The New Genetic Landscape of Alzheimer's Disease: from Amyloid Cascade to Genetically-driven Synaptic Failure Hypothesis

Supplementary Material

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Supplementary Table 1 Functional description of the genes located in the known AD risk loci. The name of the loci usually corresponds to the gene closest to the most significant genetic variant of the locus. Of note, it does not indicate that this gene is the AD functional gene of the locus. Information were manually curated from searches on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) using the name of the gene and Alzheimer and/or neuron as keywords.

Locus	Gene	General description	Relation to Aβ/APP	Relation to Tau	Other features
ABCA7 [19, 50, 95, 108, 138, 144, 240]	ABCA7	ATP binding cassette subfamily A member 7, member of the 'A' subfamily of ATPbinding cassette transporters initially characterized by their capacity to transport lipids across membranes [134]	- associated with plaque burden in AD brain [234]. Associated with Aβ deposition on in vivo imaging in human [13, 292] - regulates APP processing resulting in an inhibition of Aβ production in vitro and in vivo in APP/PS1 mice, ABCA7 deletion facilitates the processing of APP to Aβ by increasing the levels of β-site APP cleaving enzyme 1 (BACE1) [35, 214, 219] - stimulates phagocytosis in macrophages. ABCA7 loss results in 50% reduction of oAβ uptake by bone marrow-derived macrophages. ABCA7 loss doubles insoluble Aβ levels in J20 amyloidogenic mouse brain [110, 133] - highly expressed in microglia. Its loss reduces microglia phagocytic clearance of amyloid-β [69]	- associated with neurofibrillary tangle pathology in AD brain [287]	- stimulates cellular cholesterol efflux to APOE discs [35] - ABCA7 rs3764650 associated with cortical and hippocampal atrophy in MCI [203] - genetic risk factor for posterior cortical atrophy (PCA), typically a rare variant of AD [221] - its loss-of-function variants are enriched in patients with AD [78] - Lysophosphatidylcholine is one of the major transport substrates for ABCA7 in the brain and this transport may be an important function of ABCA7 [254]
ABI3 [108, 237]	*ABI3*	ABI family member 3, adaptor protein with a homeobox homology domain, a proline rich region and a SH3 domain			- highly expressed in microglia cells, coexpressed with INPP5D, important role in actin cytoskeleton organization through participation in the WAVE2 complex, a complex that regulates multiple pathways leading to T cell activation [188, 222, 237]
AC099552.4 [25]	AC099552.4	long non coding RNA			

ACE [138]	ACE	Angiotensin I converting Enzyme, peptidase activity (reviewed in [127])	- ACE is an Aβ degrading enzyme [93, 99, 192, 249, 255] - ACE expression in AD brain tissue is associated with Aβ load and AD severity. Exposing SH-SY-5Y neurons to oAβ1-42 increases ACE level and activity, suggesting Abeta may upregulate ACE in AD [179] - CSF levels of the angiotensin-converting enzyme (ACE) are associated with Aβ levels [115] and LOAD risk [126]	-	- in CSF, its levels but not activity is reduced in AD [179]
	CYB561	cytochrome b561			
	TANC2	tetratricopeptide repeat, ankyrin repeat and coiled-coil containing 2, synaptic scaffold protein			- its overexpression in cultured neurons increases the density of dendritic spines and excitatory synapses [85] - involved in the capture of KIF1A-driven dense core vesicle (DCV) at dendritic spines [244]
ADAM10 [108, 138]	ADAM10	the major α-secretase in the brain (reviewed in [213])	- component of the non-amyloidogenic pathway of APP metabolism (reviewed in [82]). - over-expression of ADAM10 in mouse models can halt Aβ production and subsequent aggregation [199]. - two rare ADAM10 mutations segregating with disease in LOAD families increased Aβ plaque load in "Alzheimer-like" mice, with diminished α-secretase activity from the mutations likely the causal mechanism [130, 248]		-numerous and fundamental functions in the development of the embryonic brain and also in the homeostasis of adult neuronal networks. Mechanistically, ADAM10 controls these functions by utilizing unique postsynaptic substrates in the central nervous system, in particular synaptic cell adhesion molecules (reviewed in [213]) - sheds TREM2 to release soluble TREM2
ADAMTS1 [138]	ADAMTS1	a disintegrin and metalloproteinase with thrombospondin motifs 1			- manifold overexpressed in brain of AD patients [176] - ADAMTS1 null female, but not male, exhibits a decline in synaptic protein levels [96]

ADAMTS4 [108]	ADAMTS4	a disintegrin and metalloproteinase with thrombospondin motifs 4	- generates N-truncated Aβ4-x species and marks oligodendrocytes as a source of amyloidogenic peptides in Alzheimer's disease [267]	- could modulate Tau phosphorylation by cleaving Reelin (reviewed in [80])	
	B4GALT3	beta-1,4-galactosyltransferase 3			
	PPOX	protoporphyrinogen oxidase			
AKAP9 [154]	AKAP9	A-kinase anchoring protein 9 AKAPs bind or tether protein kinase A (PKA) and other signaling molecules to relevant targets [275]		- AKAP9 mutations significantly increases pTau/Tau ratio in lymhoblastoid cell lines treated with phosphodiesterase-4 inhibitor rolipram, which activates protein kinase A [104]	
ALPK2 [108]	ALPK2	alpha kinase 2			
APH1B [108]	APH1B	aph-1 homolog B	- subunit of the gamma-secretase complex that cleaves APP [224]		
APOE [46]	APOE	apolipoprotein E maintains the structure of specific lipoprotein particles and directs lipoproteins to specific cell surface receptors 3 alleles/isoforms, ε2, ε3, ε4, the first and the last being protective and deleterious respectively for Alzheimer's disease	- binding to Aβ - role in Aβ production - role in Aβ aggregation - role in Aβ degradation and clearance (reviewed in [103])	- ApoE affects tau pathogenesis, neuroinflammation, and tau-mediated neurodegeneration independently of amyloid-β pathology [233]	- hypothesized to influence all the hallmarks of AD, from APP/Aβ to Tau aspects through lipid metabolism and neuroinflammation (reviewed in [243, 259])
BHMG1 / FBX046 [108]	BHMG1	basic helix-loop-helix and HMG-box containing 1			
	FBXO46	F-box protein 46, protein ubiquitin ligase			

BIN1 [108, 138, 144, 184, 225]	BIN1	bridging integrator 1, nucleocytoplasmic adaptor protein involved in endocytosis and membrane recycling, cytoskeleton regulation, DNA repair, cell cycle progression, and apoptosis [201]	- BIN1 depletion increases Aβ production through a decreased lysosomal BACE1 degradation [180] - BIN1 depletion raises Aβ generation in axons by a defective BACE1 recycling to the membrane and increased BACE1 convergence with APP in early endosomes [260] - BIN1 is found insoluble and accumulated in proximity to amyloid fibrils at the edges of amyloid deposits, suggesting a potential role for BIN1 in extracellular Aβ deposition in vivo [210]	-the functional risk allele (rs59335482) is associated with Tau loads in the brains of AD patients [37]. - loss of its Drosophila ortholog rescues Tau toxicity in Drosophila [37, 58] - BIN1 SH3 domain interacts physically with Tau Proline-Rich domain and the interaction is regulated by Tau and BIN1 phosphorylation and an isoform-dependent BIN1 intramolecular folding [37, 163, 217, 239]. - lower BIN1 levels promote the propagation of Tau pathology by increasing aggregate internalization through regulation of endocytosis and endosomal trafficking [30] - stabilizes Tau-induced actin bundles, loss of Drosophila BIN1 reduces tau-induced actin inclusions in Drosophila [60].	- Overexpression in mice results in neurodegeneration, loss of spine density, impaired LTP and behavioral deficits [52] -interacts with integrin α3A in double hybrid screen and with the Focal Adhesion Kinase (FAK) [175, 273] - physically interacts with intracellular form of CLU [299]
CASS4 [108, 138, 144]	CASS4	Cas scaffold protein family member 4, member of the CASS Scaffolding protein localized at focal adhesions, regulates cell spreading and motility [238]		- Its Drosophila ortholog modifies human Tau toxicity in Drosophila [58] - associated with CSF Tau biomarker in AD patient [204]	-physical interaction between the CASS and FAK family of protein [16]
	CSTF1	cleavage stimulation factor (CSTF) subunit 1, CSTF is involved in the polyadenylation and 3'end cleavage of pre-mRNAs			
	FAM209A	family with sequence similarity 209 member A			
	FAM209B	family with sequence similarity 209 member B			
	GCNT7	glucosaminyl (N-acetyl) transferase family member 7			

CASS4 (cont'd)	*RTFDC1*	replication termination factor 2 domain containing 1			
CD2AP [95, 108, 138, 144, 184]	CD2AP	CD2 associated protein, scaffolding protein involved in the regulation of membrane receptor endocytosis and signaling, actin cytoskeleton organization, endosomal vesicular trafficking, cell adhesion and cytokinesis [47, 61, 83, 116, 137, 157, 291]	-its loss-of-function raises Aβ generation in primary neuronal culture dendrite by increasing APP and its convergence with BACE1 in early endosomes but results in decreased cell membrane APP, decreased Aβ release and a lower Aβ42/Aβ40 ratio in N2a-APP695 cells. Complete loss of CD2AP results in a lower Aβ42/Aβ40 ratio in PS1APP mouse brain lysate but loss of one copy of CD2AP does not modify Abeta deposition or accumulation in these mice [152, 260]	- its Drosophila ortholog modifies human Tau toxicity in Drosophila [235] - associated with CSF Tau biomarker in AD patient [204]	- decreased expression in peripheral blood lymphocytes from chinese sporadic AD patients [251] - physically interacts with p130CAS (CASS1), colocalizes with F-actin and p130Cas to membrane ruffles and leading edges of cells in vitro, regulates actin cytoskeleton [135] - coordinator of Neurotrophin Signaling-Mediated Axon Arbor Plasticity [91] - regulates the signaling of the Tyrosine kinase Ret receptor in neurons [258] - CD2AP-deficient mice have reduced blood-brain barrier integrity [44] - recruited by RIN3 to RAB5a-positive early endosomes [211]
	GPR111	adhesion G protein-coupled receptor F2			
	GPR115	adhesion G protein-coupled receptor F4			

CD33 [95, 108, 184]	*CD33*	transmembrane sialic acid-binding immunoglobulin-like lectin that regulates innate immunity	- its expression is increased in microglial cells in AD brain and inhibits microglial uptake of Aβ, which correlates with increased Aβ42 levels and plaque burden in AD patient brain [27, 77] - the AD-risk allele increases the full-length CD33M isoform containing the Exon2, which inhibit Aβ uptake [162, 202]. The protective CD33m isoform is localized in peroxisome and may be protective because it does not localize to the cell membrane and neither interact directly with amyloid plaques nor engage in cell-surface signaling [236]		
CELF1 / SPI1 [138, 144]	CELF1	CUGBP Elav-like family member 1, role in RNA processing (splicing and mRNA stability mainly), role in myotonic dystrophy (reviewed in [70])		- its Drosophila ortholog, Aret, modifies Tau toxicity in Drosophila [22, 235]	
	ACP2	acid phosphatase 2, lysosomal. lysosomal membrane member of the histidine acid phosphatase family, which hydrolyze orthophosphoric monoesters to alcohol and phosphate			- *Acp2* mutant mice exhibit ataxia due to degeneration of cerebellum neurons exhibiting lysosomal storage bodies [165]
	AGBL2	ATP/GTP binding protein like 2			
	C1QTNF4	C1q and TNF related 4			
	DDB2	damage specific DNA binding protein 2, Protein that is necessary for the repair of ultraviolet light-damaged DNA	- oxidative stress generates a differential and specific DNA damage response involving overexpression of DDB2 in the presence of Aβ [67]		
	FAM180B	family with sequence similarity 180 member B			

	FNBP4	formin binding protein 4, protein containing two tryptophan-rich WW domains that binds the proline-rich formin homology 1 domains of formin family proteins, suggesting a role in the regulation of cytoskeletal dynamics during cell division and migration			
	KBTBD4	kelch repeat and BTB domain containing 4			
CELF1 / SPI1 (cont'd)	*MADD*	MAP kinase activating death domain, death domain-containing adaptor protein that interacts with the death domain of TNF-alpha receptor 1 to activate mitogen-activated protein kinase (MAPK) and regulate apoptosis	- change in MADD splice variants upon Aβ treatment, which could be protective [181]	- loss of its Drosophila ortholog enhances Tau toxicity in Drosophila [58]	- reduced expression and protein levels in the hippocampus of AD patients. MADD antisense treatment of cultured rat hippocampal neurons promoted neuronal cell death, suggesting a protective role of MADD in AD [265].
	MIR4487	microRNA 4487			
	MTCH2	mitochondrial carrier 2, member of the SLC25 family of nuclear-encoded transporters that are localized in the inner mitochondrial membrane			- loss of forebrain MTCH2 in mice decreases mitochondria motility and calcium handling and impairs hippocampal-dependent cognitive functions [6, 212]
	MYBPC3	myosin binding protein C, cardiac. cardiac isoform of myosin-binding protein C			
	NDUFS3	NADH:ubiquinone oxidoreductase core subunit S3, one of the iron-sulfur protein (IP) components of mitochondrial NADH:ubiquinone oxidoreductase (complex I)	-RNA interference knockdown of the C. elegans ortholog of NDUFS3 is associated with Aβ toxicity [183]		

	NR1H3	nuclear receptor subfamily 1 group H member 3. Also known as liver X receptor α (LXRA), member of the NR1 subfamily of the nuclear receptor superfamily, which are key regulators of macrophage function. Role in cholesterol metabolism and inflammation (reviewed in [31])	- genetic loss of either Lxrα or Lxrβ in APP/PS1 mice results in increased amyloid plaque load. Ligand activation of LXRs attenuates the inflammatory response of primary mixed glial cultures to fibrillar Aβ (fAβ) in a receptor-dependent manner and LXRs promote the capacity of microglia to maintain fAβ-stimulated phagocytosis in the setting of inflammation [288]		- involvment in cholesterol efflux in astrocytes [1]
	NUP160	Nucleoporin 160, one of the proteins that make up the 120-MD nuclear pore complex, which mediates nucleoplasmic transport			- the protective AD-associated rs9909-C allele in the 3'-UTR of NUP160 abolishes a miR target site and increases NUP160 expression, suggesting that increased expression of NUP160 might protect against the disease [53]
CELF1 / SPI1 (cont'd)	*PACSIN3*	protein kinase C and casein kinase substrate in neurons 3, member of the PACSIN family of proteins involved in synaptic vesicular membrane trafficking and endocytosis [51]			
	PSMC3	proteasome 26S subunit, ATPase 3			
	PTPMT1	protein tyrosine phosphatase, mitochondrial 1			
	RAPSN	receptor associated protein of the synapse, also known as RAPSYN, critical role in clustering and anchoring nicotinic acetylcholine receptors at neuromuscular synaptic sites by linking the receptors to the underlying postsynaptic cytoskeleton, possibly by direct association with actin or spectrin.			
	SLC39A13	solute carrier family 39 member 13 member of the LIV-1 subfamily of the ZIP transporter family			

CELF1 / SPI1 (cont'd)	*SPI1*	Spi-1 proto-oncogene, ETS-domain transcription factor that activates gene expression during myeloid and B-lymphoid cell development		- the minor allele of rs1057233 (G) shows association with delayed AD onset and lowers expression of SPI1 in monocytes and macrophages. SPI1 encodes PU.1, a transcription factor critical for myeloid cell development and function. Altered PU.1 levels affects the expression of mouse orthologs of many AD risk genes and the phagocytic activity of mouse microglial cells [100]
	LOC101928943			

CLU [90, 108, 138, 143, 144, 184]	CLU	Clusterin, multifunctional apolipoprotein (J) involved in lipid metabolism, inflammation, apoptosis, cell cycle (reviewed in [190, 272])	- increased expression and levels in AD [23, 171] - influences the regional distribution of Aβ [178] - Aβ increases intracellular clusterin and decreases clusterin protein secretion [128] - sequesters oAβ1−40 [185] - complex effect of CLU on extracellullar Aβ aggregation depending on APOE, CLU:Aβ ratio and mode of aggregation – nucleation or elongation [17, 54, 55, 193, 284]: - suppresses the toxicity of Aβ42 oligomers after they are formed in vivo [34] - mediates the clearance of Aβ from the brain by binding to LRP2/megalin receptor at the level of the blood-brain and blood-cerebrospinal barrier [18, 84, 302]. Loss of clusterin shifts amyloid deposition to the cerebrovasculature via disruption of perivascular drainage pahtways [274]. - CLU regulates Aβ toxicity via Dickkopf-1-driven induction of the wnt-PCP-JNK pathway [128]	- its rs11136000 SNP is associated with Tau CSF levels modification in AD patients [299] - its intracellular form physically interacts with Tau and BIN1 [299] - its intracellular form is upregulated in the brain of Tau overexpressing Tg4510 mice [299]	- inhibition of the complement by binding to C5b-7 component [42] - its non-synonymous mutation reduces the secretion of its protein [24] - differentially expressed in the microglia of the 5xFAD mouse model [205]
	SCARA3	scavenger receptor class A member 3, express a macrophage scavenger receptor-like protein that would protect cells from oxidative stress			

CNTNAP2 [108]	CNTNAP2	contactin associated protein like 2, encodes a member of the neurexin family which functions in the vertebrate nervous system as cell adhesion molecules and receptors		- this protein is localized at the juxtaparanodes of myelinated axons, and mediates interactions between neurons and glia during nervous system development and is also involved in localization of potassium channels within differentiating axons. - this gene has been implicated in multiple neurodevelopmental disorders
CR1 [108, 138, 143, 144, 184]	CR1	complement C3b/C4b receptor 1 (Knops blood group), member of the receptors of complement activation (RCA) family [301]	- expressed on erythrocyte, clears Aβ from the blood by binding to circulating Aβ-C3b-complement component complexes [29, 208] - association of CR1 risk allele and amyloid plaque burden/Amyloid deposition by in vivo brain imaging [41, 300] - activation of microglial CR1 is detrimental to neurons and blockade of CR1 decreases the capacity of microglia to phagocytose Aβ1-42 [48]	- decrease expression of the long CR1 isoform, decrease CR1 density per erythrocyte and increased blood soluble CR1 in AD patients [159]
ECHDC3 [57, 108, 119, 138, 153]	ECHDC3	enoyl-CoA hydratase domain containing 3		- increased expression in AD brains compared to control [57]
	USP6NL	ubiquitin-specific peptidase 6 N-terminal like		- USP6NL is a Rab5 GTPase-activating protein, which regulate the endocytosis and internalization of EGFR [146, 167] - USP6NL is also an effector of Rab5 that regulates the actin cytoskeleton [145]

EPHA1 [95, 108, 138, 144, 184]	EPHA1	Founding member of the Eph family of tyrosine kinase receptor [94]		- Drosophila ortholog of Eph receptor modifies human Tau toxicity in Drosophila [59]	- interacts with Integrin-Like Kinase and regulates cell morphology and motility through the ILK-RhoA-ROCK pathway [282] - role of ephrin/EphR in synapse development and plasticity [140] - altered distribution of its paralog EphA4 with neuritic plaques in AD [209] - EphA4 receptor regulates dendritic spine remodeling by affecting β1-integrin signaling pathways [26] - synaptic role of EphA4 in Aβ toxicity [68] - EphA4 activation of c-Abl mediates synaptic loss and LTP blockade caused by Aβ oligomers [264] - EphA4 cleaved by γ-secretase, γ-secretase-cleaved EphA4 intracellular domain regulates dendritic spine formation [105, 169]
	CASP2	caspase 2, member of the cysteine-aspartic acid protease (caspase) family involved in apoptosis	- activated upon Aβ treatment [3, 166, 257] - required for dendritic spine and behavioural alterations in J20 APP transgenic mice, as a critical mediator in the activation of the RhoA/ROCK-II signalling pathway, in the presence of Aβ [200]	- caspase-2 cleavage of tau at Asp314 impairs cognitive and synaptic function in animal and cellular models of tauopathies by promoting the missorting of tau to dendritic spines [293]	
	CLCN1	chloride voltage-gated channel 1, involved in the regulation of the electric excitability of the skeletal muscle membrane			- unexpected expression in human and mouse brain. Some CLCN1 variants are associated with epilepsy [38]
	EPHA1-AS1	EPHA1 antisense RNA 1			
	FAM131B	family with sequence similarity 131 member B			
	LOC100507507	uncharacterized LOC100507507			

EPHA1 (cont'd)	*TAS2R41*	taste 2 receptor member 41, member of the bitter taste receptor family which belong to the G protein-coupled receptor superfamily and are predominantly expressed in taste receptor cells of the tongue and palate epithelia.			
	TAS2R60	taste 2 receptor member 60, member of the bitter taste receptor family which belong to the G protein-coupled receptor superfamily and are predominantly expressed in taste receptor cells of the tongue and palate epithelia			
	ZYX	Zyxin, zinc-binding phosphoprotein that concentrates at focal adhesions and along the actin cytoskeleton, may function as a messenger in the signal transduction pathway that mediates adhesion-stimulated changes in gene expression and may modulate the cytoskeletal organization of actin bundles			- its C. elegans ortholog regulates synapse maintenance [156]
	MIR6892	microRNA 6892			
FERMT2 [138, 144]	FERMT2	fermitin family member 2, focal adhesion protein involved in integrin activation [141]	- increases Aβ peptide production by raising levels of mature APP at the cell surface and facilitating its recycling [36] - associated with brain amyloidosis on in vivo brain imaging [13]	- its Drosophila ortholog modifies human Tau toxicity in Drosophila [235]	
	ERO1A	endoplasmic reticulum oxidoreductase 1 alpha			
	GNPNAT1	glucosamine-phosphate N-acetyltransferase 1			
	GPR137C	G protein-coupled receptor 137C			
	PSMC6	proteasome 26S subunit, ATPase 6			

FERMT2 (cont'd)	*STYX*	serine/threonine/tyrosine interacting protein, it is a pseudophosphatase		
FRMD4A [142]	*FRMD4A*	FERM domain containing 4A, FERM domain-containing protein that regulates epithelial cell polarity	- regulates Tau secretion in HEK293 cells and mature cortical neurones [283]	- a homozygous mutation in FRMD4A results in a syndrome of congenital microcephaly, intellectual disability and dysmorphism [65]
KAT8 [108]	KAT8	lysine acetyltransferase 8, member of the MYST histone acetylase protein family		
	BCKDK	branched chain ketoacid dehydrogenase kinase, regulator of the valine, leucine, and isoleucine catabolic pathways		- mutations in the gene BCKDK cause autism, epilepsy, microcephaly, neurobehavioral deficits and intellectual disability [71, 189]
HESX1 / IL17RD / APPL1 [108]	*HESX1*	HESX homeobox 1, transcriptional repressor in the developing forebrain and pituitary gland		
	IL17RD	interleukin 17 receptor D		

HESX1 / IL17RD / APPL1 (cont'd)	*APPL1*	adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper 1,	- After being recruited by the β-cleaved carboxy-terminal fragment of APP, the rab5 effector APPL1 mediates rab5 overactivation in Down syndrome and AD leading to pathologically accelerated endocytosis, endosome swelling and selectively impaired axonal transport of rab5 endosomes [132]		- in AD hippocampus and not in control, APPL1 accumulates perisomatically as granules around neurons and co-localizes with glutamate receptor 2 and ubiquitin, suggesting the possible involvement of APPL1 in the synaptic modifications in AD [195] - an APPL1/Akt signaling complex regulates dendritic spine and synapse formation in hippocampal neurons [160] - adaptor protein APPL1 couples synaptic NMDA receptor with neuronal prosurvival phosphatidylinositol 3-kinase/Akt pathway [268] - APPL1 gates long-term potentiation through its plekstrin homology domain [63]
HLA [108, 138, 144]	*HLA-DQA1* *HLA-DQA2* *HLA-DQB1* *HLA-DRA* *HLA-DRB1* *HLA-DRB5*	member of the Major Histocompatibility Complex Class II (MHCII)			-highly expressed on reactive microglia (reviewed in [266, 290]) - increased HLA-DR positive microglia in AD [170, 279] - increased expression in monocytes and neutrophils in AD [64] - reactive microglia in patients with senile dementia of the Alzheimer type are positive for the histocompatibility glycoprotein HLA-DR [172]
	LOC100294145				
	MIR3135B				
HS3ST1 [57, 108]	HS3ST1	heparan sulfate-glucosamine 3-sulfotransferase 1, member of the heparan sulfate biosynthetic enzyme family			- HS3ST1 transcript expression is decreased in AD brains [57]

IGHG3 [25]	IGHG3	immunoglobulin heavy constant gamma 3, member of the IgG family	- some IgG antibodies present in human plasma recognize conformational epitopes present on Aβ fibrils and oligomers [191]. The anti-amyloidogenic activity is a general property of free human Ig gamma heavy chains. The F1 heavy chain prevents in vitro fibril growth and reduces in vivo soluble Aβ oligomer-induced impairment of rodent hippocampal long term potentiation [2]		
INPP5D [108, 138, 144]	INPP5D	member of the inositol polyphosphate-5-phosphatase (INPP5) family		- associated with CSF Tau biomarker [204]	-role in immune response [161, 290] - increased mRNA expression in the early stage which decreases with cognitive decline in Japanese AD subjects [286]
	NEU2	neuraminidase 2, glycohydrolytic enzyme which removes sialic acid residues from glycoproteins and glycolipids			- neuramidases regulate many aspect of brain physiology at the level of the cell surface carbohydrates of the central nervous system tissues [76] - NEU1 regulate APP metabolism through desialylation [12]
	NGEF	neuronal guanine nucleotide exchange factor, member of the Dbl family of proteins, which function as guanine nucleotide exchange factors for the Rho-type GTPases			- NGEF links Eph receptors to the actin cytoskeleton and are involved in axon gowth cone dynamic [226]
IQCK [138]	IQCK	IQ motif containing K, The IQ motif serves as a binding site for different EF-hand proteins such as calmodulin			
	KNOP1	lysine rich nucleolar protein 1			

IQCK (cont'd)	C16orf62	VPS35 endosomal protein sorting factor like, component of the retriever complex, which recycles endocytosed membrane protein back to the cell membrane [173]			
MAPT [118]	MAPT	microtubule associated protein tau Composing one of AD hallmarks	too huge to be reviewed here	too huge to be reviewed here	too huge to be reviewed here
MS4A [95, 108, 138, 144, 184]	*MS4A2* *MS4A3* *MS4A4A* *MS4A4E* *MS4A6A* *MS4A6E* *MS4A7*	Members of a family of membrane proteins with four transmembrane domains. Role in calcium signaling and immune function (reviewed in [123, 158])	- elevated MS4A6A expression levels associated with Braak plaque score [124]	- expression of MS4A6A significantly increases in relation to increasing AD-related neurofibrillary pathology [168]	- MS4A4A LOAD risky allele associates with higher brain expression [5]
	OOSP2	oocyte secreted protein 2			
OARD1 [138]	*OARD1*	O-acyl-ADP-ribose deacylase 1, hydrolyzes mono-ADP-ribosylation and interacts with poly-ADP-ribose chains post-translational modifications			-homozygous mutation of the OARD1 gene in patients is associated with severe neurodegeneration [227]
PFDN1 / HBEGF [119, 153]	*PFDN1*	prefoldin subunit 1, one of six subunits of prefoldin, a molecular chaperone complex that facilitates posttranslational folding of actins and other cytoskeletal proteins			-Pfdn1-deficient mice displayed phenotypes characteristic of defects in cytoskeletal function, including manifestations of ciliary dyskinesia, neuronal loss, and defects in B and T cell development and function [32]
	HBEGF	heparin binding EGF like growth factor			-HBEGF is an abundant neurotophic molecule of the brain regulating many higher brain functions [197]

PICALM [90, 108, 138, 144, 184]	PICALM	phosphatidylinositol binding clathrin assembly protein, protein involved in clathrin mediated endocytosis (reviewed in [281])	- modifies Aβ toxicity in relationship with endocytosis in yeast [256] - regulates APP endocytosis, subsequent APP metabolism and Aβ production [252, 280] - binds LC3, suggestive role in the trafficking APP-CTF from the endocytic pathway to the autophagic degradation pathway and in Aβ clearance [253] - regulates γ-secretase endocytosis and subsequent Aβ42/total Aβ ratio [120, 121] - regulates Aβ blood-brain-barrier transcytosis and clearance [294]	- regulates autophagy, Tau clearance and Tau toxicity [182] - co-localizes and coimmunoprecipitates with neurofibrillary tangles in human brains [10] - its levels correlates with Tau pathology and autophagy impairments in human brains [11]	- strongly expressed in microglia [10] - regulates the endocytosis of synaptic vesicle proteins [89, 177] - regulates the cell surface level of the AMPA receptor subunit GluR2 [88]
	CCDC83	coiled-coil domain containing 83			
PLCG2 [237]	PLCG2	phospholipase C gamma 2, transmembrane signaling enzyme converting PIP2 into IP3 and DAG second messengers			-highly expressed in microglia cells and limited expression in neurons, oligodendrocytes, astrocytes, and endothelial cells [289]

PTK2B [138, 144]	PTK2B	protein tyrosine kinase 2 beta, encode the Pyk2 protein, member of the Focal Adhesion Kinase (FAK) family of protein tyrosine kinase	- mediates Aβ neurotoxicity downstream of integrins [276] - its Aβo-induced phosphorylation is inhibited by Fyn inhibition [125] - transduces signal downstream of Aβo-PrPC-mGluR5 complexes with deleterious effects on synaptic transmission and maintenance [81, 216] - Hippocampal slices lacking Pyk2 are protected from AD-related Aβ oligomer suppression of synaptic plasticity. In APPswe/PSENΔE9 mice, deletion of Pyk2 rescues synaptic loss and learning/memory deficits [215]. Upon oAβ treatment, brain Pyk2 interacts with the RhoGAP protein Graf1 to alter dendritic spine stability via RhoA GTPase [148]. - less active in 5XFAD mice. Loss of Pyk2 in 5XFAD x Pyk2-/- double mutant mice has no effect but lentivirus-mediated Pyk2 overexpression improves synaptic markers and behavioral performance suggesting that Pyk2 is not essential for the pathogenic effects of human amyloidogenic mutations in the 5XFAD mouse model. However Pyk2 could contribute to amyloid plaque formation [74]. - activated in microglial cells upon fibrillar Aβ treatment [45]	- its Drosophila ortholog modifies human Tau toxicity in Drosophila [59] - abnormally accumulates in neuronal somata concurrently with early markers of Tau pathology in brains of the Thy-Tau22 mouse model and AD patients [59]	- PTK2B is activated by neuronal depolarization, Ca2+ and stressful conditions [75] - Role in neurite outgrowth [106] - Role in LTP and LTD [97, 102]. On hippocampal slices, Pyk2 is not required for basal synaptic transmission or long term potentiation but participates in long term depression [215] - Deficiency in mice have alterations in NMDA, PSD-95 and spines structures. Low level of PTK2B in huntington mouse model. Normalizing PTK2B levels rescues memory deficits, spines pathology and PSD-95 localization [72] - Role in the survival of cerebellar granule neurons [242] - Essential for astrocytes mobility following brain lesion [73]
	EPHX2	epoxide hydrolase 2, The protein, found in both the cytosol and peroxisomes, binds to specific epoxides and converts them to the corresponding dihydrodiols.			-its products regulate synaptic plasticity [277] - coding mutation in EPHX2 modifies the phenotype of familial hypercholoesterolemia [218]

PTK2B (cont'd)	*STMN4*	stathmin 4, belongs to a family of proteins that regulates microtubule dynamics [49]	
	TRIM35	tripartite motif containing 35, a RING-B-box-coiled-coil protein with apoptotic function	
	CHRNA2	cholinergic receptor nicotinic alpha 2 subunit, subunit of the muscle and neuronal nicotinic acetylcholine receptor	- Cholinergic transmission is strongly involved in Alzheimer with a major focus on CHRN7 (reviewed in[230])
	MIR6842	microRNA 6842	
SCIMP / RABEP1 [108, 153]	SCIMP	SLP adaptor and CSK interacting membrane protein, transmembrane adaptor protein that is expressed in antigen-presenting cells and is localized in the immunologic synapse	
	RABEP1	rabaptin, RAB GTPase binding effector protein 1,	-role in endocytosis in neurons as an effector of Rab5 [186]
SLC24A4 / RIN3 [108, 138, 144]	SLC24A4	solute carrier family 24 member 4, potassium-dependent sodium-calcium exchanger expressed in the brain [150]	- role in Ca2+ signaling in neurons controling feeding and satiety [151] - necessary for rapid response termination and proper adaptation of vertebrate olfactory sensory neurons [241]
	RIN3	Ras and Rab interactor 3, guanine nucleotide exchange factor for RAB5 and RAB31	- RIN3 recruits CD2AP to RAB5a-positive early endosomes [211]

SORL1 [20, 108, 138, 144, 187, 207, 263]	SORL1	sortilin related receptor 1, transmembrane protein, member of the sortilin family of receptors [271]	-sorts APP into the retromer recycling pathway at the expense of the late endosomal pathway where APP undergoes β- and γ-secretase cleavage to generate Aβ. Loss of SORL1 results in increased Aβ levels. SORL1 interaction and sorting of APP is dependent on APP dimerization [9, 62, 194, 207] - modulates EphA4, attenuates synaptotoxic EphA4 activation and cognitive impairment associated with Aβ-induced neurodegeneration in AD [101]		
SPPL2A [153]	SPPL2A	signal peptide peptidase like 2A, member of the GXGD family of aspartic proteases, homologue of the presenilins, located in late endosome and lysosome compartments			-Various roles in immune cells, protease of TMEM106b, a genetic risk factor for the development of frontotemporal lobar degeneration [174]
TM2D3 [107]	TM2D3	TM2 domain containing 3, the encoded protein contains a structural module related to that of the seven transmembrane domain G protein-coupled receptor superfamily	- preferentially influences uptake of Aβ aggregates during phagocytosis [86]		- Mutation in the Drosophila TM2D3 homolog, almondex, causes a phenotype similar to loss of Notch/Presenilin signaling [107] - By functional transcomplementation in Drosophila, the rare TM2D3 variant associated with LOAD, P155L, is a functionally damaging allele [107]

TREM2 [20, 79, 108, 114, 117, 138, 237]	TREM2	triggering receptor expressed on myeloid cells 2, cell surface receptor of the immunoglobulin superfamily expressed on microglial cells (reviewed in [232, 261])	- oAβ1-42 binds TREM2 on microglia and activates microglial response in a TREM2-dependent manner. The effect of the disease-associated mutations of TREM2 on its binding affinity to oAβ1-42 is debated [149, 297] - its loss alters microglia phagocytosis, including phagocytosis of Aβ [111, 136] - its TREM2 in amyloid mouse models (APPPS1-21, 5XFAD) results in defective microgliosis surrounding Aβ plaques with contradictory effects on the Aβ accumulation, whereas overexpression of TREM2 in the brain of APPswe/PS1dE9 mice ameliorated AD-related neuropathology [109, 111, 262, 269] - in vitro, human stem cell-derived monocytes and transdifferentiated microglia-like cells reveal impaired amyloid plaque clearance upon heterozygous or homozygous loss of TREM2 [43] - its deficiency reduces the efficacy of immunotherapeutic amyloid clearance [278]	-increased soluble TREM2 (sTREM2) CSF levels in AD patients that correlates with CSF Tau levels [198, 246] -its loss exacerbates Tau pathology in P301S Tau mice [112]. Increased TREM2 ameliorates the pathological effects of activated microglia on GSK3-mediated neuronal Tau hyperphosphorylation via suppression of microglial inflammatory response [113] - In contrast, glial expression of TREM2/TYROBP exacerbates Tau-mediated neurodegeneration in Drosophila [223] - In transgenic mice expressing mutant human tau, TREM2 haploinsufficiency, but not complete loss of TREM2, increases Tau pathology. The effect on microglial injury and Tauopathy would depend on the partial or complete loss of TREM2 [220]	- Promotes Microglial Survival by Activating Wnt/β-Catenin Pathway [295] - The AD-associated R47H TREM2 mutation have pleiotropic negative effects on microglia and myeloid cells that can be rescued by some TREM2-activating antibodies [39, 40] - Structural analysis reveals that Arg47 plays a critical role in maintaining the structural features of the complementarity-determining region 2 (CDR2) loop and the putative positive ligand-interacting surface (PLIS), stabilizing conformations capable of ligand interaction [247]. However AD-associated TREM2 mutant would bind Aβ with equivalent affinity but show loss of function in terms of signaling and Aβ internalization [149] - APOE is a ligand of TREM2 whose binding to TREM2 can be blocked by the high-affinity binding of oAβ to TREM2. APOE binding is reduced for R47H TREM2 [14, 15, 149]
	TREML2	triggering receptor expressed on myeloid cells like 2, structurally related to the TREM famlily but does not signal though DAP12/TYROBP (reviewed in [66])	- oligomeric amyloid-β treatment up-regulates TREML2 expression in primary microglia [296]		- has AD-associated functional variants independent of TREM2 ones [21]. - The modulation of TREM2 or TREML2 levels has opposing effect on the proliferation of primary microglia, TREM2 or TREML2 downregulation respectively decrease or increase microglia proliferation [296].

TSPOAP1 [108, 119]	TSPOAP1	TSPO associated protein 1, TSPO (translocator protein) is a key factor in the flow of cholesterol into mitochondria to permit the initiation of steroid hormone synthesis		
	MIR142	microRNA 142, abundantly expressed in hematopoietic cells with roles in inflammatory and immune responses (reviewed [228])	-upregulated in the hippocampi of rTg4510 Tau mice in the presymptomatic stage and onward. Similar to what is observed in Tau brains, overexpressing miR142 in wildtype cortical neurons augments mRNA levels of *Gfap* and *Csf1*, accompanied by a significant increase in microglia and reactive astrocyte numbers [229]	
	TSPOAP1-AS1	TSPOAP1 antisense RNA 1		
WWOX / MAF [138]	WWOX	WW domain containing oxidoreductase, member of the short-chain dehydrogenases/reductases (SDR) protein family	- WWOX is decreased in the neurons of AD hippocampi. WWOX binds to Tau through its SDR domain. Knock-down of WWOX results in Tau hyperphosphorylation [250]	- WWOX is mutated in autosomal recessive cerebellar ataxia with epilepsy and mental retardation [164]
	MAF	MAF bZIP transcription factor, DNA-binding, leucine zipper-containing transcription factor that acts as a homodimer or as a heterodimer		- MAF promotes functional differentiation and anti-inflammatory responses in myeloid cells [33] - Negative regulation of MAF mediates p53 proinflammatory responses in microglia [245] - Maf links Neuregulin1 signaling to cholesterol synthesis in myelinating Schwann cells [131] - c-Maf is required for the development of dorsal horn laminae III/IV neurons and mechanoreceptive DRG axon projections [98]

	ZCWPW1	Contain a zf-CW domain involved in histone modification reading [92]		
	ACTL6B	actin like 6B, member of a family of actin-related proteins (ARPs)		-subunit of neuron-specific chromatin remodeling complex [196] - its loss in mice results in synaptic plasticity and cocaine-associated memory defects that can be rescued by BDNF [270]
	AGFG2	ArfGAP with FG repeats 2, member of the HIV-1 Rev binding protein (HRB) family and plays a role in the Rev export pathway, which mediates the nucleocytoplasmic transfer of proteins and RNAs		
ZCWPW1 / NYAP1 [108, 138, 144]	*AP4M1*	adaptor related protein complex 4 subunit mu 1, subunit of the heterotetrameric AP-4 complex, which is involved in the recognition and sorting of cargo proteins with tyrosine-based motifs from the trans-golgi network to the endosomal-lysosomal system		-its mutation and AP-4 deficiency results in many clinical neuronal symptoms such as intellectual disability or hereditary spastic paraplegia…
	AZGP1	alpha-2-glycoprotein 1, zinc-binding, encode Zinc-α2-glycoprotein (ZAG), which is a major histocompatibility complex I molecule and a lipid-mobilizing factor.		
	C7orf43	chromosome 7 open reading frame 43		
	C7orf61	chromosome 7 open reading frame 61		
	CNPY4	canopy FGF signaling regulator 4, regulates cell surface expression of Toll-like receptor 4		

ZCWPW1 / NYAP1 (cont'd)	*COPS6*	COP9 signalosome subunit 6, one of the eight subunits of COP9 signalosome, regulator in multiple signaling pathways, whose structure is similar to that of the 19S regulatory particle of 26S proteasome.		
	CYP3A43	cytochrome P450 family 3 subfamily A member 43, The cytochrome P450 proteins are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids		
	FBXO24	F-box protein 24, F-box protein of the Fbxs class, the F-box proteins constitute one of the four subunits of the SCF ubiquitin protein ligase complex		
	GAL3ST4	galactose-3-O-sulfotransferase 4, member of the galactose-3-O-sulfotransferase protein family		
	CASTOR3	CASTOR family member 3, also named GATS		- Lower expression in AD brain [122]
	GIGYF1	GRB10 interacting GYF protein 1, member of the gyf family of adaptor proteins		- its Drosophila ortholog regulates neuronal autophagy [129] - regulates the Insulin signaling pathway [298]
	GJC3	gap junction protein gamma 3		-expressed in the myelinating glial cells [8]
	GNB2	G protein subunit beta 2, G proteins integrate signals between receptors and effector proteins		

ZCWPW1 / NYAP1 (cont'd)	*GPC2*	glypican 2, Glypicans are a group of cell-surface glycoproteins in which heparan sulfate (HS) glycosaminoglycan chains are covalently linked to a protein core, it can function as coreceptors for multiple signaling molecules.		- involved in neuronal cell adhesion and neurite outgrowth [139]
	LAMTOR4	late endosomal/lysosomal adaptor, MAPK and MTOR activator 4, subunit of the Rag-Ragulator complex, located on lysosome membrane and regulating MAPK and mTOR signaling pathways		- Lamtor4 is an essential regulator of microglia lysosomes for proper lysosome function and phagocytic flux in zebrafish microglia [231]
	LOC100128334	gap junction protein gamma 3 pseudogene		
	LRCH4	leucine rich repeats and calponin homology domain containing 4, the encoded protein resembles a membrane receptor		- Lrch4 is a Toll-Like Receptor accessory protein, which regulates innate immune response [7]
	MBLAC1	metallo-beta-lactamase domain containing 1		- differentially expressed in AD brains [28] - C.elegans MBLAC1 limits Dopaminergic (DA) neuron excitability, DA secretion, and DA-dependent behaviors through modulation of Glu signaling [87]
	MCM7	minichromosome maintenance complex component 7, subunit of the MCM complex, key component of the pre-replication complex, involved in the formation of replication forks and possessing a DNA helicase activity		
	MEPCE	methylphosphate capping enzyme, possesses histone-binding and RNA methylation activities involved in the regulation of transcription		

	MIR106B	microRNA 106b	- reduces ATG16L1 levels and autophagy In human cell lines (Lu C et al 2014)[155]
	MIR25	microRNA 25	
	MIR4658	microRNA 4658	
	MIR93	microRNA 93	- reduces ATG16L1 levels and autophagy In human cell lines [155]
	MOSPD3	motile sperm domain containing 3, encodes a multi-pass membrane protein with a major sperm protein (MSP) domain	
	NYAP1	neuronal tyrosine phosphorylated phosphoinositide-3-kinase adaptor 1	- NYAP family links PI3K to WAVE1 complex, which mediates remodelling of the actin cytoskeleton, and regulate neuronal morphogenesis [285]
ZCWPW1 / NYAP1 (cont'd)	*OR2AE1*	olfactory receptor family 2 subfamily AE member 1	
	PCOLCE	procollagen C-endopeptidase enhancer, encodes a glycoprotein which binds and drives the enzymatic cleavage of type I procollagen and heightens C-proteinase activity	
	PCOLCE-AS1	PCOLCE antisense RNA 1	
	PILRA	paired immunoglobin like type 2 receptor alpha, encode a cell surface inhibitory receptor paired with PILRB that recognizes specific O-glycosylated proteins and is expressed on various innate immune cell types including microglia	- The common missense variant (G78R, rs1859788) of PILRA could be the causal allele for the locus. The G78R mutation reduces the binding of PILRA to its ligand such as complement component 4A. It could protects individuals from AD risk via reduced inhibitory signaling in microglia [206]

	PILRB	paired immunoglobin-like type 2 receptor beta, encode a cell surface activator receptor paired with PILRB that recognizes specific O-glycosylated proteins and is expressed on various innate immune cell types including microglia		- its levels is associated with AD status [122] and with LOAD GWAS index SNPs [4]
	PPP1R35	protein phosphatase 1 regulatory subunit 35, a centrosomal protein critical for centriole elongation		
	PVRIG	PVR related immunoglobulin domain containing, a member of poliovirus receptor-like proteins and a coinhibitory receptor for human T cells		
ZCWPW1 / NYAP1 (cont'd)	*SAP25*	Sin3A associated protein 25, SAP25 associates with the mSin3A-HDAC complex in vivo and represses transcription		
	SPDYE3	speedy/RINGO cell cycle regulator family member E3		
	STAG3	stromal antigen 3, subunit of the cohesin complex which regulates the cohesion of sister chromatids during cell division		
	TAF6	TATA-box binding protein associated factor 6, component of the transcription factor IID involved in basal transcription		
	TFR2	transferrin receptor 2, This protein mediates cellular uptake of transferrin-bound iron		
	TRIM4	tripartite motif containing 4		

ZCWPW1 / NYAP1 (cont'd)	*TSC22D4*	TSC22 domain family member 4, member of the TSC22 domain family of leucine zipper transcriptional regulators	
	ZKSCAN1	zinc finger with KRAB and SCAN domains 1, encodes a member of the Kruppel C2H2-type zinc-finger family of proteins that may function as a transcription factor regulating the expression of GABA type-A receptors in the brain	
	ZNF3	zinc finger protein 3	
	ZSCAN21	zinc finger and SCAN domain containing 21	-ZSCAN21 regulates α-synuclein transcription in neuronal cells and rare genetic variants in ZSCAN21 gene occur in patients with familial forms of Parkinson's Disease [56, 147]
ZNF655 [25]	ZNF655	zinc finger protein 655	

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