Alzheimer's disease: the large gene instability hypothesis

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Abstract

All drug trials of the Alzheimer's disease (AD) have failed to slow the progression of dementia in phase III studies, and the most effective therapeutic strategy remains controversial due to our incomplete understanding of disease mechanisms. For decades, amyloid beta (Aβ) and its cascade have been the primary focus of AD drug design, but mounting evidence indicates that molecular pathways of this disease are more complex than the mainstream reductionist models.

Several genome-wide association studies (GWAS) have recently shed light on dark aspects of AD from a hypothesis-free point of view. While the newly identified AD risk loci rather raise more questions than they answer, they collectively implicate genes coding for receptors and transducers of cell adhesion pathways. Intriguingly, the classical hallmark genes of AD, including the amyloid precursor protein (APP), presenilins (PSEN), and APOE all take part in similar Aβ-independent pathways, and coordinate contact-guidance of neuronal growth cones in brain development.

Here, we have revisited function of 27 AD risk genes in pathways of normal cell physiology. Our review clearly shows that a disrupted cell adhesion signaling nexus, rather than a protein aggregation process, may be the central point of convergence in pathways of AD pathogenesis. Moreover, we conducted an exploratory bioinformatics analysis revealing that cell adhesion is the most representative ontology of extremely large human genes, and these genes are selectively expressed in the brain and take part in postsynaptic composition. We also show by statistical models that large synaptic genes may be more vulnerable to DNA damage accumulation in aging. As a prototypic example, Lrp1b codes for a giant lipoprotein receptor of the APOE protein, shows brain-specific expression, and maps to a chromosomal fragile site. Our model, the *large gene instability hypothesis*, implicates evolutionary forces of brain complexity as the etiology of AD, and warrants a paradigm shift in disease prevention and therapeutic design.

Keywords:

Alzheimer's disease; cell adhesion; integrin; focal adhesion kinase; DNA damage; anoikis

Glossary:

AD = Alzheimer's disease; **APP =** Amyloid precursor protein; **GWAS** = Genome-wide association study; **FAK** = Focal adhesion kinase; **PSD** = Postsynaptic density; **PSEN1/2** = Presenilin1/2; **SFK** = Src family kinase

Introduction

More than a century has passed since the first report of a presenile dementia case by Alois Alzheimer[1], and current understanding of AD pathophysiology mostly borrows from identification of the Aβ peptide as the main constituent of senile plaques and subsequent discovery of APP and PSEN mutations in rare forms of familial AD[2,3]. These observations were compiled to the amyloid cascade hypothesis in the pre-genomic era[4], the central model of AD etiopathogenesis that implicates Aβ species and neurofibrillary tangles as the main etiologies of neurodegeneration.

Nevertheless, due to methodological difficulties, Aβ species has hardly been validated as the causal force of neurodegeneration in humans. Despite receiving support from the preclinical models, manipulating pathways of Aβ generation and clearance has yielded disappointing results in several clinical trials so far[5]. While a handful of clinical failures do not necessarily warrant disproval of a theory *per se*, overemphasis on a single disease model is a dangerous gamble and could be one of the many explanations for the lack of progress in AD therapeutic design[6].

Accuracy of the amyloid cascade hypothesis is a topic of ongoing debate[7-12], and the alarming possibility of over-reliance on a wrong disease model warrants development of Aβ-independent hypotheses based on available evidence. In contrast to the classical hallmarks of AD including senile plaques and neurofibrillary tangles that are of questionable etiological significance[13], genetic risk factors temporally precede earliest stages of brain development, aging, and degeneration, and are expected to inform on causal disease pathways. The genetic architecture of sporadic late-onset AD is highly complex, and a number of susceptibility loci have been identified by recent genome-wide association studies[14-19]. However, mechanistic interpretation of these findings have been under powerful influence of the amyloid cascade theory.

This report servers to provide an evidence-based framework for compiling pathways of AD development from an Aβ-independent perspective. The rest of this manuscript is organized as follows; in the first section, we aim to revisit the role of classical and novel genetic risk factors of AD in pathways of normal cell physiology. We show that APP, presenilins and APOE as well as 23 other AD risk genes converge to common pathways of cell-extracellular adhesion

signaling, and coordinate neurite outgrowth in brain circuit development. In the second section, we provide a simple explanation for interaction of aging with the genetic architecture of AD using bioinformatics analysis. Finally, several testable predictions are provided for assessment of our new disease model.

1.1 The APP family proteins are evolutionarily conserved cell adhesion molecules

Derailed catabolism of the APP protein and generation of an aggregation-prone Aβ species abstract the mainstream model of AD, and several efforts have been made to block this cascade by means of Aβ immunotherapies or design of secretase inhibitors[5]. In contrast, three decades after successful cloning of the APP gene[20], the physiological role of its protein product remains elusive and may be the key to decoding disease mechanisms.

APP codes for a single-pass transmembrane protein with a high level of expression at the site of neuronal growth cones[21], structures that form motile tips of the outgrowing axons and dendrites in the developing brain. The Aβ peptide enhances interaction of neurites with extracellular adhesion molecules and promotes elongation of cell projections[22,23]. The full-length and membrane-tethered form of APP also interacts with extracellular laminin, heparan sulfate, fibronectin and collagen[24-26], i.e. extra-cellular matrix molecules that control contact-guidance of neuronal growth cones in synaptogenesis.

More specifically, interaction of APP with extracellular adhesion molecules including heparan sulfate[27] and laminin[24] stimulates assembly of hippocampal connections and outgrowth of neurites[28]. On the other hand, antisense-downregulation of APP inhibits extension of neurites[29]. APP shows a dose-effect in regulation of growth cone guidance[30] and its increased dosage in Down syndrome results in emergence of faster advancing growth cones with promoted adhesive properties and larger sizes[31]. In contrast, knockdown of the APP gene in zebrafish disrupts neurite outgrowth[32]. Intriguingly, although wild-type human APP can rescue this abnormal phenotype, the mutated APP of familial AD fails to substitute for the normal function of animal gene[32].

Several intracellular pathways are speculated to mediate the neurite-promoting effects of the APP protein. The netrin pathway of neurite guidance incorporates APP as a co-receptor[33]. In line, APP inactivation disrupts normal netrin signaling and diminishes axonal outgrowth[34]. APP also binds reelin, which is a large extracellular adhesion molecule for guidance and migration of neurons[35]. In this context, interaction of reelin with APP promotes outgrowth of hippocampal neurites[35], and this functional interaction requires presence of another cell adhesion molecule, the α3β1-integrin as well[35]. Integrin receptors are the main component of focal adhesion complexes, and show intriguing co-localization with the APP protein[36,37] at dynamic neuronal adhesion sites[38]. Interaction of integrin with APP modulates neurite outgrowth[39]. Integrin also acts as an accessory reelin receptor for cell adhesion regulation and neuronal migration[40-42]. Therefore, integrins functionally link two known AD risk genes, including APP and the APOE receptor pathway as we shall discuss later.

In addition to guiding growth cone navigation, the APP protein also moderates spatial migration of neurons during brain development[43]. In this regard, triple-knockout of the APP family genes results in a neuronal migration defect that is phenotypically similar to human lissencephaly in mice[44]. Two candidate ligands for the APP protein also orchestrate migration of neural precursor cells, including pancortin and lingo1[45-47]. It is noteworthy that from a molecular point of view, pathways of growth cone navigation and cell motility are mechanistically similar, as both of them rely on specialized membrane protrusions, namely filopodia and lamellipodia, for extracellular adhesion and cell membrane reshaping. These cell projections sense the directional gradients of extracellular contact-guidance cues by means of surface adhesion receptors including integrins. Intracellularly, adhesion receptors modulate dynamic rearrangement of the actin cytoskeleton for changing cell polarity, shape and movement direction[48].

Mounting evidence indicates that the cytoskeletal system is an important point of convergence in the APP signaling axis. Transmembrane APP is selectively localized to the cytoskeletal-rich regions of neuronal growth cones at dynamic adhesion sites[38,49], and the APP intracellular domain (AICD) affects rearrangement of the cellular actin cytoskeleton[50]. AICD interacts with a number of intracellular signal transducers, including Fe65, Tip60, KAI1, DISC1, dab1, X11, and Grb2[51-53]. All of these signal transducers influence pathways of cytoskeletal rearrangement and cell movement in diverse biological contexts;

- Fe65 and Tip60 affect the cytoskeletal system and moderate cancer cell migration[54].
- KAI1 suppresses cancer cell migration by affecting the cytoskeletal assembly[55,56].
- DISC1 coordinates remodeling of the actin cytoskeleton in migrating neurons and growth cone-like protrusions[57]. This protein rescues neuronal migration defects caused by loss of the APP gene[51].
- Dab1 is a mandatory adaptor of the lipoprotein receptors axis in the APOE/reelin signaling pathway. Dab1 controls remodeling of the actin cytoskeleton in neuronal migration[58].
- X11 is a recently discovered modulator of the reelin pathway and affects cell movement[59].
- Grb2 is an adaptor molecule that links various receptors including integrins with intracellular pathways of cytoskeletal plasticity and thereby regulates cancer cell migration[60,61].

In accordance with the common function of these cytoskeletal modulators, The APP family proteins similarly affect migration and invasion of various cancer cells by affecting the cytoskeletal pathway[62,63]. Interestingly, a feedback-like mechanism has been observed in primary hippocampal neurons in which the cytoskeletal regulator Rac1 controls expression of the APP gene[64].

Since the earliest stages of nervous system evolution, the APP paralogue of Drosophila (APPL) has promoted neuronal migration[65], and this phylogenetic evolution reveals that cell adhesion is the most prominent biological function of the APP gene family[66]. In context of evolution, the cytoplasmic tail of APP is noteworthy, as it comprises a super-conserved NPxY amino acid motif in the form of $_{682}$YE**NP**T**Y**$_{687}$ that has remained unchanged from roundworms to humans

during more than 900 million years[67]. This consensus motif is known to mediate endocytic sorting of receptors and their interaction with tyrosine-phosphorylated intracellular signal transducers[68]. Two mentioned intracellular signaling adaptors of the APP protein, including dab1 and Fe65, interact with this particular motif in a phosphorylation-dependent manner[69,70]. Moreover, the $_{682}$Tyr residue of this APP motif undergoes phosphorylation and is essential to synaptogenesis[71].

In addition to engagement of APP in neurodevelopment, this protein is also evidenced to maintain its function in mature neurons. Mouse hippocampal neurons express the APP protein under physiological conditions[72], and APP is present in close proximity to the NMDA glutamate receptors. APP controls postsynaptic trafficking of NMDA receptors and promotes synaptic transmission[73,74]. Through its conserved NPxY motif, APP also interacts with the postsynaptic scaffold protein AIDA-1[75], which is a regulator of synaptic transmission and palsticity[76]. On the other hand, loss of the APP family genes disrupts synaptic function[77], memory formation[78], and causes an aging-related synaptic loss in mice[79,80]. Further supporting such physiological roles, cleavage of the APP protein changes synaptic adhesion and assembly[81]. APP and other two members of this protein family form trans-synaptic adhesion dimers[82], and mutation of the APP gene disrupts synaptic adhesion[83]. An exhaustive review of the APP protein is beyond the scope of this manuscript and the interested reader is referred to recent publications[84-86].

1.2 The γ-secretase complex is a membrane-tethered enzyme for signaling of cell adhesion receptors

PSEN1 and PSEN2 genes code for catalytic subunits of the transmembrane γ-secretase enzyme, and various mutations in these genes cause autosomal-dominant forms of AD. As a mandatory step for Aβ generation, the APP protein is cleaved by the γ-secretase. Unexpectedly, it was recently found that PSEN mutations of familial AD may cause an almost complete loss of γ-secretase function[87] and reduce generation of the putatively-neurotoxic $A\beta_{40}$, $A\beta_{42}$ and $A\beta_{43}$ species occasionally to undetectable levels[8889]. In further contradiction, knock-in mice having the mutated PSEN1 gene of familial AD are phenotypically similar to knockout strains with total loss of γ-secretase function, and both of these strains demonstrate impaired hippocampal plasticity[90]. This novel line of evidence suggests a loss-of-function mechanism for PSEN mutations of familial AD, and may explain the paradoxical worsening of cognitive function and accelerated brain atrophy in the γ-secretase inhibitor trials of AD[91,92].

In contrast to the narrow focus on derailed pathways of APP catabolism, unbiased proteomic profiling reveals that the γ-secretase enzyme can process a broad spectrum of substrate molecules with transmembrane signaling roles[93,94]. The γ-secretase cleaves the APOE/reelin receptors[95], DSG2, TREM2 and ephrin receptors that are all coded by AD risk genes[93,96,97]. Loss of γ-secretase activity results in erroneous axonal pathfinding due to impaired netrin signaling[98], and also disrupts cell adhesion force generation[99]. Signaling of a candidate familial AD gene, Notch3[100], also relies on γ-secretase cleavage and intracellular release of the receptor fragment[101].

Recent nanoscale microscopy has revealed that expression of the γ-secretase enzyme is selectively enriched in postsynaptic compartments during normal synaptic maturation[102]. The synaptic role of the γ-secretase complex is further supported by observing that this enzyme interacts with a number of synaptic adhesion molecules, including δ-catenin and N-cadherin, as well as the glutamate receptors[102,103]. Cleavage of cell adhesion receptors by γ-secretase modulates neurotransmission and synaptic adhesion[103], and familial AD mutations disrupt this modulatory effect[104].

1.3 The APOE-lipoprotein receptor axis coordinates contact-guidance of neuronal growth cones

APOE4 is the strongest genetic risk factor of late-onset AD and explains ~6% of the risk of disease[105]. In contrast, the only observed correlation of the APP locus with late-onset AD has been recently reported in an Icelandic cohort, where a rare protective variant explained less than 0.6% of disease risk[106], but this protective variant does not modulate the AD risk in the North American population[107]. Curiously, mechanistic interpretation of the strong APOE risk locus still mostly borrows from potential influences on pathways of Aβ clearance, and the potential role of the APOE protein and its lipoprotein receptors in neurophysiology have been less investigated.

The APOE molecule moderates cellular uptake and transport of the lipoprotein particles in various organs by binding to the family of lipoprotein receptors. Although lipoprotein receptors aid in the metabolism of lipoprotein particles, they do not act as simple cargo transporters, and can stimulate a comprehensive intracellular signaling nexus of second messengers[108]. For instance, two lipoprotein receptors including APOEr2 and VLDLr moderate cell migration in canonical reelin signaling during brain development. Activation of these receptors by reelin triggers phosphorylation of the intracellular dab1 adaptor, which binds the consensus NPxY motif of the receptor intracellular domain[109]. Through dab1 activation, the reelin pathway affects various aspects of cell physiology, among which cytoskeletal remodeling and neuronal migration are central[110]. Importantly, the reelin pathway guides extension of hippocampal neurites[111] and coordinates outgrowth of the perforant path, which forms the major input to the hippocampal formation[112].

As noted, the APOE molecule shares its signaling receptors with reelin[113], and mounting evidence indicates that APOE also undertakes a similar role in guiding outgrowth of the developing neurites[113-117]. The neurite promoting effect of APOE is isoform-dependent, with the APOE3 isoform being a more potent neurite outgrowth inducer than the APOE4 isoform[115,117].

Unlike reelin, intracellular signal transducers of the APOE molecule remain less investigated in neurons, but have been explored in other cells. In macrophages, APOE activates common transducers of the reelin pathway including dab1 and PI3K[118]. In vascular pericytes, APOE affects rearrangement of the actin cytoskeleton and its knockdown deranges normal cell migration[119]. The APOE4 isoform also affects the proteomic signature of cytoskeletal regulators in peripheral nerves[120]. Taken together, this body of evidence suggests that the APOE molecule may signal through a reelin-like signaling network by incorporating the lipoprotein receptors,

and thereby affect the cytoskeletal remodeling pathway for inducing neurite outgrowth and cell movement.

In addition to the strong association of the APOE locus with AD, other risk loci further reinforce relevance of the lipoprotein receptors and their signaling paths in AD. Variants within the reelin gene are the top genetic correlates of AD-type neuropathology in postmortem human brains[121]. F-spondin (Spon1), which codes for a reelin domain-containing cell adhesion molecule, is correlated with the rate of cognitive decline in AD and also affects white matter microstructure in healthy humans[122,123]. Moreover, F-spondin interacts with the APP protein[124], and this interaction serves to activate signaling of the reelin adaptor dab1 in ganglion cells[125]. Two other AD risk loci including Sorl1[126,127] and CLU respectively code for a lipoprotein receptor and a lipoprotein receptor ligand. Sorl1 regulates cell migration[127,128] and CLU activates transducers of the reelin pathway including dab1 and PI3K/Akt in neurons[129].

Apparently unrelated to their roles in lipid metabolism, lipoprotein receptors interact with the major postsynaptic scaffold protein PSD95 and actively take part in synaptic architecture[130-132]. Expression of the lipoprotein receptors affects synaptic density in hippocampal and cortical neurons[133]. Moreover, lipoportein receptors also interact with the neurotransmitter receptors[130,132] and their activation by reelin promotes synaptic plasticity[134-136]. A recent study has further validated details of this neurobiological function for the APOEr2 receptor, by showing that postsynaptic activity of APOEr2 is critical for dab1 phosphorylation and insertion of AMPA glutamate receptors at the postsynapse during long-term potentiation[137]. Lipoprotein receptors also share several intercellular signal transducers with the APP protein, including X11, dab1, and Fe65[133,138], potentially reflecting convergent signaling paths.

1.4 AD susceptibility loci strongly implicate cell adhesion pathways

Familial early-onset AD constitutes less than one percent of all AD patients and is caused by mutations in the APP or PSEN genes. In contrast, several genome-wide association studies have recently revealed the complex polygenic landscape of the common late-onset AD[14-19]. Remarkably, the majority of novel AD risk genes engage in pathways of cell adhesion, migration and contact-guidance:

- **DSG2** (Desmoglein-2, rs8093731) is a component of desmosomal cell adhesion complexes. DSG2 gene product interacts with β8-integrin and serves focal adhesion roles in endothelial cells and regulates cytoskeletal assembly[139]. DSG2 also controls cell motility, and its depletion affects migration of malignant melanoma cells[140].
- **EPHA1** (rs11771145) codes for a member of the ephrin-A receptor family of neurite adhesion and guidance. EPHA1 moderates cell migration through integrin-linked kinase and the cytoskeletal remodeling pathway[141,142]. EPHA1 also affects invasion and metastasis of colorectal cancer cells[143].
- **FRMD4A**[144] and **FERMT2** (Kindlin-2, rs17125944) code for two members of the FERM domain family, which link integrin and focal adhesion kinase (FAK) with the intracellular actin cytoskeleton[145,146]. FERMT2 transduces cell adhesion signals and is engaged in malignant cell invasion[147].

- **GAB2** (rs2373115), one of the earliest AD susceptibility loci to be discovered by a genome-wide scan[14,148], encodes a scaffolding protein acting downstream to the integrin signaling pathway. GAB2 regulates adhesion and migration of hematopoietic cells[149] and also controls cytoskeletal remodeling in migration of breast cancer cells[150].
- **CASS4** (Hepl, rs7274581) controls focal cell adhesion[151] and the CAS family members take part in axon guidance by interacting with integrin[152]. CASS4 also affects cytoskeletal reorganization and moderates cancer cell invasion[151,153].
- **CD2AP** (rs10948363) codes for an actin cytoskeleton binding protein[154]. CD2AP regulates focal adhesion of kidney podocytes at contact sites by linking membrane adhesion complexes with the intracellular actin cytoskeleton[155].
- **PTK2B** (Pyk2, rs28834970) is a focal adhesion signal transducer and affects cytoskeletal remodeling[156,157]. PTK2B coordinates integrin-dependent migration of T-cells[158] and promotes invasion of malignant glioma cells[159].
- **PICALM** (rs10792832) is a Clathrin adaptor protein and engages in membrane receptor trafficking[160]. Clathrin regulates endocytosis of synaptic vesicles and moderates trafficking of the glutamate receptors[161]. Unbiased gene-gene interaction analysis in AD has revealed that the PICALM locus interacts with DOCK1[162], which is an actin cytoskeleton regulator and affects cell movement[163].
- **INPP5D** (SHIP-1, rs35349669) is a key modulator of the PI3K pathway. This protein regulates platelet adhesion by modulating the integrin signaling axis[164]. INPP5D also coordinates movement of neutrophils in response to focal contact and adhesion[165].
- **NYAP1** (rs1476679) codes for a signal transducer of the PI3K pathway. NYAP1 acts downstream to the Contactin5 synaptic adhesion molecule and controls cytoskeletal remodeling in neurite outgrowth[166]. Of note, Contactin5 binds the amyloid precursor-like protein 1[167].
- **Amphysin II** (BIN1, rs6733839) codes for a protein that binds to the cytoplasmic tail of integrin[168] and neuronal focal adhesion kinase[169] and is therefore probably involved in integrin-dependent cell adhesion. Moreover, Amphysin I, which has a high level of sequence similarity (71%) with this gene product, regulates outgrowth of hippocampal neurites[170] and links endocytosis mechanisms to pathways of actin cytoskeleton remodeling[171].
- **UNC5C**[172] (rs137875858) codes for a receptor of the netrin pathway of axon guidance[173]. The netrin pathway incorporates α3β1-integrin and the Down Syndrome Cell Adhesion Molecule (DSCAM) in neuronal migration process and neurite outgrowth, respectively[174,175].
- **TPBG**, a recently discovered AD risk gene[19], modulates cell adhesion and movement[176,177]. TPBG localizes at focal adhesion sites in kidney podocytes and affects formation of actin stress fibers for cell remodeling[178]. Deletion of TPBG disrupts cadherin-dependent cell adhesion and suppresses cell migration[179].
- **HBEGF**[19] (rs11168036) encodes a protein that promotes integrin-dependent cell adhesion[180]. HBEGF also regulates focal adhesion kinase and moderates cell migration by rearranging the actin cytoskeleton[181].

- **USP6NL**[19] (RNTRE, rs7920721) modulates the integrin signaling axis and controls focal adhesion turnover, thereby acting as a "brake" in cell migration[182].
- **TREM2** (rs75932628), a novel AD risk locus[183], is known to interact with the plexin-A1 adhesion molecule[184], which is an axon guidance receptor. Interaction of plexin-A1 with the TREM family has been suggested to moderate cell adhesion and movement through the cytoskeletal pathway[185]. The Plexin pathway also antagonizes the integrin signaling axis and inhibits cell movement[186].
- **TTC3**, a novel familial late-onset AD locus, maps to the Down syndrome critical region[187]. TTC3 modulates β1-integrin signaling in malignant cells[188] and its increased levels affects assembly of the actin cytoskeleton and thereby disrupts neurite extension[189].
- **PLCG2**[190] (rs72824905) codes for a phospholipase, which is activated by integrin and moderates cell migration[191]. Activation of PLCG2 downstream to the integrin pathway moderates adhesion of leukocytes[192].
- **ABI3**[190] (rs616338) affects the cytoskeletal pathway and participates in formation of membrane protrusions for cell motility[193]. Its binding partner, the ABI3 binding protein, interacts with integrin at focal adhesion sites and suppresses malignant cell migration[194,195].

Taken together, the genetic architecture of AD strongly implicates various cell adhesion regulators and pathways of cytoskeletal plasticity. Further aiding in formulation of a unified disease model, many of these gene products cross-talk with the integrin pathway of focal cell adhesion, and this convergence strongly spotlights the Aβ-independent roles of the APP protein, γ-secretase and the APOE receptors in cell adhesion regulation and synaptic function.

2 The hypothesis

By using the unbiased genetic architecture of AD as an evidence-based framework, our model puts the cell adhesion process at the center of disease pathways. Cell adhesion regulators including integrins coordinate cell migration, neurite outgrowth, and assembly of synaptic circuits in brain development. In the developed brain, these canonical pathways also undertake pivotal roles in maintaining synaptic adhesion and plasticity[196]. In the mature neuron, synaptic adhesion molecules form a dense scaffold at the postsynaptic density (PSD) sites and dendritic spines. This adhesion scaffold connects the neurotransmitter receptors and ion channels with the synaptic actin cytoskeleton and the extracellular matrix, aiding in synaptic shape maintenance and dynamic remodeling.

Synaptic adhesion molecules also act as mechano-chemical sensors and modulate trafficking of neurotransmitter receptors during plasticity events[197]. For instance, it has been shown that enhancing signaling of the synaptic integrin receptors by application of an agonist peptide modulates neurotransmission[198] in a dose-dependent manner[199]. In this context, integrin affects rearrangement of the actin cytoskeleton and promotes budding of filopodia - structures that strengthen synaptic connections[200]. Remarkably, this is the same mechanism through which the integrin pathway coordinates growth-cone adhesion and pathfinding during brain circuit development[201]. It is noteworthy that the post-developmental role of cell adhesion pathways in

synaptic physiology is not limited to integrins, and has been evidenced for several adhesion molecules (Fig. 1).

We propose that the heritable component of AD is determined by genetic factors that coordinate growth cone adhesion and robust assembly of synaptic circuits in brain development. This molecular machinery also takes part in synaptic maintenance, plasticity and functional resilience in later life. In this regard, disruption of synaptic adhesion pathways in aging may lead to synaptic failure and AD development.

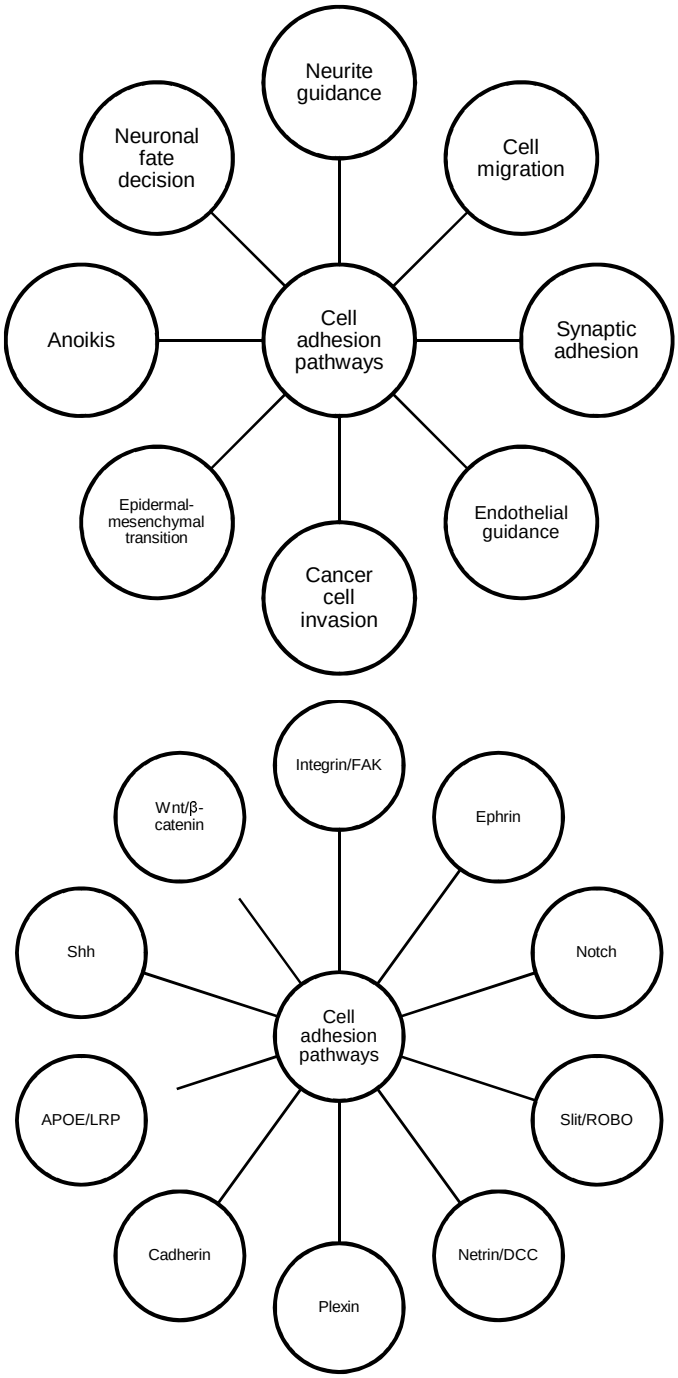

Figure 1. Biological adhesion pathways transfer extracellular signals across the cell membrane, and affect cell polarity, movement and survival (top). Various pathways of extracellular adhesion signaling coordinate rearrangement of the actin cytoskeleton and thereby control reshaping of membrane projections for cell movement and plasticity (bottom). FAK: focal adhesion kinase; LRP: lipoprotein receptor; Shh: Sonic hedgehog.

3 Aging and Alzheimer's disease

Human aging is the strongest risk factor for dementias. Considering the very high prevalence of AD in late life aging, this disease may represent a continuation of global aging process, and cellular disruptions that happen in *normal* aging may give rise to AD when accelerated[7]. An elegant work has recently revealed that frontal cortex cells of healthy humans accumulate ~37 new point mutations each year[203]. These mutations may represent the final outcome of a widespread DNA damage process resulting in accumulation of genetic and epigenetic derangements. Loss of genomic integrity has been previously implicated in AD, although its relevance to disease pathways is unknown[12,204,205].

From a statistical point of view, even if a purely random process causes accumulation of mutations in aging neurons, larger genes are expected to be disproportionately affected in late life. If the burden of 37 annual mutations is considered to be uniformly spread across the whole span of human genome at purely random positions (5.7×10^{-9} mutations/base pair.year), approximately 1% of the copies of a median-sized human gene will acquire at least one somatic mutation in the frontal cortex cells of a 65-year individual. In sharp contrast, the largest known human gene, CNTNAP2, which is more than 80× larger than a median-sized gene and codes for a synaptic adhesion protein, is expected to be highly vulnerable to somatic mutations, and only 42% of its copies are estimated to remain intact in the same individual (Fig. 2). This high variability is due to the characteristic distribution of gene size parameter in humans, which spans three-orders of magnitude with a long tail encompassing extremely large genes (Fig. 3).

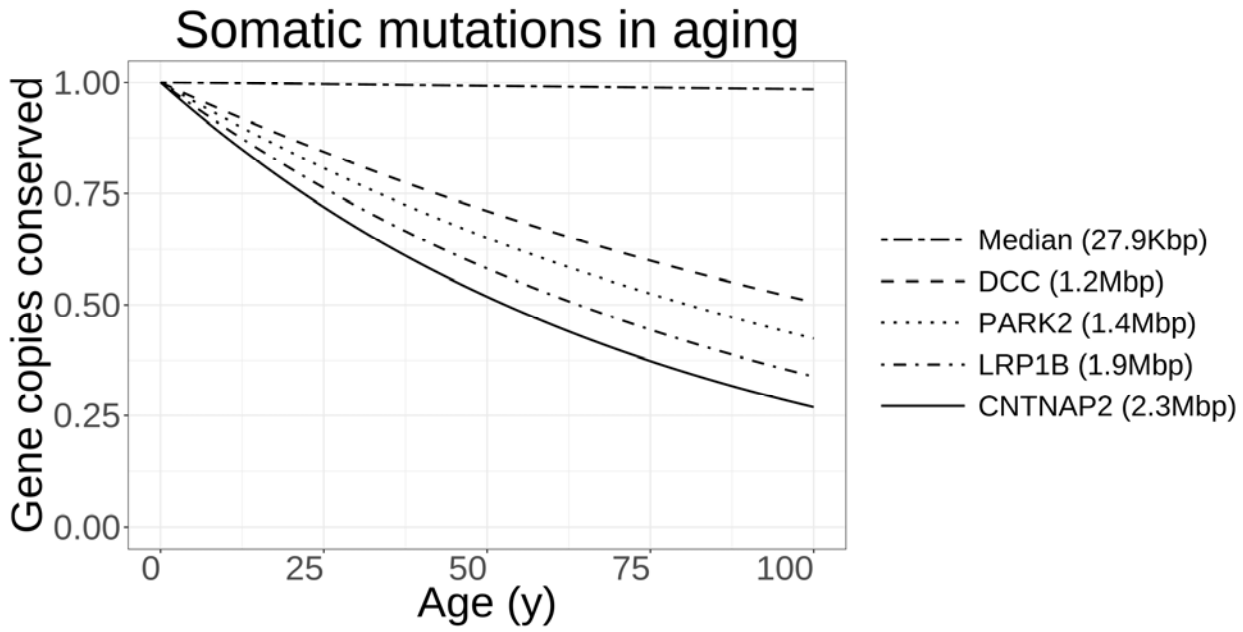

Figure 2. A simple binomial model in which somatic mutations take place at a fixed and uniform rate across the genome reveals that a median-sized human gene mostly survives the mutational burden of aging, with only ~1% of its copies being affected by any somatic mutation in a 65 year-old subject. However, larger genes will have a significantly shorter *half-lives*; many of these large genes regulate synaptic adhesion and function with relevance to neurodegenerative disorders.

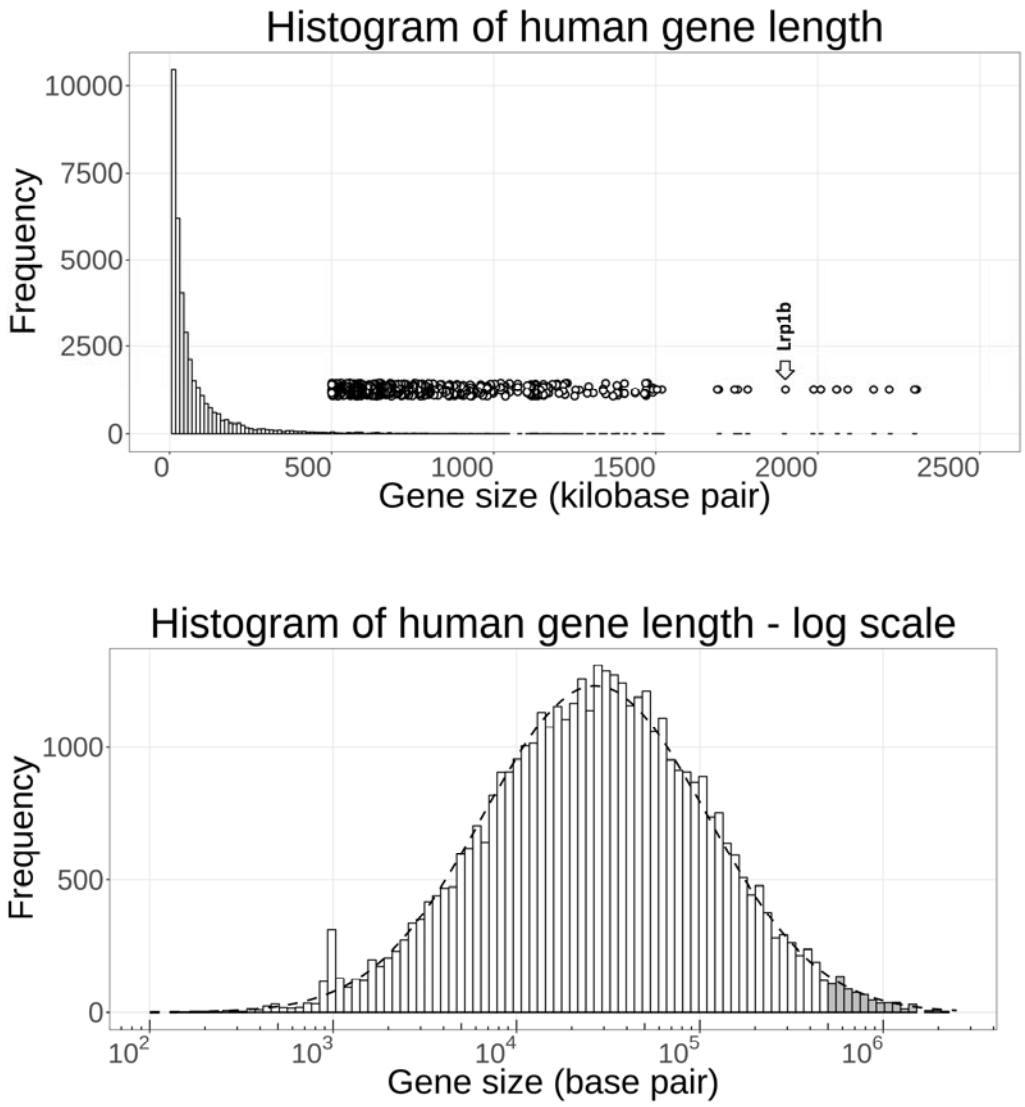

Figure 3. Human gene length distribution has a long tail that extends towards a group of extremely-large genes in the megabase pair range (top). The arrow points to the giant APOE receptor, Lrp1b. Human gene size parameter closely follows a log-normal distribution (bottom) with parameters μ=ln(26.9kbp) and σ=1.4. The outlier bin near 1 kbp represents the large family of olfactory receptors which have gone through extreme evolutionary expansion. Scattered circles (top) and grey bars (bottom) show the subgroup of large genes used in functional enrichment analyses of this paper (>500kbp).

Why has the evolution in some cases selected for extremely large genes, although they are known to map to chromosomal fragile sites[206]? We were compelled to objectively investigate whether large human genes non-randomly take part in certain biological mechanisms and cellular pathways. For this aim, we size-sorted all of the protein-coding human genes (n=19,287 NCBI RefSeq-DAVID matches), and considered the gene length threshold of >500kb for defining *large* human genes. This cut-off threshold resulted in consideration of 260 large human genes representing 1.3% of all protein-coding transcripts. Functional annotation, pathway enrichment, and tissue expression profile of this gene set of interest were investigated using a standard DAVID query[207,208].

Interestingly, the most overrepresented organ with selective expression of large genes was *brain* ($p=1.4\times10^{-19}$), followed by *amygdala* ($p=3.1\times10^{-5}$), and *hippocampus* ($p=6.6\times10^{-5}$). By showing strong enrichment statistics, *homophilic cell adhesion via plasma membrane adhesion molecules* was the most overrepresented biological process related to this gene set of interest (Table 1), and the most overrepresented cellular component was *postsynaptic membrane* (Table 2). All other enriched gene ontology terms further implicated pathways of nervous system development and physiology (Table 1). Among curated biological pathways (KEGG), four pathways were found to be statistically enriched, including *Glutamatergic synapse* (hsa04724; corrected p=0.02), *Axon guidance* (hsa04360; corrected p=0.03), *Cell adhesion molecules* (hsa04514; corrected p=0.04), and *Insulin secretion* (hsa04911; corrected p=0.04).

The very strong selectivity of large human genes to brain, synapse and cell adhesion process is an enlightening observation, and we suggest that it may reflect existence of specialized evolutionary forces driving complexity of cognitive function; these exceptional genes may have fostered adhesion and assembly of synaptic circuits in brain evolution. However, while large genes may have promoted brain complexity, as an evolutionary bottleneck, they may also be inherently costlier to be maintained in late life. In this regard, large synaptic genes may put modern humans at a neurobiological disadvantage when the burden of DNA damage is accumulated during our long lifespans, and since the average human life expectancy passed the 40-year milestone only two centuries ago[209], there has been virtually no time for evolutionary correction of disease-causing genomic variations. Taken together, increased brain complexity and rapid extension of life expectancy may have recently unmasked a DNA maintenance and repair bottleneck in humans, eventually presenting as synaptic failure, AD, and potentially other forms of aging-related disorders in the modern era.

Table 1. Enrichment of large human genes (>500 kbp) in *Gene ontology: biological process* annotations.

Gene ontology term – biological process	**Gene count**	**p-value**	**Corrected p-value**
GO:0007156~homophilic cell adhesion via plasma membrane adhesion molecules	19	1×10^{-11}	1×10^{-8}
GO:0007157~heterophilic cell-cell adhesion via plasma membrane cell adhesion molecules	11	2×10^{-9}	1×10^{-6}
GO:0007155~cell adhesion	27	2×10^{-9}	8×10^{-7}
GO:0007399~nervous system development	20	3×10^{-8}	9×10^{-6}
GO:0007416~synapse assembly	10	2×10^{-7}	5×10^{-5}
GO:0007411~axon guidance	14	4×10^{-7}	9×10^{-5}
GO:0097120~receptor localization to synapse	5	5×10^{-6}	9×10^{-4}
GO:0007165~signal transduction	37	6×10^{-6}	1×10^{-3}
GO:0007612~learning	8	2×10^{-5}	2×10^{-3}
GO:0051965~positive regulation of synapse assembly	8	3×10^{-5}	3×10^{-3}
GO:0007158~neuron cell-cell adhesion	5	6×10^{-5}	7×10^{-3}
GO:0007269~neurotransmitter secretion	7	8×10^{-5}	9×10^{-3}
GO:2000463~positive regulation of excitatory postsynaptic potential	5	2×10^{-4}	0.01
GO:0097105~presynaptic membrane assembly	4	2×10^{-4}	0.02
GO:0051966~regulation of synaptic transmission, glutamatergic	5	3×10^{-4}	0.02
GO:0007420~brain development	11	4×10^{-4}	0.03
GO:0030534~adult behavior	5	5×10^{-4}	0.03
GO:0051491~positive regulation of filopodium assembly	5	5×10^{-4}	0.03
GO:0035176~social behavior	6	6×10^{-4}	0.04
GO:0007268~chemical synaptic transmission	12	6×10^{-4}	0.04
GO:0035418~protein localization to synapse	4	6×10^{-4}	0.04

Table 2. Enrichment of large human genes (>500 kbp) in *Gene ontology: cellular component* annotations.

Gene ontology term – cellular component	**Gene count**	**p-value**	**Corrected p-value**
GO:0045211~postsynaptic membrane	22	2×10^{-12}	5×10^{-10}
GO:0030054~cell junction	29	7×10^{-11}	8×10^{-9}
GO:0005886~plasma membrane	100	3×10^{-10}	3×10^{-8}
GO:0014069~postsynaptic density	18	8×10^{-10}	5×10^{-8}
GO:0042734~presynaptic membrane	12	9×10^{-10}	4×10^{-8}
GO:0030424~axon	16	6×10^{-7}	2×10^{-5}
GO:0045202~synapse	14	2×10^{-6}	6×10^{-5}
GO:0048786~presynaptic active zone	7	3×10^{-6}	8×10^{-5}
GO:0016021~integral component of membrane	104	3×10^{-6}	7×10^{-5}
GO:0043197~dendritic spine	10	1×10^{-5}	3×10^{-4}
GO:0031225~anchored component of membrane	10	3×10^{-5}	6×10^{-4}
GO:0043005~neuron projection	14	3×10^{-5}	6×10^{-4}
GO:0042383~sarcolemma	8	2×10^{-4}	3×10^{-3}
GO:0005856~cytoskeleton	16	2×10^{-4}	4×10^{-3}
GO:0030425~dendrite	15	3×10^{-4}	4×10^{-3}

4 Predictions

Due to a combination of heritable factors and environmental exposures, AD patients may suffer faster accumulation of DNA damage in their neuronal genomes. This hypothesis may be testable by finding correlations between cognitive decline and somatic mutations, strand breaks and/or abnormal epigenetic changes in the aging neurons. More specifically, a number of synaptic adhesion genes may be exceptionally vulnerability to DNA damage accumulation in certain neuronal populations. In this regard, we predict that instability of the Lrp1b gene in amygdalar and hippocampal neurons is a prototypic example that may explain the APOE risk locus of AD (Fig. 4):

- Lrp1b has affinity to both APOE and APP proteins[211,212] and they may act as a synaptic adhesion complex.
- Lrp1b is selectivity expressed in brain[211] with hippocampal and amygdalar neurons showing the highest levels of Lrp1b transcription in humans[216] (Fig. 5). Lrp1b also interacts with the major postsynaptic protein, PSD95[131] as well as the synaptic plasticity-regulating protein PICK1[217].
- Lrp1b is the largest member of the lipoprotein receptor family and represents the 8th largest human gene overall. Potentially due to its large size and mapping to the chromosomal fragile site FRA2F, Lrp1b is among the ten most frequently deleted genes observed in 3,131 cancer specimens[210].
- The Lrp1b gene product controls focal adhesion, cytoskeletal remodeling and cell migration[213,214], pathways that functionally align with the genetic architecture of AD. Lrp1b is also cleaved by the γ-secretase enzyme and its intracellular fragment affects cell anchorage and survival[215].
- Genetic variants within the Lrp1b locus are correlated with cognitive function in aging and AD[218,219].

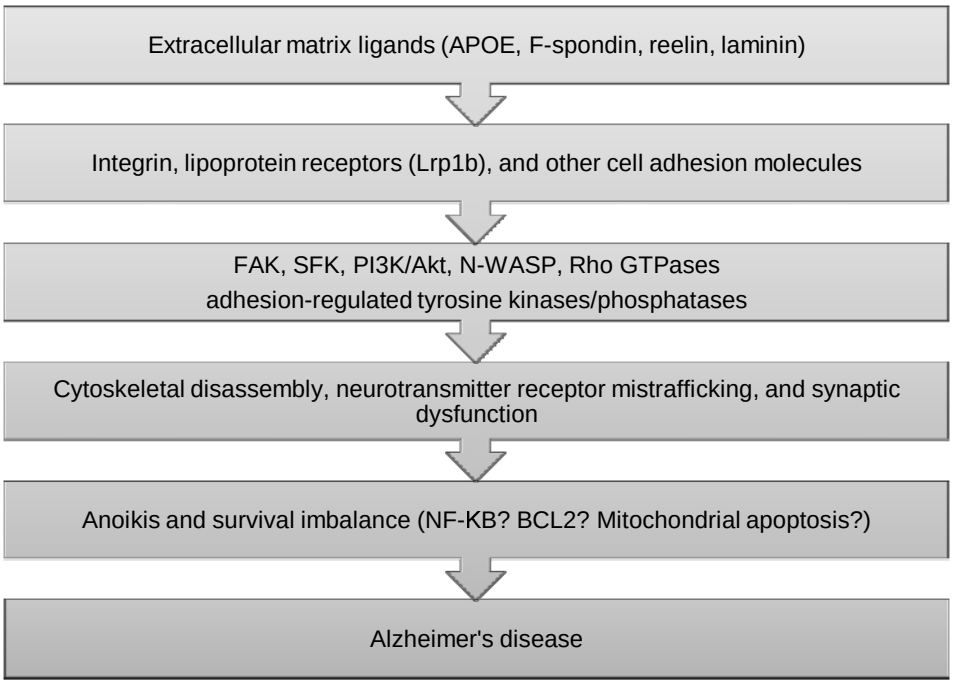

Figure 4. A simplified cascade of late-onset AD pathogenesis based on lipoprotein receptor signaling disruption. FAK: focal adhesion kinase; SFK: Src-family kinase.

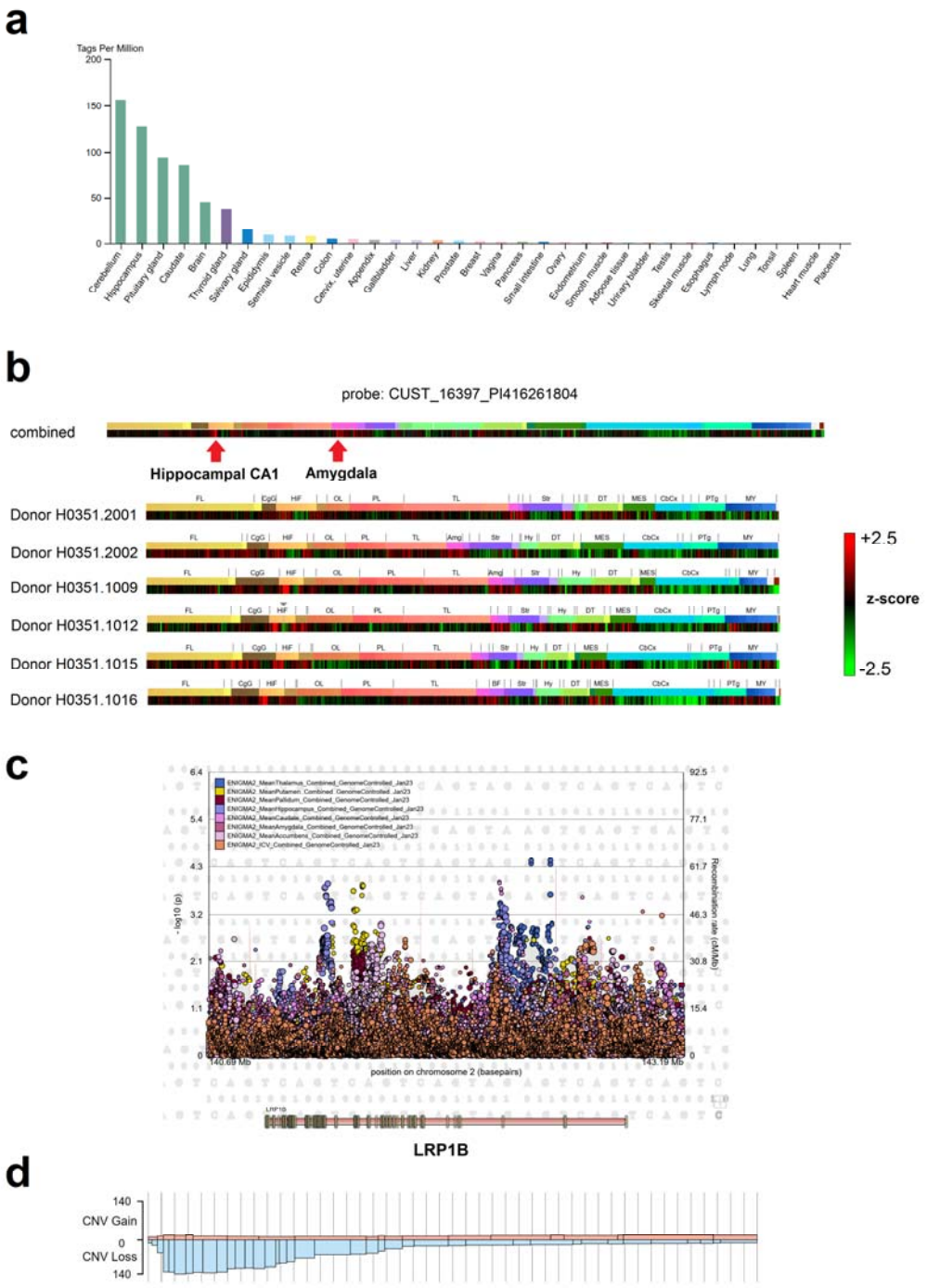

Figure 5. Tissue expression profile of Lrp1b in various organs (a) shows strong specificity to brain in FANTOM5 database. Spatial expression of Lrp1b in various brain structures in six postmortem human brain samples of the Allen human brain atlas (b). Correlation of genetic variants in the Lrp1b locus with several MRI measures of brain volume (c) in the ENIGMA-2 database[220,221]. Copy-number variation of the Lrp1b gene in 2,383 unique cancer tissue samples (d) shows higher probability for copy number loss in the 3` end of this gene.

We predict that AD-type cognitive decline is correlated with propagation of DNA damage and potentially somatic mutations in certain synaptic genes including Lrp1b, and subsequent dysfunctions in their intracellular pathways. Although previous models have already implicated oxidative stress and DNA damage mechanisms in AD[12,204,205,222], high-throughput results do not support an oxidative stress etiology for the somatic mutations observed in various organs; due to formation of free radicals, oxidative stress typically causes G:C→T:A transversions[223,224]. However, aging cells demonstrate a clock-like signature of somatic mutations with enrichment of C:G→T:A transitions[225,226]. Intriguingly, this mutational fingerprint was recently observed as the dominant type of mutations in neurons[224,227,228]. The reason for aging-related preponderance of C:G→T:A transitions is currently unknown, and may point to a common mechanism. Spontaneous cytosine deamination, transcriptional stress, and/or failure of certain DNA repair mechanisms including base and nucleotide excision repair are potential explanations[224,229].

It is noteworthy that Lrp1b only serves to provide one example of vulnerable synaptic genes in brain aging, and the true genetic landscape of AD and senile neurodegenerations may not be reducible to the lipoprotein receptor axis (Fig. 6). Similar to loss of different tumor suppressor genes by DNA damage mechanisms in various cancers, brain-wide expression of several unstable neuronal genes may underpin dementia heterogeneity in aging subjects. For instance, genetic architecture of the Parkinson's disease implicates genes of the synaptic vesicular trafficking system including the extremely large tumor suppressor PARK2 that maps to the chromosomal fragile site FRA6E[230]. Dopaminergic neurons of substantia nigra are the most vulnerable structures in Parkinson's disease, and can be distinguished by selective expression of two tumor-suppressor genes with cell adhesion roles, including DCC[231] and AJAP1[232].

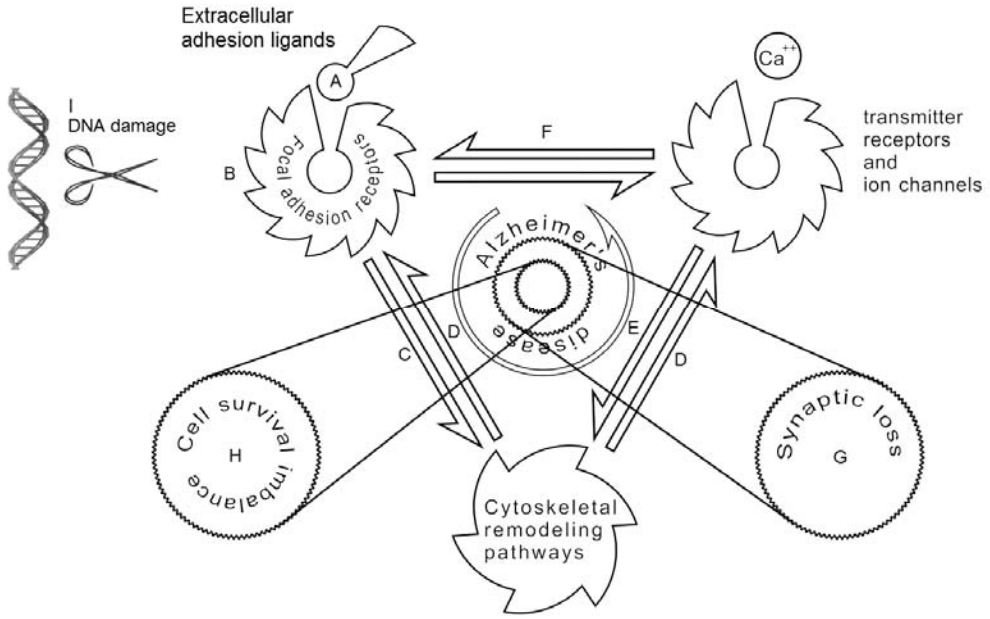

Figure 6. The proposed mechanisms of synaptic loss and neuronal death in AD. The extracellular matrix and cell adhesion molecules (A) modulate signaling of neuronal adhesion receptors (B*)*. Cell adhesion pathways affect remodeling of synaptic actin cytoskeleton as well as other mediators of plasticity, e.g. various SH3 domain containing proteins (C). The postsynaptic density is anchored to the synaptic actin cytoskeleton through scaffolding proteins, e.g. PDZ domain containing proteins (D). Normal function and trafficking of the neurotransmitter receptors are controlled by cytoskeletal plasticity pathways (E) as well as membrane adhesion complexes (F). Disruption of cell adhesion pathways in AD impairs synaptic stability and causes dendritic spine loss (G), and may eventually lead to neuronal survival imbalance by triggering anoikis cascades (H). Selective vulnerability of genes with extremely large sizes or other features causing mutational instability may be the etiology of cell adhesion disruption in aging (I).

5 Future perspectives

Mice with distal truncation of Lrp1b have no apparent phenotype[131], but a more proximally truncated Lrp1b gene product causes early embryonic lethality[233]. Conditional knockout of Lrp1b and other modulators of the lipoprotein receptor signaling axis after completion of brain development may aid in modeling AD-type synaptic loss in laboratory animals. Intriguingly, conditional knockout of the Lrp1 gene with 52% amino acid similarity to Lrp1b results in neurodegenerative changes in animals after 12 months of aging[234].

Since even the most aggressive forms of AD remain clinically silent for decades, accelerating the aging process in laboratory animals may be necessary, for instance by crossing AD models with DNA-repair defective strains. Available evidence indicates that the transcription-coupled DNA repair machinery is critical for maintaining neuronal viability[235], with the rare Cockayne syndrome of premature aging being caused by disruptions in this pathway.

Our hypothesis is not based on any form of etiological relevance for Aβ species, amyloid plaques or neurofibrillary tangles in causal disease pathways, and defines these pathological features as potential epiphenomena of other etiological factors. Even the strong APOE risk locus of sporadic AD fails to explain ~94% of the disease variance. Therefore, single pathway therapeutic approaches may provide limited benefit in clinical trials. As a potentially more effective approach, our model warrants engineering of novel gene delivery vehicles for restoring neuronal expression of unstable synaptic genes before the DNA damage accumulation reaches the high levels of clinical AD presentation.

In conclusion, our proposal, the *large gene instability hypothesis*, implicates loss of vulnerable synaptic genes due to DNA damage accumulation as the primary etiology of AD. We suggest a shift of paradigm from the protein aggregation process to genetic engineering strategies and rescuing synaptic adhesion pathways in AD drug design.

References

1. Alzheimer A. Über einen eigenartigen schweren Erkrankungsprozeβ der Hirnrinde. Neurologisches Centralblatt 1906;23:1129–113.
2. Glenner GG, Wong CW. Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. Biochem Biophys Res Commun 1984;120:885-90.
3. Goate A, Chartier-Harlin M-C, Mullan M, et al. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. Nature 1991;349:704-6.
4. Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. Science 1992;256:184.
5. Cummings JL, Morstorf T, Zhong K. Alzheimer's disease drug-development pipeline: few candidates, frequent failures. Alzheimer's Research & Therapy 2014;6:37.
6. Moreno-Treviño MG, Castillo-López J, Meester I. Moving Away from Amyloid Beta to Move on in Alzheimer Research. Frontiers in Aging Neuroscience 2015;7.
7. Josepha J, Shukitt-Hale B, Denisova NA, Martin A, Perry G, Smith MA. Copernicus revisited: amyloid beta in Alzheimer's disease. Neurobiology of aging 2001;22:131-46.
8. Castellani RJ, Smith MA. Compounding artefacts with uncertainty, and an amyloid cascade hypothesis that is 'too big to fail'. J Pathol 2011;224:147-52.
9. Morris GP, Clark IA, Vissel B. Inconsistencies and controversies surrounding the amyloid hypothesis of Alzheimer's disease. Acta Neuropathol Commun 2014;2:135.
10. Sorrentino P, Iuliano A, Polverino A, Jacini F, Sorrentino G. The dark sides of amyloid in Alzheimer's disease pathogenesis. FEBS Letters 2014;588:641-52.
11. Herrup K. The case for rejecting the amyloid cascade hypothesis. Nat Neurosci 2015:794-9.
12. Tse KH, Herrup K. Re-imagining Alzheimer's disease - the diminishing importance of amyloid and a glimpse of what lies ahead. J Neurochem 2017.
13. Reitz C. Alzheimer's disease and the amyloid cascade hypothesis: a critical review. Int J Alzheimers Dis 2012;2012:369808.
14. Reiman EM, Webster JA, Myers AJ, et al. GAB2 Alleles Modify Alzheimer's Risk in APOE ε4 Carriers. Neuron 2007;54:713-20.
15. Bertram L, Lange C, Mullin K, et al. Genome-wide association analysis reveals putative Alzheimer's disease susceptibility loci in addition to APOE. The American Journal of Human Genetics 2008;83:623-32.
16. Harold D, Abraham R, Hollingworth P, et al. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. Nature genetics 2009;41:1088-93.
17. Seshadri S, Fitzpatrick AL, Ikram MA, et al. Genome-wide analysis of genetic loci associated with Alzheimer disease. Jama 2010;303:1832-40.
18. Lambert JC, Ibrahim-Verbaas CA, Harold D, et al. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nat Genet 2013;45:1452-8.
19. Jun GR, Chung J, Mez J, et al. Transethnic genome-wide scan identifies novel Alzheimer's disease loci. Alzheimer's & dementia : the journal of the Alzheimer's Association 2017.
20. Kang J, Lemaire H-G, Unterbeck A, et al. The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor. Nature 1987;325:733-6.
21. Ferreira A, Caceres A, Kosik K. Intraneuronal compartments of the amyloid precursor protein. The Journal of Neuroscience 1993;13:3112-23.
22. Koo EH, Park L, Selkoe DJ. Amyloid beta-protein as a substrate interacts with extracellular matrix to promote neurite outgrowth. Proceedings of the National Academy of Sciences of the United States of America 1993;90:4748-52.

23. Whitson JS, Glabe CG, Shintani E, Abcar A, Cotman CW. β-Amyloid protein promotes neuritic branching in hippocampal cultures. Neuroscience Letters 1990;110:319-24.
24. Kibbey MC, Jucker M, Weeks BS, Neve RL, Van Nostrand WE, Kleinman HK. beta-Amyloid precursor protein binds to the neurite-promoting IKVAV site of laminin. Proc Natl Acad Sci U S A 1993;90:10150-3.
25. Breen KC. APP-collagen interaction is mediated by a heparin bridge mechanism. Mol Chem Neuropathol 1992;16:109-21.
26. Li X-F, Thinakaran G, Sisodia SS, Fu-Shin XY. Amyloid precursor-like protein 2 promotes cell migration toward fibronectin and collagen IV. Journal of Biological Chemistry 1999;274:27249-56.
27. Small DH, Nurcombe V, Reed G, et al. A heparin-binding domain in the amyloid protein precursor of Alzheimer's disease is involved in the regulation of neurite outgrowth. Journal of Neuroscience 1994;14:2117-27.
28. Qiu WQ, Ferreira A, Miller C, Koo EH, Selkoe DJ. Cell-surface beta-amyloid precursor protein stimulates neurite outgrowth of hippocampal neurons in an isoform-dependent manner. The Journal of neuroscience : the official journal of the Society for Neuroscience 1995;15:2157-67.
29. Allinquant B, Hantraye P, Mailleux P, Moya K, Bouillot C, Prochiantz A. Downregulation of amyloid precursor protein inhibits neurite outgrowth in vitro. The Journal of cell biology 1995;128:919-27.
30. Sosa LJ, Bergman J, Estrada-Bernal A, Glorioso TJ, Kittelson JM, Pfenninger KH. Amyloid precursor protein is an autonomous growth cone adhesion molecule engaged in contact guidance. PLoS One 2013;8:e64521.
31. Sosa LJ, Postma NL, Estrada-Bernal A, et al. Dosage of amyloid precursor protein affects axonal contact guidance in Down syndrome. FASEB journal : official publication of the Federation of American Societies for Experimental Biology 2014;28:195-205.
32. Song P, Pimplikar SW. Knockdown of Amyloid Precursor Protein in Zebrafish Causes Defects in Motor Axon Outgrowth. PLoS ONE 2012;7:e34209.
33. Lourenco FC, Galvan V, Fombonne J, et al. Netrin-1 interacts with amyloid precursor protein and regulates amyloid-beta production. Cell death and differentiation 2009;16:655-63.
34. Rama N, Goldschneider D, Corset V, Lambert J, Pays L, Mehlen P. Amyloid precursor protein regulates netrin-1-mediated commissural axon outgrowth. The Journal of biological chemistry 2012;287:30014-23.
35. Hoe HS, Lee KJ, Carney RS, et al. Interaction of reelin with amyloid precursor protein promotes neurite outgrowth. The Journal of neuroscience : the official journal of the Society for Neuroscience 2009;29:7459-73.
36. Young-Pearse TL, Chen AC, Chang R, Marquez C, Selkoe DJ. Secreted APP regulates the function of full-length APP in neurite outgrowth through interaction with integrin beta1. Neural Dev 2008;3:15.
37. Yamazaki T, Koo EH, Selkoe DJ. Cell surface amyloid β-protein precursor colocalizes with β1 integrins at substrate contact sites in neural cells. The Journal of neuroscience 1997;17:1004-10.
38. Sabo SL, Ikin AF, Buxbaum JD, Greengard P. The Alzheimer amyloid precursor protein (APP) and FE65, an APP-binding protein, regulate cell movement. The Journal of cell biology 2001;153:1403-14.
39. Young-Pearse TL, Chen AC, Chang R, Marquez C, Selkoe DJ. Secreted APP regulates the function of full-length APP in neurite outgrowth through interaction with integrin beta1. Neural Development 2008;3:15-.
40. Lin L, Yan F, Zhao D, et al. Reelin promotes the adhesion and drug resistance of multiple myeloma cells via integrin beta1 signaling and STAT3. Oncotarget 2016;7:9844-58.
41. Dulabon L, Olson EC, Taglienti MG, et al. Reelin binds alpha3beta1 integrin and inhibits neuronal migration. Neuron 2000;27:33-44.

42. Schmid RS, Jo R, Shelton S, Kreidberg JA, Anton ES. Reelin, Integrin and Dab1 Interactions during Embryonic Cerebral Cortical Development. Cerebral Cortex 2005;15:1632-6.
43. Ramaker JM, Swanson TL, Copenhaver PF. Amyloid precursor proteins interact with the heterotrimeric G protein Go in the control of neuronal migration. J Neurosci 2013;33:10165-81.
44. Herms J, Anliker B, Heber S, et al. Cortical dysplasia resembling human type 2 lissencephaly in mice lacking all three APP family members. The EMBO Journal 2004;23:4106-15.
45. Rice HC, Townsend M, Bai J, et al. Pancortins interact with amyloid precursor protein and modulate cortical cell migration. Development 2012;139:3986-96.
46. Rice HC, Young-Pearse TL, Selkoe DJ. Systematic evaluation of candidate ligands regulating ectodomain shedding of amyloid precursor protein. Biochemistry 2013;52:3264-77.
47. Mathis C, Schröter A, Thallmair M, Schwab ME. Nogo-A Regulates Neural Precursor Migration in the Embryonic Mouse Cortex. Cerebral Cortex (New York, NY) 2010;20:2380-90.
48. Guan K-L, Rao Y. Signalling mechanisms mediating neuronal responses to guidance cues. Nat Rev Neurosci 2003;4:941-56.
49. Sabo SL, Ikin AF, Buxbaum JD, Greengard P. The amyloid precursor protein and its regulatory protein, FE65, in growth cones and synapses in vitro and in vivo. The Journal of neuroscience : the official journal of the Society for Neuroscience 2003;23:5407-15.
50. Müller T, Concannon CG, Ward MW, et al. Modulation of gene expression and cytoskeletal dynamics by the amyloid precursor protein intracellular domain (AICD). Molecular biology of the cell 2007;18:201-10.
51. Young-Pearse TL, Suth S, Luth ES, Sawa A, Selkoe DJ. Biochemical and functional interaction of DISC1 and APP regulates neuronal migration during mammalian cortical development. The Journal of neuroscience : the official journal of the Society for Neuroscience 2010;30:10431-40.
52. Slomnicki LP, Lesniak W. A putative role of the Amyloid Precursor Protein Intracellular Domain (AICD) in transcription. Acta Neurobiol Exp (Wars) 2008;68:219-28.
53. Zhou D, Noviello C, D'Ambrosio C, Scaloni A, D'Adamio L. Growth Factor Receptor-bound Protein 2 Interaction with the Tyrosine-phosphorylated Tail of Amyloid β Precursor Protein Is Mediated by Its Src Homology 2 Domain. Journal of Biological Chemistry 2004;279:25374-80.
54. Sun Y, Sun J, Lungchukiet P, et al. Fe65 Suppresses Breast Cancer Cell Migration and Invasion through Tip60 Mediated Cortactin Acetylation. Scientific reports 2015;5.
55. Zhou B, Liu L, Reddivari M, Zhang XA. The Palmitoylation of Metastasis Suppressor KAI1/CD82 Is Important for Its Motility- and Invasiveness-Inhibitory Activity. Cancer Research 2004;64:7455-63.
56. Liu WM, Zhang F, Moshiach S, et al. Tetraspanin CD82 inhibits protrusion and retraction in cell movement by attenuating the plasma membrane-dependent actin organization. PLoS One 2012;7:e51797.
57. Steinecke A, Gampe C, Nitzsche F, Bolz J. DISC1 knockdown impairs the tangential migration of cortical interneurons by affecting the actin cytoskeleton. Frontiers in cellular neuroscience 2014;8:190.
58. Suetsugu S, Tezuka T, Morimura T, et al. Regulation of actin cytoskeleton by mDab1 through N-WASP and ubiquitination of mDab1. Biochemical Journal 2004;384:1-8.
59. Minami SS, Sung YM, Dumanis SB, et al. The cytoplasmic adaptor protein X11α and extracellular matrix protein Reelin regulate ApoE receptor 2 trafficking and cell movement. The FASEB Journal 2010;24:58-69.
60. Cheng SYS, Sun G, Schlaepfer DD, Pallen CJ. Grb2 Promotes Integrin-Induced Focal Adhesion Kinase (FAK) Autophosphorylation and Directs the Phosphorylation of Protein Tyrosine Phosphatase α by the Src-FAK Kinase Complex. Molecular and cellular biology 2014;34:348-61.
61. Giubellino A, Burke TR, Bottaro DP. Grb2 Signaling in Cell Motility and Cancer. Expert opinion on therapeutic targets 2008;12:1021-33.

62. Pandey P, Sliker B, Peters HL, et al. Amyloid precursor protein and amyloid precursor-like protein 2 in cancer. Oncotarget 2016;7:19430-44.
63. Pandey P, Rachagani S, Das S, et al. Amyloid precursor-like protein 2 (APLP2) affects the actin cytoskeleton and increases pancreatic cancer growth and metastasis. Oncotarget 2015;6:2064-75.
64. Wang PL, Niidome T, Akaike A, Kihara T, Sugimoto H. Rac1 inhibition negatively regulates transcriptional activity of the amyloid precursor protein gene. Journal of neuroscience research 2009;87:2105-14.
65. Copenhaver PF, Ramaker JM. Neuronal migration during development and the amyloid precursor protein. Current opinion in insect science 2016;18:1-10.
66. Coulson E, Paliga K, Beyreuther K, Masters C. What the evolution of the amyloid protein precursor supergene family tells us about its function. Neurochemistry international 2000;36:175-84.
67. Shariati SAM, De Strooper B. Redundancy and divergence in the amyloid precursor protein family. FEBS letters 2013;587:2036-45.
68. Kavanaugh WM, Williams LT. An alternative to SH2 domains for binding tyrosine-phosphorylated proteins. Science 1994;266:1862-5.
69. Young-Pearse TL, Bai J, Chang R, Zheng JB, LoTurco JJ, Selkoe DJ. A critical function for beta-amyloid precursor protein in neuronal migration revealed by in utero RNA interference. The Journal of neuroscience : the official journal of the Society for Neuroscience 2007;27:14459-69.
70. Minami SS, Hoe H-S, Rebeck GW. Fyn kinase regulates the association between amyloid precursor protein and Dab1 by promoting their localization to detergent-resistant membranes. Journal of neurochemistry 2011;118:879-90.
71. Barbagallo APM, Wang Z, Zheng H, D'Adamio L. A Single Tyrosine Residue in the Amyloid Precursor Protein Intracellular Domain Is Essential for Developmental Function. The Journal of biological chemistry 2011;286:8717-21.
72. Del Turco D, Paul MH, Schlaudraff J, et al. Region-Specific Differences in Amyloid Precursor Protein Expression in the Mouse Hippocampus. Frontiers in Molecular Neuroscience 2016;9:134.
73. Cousins SL, Hoey SE, Anne Stephenson F, Perkinton MS. Amyloid precursor protein 695 associates with assembled NR2A- and NR2B-containing NMDA receptors to result in the enhancement of their cell surface delivery. Journal of neurochemistry 2009;111:1501-13.
74. Hoe H-S, Fu Z, Makarova A, et al. The Effects of Amyloid Precursor Protein on Postsynaptic Composition and Activity. The Journal of biological chemistry 2009;284:8495-506.
75. Smirnova E, Shanbhag R, Kurabi A, Mobli M, Kwan JJ, Donaldson LW. Solution Structure and Peptide Binding of the PTB Domain from the AIDA1 Postsynaptic Signaling Scaffolding Protein. PLOS ONE 2013;8:e65605.
76. Tindi JO, Chavez AE, Cvejic S, Calvo-Ochoa E, Castillo PE, Jordan BA. ANKS1B Gene Product AIDA-1 Controls Hippocampal Synaptic Transmission by Regulating GluN2B Subunit Localization. J Neurosci 2015;35:8986-96.
77. Klevanski M, Saar M, Baumkotter F, Weyer SW, Kins S, Muller UC. Differential role of APP and APLPs for neuromuscular synaptic morphology and function. Mol Cell Neurosci 2014;61:201-10.
78. Mileusnic R, Lancashire CL, Johnston AN, Rose SP. APP is required during an early phase of memory formation. The European journal of neuroscience 2000;12:4487-95.
79. Tyan SH, Shih AY, Walsh JJ, et al. Amyloid precursor protein (APP) regulates synaptic structure and function. Mol Cell Neurosci 2012;51:43-52.
80. Dawson GR, Seabrook GR, Zheng H, et al. Age-related cognitive deficits, impaired long-term potentiation and reduction in synaptic marker density in mice lacking the beta-amyloid precursor protein. Neuroscience 1999;90:1-13.
81. Stahl R, Schilling S, Soba P, et al. Shedding of APP limits its synaptogenic activity and cell adhesion properties. Frontiers in Cellular Neuroscience 2014;8:410.

82. Soba P, Eggert S, Wagner K, et al. Homo- and heterodimerization of APP family members promotes intercellular adhesion. The EMBO Journal 2005;24:3624-34.
83. Munter L-M, Voigt P, Harmeier A, et al. GxxxG motifs within the amyloid precursor protein transmembrane sequence are critical for the etiology of Aβ42. The EMBO Journal 2007;26:1702-12.
84. Deyts C, Thinakaran G, Parent AT. APP Receptor? To Be or Not To Be. Trends in Pharmacological Sciences;37:390-411.
85. Swistowski A, Zhang Q, Orcholski ME, et al. Novel mediators of amyloid precursor protein signaling. The Journal of neuroscience : the official journal of the Society for Neuroscience 2009;29:15703-12.
86. Hoe HS, Lee HK, Pak DT. The upside of APP at synapses. CNS Neurosci Ther 2012;18:47-56.
87. De Strooper B. Loss-of-function presenilin mutations in Alzheimer disease. Talking Point on the role of presenilin mutations in Alzheimer disease. EMBO Reports 2007;8:141-6.
88. Heilig EA, Xia W, Shen J, Kelleher RJ, 3rd. A presenilin-1 mutation identified in familial Alzheimer disease with cotton wool plaques causes a nearly complete loss of gamma-secretase activity. The Journal of biological chemistry 2010;285:22350-9.
89. Xia D, Kelleher RJ, 3rd, Shen J. Loss of Abeta43 Production Caused by Presenilin-1 Mutations in the Knockin Mouse Brain. Neuron 2016;90:417-22.
90. Xia D, Watanabe H, Wu B, et al. Presenilin-1 knockin mice reveal loss-of-function mechanism for familial Alzheimer's disease. Neuron 2015;85:967-81.
91. Doody RS, Raman R, Farlow M, et al. A Phase 3 Trial of Semagacestat for Treatment of Alzheimer's Disease. New England Journal of Medicine 2013;369:341-50.
92. Coric V, Salloway S, van Dyck CH, et al. Targeting Prodromal Alzheimer Disease With Avagacestat: A Randomized Clinical Trial. JAMA neurology 2015;72:1324-33.
93. Hemming ML, Elias JE, Gygi SP, Selkoe DJ. Proteomic Profiling of ?-Secretase Substrates and Mapping of Substrate Requirements. PLoS Biol 2008;6:e257.
94. Haapasalo A, Kovacs DM. The Many Substrates of Presenilin/γ-Secretase. Journal of Alzheimer's Disease 2011;25:3-28.
95. May P, Bock HH, Nimpf J, Herz J. Differential glycosylation regulates processing of lipoprotein receptors by gamma-secretase. The Journal of biological chemistry 2003;278:37386-92.
96. Wunderlich P, Glebov K, Kemmerling N, Tien NT, Neumann H, Walter J. Sequential proteolytic processing of the triggering receptor expressed on myeloid cells-2 (TREM2) protein by ectodomain shedding and gamma-secretase-dependent intramembranous cleavage. The Journal of biological chemistry 2013;288:33027-36.
97. Inoue E, Deguchi-Tawarada M, Togawa A, et al. Synaptic activity prompts gamma-secretase-mediated cleavage of EphA4 and dendritic spine formation. J Cell Biol 2009;185:551-64.
98. Bai G, Chivatakarn O, Bonanomi D, et al. Presenilin-Dependent Receptor Processing Is Required for Axon Guidance. Cell 2011;144:106-18.
99. Waschbusch D, Born S, Niediek V, et al. Presenilin 1 affects focal adhesion site formation and cell force generation via c-Src transcriptional and posttranslational regulation. The Journal of biological chemistry 2009;284:10138-49.
100. Guerreiro RJ, Lohmann E, Kinsella E, et al. Exome sequencing reveals an unexpected genetic cause of disease: NOTCH3 mutation in a Turkish family with Alzheimer's disease. Neurobiol Aging 2012;33:1008.e17-23.
101. Groot AJ, Habets R, Yahyanejad S, et al. Regulated Proteolysis of NOTCH2 and NOTCH3 Receptors by ADAM10 and Presenilins. Molecular and cellular biology 2014;34:2822-32.
102. Schedin-Weiss S, Caesar I, Winblad B, Blom H, Tjernberg LO. Super-resolution microscopy reveals γ-secretase at both sides of the neuronal synapse. Acta Neuropathologica Communications 2016;4:29.

103. Restituito S, Khatri L, Ninan I, et al. Synaptic Autoregulation by Metalloproteases and γ-Secretase. The Journal of neuroscience : the official journal of the Society for Neuroscience 2011;31:12083-93.
104. Marambaud P, Wen PH, Dutt A, et al. A CBP Binding Transcriptional Repressor Produced by the PS1/ϵ-Cleavage of N-Cadherin Is Inhibited by PS1 FAD Mutations. Cell;114:635-45.
105. Ridge PG, Mukherjee S, Crane PK, Kauwe JSK, Alzheimer?s Disease Genetics C. Alzheimer?s Disease: Analyzing the Missing Heritability. PLoS ONE 2013;8:e79771.
106. Jonsson T, Atwal JK, Steinberg S, et al. A mutation in APP protects against Alzheimer's disease and age-related cognitive decline. Nature 2012;488:96-9.
107. Wang LS, Naj AC, Graham RR, et al. Rarity of the Alzheimer disease-protective APP A673T variant in the United States. JAMA Neurol 2015;72:209-16.
108. Zhou TB. Signaling pathways of apoE and its role of gene expression in glomerulus diseases. J Recept Signal Transduct Res 2013;33:73-8.
109. Reddy SS, Connor TE, Weeber EJ, Rebeck W. Similarities and differences in structure, expression, and functions of VLDLR and ApoER2. Molecular Neurodegeneration 2011;6:30-.
110. Lee GH, D'Arcangelo G. New Insights into Reelin-Mediated Signaling Pathways. Frontiers in cellular neuroscience 2016;10.
111. Del Rio JA, Heimrich B, Borrell V, et al. A role for Cajal-Retzius cells and reelin in the development of hippocampal connections. Nature 1997;385:70-4.
112. Wu P, Li MS, Yu DM, Deng JB. Reelin, a guidance signal for the regeneration of the entorhino-hippocampal path. Brain research 2008;1208:1-7.
113. Nathan BP, Jiang Y, Wong GK, Shen F, Brewer GJ, Struble RG. Apolipoprotein E4 inhibits, and apolipoprotein E3 promotes neurite outgrowth in cultured adult mouse cortical neurons through the low-density lipoprotein receptor-related protein. Brain research 2002;928:96-105.
114. Handelmann GE, Boyles JK, Weisgraber KH, Mahley RW, Pitas RE. Effects of apolipoprotein E, beta-very low density lipoproteins, and cholesterol on the extension of neurites by rabbit dorsal root ganglion neurons in vitro. Journal of lipid research 1992;33:1677-88.
115. Bellosta S, Nathan BP, Orth M, Dong L-M, Mahley RW, Pitas RE. Stable expression and secretion of apolipoproteins E3 and E4 in mouse neuroblastoma cells produces differential effects on neurite outgrowth. Journal of Biological Chemistry 1995;270:27063-71.
116. Huang Y. Abeta-independent roles of apolipoprotein E4 in the pathogenesis of Alzheimer's disease. Trends Mol Med 2010;16:287-94.
117. Hussain A, Luong M, Pooley A, Nathan BP. Isoform-specific effects of ApoE on neurite outgrowth in Olfactory Epithelium culture. Journal of Biomedical Science 2013;20:49-.
118. Chen X, Guo Z, Okoro EU, et al. Up-regulation of ATP Binding Cassette Transporter A1 Expression by Very Low Density Lipoprotein Receptor and Apolipoprotein E Receptor 2. Journal of Biological Chemistry 2012;287:3751-9.
119. Casey CS, Atagi Y, Yamazaki Y, et al. Apolipoprotein E Inhibits Cerebrovascular Pericyte Mobility through a RhoA Protein-mediated Pathway. The Journal of biological chemistry 2015;290:14208-17.
120. Comley LH, Fuller HR, Wishart TM, et al. ApoE isoform-specific regulation of regeneration in the peripheral nervous system. Human molecular genetics 2011;20:2406-21.
121. Kramer PL, Xu H, Woltjer RL, et al. Alzheimer Disease Pathology in Cognitively Healthy Elderly:A Genome-wide Study. Neurobiology of aging 2011;32:2113-22.
122. Sherva R, Tripodis Y, Bennett DA, et al. Genome-wide association study of the rate of cognitive decline in Alzheimer's disease. Alzheimer's & dementia : the journal of the Alzheimer's Association 2014;10:45-52.

123. Jahanshad N, Rajagopalan P, Hua X, et al. Genome-wide scan of healthy human connectome discovers SPON1 gene variant influencing dementia severity. Proceedings of the National Academy of Sciences 2013;110:4768-73.
124. Ho A, Südhof TC. Binding of F-spondin to amyloid-β precursor protein: A candidate amyloid-β precursor protein ligand that modulates amyloid-β precursor protein cleavage. Proceedings of the National Academy of Sciences of the United States of America 2004;101:2548-53.
125. Peterziel H, Sackmann T, Strelau J, et al. F-spondin regulates neuronal survival through activation of disabled-1 in the chicken ciliary ganglion. Mol Cell Neurosci 2011;46:483-97.
126. Rogaeva E, Meng Y, Lee JH, et al. The neuronal sortilin-related receptor SORL1 is genetically associated with Alzheimer disease. Nature genetics 2007;39:168-77.
127. Taira K, Bujo H, Hirayama S, et al. LR11, a mosaic LDL receptor family member, mediates the uptake of ApoE-rich lipoproteins in vitro. Arteriosclerosis, thrombosis, and vascular biology 2001;21:1501-6.
128. Zhu Y, Bujo H, Yamazaki H, et al. LR11, an LDL receptor gene family member, is a novel regulator of smooth muscle cell migration. Circulation research 2004;94:752-8.
129. Leeb C, Eresheim C, Nimpf J. Clusterin is a ligand for apolipoprotein E receptor 2 (ApoER2) and very low density lipoprotein receptor (VLDLR) and signals via the Reelin-signaling pathway. The Journal of biological chemistry 2014;289:4161-72.
130. May P, Rohlmann A, Bock HH, et al. Neuronal LRP1 functionally associates with postsynaptic proteins and is required for normal motor function in mice. Molecular and cellular biology 2004;24:8872-83.
131. Marschang P, Brich J, Weeber EJ, et al. Normal Development and Fertility of Knockout Mice Lacking the Tumor Suppressor Gene LRP1b Suggest Functional Compensation by LRP1. Molecular and Cellular Biology 2004;24:3782-93.
132. Hoe HS, Pocivavsek A, Chakraborty G, et al. Apolipoprotein E receptor 2 interactions with the N-methyl-D-aspartate receptor. The Journal of biological chemistry 2006;281:3425-31.
133. Dumanis SB, Cha HJ, Song JM, et al. ApoE receptor 2 regulates synapse and dendritic spine formation. PLoS One 2011;6:e17203.
134. Weeber EJ, Beffert U, Jones C, et al. Reelin and ApoE receptors cooperate to enhance hippocampal synaptic plasticity and learning. The Journal of biological chemistry 2002;277:39944-52.
135. Qiu S, Zhao LF, Korwek KM, Weeber EJ. Differential reelin-induced enhancement of NMDA and AMPA receptor activity in the adult hippocampus. The Journal of neuroscience : the official journal of the Society for Neuroscience 2006;26:12943-55.
136. Chen Y, Durakoglugil MS, Xian X, Herz J. ApoE4 reduces glutamate receptor function and synaptic plasticity by selectively impairing ApoE receptor recycling. Proceedings of the National Academy of Sciences of the United States of America 2010;107:12011-6.
137. Pfennig S, Foss F, Bissen D, et al. GRIP1 Binds to ApoER2 and EphrinB2 to Induce Activity-Dependent AMPA Receptor Insertion at the Synapse. Cell Rep 2017;21:84-96.
138. Klug W, Dietl A, Simon B, Sinning I, Wild K. Phosphorylation of LRP1 regulates the interaction with Fe65. FEBS Lett 2011;585:3229-35.
139. Giusti B, Margheri F, Rossi L, et al. Desmoglein-2-integrin Beta-8 interaction regulates actin assembly in endothelial cells: deregulation in systemic sclerosis. PLoS One 2013;8:e68117.
140. Peitsch WK, Doerflinger Y, Fischer-Colbrie R, et al. Desmoglein 2 Depletion Leads to Increased Migration and Upregulation of the Chemoattractant Secretoneurin in Melanoma Cells. PLoS ONE 2014;9:e89491.
141. Carter N, Nakamoto T, Hirai H, Hunter T. EphrinA1-induced cytoskeletal re-organization requires FAK and p130cas. Nature cell biology 2002;4:565-73.

142. Yamazaki T, Masuda J, Omori T, Usui R, Akiyama H, Maru Y. EphA1 interacts with integrin-linked kinase and regulates cell morphology and motility. J Cell Sci 2009;122:243-55.
143. Dong Y, Wang J, Sheng Z, et al. Downregulation of EphA1 in colorectal carcinomas correlates with invasion and metastasis. Modern Pathology 2009;22:151-60.
144. Lambert JC, Grenier-Boley B, Harold D, et al. Genome-wide haplotype association study identifies the FRMD4A gene as a risk locus for Alzheimer's disease. Mol Psychiatry 2013;18:461-70.
145. Moleirinho S, Tilston-Lunel A, Angus L, Gunn-Moore F, Reynolds Paul A. The expanding family of FERM proteins. Biochemical Journal 2013;452:183-93.
146. Frame MC, Patel H, Serrels B, Lietha D, Eck MJ. The FERM domain: organizing the structure and function of FAK. Nat Rev Mol Cell Biol 2010;11:802-14.
147. Shen Z, Ye Y, Dong L, et al. Kindlin-2: a novel adhesion protein related to tumor invasion, lymph node metastasis, and patient outcome in gastric cancer. The American Journal of Surgery 2012;203:222-9.
148. Schjeide B-MM, Hooli B, Parkinson M, et al. GAB2 as an Alzheimer Disease Susceptibility Gene: Follow-up of Genomewide Association Results. Archives of neurology 2009;66:250-4.
149. Yu WM, Hawley TS, Hawley RG, Qu CK. Role of the docking protein Gab2 in beta(1)-integrin signaling pathway-mediated hematopoietic cell adhesion and migration. Blood 2002;99:2351-9.
150. Herrera Abreu MT, Hughes WE, Mele K, et al. Gab2 regulates cytoskeletal organization and migration of mammary epithelial cells by modulating RhoA activation. Mol Biol Cell 2011;22:105-16.
151. Singh MK, Dadke D, Nicolas E, et al. A novel Cas family member, HEPL, regulates FAK and cell spreading. Mol Biol Cell 2008;19:1627-36.
152. Huang Z, Yazdani U, Thompson-Peer KL, Kolodkin AL, Terman JR. Crk-associated substrate (Cas) signaling protein functions with integrins to specify axon guidance during development. Development 2007;134:2337-47.
153. Guerrero MS, Parsons JT, Bouton AH. Cas and NEDD9 contribute to tumor progression through dynamic regulation of the cytoskeleton. Genes & cancer 2012;3:371-81.
154. Lehtonen S, Zhao F, Lehtonen E. CD2-associated protein directly interacts with the actin cytoskeleton. American Journal of Physiology-Renal Physiology 2002;283:F734-F43.
155. van Duijn TJ, Anthony EC, Hensbergen PJ, Deelder AM, Hordijk PL. Rac1 Recruits the Adapter Protein CMS/CD2AP to Cell-Cell Contacts. The Journal of biological chemistry 2010;285:20137-46.
156. Taniyama Y, Weber DS, Rocic P, et al. Pyk2-and Src-dependent tyrosine phosphorylation of PDK1 regulates focal adhesions. Molecular and cellular biology 2003;23:8019-29.
157. Du Q-S, Ren X-R, Xie Y, Wang Q, Mei L, Xiong W-C. Inhibition of PYK2-induced actin cytoskeleton reorganization, PYK2 autophosphorylation and focal adhesion targeting by FAK. Journal of Cell Science 2001;114:2977-87.
158. Cheung SMS, Ostergaard HL. Pyk2 Controls Integrin-Dependent CTL Migration through Regulation of De-Adhesion. The Journal of Immunology 2016.
159. Lipinski CA, Tran NL, Menashi E, et al. The tyrosine kinase pyk2 promotes migration and invasion of glioma cells. Neoplasia 2005;7:435-45.
160. Tebar F, Bohlander SK, Sorkin A. Clathrin assembly lymphoid myeloid leukemia (CALM) protein: localization in endocytic-coated pits, interactions with clathrin, and the impact of overexpression on clathrin-mediated traffic. Molecular biology of the cell 1999;10:2687-702.
161. Man HY, Lin JW, Ju WH, et al. Regulation of AMPA receptor-mediated synaptic transmission by clathrin-dependent receptor internalization. Neuron 2000;25:649-62.
162. Becker T, Ramirez A, Herold C, et al. COMPREHENSIVE GENE-GENE INTERACTION META-ANALYSIS OF IGAP GWA STUDIES. Alzheimer's & Dementia: The Journal of the Alzheimer's Association;10:P245.

163. Para A, Krischke M, Merlot S, et al. Dictyostelium Dock180-related RacGEFs Regulate the Actin Cytoskeleton during Cell Motility. Molecular Biology of the Cell 2009;20:699-707.
164. Maxwell MJ, Yuan Y, Anderson KE, Hibbs ML, Salem HH, Jackson SP. SHIP1 and Lyn Kinase Negatively Regulate Integrin alpha IIb beta 3 signaling in platelets. The Journal of biological chemistry 2004;279:32196-204.
165. Mondal S, Subramanian KK, Sakai J, Bajrami B, Luo HR. Phosphoinositide lipid phosphatase SHIP1 and PTEN coordinate to regulate cell migration and adhesion. Mol Biol Cell 2012;23:1219-30.
166. Yokoyama K, Tezuka T, Kotani M, et al. NYAP: a phosphoprotein family that links PI3K to WAVE1 signalling in neurons. The EMBO Journal 2011;30:4739-54.
167. Shimoda Y, Koseki F, Itoh M, Toyoshima M, Watanabe K. A cis-complex of NB-2/contactin-5 with amyloid precursor-like protein 1 is localized on the presynaptic membrane. Neuroscience letters 2012;510:148-53.
168. Wixler V, Laplantine E, Geerts D, et al. Identification of novel interaction partners for the conserved membrane proximal region of α-integrin cytoplasmic domains. FEBS Letters 1999;445:351-5.
169. Messina S, Onofri F, Bongiorno-Borbone L, et al. Specific interactions of neuronal focal adhesion kinase isoforms with Src kinases and amphiphysin. J Neurochem 2003;84:253-65.
170. Mundigl O, Ochoa GC, David C, Slepnev VI, Kabanov A, De Camilli P. Amphiphysin I antisense oligonucleotides inhibit neurite outgrowth in cultured hippocampal neurons. J Neurosci 1998;18:93-103.
171. Yamada H, Padilla-Parra S, Park SJ, et al. Dynamic interaction of amphiphysin with N-WASP regulates actin assembly. The Journal of biological chemistry 2009;284:34244-56.
172. Wetzel-Smith MK, Hunkapiller J, Bhangale TR, et al. A rare mutation in UNC5C predisposes to late-onset Alzheimer's disease and increases neuronal cell death. Nature medicine 2014;20:1452-7.
173. Burgess RW, Jucius TJ, Ackerman SL. Motor axon guidance of the mammalian trochlear and phrenic nerves: dependence on the netrin receptor Unc5c and modifier loci. Journal of Neuroscience 2006;26:5756-66.
174. Ly A, Nikolaev A, Suresh G, Zheng Y, Tessier-Lavigne M, Stein E. DSCAM is a netrin receptor that collaborates with DCC in mediating turning responses to netrin-1. Cell 2008;133:1241-54.
175. Stanco A, Szekeres C, Patel N, et al. Netrin-1–α3β1 integrin interactions regulate the migration of interneurons through the cortical marginal zone. Proceedings of the National Academy of Sciences 2009;106:7595-600.
176. Carsberg CJ, Myers KA, Stern PL. Metastasis-associated 5T4 antigen disrupts cell-cell contacts and induces cellular motility in epithelial cells. Int J Cancer 1996;68:84-92.
177. He P, Jiang S, Ma M, et al. Trophoblast glycoprotein promotes pancreatic ductal adenocarcinoma cell metastasis through Wnt/planar cell polarity signaling. Molecular medicine reports 2015;12:503-9.
178. Murakami T, Abe H, Nagai K, et al. Trophoblast glycoprotein: possible candidate mediating podocyte injuries in glomerulonephritis. American journal of nephrology 2010;32:505-21.
179. Spencer HL, Eastham AM, Merry CLR, et al. E-Cadherin Inhibits Cell Surface Localization of the Pro-Migratory 5T4 Oncofetal Antigen in Mouse Embryonic Stem Cells. Molecular Biology of the Cell 2007;18:2838-51.
180. Su Y, Yang J, Besner GE. HB-EGF promotes intestinal restitution by affecting integrin–extracellular matrix interactions and intercellular adhesions. Growth factors 2013;31:39-55.
181. Su Y, Besner GE. HB-EGF Promotes Cell Migration and Adhesion via Focal Adhesion Kinase. The Journal of surgical research 2014;189:222-31.
182. Palamidessi A, Frittoli E, Ducano N, et al. The GTPase-activating protein RN-tre controls focal adhesion turnover and cell migration. Current biology : CB 2013;23:2355-64.
183. Guerreiro R, Wojtas A, Bras J, et al. TREM2 Variants in Alzheimer's Disease. New England Journal of Medicine 2013;368:117-27.

184. Takegahara N, Takamatsu H, Toyofuku T, et al. Plexin-A1 and its interaction with DAP12 in immune responses and bone homeostasis. Nat Cell Biol 2006;8:615-22.
185. Ford JW, McVicar DW. TREM and TREM-like receptors in inflammation and disease. Current Opinion in Immunology 2009;21:38-46.
186. Barberis D, Artigiani S, Casazza A, et al. Plexin signaling hampers integrin-based adhesion, leading to Rho-kinase independent cell rounding, and inhibiting lamellipodia extension and cell motility. The FASEB journal 2004;18:592-4.
187. Beecham GW, Vardarajan BN, Blue E, et al. WHOLE GENOME SEQUENCING IN FAMILIAL LATE-ONSET ALZHEIMER’S DISEASE IDENTIFIES VARIATIONS IN TTC3 AND FSIP2. Alzheimer's & Dementia: The Journal of the Alzheimer's Association;12:P197.
188. Dey-Guha I, Alves CP, Yeh AC, et al. A MECHANISM FOR ASYMMETRIC CELL DIVISION RESULTING IN PROLIFERATIVE ASYNCHRONICITY. Molecular cancer research : MCR 2015;13:223-30.
189. Berto GE, Iobbi C, Camera P, et al. The DCR Protein TTC3 Affects Differentiation and Golgi Compactness in Neurons through Specific Actin-Regulating Pathways. PLOS ONE 2014;9:e93721.
190. Sims R, van der Lee SJ, Naj AC, et al. Rare coding variants in PLCG2, ABI3, and TREM2 implicate microglial-mediated innate immunity in Alzheimer's disease. Nature genetics 2017.
191. Tvorogov D, Wang X-J, Zent R, Carpenter G. Integrin-dependent PLC-γ1 phosphorylation mediates fibronectin-dependent adhesion. Journal of cell science 2005;118:601-10.
192. Mueller H, Stadtmann A, Van Aken H, et al. Tyrosine kinase Btk regulates E-selectin–mediated integrin activation and neutrophil recruitment by controlling phospholipase C (PLC) γ2 and PI3Kγ pathways. Blood 2010;115:3118-27.
193. Sekino S, Kashiwagi Y, Kanazawa H, et al. The NESH/Abi-3-based WAVE2 complex is functionally distinct from the Abi-1-based WAVE2 complex. Cell Communication and Signaling 2015;13:41.
194. Hodgkinson CP, Naidoo V, Patti KG, et al. Abi3bp is a multifunctional autocrine/paracrine factor that regulates mesenchymal stem cell biology. Stem cells (Dayton, Ohio) 2013;31:1669-82.
195. Ichigotani Y, Yokozaki S, Fukuda Y, Hamaguchi M, Matsuda S. Forced expression of NESH suppresses motility and metastatic dissemination of malignant cells. Cancer research 2002;62:2215-9.
196. Hortsch M, Umemori H. The sticky synapse: Springer; 2009.
197. Missler M, Sudhof TC, Biederer T. Synaptic cell adhesion. Cold Spring Harbor perspectives in biology 2012;4:a005694.
198. Lin B, Arai AC, Lynch G, Gall CM. Integrins regulate NMDA receptor-mediated synaptic currents. Journal of neurophysiology 2003;89:2874-8.
199. Juhász G, Vass G, Bozsó Z, Budai D, Penke B, Szegedi V. Integrin activation modulates NMDA and AMPA receptor function of CA1 cells in a dose-related fashion in vivo. Brain Research 2008;1233:20-6.
200. Shi Y, Ethell IM. Integrins Control Dendritic Spine Plasticity in Hippocampal Neurons through NMDA Receptor and Ca2+/Calmodulin-Dependent Protein Kinase II-Mediated Actin Reorganization. The Journal of Neuroscience 2006;26:1813-22.
201. Myers JP, Santiago-Medina M, Gomez TM. Regulation of axonal outgrowth and pathfinding by integrin-ECM interactions. Developmental neurobiology 2011;71:901-23.
202. Kerrisk ME, Cingolani LA, Koleske AJ. ECM receptors in neuronal structure, synaptic plasticity, and behavior. Progress in brain research 2014;214:101-31.
203. Hoang ML, Kinde I, Tomasetti C, et al. Genome-wide quantification of rare somatic mutations in normal human tissues using massively parallel sequencing. Proceedings of the National Academy of Sciences 2016:201607794.
204. Robison SH, Munzer JS, Tandan R, Bradley WG. Alzheimer's disease cells exhibit defective repair of alkylating agent-induced DNA damage. Annals of neurology 1987;21:250-8.

205. Anderson A, Su J, Cotman C. DNA damage and apoptosis in Alzheimer's disease: colocalization with c- Jun immunoreactivity, relationship to brain area, and effect of postmortem delay. The Journal of Neuroscience 1996;16:1710-9.
206. Smith DI, Zhu Y, McAvoy S, Kuhn R. Common fragile sites, extremely large genes, neural development and cancer. Cancer letters 2006;232:48-57.
207. Consortium TU. The Universal Protein Resource (UniProt). Nucleic acids research 2008;36:D190-D5.
208. Huang da W, Sherman BT, Lempicki RA. Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. Nat Protoc 2009;4:44-57.
209. Rose MR, Mueller LD. Evolution of human lifespan: past, future, and present. American journal of human biology 1998;10:409-20.
210. Beroukhim R, Mermel CH, Porter D, et al. The landscape of somatic copy-number alteration across human cancers. Nature 2010;463:899-905.
211. Haas J, Beer AG, Widschwendter P, et al. LRP1b shows restricted expression in human tissues and binds to several extracellular ligands, including fibrinogen and apoE – carrying lipoproteins. Atherosclerosis 2011;216:342-7.
212. Cam JA, Zerbinatti CV, Knisely JM, Hecimovic S, Li Y, Bu G. The Low Density Lipoprotein Receptor-related Protein 1B Retains β-Amyloid Precursor Protein at the Cell Surface and Reduces Amyloid-β Peptide Production. Journal of Biological Chemistry 2004;279:29639-46.
213. Ni S, Hu J, Duan Y, et al. Down expression of LRP1B promotes cell migration via RhoA/Cdc42 pathway and actin cytoskeleton remodeling in renal cell cancer. Cancer science 2013;104:817-25.
214. Wang Z, Sun P, Gao C, et al. Down-regulation of LRP1B in colon cancer promoted the growth and migration of cancer cells. Experimental cell research 2017;357:1-8.
215. Liu CX, Ranganathan S, Robinson S, Strickland DK. gamma-Secretase-mediated release of the low density lipoprotein receptor-related protein 1B intracellular domain suppresses anchorage-independent growth of neuroglioma cells. The Journal of biological chemistry 2007;282:7504-11.
216. Hawrylycz MJ, Lein S, Guillozet-Bongaarts AL, et al. An anatomically comprehensive atlas of the adult human brain transcriptome. Nature 2012;489:391.
217. Shiroshima T, Oka C, Kawaichi M. Identification of LRP1B-interacting proteins and inhibition of protein kinase Cα-phosphorylation of LRP1B by association with PICK1. FEBS letters 2009;583:43-8.
218. Shang Z, Lv H, Zhang M, et al. Genome-wide haplotype association study identify TNFRSF1A, CASP7, LRP1B, CDH1 and TG genes associated with Alzheimer's disease in Caribbean Hispanic individuals. Oncotarget 2015;6:42504.
219. Poduslo S, Huang R, Spiro A. A genome screen of successful aging without cognitive decline identifies LRP1B by haplotype analysis. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics 2010;153:114-9.
220. Hibar DP, Stein JL, Renteria ME, et al. Common genetic variants influence human subcortical brain structures. Nature 2015;520:224-9.
221. Novak NM, Stein JL, Medland SE, Hibar DP, Thompson PM, Toga AW. EnigmaVis: online interactive visualization of genome-wide association studies of the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) consortium. Twin Res Hum Genet 2012;15:414-8.
222. Coppede F, Migliore L. DNA damage and repair in Alzheimer's disease. Current Alzheimer research 2009;6:36-47.
223. Itsara LS, Kennedy SR, Fox EJ, et al. Oxidative Stress Is Not a Major Contributor to Somatic Mitochondrial DNA Mutations. PLoS Genetics 2014;10:e1003974.
224. Lodato MA, Woodworth MB, Lee S, et al. Somatic mutation in single human neurons tracks developmental and transcriptional history. Science (New York, NY) 2015;350:94-8.

225. Alexandrov LB, Jones PH, Wedge DC, et al. Clock-like mutational processes in human somatic cells. Nature genetics 2015;47:1402-7.
226. Podolskiy DI, Lobanov AV, Kryukov GV, Gladyshev VN. Analysis of cancer genomes reveals basic features of human aging and its role in cancer development. Nature Communications 2016;7.
227. Busuttil RA, Garcia AM, Reddick RL, et al. Intra-organ variation in age-related mutation accumulation in the mouse. PloS one 2007;2:e876.
228. Hazen JL, Faust GG, Rodriguez AR, et al. The Complete Genome Sequences, Unique Mutational Spectra, and Developmental Potency of Adult Neurons Revealed by Cloning. Neuron 2016;89:1223-36.
229. Tubbs A, Nussenzweig A. Endogenous DNA damage as a source of genomic instability in cancer. Cell 2017;168:644-56.
230. Zhang Y, Gao J, Chung KK, Huang H, Dawson VL, Dawson TM. Parkin functions as an E2-dependent ubiquitin- protein ligase and promotes the degradation of the synaptic vesicle-associated protein, CDCrel-1. Proceedings of the National Academy of Sciences of the United States of America 2000;97:13354-9.
231. Osborne PB, Halliday GM, Cooper HM, Keast JR. Localization of immunoreactivity for deleted in colorectal cancer (DCC), the receptor for the guidance factor netrin-1, in ventral tier dopamine projection pathways in adult rodents. Neuroscience 2005;131:671-81.
232. La Manno G, Gyllborg D, Codeluppi S, et al. Molecular Diversity of Midbrain Development in Mouse, Human, and Stem Cells. Cell 2016;167:566-80.e19.
233. Dietrich MF, Van Der Weyden L, Prosser HM, Bradley A, Herz J, Adams DJ. Ectodomains of the LDL receptor-related proteins LRP1b and LRP4 have anchorage independent functions in vivo. PLoS One 2010;5:e9960.
234. Liu Q, Trotter J, Zhang J, et al. Neuronal LRP1 knockout in adult mice leads to impaired brain lipid metabolism and progressive, age-dependent synapse loss and neurodegeneration. The Journal of neuroscience : the official journal of the Society for Neuroscience 2010;30:17068-78.
235. Jaarsma D, van der Pluijm I, de Waard MC, et al. Age-related neuronal degeneration: complementary roles of nucleotide excision repair and transcription-coupled repair in preventing neuropathology. PLoS Genet 2011;7:e1002405.