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Review

Translational approaches to understanding resilience to Alzheimer's disease

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Individuals who maintain cognitive function despite high levels of Alzheimer's disease (AD)-associated pathology are said to be 'resilient' to AD. Identifying mechanisms underlying resilience represents an exciting therapeutic opportunity. Human studies have identified a number of molecular and genetic factors associated with resilience, but the complexity of these cohorts prohibits a complete understanding of which factors are causal or simply correlated with resilience. Genetically and phenotypically diverse mouse models of AD provide new and translationally relevant opportunities to identify and prioritize new resilience mechanisms for further cross-species investigation. This review will discuss insights into resilience gained from both human and animal studies and highlight future approaches that may help translate these insights into therapeutics designed to prevent or delay AD-related dementia.

Prevalence of resilience to Alzheimer's neuropathology

AD is characterized clinically by a progressive loss of memory functions that impact daily life [1]. Dementia is preceded pathologically by progressive neurodegeneration, deposition of extracellular beta amyloid (A β) aggregates, and intracellular accumulation of hyperphosphorylated tau-containing neurofibrillary tangles [2]. These proteinopathies are thought to be drivers of the neuronal dysfunction and cognitive impairment that characterize the disease [3], in part due to the identification of inherited mutations in amyloid precursor protein (*APP*) that cause familial forms of autosomal dominant AD [4].

Despite the strong genetic link between amyloid and AD, a significant proportion of individuals with brain amyloid deposition remain non-demented throughout their lifespan [5]. These individuals are referred to in the literature as 'resilient' to AD pathology and represent a clinically interesting subset of the population, as they are able to cope with the presence of amyloid and/or tau while escaping the deficits typically associated with these pathological hallmarks. In large-scale studies, up to one-third of elderly individuals are estimated to reach this criterion as measured by either cerebrospinal fluid (CSF) biomarker monitoring, amyloid- or tau-specific imaging techniques, or autopsy [6–8]. A better understanding of the mechanisms that confer protection against cognitive decline in these individuals represents an outstanding therapeutic opportunity; information gained from studying these 'resilient' individuals could provide the key to preventing or delaying the onset of dementia in susceptible individuals. This review will primarily focus on studies aimed at identifying cellular and molecular mediators of preserved cognition in the face of amyloid and/or tau neuropathology. In addition, we will discuss how animal models can be used to nominate, prioritize, and investigate potential therapeutic targets.

Features of resilient individuals

A number of definitions have been used in recent years to attempt to describe and understand resilient individuals (Box 1 and Figure 1). A comprehensive histopathological study comparing

Highlights

Some individuals retain cognitive function despite high levels of Alzheimer's disease (AD) pathology. Understanding the biology behind this form of 'AD resilience' may lead to opportunities for therapeutic development.

Human genetic studies and postmortem analyses have identified a number of factors associated with cognitive resilience to AD pathology, including overall maintenance of synapse structure and candidate molecular mediators (e.g., REST, NRN1, among others).

Genetically and phenotypically diverse mouse models of AD provide new and translationally relevant opportunities to identify and prioritize new resilience mechanisms.

Approaches integrating results from both human and mouse studies will provide an effective path toward the development of therapeutics promoting resilience in susceptible human populations.

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Box 1. Defining AD resilience

Generally, resilient individuals are those who evade cognitive decline associated with observed levels of amyloid and/or tau neuropathology and/or inheritance of deleterious autosomal dominant AD mutations [74–76] (see Figure 1A,B in main text). It has been hypothesized that these individuals exhibit higher levels of ‘cognitive reserve’, where functional brain processes are better able to cope with changes induced by neuropathology, or ‘brain reserve’, where variation in structural characteristics of the brain (e.g., neuron or synapse numbers) increases the ability of an individual’s brain to deal with neuropathological insults [77].

To understand the mechanisms and specific factors that differentiate resilient versus susceptible individuals, individuals can be grouped into bins (e.g., non-demented with AD pathology versus demented with AD pathology). Historically, this has been done postmortem using classifications from autopsy-based neuropathological scores on standardized scales such as the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) score for neuritic plaques [78] and Braak staging of neurofibrillary tangles [79] in combination with antemortem scores on standardized cognitive tests.

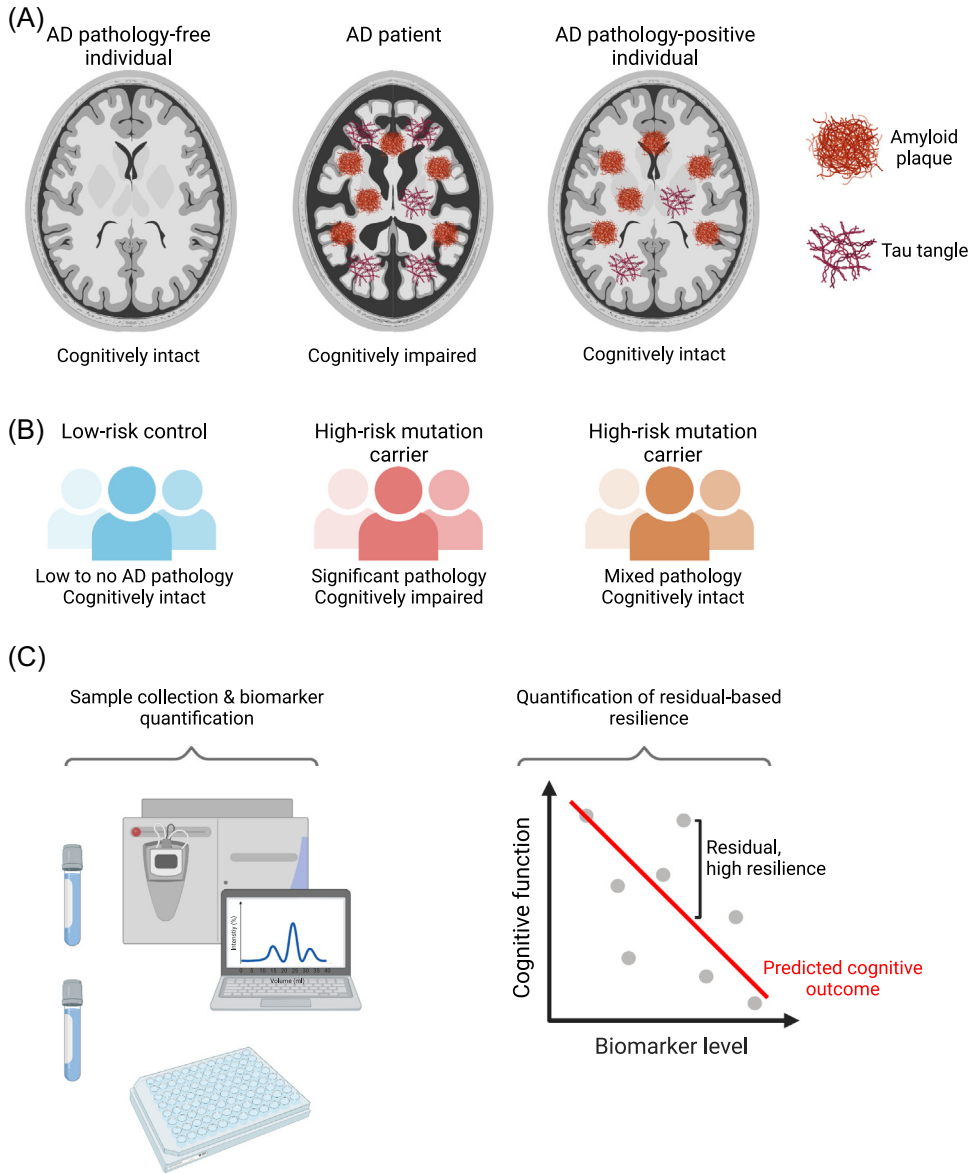
Beyond discrete classification systems, the development of approaches that define resiliency as a continuous metric has been aided by the development of quantitative measurements of pathology, including CSF biomarkers, uptake of amyloid- and tau-specific ligands measured via positron emission tomography (PET) imaging, and structural magnetic resonance imaging (MRI) that quantifies various metrics such as brain volume. The measures are aggregated to calculate a predicted cognitive outcome given an individual’s measured pathology; this predicted value is compared with the same individual’s actual cognitive performance. The discrepancy between the predicted and observed outcome, or the proportion of the cognitive score not explained by neuropathology (i.e., the model residuals), is used to quantify an individual’s level of resilience (see Figure 1B in main text). Nonresidual-based continuous metrics have also been developed [80], such as the AD Cognitive Resilience (AD-CR) score. This score is computed using a global measure of cognition obtained proximal to death and postmortem AD pathology. Machine learning algorithms trained using this information may eventually be able to predict whether an individual will have an extremely high or low AD-CR score and thus be at extremely high or low risk for progressing into AD dementia. Across these measures, individuals that perform better than predicted given an observed level of pathology are said to have high resilience. The main benefit of these approaches is that they do not exclude individuals that do not fit neatly into discrete bins but allow for interrogation of the entire study population.

pathology-positive non-demented individuals with AD cases and pathology-free controls found a striking preservation of neuron numbers, synaptic markers, and axonal morphology in resilient individuals compared with the demented cases [7] (Table 1). In addition, resilient individuals exhibited a unique cytokine profile consisting of higher levels of anti-inflammatory cytokines and neurotrophins along with lower levels of chemokines associated with microglial recruitment and activation [9]. Spine density was found to be significantly reduced in AD patients relative to both pathology-free controls and pathology-positive non-demented individuals [10], suggesting maintenance of critical brain structures is an important determinant of maintained cognitive function in the face of pathology. Interestingly, studies have found that resilient individuals have lower levels of hyperphosphorylated tau accumulation in the synaptic compartment [7] and neocortical areas [11], despite comparable levels of amyloid. Across studies, tau pathology seems to be more strongly linked to cognitive outcomes than amyloid pathology [12–14], suggesting resilience to tau pathology is less common than resilience to amyloid pathology.

Beyond discrete classification systems, a number of studies have used a residual-based approach to identify features common to resilient individuals (Box 1 and Table 1). For example, cortical thickness is associated with cognitive resilience to pathological tau [15], while younger age and higher education was well correlated with resilience to structural changes and CSF/plasma-based biomarker metrics [15–17]. An additional benefit to studies that incorporate relatively noninvasive measurements is their ability to be repeated over time. There is some evidence that resilience capacity can change over time, with overall levels of resilience decreasing with age [18]. While cross-sectional measures of residual-based resilience were indeed associated with cognitive outcomes [19], there is some evidence that change in resilience metrics over time is even more useful for predicting cognitive decline over time and identifying those individuals most at risk of developing dementia [18], which is important for identifying when individuals stand to benefit most from early intervention and preventative-based therapeutics and clinical trials.

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Trends in Neurosciences

Figure 1. Strategies to identify resilient individuals in human populations. (A) Example of a discrete classification system used to identify resilient individuals. In this classification, each individual is assigned into one of the three groups: cognitively unimpaired individuals, free from significant Alzheimer’s disease (AD) pathology (left); AD patients, with brain atrophy, amyloid plaques, and hyperphosphorylated tau tangles (middle); and ‘resilient’ individuals, with no apparent cognitive impairment despite the presence of AD pathology (right). Preservation of brain volume and decreased accumulation of tau tangles have been associated with resilience, although specific features of resilient individuals can vary across studies and cohorts. (B) Resilient individuals can also be identified based on susceptibility to mutations typically associated with increased risk for AD. A subset of the population is at relatively low genetic risk for AD and will exhibit limited accumulation of AD pathology and has a high likelihood of remaining cognitively intact (left). Another subset will inherit deleterious mutations associated with increased risk for AD: some of these individuals will go on to develop AD pathology and dementia as expected (middle), while a resilient subset will remain cognitively intact throughout the lifespan (right), despite varying levels of pathology. (C) Resilience can also be quantified as a continuous metric. In this approach, diagnostic samples are first collected and biomarkers are quantified (left). These measures are aggregated with other demographic factors including, for instance, age, sex, and educational status, to predict an individual’s expected cognitive

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Targeted investigation of genetic and molecular mediators of resilience

Identification of the specific genetic factors that promote resilience to AD pathology or autosomal dominant familial AD mutations may provide a starting point for uncovering novel therapeutic targets. Specific populations at high genetic risk for AD represent an opportunity to interrogate mechanisms that enable some mutation carriers to ‘escape’ the predicted effect of the mutation on cognitive outcomes. For example, a recent case study reported a carrier of a *PSEN1* mutation (*PSEN1* E280A) who did not develop mild cognitive impairment until her seventies despite high levels of amyloid [20]. Carriers of the *PSEN1* E280A mutation exhibit an average age of dementia onset at 49 years [21,22], so this individual seemed highly resilient to the typically deleterious effects of the mutation [20]. This specific incidence of resilience was attributed to the presence of a homozygous *APOE* variant known as the Christchurch mutation [23] that confers reductions in low-density lipoprotein receptor and heparin binding [20], implicating these mechanisms as putative drivers of resilience in the face of high amyloid deposition. The value of these pathways as therapeutic targets remains to be elucidated, as the Christchurch mutation was also linked to reduced tau pathology in the *PSEN1* E280A carrier [20], which suggests some of the benefits of the mutation may be conferred through resistance to developing primary pathologies associated with AD rather than true resilience as defined earlier.

Populations at high genetic risk for AD provide several other important opportunities for the investigation of resilience. One approach, for instance, involved genome-wide searches for the modifiers of the age at onset of cognitive decline in families carrying what are typically considered highly penetrant mutations. These studies have identified several putatively involved genes [24,25] (Table 1). In addition, these populations provide the opportunity for targeted investigation into hypothesized resilience factors such as *BDNF*. For example, it was found that an SNP in *BDNF* (*BDNF*_{Val66Met}) was associated with worsened neurodegeneration and cognitive decline given amyloid pathology across individuals with autosomal dominant AD, studied as part of the Dominantly Inherited Alzheimer Network (DIAN) cohort [26]. Individuals with *APOE*- ϵ 4 genotype provide a similar opportunity. Although *APOE*- ϵ 4 has been identified as the most significant genetic risk factor for AD, some ϵ 4 homozygous individuals do not develop AD as expected. Several candidate genes (Table 1) have been associated with reduced AD risk in *APOE*- ϵ 4-positive individuals [27,28], highlighting these genes as potential therapeutic intervention points. For example, levels of the soluble form of the AD risk gene *TREM2* (sTREM2) found in the CSF of biomarker-positive AD patients were found to significantly modify the effect of an *APOE*- ϵ 4 allele independent of primary AD pathology [29]. Higher CSF levels of sTREM2 were also found to be associated with slower decline in memory and cognition in biomarker-positive AD patients [30]. It is worth noting that some of the ‘resilience’ genes identified have also been associated with reduced levels of pathology [31,32], highlighting the need to disentangle effects associated with true resilience to pathology from resistance to developing these pathologies.

Genome-wide approaches to discover genetic and molecular mediators of resilience

With the advent of more affordable genetic profiling, higher-throughput monitoring of relevant biomarker metrics including CSF-, plasma-, and imaging-based metrics, as well as quantitative, continuous metrics of resilience, whole-genome discovery-based studies of resilience are now feasible. Here, residual resilience metrics are calculated across a population and treated as a

performance (prediction line in red). Results are then compared with the same individual’s actual cognitive performance, and the discrepancy between these two values (i.e., the residual) is used to quantify resilience. Individuals with better than predicted cognitive function (above red line) are said to exhibit high resilience, while those with worse than predicted cognitive function (below red line) are said to exhibit low resilience.

Table 1. Select factors correlated with resilience in humans^a

Trait	Cohort	Directionality	Refs
Structural			
Cortical thickness	A β -positive individuals with MCI or dementia; residual metrics used to define resilience	Increased thickness associated with cognitive resilience to tau pathology	[15]
Spine density	AD patients vs. pathology-free controls vs. pathology-positive, non-demented controls	Spine density and numbers of thin and mushroom spines reduced in AD cases only	[10]
Neuron numbers, synaptic markers	AD vs. pathology-free controls vs. pathology-positive, non-demented	Preservation of these features observed in pathology-positive controls	[7]
Glial activation	AD vs. pathology-free controls vs. pathology-positive, non-demented	Lower activation in resilient individuals	[7]
Molecular			
Cortical proteins including NRN1, EPHX4, SGTB, CPLX1	ROSMAP	Higher levels of these proteins associated with greater resilience to several pathologies	[35]
REST protein levels	Pathology-positive controls vs. AD patients	Nuclear REST levels higher in cognitively intact individuals	[53]
CSF levels of VEGF	ADNI	Elevated CSF VEGF associated with better cognitive outcomes in pathology-positive individuals	[86]
IGFBP5, HSPB2, AK4, ITPK1 protein in DLPFC	ROSMAP	IGFBP5, HSPB2, AK4 – higher protein levels associated with faster cognitive function, opposite for ITPK1. Associations not explained by neuropathology.	[87]
<i>ENC1</i> , <i>UNC5C</i>	ROSMAP	Multomics approach (genetic, epigenetic, transcriptomic) prioritized the aforementioned genes; increased <i>UNC5C</i> RNA associated with worse residual-based resilience and increased <i>ENC1</i> associated with increased residual-based resilience	[33]
Cytokine profiles in entorhinal cortex and superior temporal sulcus	Non-demented individuals with (i) no, (ii) moderate, (iii) high pathology and AD patients	Resilient cases had unique profile – increased anti-inflammatory cytokines, increased neurotrophic factors, decreased microglial recruitment chemokines	[9]
sTREM2 levels in CSF	Subjects with AD defined by CSF biomarkers	Higher CSF sTREM2 associated with attenuated decline in memory and cognition	[30]
<i>MEF2C</i>	Pathology-positive subjects with or without AD dementia	Higher <i>MEF2C</i> observed in resilient individuals, specifically within a subset of translationally active excitatory neurons	[38]
LAP3, MACROD1, SEMA7A protein in synapse	Pathology-positive cognitively intact 'resilient' patients vs. AD patients	Resilient subjects had lower levels of these proteins in synapses compared with AD patients	[37]
Proteins involved in serotonin release, oxidative phosphorylation, glycolysis, and proteasome function	Pathology-positive cognitively intact 'resilient' patients vs. AD patients	Resilient subjects had an enrichment for serotonin- and oxidative phosphorylation-related proteins in the synapse, as well as depletion of glycolysis- and proteasome-related proteins in the synapse	[37]
Genetic			
<i>APOE</i> Christchurch mutation	<i>PSEN1</i> E280A carrier	Homozygous mutation protected against high levels of pathology	[20]
<i>BDNF</i> Val66Met mutation	DIAN, among others	Mutation associated with worsened neurodegeneration and cognitive decline	[26,88–90]
<i>Klotho</i> haplotype VS	<i>APOE</i> - ϵ 4 positive individuals	One copy of haplotype lowered AD risk (but also reduced A β and tau positivity on PET)	[28,31,32]
<i>SNX25</i> , <i>PDLIM3</i> , <i>SORBS2</i>	Caribbean Hispanics with <i>PSEN1</i> p.G206A mutation	Association with age at onset in early- and late-onset AD	[24]
Gene variants near <i>CD44</i> , <i>NPHP1</i> , <i>CADPS2</i> , <i>GREM2</i>	Families carrying <i>PSEN1</i> E280A mutation	Variants associated with age at onset of AD	[25]

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Table 1. (continued)

Trait	Cohort	Directionality	Refs
Gene variants near <i>CASP7</i> , <i>SERPINA3</i>	APOE-ε4 carriers	Variants associated with AD risk	Reviewed in [27]
Variant upstream <i>ATP8B1</i>	Four cohorts: A4, ROSMAP, ADNI, ACT	Variant associated with combined (i.e., cognitive and brain structural based) resilience in cognitively intact subset of patients	[17]
Variation at chromosome 8 locus	Mayo Clinic Study of Aging and ADNI	Variant associated with differential cognitive resilience to brain amyloid	[34]
Lifestyle			
Educational attainment	Various	Higher education is associated with increased resilience across cohorts and studies	[15–17,91], among others
Early-life cognitive enrichment	MAP	Cognitive enrichment was associated with less cognitive decline, 80% of the effect was independent of neuropathology	[92]

^aAbbreviations: A4, Anti-Amyloid Treatment in Asymptomatic Alzheimer’s study; ACT, Adult Changes in Thought study; AD, Alzheimer’s disease; ADNI, Alzheimer’s Disease Neuroimaging Initiative; DLPFC, dorsolateral prefrontal cortex; GWAS, genome-wide association studies; MCI, mild cognitive impairment; ROSMAP, Religious Orders Study/Memory and Aging Project.

quantitative variable for association studies in order to identify specific variants, genes, proteins, and/or pathways associated with the resilience phenotype [18]. As sample sizes are generally still small compared with traditional case–control genome-wide association studies (GWAS), relatively few genome-wide significant associations have been found [17,33,34]. Hits have been prioritized by combining genetic data with various additional functional omics datasets, including methylation data and dorsolateral prefrontal cortex (DLPFC) RNA expression [33]. At the pathway level, associations with resilience included amino acid metabolism, prolactin receptor signaling, and the dehydrogenase pathway [17] as well as integrin-related cell adhesion and T-cell factor signaling related to the Wnt/B-catenin pathway [34], nominating relatively broad biological categories for therapeutic intervention rather than specific therapeutic targets. Beyond genetic mediators of resilience, unbiased proteomics has identified cortical proteins strongly associated with levels of resilience [35], including NRN1 (Table 1), which, similar to BDNF, is a neurotrophic factor known to play important roles in synaptic function and plasticity as well as maintenance of axonal morphology [36]. An additional study uniquely focused on synaptic proteins identified decreased levels of proteins including MAP3 and SEMA7A in synapses from resilient individuals relative to AD patients, as well as an overall enrichment for proteins involved in the serotonin release cycle and oxidative phosphorylation and depletion of protein involved in glycolysis and proteasome-related processes [37] (Table 1). Single-nuclear sequencing has also been used to identify a resilience-related increase in MEF2C in a specific subpopulation of translationally active excitatory neurons [38] (Table 1), demonstrating the utility of these high-dimensional and unbiased assays to identify specific molecular mediators of resilience to AD pathology.

Using animal models to study resilience

While human-focused studies of resilience are crucial, drawbacks to these studies exist (Box 2), calling for complementary research approaches. Model organism studies provide an important resource to begin to address the outstanding questions surrounding resilience mechanisms through longitudinal, mechanistic, and/or interventional studies with controlled environmental factors. Mice have emerged as a particularly useful model organism due to their affordability, shared genetic features with humans, short generation time, and the vast array of mouse-specific genetic engineering resources. As mice do not naturally develop AD, genetic engineering is necessary to introduce human genes harboring mutations that lead to early-onset AD. These mutations typically drive the overproduction of amyloid, which accumulates in the brain of these animals

Box 2. Potential drawbacks to human-based studies of resilience

While both targeted and genome-wide studies identified correlates with resilience in the human population, it is important to note several limitations of these types of analyses. Because brain tissue from individuals in these cohorts is not accessible during their lives, many studies use postmortem tissue to identify molecules (e.g., RNA, protein) that are associated with performance on cognitive tests prior to death. However, in these studies, brain regions used to examine the molecular mediators of resilience are typically selected based on already-known involvement in disease risk (e.g., hippocampus and prefrontal cortex). It is possible that molecular changes that confer resilience originate in brain regions outside those classically affected in AD and are thus not typically selected for analyses. In addition, mechanisms and molecules important for resilience are likely expressed and act well before the time at which these tissues can be accessed. This lack of access to brain tissue early in the disease course is a significant barrier to understanding the molecules most closely associated with the onset of resilience (and/or dementia). In addition, the ability to test mechanistic hypotheses is generally limited in human populations, as the identification of molecules associated with cognitive outcomes is largely correlative [81]. Other potential caveats and considerations, such as the limitations associated with retrospective group assignments, have been highlighted elsewhere [81]. Together, these factors have precluded a clear understanding of when in disease course and where in the brain differences between resilient and susceptible individuals are first detectable, a key piece of information that will enable the eventual development of targeted therapeutics. These limitations create a critical need for innovative approaches to synergize the power of animal AD models with the wealth of medically relevant human data presently available to parse out the spatial and temporal origins of resilience, as well as to establish causation and screen actionable resilience interventions.

and induces AD-relevant symptoms including cognitive decline, synaptic dysfunction, and neurodegeneration.

Historically, model organism studies have varied one condition in genetically identical individuals (e.g., inbred mice) to evaluate the impact on disease outcomes. While many important insights into disease pathogenesis have been achieved using this approach, recently the importance of expanding model organism studies to include additional unique genotypes has been receiving growing recognition. Specifically, genetic reference panels (GRPs) have emerged as a useful tool to incorporate genetic diversity into mouse studies in a systematic way (Box 3). Another notable development is that in addition to various forms of inbred lines, studies have begun to incorporate genetic diversity in the form of outbred mice, particularly the Diversity Outbred (DO) panel population of systematically outbred mice originating from the same eight founder strains as the Collaborative Cross (CC) GRP [39].

Hypothesis-driven approaches to understanding mechanisms of resilience in mouse models

Animal models offer opportunities to test the causality of resilience factors identified in human studies. As mentioned previously, historically, this has often been performed in a single inbred line where the intervention or treatment is the only factor being manipulated to assess causality of the putative resilience factor. For example, viral delivery or overexpression of BDNF in various

Box 3. Mouse genetic reference panels

Two of the most well-characterized genetic reference panels (GRPs) are (i) the BXDs, named for the parental common inbred strains C57BL/6J (B) and DBA/2J (D) from which it is derived, and (ii) the Collaborative Cross (CC), derived from a systematic crossing scheme incorporating five common inbred strains and three wild-derived inbred strains [82]. In these GRPs, mice with unique combinations of each parental genotype are inbred until a new stable inbred line is created. The result is a large number of related inbred strains (the BXD GRP currently comprises 140 unique strains, while the CC GRP contains ~70 strains), each of which can be reproducibly studied across time, laboratories, and under different environmental conditions [72]. In addition, functional data such as transcriptional, proteomic, and behavioral profiles for each strain can be collected, combined, and shared in order to better prioritize nominated candidates as described in the main text for human data. GRPs allow for intense community collaboration, and a wealth of resources exist for each system (e.g., GeneNetwork.orgⁱⁱⁱ [83], Systems-Genetics.org^{iv} [84], and the Mouse Phenome Database^v [85] allow for data mining, visualization, and investigations of relationships between measures of interest). These resources enable investigation into the downstream effects of prioritized candidate genes and SNPs associated with traits of interest and facilitate the identification of relevant SNPs and molecular mechanisms from a large number of putative candidates.

animal models of AD has been shown to improve outcomes, as assessed via various markers of disease including hippocampal connectivity and cognitive tests, independent of any effects on amyloid or tau neuropathology [40,41] (Table 2). Similarly, overexpression of *Mef2* family transcription factors in neurons of a mouse model of tauopathy was sufficient to improve cognitive outcomes and rescue pathology-induced neuronal hyperexcitability without altering tau pathology [38] (Table 2).

Beyond the testing of specific gene candidates, animal models also enable targeted experimental investigation into pathways hypothesized to mediate resilience. In resilient patients, preservation of dendritic spines is consistently observed, raising the question of what are the mechanisms and pathways that preserve spines. Using cell and animal models, A β 42-induced spine loss was identified to be mediated, at least in part, through Rho-associated kinase ROCK2 and downstream activation of the kinase LIMK1 [42]. Treatment of AD model mice with a LIMK1 inhibitor rescued A β -induced hippocampal spine loss and morphological aberrations [42]. In addition, an intriguing observation across human populations is that despite similar levels of A β and tau, men show worse cognition [43], greater cognitive decline [44], increased neurodegeneration [45], and increased mortality [46] compared with women, suggesting an effect of sex on resilience and reduced resilience in men. A study in transgenic animal models found that the presence of an additional X chromosome either in males or females consistently improved A β -related mortality, cognitive deficits, and cellular viability [46]. The authors localized the protective effect to the gene *Kdm6a*, a histone demethylase that escapes X chromosome inactivation and is enriched in the brain. Overexpression of *Kdm6a* attenuated A β -induced neurotoxicity and cognitive

Table 2. Select factors associated with resilience in mouse models^a

Trait	Cohort	Directionality	Refs
Intrinsic neuronal excitability	B6SJL 5XFAD	Decreased neuronal excitability in 'weak-learners'	[50]
<i>Pla2g4e</i> expression and genotype	Tg2576	Increased <i>Pla2g4e</i> observed in 'resilient' mice	[51]
Synaptic protein levels	Tg2576	Increased in 'resilient' mice	[51]
Several gene networks, including immune- and amyloid degradation-related networks	Tg2576	Results suggest reduced CD4+ T cell infiltration in resilient mice	[49]
BDNF	J20 (amyloid transgenic) P301L (tau transgenic) mouse models	Overexpression improved AD-related outcomes independent of pathological changes	[40,41]
<i>Mef2</i> family of transcription factors	P301S tauopathy model	Overexpression of <i>Mef2a/c</i> improved cognitive outcomes and rescued neuronal hyperexcitability without changing tau pathology	[38]
<i>ApoE</i> genotype	AD-BXD	<i>D</i> allele associated with worsened cognitive outcomes	[56]
Genetic risk score derived from common AD risk genes	AD-BXD	Genotype at common AD risk genes associated with late-life cognitive outcomes	[56]
Several gene networks, including vascular- and immune-related networks	AD-BXD	Higher expression of immune-enriched networks early in life correlated with worse cognitive outcomes later in life, reverse was true for expression of vascular-related networks	[57]
Variation at chromosome 2 locus	AD-BXD	Genotype at identified locus regulated immune-related network expression	[57]
X chromosome, putatively <i>Kdm6a</i>	Transgenically modified mice with altered numbers of sex chromosomes and hAPP model mice	Additional X chromosome in either males or females improved A β -related mortality, cognitive deficits, and cellular viability. Overexpression of <i>Kdm6a</i> , which escapes X inactivation, was sufficient to recapitulate this effect in cell and animal models	[46]

^aAbbreviations: 5XFAD, common AD transgene incorporating five mutations known to cause familial AD in humans; AD, Alzheimer's disease; AD-BXD, F1 genetic reference panel generated by introducing the 5XFAD transgene into the BXD panel (see Box 3 for details); B6SJL, mixed background strain derived from the inbred strains C57BL/6J and SJL/J; BDNF, brain-derived neurotrophic factor.

impairment in both cell and animal models [46], nominating *Kdm6a* as a putative mechanistic driver of resilience.

Exploiting phenotypic diversity to identify resilience mechanisms

Beyond mechanistic investigation of previously identified resilience factors [40,41,47], mouse models also provide a powerful tool to investigate differential susceptibility to typically highly deleterious AD mutations – similar to the approach described previously using families harboring autosomal dominant AD mutations (Figure 2). In animal model studies, various studies have shown that even within a single inbred strain, mice are not uniformly susceptible to the cognitive effects of amyloid and/or tau accumulation [48–51]. For example, two independent groups found that when mice are subjected to paradigms meant to measure learning and memory, age-matched AD mice could be divided into either ‘weak-learner’ or ‘strong-learner’ subsets [49–51]. Across studies, whether a particular mouse exhibited cognitive deficits was not significantly associated with amyloid plaque density, levels of tau hyperphosphorylation, or markers of glial activation, suggesting that the ‘strong-learners’ were exhibiting resilience to neuropathology [50,51]. The identification of these independent subsets provides an opportunity to investigate causal mechanisms driving resilience. In the case of Tg2576 transgenic mice, resilient animals exhibited higher levels of synaptic proteins, suggesting preserved synaptic function [51] (Table 2). Similarly, resilient mice carrying the 5XFAD transgene exhibited a higher degree of learning-related intrinsic neuronal plasticity relative to 5XFAD weak-learners [50] (Table 2). Together, these studies highlight

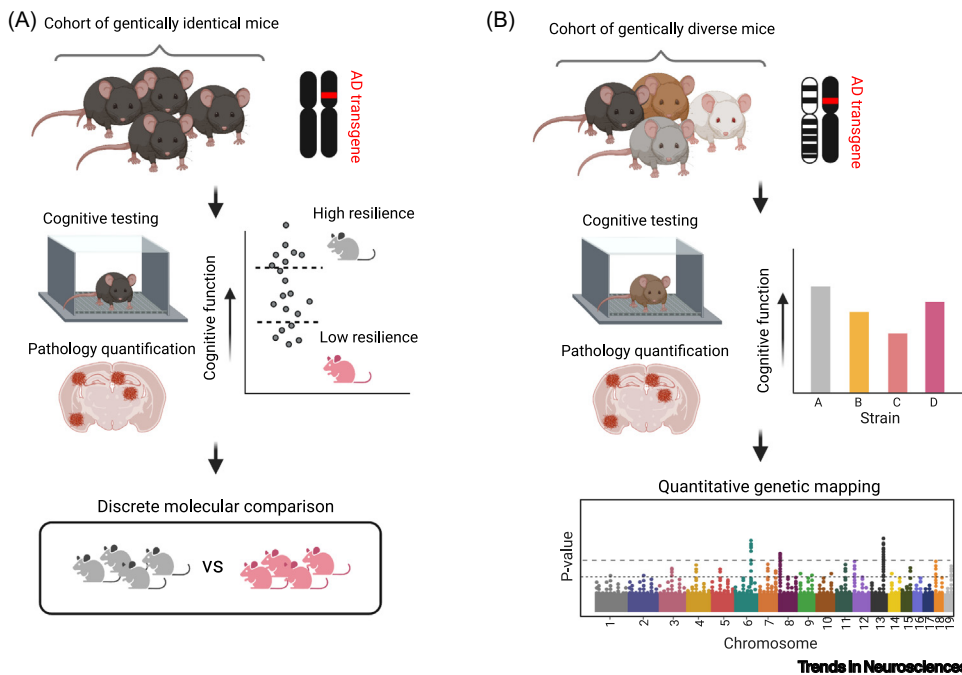


Figure 2. Exploiting phenotypic or genetic diversity in mouse populations to investigate molecular and genetic mediators of resilience. (A) Phenotypic diversity among genetically homogenous strains of mice harboring Alzheimer’s disease (AD) transgenes can be harnessed to classify individuals into discrete ‘high resilience’ (i.e., strong-learner) or ‘low resilience’ (i.e., weak-learner) categories. Pathology can be quantified using a range of techniques including immunohistochemistry to account for differences in amyloid and/or hyperphosphorylated tau accumulation. (B) Traditional animal models do not incorporate genetic diversity, which in human populations contributes to differing levels of resilience. By introducing AD transgenes into diverse models including the BXDs, Collaborative Cross, or Diversity Outbred panels, strain-by-strain differences in cognitive outcomes and pathology can be quantified and used for genetic mapping in order to identify specific genetic mediators of resilience.

maintenance of synaptic structure and neuronal excitability as an important mechanism mediating resilience to AD pathology. Transcriptomic analysis comparing Tg2576 resilient and susceptible mice identified the gene *Pla2g4e* (phospholipase A2 group IVE) as a putative driver of resilience [51]. Subsequent overexpression of *Pla2g4e* in hippocampal neurons of AD mice was sufficient to completely restore cognitive function and increase spine number without affecting amyloid or tau pathology [51]. In addition, *PLA2G4E* was found to be decreased in the brains of late-stage AD human patients, suggesting this approach identified a translationally relevant therapeutic target. A similar transcriptomic analysis also identified several additional pathways putatively involved in resilience and predicted a reduced infiltration of peripheral immune cells into the brains of resilient mice [49]. A previous investigation into the hippocampal membrane proteome of 5XFAD strong-learners and weak-learners identified several putative drivers of resilience, including the epigenetic modifier REST [52] previously associated with resilience to pathology in human populations [53] (Table 2). Together, these findings demonstrate the powerful translational potential of harnessing variable AD susceptibility in animal models.

Exploiting genetic diversity to identify resilience mechanisms

Traditionally, animal model studies of resilience to AD have often relied on experiments within a single strain. While variable susceptibility within a single strain provides important mechanistic insight into resilience, focusing on a single strain leads to a scenario that is distant from the degree of genetic diversity of human populations. Comparison of genetically distinct mouse strains harboring identical amyloid- or tau-overexpressing transgenes has confirmed the presence of variable susceptibility across strains to disease outcomes including pathological burden and overall survival [48,54,55]. To specifically use GRPs (Box 3) to identify resilience factors, a new F1 mouse population was generated by introducing the well-established 5XFAD transgene into almost 30 BXD strains [56]. This panel, referred to as the AD-BXDs, was thoroughly characterized for a variety of disease-relevant traits, including amyloid deposition and cognitive decline. As hypothesized, a wide range of cognitive outcomes was observed across the strains despite similar levels of amyloid pathology [56], demonstrating differing levels of cognitive resilience depending on an individual strain's genetic makeup. Notably, genotype at well-defined late-onset AD risk factors including *ApoE*, *Bin1*, and *Clu*, among others, influenced cognitive outcomes in the AD-BXDs, suggesting this novel panel represents a resource with high translational potential [56] (Table 2). Of note, the single *ApoE* mutation segregating across the AD-BXDs occurs near the receptor-binding region of the protein, where the highly protective Christchurch mutation occurs in human populations. This suggests that the AD-BXDs, in addition to their utility in identifying modifiers of familial AD, could be useful for identifying more general modifiers of late-onset AD susceptibility.

The reproducible nature of an F1 GRP design provides an opportunity to understand genetic and molecular drivers of resilience. Specifically, transcriptional networks present early in life, at a time point at which the AD-BXDs were not impaired as a population relative to their wild-type littermates, were related to strain-specific cognitive outcomes in later life [57]. Networks related to neuroinflammation, brain vasculature, extracellular matrix organization, and synaptic signaling were associated with cognitive resilience in this population [57], mirroring some of the pathways (e.g., vascular risk, synaptic structure) important in regulating human resilience (Table 2) and highlighting these as mechanisms that may drive resilience. Due to the genetic structure of the AD-BXDs, genetic mapping can be used to identify specific regions associated with traits of interest. A region on chromosome 2 was identified as containing variants that directly modulate expression of identified resilience networks in AD-BXD mice [57]. Interestingly, the human equivalent of this region was also associated with age at AD onset in familial AD studies [58,59], further demonstrating the translational relevance of this panel for identifying drivers of resilience that may be harnessed for future therapeutic development. Notably, beyond specific resilience to AD

pathology, the AD-BXDs can also be combined with their wild-type or non-transgenic littermates (i.e., the Ntg-BXDs) to understand and identify mechanisms that promote cognitive longevity across disease and normal aging [60,61].

Future directions for animal studies of resilience

Translating findings from animal models to the human condition is not without challenges. For example, microglia, the resident immune cells of the brain, have been identified as cells involved in disease progression [62]. However, significant differences exist between the mouse and human immune systems, and these could translate into marked differences in the microglial response to amyloid [63]. In addition, most transgenes used to study AD in mouse models overexpress human mutant *APP* and *PSEN1* in a cell-type-specific manner. In humans, mutations are presumably expressed in all cell types, so the expression of transgenes only in a single cell type, typically neurons, prohibits the identification of how these mutations may drive disease through effects on intercell communication or non-neuronal mechanisms. Newer models incorporating AD mutations directly into the mouse orthologs have not replicated all findings in earlier transgenic models, raising the concern that some aspects of disease in these mice are driven purely by overexpression artifacts rather than mutation status [64]. Finally, most of the widely used animal models of AD produce no detectable tau pathology. This is primarily because variants in the gene encoding for tau, *MAPT*, have not been genetically associated with AD and were therefore thought not to be a valid way to genetically model AD in the mouse. However, because tau pathology is part of the diagnostic criteria for AD, models that incorporate some degree of tau pathology likely come closer to recapitulating the human disease. A recent study identified the MEF2 family of transcription factors as potential mediator(s) of resilience to tau pathology with high translational relevance, demonstrating the utility and potential of this approach [38]. As such, incorporating tau pathology into future studies of resilience to AD will be critical. For example, the AD-BXD reference panel could be regenerated using alternative AD models harboring tau mutations. This approach could provide important insight into the overlap or discordance between the genetic mediators of resilience to amyloid or tau pathology. Importantly, as tau pathology appears to be more intimately coupled to cognitive outcomes than amyloid in human populations, understanding the genetic mechanisms that enable resilience to tau pathology may provide the most broadly applicable therapeutic targets.

While the BXD family contains six million SNPs [65], this degree of genetic diversity does not reach what is observed across the human population. By contrast, the wild-derived strains used to generate the CC and DO panels harbor almost 40 million SNPs relative to the reference C57BL6J genome [39]. Introduction of AD transgenes into these wild-derived strains themselves produces a wide variation in amyloid deposition, neuronal cell loss, and microglial morphology and activation [66,67]. Similar to the approach used to generate the AD-BXDs discussed earlier, future studies incorporating AD transgenes into CC strains could provide insights into which, if any, CC strains exhibit cognitive resilience to amyloid deposition and could offer opportunities to identify novel resilience factors that may not exhibit genetic variation in the BXD GRP. The areas of oncology and immunology offer some precedents in that regard: the introduction of disease-causative transgenes into the DO population has proven useful in identifying mediators of prostate cancer [68] and immune dysfunction [69,70]. Possibly, the DO panel may prove similarly useful in nominating specific genetic resilience candidates. Encouraging data pointing in this direction are the differential resilience to normal cognitive aging in the DO panel, driven by genotype at *Dlgap2* and presumably subsequent alterations in spine morphology [71].

Laboratory mice also provide a unique opportunity to begin to understand the mechanisms by which various lifestyle factors may contribute to resilience [72]. Because of the well-defined

environment in which laboratory mice are housed, researchers can systematically vary a single lifestyle factor, such as diet, physical activity, or cognitive enrichment. The effect of each of these well-defined manipulations on cognitive outcomes can then be interrogated and mechanisms can be investigated, providing insight into how each of these interventions may influence disease outcomes. There is abundant evidence that environmental enrichment and physical activity improve disease outcomes in animal models of AD [73], but most of these studies have been conducted only in single inbred strains. Given that genetic heterogeneity may influence the effects of these interventions, it would be valuable to pair these approaches with genetically diverse models [72]. These approaches may also help identify specific human populations that stand to benefit most from certain lifestyle interventions, providing a pathway to personalized recommendations to promote resilience.

Finally, future studies utilizing genetically diverse animal models should continually strive to complement their findings with human data in order to maximize their translational relevance. Due to the combination of increased availability of large-scale human datasets and increased collaboration through consortia such as the Collaboratory on Research Definitions for Reserve and Resilience in Cognitive Aging and Dementia¹ and Resilience-ADⁱⁱ, it has become increasingly possible to perform cross-species analyses. Often, human studies that aim to identify resilience mediators by testing many genes or variants for association with cognitive function simultaneously suffer from low power due to low sample size and high statistical burden. Using prior knowledge gained from animal studies to test specific variants or genes for association with cognitive function in humans, rather than performing genome-wide searches, enables researchers to nominate new resilience mediators that may have been previously overlooked in these complex studies. It is worth noting that the approaches described here to understand resilience to AD, including incorporating genetic and phenotypic diversity across animal models of disease, are broadly applicable to a range of complex diseases. As these studies require large numbers of animals and phenotyping tests, and also generate large amounts of data, the continued development of high-throughput tools (e.g., automated behavioral assays, imaging, and biomarker analysis platforms) will be essential for effective progress.

Concluding remarks

Understanding how some individuals can retain cognitive function despite high levels of neuropathology is critical for developing therapeutics to prevent or delay the onset of dementia in the larger population. Initial studies have identified several factors that contribute to resilience to AD pathology, including the ability to maintain brain synapse structure and functional connectivity, potentially through the maintenance of neurotrophic factors including NRN1 and BDNF. Recent advances in the ability to quantitatively define resilience across large populations, in combination with relatively noninvasive CSF/plasma biomarkers and structural imaging measurements, have facilitated the search for genetic contributors to resilience.

To facilitate the identification of actionable resilience factors, a major goal for future work is to better understand which brain regions are involved, and at what time point in disease progression resilience mechanisms act (see [Outstanding questions](#)). This will necessitate brain-wide assessment at various time points throughout the lifespan, in contrast to profiling a single region with a single technology (e.g., PFC- and hippocampus-specific RNA sequencing). Understanding where in the brain (or body) resilience originates, when in the disease course it emerges, and how it progresses with age will provide critical insight for the development of effective therapies. Each of these questions can be systematically addressed when paired with both comprehensive human data and innovative mouse models that harness genetic complexity under well-defined environmental conditions. With these techniques, the field is hopefully well positioned to identify new avenues for therapeutic development in the coming years.

Outstanding questions

Quantifying resilience as a continuous metric eliminates the need to 'discard' data from patients that do not fit into discrete classification bins. This perspective, combined with noninvasive techniques to evaluate AD pathology, allows performing large-scale analyses of the genetic and molecular mediators of resilience. Will the use of larger cohorts result in the identification and prioritization of novel mediators of resilience to AD pathology?

Previous studies identified candidate features of resilience. Can these various metrics be integrated to identify individuals who may have low levels of innate resilience and thus be at a higher risk for developing dementia due to AD? Can this information be used to begin early intervention and/or optimize clinical trial enrollment? Is early intervention necessary, or can treatments which intervene after the onset of cognitive decline be effective?

While the use of the BXD genetic reference panel improved translational relevance of AD mouse models, the genetic diversity present in this panel does not approach the diversity present in the human population. Will the introduction of AD transgenes into more complex animal models of genetic diversity (i.e., CC, DO – [Box 3](#)) yield new insights into mediators of resilience?

As tau pathology is more closely linked to cognitive outcomes than amyloid and is a diagnostic criterion for AD, is inclusion of tau pathology necessary to identify translationally relevant mediators of resilience? What is the best translationally relevant model(s) for pre-clinical studies of therapeutic targets?

The exact brain region(s) and molecular mediator(s) for conferring enhanced resilience to AD pathology remain unclear. Can brain-wide studies designed to survey putative mediators at multiple levels (i.e., DNA, RNA, protein) help pinpoint which brain regions or molecules may be most highly associated with resilience? In addition, when do 'resilient' and 'susceptible' individuals first start to deviate?

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Declaration of interests

T.J.H. serves on the Scientific Advisory Board for Vivid Genomics. All other authors have no conflicts of interest to declare in relation to this work.

Resources

ⁱ<https://reserveandresilience.com>

ⁱⁱ<https://adknowledgeportal.synapse.org/Explore/Programs/DetailsPage?Program=Resilience-AD>

ⁱⁱⁱ<http://GeneNetwork.org>

^{iv}<http://Systems-Genetics.org>

^v<http://phenome.jax.org>

References

- Selkoe, D.J. (1991) The molecular pathology of Alzheimer's disease. *Neuron* 6, 487–498
- Gao, Y. *et al.* (2018) Tau in Alzheimer's disease: mechanisms and therapeutic strategies. *Curr. Alzheimer Res.* 15, 283–300
- Hardy, J.A. and Higgins, G.A. (1992) Alzheimer's disease: the amyloid cascade hypothesis. *Science* 256, 184–185
- Goate, A. *et al.* (1991) Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. *Nature* 349, 704–706
- Rahimi, J. and Kovacs, G.G. (2014) Prevalence of mixed pathologies in the aging brain. *Alzheimers Res. Ther.* 6, 82
- Aizenstein, H.J. *et al.* (2008) Frequent amyloid deposition without significant cognitive impairment among the elderly. *Arch. Neurol.* 65, 1509–1517
- Perez-Nievas, B.G. *et al.* (2013) Dissecting phenotypic traits linked to human resilience to Alzheimer's pathology. *Brain* 136, 2510–2526
- Schneider, J.A. *et al.* (2009) The neuropathology of older persons with and without dementia from community versus clinic cohorts. *J. Alzheimers Dis.* 18, 691–701
- Barroeta-Espar, I. *et al.* (2019) Distinct cytokine profiles in human brains resilient to Alzheimer's pathology. *Neurobiol. Dis.* 121, 327–337
- Boros, B.D. *et al.* (2017) Dendritic spines provide cognitive resilience against Alzheimer's disease. *Ann. Neurol.* 82, 602–614
- Latimer, C.S. *et al.* (2019) Resistance and resilience to Alzheimer's disease pathology are associated with reduced cortical pTau and absence of limbic-predominant age-related TDP-43 encephalopathy in a community-based cohort. *Acta Neuropathol. Commun.* 7, 91
- van Rossum, I.A. *et al.* (2012) Injury markers but not amyloid markers are associated with rapid progression from mild cognitive impairment to dementia in Alzheimer's disease. *J. Alzheimers Dis.* 29, 319–327
- Arriagada, P.V. *et al.* (1992) Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. *Neurology* 42, 631–639
- Hyman, B.T. *et al.* (2012) National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. *Alzheimers Dement.* 8, 1–13
- Ossenkopppele, R. *et al.* (2020) Assessment of demographic, genetic, and imaging variables associated with brain resilience and cognitive resilience to pathological tau in patients with Alzheimer disease. *JAMA Neurol.* 77, 632–642
- Lin, L. *et al.* (2021) Resilience to plasma and cerebrospinal fluid amyloid-beta in cognitively normal individuals: findings from two cohort studies. *Front. Aging Neurosci.* 13, 610755
- Dumitrescu, L. *et al.* (2020) Genetic variants and functional pathways associated with resilience to Alzheimer's disease. *Brain* 143, 2561–2575
- Bocancea, D.I. *et al.* (2021) Measuring resilience and resistance in aging and Alzheimer disease using residual methods: a systematic review and meta-analysis. *Neurology* 97, 474–488
- Hohman, T.J. *et al.* (2016) Asymptomatic Alzheimer disease: defining resilience. *Neurology* 87, 2443–2450
- Arboleda-Velasquez, J.F. *et al.* (2019) Resistance to autosomal dominant Alzheimer's disease in an APOE3 Christchurch homozygote: a case report. *Nat. Med.* 25, 1680–1683
- Quiroz, Y.T. *et al.* (2018) Association between amyloid and tau accumulation in young adults with autosomal dominant Alzheimer disease. *JAMA Neurol.* 75, 548–556
- Acosta-Baena, N. *et al.* (2011) Pre-dementia clinical stages in presenilin 1 E280A familial early-onset Alzheimer's disease: a retrospective cohort study. *Lancet Neurol.* 10, 213–220
- Wardell, M.R. *et al.* (1987) Apolipoprotein E2-Christchurch (136 Arg—Ser). New variant of human apolipoprotein E in a patient with type III hyperlipoproteinemia. *J. Clin. Invest.* 80, 483–490
- Lee, J.H. *et al.* (2015) Genetic modifiers of age at onset in carriers of the G206A mutation in PSEN1 with familial Alzheimer disease among Caribbean Hispanics. *JAMA Neurol.* 72, 1043–1051
- Velez, J.I. *et al.* (2013) Pooling/bootstrap-based GWAS (pbGWAS) identifies new loci modifying the age of onset in PSEN1 p.Glu280Ala Alzheimer's disease. *Mol. Psychiatry* 18, 568–575
- Franzmeier, N. *et al.* (2021) The BDNFVal66Met SNP modulates the association between beta-amyloid and hippocampal disconnection in Alzheimer's disease. *Mol. Psychiatry* 26, 614–628
- Huq, A.J. *et al.* (2019) Genetic resilience to Alzheimer's disease in APOE ε4 homozygotes: a systematic review. *Alzheimers Dement.* 15, 1612–1623
- Belloy, M.E. *et al.* (2020) Association of Klotho-VS heterozygosity with risk of Alzheimer disease in individuals who carry APOE4. *JAMA Neurol.* 77, 849–862
- Franzmeier, N. *et al.* (2020) Higher CSF sTREM2 attenuates ApoE4-related risk for cognitive decline and neurodegeneration. *Mol. Neurodegener.* 15, 57
- Ewers, M. *et al.* (2019) Increased soluble TREM2 in cerebrospinal fluid is associated with reduced cognitive and clinical decline in Alzheimer's disease. *Sci. Transl. Med.* 11, eaav6221
- Neitzel, J. *et al.* (2021) KL-VS heterozygosity is associated with lower amyloid-dependent tau accumulation and memory impairment in Alzheimer's disease. *Nat. Commun.* 12, 3825
- Belloy, M.E. *et al.* (2021) KL-VS heterozygosity reduces brain amyloid in asymptomatic at-risk APOE *4 carriers. *Neurobiol. Aging* 101, 123–129

33. White, C.C. *et al.* (2017) Identification of genes associated with dissociation of cognitive performance and neuropathological burden: multistep analysis of genetic, epigenetic, and transcriptional data. *PLoS Med.* 14, e1002287
34. Ramanan, V.K. *et al.* (2021) Coping with brain amyloid: genetic heterogeneity and cognitive resilience to Alzheimer's pathophysiology. *Acta Neuropathol. Commun* 9, 48
35. Yu, L. *et al.* (2020) Cortical proteins associated with cognitive resilience in community-dwelling older persons. *JAMA Psychiatry* 77, 1172–1180
36. Yao, J.J. *et al.* (2018) Functions and the related signaling pathways of the neurotrophic factor neuritin. *Acta Pharmacol. Sin.* 39, 1414–1420
37. Carlyle, B.C. *et al.* (2021) Synaptic proteins associated with cognitive performance and neuropathology in older humans revealed by multiplexed fractionated proteomics. *Neurobiol. Aging* 105, 99–114
38. Barker, S.J. *et al.* (2021) MEF2 is a key regulator of cognitive potential and confers resilience to neurodegeneration. *Sci. Transl. Med.* 13, eabd7695
39. Churchill, G.A. *et al.* (2012) The Diversity Outbred mouse population. *Mamm. Genome* 23, 713–718
40. Nagahara, A.H. *et al.* (2009) Neuroprotective effects of brain-derived neurotrophic factor in rodent and primate models of Alzheimer's disease. *Nat. Med.* 15, 331–337
41. Jiao, S.S. *et al.* (2016) Brain-derived neurotrophic factor protects against tau-related neurodegeneration of Alzheimer's disease. *Transl. Psychiatry* 6, e907
42. Henderson, B.W. *et al.* (2019) Pharmacologic inhibition of LIMK1 provides dendritic spine resilience against beta-amyloid. *Sci. Signal.* 12, eaaw9318
43. Buckley, R.F. *et al.* (2018) Sex, amyloid, and APOE ϵ 4 and risk of cognitive decline in preclinical Alzheimer's disease: findings from three well-characterized cohorts. *Alzheimers Dement.* 14, 1193–1203
44. Jack Jr., C.R. *et al.* (2015) Age, sex, and APOE ϵ 4 effects on memory, brain structure, and beta-amyloid across the adult life span. *JAMA Neurol.* 72, 511–519
45. Jack Jr., C.R. *et al.* (2016) Transition rates between amyloid and neurodegeneration biomarker states and to dementia: a population-based, longitudinal cohort study. *Lancet Neurol.* 15, 56–64
46. Davis, E.J. *et al.* (2020) A second X chromosome contributes to resilience in a mouse model of Alzheimer's disease. *Sci. Transl. Med.* 12, eaaz5677
47. Dubal, D.B. *et al.* (2015) Life extension factor klotho prevents mortality and enhances cognition in hAPP transgenic mice. *J. Neurosci.* 35, 2358–2371
48. Swarup, V. *et al.* (2019) Identification of evolutionarily conserved gene networks mediating neurodegenerative dementia. *Nat. Med.* 25, 152–164
49. Perez-Gonzalez, M. *et al.* (2021) Identifying the main functional pathways associated with cognitive resilience to Alzheimer's disease. *Int. J. Mol. Sci.* 22, 9120
50. Kaczorowski, C.C. *et al.* (2011) Mechanisms underlying basal and learning-related intrinsic excitability in a mouse model of Alzheimer's disease. *Neurobiol. Aging* 32, 1452–1465
51. Perez-Gonzalez, M. *et al.* (2020) PLA2G4E, a candidate gene for resilience in Alzheimer's disease and a new target for dementia treatment. *Prog. Neurobiol.* 191, 101818
52. Neuner, S.M. *et al.* (2017) Hippocampal proteomics defines pathways associated with memory decline and resilience in normal aging and Alzheimer's disease mouse models. *Behav. Brain Res.* 322, 288–298
53. Lu, T. *et al.* (2014) REST and stress resistance in ageing and Alzheimer's disease. *Nature* 507, 448–454
54. Jackson, H.M. *et al.* (2015) DBA/2J genetic background exacerbates spontaneous lethal seizures but lessens amyloid deposition in a mouse model of Alzheimer's disease. *PLoS One* 10, e0125897
55. Sipe, J.D. *et al.* (1993) Characterization of the inbred CE/J mouse strain as amyloid resistant. *Am. J. Pathol.* 143, 1480–1485
56. Neuner, S.M. *et al.* (2019) Harnessing genetic complexity to enhance translatability of Alzheimer's disease mouse models: a path toward precision medicine. *Neuron* 101, 399–411.e5
57. Neuner, S.M. *et al.* (2019) Identification of pre-symptomatic gene signatures that predict resilience to cognitive decline in the genetically diverse AD-BXD model. *Front. Genet.* 10, 35
58. Kehoe, P. *et al.* (1999) A full genome scan for late onset Alzheimer's disease. *Hum. Mol. Genet.* 8, 237–245
59. Pericak-Vance, M.A. *et al.* (2000) Identification of novel genes in late-onset Alzheimer's disease. *Exp. Gerontol.* 35, 1343–1352
60. Heuer, S.E. *et al.* (2020) Identifying the molecular systems that influence cognitive resilience to Alzheimer's disease in genetically diverse mice. *Learn. Mem.* 27, 355–371
61. Dunn, A.R. *et al.* (2020) Identifying mechanisms of normal cognitive aging using a novel mouse genetic reference panel. *Front. Cell Dev. Biol.* 8, 562662
62. Novikova, G. *et al.* (2021) Integration of Alzheimer's disease genetics and myeloid genomics identifies disease risk regulatory elements and genes. *Nat. Commun.* 12, 1610
63. Zhou, Y. *et al.* (2020) Human and mouse single-nucleus transcriptomics reveal TREM2-dependent and TREM2-independent cellular responses in Alzheimer's disease. *Nat. Med.* 26, 131–142
64. Sasaguri, H. *et al.* (2017) APP mouse models for Alzheimer's disease preclinical studies. *EMBO J.* 36, 2473–2487
65. Ashbrook, D.G. *et al.* (2021) A platform for experimental precision medicine: the extended BXD mouse family. *Cell Syst.* 12, 235–247.e9
66. Onos, K.D. *et al.* (2019) Enhancing face validity of mouse models of Alzheimer's disease with natural genetic variation. *PLoS Genet.* 15, e1008155
67. Yang, H.S. *et al.* (2021) Natural genetic variation determines microglia heterogeneity in wild-derived mouse models of Alzheimer's disease. *Cell Rep.* 34, 108739
68. Winter, J.M. *et al.* (2017) Mapping complex traits in a Diversity Outbred F1 mouse population identifies germline modifiers of metastasis in human prostate cancer. *Cell Syst.* 4, 31–45.e6
69. Wei, W.Z. *et al.* (2020) Diversity Outbred mice reveal the quantitative trait locus and regulatory cells of HER2 immunity. *J. Immunol.* 205, 1554–1563
70. Hackett, J.B. *et al.* (2021) A Diversity Outbred F1 mouse model identifies host-intrinsic genetic regulators of response to immune checkpoint inhibitors. *bioRxiv* Published online February 14, 2022. <https://doi.org/10.1101/2021.10.07.463570>
71. Ouellette, A.R. *et al.* (2020) Cross-species analyses identify Dlgap2 as a regulator of age-related cognitive decline and Alzheimer's dementia. *Cell Rep.* 32, 108091
72. Dunn, A.R. *et al.* (2019) Gene-by-environment interactions in Alzheimer's disease and Parkinson's disease. *Neurosci. Biobehav. Rev.* 103, 73–80
73. Shepherd, A. *et al.* (2018) Transgenic mouse models as tools for understanding how increased cognitive and physical stimulation can improve cognition in Alzheimer's disease. *Brain Plast.* 4, 127–150
74. Bekris, L.M. *et al.* (2010) Genetics of Alzheimer disease. *J. Geriatr. Psychiatry Neurol.* 23, 213–227
75. Reitz, C. *et al.* (2020) Late-onset vs nonmendelian early-onset Alzheimer disease: a distinction without a difference? *Neurol. Genet.* 6, e512
76. Cruchaga, C. *et al.* (2012) Rare variants in APP, PSEN1 and PSEN2 increase risk for AD in late-onset Alzheimer's disease families. *PLoS One* 7, e31039
77. Stern, Y. *et al.* (2020) Whitepaper: defining and investigating cognitive reserve, brain reserve, and brain maintenance. *Alzheimers Dement.* 16, 1305–1311
78. Fillenbaum, G.G. *et al.* (2008) Consortium to Establish a Registry for Alzheimer's Disease (CERAD): the first twenty years. *Alzheimers Dement.* 4, 96–109
79. Braak, H. *et al.* (2006) Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. *Acta Neuropathol.* 112, 389–404
80. Yao, T. *et al.* (2020) Quantifying cognitive resilience in Alzheimer's disease: the Alzheimer's Disease Cognitive Resilience Score. *PLoS One* 15, e0241707

81. Arenaza-Urquijo, E.M. and Vemuri, P. (2018) Resistance vs resilience to Alzheimer disease: clarifying terminology for preclinical studies. *Neurology* 90, 695–703
82. Churchill, G.A. *et al.* (2004) The Collaborative Cross, a community resource for the genetic analysis of complex traits. *Nat. Genet.* 36, 1133–1137
83. Mulligan, M.K. *et al.* (2017) GeneNetwork: a toolbox for systems genetics. *Methods Mol. Biol.* 1488, 75–120
84. Li, H. *et al.* (2018) An integrated systems genetics and omics toolkit to probe gene function. *Cell Syst.* 6, 90–102.e4
85. Bogue, M.A. *et al.* (2020) Mouse Phenome Database: a data repository and analysis suite for curated primary mouse phenotype data. *Nucleic Acids Res.* 48, D716–D723
86. Hohman, T.J. *et al.* (2015) The role of vascular endothelial growth factor in neurodegeneration and cognitive decline: exploring interactions with biomarkers of Alzheimer disease. *JAMA Neurol.* 72, 520–529
87. Yu, L. *et al.* (2018) Targeted brain proteomics uncover multiple pathways to Alzheimer's dementia. *Ann. Neurol.* 84, 78–88
88. Lim, Y.Y. *et al.* (2016) BDNF Val66Met moderates memory impairment, hippocampal function and tau in preclinical autosomal dominant Alzheimer's disease. *Brain* 139, 2766–2777
89. Lim, Y.Y. *et al.* (2015) APOE and BDNF polymorphisms moderate amyloid β -related cognitive decline in preclinical Alzheimer's disease. *Mol. Psychiatry* 20, 1322–1328
90. Lim, Y.Y. *et al.* (2018) Effect of BDNFVal66Met on disease markers in dominantly inherited Alzheimer's disease. *Ann. Neurol.* 84, 424–435
91. Busatto, G.F. *et al.* (2020) In vivo imaging evidence of poor cognitive resilience to Alzheimer's disease pathology in subjects with very low cognitive reserve from a low-middle income environment. *Alzheimers Dement. (Amst)* 12, e12122
92. Oveisgharan, S. *et al.* (2020) Association of early-life cognitive enrichment with Alzheimer disease pathological changes and cognitive decline. *JAMA Neurol.* 77, 1217–1224