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

Supplementary Material

Pierre Dourlen, Devrim Kilinc, Nicolas Malmanche, Julien Chapuis, Jean-Charles Lambert

Inserm, U1167, RID-AGE-Risk Factors and Molecular Determinants of Aging-Related Diseases, Lille, France; Institut Pasteur de Lille, Lille, France; University Lille, U1167-Excellence Laboratory LabEx DISTALZ, Lille, France.
**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/](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 ATP binding 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] <br> - 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] <br> - 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] <br> - 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] <br> - ABCA7 rs3764650 associated with cortical and hippocampal atrophy in MCI [203] <br> - genetic risk factor for posterior cortical atrophy (PCA), typically a rare variant of AD [221] <br> - its loss-of-function variants are enriched in patients with AD [78] <br> - 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 | | | |
| Gene/Protein  | Description                                                                 | Functions and Observations                                                                                                                                                                                                                   |
|--------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 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                                                              | - 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]                                                                                      |
| TANC2        | tetra tricopeptide repeat, ankyrin repeat and coiled-coil containing 2, synaptic scaffold protein |                                                                                                                                                                                                                                         |
| 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      | 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]                                                                                                                                               |
| Gene                  | Function and Relevance                                                                 | Notes                                                                 |
|-----------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------|
| 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 lymphoblastoid 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 / FBXO46 [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] | Bridging integrator 1 (BIN1), 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                           | 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] |
| CASS4 [108, 138, 144]          | Physically 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] | 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 Aβeta 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 RAB5-positive early endosomes [211] |
| GPR111 | adhesion G protein-coupled receptor F2 |
| GPR115 | adhesion G protein-coupled receptor F4 |
| Gene                | Description                                                                 | Regulation and Function                                                                                                               |
|---------------------|-----------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|
| CD33 [95, 108, 184] | 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               | 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                                |                                                                                                                                       |
| Gene Symbol | Description |
|-------------|-------------|
| **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 |
| **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 |
| **MIR4487** | microRNA 4487 |
| **MTCH2**  | mitochondrial carrier 2, member of the SLC25 family of nuclear-encoded transporters that are localized in the inner mitochondrial membrane |
| **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) |

- **MADD**
  - change in MADD splice variants upon Aβ treatment, which could be protective [181]
  - loss of its Drosophila ortholog enhances Tau toxicity in Drosophila [58]

- **MTCH2**
  - loss of forebrain MTCH2 in mice decreases mitochondria motility and calcium handling and impairs hippocampal-dependent cognitive functions [6, 212]

- **MYBPC3**
  - 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].

- **NDUFS3**
  - RNA interference knockdown of the C. elegans ortholog of NDUFS3 is associated with Aβ toxicity [183].
| Gene   | Description                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Reference |
|--------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| 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 LXRα attenuates the inflammatory response of primary mixed glial cultures to fibrillar Aβ (fAβ) in a receptor-dependent manner and LXRα promote the capacity of microglia to maintain fAβ-stimulated phagocytosis in the setting of inflammation [288]. | [31]      |
| NUP160 | Nucleoporin 160, one of the proteins that make up the 120-MD nuclear pore complex, which mediates nucleoplasmic transport. - Involvement in cholesterol efflux in astrocytes [1].                                                                                                                                                                                                                                                                                      | [1]       |
| 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].                                                                                                                                                                                                                                                                                  | [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 |
|----------------------|------|----------------------------------------------------------------------------------------------------------------------------------|
|                      | LOC1019289 | - 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] |

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CLU [90, 108, 138, 143, 144, 184]

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 αAβ1–40 [185]  
- complex effect of CLU on extracellular 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 pathways [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
| Gene   | Description |
|--------|-------------|
| 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. |
| CR1    | Complement C3b/C4b receptor 1 (Knops blood group), member of the receptors of complement activation (RCA) family. |
| ECHDC3 | Enoyl-CoA hydratase domain containing 3. |
| USP6NL | Ubiquitin-specific peptidase 6 N-terminal like. |

**CR1**
- 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**
- Increased expression in AD brains compared to control [57].

**USP6NL**
- 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].
| **Gene** | Description | Function |
|---------|-------------|----------|
| **EPHA1** | Founding member of the Eph family of tyrosine kinase receptor [94] | - Drosophila ortholog of Eph receptor modifies human Tau toxicity in Drosophila [59] |
| **EPHA1-AS1** | EPHA1 antisense RNA 1 | |
| **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] |
| **FAM131B** | Family with sequence similarity 131 member B | |
| **LOC100507507** | Uncharacterized LOC100507507 | |

- 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]
| Gene       | Description                                                                                                                                   |
|------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| **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. |
| **MIR6892**| microRNA 6892                                                                                                                                |
| **FERMT2** | - 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]                                                                    |
| **ER01A**  | endoplasmic reticulum oxidoreductase 1 alpha                                                                                                  |
| **GNPNAT1**| glucosamine-phosphate N-acetyltransferase 1                                                                                                |
| **GPR137C**| G protein-coupled receptor 137C                                                                                                                |
| **PSMC6**  | proteasome 26S subunit, ATPase 6                                                                                                              |
| Gene Symbol | Gene Name | Description | Function | Remarks |
|-------------|-----------|-------------|----------|---------|
| FERMT2      | 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 |         |         |
| L17RD       | 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 | HLA-DQA1<br>HLA-DQA2<br>HLA-DQB1<br>HLA-DRA<br>HLA-DRB1<br>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] |

| LOC1002941 | 45 |

| 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] |
| Gene Symbol | Description | Functional Note |
|-------------|-------------|----------------|
| IGHG3 [25] | 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] | member of the inositol polyphosphate-5-phosphatase (INPP5) family | - associated with CSF Tau biomarker [204] |
| 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 growth cone dynamic [226] |
| IQCK [138] | 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 | Ooocyte 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 neurotrophic molecule of the brain regulating many higher brain functions [197] |
| Gene | Description | Functions |
|------|-------------|-----------|
| 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] |
| PLCG2 | Phospholipase C gamma 2, transmembrane signaling enzyme converting PIP2 into IP3 and DAG second messengers | - 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**  
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]
| Gene      | Description                                                                                      | Notes                                                                                   |
|-----------|-------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 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/PSEN1E9 mice, deletion of Pyk2 rescues synaptic loss and learning/memory deficits [215]. Upon oAβ treatment, brain Pyk2 interacts with the RhosGAP protein Gra1 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 hypercholesterolemia [218] |
| Gene Symbol | Description | Notes |
|-------------|-------------|------|
| 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 |
| MIR6842     | microRNA 6842 |
| SCIMP / RABEP1 [108, 153] | 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, |
| SLC24A4 / RIN3 [108, 138, 144] | solute carrier family 24 member 4, potassium-dependent sodium-calcium exchanger expressed in the brain [150] |
| RIN3        | Ras and Rab interactor 3, guanine nucleotide exchange factor for RAB5 and RAB31 |

- Cholinergic transmission is strongly involved in Alzheimer with a major focus on CHRN7 (reviewed in [230])

- role in endocytosis in neurons as an effector of Rab5 [186]

- role in Ca2+ signaling in neurons controlling feeding and satiety [151]

- necessary for rapid response termination and proper adaptation of vertebrate olfactory sensory neurons [241]

- RIN3 recruits CD2AP to RAB5a-positive early endosomess [211]
| Gene   | Description                                                                 | Function                                                                                                                                  |
|--------|------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| 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 | 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  | 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

| TREM2 | TREML2 |
|-------|--------|
| Trem2, triggering receptor expressed on myeloid cells 2, cell surface receptor of the immunoglobulin superfamily expressed on microglial cells (reviewed in [232, 261]) | TREML2, triggering receptor expressed on myeloid cells like 2, structurally related to the TREM family but does not signal though DAP12/TYROBP (reviewed in [66]) |
| - 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] | - oligomeric amyloid-β treatment up-regulates TREML2 expression in primary microglia [296] |
| - 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] | - 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]. |
| - 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] | - 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 high-affinity binding of oAβ to TREM2. APOE binding is reduced for R47H TREM2 [14, 15, 149] |
| Gene        | Description                                                                 | Notes                                                                 |
|-------------|-----------------------------------------------------------------------------|----------------------------------------------------------------------|
| 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        | 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. Knockdown of WWOX results in Tau hyperphosphorylation [250] | WWOX is mutated in autosomal recessive cerebellar ataxia with epilepsy and mental retardation [164] |
| WWOX / MAF  | WWOX / MAF [138]                                                            |                                                                      |
| 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] |
| Gene | Description |
|------|-------------|
| 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) |
| 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] | - 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] |
| 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 |
| 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 |
| Gene   | Description                                                                                                                                 |
|--------|--------------------------------------------------------------------------------------------------------------------------------------------|
| 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                                                                                                                                                                      |
| GIGYF1 | GRB10 interacting GYF protein 1, member of the gyl family of adaptor proteins                                                                                                                                 |
| GJC3   | gap junction protein gamma 3                                                                                                                                                                                |
| GNB2   | G protein subunit beta 2, G proteins integrate signals between receptors and effector proteins                                                                                                |

- Lower expression in AD brain [122]
- its Drosophila ortholog regulates neuronal autophagy [129]
- regulates the Insulin signaling pathway [298]
- expressed in the myelinating glial cells [8]
| Gene   | Description                                                                                                                                  |
|--------|----------------------------------------------------------------------------------------------------------------------------------------------|
| 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. |
| 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 |
| LOC1001283 34 | gap junction protein gamma 3 pseudogene                                                                                                           |
| LRCH4  | leucine rich repeats and calponin homology domain containing 4, the encoded protein resembles a membrane receptor                                 |
| MBLAC1 | metallo-beta-lactamase domain containing 1                                                                                                      |
| 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              |
| Gene     | Description                                                                                   | Notes                                                                 |
|----------|---------------------------------------------------------------------------------------------|----------------------------------------------------------------------|
| **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] |
| **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 immunoglobulin 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] |
| Gene      | Description                                                                                                                                                                                                 |notes |
|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| PILRB     | paired immunoglobulin-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                                                                          |      |
| 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                                                                                                                                                                              |      |
| Gene       | Description                                                                                                                                                                                                 |
|------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| **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                                                                                                                                                                  |
| **ZNF655** | Zinc finger protein 655                                                                                                                                                                                   |

*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]*
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