African ancestry at this locus were associated with AD [24]. Rs3764647 increases AD risk by 30–50% (odds ratio (OR) = 1.32–1.47) [25, 39, 40], while rs3752232, which is in linkage disequilibrium with rs3764647 [40], increases AD risk by 25% in African American/Black adults (OR = 1.24) [43]. It is possible that the difference in conferred risk between these two SNPs, despite being in linkage disequilibrium, is due to the relatively small sample sizes of the supporting

studies (538 [40] to 1,929 [43]). Another missense mutation, rs3752246, which is in linkage disequilibrium with rs3764650 [44] and rs4147929 [35], was associated with AD (OR = 1.15) in a meta-analysis of four large genome-wide association study (GWAS) datasets performed by the Alzheimer Disease Genetics Consortium that included data from >20,000 individuals of multiple racial backgrounds [45]; however, rs3752246 was not associated with AD in two studies of >500 African American/Black adults with normal cognition or who had AD [40]. Lastly, rs59851484 was recently associated with a 50% increase in AD risk in African American/Black adults (OR = 1.49) [43].

On the other hand, the rarer mutations tend to occur in < 1% of individuals with normal cognition and < 2% of individuals with AD but increase AD risk by > 70% (Table 1). This group includes rs3752239, which increases AD risk 4x (OR = 4.06) [40]. Interestingly, the C allele of this SNP that is associated with AD risk in African American/Black adults has been reported to have a protective effect against AD in non-Hispanic White adults [46]. Rs115550680 has also been associated with AD in African American/Black adults, with an effect size similar to that of the *APOE* ϵ 4 allele (OR = 1.79) leading to a 70–80% increase in AD risk [19, 23]. This group also includes the frameshift mutations rs142076058 and rs567222111, both of which more than double AD risk in African American/Black adults (OR = 2.13 and 2.42, respectively) [25, 43]. Rs142076058 occurs more frequently in African American/Black adults than in non-Hispanic White adults [25].

CONTRIBUTIONS OF ABCA7 VARIANTS TO AD PATHOGENESIS

The potential contributions of these *ABCA7* variants to AD pathogenesis are discussed in this section and are summarized in Fig. 1.

Impacts on ABCA7 structure

ATP-binding cassette (ABC) transporters are membrane-associated machines that transport a wide variety of substrates across extra- and intracellular membranes, including metabolic products, lipids, and sterols, as well as drugs [27, 47]. In general, ABC transporters contain two highly conserved nucleotide-binding domains (NBDs) which are connected to two integral transmembrane domains (TMDs), each containing 6–10 transmembrane-spanning helices (Fig. 2) [47]. High-resolution structures of ABC transporters have provided insight into how these proteins use ATP to transport molecules out of the cell [48–50]. ABC transporters utilize energy from intracellular ATP that induces conformational changes allowing various molecules, such as lipids or cholesterol, to be transported from the cell membrane to bind to extracellular proteins including apolipoprotein A-I (apoA-I) or apoE [51, 52].

ABC transporter subfamily A (ABCA) transporters are distinct from other ABC subfamilies because they possess two large extracellular domains (ECDs) that are often glycosylated [53]. Current information about ABCA7 comes from our understanding of its closest homologue, ABCA1, which has been studied extensively and serves as the prototype for other ABCA transporters [54, 55]. The presence of ECD1 and ECD2 in ABCA1 and ABCA7 is an essential factor in their function due to their interactions with apolipoproteins (Fig. 2). Sequence alignment of the ECD1 domains between ABCA1 and ABCA7 shows

39.97% homology (Fig. 3). Structural/functional studies of ABCA1 show that these domains contain two intramolecular disulfide bonds (Cys75 and Cys309) needed for apoA-I-dependent cholesterol efflux [56]. ApoA-I is predicted to directly bind to ABCA1, which triggers signal transduction pathways to mediate lipid transport [57–59]. Nagao et al. (2012) demonstrated that the intracellular hydrolysis of ATP in both of the NBDs of ABCA1 induces conformational changes that signal the ECDs to bind apoA-I [60]. This conformational change couples ATP hydrolysis with apoA-I binding and cholesterol efflux. Despite the extensive information on ABCA1, the precise molecular details of its interaction with apoA-I are unknown. However, this interaction is necessary for apoA-I's downstream signaling to activate cellular cyclic adenosine monophosphate (cAMP) signaling and mediate cellular lipid efflux [61].

Mutations in *ABCA1*, including R587W, W590S, Q597R, C1477R, and S1506L, disrupt its interaction with apoA-I and have been linked to a rare lipoprotein metabolism disorder called Tangier disease [62–64]. Several of these mutations (R587W, W590S, Q597R) occur within the ECD1 of ABCA1, which spans residues 43–639. The W590S mutation is located at the end of ECD1, in close proximity to the cellular membrane. All three of these mutations reduce apoA-I-mediated lipid efflux and corresponding high-density lipoprotein (HDL) generation in human embryonic kidney (HEK) 293 cells [62]. Interestingly, the R587W and Q597R mutants were retained in the endoplasmic reticulum (ER), while the W590S mutant still localized to the plasma membrane similar to wild-type ABCA1, suggesting that the impact of the W590S mutation was functionally distinct from that of the R587W and Q597R mutations [62].

The ECDs of membrane proteins serve a distinct purpose to allow cell-cell communication. It is unclear why two missense mutations (rs3752232 and rs3764647 [40]) in the ECD1 of ABCA7 are strongly associated with AD in African American/Black adults, or why the rs72973581 variant, also located within ECD1, seems to have a protective effect [42]. Interestingly, the mutations identified in *ABCA1* that disrupt binding of apoA-I are conserved in *ABCA7*. These mutations seem to cluster toward the end of ECD1. The missense *ABCA7* mutations, however, are situated away from this small cluster of *ABCA1* mutations, which appears to be a binding pocket and may alter ABCA7's ability to bind lipid substrates instead. Rs3752232 causes a threonine to alanine substitution at position 319, and rs3764647 leads to a histidine to arginine substitution at position 395. Neither of these mutations is predicted to have harmful functional effects, such that they may contribute to AD risk via more subtle effects on ABCA7 protein's structure or function [40]. Our recent study of rs3752232 supports this hypothesis, as we found that this mutation had subtle structural effects on ABCA7 protein's ability to bind various lipids such as phosphatidylinositol 4,5-bisphosphate (PIP₂) [65]. Another missense mutation located in ECD2, rs3752246, results in a glycine to alanine substitution at position 1527 and is also not predicted to affect ABCA7 protein's function [66]. In the first intracellular domain of the protein, rs3752239 leads to a missense mutation changing an asparagine to a threonine at position 718 [40]. This mutation could lead to potentially damaging effects on the protein, though this remains to be investigated. Additionally, a low-frequency missense variant, rs72973581 (minor allele frequency = 4.3%), has been reported to confer modest but statistically significant protection against AD ($p=0.024$, OR = 0.57, 95% confidence interval

= 0.41–0.80) [42]. This variant results in a glycine to serine substitution at position 215 (G215S), also located within ECD1. Taken together, mutations within the ECDs likely affect which lipid substrates get transported out of the cell to apolipoproteins. The mechanistic details of this function are critical to understand since lipoproteins such as apoA-I and apoE are cholesterol/lipid delivery carriers and alterations in their cargo due to *ABCA7* variants can have significant downstream effects that promote AD.

On the other hand, *ABCA7* frameshift mutations rs142076058 and rs567222111 are also associated with AD and cause significant structural changes to the *ABCA7* protein. Rs142076058 is a 44 bp deletion that causes a frameshift (Arg578Alafs) and premature termination codon, producing a truncated protein missing many TMDs and both NBDs, likely with significant functional impact [3]. Rs567222111 leads to an 11 bp deletion and frameshift (Leu396fs) and is also hypothesized to lead to *ABCA7* protein loss-of-function [43]. It is also possible that the shortened transcripts resulting from both of these mutations could undergo nonsense-mediated decay, which may be phenotypically comparable to a knockout, or lead to significantly decreased *ABCA7* protein levels as have previously been associated with AD [25, 31, 67].

Impact on *ABCA7* functions

Lipid metabolism and transport—*ABCA7* is predicted to play a large role in regulating lipid metabolism and transporting newly synthesized lipids. *ABCA7* transports primarily phospholipids such as phosphatidylcholines and phosphatidylserines across the cell membranes to apolipoproteins apoA-I and apoE, though it has a lesser ability to transport cholesterol [29, 68]. While the full repertoire of *ABCA7* lipid substrates is not known, the preference of *ABCA7* lipid export differs from that of *ABCA1*. *ABCA7* preferred to export phosphatidylcholine (PC) > lysophosphatidylcholine (lysoPC) > sphingomyelin (SM) = phosphatidylethanolamine (PE), whereas *ABCA1* preferred to export PC >> SM > PE = lysoPC [69]. The authors of this study suggested that lysoPC export may be critical for *ABCA7* function in the brain. However, *ABCA7* expression is inversely correlated with cholesterol levels via the sterol regulatory element-binding protein 2 (SREBP2) pathway and reverse cholesterol transport [31]. The endogenous expression of *ABCA7* stimulates cholesterol efflux to apoE, in turn suppressing A β production [30]. When *ABCA7* function is lost (i.e., *ABCA7* knockout), disruption in the microglial A β clearance pathway leads to a cholesterol deficiency, triggering accelerated A β production both *in vitro* and *in vivo* [25, 31]. This accelerated A β production causes A β plaques to form [70]. Therefore, it is well established that loss of *ABCA7* function significantly increases the progression of AD [71].

Furthermore, decreased levels of *ABCA7* can also lead to altered lipid homeostasis, which is linked to ER stress. In mice, *ABCA7* knockout alters the brain phospholipid profile [71], decreases serum HDL and cholesterol levels [72], and disrupts lipid rafts on the plasma membrane [73]. *ABCA7* knockdown induced ER stress in cultures of primary mouse neurons, as observed by increased protein kinase R-like ER kinase (PERK) levels which then activates eukaryotic initiation factor 2 α (eIF2 α) [71]. EIF2 α phosphorylation increases β -secretase 1 (BACE1) expression, thus increasing A β generation [74]. Amyloid precursor

protein/presenilin-1 double mutant (*APP/PS1*); *ABCA7*^{-/-} mice also had increased levels of phosphorylated extracellular regulated kinase (ERK) in the brain, specifically in neurons, compared to *APP/PS1* mice [71]. These findings suggest that *ABCA7* deficiency, resulting from *ABCA7* knockout, may be associated with abnormal activation of the ERK pathway, which leads to declines in cognition and synaptic integrity [75].

Mutations in the structurally similar *ABCA1* protein disrupt efflux of phospholipids and cholesterol across cell membranes to extracellular apoA-I and apoE, and consequently HDL is unable to transport cholesterol and phospholipids from peripheral tissues, such as the heart, to the liver [29, 68]. Although *ABCA7* knockout mice had altered lipid levels as described above, apoA-I-mediated phospholipid and cholesterol efflux were not affected [72]. Our study of rs3752232 in HEK 293 cells yielded similar results, wherein subtle structural changes in the mutant *ABCA7* protein affected PIP₂ binding compared to wild-type *ABCA7*, yet the impact on the cellular proteome was minimal without evidence for effects on lipid transport proteins [65]. Taken together, these findings suggest that *ABCA7* risk mutations likely cause more significant functional changes outside of lipid metabolism and transport pathways that contribute to AD pathogenesis.

While rs3752246 is not predicted to adversely affect *ABCA7* function, an *in vitro* study of Chinese hamster ovary (CHO) cells transfected with the human APP expressing the Swedish mutation (*APP*_{Swe}) found that this SNP resulted in a modified form of *ABCA7* with altered function, due to the lack of a myristoylation site [76]. This led to increased Aβ production via increased BACE1 activity, likely due to protein-protein interactions favoring BACE1 activity resulting from the lack of the myristate (14-carbon saturated fatty acid) posttranslational modification at position 1527. Rs3752246 has also been associated with increased amyloid deposition in individuals with normal cognition or mild cognitive impairment (MCI) in two different cohorts [77, 78], further supporting that this mutation contributes to AD via amyloid pathology, particularly early in disease progression. Contrary to the *ABCA7* missense mutations, the frameshift mutations (rs142076058 and rs567222111) cause more significant protein structure changes that likely impair its lipid transport functions [3], thus leading to increased Aβ pathology and ER stress.

Immune functions and phagocytosis—*ABCA7* plays an important role in immune response and synaptic function (specifically regarding phagocytosis), which are both affected by AD. The normal function of *ABCA7* helps create the lipid rafts in the plasma membranes of antigen-presenting cells and thymocytes and promote phagocytosis of apoptotic debris [29]. In *ABCA7* knockout mice the disruption of lipid rafts in thymocytes and antigen-presenting cells occurs [31], causing the plasma membrane of these cells to be malformed and ineffective. *ABCA7* enhances phagocytosis [31, 79] and has high homology and similarity to the ABC transporter *ced-7* (*ced-7*) gene in *C. elegans* involved in apoptotic cell engulfment [29]. In mouse macrophages, *ABCA7* but not *ABCA1* knockout affected phagocytosis both *in vitro* and *in vivo* [31, 80]. *ABCA7* knockout creates AD-related phenotypes by decreasing phagocytic activity in macrophages, which results in larger A aggregates [25].

ABCA7 knockout and mutations have only shown modest effects on lipid homeostasis, as discussed in the previous section, suggesting that *ABCA7* likely affects AD risk via its phagocytic functions [81]. *ABCA7* is involved in the phagocytosis of apoptotic cells through the complement component 1q pathway in macrophages. Increased *ABCA7* expression increases microglial phagocytosis as well as A uptake [82]. On the other hand, *ABCA7* knockout mice showed reduced oligomeric uptake of A β proteins in macrophages and microglia, suggesting that suppression of *ABCA7* negatively affects the phagocytosis of A β aggregates [31, 83]. *ABCA7* knockdown in macrophages also results in incomplete phagocytosis of apoptotic debris [84]. Lack of clearance of such debris could potentially cause neuroinflammation and thus contribute to AD pathogenesis [29]. Additionally, *ABCA7* haplodeficient mice had reduced proinflammatory responses to acute inflammation in the brain due to impaired monocyte differentiation antigen CD14 (CD14) expression [67]. CD14 deficit also suppresses microglial uptake of A β [85–87]. When *ABCA7* haplodeficient mice were crossed with *APP^{NL-G-F}* mice, these mice had increased A β accumulation in the brain and enlarged endosomes in microglia [67]. The observed disruption of cell membrane organization likely alters microglial responses to acute and chronic brain inflammation. Though one study in *APP/PS1* mice found that *ABCA7* knockout had no effect on microglial activation [71], the majority of this research supports *ABCA7* microglial expression in AD [29, 82, 88] and provides further evidence that *ABCA7* deficiency (from either *ABCA7* knockout or haplodeficiency) contributes to AD pathogenesis.

The impact of *ABCA7* risk mutations on its immune and phagocytic functions has been understudied to date. Cukier et al. recently studied rs142076058 in induced pluripotent stem cells (iPSCs) differentiated into cortical neurons and microglia [89]. In this study, the iPSCs were derived from African American/Black individuals with AD with this deletion and matched cognitively normal individuals. The deletion led to reduced A β clearance in microglia, along with increased A β production in cortical neurons. Additionally, some SNPs (rs3752246, rs3764650) have been associated with increased brain amyloid deposition [77, 78, 90], which could be due in part to disruption of *ABCA7*'s phagocytic functions. Mechanistic studies are necessary to elucidate the specific functional consequences of these mutations that lead to the observed increase in amyloid deposition.

Contributions to cognitive decline

The role of *ABCA7* in cognitive decline has been studied in both mice and humans. *ABCA7* knockout mice had impaired spatial memory [25, 71] and were unable to develop short-term novel object recognition [25]. On the other hand, in the J20 mouse model of AD, *ABCA7* knockout did not cause any further cognitive deficits, despite doubling insoluble A β and plaques in the brain and reducing macrophage A β uptake by half [83]. These findings suggest that, in mice, *ABCA7* knockout exerts specific (i.e., related to spatial memory) though minimal effects on cognition.

The effects of certain AD-associated *ABCA7* SNPs on cognition and brain morphology changes associated with cognitive decline have been studied in humans, with rs3764650 being the most studied. In a study of the University of California, Los Angeles' Imaging

and Genetic Biomarkers for AD (ImaGene) cohort, rs3764650 was associated with increased atrophy in both hippocampus and cortex of individuals with normal cognition or MCI [91]. This mutation has also been associated with more postmortem amyloid plaques in the brain in a cohort of individuals with normal cognition, MCI, or AD [90] and faster rates of decline in memory in individuals with final diagnoses of MCI or AD [92]. Rs3764650 was also associated with lower baseline episodic memory scores in individuals with normal cognition over the age of 60 from the Personality and Total Health cohort in Australia [93], but not with decline in any cognitive domains by others [94]. It is important to note that these studies either were exclusively Caucasian or individuals of European ancestry [92, 93] or did not disclose racial/ethnic group information for their cohorts [90, 91].

Some cognitive effects of rs3764650 have only been identified in specific subpopulations. For example, this SNP resulted in a faster rate of cognitive decline only in individuals who were cognitively normal at baseline and became cognitively impaired longitudinally [95]. Additionally, rs3764650 was associated with cognitive decline in males [96]. Another study identified a significant *APOE-ABCA7* interaction associated with memory scores and default mode network activity, and showed that, of individuals with *ABCA7*rs3764650, *APOE* ϵ 4 carriers had worse memory scores than *APOE* ϵ 4 non-carriers [97]. However, both rs3764650 and rs3752246 have also been shown to be protective against memory decline in *APOE* ϵ 4-positive individuals [98]. *ABCA7* interactions with other genes such as clusterin (*CLU*) also impact cognition [99]. Specifically, interactions between *ABCA7* rs3764650 and *CLU* rs9331888 resulted in decreased functional connectivity in different brain regions in healthy, middle-aged adults [99]. Interestingly, rs3764650 may prevent older African American/Black adults with normal cognition from receiving the benefits of aerobic exercise on brain health and cognition [33, 100, 101]. Specifically, rs3764650 moderated the association between aerobic fitness and hippocampus-related generalization, measured by a concurrent discrimination and generalization task, in older African American/Black adults [100]. Overall, rs3764650 has generally minimal effects on cognition, though these effects may vary in subgroups based on genetics (*APOE* ϵ 4 positive versus negative), sex, and cognitive status [31].

The impact of other *ABCA7* SNPs on cognitive decline has been much less studied. The *ABCA7* SNP rs3752246 was associated with decreased gray matter density in dementia patients in a study of ~1500 individuals from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort [102]. The *ABCA7* SNP rs3752232 was associated with increased decline in visuospatial function, including working and visual memory, in a cohort of Korean AD patients [103], though this association has not been studied in African American/Black adults to date. This mutation did not correlate with other domains such as executive function, language, attention, and memory. Additionally, older African American/Black adults (ages 63–90 years) with rs11550680 had impaired functional connectivity of the medial temporal lobe with other brain regions and smaller anterolateral entorhinal cortices compared to matched African American/Black adults without the risk SNP [41]. The entorhinal cortex is among the first brain region to be affected by AD neuropathology and smaller volumes in this brain region have been associated with cognitive decline [104]. These differences may indicate an interaction between amyloid and tau pathology in the entorhinal cortex in individuals with this mutation, whereby increased amyloid leads to

increased tau pathogenesis in this region [33, 105]. However, further studies of these *ABCA7* SNPs are necessary to fully elucidate their contributions to cognitive decline, particularly in diverse racial/ethnic groups.

Summary

Overall, these findings implicate *ABCA7* variants in multiple aspects of AD pathogenesis, including cognitive decline, brain morphology changes, amyloid pathology, neuroinflammation, and ER stress (Fig. 1). Many of these roles contribute to or are enhanced by amyloid pathology, either directly or indirectly, but interestingly, no relation of *ABCA7*'s functions to tau pathology have been noted. These variants result in various structural and functional impacts on the *ABCA7* protein that likely contribute to AD pathogenesis by causing *ABCA7* dysfunction [25] (particularly of its phagocytic functions [35]), reduced levels or expression, or loss of function [25, 31, 67]. A recent comprehensive review of *ABCA7*'s role in AD focusing on data from genomics, transcriptomics, and methylomics similarly concluded that 'omics studies in humans point to *ABCA7* loss or partial loss as the mechanism behind its contribution to AD pathogenesis [31]. However, further mechanistic studies of *ABCA7* in AD are necessary to elucidate the specific roles of these variants.

Though significant research has been performed to identify and study the *ABCA7* SNPs associated with AD at the genetic level, it is necessary to study the functional impacts of these genetic variants, i.e., at the protein level. In their review, De Roeck et al. stated that studying these SNPs at the gene and transcript level does not provide "sufficient insight" into how *ABCA7* variants contribute to AD [31]. Other 'omics, such as proteomics, lipidomics, and metabolomics, can be useful to interrogate the downstream effects of genetic variants in both model systems and human biospecimens. As *ABCA7* has known lipid transport and metabolism functions *ABCA7* variants have the potential to alter the profiles of these molecules, which 'omics techniques are particularly poised to reveal. 'Omics analyses can provide valuable insight into genetic variants both on their own and in combination with other methods. For example, we recently applied both proteomics and structural methods to study rs3752232. Combining these analyses allowed us to determine that slight structural differences caused by this mutation may impact *ABCA7*'s ability to bind lipids such as PIP₂ and also that this mutation had subtle effects on the HEK 293 cell proteome [65]. Further 'omics studies of *ABCA7* AD variants are crucial to advance our understanding of the contributions of these variants to AD pathogenesis and AD risk in African American/Black adults.

Moreover, there is an overarching need for mechanistic studies of *ABCA7* variants in AD in African American/Black adults. Development of preclinical models, such as the iPSC model described by Cukier et al. [89], that allow study of *ABCA7* mutations in systems with African American/Black backgrounds will enhance understanding of the functional implications of these mutations and enable more informed studies in humans. Leveraging existing studies and biospecimens from African American/Black adults for 'omics and other mechanistic studies of *ABCA7* variants is also a key step to address this need. Recent studies have made significant efforts towards recruitment of individuals from underrepresented groups in research including African American/Black adults, such as

the nationwide All of Us research program [106] and the African Ancestry Neuroscience Research Initiative [107], providing valuable resources to empower these necessary investigations. In addition to the need for sufficient numbers of biospecimens, it will also be important to expand the scope of data collected to characterize such existing and future samples to include more social, educational, cultural, and other factors that can impact health of African American/Black adults and thus need to be considered as confounding factors [108], towards which All of Us is also making efforts. Furthermore, generating additional functional data on *ABCA7* variants in African American/Black adults from the described studies may lead to effective personalized therapeutics for individuals with specific variants. Beyond these necessary studies in African American/Black adults, investigations of *ABCA7* variants and AD in non-American African populations could further expand understanding of *ABCA7*'s mechanisms in AD in the absence of Western cultural influences. These proposed studies are critical to address missing pieces in the puzzle of *ABCA7* genetic risk of AD in African American/Black adults and advance fundamental molecular understanding of how *ABCA7* variants contribute to AD pathogenesis.

Conclusions

Mutations within the *ABCA7* gene account for a significant proportion of genetic risk for AD in African American/Black adults. The *ABCA7* protein is involved in lipid metabolism and transport and phagocytosis processes, which may become dysfunctional in AD and lead to increased A β production and decreased A β clearance, impaired microglial response to inflammation, and ER stress. The impact of individual variants on *ABCA7* function varies, as some AD-associated mutations are not predicted to affect protein function while others likely produce an aberrant, truncated protein. However, the implications of the majority of these *ABCA7* mutations on protein function are predicted or hypothesized. Additional studies investigating the downstream effects of these mutations relative to *ABCA7* protein function in both model systems and human samples are necessary to reveal the specific mechanisms by which these mutations are contributing to AD pathogenesis to understand their role in risk for AD among diverse racial/ethnic groups and the design of personalized therapeutics.

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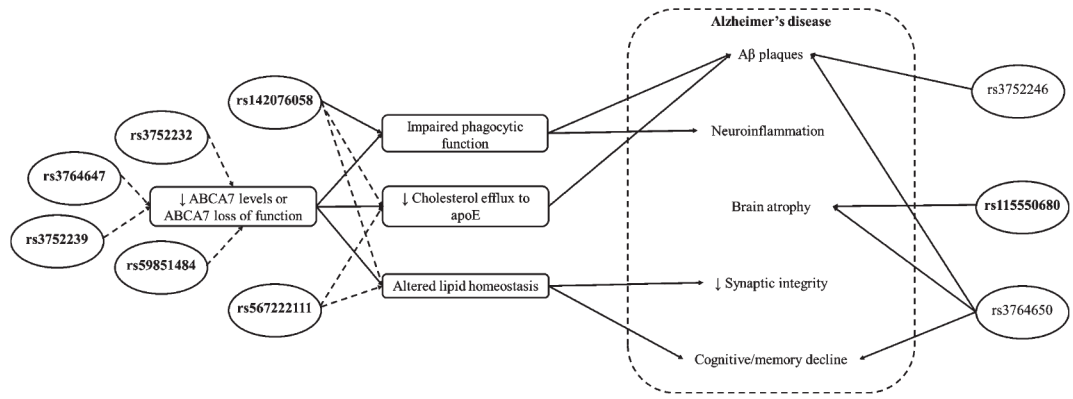


Fig. 1. Summary of ABCA7 variant contributions to AD pathogenesis. ABCA7 SNPs that increase AD risk in African American/Black adults are shown in ovals, with bold text indicating risk SNPs specific to African American/Black adults. Solid arrows indicate proven effects of SNPs; dashed arrows indicate predicted or hypothesized effects of SNPs. ABCA7, phospholipid-transporting ATPase ABCA7; apoE, apolipoprotein E; A, amyloid-beta.

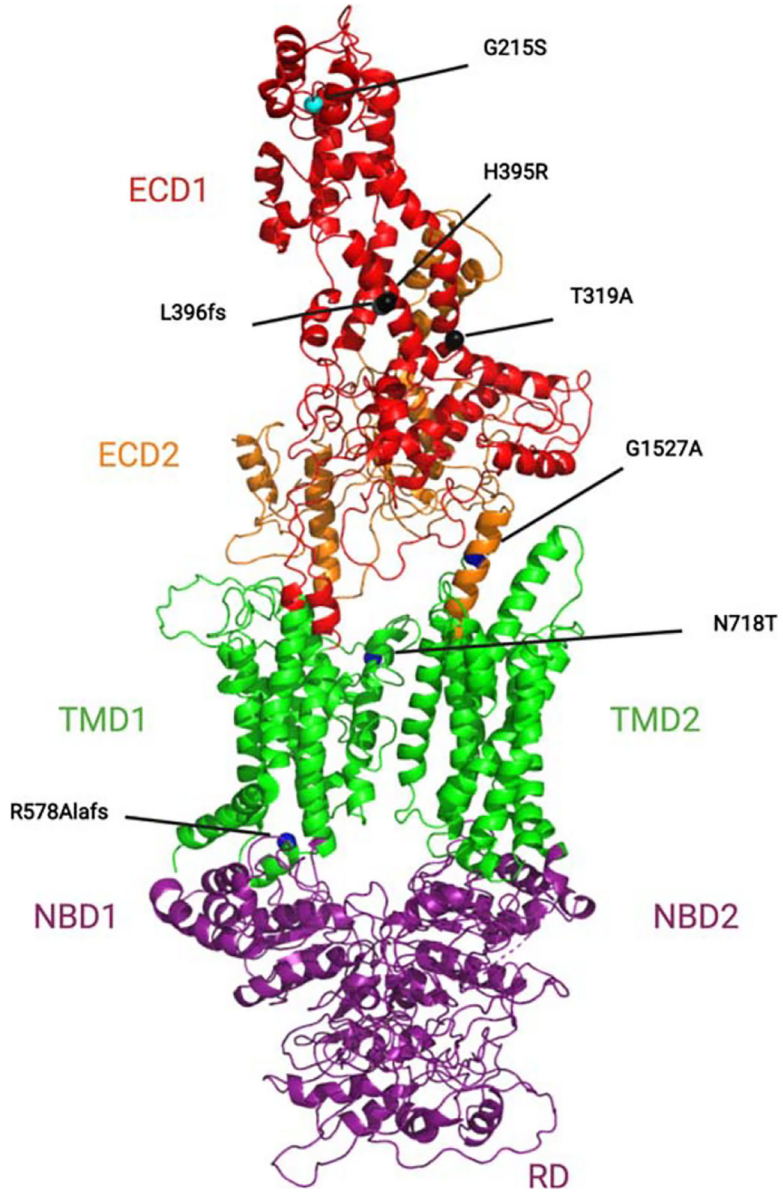


Fig. 2. Cartoon homology model of full-length ABCA7. A homology model of full-length ABCA7 was generated using MODELLER [109] based on the alignment with the ABCA1 structure (PDB: 5xjy) and validated using the Structural Analysis and Verification Server (SAVES) server [110, 111]. AD-associated variants (Table 1) are noted and highlighted here as spheres. ECD, extracellular domain; TMD, transmembrane domain; NBD, nucleotide binding domain; RD, regulatory domain.

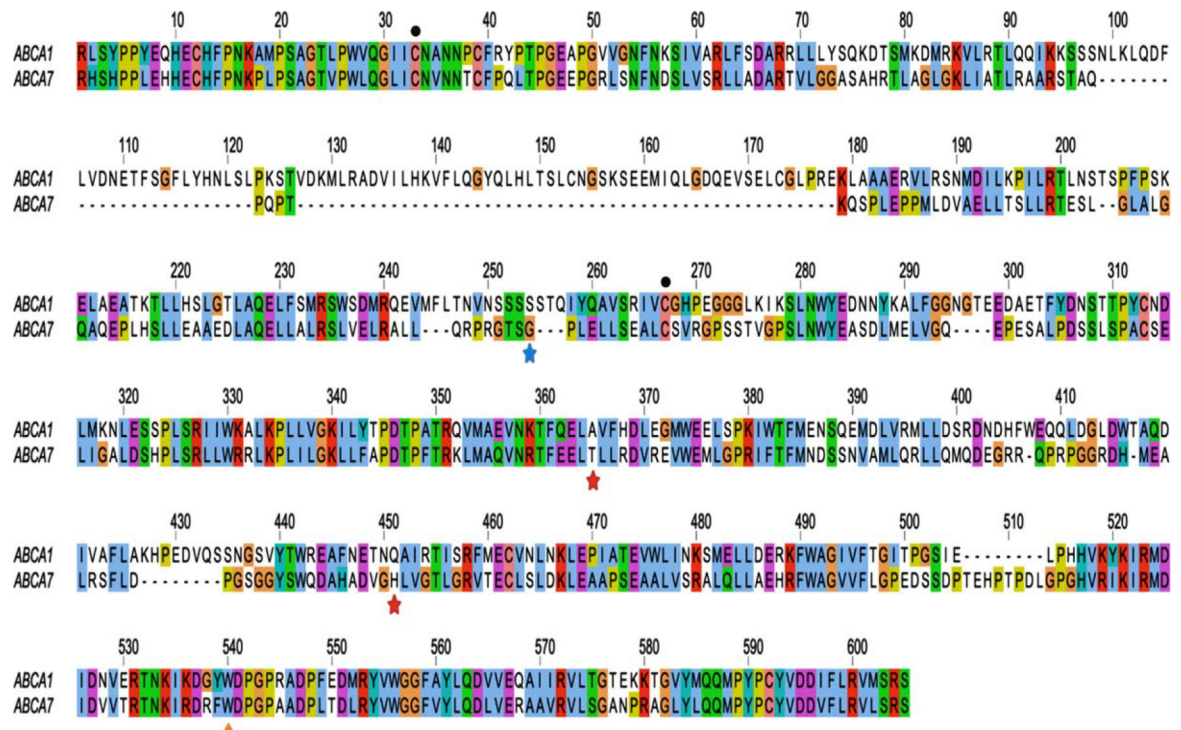


Fig. 3.

Sequence alignment of ECD1 domains of ABCA1 and ABCA7. Amino acid sequences for the corresponding ECD1s were obtained from UniProt.org (ABCA1 ID: O95477, residues 43–639; ABCA7 ID: Q8IZY2, residues 43–549). The numbering of the alignment starts with the beginning of the ECD1. The location of the missense variants that confer AD risk in African American/Black adults (T319A, H395R) and the missense variant predicted to have a protective effect (G215S) are indicated by stars. Intramolecular disulfide bonds implicated in apoA-I-dependent cholesterol efflux are denoted by circles. The Trp residue at position 590 linked to Tangier disease in ABCA1 is conserved in ABCA7 and highlighted by a triangle. Sequences were aligned using the Tcoffee multiple sequence alignment in Jalview [112]. The alignment was color coded using the ClustalX scheme. Colors represent categories of amino acids; white indicates gap/unconserved residues.

Table 1

ABCA7 SNPs associated with AD in various racial/ethnic groups^a

SNP	Mutation	Populations Associated with AD	Frequency ^b	Effect Size	Sources
rs3752232	Thr319Ala	African American/Black	27.2% AD 23.2% CN	1.24	N’Songo et al. 2017 [40] Logue et al. 2018 [43]
rs3752239	Asn718Thr	African American/Black	1.8% AD 0.4% CN	4.06	N’Songo et al. 2017 [40]
rs3752246	Gly1527Ala	Multiple racial groups	ND	1.35	Feheretal. 2019 [113]; Hollingworth et al. 2011 [44]; 1.15 Naj et al. 2011 [45]
rs3764647	His395Arg	African American/Black	26.2–29.8% AD 21.6–23.1% CN	1.32 1.29 1.47	Logue et al. 2011 [39]; Logue et al. 2018 [43] N’Songo et al. 2017 [40]
rs3764650	Intron variant	African American/Black	ND	1.27	Hohman et al. 2016 [24]; Logue et al. 2011 [39]
		Asian		8.32	Li et al. 2017 [114];
		Colombian		1.09	Zhou et al. 2017 [115]
		Non-Hispanic White		1.7 1.25	Moreno et al. 2017 [37] Almeida et al. 2018 [38];
		Multiple racial groups		1.25 1.23	Zhou et al. 2017 [115] Hollingworth et al. 2011 [44]
rs4147929		Danish	ND	1.07	Kjeldsen et al. 2017 [35]
		Non-Hispanic White		1.66	Monsell et al. 2017 [116]
		Multiple racial groups		1.15	Lambert et al. 2013 [46]
rs59851484		African American/Black	14.8% AD 10.5% CN	1.49	Logue et al. 2018 [43]
rs78117248	Intron variant	Belgian	3.8% AD 1.8% CN	2.07	Cuyvers et al. 2015 [36]
		Non-Hispanic White	ND	1.56	Kunkle et al. 2017 [117]
rs115550680		African American/Black	ND	1.79	Reitz et al. 2013 [23]
rs142076058	Arg578Alafs	African American/Black	9.2–15.2% AD 7.4–9.7% CN	2.13 1.27	Cukier et al. 2016 [3] Logue et al. 2018 [43]
rs200538373	Splice donor variant	Icelandic	ND	1.91	Steinberg et al. 2015 [34]
		Non-Hispanic White		2.12	Kunkle et al. 2017 [117]
rs567222111	Leu396fs	African American/Black	1.1% AD 0.3% CN	2.42	Logue et al. 2018 [43]

^aUpdated from [118].

^bND indicates that this information was not available for the denoted SNP. SNP, single nucleotide polymorphism; AD, Alzheimer’s disease; CN, cognitively normal.