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Protective genetic variants against Alzheimer's disease

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Abstract

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Contributors

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Declaration of interests

YTQ and FL are named as co-inventors in patents filed by Mass General Brigham-related Alzheimer's therapeutics targeting APOE and Reelin. YTQ and FL serve as consultants for Biogen. All other authors declare no competing conflicts.

Genetic studies can offer powerful insights for the development of disease-modifying therapies for Alzheimer's disease. Protective genetic variants that delay the onset of cognitive impairment have been found in people with sporadic Alzheimer's disease and in carriers of mutations that usually cause autosomal-dominant Alzheimer's disease in mid-life. The study of families who carry autosomal dominant mutations provides a unique opportunity to uncover genetic modifiers of disease progression, including rare variants in genes such as *APOE* and *RELN*. Understanding how these variants confer protection can help identify the biological pathways that contribute to cognitive resilience, such as the heparan-sulphate proteoglycan–APOE receptor pathway, the TREM-2-driven signalling pathways in the microglia, and phagocytosis. Therapies able to replicate the beneficial effects of these natural defences could provide novel strategies for slowing or preventing the progression of Alzheimer's disease.

Introduction

Alzheimer's disease, the most common form of dementia, is characterised neuropathologically by amyloid β peptide plaques and neurofibrillary tangles.[1] Advances in understanding amyloid and tau pathology led to the development of biomarkers for presymptomatic and early diagnosis,[2] and to the accurate postmortem diagnosis of Alzheimer's disease.[3-5] However, progress in treatment remains slow. Animal models have reinforced the link between toxic amyloid β and phosphorylated tau (p-tau) intermediates with cognitive decline,[1] emphasising the importance of early detection of atypical concentrations of these proteins through fluid or imaging biomarkers.[5] Pathological amyloid β and p-tau aggregates first appear in specific cortical and subcortical areas,[6] with tau pathology more closely linked to clinical progression of Alzheimer's disease than amyloid β deposition.[7]

Compared with the extensive research on Alzheimer's disease risk so far, less is known about the mechanisms underlying resistance and resilience to the disease. Two cases of autosomal-dominant Alzheimer's disease showcase these protective phenomena.[8,9] A carrier of the *PSEN1* Glu280Ala mutation who was homozygous for the *APOE3* Christchurch variant (also known as Arg136Ser and abbreviated throughout as *APOE3Ch*) had region-specific resistance to tau pathology.[8,10] The other case was that of a *PSEN1* Glu280Ala mutation carrier with a rare *RELN* gene variant (His3447Arg and referred to throughout as *RELN-COLBOS*).[9] In both cases, symptom onset was delayed by more than two decades compared with typical *PSEN1* Glu280Ala carriers from the same Colombian kindred, who usually develop mild cognitive impairment by age 44 years and dementia by age 49 years.[11] These cases help distinguish resistance (a term that refers to the cellular or molecular processes that prevent or reduce pathology) from resilience (a term that refers to the capacity of certain individuals for maintaining cognitive functions despite having typical Alzheimer's disease pathology).[12]

In this Review, we describe the evidence on protective genetic variants in Alzheimer's disease and evaluate how these findings could guide the development of novel treatment strategies aiming to slow or prevent disease progression by mimicking or boosting these natural defence mechanisms.

Protective genetic variants against sporadic Alzheimer's disease

Genome-wide association studies have allowed the discovery of several genetic variants that are protective against sporadic Alzheimer's disease, beyond the widely known *APOE* allele ε*2*.[13-15] The development of geneticbased metrics seems crucial for identifying and monitoring individuals at high risk of sporadic Alzheimer's disease, and for selecting participants for clinical trials testing early-stage interventions.[16-18] Additionally, identification of resilience-associated variants can inform the development of disease-modifying therapies by uncovering biological pathways involved in Alzheimer's disease progression (panel).[16,19]

Among genetic risk factors, *APOE* remains the strongest and most prevalent risk factor for sporadic Alzheimer's disease, comprising three major allelic variants: *APOE*ε*2*, *APOE*ε*3*, and *APOE*ε*4*, with either a protective (*APOE*ε*2*), physiologically neutral (*APOE*ε*3*), or detrimental (*APOE*ε*4*) effect on Alzheimer's disease pathology.[20] In sporadic Alzheimer's disease, the *APOE*ε*2* allele (which encodes ApoE2) is the most common protective variant, with an allele frequency estimated to be at 7% of the population worldwide, albeit with geographical variability.[21-23] People who carry *APOE*ε*2* have a 10-year delay in age of disease onset as compared with those who carry *APOE*ε*4*, who have an age of onset between 63·8 years and 76·0 years for people who are homozygous for the ε4 allele, and between 66·1 and 80·5 years for those who are heterozygous (ε3/ε4).[24,25]

In 4-month-old *APP/PS1/APOE4* mouse models of Alzheimer's disease pathology, the intracerebral injection of viral vectors expressing *APOE*ε*2* in the ventricles has been associated with reduced amyloid β plaque deposition in the cortex, decreased synaptic loss, and less microglial activation 2 months after injection, compared with vehicle control-treated mice.[26] In addition to *APOE*ε*2*, other *APOE* variants have been linked to protective effects. Among them, two rare missense variants in *APOE*ε*3* (Val236Glu or ApoE3-Jacksonville) and *APOE*ε*4* (Arg251Gly) have been reported to substantially lower the risk of Alzheimer's disease by more than 60% and more than 50%, respectively.[27,28] The *APOE*ε*4* allele, conversely, is the strongest genetic risk factor for Alzheimer's disease.[20] *APOE*ε*4* knockout has therefore been proposed as a therapeutic strategy. This hypothesis is supported by evidence showing that loss-of-function variants on *APOE*ε*4* are associated with Alzheimer's disease protection in human beings.[29] Lowered ApoE concentrations in a P301S/APOEε4 mouse model, by use of antisense oligonucleotides targeting APOE mRNA, were associated with reduced tauopathy, brain atrophy, inflammation, and synaptic loss.[30]

Findings from genome-wide association studies suggest an association between *APOE* and other genes, such as *TMEM106B*, in influencing Alzheimer's disease risk.[31] Specifically, a study with human samples found that *TMEM106B*, *APOE*, and amyloid β effects converge to alter myelination and lysosomal gene expression, whereas the *TMEM* rs1990621 variant has been associated with increased neuronal density.[32,33] Another key gene, *TREM-2*, is expressed in microglia.[34] This gene plays a crucial role in microglia proliferation, survival, migration, and phagocytosis.[35] In mouse models of Alzheimer's disease, *TREM-2* haplodeficiency and deficiency can lead to reduced microglial clustering around amyloid β plaques, suggesting that *TREM-2* is required for plaque-associated microglial responses.[36]

Stimulating *TREM-2* with agonistic antibodies could be a new therapeutic approach, as it can enhance microglial metabolism in several models of Alzheimer's disease.[37,38]

Additionally, *ABCA7* has been highlighted by genomics, transcriptomics, and methylomics approaches for its roles in amyloid β clearance via phagocytosis and in lipid metabolism by promoting the release of phospholipids and cholesterol. Several *ABCA7* variants have been highlighted as protective, such as rs72973581[31] and Val1613Met, via a suggested gain-of-function mechanism.[39] Conversely, loss-of-function variants, such as rs4147929, have been associated with increased Alzheimer's disease risk in Icelandic populations (OR 2·12) and in European and US populations (combined OR 2·03).[40] These findings highlight *ABCA7* as a possible genetic biomarker for Alzheimer's disease, warranting further investigation into its precise mechanisms[41] given that some variants have been associated with increased risk for Alzheimer's disease in specific populations, such as African American populations (rs11550680, rs14076058, rs567222111, rs10405305, and rs3764647) and Asian populations (rs3764650).[42]

APP, which encodes the amyloid precursor protein, is central to Alzheimer's disease pathology. Successive cleavages of the amyloid precursor protein by β secretase and γ secretase produce amyloid β peptides that can aggregate and form plaques in the brain. In addition to *APP*, mutations in the *PSEN1* and *PSEN2* genes are generally associated with autosomal dominant Alzheimer's disease, as these genes encode the major enzymatic component of γ secretase.[43] In a set of wholegenome sequencing data from 1795 Icelandic individuals, the Ala673Thr mutation of the *APP* gene was found to be more prevalent in the healthy control population than in people with Alzheimer's disease.[44] This mutation also dampened amyloid β toxicity in a mouse model.[45]

Emerging evidence suggests that the *PICALM* gene modulates multiple pathways of Alzheimer's disease pathogenesis, including the processing of the amyloid precursor protein and amyloid β transcytosis, and substantially affects the progression of tau pathology in Alzheimer's disease models.[46] The *PICALM* rs3851179A single nucleotide polymorphism (SNP) has shown protective effects against Alzheimer's disease in populations from France, Italy, Lebanon, Spain, and Türkiye.[47]

Independently from previous findings on genes such as *PICALM* and *APP*, multiple genome-wide association studies have reported the rs11136000 SNP of the *CLU* gene, encoding for clusterin, as a protective locus for Alzheimer's disease risk in European and US cohorts. This variant seems to upregulate clusterin concentrations in the temporal cortex of carriers.[48-50] Furthermore, a case–control association study in a cohort of Czech individuals[51] replicated this protective effect, also involving reduced aggregation of amyloid β.[48,51]

The expression of another gene of interest, *PLCG2*, is increased in several brain regions in patients with late-onset Alzheimer's disease compared with cognitively unimpaired participants.[52] Increased *PLCG2* is also highly correlated with brain amyloid burden in both patients with late-onset Alzheimer's disease and in Alzheimer's disease model mice.[53] Specifically, the Pro522Arg variant could reduce Alzheimer's disease progression

by mitigating tau pathology in the presence of amyloid pathology by acting as a functional hypermorph, or in other words, a gain-of-function variant.[53,54] *TREML2* rs3747742 and rs6915083 SNPs were associated with reduced Alzheimer's disease risk in separate studies.[55,56] *TREML2* is involved in the regulation of inflammation by regulating microglia function.[57]

Finally, a study conducted in the Alzheimer's Disease Genetics Consortium, Alzheimer's Disease Sequencing Project, and UKB cohorts reported that two missense, potential loss-of-function variants in the fibronectin 1 (*FN1*) gene might protect against *APOE*ε4-mediated Alzheimer's disease pathology. In cognitively unimpaired individuals homozygous for *APOE*ε4, brain expression showed statistically significantly lower *FN1* deposition and reduced reactive gliosis compared with people with homozygous *APOE*ε4 and Alzheimer's disease. Furthermore, fibronectin loss of function in zebrafish models can enhance gliovascular remodelling at the blood–brain barrier, increase microglial activity, and reduce gliosis. These findings suggest that FN1 could act as a downstream driver of *APOE*ε4-mediated pathology and cognitive decline in Alzheimer's disease.[58]

Protective genetic variants against autosomal dominant Alzheimer's disease

In a Colombian woman carrying the *PSEN1* Glu280Ala variant who was homozygous for the *APOE3Ch* variant, the onset of cognitive symptoms was delayed by more than 30 years, compared with typical carriers from the same kindred, who generally develop mild cognitive impairment around age 44 years and progress to dementia by age 49 years.[8] In this woman, PET imaging using ^{18}F flortaucipir as a tracer revealed an atypical pattern of tau accumulation, of reduced magnitude and confined primarily to the occipital cortex, with little involvement of medial temporal and other cortical regions. Postmortem analysis confirmed sparse tau neuropathology, with a higher concentration in posterior regions than in the frontal cortex. This analysis also showed homoeostatic astrocytes and minimal vascular pathology, even in the presence of an elevated amyloid burden.[8,59,60] Morphological analyses of her brain consistently confirmed the presence of a larger and more complex astroglia morphology and reduced vascular pathology, compared with *PSEN1* Glu280Ala carriers without the *APOE3Ch* variant. Furthermore, the astrocyte distribution in the cortical layer II was very similar to that found in healthy brains, and low concentrations of p-tau were found in layers I-III of the frontal cortex, which possibly contributed to her cognitive resilience.[60] Heterozygous carriers of *APOE3Ch* and *PSEN1* Glu280Ala from the same Colombian kindred, including both female and male individuals, have also been studied. These individuals showed a delay of approximately 5 years in the onset of mild cognitive impairment and 4 years in dementia onset compared with typical *PSEN1* Glu280Ala carriers. A neuroimaging study in two *APOE3Ch* carriers revealed reduced tau deposition and relatively preserved brain metabolism compared with non-carriers, whereas postmortem analyses showed less amyloid-related vascular pathology in these two individuals than in *APOE3Ch* non-carriers.[60,61]

Contrasting the protective effect observed in Colombian carriers, a study of a family from Spain reported a case of early-onset Alzheimer's disease at age 53 years in a male individual who was heterozygous for the *APOE3Ch* variant, and without any mutation causing Alzheimer's disease, whereas a female sibling with the same variant developed Alzheimer's disease at age 66 years. Postmortem analysis of the male carrier showed amyloid angiopathy and Lewy body copathology consistent with advanced Alzheimer's disease.[62] These findings suggest that *APOE3Ch* heterozygosity does not universally confer protection against Alzheimer's disease and highlight the complexity of gene–environment and gene–gene interactions.

Experimental studies have examined the mechanisms underlying the protective effects of *APOE3Ch*, and findings suggest that this genetic variant reduces its interaction with heparan sulfate proteoglycans.[63] This reduced binding of ApoE3Ch to heparan sulphate proteoglycans appears to limit tau deposits in brain regions that are typically affected in Alzheimer's disease, such as the medial temporal lobe.[8,59] By interfering with this pathway, ApoE3Ch might help modulate downstream processes that drive neurodegeneration.

Neurons obtained from induced human and mouse pluripotent stem cells carrying human *APOE4* and either the homozygous or heterozygous Christchurch variant have also uncovered some potential mechanisms of neuroprotection.[64-66] Specifically, given that *APOE4* is a established major risk factor for sporadic Alzheimer's disease,[20] establishing whether the Christchurch variant could also protect in the presence of the *APOE4* allele was crucial. Findings have confirmed that the homozygous *APOE4Ch* variant provided protection against tau pathology, neurodegeneration, and neuroinflammation, whereas heterozygotes showed a partial protection against neurodegeneration and neuroinflammation, but not against tau pathology.[65] A novel antibody designed to bind to the heparin-binding domain of ApoE3 in the R136 region, the 7C11 antibody, has been tested in both *APOE4* knock-in and *MAPT*^{P301S} transgenic murine models, showing reduced tau phosphorylation (p-tau S396) in the brains of systemically treated *APOE4* knock-in mice,[67] and reduced tau pathology in the retina of *MAPT*^{P301S} mice. In murine models carrying *APOE3Ch*, positive effects on amyloid pathology, amyloid-induced tauopathy, and tau-driven neurodegeneration have been shown.[68] Additionally, improvements in microglial response and enhanced myeloid cell phagocytosis have been observed.[64] Despite these findings, the optimal balance between microglial activation and suppression remains uncertain.

Overall, inhibiting the interaction between ApoE and heparan sulphate proteoglycans might serve as a promising therapeutic strategy that could affect tau aggregation and spreading. Additionally, this inhibition might influence the severity, progression, and clinical presentation of autosomal-dominant Alzheimer's disease by reducing ApoE-mediated neurotoxicity and tau hyperphosphorylation. Findings on *APOE3Ch* also support that the interaction between ApoE and heparan sulphate proteoglycans could serve as a promising therapeutic target for Alzheimer's disease.[67]

A resilient male individual from the Colombian *PSEN1* Glu280Ala kindred who remained cognitively unimpaired until his late 60s (more than 20 years after the expected age

of dementia onset) was found to be a carrier of the rare *RELN-COLBOS* variant.[9] In vitro and in vivo molecular genetic studies found that Reelin-COLBOS statistically significantly increased the phosphorylation concentrations of phosphorylated disabled homolog 1 (DAB1) in neurons, possibly via the higher binding affinity of Reelin-COLBOS to heparan sulphate proteoglycans, thus favouring increased local concentrations of Reelin in the vicinity of the APOE receptors. To further validate the protective mechanism of *RELN-COLBOS*, a knock-in mouse model carrying the *RELN-COLBOS* variant homologous to the human variant confirmed a gain-of-function effect via increased phosphorylated DAB1 concentrations; this effect was associated with reduced tau pathology and preserved cognitive performance when these mice were crossed with a transgenic model of tau pathology. Interestingly, the mouse model also indicated a sexually dimorphic effect of the *RELN-COLBOS* variant, with statistically significantly increased phosphorylated DAB1 concentrations only in male mice.

Postmortem examination of the resilient Colombian male carrier of the *RELN-COLBOS* variant showed severe Alzheimer's disease pathology despite having high neuronal density and low tau pathology in the entorhinal cortex, compared with other individuals from the same kindred. These findings further support the protective role of this *RELN-COLBOS* variant.[9] The unique characteristics of this example provide valuable insights, complemented by in vitro and animal studies, and support the role of Reelin in Alzheimer's disease resilience and as a potential therapeutic target that could be used to mimic the effect of *RELN-COLBOS*.[9] Physiologically, the glycoprotein Reelin, encoded by the *RELN* gene, has several important functions in the brain, such as regulating neuronal migration, dendritic growth and branching, dendritic spine formation, synaptogenesis, and synaptic plasticity.[69] Reelin promotes long-term potentiation in the hippocampus by activating ApoEr2 and VLDL receptors and their downstream signalling via Dab1, which strengthens NMDA receptor function.[70] Experimental models show that reduced Reelin signalling can worsen age-related learning and memory deficits when combined with Alzheimer's disease-related tau mutations.[71] Additionally, Reelin mitigates amyloid β toxicity and tau hyperphosphorylation, two hallmarks of Alzheimer's disease, supporting its role in preserving cognitive function with ageing.[70] Other evidence suggests that Reelin signalling might contribute to cognitive resilience and potentially lower dementia risk.[69-71] Studies in mice have shown that the *RELN* gene provides protection against amyloid β toxicity, compared with the low *RELN* expression in conditional knock-out mouse models.[72] A study reporting a single-cell transcriptomics atlas identified vulnerable excitatory and inhibitory neurons that are depleted in specific brain regions in Alzheimer's disease, providing evidence that the Reelin signalling pathway influences their vulnerability.[73]

Lowering Reelin in entorhinal cortex layer II neurons through microRNA-mediated knock down reduces intracellular amyloid β without affecting amyloid precursor proteins, which suggests a direct link between Reelin and intracellular amyloid β accumulation.[74] Impaired Reelin signalling through amyloid β peptide binding to Reelin, alterations in Reelin processing and glycosylation, or reduced formation of active Reelin homodimers correlates statistically with higher tau phosphorylation in cultures of primary neurons treated with amyloid β, in the lateral entorhinal cortex of rats aged 24 months with cognitive impairment, and in various mouse models of tauopathy.[75] Furthermore, Reelin overexpression can

improve memory and counter tau pathology in transgenic mouse models expressing human tau.[76] Patients with Alzheimer's disease have distinct Reelin proteolytic fragments in CSF, including an approximately 500 kDa Reelin species, and increased expression of genes of the Reelin pathway, highlighting its potential role in Alzheimer's disease.[77]

A longitudinal analysis of a cohort of individuals carrying the *PSEN2* p.Asn141Ile mutation, causative of autosomal-dominant Alzheimer's disease usually by age 50 years, reported an individual with exceptional resilience in whom cognitive decline was delayed by almost 18 years.[78] This individual did not carry the *RELN-COLBOS* or *APOE3Ch* variants, and PET imaging showed less tau spreading compared with individuals with autosomal-dominant Alzheimer's disease. Genetic analyses revealed the presence of a rare variant in the *MAPT* gene (*MAPT* p.Tyr441His), encoding for tau. Although more studies are needed to validate the genetic variants conferring resilience in this individual, these findings validate the crucial role of tau pathology in Alzheimer's disease progression.[78]

Pathways for cognitive resilience and resistance to dementia

Understanding the pathways that contribute to resilience and resistance (table) to dementia requires a multifaceted, comprehensive approach that encompasses the study of genetic, cellular, and environmental factors. Notably, the identification of protective variants in the *APOE* and *RELN* genes, which appear to influence the onset of cognitive decline in individuals with autosomal-dominant Alzheimer's disease, suggests the existence of a crucial pathway for cognitive resilience. This pathway involves differential binding to heparan sulphate proteoglycans and ApoE receptors.[8,9] Specifically, ApoE3Ch and ApoE3-Jacksonville bind less to heparan sulphate proteoglycans, compared with ApoE4, thus supporting their protective role.[8,27] Higher ApoE4 concentrations and other diseaserelevant heparin-binding proteins have been found in plasma isolated from individuals with Alzheimer's disease, compared with healthy control participants.[79] Conversely, the *RELN-COLBOS* variant seems to enhance binding to heparan sulphate proteoglycans via electrostatic interactions promoted by the presence of an additional arginine, thus leading to a gain of function.[9] This opposite binding affinity to heparan sulphate proteoglycans of ApoE3Ch and *RELN-COLBOS* aligns with different binding affinities to ApoE receptors, particularly LRP-8 (or ApoEr2) and the VLDL receptor.[80]

The ApoE–Reelin pathway has been shown to play a crucial role in synaptic plasticity, memory formation, and the suppression of tau phosphorylation. At the cortical level, Reelin is secreted by GABAergic interneurons and binds to ApoEr2 and VLDL receptors. These receptors are mainly located in neurons involved in synaptic plasticity, such as the subgranular zone of the dentate gyrus in the hippocampus.[81] This binding leads to the activation of Src kinases responsible for the phosphorylation of DAB1. DAB1 phosphorylation is a key event of Reelin signalling that leads to the activation of several downstream pathways before its ubiquitination and degradation. One of these downstream pathways involves AKT activation, which leads to inhibition of pGSK3β and results in reduced tau phosphorylation and downstream neuroprotection (figure 1). Furthermore, the observation of increased neuronal density in the entorhinal cortex of the carrier of the *RELN-COLBOS* variant, along with the fact that he was cognitively unimpaired, suggests

that a gain of function of Reelin contributes to preserved neuronal activity and synaptic plasticity, thus resulting in enhanced memory and protection from cognitive decline.

Tau hyperphosphorylation is crucial and correlates with cognitive impairment in individuals with Alzheimer's disease. Given that the *APOE*ε4 variant is a major risk factor for sporadic Alzheimer's disease, and as the ApoE4 isoform interferes with the Reelin–ApoE pathway, a gain of function of this pathway could promote resilience against tau-induced neuropathology.[82] ApoE4 is known to antagonise Reelin–ApoE receptor binding more strongly than other isoforms, thus supporting the hypothesis that upregulation of the Reelin pathway might be a key mechanism of resilience. Upregulation of the Reelin pathway was linked to a reduction of tau pathology in a person carrying the *PSEN1* Glu280Ala variant.[8,9]

The interaction between Reelin and ApoE receptors plays a pivotal role in regulating synaptic plasticity, facilitating long-term potentiation, modulating ApoE receptor functions, and promoting presynaptic vesicle release, a process also regulated by phosphorylated DAB1.[80] The protective effects of the *RELN-COLBOS* variant regarding increased neuronal density in the resilient individual who carried an autosomal-dominant mutation suggest the existence of a preserved neuronal network linked to the Reelin pathway and its increased binding to heparan sulphate proteoglycans, followed by a preserved interaction with APOE receptors (VLDL receptor and ApoEr2), and the consequent intraneuronal upregulation of DAB1 concentrations.[69] ApoE3Ch binds with stronger affinity to neurotoxic tau than ApoE3, thus blocking tau spreading and subsequent neurotoxicity both in culture and in two different animal models, 5xFAD and *P301S* transgenic mice.[83] These findings strongly suggest that multiple mechanisms contribute to neuroprotection in people who carry these protective variants.

On a cellular level, another possible hallmark of resilience could be the presence of abundant *RORB*-positive excitatory neurons, identified as susceptible to Alzheimer's disease pathology,[84] and detected by snRNA sequencing in p-tau-protected areas, such as the frontal cortex, of the autosomal-dominant Alzheimer's disease *APOE3Ch* carrier.[10] The high neuronal density of layer II pyramidal neurons in the entorhinal cortex of the individual with *RELN-COLBOS* autosomal-dominant Alzheimer's disease suggested the survival of neurons that are usually vulnerable by Alzheimer's disease pathology.[9] Reelin-positive neurons were identified as vulnerable in Alzheimer's disease in a study using snRNA sequencing in several cortical areas of human brains of individuals ranging from 75 years to more than 90 years of age.[73] Thus, the discovery of genetic variants that confer resistance or resilience to Alzheimer's disease and the identification of the specific cell populations that benefit from these protective traits present a valuable opportunity to develop treatments promoting the survival of such cells.

Neuroinflammation

Gliosis and neuroinflammation are recognised contributors to the pathogenesis of Alzheimer's disease.[85] The protective mechanisms offered by the *APOE3Ch* and *RELN-COLBOS* variants suggest that the Reelin–ApoE pathway not only affects neurons but also modulates glial cells, such as microglia and astrocytes. On the basis of clinical observations in the *APOE3Ch*[8] and *RELN-COLBOS*[9] protected cases, these pathways are

thought to have a crucial contribution to the preserved metabolic activity in brains resilient to Alzheimer's disease pathology, as measured by fluorodeoxyglucose PET (figure 2).

RNA-sequencing analyses of the *APOE3Ch* carrier compared with non-protected *PSEN1* Glu280Ala carriers have shown that ApoE3Ch elevates concentrations of the ApoE receptor LRP-1 in astrocytes in the frontal cortex, hinting at a potential resilience mechanism tied to the upregulation of LRP-1.[59] Furthermore, studies using transgenic mouse models indicate that APOE3Ch has a direct effect on microglia that results in enhanced clustering and activation, and ultimately leads to improved amyloid β clearance and reduced tau spreading.[64] Conversely, microglial ApoE4 has been shown to impair the microglial response to neurodegeneration[64] and to reduce capacity for phagocytosis and response to inflammation,[86] thus explaining its detrimental role in Alzheimer's disease. Specifically, ApoE4 negatively affects the induction of the neurodegenerative microglia phenotype, which is associated with neuroprotection. In Alzheimer's disease models, the deletion of microglial ApoE4 restores the neurodegenerative microglia phenotype and reduces pathology, suggesting a detrimental role of ApoE4 in microglial function.[86] In contrast to the effects of ApoE4 in lipid metabolism and microglial activation, microglia expressing the protective variant ApoE2 have been reported to do a better clearance of pathological proteins such as amyloid β, thus strengthening the role of the ApoE pathways in Alzheimer's disease.[86]

The interaction between ApoE and TREM-2 is crucial for optimal microglial function. Studies have indicated that TREM-2-mediated microglial activation enhances the beneficial effects of ApoE3, whereas deficiency of TREM-2 exacerbates the detrimental effects of ApoE4 on aberrant microglia activation.[87] Moreover, Reelin is thought to influence the differentiation of astrocytic morphology and molecular profiles according to neuronal layers via DAB1 signalling, thus ensuring their proper function.[88] Reelin might modulate the phagocytic response of microglia via ApoEr2-dependent and VLDL receptor-dependent pathways.[89] The unique neuronal density pattern seen in the *RELN-COLBOS* protected individual could be also interpreted as a result of the homoeostatic environment associated with a particular glial profile.

Preserved dendritic spine morphology has been reported in a cohort of cognitively unimpaired individuals with postmortem hallmarks of Alzheimer's disease neuropathology (ie, individuals without dementia but with Alzheimer's disease neuropathology),[90] suggesting that improved synaptic functions might mitigate tau phosphorylation and spreading. Reduced tau phosphorylation and misfolding into toxic aggregates correlate with cognitive resilience.[91] A study validated that oligomeric tau is cleared from synapses in individuals without dementia but with Alzheimer's disease neuropathology, as compared with synapses of people with sporadic Alzheimer's disease.[91] Altogether, these findings confirm the crucial role in both resilience and resistance of the pathways that contribute to low concentrations of neurotoxic tau species and preserve synaptic integrity.

Additionally, *TREM-2*-driven phagocytic activity is enhanced in individuals without dementia but with Alzheimer's disease neuropathology compared with non-protected individuals with Alzheimer's disease, which aids in the maintenance of synaptic resilience.

These individuals have preserved axonal and dendritic structures near amyloid β plaques, that are known hallmarks of Alzheimer's disease (figure 3). This preservation is associated with elevated *TREM-2* expression and activity, suggesting that *TREM-2* plays a protective role against synaptic loss and cognitive decline.[92]

Conclusions and future directions

Alzheimer's disease is a heterogeneous disease that affects millions of people worldwide. Few disease-modifying treatments are available, and those that are available can cause substantial side-effects. In this Review, we have covered recent findings on protective variants against both sporadic and autosomal-dominant Alzheimer's disease (table), with a particular focus on the variants identified in families carrying the autosomal-dominant *PSEN1* Glu280Ala mutation. Notably, individuals with the *APOE3Ch* or the *RELN-COLBOS* variants had a delay in cognitive decline of almost three decades, underscoring the therapeutic potential of mapping the downstream pathways responsible for their protection.

Individuals who carry the *APOE3Ch* or the *RELN-COLBOS* variants but without dementia, and with Alzheimer's disease neuropathology have unique protective mechanisms against either familial or sporadic forms of Alzheimer's disease. Despite differing genetic and molecular backgrounds, these individuals share common biological traits that contribute to their protection against Alzheimer's disease pathology, including preserved synaptic integrity, reduced tau pathology, and lower concentrations of neuro-inflammatory markers. These shared traits suggest promising therapeutic targets for developing interventions that enhance brain resilience and slow or prevent cognitive decline. Furthermore, each individual case presents a distinctive pathological profile: *APOE3Ch* reflects a case of resistance, given the reduced Alzheimer's pathology and preserved cognition, whereas *RELN-COLBOS* is characterised by resilience. This distinction implies that there might be multiple strategies of protection against Alzheimer's disease, which might converge on shared mechanisms. Although more research is needed to fully elucidate the molecular pathways and develop targeted treatments, these findings support the hypothesis that resilience to Alzheimer's disease is linked to the Reelin–ApoE pathway.

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References

1. Scheltens P, De Strooper B, Kivipelto M, et al. Alzheimer's disease. Lancet 2021; 397: 1577–90. [PubMed: 33667416]

2. Jack CR Jr, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. Alzheimers Dement 2024; 20: 5143–69. [PubMed: 38934362]
3. McAleese KE, Colloby SJ, Thomas AJ, et al. Concomitant neurodegenerative pathologies contribute to the transition from mild cognitive impairment to dementia. Alzheimers Dement 2021; 17: 1121–33. [PubMed: 33663011]
4. Ferrari C, Sorbi S. The complexity of Alzheimer's disease: an evolving puzzle. Physiol Rev 2021; 101: 1047–81. [PubMed: 33475022]
5. Murray ME, Graff-Radford NR, Ross OA, Petersen RC, Duara R, Dickson DW. Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: a retrospective study. Lancet Neurol 2011; 10: 785–96. [PubMed: 21802369]
6. Thal DR, Attems J, Ewers M. Spreading of amyloid, tau, and microvascular pathology in Alzheimer's disease: findings from neuropathological and neuroimaging studies. J Alzheimers Dis 2014; 42 (suppl 4): S421–29. [PubMed: 25227313]
7. Bejanin A, Schonhaut DR, La Joie R, et al. Tau pathology and neurodegeneration contribute to cognitive impairment in Alzheimer's disease. Brain 2017; 140: 3286–300. [PubMed: 29053874]
8. Arboleda-Velasquez JF, Lopera F, O'Hare M, et al. Resistance to autosomal dominant Alzheimer's disease in an APOE3 Christchurch homozygote: a case report. Nat Med 2019; 25: 1680–83. [PubMed: 31686034]
9. Lopera F, Marino C, Chandrahas AS, et al. Resilience to autosomal dominant Alzheimer's disease in a Reelin-COLBOS heterozygous man. Nat Med 2023; 29: 1243–52. [PubMed: 37188781]
10. Sepulveda-Falla D, Sanchez JS, Almeida MC, et al. Distinct tau neuropathology and cellular profiles of an APOE3 Christchurch homozygote protected against autosomal dominant Alzheimer's dementia. Acta Neuropathol 2022; 144: 589–601. [PubMed: 35838824]
11. Sepulveda-Falla D. Resistant and Resilient mutations in protection against familial Alzheimer's disease: learning from nature. Mol Neurodegener 2023; 18: 36. [PubMed: 37264439]
12. Oh J, Eser RA, Ehrenberg AJ, et al. Profound degeneration of wake-promoting neurons in Alzheimer's disease. Alzheimers Dement 2019; 15: 1253–63. [PubMed: 31416793]
13. Schwartzentruber J, Cooper S, Liu JZ, et al. Genome-wide meta-analysis, fine-mapping and integrative prioritization implicate new Alzheimer's disease risk genes. Nat Genet 2021; 53: 392–402. [PubMed: 33589840]
14. Dumitrescu L, Mahoney ER, Mukherjee S, et al. Genetic variants and functional pathways associated with resilience to Alzheimer's disease. Brain 2020; 143: 2561–75. [PubMed: 32844198]
15. Bellenguez C, Küçükali F, Jansen IE, et al. New insights into the genetic etiology of Alzheimer's disease and related dementias. Nat Genet 2022; 54: 412–36. [PubMed: 35379992]
16. Hou J, Hess JL, Armstrong N, et al. Polygenic resilience scores capture protective genetic effects for Alzheimer's disease. Transl Psychiatry 2022; 12: 296. [PubMed: 35879306]
17. Choi SW, Mak TS-H, O'Reilly PF. Tutorial: a guide to performing polygenic risk score analyses. Nat Protoc 2020; 15: 2759–72. [PubMed: 32709988]
18. Hess JL, Tylee DS, Mattheisen M, et al. A polygenic resilience score moderates the genetic risk for schizophrenia. Mol Psychiatry 2021; 26: 800–15. [PubMed: 31492941]
19. Seto M, Weiner RL, Dumitrescu L, Hohman TJ. Protective genes and pathways in Alzheimer's disease: moving towards precision interventions. Mol Neurodegener 2021; 16: 29. [PubMed: 33926499]
20. Raulin AC, Doss SV, Trottier ZA, Ikezu TC, Bu G, Liu CC. ApoE in Alzheimer's disease: pathophysiology and therapeutic strategies. Mol Neurodegener 2022; 17: 72. [PubMed: 36348357]
21. Singh PP, Singh M, Mastana SS. APOE distribution in world populations with new data from India and the UK. Ann Hum Biol 2006; 33: 279–308. [PubMed: 17092867]
22. Abondio P, Sazzini M, Garagnani P, et al. The genetic variability of *APOE* in different human populations and its implications for longevity. Genes 2019; 10: 222. [PubMed: 30884759]
23. Belloy ME, Andrews SJ, Le Guen Y, et al. APOE genotype and Alzheimer disease risk across age, sex, and population ancestry. JAMA Neurol 2023; 80: 1284–94. [PubMed: 37930705]

24. Reiman EM, Arboleda-Velasquez JF, Quiroz YT, et al. Exceptionally low likelihood of Alzheimer's dementia in APOE2 homozygotes from a 5,000-person neuropathological study. Nat Commun 2020; 11: 667. [PubMed: 32015339]
25. Husain MA, Laurent B, Plourde M. APOE and Alzheimer's disease: from lipid transport to physiopathology and therapeutics. Front Neurosci 2021; 15: 630502. [PubMed: 33679311]
26. Jackson RJ, Keiser MS, Meltzer JC, et al. APOE2 gene therapy reduces amyloid deposition and improves markers of neuroinflammation and neurodegeneration in a mouse model of Alzheimer disease. Mol Ther 2024; 32: 1373–86. [PubMed: 38504517]
27. Liu CC, Murray ME, Li X, et al. *APOE3*-Jacksonville (V236E) variant reduces self-aggregation and risk of dementia. Sci Transl Med 2021; 13: eabc9375. [PubMed: 34586832]
28. Le Guen Y, Belloy ME, Grenier-Boley B, et al. Association of rare APOE missense variants V236E and R251G with risk of Alzheimer disease. JAMA Neurol 2022; 79: 652–63. [PubMed: 35639372]
29. Chemparathy A, Le Guen Y, Chen S, et al. APOE loss-of-function variants: compatible with longevity and associated with resistance to Alzheimer's disease pathology. Neuron 2024; 112: 1110–1116.e5. [PubMed: 38301647]
30. Litvinchuk A, Huynh TV, Shi Y, et al. Apolipoprotein E4 reduction with antisense oligonucleotides decreases neurodegeneration in a tauopathy model. Ann Neurol 2021; 89: 952–66. [PubMed: 33550655]
31. Sassi C, Nalls MA, Ridge PG, et al. ABCA7 p.G215S as potential protective factor for Alzheimer's disease. Neurobiol Aging 2016; 46: 235.e1–9.
32. Li Z, Farias FHG, Dube U, et al. The TMEM106B FTLD-protective variant, rs1990621, is also associated with increased neuronal proportion. Acta Neuropathol 2020; 139: 45–61. [PubMed: 31456032]
33. Jun G, Ibrahim-Verbaas CA, Vronskaya M, et al. A novel Alzheimer disease locus located near the gene encoding tau protein. Mol Psychiatry 2016; 21: 108–17. [PubMed: 25778476]
34. Shi Q, Gutierrez RA, Bhat MA. Microglia, TREM2, and neurodegeneration. Neuroscientist 2025; 31: 159–76. [PubMed: 38769824]
35. Li Y, Xu H, Wang H, Yang K, Luan J, Wang S. TREM2: potential therapeutic targeting of microglia for Alzheimer's disease. Biomed Pharmacother 2023; 165: 115218. [PubMed: 37517293]
36. Zhou Y, Ulland TK, Colonna M. TREM2-dependent effects on microglia in Alzheimer's disease. Front Aging Neurosci 2018; 10: 202. [PubMed: 30038567]
37. Schlepckow K, Morenas-Rodríguez E, Hong S, Haass C. Stimulation of TREM2 with agonistic antibodies-an emerging therapeutic option for Alzheimer's disease. Lancet Neurol 2023; 22: 1048–60. [PubMed: 37863592]
38. van Lengerich B, Zhan L, Xia D, et al. A TREM2-activating antibody with a blood-brain barrier transport vehicle enhances microglial metabolism in Alzheimer's disease models. Nat Neurosci 2023; 26: 416–29. [PubMed: 36635496]
39. Butler CA, Mendoza Arvilla A, Milinkeviciute G, et al. The Abca7^{V1613M} variant reduces Aβ generation, plaque load, and neuronal damage. Alzheimers Dement 2024; 20: 4914–34. [PubMed: 38506634]
40. Steinberg S, Stefansson H, Jonsson T, et al. Loss-of-function variants in ABCA7 confer risk of Alzheimer's disease. Nat Genet 2015; 47: 445–47. [PubMed: 25807283]
41. De Roeck A, Van Broeckhoven C, Sleegers K. The role of ABCA7 in Alzheimer's disease: evidence from genomics, transcriptomics and methylomics. Acta Neuropathol 2019; 138: 201–20. [PubMed: 30903345]
42. Gialama V, Siokas V, Liampas I, et al. Alzheimer's disease and effects of *ABCA7* polymorphisms: a review. J Integr Neurosci 2024; 23: 164. [PubMed: 39344232]
43. Petit D, Fernández SG, Zoltowska KM, et al. Aβ profiles generated by Alzheimer's disease causing PSEN1 variants determine the pathogenicity of the mutation and predict age at disease onset. Mol Psychiatry 2022; 27: 2821–32. [PubMed: 35365805]
44. Jonsson T, Atwal JK, Steinberg S, et al. A mutation in APP protects against Alzheimer's disease and age-related cognitive decline. Nature 2012; 488: 96–99. [PubMed: 22801501]

45. Célestine M, Jacquier-Sarlin M, Borel E, et al. Transmissible long-term neuroprotective and pro-cognitive effects of 1-42 beta-amyloid with A2T icelandic mutation in an Alzheimer's disease mouse model. Mol Psychiatry 2024; 29: 3707–21. [PubMed: 38871852]
46. Ando K, Nagaraj S, Küçükali F, et al. PICALM and Alzheimer's disease: an update and perspectives. Cells 2022; 11: 3994. [PubMed: 36552756]
47. Masri I, Salami A, El Shamieh S, Bissar-Tadmouri N. rs3851179G>A in PICALM is protective against Alzheimer's disease in five different countries surrounding the Mediterranean. Curr Aging Sci 2020; 13: 162–68. [PubMed: 31648652]
48. Harold D, Abraham R, Hollingworth P, et al. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. Nat Genet 2009; 41: 1088–93. [PubMed: 19734902]
49. Allen M, Zou F, Chai HS, et al. Novel late-onset Alzheimer disease loci variants associate with brain gene expression. Neurology 2012; 79: 221–28. [PubMed: 22722634]
50. Ma J, Qiu S. Genetic variant rs11136000 upregulates clusterin expression and reduces Alzheimer's disease risk. Front Neurosci 2022; 16: 926830. [PubMed: 36033622]
51. Balcar VJ, Zeman T, Janout V, Janoutová J, Lochman J, Šerý O. Single nucleotide polymorphism rs11136000 of CLU gene (Clusterin, ApoJ) and the risk of late-onset Alzheimer's disease in a central European population. Neurochem Res 2021; 46: 411–22. [PubMed: 33206315]
52. Tsai AP, Dong C, Lin PB, et al. PLCG2 is associated with the inflammatory response and is induced by amyloid plaques in Alzheimer's disease. Genome Med 2022; 14: 17. [PubMed: 35180881]
53. Magno L, Lessard CB, Martins M, et al. Alzheimer's disease phospholipase C-gamma-2 (PLCG2) protective variant is a functional hypermorph. Alzheimers Res Ther 2019; 11: 16. [PubMed: 30711010]
54. Kleineidam L, Chouraki V, Próchnicki T, et al. PLCG2 protective variant p.P522R modulates tau pathology and disease progression in patients with mild cognitive impairment. Acta Neuropathol 2020; 139: 1025–44. [PubMed: 32166339]
55. Benitez BA, Jin SC, Guerreiro R, et al. Missense variant in TREML2 protects against Alzheimer's disease. Neurobiol Aging 2014; 35: 1510. e19–26.
56. Li JQ, Zhong XL, Song JH, et al. Associations between TREML2 gene variants and Alzheimer's disease: biomarkers, neuroimage, and cognition. J Alzheimers Dis 2023; 96: 1555–63. [PubMed: 37980675]
57. Wang SY, Gong PY, e Y, Zhang YD, Jiang T. The role of TREML2 in Alzheimer's disease. J Alzheimers Dis 2020; 76: 799–806. [PubMed: 32568208]
58. Bhattarai P, Gunasekaran TI, Belloy ME, et al. Rare genetic variation in fibronectin 1 (FN1) protects against APOEε4 in Alzheimer's disease. Acta Neuropathol 2024; 147: 70. [PubMed: 38598053]
59. Almeida MC, Eger SJ, He C, et al. Single-nucleus RNA sequencing demonstrates an autosomal dominant Alzheimer's disease profile and possible mechanisms of disease protection. Neuron 2024; 112: 1778–1794.e7. [PubMed: 38417436]
60. Henao-Restrepo J, López-Murillo C, Valderrama-Carmona P, et al. Gliovascular alterations in sporadic and familial Alzheimer's disease: APOE3 Christchurch homozygote glioprotection. Brain Pathol 2023; 33: e13119. [PubMed: 36130084]
61. Quiroz YT, Aguillon D, Aguirre-Acevedo DC, et al. *APOE3* Christchurch heterozygosity and autosomal dominant Alzheimer's disease. N Engl J Med 2024; 390: 2156–64. [PubMed: 38899694]
62. Hernandez I, Gelpi E, Molina-Porcel L, et al. Heterozygous APOE Christchurch in familial Alzheimer's disease without mutations in other Mendelian genes. Neuropathol Appl Neurobiol 2021; 47: 579–82. [PubMed: 33095930]
63. Mah D, Zhu Y, Su G, et al. Apolipoprotein E recognizes Alzheimer's disease associated 3-o sulfation of heparan sulfate. Angew Chem Int Ed Engl 2023; 62: e202212636. [PubMed: 37014788]
64. Chen Y, Song S, Parhizkar S, et al. APOE3ch alters microglial response and suppresses Aβ-induced tau seeding and spread. Cell 2024; 187: 428–445.e20. [PubMed: 38086389]

65. Nelson MR, Liu P, Agrawal A, et al. The APOE-R136S mutation protects against APOE4-driven tau pathology, neurodegeneration and neuroinflammation. Nat Neurosci 2023; 26: 2104–21. [PubMed: 37957317]
66. Perez-Corredor P, Vanderleest TE, Vacano GN, et al. *APOE3* Christchurch modulates β-catenin/Wnt signaling in iPS cell-derived cerebral organoids from Alzheimer's cases. Front Mol Neurosci 2024; 17: 1373568. [PubMed: 38571814]
67. Marino C, Perez-Corredor P, O'Hare M, et al. APOE Christchurch-mimetic therapeutic antibody reduces APOE-mediated toxicity and tau phosphorylation. Alzheimers Dement 2024; 20: 819–36. [PubMed: 37791598]
68. Chen Y, Holtzman DM. New insights into innate immunity in Alzheimer's disease: from APOE protective variants to therapies. Trends Immunol 2024; 45: 768–82. [PubMed: 39278789]
69. Jossin Y Reelin functions, mechanisms of action and signaling pathways during brain development and maturation. Biomolecules 2020; 10: 964. [PubMed: 32604886]
70. Katsuyama Y, Hattori M. REELIN ameliorates Alzheimer's disease, but how? Neurosci Res 2024; 208: 8–14. [PubMed: 39094979]
71. Marckx AT, Fritschle KE, Calvier L, Herz J. Reelin changes hippocampal learning in aging and Alzheimer's disease. Behav Brain Res 2021; 414: 113482. [PubMed: 34333070]
72. Lane-Donovan C, Philips GT, Wasser CR, et al. Reelin protects against amyloid β toxicity in vivo. Sci Signal 2015; 8: ra67. [PubMed: 26152694]
73. Mathys H, Boix CA, Akay LA, et al. Single-cell multiregion dissection of Alzheimer's disease. Nature 2024; 632: 858–68. [PubMed: 39048816]
74. Kobro-Flatmoen A, Battistin C, Nair RR, et al. Lowering levels of reelin in entorhinal cortex layer II-neurons results in lowered levels of intracellular amyloid-β. Brain Commun 2023; 5: fcad115. [PubMed: 37091586]
75. Joly-Amado A, Kulkarni N, Nash KR. Reelin signaling in neurodevelopmental disorders and neurodegenerative diseases. Brain Sci 2023; 13: 1479. [PubMed: 37891846]
76. Rossi D, Gruart A, Contreras-Murillo G, et al. Reelin reverts biochemical, physiological and cognitive alterations in mouse models of tauopathy. Prog Neurobiol 2020; 186: 101743. [PubMed: 31870804]
77. Lopez-Font I, Lennol MP, Iborra-Lazaro G, Zetterberg H, Blennow K, Sáez-Valero J. Altered balance of reelin proteolytic fragments in the cerebrospinal fluid of Alzheimer's disease patients. Int J Mol Sci 2022; 23: 7522. [PubMed: 35886870]
78. Llibre-Guerra JJ, Fernandez MV, Joseph-Mathurin N, et al. Longitudinal analysis of a dominantly inherited Alzheimer disease mutation carrier protected from dementia. Nat Med 2025; published online Feb 10. 10.1038/s41591-025-03494-0.
79. Guo Q, Ping L, Dammer EB, et al. Heparin-enriched plasma proteome is significantly altered in Alzheimer's disease. Mol Neurodegener 2024; 19: 67. [PubMed: 39380021]
80. Yi LX, Zeng L, Wang Q, Tan EK, Zhou ZD. Reelin links apolipoprotein E4, tau, and amyloid-β in Alzheimer's disease. Ageing Res Rev 2024; 98: 102339. [PubMed: 38754634]
81. Weeber EJ, Beffert U, Jones C, et al. Reelin and ApoE receptors cooperate to enhance hippocampal synaptic plasticity and learning. J Biol Chem 2002; 277: 39944–52. [PubMed: 12167620]
82. Ramsden CE, Zamora D, Horowitz MS, et al. ApoER2-Dab1 disruption as the origin of pTau-associated neurodegeneration in sporadic Alzheimer's disease. Acta Neuropathol Commun 2023; 11: 197. [PubMed: 38093390]
83. Chen G, Wang M, Zhang Z, et al. ApoE3 R136S binds to tau and blocks its propagation, suppressing neurodegeneration in mice with Alzheimer's disease. Neuron 2025; 113: 719–736.e5. [PubMed: 39814008]
84. Leng K, Li E, Eser R, et al. Molecular characterization of selectively vulnerable neurons in Alzheimer's disease. Nat Neurosci 2021; 24: 276–87. [PubMed: 33432193]
85. Leng F, Edison P. Neuroinflammation and microglial activation in Alzheimer disease: where do we go from here? Nat Rev Neurol 2021; 17: 157–72. [PubMed: 33318676]
86. Wang N, Wang M, Jeevaratnam S, et al. Opposing effects of APOE2 and APOE4 on microglial activation and lipid metabolism in response to demyelination. Mol Neurodegener 2022; 17: 75. [PubMed: 36419137]

87. Fitz NF, Nam KN, Wolfe CM, et al. Phospholipids of APOE lipoproteins activate microglia in an isoform-specific manner in preclinical models of Alzheimer's disease. Nat Commun 2021; 12: 3416. [PubMed: 34099706]

88. Lanjakornsiripan D, Pior BJ, Kawaguchi D, et al. Layer-specific morphological and molecular differences in neocortical astrocytes and their dependence on neuronal layers. Nat Commun 2018; 9: 1623. [PubMed: 29691400]

89. Rahimi-Balaei M, Jiao X, Dalvand A, et al. Mutations in the reelin pathway are associated with abnormal expression of microglial IgG FC receptors in the cerebellar cortex. Mol Biol Rep 2020; 47: 5323–31. [PubMed: 32594343]

90. Guptarak J, Scaduto P, Tumurbaatar B, et al. Cognitive integrity in non-demented individuals with Alzheimer's neuropathology is associated with preservation and remodeling of dendritic spines. Alzheimers Dement 2024; 20: 4677–91. [PubMed: 38829680]

91. Singh A, Allen D, Fracassi A, et al. Functional integrity of synapses in the central nervous system of cognitively intact individuals with high Alzheimer's disease neuropathology is associated with absence of synaptic tau oligomers. J Alzheimers Dis 2020; 78: 1661–78. [PubMed: 33185603]

92. Fracassi A, Marcatti M, Tumurbaatar B, Woltjer R, Moreno S, Taglialatela G. TREM2-induced activation of microglia contributes to synaptic integrity in cognitively intact aged individuals with Alzheimer's neuropathology. Brain Pathol 2023; 33: e13108. [PubMed: 35816404]

Panel: Genome-wide association studies and polygenic analyses as powerful tools for the identification of genetic variants

Genome-wide association studies (GWAS) involve the DNA analysis of a large population, which enables the identification of associations between genetic variants (ie, single-nucleotide polymorphisms) and specific diseases or phenotypes. The identification of genetic risk factors for Alzheimer's disease and related neurodegenerative diseases is feasible through GWAS. Analyses focused on families with a particular family history of a disease are referred to as GWAX or GWAS by proxy.[13-15]

Polygenic analysis involves the study of the effects of multiple genetic variants across the genome on different diseases. Polygenic risk scores are calculated as the weighted sum of risk alleles identified by a discovery GWAS.[17] The resulting polygenic risk score is a parameter that allows the establishment of the genetic predisposition to a specific disease or phenotype.[18]

A polygenic resilience score represents the weighted sum of alleles associated with the absence of a condition in individuals with high polygenic risk scores.[18] Polygenic resilience score is a novel genetic measure that quantifies an individual's potential to resist or overcome the genetic risk for complex disorders, such as schizophrenia or Alzheimer's disease. The identification of resilience-associated variants can inform the development of disease-modifying therapies by uncovering biological pathways involved in Alzheimer's disease progression.[16]

GWAS and polygenic analyses allow identification of common genomic loci that confer either risk or resilience to sporadic Alzheimer's disease.[13-15] The novel development of polygenic risk and polygenic resilience scores is crucial for clinical studies evaluating disease-modifying and prophylactic interventions against Alzheimer's disease. A study from 2020 used data from four publicly available clinical cohorts (ACT, ROSMAP, ADNI, and A4) to investigate the genetic covariances between the participants' cognitive resilience, given their amyloid burden, and 67 other complex traits, including educational attainment, mental health, and various physiological characteristics.[14] The authors identified important genetic correlations between resilience phenotypes and traits, such as education, smoking behaviour, and neuropsychiatric conditions.[14] Furthermore, a large GWAS involving 111 326 clinically diagnosed individuals with Alzheimer's disease and 677 663 healthy control participants contributed to the discovery of 42 new risk loci.[15] Collectively, evidence from these large-scale studies support that amyloid plaque, neurofibrillary tangle formation, cholesterol metabolism, endocytosis, phagocytosis, and innate immune system function are the pathways influencing Alzheimer's disease risk.[15,19]

Search strategy and selection criteria

We searched the National Institute on Aging database, the ALZFORUM databases (including, AlzBiomarker, AlzRisk), and PubMed between Jan 1, 2019 and March 1, 2025 for studies describing protective genetic variants against sporadic and familial Alzheimer's disease, using the keywords "Alzheimer's disease" and "resilience", "resistance", "Christchurch", "Reelin", "RELN-COLBOS", "genetic risk factors", "pathology", "protect", "protective", "variant", "GWAS", "TREM-2", "pathways", and "HSPG". Additionally, our selection criteria aimed to help us identify current challenges in developing effective treatments for Alzheimer's disease and elucidating pathways and genetic variants that promote resilience or resistance against the disease. We omitted studies where the full text was unavailable, preventing a thorough evaluation of their quality and relevance to the scope of this Review. Only articles published in English were consulted.

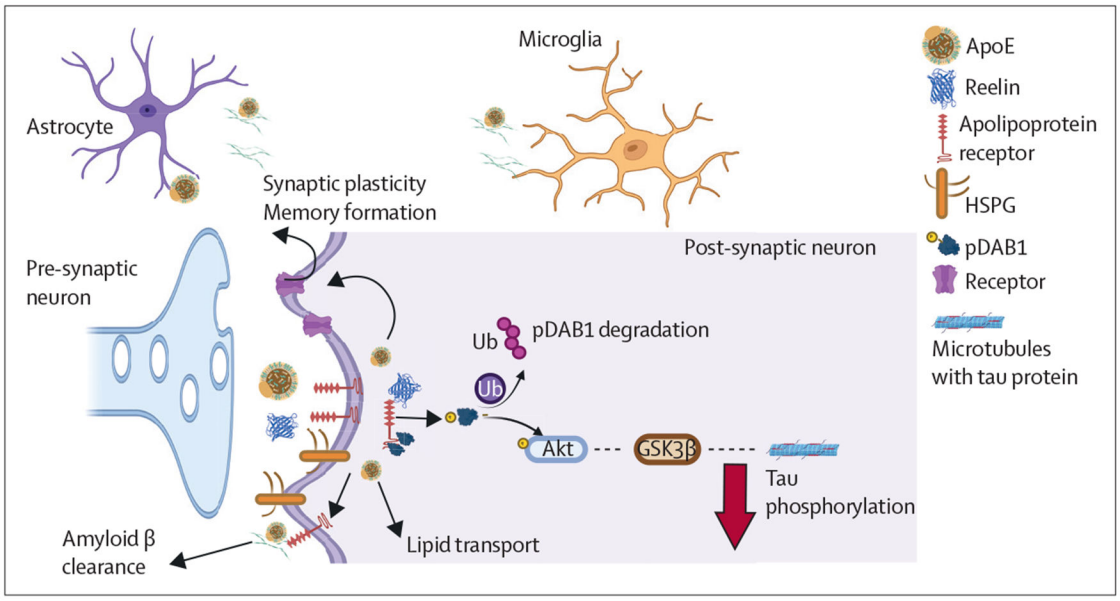

Figure 1: The ApoE–Reelin pathway of resilience in neurons

The intraneuronal pathway is activated upon interaction between Reelin or ApoE and heparan sulphate proteoglycans, followed by binding to the ApoE receptor. Once the Reelin–ApoE receptor complex is internalised, the rapid phosphorylation of DAB1 leads to AKT activation and subsequent inhibition of GSK3β, thus resulting in reduced tau phosphorylation. pDAB1 activity is controlled by fast ubiquitination and degradation. HSPG=heparan sulfate proteoglycans. Figure created with BioRender.com.

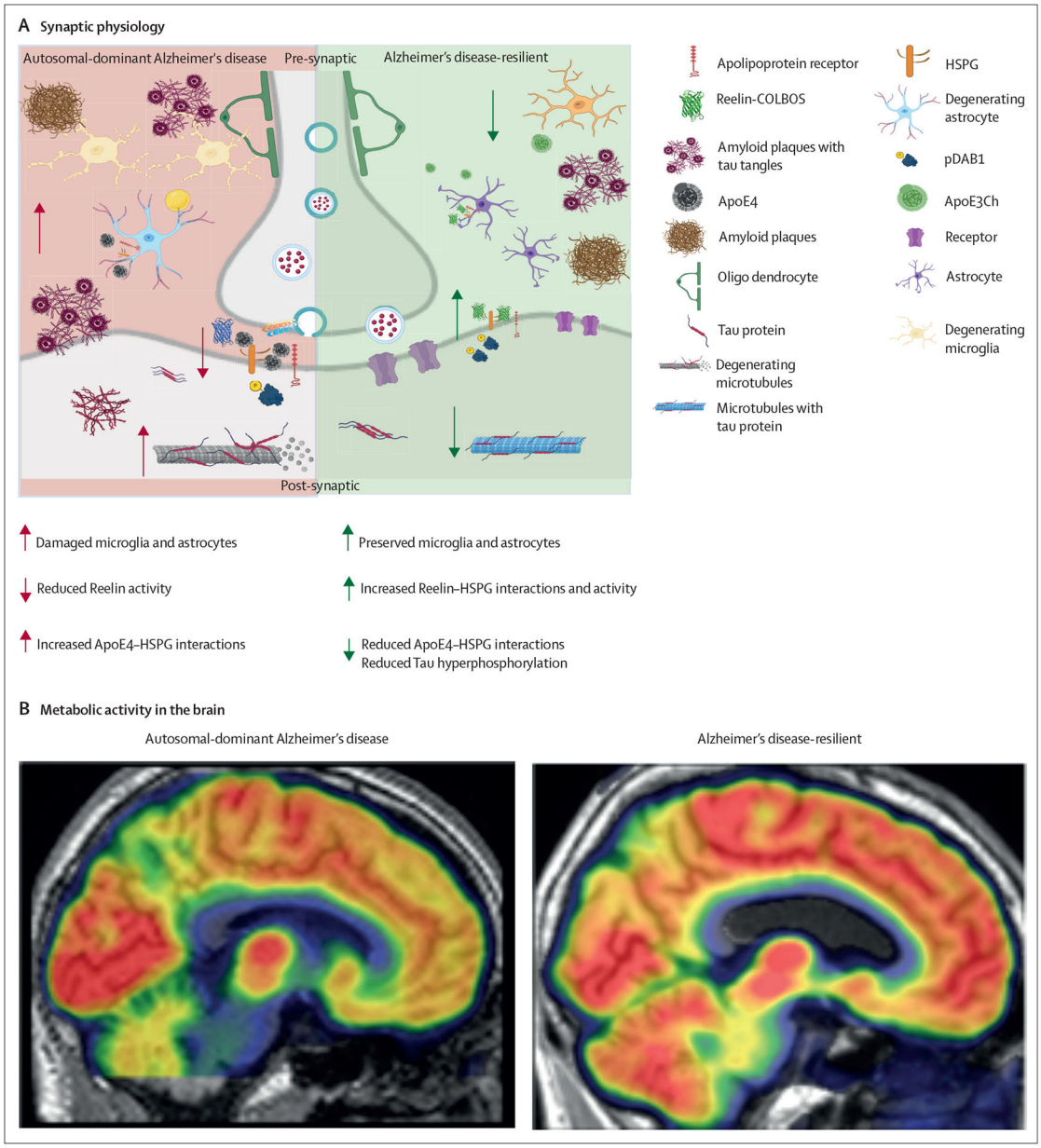

Figure 2: Differences between individuals susceptible or resilient to Alzheimer's disease.

(A) ApoE3 and Reelin variants contribute to maintain the homoeostatic balance between glia and neuronal transmission. In people with autosomal-dominant Alzheimer's disease or sporadic Alzheimer's disease, microglia, astrocytes, and synaptic transmission are severely affected. *APOE4* contributes to impaired Reelin activity due to increased binding affinity to heparan sulphate proteoglycans, thus contributing to tau hyperphosphorylation. The effects of Alzheimer's disease-inducing pathological variants are counterbalanced by the presence of protective variants such as *APOE3Ch*. *Reelin-COLBOS* contributes to preserved microglia, astrocytes, and neuronal function thanks to up-regulated reelin activity and reduced tau phosphorylation. (B) Representative fluorodeoxyglucose PET scans of the brain of an individual with autosomal-dominant Alzheimer's disease (left) and the brain

of a *Reelin-COLBOS* resilient individual (right) showing that the metabolic activity of the brain is severely affected in the presence of Alzheimer's disease pathology, whereas in the presence of protective variants, metabolism is preserved. Adapted from Lopera et al.[9] APOE3CH=*APOE3* Christchurch (Arg136Ser) variant. HSPG=heparan sulfate proteoglycans. Figure created with BioRender.com.

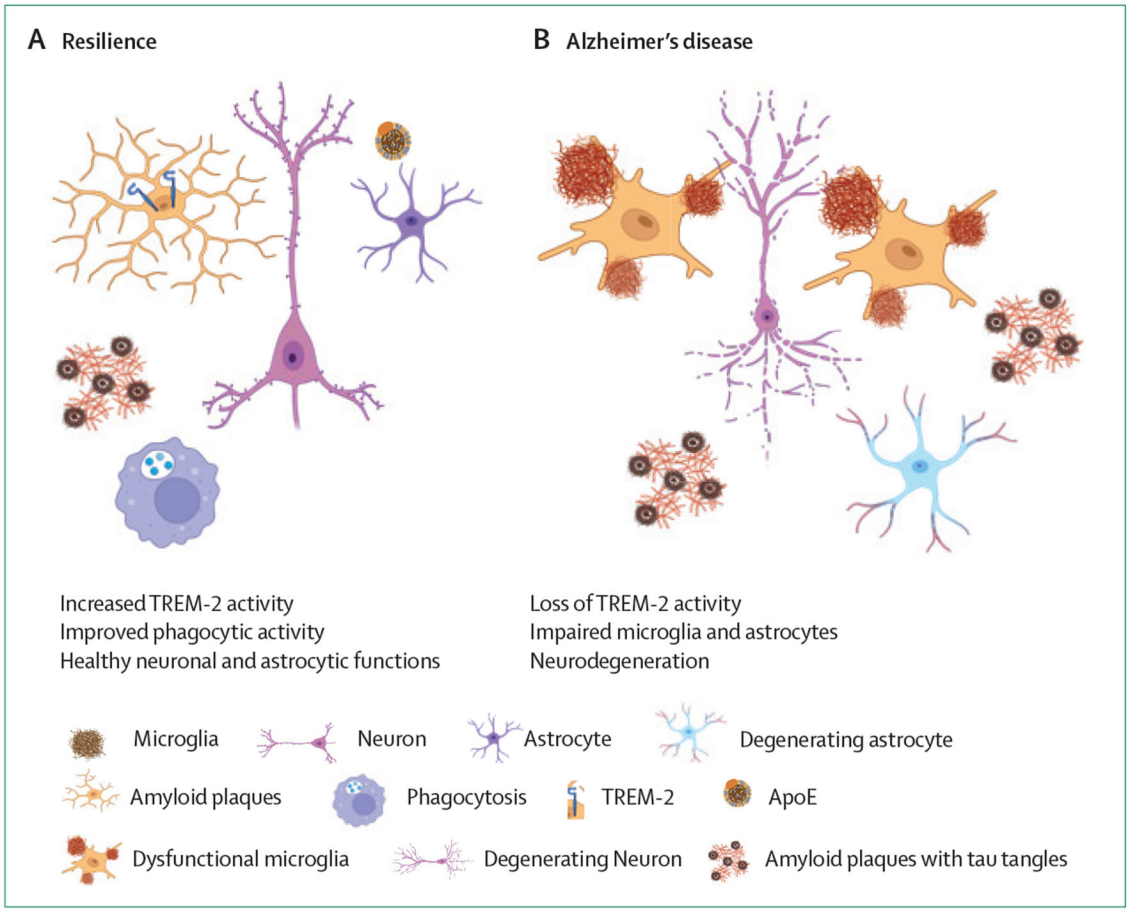

Figure 3: The protective role of TREM-2 in microglia

(A) Increased TREM-2 activity leads to preserved microglia activity, whereas the crosstalk of TREM-2 with ApoE leads to preserved astrocyte function, increased phagocytosis, and preserved neuronal activity in individuals with resilience. (B) The loss of function of TREM-2 activity leads to impaired microglia activity that, along with degenerating astrocytes, contributes to neurodegeneration in people with Alzheimer's disease. Figure created with BioRender.com.

Table:

Protective genetic variants against sporadic or autosomal dominant Alzheimer's disease

	Protective variants	Downstream pathways	Effect
ABCA7	*ABCA7* rs72973581*; ABCA7* Val1613Met	Lipid homoeostasis and phagocytosis, amyloid β clearance, and release of phospholipids and cholesterol[31,39]	Improvement of phospholipid and cholesterol transport
APOE	*APOEε2*	Amyloid β clearance and lipid transport[23,24]	Promotion of amyloid β clearance and reductions in tau pathology and amyloid plaques deposition
APOE	*APOE3* V236E	Amyloid β clearance and lipid transport[27,28]	Reduced tau pathology
APOE	*APOE3Ch*	Amyloid β and tau aggregation and clearance[8,11,61]	Reduced tau pathology and reduced amyloid β aggregation
APP	*APP* Ala673Thr	APP processing[44,45]	Promotion of non-amyloidogenic APP processing and reduced amyloid β release
CLU	*CLU* rs11136000	Clusterin production and chaperone activity[48,49,51]	Reduced amyloid β aggregation
PICALM	*PICALM* rs3851179A	Amyloid β cascade[47]	Reduced proamyloidogenic processing and tau pathology
PLCG2	*PLCG2* Pro522Arg	Antigen presentation to microglia and cascade of neuronal immune response[52,53]	Reduced tau pathology
RELN	*RELN-COLBOS* His3447Arg	Reelin signalling, brain development, and synaptic plasticity[9]	Reduced tau pathology and preserved synaptic plasticity
TREM2	*TMEM106B; rs1990621*	Microglia proliferation, survival and migration, and phagocytosis[55-57]	Preserved neuronal density and microglial function

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