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An Amyloid Agnostic Reformulation of the Alzheimer's Disease: the Long Gene Vulnerability Hypothesis

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Abstract

Alzheimer's disease (AD) is a genetically complex senile neurodegeneration with unknown etiology. The first gene discovered to be mutated in early-onset AD, the amyloid precursor protein (APP), has been widely assumed as a causal factor in the disease cascade due to its generation of Aβ species. APP has an evolutionarily conserved biological role and activates a signaling program with notable similarities to integrin—a cell adhesion receptor with a wide array of functions. Intriguingly, several AD genome-wide association study (GWAS) candidate genes, including the SHARPIN locus recently reported by us and others, influence signaling of the integrin pathway. Integrins are focal adhesion regulators and serve in nervous system development, synaptic plasticity, and Tau phosphorylation. These observations suggest that the function of APP probably goes beyond Aβ generation in AD.

Aging—the strongest risk factor for AD—is associated with various clock-like events in cells. For instance, neurons are continuously impacted by stochastic 'hits' to their genomes in aging, in the forms of DNA damage, insertion-deletions, copy-number variations (CNVs) and other types of somatic mutations. DNA damage and somatic mutations can result in neoplastic changes and cancer in mitotically active cells. However, their consequences in post-mitotic cells such as aging neurons are less defined.

The current hypothesis holds that the stochastic loss of DNA sequence data at random loci in aging affects longer genes by chance more frequently. As a result, the biological processes coordinated by long genes may be more vulnerable to such random aging effects. Curiously, as shown by us and others, long genes are strongly enriched for *synapse*- and *cell adhesion*-related ontologies, more than any other biological process or cellular compartment. In addition, among various cell types, neurons possess the highest levels of long gene expression and are therefore more vulnerable to such harmful effects. The long gene vulnerability hypothesis provides a simple link between aging and the genetic landscape of AD and warrants new strategies for disease modification.

Keywords: Alzheimer's disease, DNA damage, somatic mutation, integrin, synaptic adhesion

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Introduction

The Aβ fragment of the APP protein[1] has been the centerpiece of AD pathogenesis research and drug design following the amyloid cascade theory[2]. However, more than three decades after the successful cloning of the APP gene[3], the biological function of its encoded protein remains speculative in the brain and elsewhere. Mounting evidence indicates that APP acts as a cell surface receptor and activates an intracellular signaling program[4,5] for synaptic function and plasticity[6]. Still, this essential biological function has received less attention in the field.

Sporadic late-onset AD is a genetically complex disease with a heritability of 60-80%[7]. GWAS and next-generation sequencing have identified multiple risk loci for late-onset AD in the last decade[8-11]. These loci provide a hypothesis-free glimpse of the underlying molecular pathways in AD and bring opportunities for revising disease models in a data-driven way. APP, presenilins (PSENs), and Tau variants have shown small contributions to the total heritability of late-onset AD[10,12], whereas the APOE locus explains approximately a quarter of the disease heritability[13]. The GWAS loci have been suggested to highlight several pathways in AD pathogenesis, spanning microglial activation, lipid metabolism, focal adhesion, and Aβ turnover[14-17]. Nevertheless, the causal significance of Aβ in AD is a matter of ongoing debate[18-20]. The correlation between Aβ and brain atrophy seems to be weak, absent, and in recent reports paradoxically negative[21].

It is argued here that the model of AD pathogenesis can be surprisingly simplified by reimagining Aβ deposition and Tau phosphorylation as potential consequences of the disease process rather than causal factors. Several testable predictions are proposed together with new disease modification strategies.

APP may be a synaptic adhesion molecule: the evolutionarily-conserved NPxY motif

Three APP family genes are present in the human genome, including APP, APLP1, and APLP2. The common function of this gene family, biological adhesion[22], has been highly conserved in evolution. As a receptor-like protein, transmembrane APP transfers extracellular signals to the internal actin cytoskeleton and affects focal adhesion stability[4,23]. Specifically, APP interacts with many extracellular molecules that are classical ligands for integrins, such as heparan sulfate, laminin, and fibronectin[24-27]. Similar to the integrin pathway, APP moderates neuronal growth cone adhesion and movement[28,29]. For example, the APP protein directly interacts with β1 integrin at cell membranes and influences focal adhesion[30,31], cell motility[32], and hippocampal neurite outgrowth[33,34]. In addition to direct interaction with integrin, APP also binds to two extracellular adhesion molecules that act as integrin-activating ligands[34,35], including reelin[34] and netrin[36,37]. This biological convergence with integrin suggests that APP may take part in the integrin adhesion complex and modulate its downstream signaling effects on the cytoskeleton.

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The intracellular domain of APP attracts adaptor molecules with signaling activity[38-40]. Specifically, the APP intracellular domain constitutes an NPxY amino acid motif that has been super-conserved from roundworms to humans for more than 900 million years of evolution[41]. NPxY is a consensus motif for receptor sorting and intracellular signaling. For instance, integrins recruit their cytoplasmic adaptors (e.g., kindlin and talin) via a cytoplasmic NPxY motif, and this event ultimately affects the remodeling of the actin cytoskeleton[42]. Similarly, the NPxY-binding APP intracellular adaptors converge to the same cytoskeletal actin pathway[4,23] (table 1). Notably, APOE lipoprotein receptors also recruit the same NPxY motif for signaling (as shall be discussed in the next sections).

Several lines of evidence suggest that APP may be a synaptic protein. At the postsynapse, APP interacts with AIDA1, a synaptic plasticity regulator, via its NPxY site[43,44]. The APP family proteins form trans-synaptic adhesion dimers, stabilize synaptic connections[45] and coordinate neurotransmitter receptor function[46,47]. Taken together, the signaling function of APP[6] seems to overlap with that of integrin cell adhesion and its influence on synaptic plasticity[48,49]. This amyloid-independent role of APP dovetails with the body of GWAS evidence and the genetic architecture of AD.

Table 1. Extracellular and intracellular APP binding molecules

	Binding site	Function	Integrin modulation
FE65/TIP60	AICD	Cell adhesion and migration, cytoskeletal remodeling[50,51]	β1 integrin[52]
KAI1	AICD	Cell migration, cytoskeletal assembly[53,54]	β1 integrin[55]
DISC1	AICD	Neuronal migration and cytoskeletal remodeling[56,57]	β1 integrin[58]
DAB1	AICD	Neuronal migration and cytoskeletal remodeling[59]	β1 integrin[60]
MINT1	AICD	Cell migration[61]	Unknown
GRB2	AICD	Cell migration[62,63]	β1 integrin[62]
SHC	AICD	Cell adhesion and migration[63,64]	β1 integrin[65]
GRB7	AICD	Cell adhesion and migration[66]	(β1-)integrin[67]
CRK	AICD	Cell migration and cytoskeletal remodeling[68]	β1 integrin[69]
PIN1	AICD	Cell migration[70]	β1 integrin[71]
Lingo1	Extracellular	Cell migration[72,73]	β1 integrin[74]
Pancortin	Extracellular	Cell migration[75]	Unknown
Reelin	Extracellular	Cell migration[76]	β1 integrin[76]
Netrin1	Extracellular	Cell migration and synaptic actin remodeling[77,78]	β1 integrin[79]
F-spondin	Extracellular	Cell adhesion and migration[80,81]	β3 integrin[82]

AICD: APP intracellular domain

Γ-secretase may be a synaptic adhesion modulator

Although γ-secretase dysfunction has been primarily researched in the context of Aβ generation, the function of this transmembrane protease is not limited to APP cleavage[83]. Several receptors such as notch[84], which is a novel familial AD candidate gene[85], rely on γ-cleavage for normal signaling. Other γ-secretase substrates associated with AD include the APOE lipoprotein receptors (LRPs[86]) and the ephrin synaptic adhesion receptors[87], both of which regulate

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neurotransmission[86,88] and interact with the integrin adhesion complex[89,90]. Synaptic maturation is accompanied by an increased expression of γ-secretase at the postsynaptic membranes[91], where this enzyme is anchored to various cell adhesion molecules[91-93]. Loss of γ-secretase activity disrupts membrane adhesion force generation[94] and causes erroneous axonal pathfinding[95]. Taken together, γ-secretase is essential to the signaling of multiple synaptic adhesion receptors other than APP, a physiological cleavage process that has been hardly explored in AD pathogenesis.

The genome-wide landscape of AD and synaptic adhesion

Pioneered by Lambert et al., multiple GWAS risk loci have been discovered for late-onset AD in the last decade[12,96]. Curiously, GWAS candidate genes seem to strongly converge to the integrin cell adhesion pathway—a mechano-chemical signaling event that transfers extracellular matrix (ECM) signals to the internal actin cytoskeleton and vice versa. Integrins are heterodimeric receptors generated from 18 α and eight β subunits in humans. These cell adhesion receptors coordinate bidirectional communications between the cell and the ECM, for instance, in synapse development and plasticity modulation[48]. Many of the GWAS loci code for proteins that interact with the β1 integrin pathway, such as the Src family kinases (SFKs), focal adhesion kinase (FAK), and actin reorganizers (table 2 and Fig. 1). Notably, the integrin pathway prevents Tau phosphorylation via integrin-linked kinase (ILK). In this context, tau phosphorylation and ILK change the plasticity of cytoskeletal actin in neurites, an essential process for synaptic reshaping and outgrowth[97-101].

The endocytosis machinery has been implicated by multiple risk loci of AD, including BIN1, PICALM,[102] and ABCA7[103]. Endocytosis via clathrin[104] and IDOL-dependent pathways[105] regulates synaptic biology. Synaptic endocytosis modulates the strength of transmission by redistributing the pool of transmitter receptors from the postsynaptic density membrane (active state) to the intrasynaptic space (inactive state). For instance, LRPs are endocytic receptors of the APOE molecule and modulate postsynaptic glutamate receptor trafficking and plasticity[106,107]. Both LRPs and integrins recruit the clathrin-mediated endocytosis machinery via their NPxY motifs[108]. Intriguingly, kindlin-2, a known AD risk locus, links the LRP-mediated endocytosis to the integrin cell adhesion pathway[109].

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Table 2. AD risk genes and their implication of the integrin cell adhesion pathway

	Cell adhesion function	Interaction with integrin and focal adhesion	Actin cytoskeleton reorganization
EPHA1	Cancer cell invasion[110]	β1 integrin[111,112]	RhoA, ROCK pathway[112]
FRMD4A	Cell adhesion and invasion[113]	FAK[114,115]	Arf6[116]
FERMT2	Cell invasion[117]	FAK[114,115]	Unknown
GAB2	Cell adhesion and migration[118]	β1 integrin[118]	Rho pathway[119]
CASS4	Axon guidance[120], cell migration[121]	Integrin[120] and FAK[121]	Rho, Rac1, Rap1 pathway[122]
CD2AP	Podocyte focal adhesion[123]	α3 integrin[123]	Direct actin binding[124]
PTK2B	Cell migration[125]	FAK, SRC[126]	Actin reorganization[126]
INPP5D	Cell movement[127]	β3 integrin[127,128]	TREM2-mediated cytoskeletal rearrangement[129]
NYAP1	Neuronal migration[130]	Fyn[130]	PI3K/WAVE1 pathway[131]
BIN1	Clathrin-mediated endocytosis, focal adhesion[132]. AMPH (71% sequence similarity) affects hippocampal neurite outgrowth[133]	β1 integrin[132], α-integrin[134], FAK[135]	Tau-mediated actin dynamics[136]
PICALM	Unknown; Clathrin-mediated endocytosis[137,138]	Unknown, β1 integrin endocytosis through clathrin?[139,140]	Genetic interaction with the actin regulator DOCK1[141]
ABCA7	Unknown; Clathrin-mediated endocytosis[142]	Unknown	Unknown
UNC5C	Axon repulsion[143]	α6 integrin[144]	Unknown
TPBG	Cell adhesion and movement[145-147]	Focal adhesion[148]	Rho pathway[148]
HBEGF	integrin-dependent cell adhesion[149]	α5β1 Integrin[149], FAK[150]	ErbB-1[150]
USP6NL	Cell migration[151]	β1 integrin endocytosis[151]	Rab5[151]
TREM2	Unknown	β1 and β3 integrin[152]	DAP12-mediated cytoskeletal reorganization[129]
TTC3	Unknown	β1 integrin/FAK[153]	RhoA, ROCK[154]
PLCG2	Cell migration[155]	β1 and β2 integrin, SFK[155,156]	Unknown
ABI3	Cell migration[157]	ABI3 binding protein activates β1 integrin and FAK[158,159]	WAVE[160]
CLU	Cell adhesion[161] and migration[162]	Unknown	LIMK1[161] and PI3K/AKT pathways[162]
SHARPIN	Cell adhesion and migration[163,164]	β1 integrin[165]	Postsynaptic actin[166], Rap1, Rho GTPase[164]
ADAM10	Cell migration[167]	β1 integrin[167]	Unknown
HLA-DRB1	Cell adhesion and movement[168]	β1 integrin, FAK, Src[169,170]	Rho GTPase[171], Src, FAK and Erk[170]
NCK2	Cell adhesion and movement[172]	Integrin linked kinase[173] and FAK[174]	Cdc42, Rac[172], PINCH and N-WASP[175]
ACE	Unknown	β1 and α5 integrins[176]	Unknown

Long synaptic adhesion genes implicate DNA damage as the cause of AD

Cell adhesion enlightens new mechanisms of AD pathogenesis. Curiously, among all pathways and cell compartments documented in the gene ontology (GO) database, *cell adhesion*- and *synapse*-related ontologies show the strongest enrichment of long genes[177]. In addition, gene

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expression data shows that neurons highly express long genes, more than any other cell type[178]. While the reason for this statistical overrepresentation is elusive, it may be speculated that long genes may have increased the complexity of cell signaling pathways in evolution, such as those of brain development and synaptic connectivity. Long genes often possess long introns and more transcription factor binding sites. Also, long genes usually code for larger proteins with larger surface areas and more interaction sites. Elements of the neurodevelopmental program, such as axon guidance, neural migration and synapse formation, may rely on signaling complexities enabled by long gene products. Importantly, these large molecules also contribute to the post-developmental plasticity of the synapse[179].

Several independent groups have recently reported that somatic mutations and insertion-deletions (indels) accumulate in aging brain neurons at a more or less linear rate[180-183]. A long synaptic gene may be more vulnerable to such DNA damage events and somatic mutations (genosenium) that emerge in aging cells. Also, long neuronal genes often reside in chromosomal fragile sites and hot-spots of genome instability[184,185], a feature that may render them more vulnerable to DNA damage in aging. Loss of long neuronal genes due to DNA damage accumulation may be more or less similar to the mutational loss of long tumor suppressor genes in cancers[186], albeit with some distinctive features due to the post-mitotic state of neurons.

The biological pathways coordinated by long genes, synapse and cell adhesion, compile the genome-wide landscape of AD with APP, γ-secretase and APOE. Aβ generation and Tau phosphorylation may be downstream consequences of this causal mechanism (please see the next sections).

Testing the hypothesis: LRP1b, DAB1 and CSMD1 under the spotlight

The medial temporal lobe neurons express certain synaptic genes such as the NMDA receptor subunits for regulating plasticity and memory formation. NMDA receptors are coupled with synaptic adhesion molecules and cytoskeletal actin (Fig. 1). Due to such proteomic diversity in different brain regions and cells, some neurons may be more vulnerable to aging and DNA damage, for example if they incorporate multiple genes that are mutationally fragile in aging. While an extensive and exploratory search of long and fragile genes in AD may be helpful, three genes have interesting features warranting focused research (table 3):

- **LRP1b** codes for a receptor of the APOE molecule. LRP1b is the ninth-longest gene in the human genome and is selectively expressed in the hippocampal formation[187,188] (Fig. 2). This giant receptor maps to the chromosomal fragile site FRA2F and is among the top-ten genes frequently deleted in cancers[189]. Considering its interaction with the postsynaptic density protein PSD95[190], the synaptic plasticity regulator PICK1[191], and the APP protein[192], LRP1b may have postsynaptic roles. The biological functions of its closest homolog, LRP1 (with 59% sequence similarity), may help speculate potential synaptic roles of LRP1b. LRP1 regulates postsynaptic glutamate receptor trafficking, long-term potentiation[193] and integrin signaling[194]. Both of these receptors have two NPxY motifs.

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- **DAB1** is a mandatory signaling adaptor of the APOE/RELN signaling axis, an essential biological pathway in the perforant synaptic path of the medial temporal lobes[195,196]. DAB1 is coded by the 13th longest gene in the human genome and maps to the chromosomal fragile site FRA1B.

- **CSMD1** is another long synaptic gene with tumor-suppressor-like fragility[197]. This gene, which is the sixth-longest gene in the human genome, resides at the chromosomal fragile site FRA8B and prevents activation of the complement system[198]. As a giant synaptic membrane adhesion molecule, CSMD1 is strongly expressed in the hippocampal formation[188]. These features warrant research into the potential loss of CSMD1 in the aging brain and its possible influence on complement activation, synaptic pruning[199] and integrin signaling[200]. Notably, the C3b-4b complement complex—a cognate ligand for the AD risk locus CR1 receptor—is degraded by CSMD1[198].

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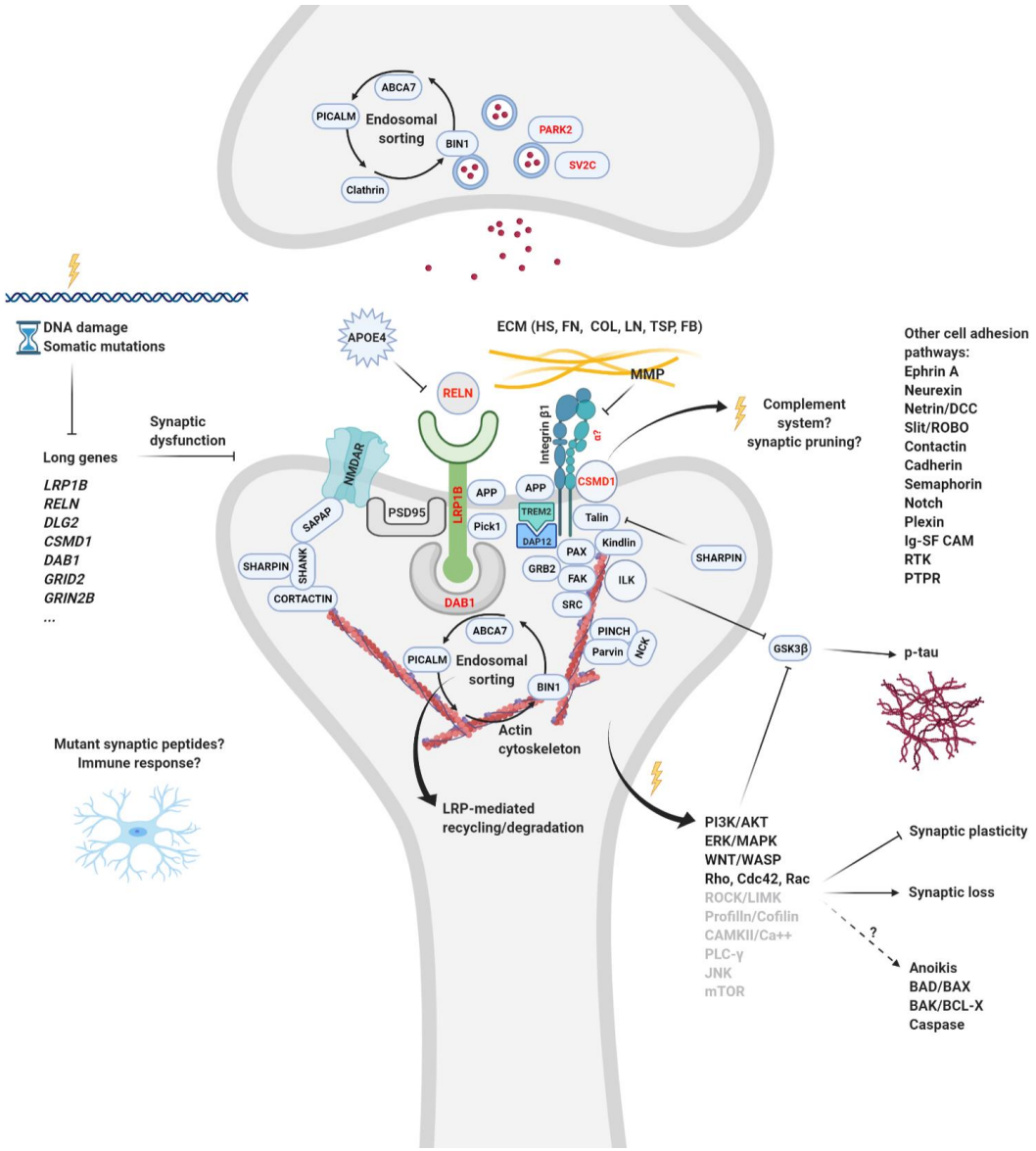

Figure 1. The postsynaptic adhesion pathway. The integrin cell adhesion pathway interacts with several candidate AD risk gene products. A number of aging-vulnerable neuronal genes in this molecular interactome (red) may be affected by DNA damage in aging, causing other genes to appear as disease risk loci. PAX: paxillin, RELN: reelin, RTK: receptor tyrosine kinase, PTPR: protein tyrosine phosphatase receptor, MMP: matrix metalloproteinase, FN: fibronectin, LN: laminin, TSP: thrombospondin. Ig-SF CAM: immunoglobulin-superfamily cell adhesion molecule.

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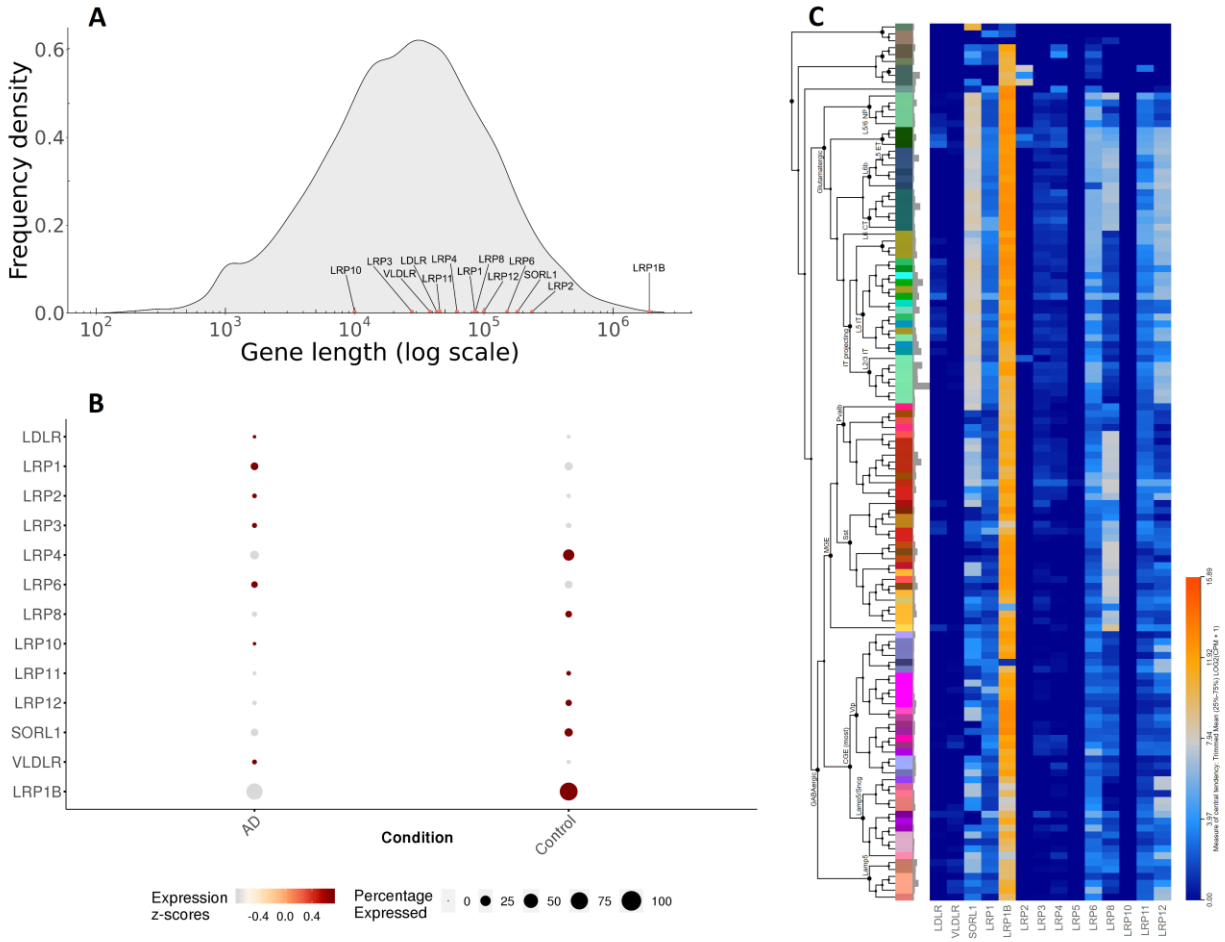

Figure 2. The lipoprotein receptor family. All protein-coding human genes are shown in the frequency density plot (n=20,006 genes, Ensembl v99). The lengths of all APOE receptor genes (LRPs) are indicated **(A)**. Expression of LRPs in single entorhinal cortical neurons of non-demented and AD subjects (RNA-seq data; retrieved from http://adsn.ddnetbio.com[201]) **(B)**. Single-cell expression of LRPs in subtypes of human cortical neurons (RNA-seq data; retrieved from https://portal.brain-map.org) (**C**). LRP1b is a positive outlier in all three plots.

Long gene vulnerability and the DNA damage theory of aging

In the 1950s, Failla and Szilard attributed aging to the *'accumulation of spontaneous somatic mutations in all body cells*[202]*'* and the buildup of random events that *'destroy chromosomes*[203]*'*. DNA damage has been suspected as a mechanism of neurodegeneration and AD for some time[18,204-206]. Single-cell sequencing has recently revealed an accumulation of somatic mutations in human brain neurons[181-183,207,208], a process termed genosenium. A number of preliminary works have surveyed somatic mutations in AD and non-demented brain neurons with inconsistent results[183]. It is noteworthy that the survivorship bias probably confounds single-cell mutational readouts, since different subtypes of neurons show variable degrees of vulnerability to

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AD. As much as 90% of vulnerable neurons may be lost in severe AD[209]. In support of this notion, healthy brains seem to lose a substantial proportion of neurons with higher mutational loads in aging[210]. Compared to non-demented brains, AD brains show a reduced number of somatic mutations. While inconclusive, this observation may suggest that neurons with higher mutational loads are generally more vulnerable in the aging brain and are (more) easily depleted in AD. In addition to single nucleotide variant (sSNV), further studies are needed to quantify copy number variations (CNVs) and indels in AD neurons, since these less-explored types of somatic mutations frequently impair long genes at fragile sites, some of which have neuronal roles[211]. Considering the post-mitotic state of neurons, an interesting question is whether DNA strand break and repair cycles in neurons affect fragile site genes similar to the effect of cell division cycles in cancer pathogenesis[212].

The current hypothesis brings new elements to the DNA damage theory of aging. Long genes are postulated to be more susceptible to DNA damage and its consequences, such as somatic CNVs and SNVs. This phenomenon is predicted to disable long genes and affect essential synaptic processes, such as the postsynaptic adhesion complex and fragile site genes (table 3).

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Table 3. The top 40 longest genes and common fragile sites

Rank	Gene	Transcript length (bp)[¥]	Exon count	Total exon length (bp)	Fragile site	Disease/pathway
1	RBFOX1	2,471,657	20	3,651		
2	CNTNAP2	2,304,198	24	9,454	FRA7I	Autism
3	DLG2	2,169,352	28	7,959	FRA11F	Schizophrenia, Parkinson's disease
4	DMD	2,092,292	79	1,3992	FRAXC	
5	PTPRD	2,084,572	17	1,697		
6	CSMD1†	2,059,554	70	1,4417	FRA8B	Schizophrenia, cognitive function
7	MACROD2	2,057,829	17	4,994		
8	EYS	1,987,247	43	10,590		
9	LRP1B*†	1,900,279	91	15,850	FRA2F	APOE receptor
10	CTNNA3	1,783,673	18	10,696	FRA10D	
11	ROBO2	1,740,816	27	5,919	FRA3R	
12	NRXN3	1,691,661	21	12,048	FRA14C	
13	DAB1*	1,548,836	15	5,301	FRA1B	APOE/RELN signaling
14	PDE4D	1,513,420	17	2,478		
15	FHIT	1,504,176	10	3,116	FRA3B	
16	AGBL4	1,491,101	14	2,989		
17	CCSER1	1,474,329	11	5,847		
18	GRID2	1,470,601	16	5,783	FRA4G	Glutamate receptor
19	GPC5	1,468,617	8	2,943	FRA13D	
20	CTNNA2	1,463,549	22	4,349	FRA2E	
21	MAGI2	1,436,613	22	6,975		
22	RBMS3	1,427,860	17	1,973		
23	AC098650.1	1,418,360	14	3,535		
24	DPP10	1,403,454	26	5,964		
25	PRKN	1,380,350	12	4,178	FRA6E	Parkinson's disease
26	IL1RAPL1	1,369,273	11	3,615	FRAXC	
27	LRRC4C	1,345,481	5	2,669		
28	AF241726.2	1,338,345	9	954		
29	CNTN5	1,337,937	25	6,499		
30	PRKG1	1,307,463	18	6,957	FRA10C	
31	TBC1D5	1,284,446	22	7,854		
32	PCDH15	1,249,127	28	9,366		
33	ANKS1B	1,248,816	17	6,874		
34	GALNTL6	1,228,156	9	2,370		
35	KAZN	1,225,252	71	1,3052		
36	KCNIP4	1,220,167	11	3,101		
37	NRG1†	1,215,008	12	5,931		
38	CSMD3	1,214,012	19	7,469		
39	IL1RAPL2	1,201,631	9	7,121		
40	DCC†‡	1,195,703	19	10,181	FRA18B	

*APOE/LRP signaling
†Integrin signaling
‡ APP/Netrin-1 signaling[213]

Long gene vulnerability and the amyloid cascade theory

The APP molecule is probably one member of a large synaptic adhesion interactome, rather than a central disease factor (Fig. 1). Some members of this interactome may be vulnerable to DNA damage in aging, causing others to appear as disease risk loci. For example, mutational loss of

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the LRP1b gene, whose protein product binds APP and affects its cleavage[192], may increase Aβ generation as an indirect effect of DNA damage. As noted for its closest homolog LRP1[97-100], another potential consequence of this event is β1 integrin dysfunction, with Tau phosphorylation taking place in this cascade[98]. Taken together, neuropathology and the proteinopathy in AD may represent consequences of altered signaling events, rather than causal factors. Following this assumption, the current hypothesis is incompatible with the amyloid cascade theory.

Glial cells, innate and adaptive immunity and the complement system

As a part of the innate immune system, the complement cascade controls synaptic pruning in the developing brain and in psychiatric disorders by tagging unwanted synapses for removal[214]. Microglia cells recognize activated complement proteins deposited on the synapse via a ligand-receptor interaction[215]. The genetic architecture of AD seems to implicate some degree of overlap between glial-specific genes and neurodegeneration. In support of the complement system and its potential role AD, the extremely long and fragile synapses gene, CSMD1, prevents complement activation (please see above). Nevertheless, it remains unknown whether neuroinflammation is a cause or a consequence of the disease pathogenesis mechanisms. Notably, somatic mutations in cancer cells result in the generation of novel peptides (neoantigens) that are unknown to the immune system and elicit an immune response[216]. Whether somatic mutations in synaptic genes may cause immune activation remains an open and interesting question.

Conclusion

Aging is associated with an accumulation of random ‘hits’ to the DNA base sequence in the form of DNA damage, CNVs, SNVs and other types of somatic mutations. This process can result in carcinogenesis in mitotically active cells, but its effects have yet to be understood in post-mitotic neurons. Long synaptic genes may be more vulnerable to this random process and form a bottleneck in healthy brain aging, since they contain more ‘information’ (lower entropy) that is more probable to be lost in time. In addition, long genes often map to chromosomal fragile sites and mutational hotspots. Compared to healthy individuals, the pace of the mutational accumulation may be higher in AD patients, and/or the resistance threshold of neurons to such harmful effects of aging may be lower, causing earlier cell death or dysfunction. Long gene vulnerability warrants new disease modification strategies for the treatment of AD.

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