Review

The role of genetic risk factors of Alzheimer's disease in synaptic dysfunction

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ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative disease characterized by the progressive deterioration of cognitive functions. Due to the extended global life expectancy, the prevalence of AD is increasing among aging populations worldwide. While AD is a multifactorial disease, synaptic dysfunction is one of the major neuropathological changes that occur early in AD, before clinical symptoms appear, and is associated with the progression of cognitive deterioration. However, the underlying pathological mechanisms leading to this synaptic dysfunction remains unclear. Recent large-scale genomic analyses have identified more than 40 genetic risk factors that are associated with AD. In this review, we discuss the functional roles of these genes in synaptogenesis and synaptic functions under physiological conditions, and how their functions are dysregulated in AD. This will provide insights into the contributions of these encoded proteins to synaptic dysfunction during AD pathogenesis.

1. Introduction

Alzheimer's disease (AD), the most common form of dementia, is characterized by the progressive deterioration of cognitive functions, typically in memory as well as language, comprehension, judgment and orientation. Profound brain changes occur decades before observable clinical pathologies appear. The major neuropathological hallmarks of AD include amyloid plaque deposition (i.e., the extracellular aggregation of amyloid-beta [Aβ]) surrounded by dystrophic neurites and neurofibrillary tangles (i.e., the intraneuronal accumulation of hyperphosphorylated tau protein). Other pathological features of AD include microgliosis, neuroinflammation, and synaptic loss [1]. Evidence suggests that the impairment of synapse functions occurs early before the clinical manifestation of AD, and that synapse loss is correlated with the clinical stages of AD progression [2]. Histological studies of post-mortem AD brains demonstrate that AD brains show significant synapse loss and postsynaptic density disruption when compared with aged-matched control brains [3,4]. Consistently, multiple transgenic mouse models of AD exhibit synaptic loss and dysfunction that are correlated with the cognitive impairments [5,6].

There are two types of AD: autosomal dominant early-onset AD (EOAD; onset between ages 30–65), which contributes to ~5% of AD cases, and sporadic late-onset AD (LOAD; onset after age 65). Three causative genes—*APP, PSEN1,* and *PSEN2*—for EOAD encode amyloid precursor protein (APP) and the catalytic subunits of γ-secretase presenilin 1 (PS1) and presenilin 2 (PS2), respectively. APP undergoes sequential proteolytic cleavage of the amyloidogenic pathway to generate the pathological agent of AD, Aβ. APP is first cleaved by β-secretase to generate a C99 fragment and secreted APPβ (sAPPβ), and the C99 fragment is subsequently cleaved by γ-secretase to generate Aβ peptides and the APP intracellular domain (AICD). APP processing undergoes a non-amyloidogenic pathway that is initially cleaved by α-secretase followed by γ-secretase, which prevents Aβ formation [7]. The increased generation of Aβ peptides leads to the aggregation of soluble Aβ oligomers, which plays a central role in mediating the impairment of synaptic functions, triggering synapse loss, and inducing neurotoxicity (review in [8]). However, the underlying signaling mechanisms of Aβ-induced synaptic impairments have not clearly

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understood. LOAD is a multifactorial disease and involves polygenic risk factors. High-throughput genomic analyses such as genome-wide association studies (GWASs) have identified more than 40 AD-associated genes [9]. Network analysis reveals that most of these genes are associated with biological processes involved in glia and neurons, including the production, aggregation, degradation, and clearance of Aβ as well as lipid metabolism and innate immune response [10]. Some of these genes also play critical roles in regulating synaptogenesis, synaptic functions, and synaptic plasticity. Deregulated expression and altered functions of these proteins may contribute to the early impairment of synaptic functions in AD before clinical symptoms occur. Herein, we present an overview of the AD-associated genes that have been implicated in synaptic functions (Fig. 1). Specifically, we will focus on those genetic risk factors that are most prevalent or validated for LOAD, including *SORL1*, *BIN1*, *PICALM*, *CD2AP, CLU, PTK2B, APOE*, and *TREM2*. Moreover, we will discuss genetic risk factors whose deregulated activities are suggested to be involved in synaptic dysfunction in AD, including *LILRB2*, *IL33*, and *ADAM10*.

1.1. Neuronal genes

Synapses, basic units that connect neurons in the neuronal network to transmit and process information, are formed upon the innervation of the presynaptic axonal terminal from one neuron to the postsynaptic specialization located on the dendrite or neuronal soma of another neuron. Activity-dependent changes of synaptic properties, such as synapse size and density, release probability, and postsynaptic receptor composition, can impact the efficacy of synaptic transmission. AD-associated genetic risk factors, including *SORL1*, *BIN1*, *PICALM*, *CD2AP, CLU, PTK2B, LILRB2*, and *ADAM10*, are expressed in neurons and exert functional roles in synapse morphogenesis as well as synaptic plasticity. They regulate synaptic vesicle (SV) recycling for mediating neurotransmitter release at presynaptic terminals, and trafficking and functions of neurotransmitter receptors at postsynaptic specializations.

SORL1, BIN1, PICALM, and *CD2AP*—these four AD-associated genetic risk factors are critical players in mediating protein trafficking and endosomal pathways, which are required for SV maturation, neurotransmitter exocytosis, and SV endocytosis at the presynaptic terminals. These pathways are also necessary for the post-translational modification of neurotransmitter receptors and the regulation of balancing the insertion or removal of neurotransmitter receptors at the postsynaptic sites. Thus, deregulation of these pathways would affect synapse maturation and impair the efficacy of synaptic transmission.

The **SORL1** (sortilin related receptor 1) gene encodes a protein known as SorLA, SorLA1, or LR11. SorLA is a membrane-bound receptor that contains various extracellular domains including a VPS10 domain and a YWTD/EGF-type repeat domain for protein interaction [11]. More than a hundred *SORL*1 variants are associated with increased risk of AD; many of them are loss-of-function variants or related to altered functions of SorLA. SorLA is involved in protein sorting and trafficking within the trans-Golgi network to the membrane, and in targeting proteins to the endosomal/lysosomal system [11]. It is a critical player in regulating APP processing and trafficking and has been shown to target Aβ peptides to lysosomal degradation, thus preventing Aβ overproduction [12,13].

Besides APP, SorLA also regulates the trafficking or signaling of other cell surface receptors, such as TrkB, GFRα1/RET, and EphA4 [14–16], that are well known to be located at synapses and important for the regulation of synapse formation and synaptic functions. These findings suggest that SorLA dysfunction may impact synaptic functions. TrkB and its cognate ligand, brain-derived neurotrophic factor (BDNF), play
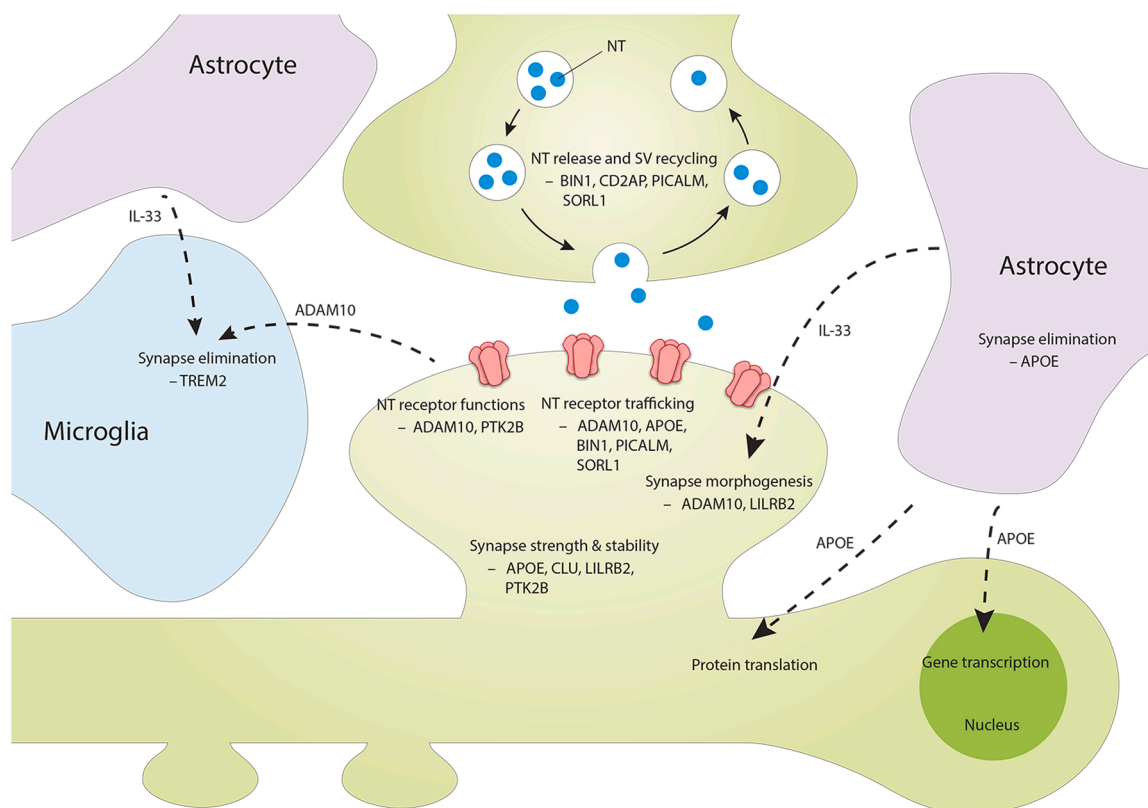

Fig. 1. Diagram illustrates the functional roles of Alzheimer's disease-associated genetic risk factors at synapses. These genes/proteins are involved in synapse morphogenesis as well as synaptic strengthening and stability. They have regulatory roles in the release of neurotransmitters (NT) and synaptic vesicle (SV) recycling at presynaptic terminals, and regulate the trafficking and functions of NT receptors at postsynaptic specializations. They also modulate the expression of synaptic proteins through altering their gene transcription and protein translation in neurons. Moreover, some of these factors are prominently expressed in glial cells (i.e. microglia and astrocytes) to modulate synaptic connectivity through the regulation of synaptic elimination.

pleiotropic roles in synaptic formation and functions [17]. Specifically, SorLA mediates TrkB receptor trafficking; it interacts with TrkB via its VPS10 domain, resulting in increased TrkB expression in the synaptic plasma membranes, which in turn regulates the response of BDNF-induced TrkB downstream signaling activation [14]. GDNF/GFRα1/RET signaling is involved in regulating neuronal survival and axon guidance during development as well as eliciting synaptogenic effects in hippocampal neurons [18]. SorLA regulates the degradation and subcellular localization of the GDNF/GFRα1/RET signaling complex [16]. It interacts with GDNF and GFRα1 to regulate the endosomal pathway and recycling of the GDNF/GFRα1/RET complex. SorLA sorts the GDNF/GFRα1/RET complex to the endosome. In the endosome, GDNF is directed to lysosomal degradation, but GFRα1 is recycled to the cell surface. The GFRα1/SorLA complex also sorts RET to early endosomes independent of GDNF, thereby affecting the cellular distribution of RET and dampening the strength of GDNF/GFRα1/RET signaling [16]. Ephrin-induced EphA4 signaling plays important roles in homeostatic plasticity by mediating the degradation of the AMPA receptor subunit GluA1 via the proteasomal degradation pathway and in the retraction of dendritic spines [19–21]. Hippocampi in AD transgenic APP/PS1 mice show aberrant EphA4 activation at the stage in which amyloid plaque deposition is just initiated. This aberrant EphA4 activation is induced by soluble oligomer Aβ, which leads to impaired hippocampal synaptic plasticity [22]. SorLA can interact with EphA4 and attenuate the Aβ-induced EphA4 activation [15]. Thus, SorLA acts as a negative regulator of EphA4 signaling-mediated synapse loss, probably in AD. SorLA overexpression in transgenic mice protects spatial memory and synapse preservation in the dentate gyrus (DG) upon Aβ challenge [15].

The SorLA coding mutation F193S and N466S are associated with EOAD [23], whereas E270K and A528T are identified from LOAD [24]. The four mutations are located in the VPS10P domain that is critical for interacting with different signaling molecules, e.g. TrkB receptor and GDNF/GFRα1/RET receptor complex [14,16], to mediate protein sorting and trafficking [25]. The effects of distinct mutations on EOAD and LOAD may attribute to their interaction with different signaling molecules. Thus, studies on how these mutants affect respective signaling processes, including APP processing, TrkB and GDNF signalings, may help to illustrate the pathological mechanisms of SorLA in AD. Another SorLA coding mutation T947M, in the YWTD/EGF-like repeat domain of SorLA, is associated with LOAD. It has been shown that T947M lowers the expression of SorLA on cell membranes [24], thus, reducing the ability of SorLA to interact with EphA4 and attenuate the receptor activation [15]. Thus, SorLA dysfunction alters the expression of cell surface receptors at synapses, and hence their signaling, that contributes to the deregulation of synaptic dysfunction.

BIN1 (bridging integrator 1), also known as amphiphysin II, is a member of the Bin/amphiphysin/Rvs (BAR) family that regulates membrane dynamics and mediates protein trafficking and endocytosis. The AD risk variants of BIN1 are mostly located in the noncoding region and are associated with changes in the expression of the protein [26]. In neurons, BIN1 is prominently expressed at excitatory presynaptic terminals, but is also detected in postsynaptic compartments with a lower expression [27]. Altered BIN1 expression is associated with Aβ peptide generation in axons [28] and tau spreading within the circuit connectivity in AD [29,30]. Conditional knockout mice with BIN1 deletion in excitatory neurons show defects in spatial memory consolidation and impaired synaptic transmission in hippocampal neurons. [27]. BIN1-depleted neurons show a deficit in neurotransmitter release, resulting from disorganized clusters of protein components of the SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) complex, which is critical for mediating SV fusion at presynaptic terminals [27]. Meanwhile, in cultured neuronal systems, suppressed expression of postsynaptic BIN1 slightly reduces the size of dendritic spines and attenuates synaptic membrane expression of GluA1, resulting in decreased efficacy of excitatory transmission with decreased

amplitude of miniature excitatory postsynaptic currents (mEPSCs) [31]. BIN1 also regulates the network activity via regulating the trafficking of L-type voltage-gated calcium channels (LVGCCs) to membranes, which results in enhanced Ca^{2+} response [32]. The interaction of BIN1 and LVGCCs is in a tau-dependent manner and involves the direct binding of the SH3 domains of BIN1 and LVGCCs together with the central proline rich region of tau. Indeed, BIN1 overexpression in cultured neurons leads to network hyperexcitability with increased spontaneous excitatory and inhibitory synaptic transmission, while the decreasing of tau protein abolishes these effects [32]. These findings suggest that it would be of interest to investigate whether the deregulated expression of BIN1 and its interaction with tau contributes to the impaired neuronal activity in AD.

The **PICALM** (phosphatidylinositol binding clathrin assembly protein) gene encodes a protein known as CALM (clathrin assembly lymphoid myeloid), which plays roles in the recruitment and assembly of the clathrin-associated proteins required for clathrin-mediated endocytosis and endosome trafficking. Two single-nucleotide polymorphisms (SNPs) of PICALM are identified with increased CALM expression and are associated with decreased occurrence of AD [33]. In neurons, CALM is found in both presynaptic and postsynaptic compartments, and has a critical role in regulating SV recycling. While VAMP2/synaptobrevin is a component of the SNARE complex for mediating SV fusion triggered by fast calcium, CALM directly interacts with VAMP2 to mediate SV endocytosis after neurotransmitter release. [34,35]. Moreover, CALM regulates synaptic transmission through modulating the expression levels of vesicular glutamate transporters (VGLUTs) that are involved in loading glutamate into SVs at presynaptic terminals, as well as the expression of glutamate receptors at the postsynaptic membrane. The roles of CALM in synaptic dysfunction in AD are supported in Drosophila. Aβ attenuates synaptic transmission and leads to excitotoxicity in Drosophila; this involves the presynaptic accumulation of VGLUTs to enhance spontaneous glutamate release and alter the regulatory subunits of GluRII receptors at the postsynaptic membrane that impact receptor sensitivity. Overexpression of lap, the Drosophila ortholog of CALM, restores the synaptic impairment induced by Aβ [36].

The **CD2AP** (CD2-associated protein) gene encodes an actin-binding adaptor protein that mediates the assembly of the cytoskeleton and adhesion complexes [37]. It also plays a role in receptor-mediated endocytosis [38]. CD2AP is enriched in brain endothelial cells and CD2AP deficient mice exhibit an impairment in blood-brain barrier [39]. Reduced CD2AP in endothelial cells thus may affect the transcytosis of Aβ across the blood-brain barrier [40]. CD2AP protein in neurons regulates APP trafficking, decreased expression facilitates amyloidogenic pathway in dendritic early endosomes, resulting in increased Aβ generation in neurons [28]. Thus, deregulated CD2AP signaling may impact amyloid pathology in AD. On the other hand, CD2AP also regulates the collateral sprouting of intact axons via TrkA signaling that may affect the number of nerve terminals [41]. In Drosophila, deletion of the expression of cindr, the Drosophila homolog of *CD2AP*, leads to impaired synapse maturation as well as defects in synaptic transmission caused by an inability to maintain SV release and recycling. Cindr/14–3–3ζ signaling regulates the ubiquitin proteasome system to mediate the turnover of synapsin, a protein critical for mobilization of SVs, which results in reduced efficacy of synaptic transmission [42]. A similar role of CD2AP in regulating the ubiquitin proteasome system is also found in the mammalian system [42]. Multiple CD2AP variants are identified to associate with LOAD risk; and reduced expression or activity of CD2AP are shown to play critical roles in LOAD development [43]. Recently, an SNP associated with both LOAD and EOAD is correlated with increased expression of *CD2AP* in the thalamus and cerebellar cortex [44]. These findings suggest that proper *CD2AP* expression in specific cell types plays critical roles in AD pathogenesis, whether altered *CD2AP* expression in AD contributes to the development of synaptic dysfunctions remains to be determined.

The modeling of synaptic connectivity and the efficacy of synaptic transmission involve the coordination of multiple modulatory signals in neurons and glial cells. PTK2B and LILRB2 are 2 signaling molecules involved in modulating synaptic functions; more importantly, both are the critical downstream signals for Aβ-mediated synapse loss [45,46]. The **PTK2B** (protein tyrosine kinase 2β) gene, also known as Pyk2 and Fak2, encodes a non-receptor tyrosine kinase related to focal adhesion kinase. It is a downstream signaling molecule for various signaling cascades including integrin [47] and NRG1/ErbB4 [48]. Pyk2 is highly expressed in the hippocampus. Pyk2 expression and activation at synapses are regulated by synaptic activity. Specifically, NMDA receptor activation-mediated Ca^{2+} influx recruits Pyk2 to synapses via its interaction with scaffold proteins PSD-95 and SAP102 at dendritic spines [49]. Pyk2 activation (i.e., revealed by its phosphorylation at Tyr 402) induced by NMDA receptor activation plays critical roles in dendritic spine structure. Activated Pyk2 also coordinates with Src family kinases to phosphorylate PSD-95 and NMDA receptors, which results in enhanced functions of NMDA receptors [48,50]. Multiple studies report the roles of Pyk2 in synaptic plasticity regulation. Absence of Pyk2 impairs long-term depression (LTD) in hippocampal slices [51]. Contradictory findings are observed regarding the roles of Pyk2 in long-term potentiation (LTP), which may be due to the different experimental models used across studies (review in [52]). A recent report suggests that Pyk2 participates in high frequency stimulation-LTP but not in theta burst stimulation-LTP [53]. Nonetheless, Pyk2$^{-/-}$ mice exhibit impaired spatial memory [53].

In AD, genetic variants of *PYK2B* are correlated with increased Pyk2 expression, which is associated with increased disease risk [52]. Pyk2 signaling is involved in Aβ oligomer-triggered synapse loss [45]. Aβ binding to the cellular prion protein (PrP^C) stimulates synaptic localization and Pyk2 activation. In turn, activated Pyk2 inhibits the activity of Graf1c, a Rho GTPase-activating protein (GAP), resulting in increased RhoA activity which leads to the destabilization of actin dynamics [45]. Pyk2 depletion in AD transgenic APP/PS1 mice ameliorates synapse loss and exhibits better reservation of spatial memory without significantly affecting amyloid pathology [54].

The **LILRB2** (leukocyte immunoglobulin-like receptor B2) gene encodes the receptor for major histocompatibility complex class I (MHC I) proteins that mediate immune responses in the peripheral system. Mouse PirB is the human ortholog for LILRB2. In the adult mouse cerebrum, PirB is widely expressed in pyramidal neurons [55]. PirB$^{-/-}$ mice have better performance in acquiring, and flexibility in hippocampal-dependent learning and memory [56]. These PirB$^{-/-}$ mice show abnormally higher dendritic spine density associated with increased neurotransmission (i.e., higher mEPSC frequency) in the pyramidal neurons of the visual cortex and hippocampus [56–58]. This excessive increase of spine density in PirB-deficient pyramidal neurons shifts Hebbian synaptic plasticity toward synaptic strengthening, which enhances LTP but impairs LTD at L4–L2/3 synapses in the visual cortex and at Schaffer collateral–CA1 synapses in the hippocampus [56–58]. Thus, PirB signaling is important for maintaining synapse density and synaptic plasticity. *In vivo* imaging suggests that this increase of dendritic spines in PirB-deficient neurons may be contributed by the more stable and less motile dendritic spines [57]. Several downstream signalings of PirB—including Shp-1, Shp-2, and cofilin—are critical actin regulators [55,57,59], suggesting that the molecular roles of PirB in dendritic spine mobility involves modulating actin dynamics.

A recent large-scale GWAS identified *LILRB2* as a genetic risk for LOAD [60]. In fact, LILRB2 is the receptor for Aβ oligomers with nanomolar affinity [59]. Aβ-dependent impairment of synaptic plasticity is mediated through the activation of PirB signaling. The Aβ oligomer-stimulated attenuation of LTP is abolished in hippocampal slices prepared from PirB$^{-/-}$ mice. Moreover, deletion of PirB in APP/PS1 mice leads to an amelioration of impairment in learning and memory performance. Proteomic screening of AD transgenic mouse brains have identified downstream signaling proteins of Aβ/PirB that are associated

with enhancing cofilin signaling and that contribute to actin dynamic instability [59]. Thus, it would be of interest to examine the mechanisms of *LILRAB2* risk associated with synaptic dysfunction in LOAD pathology.

Most proteins undergo sequential proteolytic processing for maturation and activation. The **ADAM10** (A disintegrin and metalloprotease domain-containing protein 10) gene, which encodes α-secretase, mediates the ectodomain shedding of target membrane proteins to generate secretory domains and membrane-associated domains, resulting in mediating the downstream signaling of these membrane proteins [61]. Multiple genome-wide analyses have identified a number of genetic variants, including non-coding variants and coding variants, of ADAM10 [62–64]. Mice with conditional knockout of neuronal ADAM10 at postnatal stages exhibit learning and memory deficits. These transgenic mice have normal synaptic transmission but impaired synaptic plasticity in the hippocampal CA1 region at the adult stage. They also exhibit altered synapse morphology, with decreased dendritic spine density and more stubby-shaped spines. [65].

More than 40 transmembrane proteins are substrates of ADAM10 [66]. A number of these transmembrane proteins—including APP, N-cadherin, neurexin-1, neuroligin-1, and Cx3CL1—are involved in different aspects of synapse formation and maintenance as well as synaptic plasticity. The synaptic roles of these proteins can be regulated by their shedding by ADAM10. For example, APP and its cleavage products regulate synaptic maturation and synaptic plasticity in physiological conditions [67]. However, excessive production of sAPPα by increased ADAM10 expression leads to an increased formation of immature dendritic spines [68]. N-cadherin, a homophilic cell adhesion protein, undergoes sequential cleavage by ADAM10 and γ-secretase upon NMDA receptor activation. N-cadherin is critical for the regulation of synapse morphology as well as the composition and functions of neurotransmitter receptors at synapses [69]. Neurexin-1, a presynaptic cell adhesion molecule, and its postsynaptic ligand neuroligin-1 are critical for axon pathfinding and synapse formation [70]. Both N-cadherin and neurexin-1 are substrates for ADAM10. Blockade of ADAM10-mediated cleavage of neurexin-1 increases synaptic expression of neurexin-1, which contributes to an increase of excitatory synapses [71]. Activity-regulated shedding of neuroligin-1 negatively regulates excitatory synaptic connection in hippocampal granule cells [72]. Cx3CL1 is a chemokine in cortical neurons that is cleaved by ADAM10 in response to reduced neuronal activity in the barrel cortex in mouse due to whisker lesioning. The secreted form of Cx3CL1 binds to its cognate fractalkine receptor, CX3CR1, which is expressed in microglia to mediate synapse engulfment [73].

The synaptic localization of ADAM10 can be regulated by neuronal activity that affects its action on protein shedding. For example, LTD induces an interaction of ADAM10 with SAP97 and promotes the trafficking of ADAM10 to synapses; and LTP induces removal of ADAM10 from membranes by clathrin-mediated endocytosis and reduces its activity [74,75]. Furthermore, the maturation of ADAM10 requires the removal of its prodomain by proprotein convertases (e.g., furin) to expose its catalytic domain during trafficking [76]. Q170H and R181G of ADAM10 are rare coding variants identified in AD that attenuate the maturation of the protein by impairing the cleavage of the ADAM10 prodomain [62]. TspanC8, a subfamily member of tetraspanins, is identified to be a critical regulator for the trafficking and maturation of ADAM10 [77]. A locus near **TSPAN14**, a member of the Tspanc8 subfamily, was recently identified to be associated with AD risk [78]. However, it remains unclear whether this TSPAN14 variant affects expression and activity of ADAM10 and contributes to synaptic deficits.

1.2. Astrocytic genes

Astrocytes integrate into neural networks via their intricate processes, which interact with pre- and postsynaptic neurons to form "tripartite synapses." The roles of astrocytes in synaptogenesis, synaptic

connectivity, synaptic transmission, and synaptic plasticity have been extensively studied [79].

The *IL33* gene encodes a member of the interleukin (IL)– 1 family of cytokines, IL-33, which has critical roles in immune homeostasis [80]. IL-33 binds to its cognate receptor, ST2 (suppression of tumorigenicity 2) and then recruits IL-1RAcP (interleukin-1 receptor accessory protein) to trigger downstream signaling pathways [80]. IL-33 is prominently expressed in astrocytes and oligodendrocytes, but is also found to be expressed in neurons [81–83]. *Il33*$^{-/-}$ mice or mice administered with soluble ST2 (an endogenous decoy receptor of IL-33/ST2 signaling) exhibit impairment of synaptic plasticity and dysfunction in learning and memory [82–84]. Both neuronal and astrocytic IL-33 play critical roles in modeling synaptic connectivity, but IL-33/ST2 signaling exerts specific functional and mechanistic roles in distinct neuronal circuitry at different developmental stages [82,83,85]. In the critical period of neural circuitry refinement in postnatal development, astrocyte-derived IL-33 binds to ST2 in microglia in the thalamus and spinal cord to mediate microglial synaptic pruning [85]. In the hippocampi of adult mice, astrocytic expression and IL-33 secretion increases upon neuronal activity blockade, and that elevated IL-33 increases excitatory synapse numbers and synaptic transmission through the activation of ST2 on CA1 neurons in order to maintain network homeostasis [82]. In the DG, a subgroup of neurons expresses IL-33 in response to experience, and that neuronal-released IL-33 instructs the nearby ST2-positive microglia to phagocytose extracellular matrix proteins, resulting in enhanced synapse formation and the promotion of structural plasticity [83]. SNPs of IL-33 are identified in AD and are associated with decreased IL-33 expression [86]. Moreover, decreased plasma level of IL-33 protein and increased soluble ST2 are associated with patients with AD [87–89]. Importantly, replenishment of IL-33 rescues impaired hippocampal LTP and hippocampal-dependent memory in APP/PS1 transgenic mice [88], suggesting decreased IL-33/ST2 signaling contributes to synaptic impairment in disease progression. Thus, it would be of great interest to further examine the specific cellular roles of IL-33 and ST2 in synaptic impairment in AD.

The *APOE* (apolipoprotein E) gene is the most significant genetic risk factor for AD. APOE is a lipoprotein with three human APOE isoforms—*APOEε2, APOEε3*, and *APOEε4*—that are associated with the probability of AD development. *APOEε3* is the most common form, whereas *APOEε4* carriers are more susceptible to AD and the gene dosage of the *APOEε4* allele is inversely related to age of AD onset. In the human brain, under physiological conditions, APOE-containing lipoproteins are secreted from astrocytes, a major source of these lipoproteins. Under pathological conditions, APOE-containing lipoproteins can be secreted from microglia as well as from neurons in some injury conditions. APOE binds to the members of the low-density lipoprotein receptor (LDLR) family, including the LDLR, apolipoprotein E receptor 2 (ApoER2), very-low-density lipoprotein receptor (VLDLR), and LDLR-related protein 1 (Lrp1). Besides acting as a lipid-transporter from astrocytes to neurons in physiological conditions, APOE also participates in multiple biological pathways—including neuronal morphogenesis, protein trafficking, and calcium homeostasis—involved in the development, maintenance, and repair of the central nervous system (CNS) (review in [90]). APOE plays critical roles in amyloid pathology that affect APP processing, fibrillation, and Aβ secretion in neurons. The secreted form of APOE binds to Aβ to facilitate its uptake and clearance by microglia. APOE also affects the progression of tau pathology and tau-mediated neurodegeneration (review in [91]). In addition, APOE signaling is involved in regulating synaptic functions. Roles of different APOE isoforms associated with synapse loss and dysfunction are reported in AD progression: in patients with AD who carry the APOE ε4 allele, synatotoxic Aβ oligomers have an increased association with synapses [92]. This suggests APOE4 is involved in Aβ-mediated synapse loss and dysfunction.

Extensive studies have characterized the effects of APOE isoforms in synapse formation and maintenance, synaptic functions, and cognitive functions using different APOE2, APOE3, and APOE4 transgenic mouse models. Kim et al. and Lewandowski et al. provide comprehensive summaries on the characterization of different APOE mouse models, specifically on synaptic structure, synaptic functions, and different behavioral tests [93,94]. In brief, these transgenic mice studies suggest APOE4 has aversive effects on synapse integrity and functions. APOE4-harboring induced pluripotent stem cells (iPSCs) exhibit accelerated neuronal differentiation; and neurons or organoids derived from these APOE4 human iPSCs or embryonic stem cells have more synapses and increased synaptic transmission efficiency when compared to that of APOE3-carrying iPSC-derived neurons. Similarly, iPSC-derived cerebral organoids from patients with AD carrying the APOE4 allele show faster synapse formation and maturation in early organoid development. However, the APOE4-expressing organoids show an increase in synapse loss and neuronal apoptosis together with Aβ accumulation at later stages [95–98]. Thus, iPSC-derived neural cell systems may provide a good cellular model for further study of the impacts of different APOE isoforms on synaptic functions.

Different mechanisms of how the APOE4 protein causes disturbances in synaptogenesis and synaptic functions have been suggested. Mice with APOE4 expression have higher neurotransmitter glutamine levels in the brain, contributed by a disturbance of the glutamate-glutamine cycle, which result in neuronal excitotoxicity [99]. Postsynaptically, APOE4 attenuates NMDA-dependent LTP via sequestering glutamate receptors in intracellular compartments and preventing their membrane expression, leading to decreased NMDA receptor-mediated Ca^{2+} influx and impaired synaptic plasticity [100]. Moreover, APOE4 attenuates the maturation and function of synapses by altering the expression of neuronal and synaptic proteins at both transcription and translation levels [95–97,101]. Specifically, APOE4 signaling suppresses the activities of transcription factors such as CaMKIIα and CREB in neurons, which leads to altered synaptic gene expression and impaired synaptic plasticity [101]. APOE signaling also participates in the epigenetic regulation of gene expression by modulating the activity of the transcription repressor REST (RE1-silencing transcription factor) in neurons; APOE4 decreases the nuclear translocation and chromatin binding of REST, which leads to the altered transcription of neuronal genes [96]. On the other hand, astrocyte APOE4 signaling attenuates synaptic gene expression in neurons through regulating the accumulation of acetyl-CoA and the subsequent histone acetylation. Astrocyte-derived APOE-containing particles carry miRNA into neurons that specifically suppress the translation of genes associated with cholesterol biosynthesis, resulting in the accumulation of acetyl-CoA, an initiating substrate for cholesterol biosynthesis. Acetyl-CoA is also a predominant donor for histone acetylation, and its accumulation in neurons leads to the promotion of gene transcription related to axonogenesis and synaptogenesis. However, APOE4-containing particles have lower miRNA content, which enables cholesterol biosynthesis and lowers acetyl-CoA and leads to decreased histone acetylation and gene transcription [102]. Neuronal APOE4 signaling also attenuates the protein translation of synaptic proteins by stimulating eukaryotic translation elongation factor (eEF2) phosphorylation in response to neuronal activity changes [103]. Indeed, APOE signaling is also involved in sculpting synaptic connectivity through regulating the phagocytic activity of glial cells. During postnatal developmental stage, compared with APOE2 and APOE3 knock-in (KI mice), astrocytes have a lower phagocytic activity for synapse elimination in the dorsal lateral geniculate nucleus of APOE4 KI mice [104]. Moreover, C1q is a recognition ligand of the classical complement cascade and is involved in tagging weak synapses in neurons to signal the microglia for synapse engulfment through complement component-3 receptors [105]. Aged APOE4 KI mice have increased C1q accumulation in hippocampus, suggest that APOE4 affects the microglial synaptic pruning [104]. Transcriptomic and proteomics analyses of the brains of APOE4-expressing transgenic mouse models, post-mortem human brains carrying different APOE isoforms, and human iPSC cells further suggest the underlying mechanisms of

APOE isoforms in altering synaptic functions. In these studies, proteins associated with energy metabolism, phospholipid metabolism, immune response, neuroinflammation, synapse organization, and synaptic transmission are most differentially altered between APOE isoforms [95, 98,106–109].

The **CLU** gene encodes a lipoprotein called clusterin (also known as APOJ) that is prominently expressed in astrocytes in the brain, while its secreted form is enriched in plasma. CLU is a multifunction protein that acts as an extracellular chaperone, which is involved in lipid metabolism and immune modulation [110]. In LOAD, CLU is the third-most significant genetic risk factor. CLU is found to be colocalized with Aβ deposition, and involved in both Aβ generation, fibrillization, and clearance. A number of SNPs have been identified, including ones that are shown to affect gene transcription, isoform expression, and protein trafficking or secretion, while the roles of the identified CLU variants in association with AD are not clearly understood (review in [110,111]). A recent study suggested that astrocyte-secreted CLU also plays a role in synaptic function, where it is found to bind at excitatory but not inhibitory presynaptic sites. CLU knockout mice have impaired excitatory synaptic transmission with decreased mEPSC frequency in hippocampal neurons. This synaptic defect in CLU knockout neurons is contributed by decreased neurotransmitter release probability and dendritic spine density. In contrast, increased CLU expression in astrocytes by viral injection not only ameliorates the amyloid pathology but also rescues decreased mEPSC frequency in 5xFAD, an AD transgenic mouse model [112].

1.3. Microglial genes

Microglia are the resident immune cells in the CNS that are responsible for the surveillance of the environment, mediation of neuroinflammation, and clearance of pathogen/debris. During postnatal development and in response to experiences, microglial-mediated synapse pruning is critical for refining and sculpting synaptic connectivity and mediating structural plasticity. Deregulation of these pathways affects synaptic transmission efficacy and plasticity in pathological condition. [105].

TREM2 (triggering receptor expressed on myeloid cell 2) is a transmembrane glycoprotein that is mainly expressed on the immune cells of myeloid origin. TREM2 can be activated by different classes of ligands including lipids, apolipoproteins, and DNA. Upon binding with its ligand, TREM2 couples with an adaptor protein, DNAX-activating protein of 12 kDa (DAP12, also known as TYROBP) to recruit and activate downstream signaling in microglia [113]. In physiological conditions, TREM2 signaling is involved in promoting cell proliferation and survival, anabolic metabolism, restricting inflammation, and phagocytosis [114]. In AD, TREM2 is well known for its roles in mediating the transition of disease-associated microglia (DAM) from homeostatic microglia, and TREM2$^+$ microglia are localized in close proximity to amyloid plaques[113,115].

TREM2 also acts as a microglial signal that regulates synapse elimination. Proper regulation of its expression and activity is crucial for sculpting synaptic connectivity and proper synaptic functions during development. TREM2$^{-/-}$ mice show an increase in excitatory synapse numbers in the hippocampus at postnatal development with a higher mEPSC frequency, whereas overexpressed TREM2 in microglia enhances their phagocytic activity and contributes to synaptic impairment in young adult mice [116]. Young adult TREM2$^{-/-}$ mice (6–8 months old) do not show any cognitive impairments [117], whereas aged TREM2$^{-/-}$ mice (>18 months old) have better preservation of dendritic spines in hippocampal pyramidal neurons that contribute to maintaining normal basal synaptic transmission with enhanced hippocampal LTP. These transgenic mice also have better cognitive performance than that of aged wild-type mice. Interestingly, in the early pathological stage of AD, reduced TREM2 activity indeed is associated with prevention of synapse loss. Depleted TREM2 expression in cortical and hippocampal microglia

of APP/PS1 mice at the early to middle pathological transition stage (i. e., 4–8 months old) leads to decreased microglial phagocytic activity; these transgenic mice preserve excitatory synapse numbers, hippocampal LTP, and spatial memory without affecting amyloidosis. However, these transgenic mice with depleted TREM2 expression at the middle to late pathological transition stage (~6–10 months old) exacerbates synaptic dysfunction and cognitive impairment [116]. Moreover, compared with ordinary 5xFAD mice, 5xFAD mice with increased microglial TREM2 expression show ameliorated amyloid pathology and better cognitive performance. Bulk transcriptomic analysis of the brains from these mice revealed that, not only was decreased expression shown in the gene signature of DAM, which is otherwise found to be prominently induced in ordinary 5xFAD mice, decreased expression of some of the neuronal and synaptic genes was also restored [118]. Further studies are required to better understand the mechanistic roles of TREM2 signaling in mediating the synaptic deficits at different pathological stages of AD progression.

Most AD-associated TREM2 variants are loss-of-function variants that are associated with reduced expression or reduced activity of the protein. The most prevalent variant, R47H TREM2, is associated with elevated AD risk [119]. TREM2 R47H KI young adult rats exhibit enhanced glutamatergic transmission and decreased inhibitory transmission in hippocampal pyramidal neurons that result in impaired (excitation/inhibition) E/I balance. These transgenic rats also show impaired synaptic plasticity with reduced LTP at Schaffer collateral–CA1 synapses [120,121]. Thus, the R47H variant of TREM2 plays a role in deregulating synaptic connectivity and synaptic function at the early stages of AD before clinical symptoms appear.

2. Conclusion

In the past two to three decades, therapeutic interventions for AD have been based on the amyloid hypothesis. However, with the continued failure of clinical trials, researchers have turned their focus to understanding the underlying multifactorial mechanisms of AD to develop novel therapeutic approaches. The deterioration of synaptic functions is highly associated with the progression of cognitive impairments in various neurodegenerative diseases [122]. In AD, synaptic dysfunction is one of the neuropathological changes that occur in the brain before clinical symptoms appear. Aβ oligomers and abnormal hyperphosphorylated tau are two critical players for initiating the synaptic dysfunction and synaptic loss in AD [8]. They can act on multiple signaling pathways to exert damage to the cellular processes on presynaptic terminals, postsynaptic specializations, and glial cells wrapped around synapses. Using the latest bioinformatics and quantitative tools, including genomics, proteomics, and epidemiological studies, have identified more genetic risks and biomarkers associated with AD progression. Understanding of how these AD-associated variants/biomarkers regulate the homeostasis of synaptic circuitry and function may help uncover the disease mechanisms and develop early interventions for AD.

Declaration of Competing Interest

Data availability

Acknowledgments

References

[1] A. Serrano-Pozo, M.P. Frosch, E. Masliah, B.T. Hyman, Neuropathological alterations in Alzheimer disease, Cold Spring Harb. Perspect. Med. (2011), https://doi.org/10.1101/cshperspect.a006189.

[2] T.L. Spires-Jones, B.T. Hyman, The intersection of amyloid beta and tau at synapses in Alzheimer's disease, Neuron 82 (2014) 756–771, https://doi.org/10.1016/j.neuron.2014.05.004.

[3] S.T. DeKosky, S.W. Scheff, Synapse loss in frontal cortex biopsies in Alzheimer's disease: correlation with cognitive severity, Ann. Neurol. 27 (1990) 457–464, https://doi.org/10.1002/ana.410270502.

[4] P.H. Reddy, G. Mani, B.S. Park, J. Jacques, G. Murdoch, W. Whetsell, J. Kaye, M. Manczak, Differential loss of synaptic proteins in Alzheimer's disease: implications for synaptic dysfunction, J. Alzheimer's Dis. 7 (2005) 103–117, https://doi.org/10.3233/JAD-2005-7203.

[5] J. Subramanian, J.C. Savage, M.È. Tremblay, Synaptic loss in Alzheimer's disease: mechanistic insights provided by two-photon in vivo imaging of transgenic mouse models, Front. Cell. Neurosci. 14 (2020) 1–13, https://doi.org/10.3389/fncel.2020.592607.

[6] R. Nisticò, M. Pignatelli, S. Piccinin, N.B. Mercuri, G. Collingridge, Targeting synaptic dysfunction in Alzheimer's disease therapy, Mol. Neurobiol. 46 (2012) 572–587, https://doi.org/10.1007/s12035-012-8324-3.

[7] C. Haass, C. Kaether, G. Thinakaran, S. Sisodia, Trafficking and proteolytic processing of APP, Cold Spring Harb. Perspect. Med. 2 (2012) 1–26, https://doi.org/10.1101/cshperspect.a006270.

[8] Y. Chen, A.K.Y. Fu, N.Y. Ip, Synaptic dysfunction in Alzheimer's disease: mechanisms and therapeutic strategies, Pharmacol. Ther. 195 (2019) 186–198, https://doi.org/10.1016/j.pharmthera.2018.11.006.

[9] C. Bellenguez, B. Grenier-Boley, J.C. Lambert, Genetics of Alzheimer's disease: where we are, and where we are going, Curr. Opin. Neurobiol. 61 (2020) 40–48, https://doi.org/10.1016/j.conb.2019.11.024.

[10] R.E. Tanzi, The genetics of Alzheimer disease, Cold Spring Harb. Perspect. Med. 2 (2012) a006296, https://doi.org/10.1101/cshperspect.a006296.

[11] V. Schmidt, A. Subkhangulova, T.E. Willnow, Sorting receptor SORLA: cellular mechanisms and implications for disease, Cell. Mol. Life Sci. 74 (2017) 1475–1483, https://doi.org/10.1007/s00018-016-2410-z.

[12] S. Caglayan, S. Takagi-Niidome, F. Liao, A.-S. Carlo, V. Schmidt, T. Burgert, Y. Kitago, E.-M. Füchtbauer, A. Füchtbauer, D.M. Holtzman, J. Takagi, T. E. Willnow, Lysosomal sorting of amyloid-β by the SORLA receptor is impaired by a familial Alzheimer's disease mutation, Sci. Transl. Med. 6 (2014), https://doi.org/10.1126/scitranslmed.3007747.

[13] O.M. Andersen, J. Reiche, V. Schmidt, M. Gotthardt, R. Spoelgen, J. Behlke, C.A. F. Von Arnim, T. Breiderhoff, P. Jansen, X. Wu, K.R. Bales, R. Cappai, C. L. Masters, J. Gliemann, E.J. Mufson, B.T. Hyman, S.M. Paul, A. Nykjær, T. E. Willnow, Neuronal sorting protein-related receptor sorLA/LR11 regulates processing of the amyloid precursor protein, Proc. Natl. Acad. Sci. USA 102 (2005) 13461–13466, https://doi.org/10.1073/pnas.0503689102.

[14] M. Rohe, D. Hartl, A.N. Fjorback, J. Klose, T.E. Willnow, SORLA-mediated trafficking of TrkB enhances the response of neurons to BDNF, PLoS One 8 (2013), https://doi.org/10.1371/journal.pone.0072164.

[15] T.Y. Huang, Y. Zhao, L. Jiang, X. Li, Y. Liu, Y. Sun, J.C. Piña-Crespo, B. Zhu, E. Masliah, T.E. Willnow, E.B. Pasquale, H. Xu, SORLA attenuates EphA4 signaling and amyloid β–induced neurodegeneration, J. Exp. Med. 214 (2017) 3669–3685, https://doi.org/10.1084/jem.20171413.

[16] S. Glerup, M. Lume, D. Olsen, J.R. Nyengaard, C.B. Vaegter, C. Gustafsen, E. I. Christensen, M. Kjolby, A. Hay-Schmidt, D. Bender, P. Madsen, M. Saarma, A. Nykjaer, C.M. Petersen, SorLA controls neurotrophic activity by sorting of GDNF and its receptors GFRα1 and RET, Cell Rep. 3 (2013) 186–199, https://doi.org/10.1016/j.celrep.2012.12.011.

[17] C.S. Wang, E.T. Kavalali, L.M. Monteggia, BDNF signaling in context: from synaptic regulation to psychiatric disorders, Cell 185 (2022) 62–76, https://doi.org/10.1016/j.cell.2021.12.003.

[18] C.F. Ibáñez, J.O. Andressoo, Biology of GDNF and its receptors — relevance for disorders of the central nervous system, Neurobiol. Dis. 97 (2017) 80–89, https://doi.org/10.1016/j.nbd.2016.01.021.

[19] A.K.Y. Fu, K.W. Hung, W.Y. Fu, C. Shen, Y. Chen, J. Xia, K.O. Lai, N.Y. Ip, APCCdh1 mediates EphA4-dependent downregulation of AMPA receptors in homeostatic plasticity, Nat. Neurosci. 14 (2011) 181–191, https://doi.org/10.1038/nn.2715.

[20] W.Y. Fu, Y. Chen, M. Sahin, X.S. Zhao, L. Shi, J.B. Bikoff, K.O. Lai, W.H. Yung, A. K.Y. Fu, M.E. Greenberg, N.Y. Ip, Cdk5 regulates EphA4-mediated dendritic spine retraction through an ephexin1-dependent mechanism, Nat. Neurosci. 10 (2007) 67–76, https://doi.org/10.1038/nn1811.

[21] L.M. Vargas, N. Leal, L.D. Estrada, A. González, F. Serrano, K. Araya, K. Gysling, N.C. Inestrosa, E.B. Pasquale, A.R. Alvarez, EphA4 activation of c-Abl mediates synaptic loss and LTP blockade caused by amyloid-β oligomers, PLoS One 9 (2014), https://doi.org/10.1371/journal.pone.0092309.

[22] A.K.Y. Fu, K.W. Hung, H. Huang, S. Gu, Y. Shen, E.Y.L. Cheng, F.C.F. Ip, X. Huang, W.Y. Fu, N.Y. Ip, Blockade of EphA4 signaling ameliorates hippocampal synaptic dysfunctions in mouse models of Alzheimer's disease, Proc. Natl. Acad. Sci. USA 111 (2014) 9959–9964, https://doi.org/10.1073/pnas.1405803111.

[23] G. Qiu, F.Q. Zhu, C. Xu, Identification of two pathogenic mutations in SORL1 in early-onset Alzheimer's disease, J. Clin. Neurosci. 89 (2021) 243–248, https://doi.org/10.1016/j.jocn.2021.05.020.

[24] B.N. Vardarajan, Y. Zhang, J.H. Lee, R. Cheng, C. Bohm, M. Ghani, C. Reitz, D. Reyes-Dumeyer, Y. Shen, E. Rogaeva, P. George-Hyslop St, R. Mayeux, Coding mutations in SORL1 and Alzheimer disease, Ann. Neurol. 77 (2015) 215–227, https://doi.org/10.1002/ana.24305.

[25] A.R. Malik, T.E. Willnow, VPS10P domain receptors: sorting out brain health and disease, Trends Neurosci. 43 (2020) 870–885, https://doi.org/10.1016/j.tins.2020.08.003.

[26] J.C. Lambert, C.A. Ibrahim-Verbaas, D. Harold, A.C. Naj, R. Sims, C. Bellenguez, G. Jun, A.L. DeStefano, J.C. Bis, G.W. Beecham, B. Grenier-Boley, G. Russo, T. A. Thornton-Wells, N. Jones, A.V. Smith, V. Chouraki, C. Thomas, M.A. Ikram, D. Zelenika, B.N. Vardarajan, Y. Kamatani, C.F. Lin, A. Gerrish, H. Schmidt, B. Kunkle, N. Fiévet, P. Amouyel, F. Pasquier, V. Deramecourt, R.F.A.G. De Bruijn, N. Amin, A. Hofman, C.M. Van Duijn, M.L. Dunstan, P. Hollingworth, M. J. Owen, M.C. O'Donovan, L. Jones, P.A. Holmans, V. Moskvina, J. Williams, C. Baldwin, L.A. Farrer, S.H. Choi, K.L. Lunetta, A.L. Fitzpatrick, T.B. Harris, B. M. Psaty, J.R. Gilbert, K.L. Hamilton-Nelson, E.R. Martin, M.A. Pericak-Vance, J. L. Haines, V. Gudnason, P.V. Jonsson, G. Eiriksdottir, M.T. Bihoreau, M. Lathrop, O. Valladares, L.B. Cantwell, L.S. Wang, G.D. Schellenberg, A. Ruiz, M. Boada, C. Reitz, R. Mayeux, A. Ramirez, W. Maier, O. Hanon, W.A. Kukull, J. D. Buxbaum, D. Campion, D. Wallon, D. Hannequin, P.K. Crane, E.B. Larson, T. Becker, C. Cruchaga, A.M. Goate, D. Craig, J.A. Johnston, B. Mc-Guinness, S. Todd, P. Passmore, C. Berr, K. Ritchie, O.L. Lopez, P.L. De Jager, D. Evans, S. Lovestone, P. Proitsi, J.F. Powell, L. Letenneur, P. Barberger-Gateau, C. Dufouil, J.F. Dartigues, F.J. Morón, D.C. Rubinsztein, P. George-Hyslop St., K. Sleegers, K. Bettens, C. Van Broeckhoven, M.J. Huentelman, M. Gill, K. Brown, K. Morgan, M.I. Kamboh, L. Keller, L. Fratiglioni, R. Green, A.J. Myers, S. Love, E. Rogaeva, J. Gallacher, A. Bayer, J. Clarimon, A. Lleo, D.W. Tsuang, L. Yu, D. A. Bennett, M. Tsolaki, P. Bossù, G. Spalletta, J. Collinge, S. Mead, S. Sorbi, B. Nacmias, F. Sanchez-Garcia, M.C. Deniz Naranjo, N.C. Fox, J. Hardy, P. Bosco, R. Clarke, C. Brayne, D. Galimberti, M. Mancuso, F. Matthews, S. Moebus, P. Mecocci, M. Del Zompo, H. Hampel, A. Pilotto, M. Bullido, F. Panza, P. Caffarra, M. Mayhaus, S. Pichler, W. Gu, M. Riemenschneider, L. Lannfelt, M. Ingelsson, H. Hakonarson, M.M. Carrasquillo, F. Zou, S.G. Younkin, D. Beekly, V. Alvarez, E. Coto, C. Razquin, P. Pastor, I. Mateo, O. Combarros, K.M. Faber, T. M. Foroud, H. Soininen, M. Hiltunen, D. Blacker, T.H. Mosley, C. Graff, C. Holmes, T.J. Montine, J.I. Rotter, A. Brice, M.A. Nalls, J.S.K. Kauwe, E. Boerwinkle, R. Schmidt, D. Rujescu, C. Tzourio, M.M. Nöthen, L.J. Launer, S. Seshadri, Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease, Nat. Genet. 45 (2013) 1452–1458, https://doi.org/10.1038/ng.2802.

[27] P. De Rossi, T. Nomura, R.J. Andrew, N.Y. Masse, V. Sampathkumar, T.F. Musial, A. Sudwarts, A.J. Recupero, T. Le Metayer, M.T. Hansen, H.N. Shim, S.V. Krause, D.J. Freedman, V.P. Bindokas, N. Kasthuri, D.A. Nicholson, A. Contractor, G. Thinakaran, Neuronal BIN1 regulates presynaptic neurotransmitter release and memory consolidation, e7, Cell Rep. 30 (2020) 3520–3535, https://doi.org/10.1016/j.celrep.2020.02.026.

[28] F. Ubelmann, T. Burrinha, L. Salavessa, R. Gomes, C. Ferreira, N. Moreno, C. Guimas Almeida, Bin1 and CD2AP polarise the endocytic generation of beta-amyloid, EMBO Rep. 18 (2017) 102–122, https://doi.org/10.15252/embr.201642738.

[29] S. Calafate, W. Flavin, P. Verstreken, D. Moechars, Loss of Bin1 promotes the propagation of tau pathology, Cell Rep. 17 (2016) 931–940, https://doi.org/10.1016/J.CELREP.2016.09.063.

[30] A. Crotti, H.R. Sait, K.M. McAvoy, K. Estrada, A. Ergun, S. Szak, G. Marsh, L. Jandreski, M. Peterson, T.L. Reynolds, I. Dalkilic-Liddle, A. Cameron, E. Cahir-McFarland, R.M. Ransohoff, H. Rajamohamend Sait, K.M. McAvoy, K. Estrada, A. Ergun, S. Szak, G. Marsh, L. Jandreski, M. Peterson, T.L. Reynolds, I. Dalkilic-Liddle, A. Cameron, E. Cahir-McFarland, R.M. Ransohoff, BIN1 favors the spreading of Tau via extracellular vesicles, Sci. Rep. 9 (2019) 1–20, https://doi.org/10.1038/s41598-019-45676-0.

[31] B. Schürmann, D.P. Bermingham, K.J. Kopeikina, K. Myczek, S. Yoon, K.E. Horan, C.J. Kelly, M.D. Martin-de-Saavedra, M.P. Forrest, J.M. Fawcett-Patel, K.R. Smith, R. Gao, A. Bach, A.C. Burette, J.Z. Rappoport, R.J. Weinberg, M. Martina, P. Penzes, A novel role for the late-onset Alzheimer's disease (LOAD)-associated protein Bin1 in regulating postsynaptic trafficking and glutamatergic signaling, Mol. Psychiatry 25 (2020) 2000–2016, https://doi.org/10.1038/s41380-019-0407-3.

[32] Y. Voskobiynyk, J.R. Roth, J.N. Cochran, T. Rush, N.V.N. Carullo, J.S. Mesina, M. Waqas, R.M. Vollmer, J.J. Day, L.L. McMahon, E.D. Roberson, Alzheimer's disease risk gene BIN1 induces Tau-dependent network hyperexcitability, Elife 9 (2020) 1–25, https://doi.org/10.7554/eLife.57354.

[33] F.-F. Zeng, J. Liu, H. He, X.-P. Gao, M.-Q. Liao, X.-X. Yu, Y.-H. Liu, S. Zhu, C.-X. Jing, Association of PICALM gene polymorphisms with Alzheimer's disease: evidence from an updated meta-analysis, Curr. Alzheimer Res. 16 (2020) 1196–1205, https://doi.org/10.2174/1567205016666190805165607.

[34] R.S. Petralia, Y.X. Wang, F.E. Indig, I. Bushlin, F. Wu, M.P. Mattson, P.J. Yao, Reduction of AP180 and CALM produces defects in synaptic vesicle size and density, Neuro Mol. Med. 15 (2013) 49–60, https://doi.org/10.1007/s12017-012-8194-x.

[35] S.J. Koo, S. Markovic, D. Puchkov, C.C. Mahrenholz, F. Beceren-Braun, T. Maritzen, J. Dernedde, R. Volkmer, H. Oschkinat, V. Haucke, SNARE motif-mediated sorting of synaptobrevin by the endocytic adaptors clathrin assembly lymphoid myeloid leukemia (CALM) and AP180 at synapses, Proc. Natl. Acad. Sci. USA 108 (2011) 13540–13545, https://doi.org/10.1073/pnas.1107067108.

[36] Y. Yu, T. Niccoli, Z. Ren, N.S. Woodling, B. Aleyakpo, G. Szabadkai, L. Partridge, PICALM rescues glutamatergic neurotransmission, behavioural function and survival in a Drosophila model of Aβ42 toxicity, Hum. Mol. Genet. 29 (2020) 2420–2434, https://doi.org/10.1093/hmg/ddaa125.

[37] R.I. Johnson, M.J. Seppa, R.L. Cagan, The Drosophila CD2AP/CIN85 orthologue Cindr regulates junctions and cytoskeleton dynamics during tissue patterning, J. Cell Biol. 180 (2008) 1191–1204, https://doi.org/10.1083/jcb.200706108.

[38] D.K. Lynch, S.C. Winata, R.J. Lyons, W.E. Hughes, G.M. Lehrbach, V. Wasinger, G. Corthals, S. Cordwell, R.J. Daly, A cortactin-CD2-associated protein (CD2AP) complex provides a novel link between epidermal growth factor receptor endocytosis and the actin cytoskeleton, J. Biol. Chem. 278 (2003) 21805–21813, https://doi.org/10.1074/jbc.M211407200.

[39] J.N. Cochran, T. Rush, S.C. Buckingham, E.D. Roberson, The Alzheimer's disease risk factor CD2AP maintains blood–brain barrier integrity, Hum. Mol. Genet. 24 (2015) 6667–6674, https://doi.org/10.1093/hmg/ddv371.

[40] M. Vandal, C. Gunn, A. Institoris, P. Bourassa, R.C. Mishra, G. Peringod, C. Belzil, Y. Jiang, L. Reveret, C. Tremblay, M. Hashem, W. Nicola, J. Körbelin, J.F. Dunn, A.P. Braun, D.A. Bennett, G.R.J. Gordon, F. Calon, M. Dang Nguyen, Deregulation of brain endothelial CD2AP in Alzheimer's disease impairs Reelin-mediated neurovascular coupling, (n.d.). https://doi.org/10.1101/2020.12.10.419598.

[41] B.J. Harrison, B. Venkat, J.L. Lamb, T.H. Hutson, C. Drury, K.K. Rau, M.B. Bunge, L.M. Mendell, F.H. Gage, R.D. Johnson, C.E. Hill, E.C. Rouchka, L.D.F. Moon, J.C. Petruska, The adaptor protein CD2AP is a coordinator of neurotrophin signaling-mediated axon arbor plasticity, J. Neurosci. 36 (2016) 4259–4275, https://doi.org/10.1523/JNEUROSCI.2423-15.2016.

[42] S.A. Ojelade, T.V. Lee, N. Giagtzoglou, L. Yu, B. Ugur, Y. Li, L. Duraine, Z. Zuo, V. Petyuk, P.L. De Jager, D.A. Bennett, B.R. Arenkiel, H.J. Bellen, J.M. Shulman, cindr, the Drosophila homolog of the CD2AP Alzheimer's disease risk gene, is required for synaptic transmission and proteostasis, e5, Cell Rep. 28 (2019) 1799–1813, https://doi.org/10.1016/j.celrep.2019.07.041.

[43] Q.-Q. Tao, Y.-C. Chen, Z.-Y. Wu, The role of CD2AP in the pathogenesis of Alzheimer's disease, Aging Dis. 10 (2019) 901, https://doi.org/10.14336/AD.2018.1025.

[44] Y. Yan, A. Zhao, Y. Qui, Y. Li, R. Yan, Y. Wang, W. Xu, Y. Deng, Genetic association of FERMT2, HLA-DRB1, CD2AP, and PTK2B polymorphisms with Alzheimer's disease risk in the Southern Chinese population, Front. Aging Neurosci. 12 (2020) 1–9, https://doi.org/10.3389/fnagi.2020.00016.

[45] S. Lee, S.V. Salazar, T.O. Cox, S.M. Strittmatter, Pyk2 signaling through graf1 and rhoA GTPase is required for amyloid-β oligomer-triggered synapse loss, J. Neurosci. 39 (2019) 1910–1929, https://doi.org/10.1523/JNEUROSCI.2983-18.2018.

[46] T. Kim, G.S. Vidal, M. Djurisic, C.M. William, M.E. Birnbaum, K.C. Garcia, B.T. Hyman, C.J. Shatz, Human LilrB2 Is a β-amyloid receptor and its murine PirB regulates synaptic plasticity in an Alzheimer's model, Science 80 (341) (2013) 1399–1404, https://doi.org/10.1126/science.1242077.

[47] J.A. Bernard-Trifilo, E.A. Kramár, R. Torp, C.Y. Lin, E.A. Pineda, G. Lynch, C.M. Gall, Integrin signaling cascades are operational in adult hippocampal synapses and modulate NMDA receptor physiology, J. Neurochem. 93 (2005) 834–849, https://doi.org/10.1111/j.1471-4159.2005.03062.x.

[48] M. Bjarnadottir, D.L. Misner, S. Haverfield-Gross, S. Bruun, V.G. Helgason, H. Stefansson, A. Sigmundsson, D.R. Firth, B. Nielsen, R. Stefansdottir, T.J. Novak, K. Stefansson, M.E. Gurney, T. Andresson, Neuregulin1 (NRG1) signaling through fyn modulates NMDA receptor phosphorylation: differential synaptic function in NRG1+/- knock-outs compared with wild-type mice, J. Neurosci. 27 (2007) 4519–4529, https://doi.org/10.1523/JNEUROSCI.4314-06.2007.

[49] G.K. Seabold, A. Burette, I.A. Lim, R.J. Weinberg, J.W. Hell, Interaction of the tyrosine kinase Pyk2 with the N-methyl-D-aspartate receptor complex via the Src homology 3 domains of PSD-95 and SAP102, J. Biol. Chem. 278 (2003) 15040–15048, https://doi.org/10.1074/jbc.M212825200.

[50] C. Zhao, C.P. Du, Y. Peng, Z. Xu, C.C. Sun, Y. Liu, X.Y. Hou, The upregulation of NR2A-containing N-methyl-d-aspartate receptor function by tyrosine phosphorylation of postsynaptic density 95 via facilitating Src/proline-rich tyrosine kinase 2 activation, Mol. Neurobiol. 51 (2015) 500–511, https://doi.org/10.1007/s12035-014-8796-4.

[51] H. Hsin, M.J. Kim, C.F. Wang, M. Sheng, Proline-rich tyrosine kinase 2 regulates hippocampal long-term depression, J. Neurosci. 30 (2010) 11983–11993, https://doi.org/10.1523/JNEUROSCI.1029-10.2010.

[52] B. de Pins, T. Mendes, A. Giralt, J.-A. Girault, The non-receptor tyrosine kinase Pyk2 in brain function and neurological and psychiatric diseases, Front. Synaptic Neurosci. 13 (2021) 1–27, https://doi.org/10.3389/fnsyn.2021.749001.

[53] V. Mastrolia, O. al Massadi, B. de Pins, J.A. Girault, Pyk2 in dorsal hippocampus plays a selective role in spatial memory and synaptic plasticity, Sci. Rep. 11 (2021) 1–13, https://doi.org/10.1038/s41598-021-95813-x.

[54] S.V. Salazar, T.O. Cox, S. Lee, A.H. Brody, A.S. Chyung, L.T. Haas, S.M. Strittmatter, Alzheimer's disease risk factor Pyk2 mediates amyloid-β-induced synaptic dysfunction and loss, J. Neurosci. 39 (2019) 758–772, https://doi.org/10.1523/JNEUROSCI.1873-18.2018.

[55] J. Syken, T. GrandPre, P.O. Kanold, C.J. Shatz, PirB restricts ocular-dominance plasticity in visual cortex, Science 313 (80) (2006) 1795–1800, https://doi.org/10.1126/science.1128232.

[56] M. Djurisic, B.K. Brott, N.L. Saw, M. Shamloo, C.J. Shatz, Activity-dependent modulation of hippocampal synaptic plasticity via PirB and endocannabinoids, Mol. Psychiatry 24 (2019) 1206–1219, https://doi.org/10.1038/s41380-018-0034-4.

[57] M. Djurisic, G.S. Vidal, M. Mann, A. Aharon, T. Kim, A. Ferrao Santos, Y. Zuo, M. Hubener, C.J. Shatz, PirB regulates a structural substrate for cortical plasticity, Proc. Natl. Acad. Sci. USA 110 (2013) 20771–20776, https://doi.org/10.1073/pnas.1321092110.

[58] G.S. Vidal, M. Djurisic, K. Brown, R.W. Sapp, C.J. Shatz, Cell-autonomous regulation of dendritic spine density by PirB, ENeuro 3 (2016), https://doi.org/10.1523/ENEURO.0089-16.2016.

[59] T. Kim, G.S. Vidal, M. Djurisic, C.M. William, M.E. Birnbaum, K.C. Garcia, B.T. Hyman, C.J. Shatz, Human LilrB2 is a β-amyloid receptor and its murine homolog PirB regulates synaptic plasticity in an Alzheimer's model, Science 341 (80) (2013) 1399–1404, https://doi.org/10.1126/science.1242077.

[60] D.P. Wightman, I.E. Jansen, J.E. Savage, A.A. Shadrin, S. Bahrami, D. Holland, A. Rongve, S. Børte, B.S. Winsvold, O.K. Drange, A.E. Martinsen, A.H. Skogholt, C. Willer, G. Bråthen, I. Bosnes, J.B. Nielsen, L.G. Fritsche, L.F. Thomas, L.M. Pedersen, M.E. Gabrielsen, M.B. Johnsen, T.W. Meisingset, W. Zhou, P. Proitsi, A. Hodges, R. Dobson, L. Velayudhan, M. Agee, S. Aslibekyan, E. Babalola, R.K. Bell, J. Bielenberg, K. Bryc, E. Bullis, B. Cameron, D. Coker, G.C. Partida, D. Dhamija, S. Das, S.L. Elson, T. Filshtein, K. Fletez-Brant, P. Fontanillas, W. Freyman, P.M. Gandhi, B. Hicks, D.A. Hinds, K.E. Huber, E.M. Jewett, Y. Jiang, A. Kleinman, K. Kukar, V. Lane, K.H. Lin, M. Lowe, M.K. Luff, J.C. McCreight, M.H. McIntyre, K.F. McManus, S.J. Micheletti, M. Moreno, J.L. Mountain, S.V. Mozaffari, P. Nandakumar, E.S. Noblin, J. O'Connell, A.A. Petrakovitz, G.D. Poznik, M. Schumacher, A.J. Shastri, J.F. Shelton, J. Shi, S. Shringarpure, C. Tian, V. Tran, J.Y. Tung, X. Wang, W. Wang, C.H. Weldon, P. Wilton, J.M. Sealock, L.K. Davis, N.L. Pedersen, C.A. Reynolds, I.K. Karlsson, S. Magnusson, H. Stefansson, S. Thordardottir, P.V. Jonsson, J. Snaedal, A. Zettergren, I. Skoog, S. Kern, M. Waern, H. Zetterberg, K. Blennow, E. Stordal, K. Hveem, J.A. Zwart, L. Athanasiu, P. Selnes, I. Saltvedt, S.B. Sando, I. Ulstein, S. Djurovic, T. Fladby, D. Aarsland, G. Selbæk, S. Ripke, K. Stefansson, O.A. Andreassen, D. Posthuma, A genome-wide association study with 1,126,563 individuals identifies new risk loci for Alzheimer's disease, Nat. Genet. 53 (2021) 1276–1282, https://doi.org/10.1038/s41588-021-00921-z.

[61] F. Tosetti, M. Alessio, A. Poggi, M.R. Zocchi, Adam10 site-dependent biology: keeping control of a pervasive protease, Int. J. Mol. Sci. 22 (2021), https://doi.org/10.3390/ijms22094969.

[62] J. Suh, S.H. Choi, D.M. Romano, M.A. Gannon, A.N. Lesinski, D.Y. Kim, R.E. Tanzi, ADAM10 missense mutations potentiate β-amyloid accumulation by impairing prodomain chaperone function, Neuron 80 (2013) 385–401, https://doi.org/10.1016/j.neuron.2013.08.035.

[63] A. Okbay, J.P. Beauchamp, M.A. Fontana, J.J. Lee, T.H. Pers, C.A. Rietveld, P. Turley, G.B. Chen, V. Emilsson, S.F.W. Meddens, S. Oskarsson, J.K. Pickrell, K. Thom, P. Timshel, R. De Vlaming, A. Abdellaoui, T.S. Ahluwalia, J. Bacelis, C. Baumbach, G. Bjornsdottir, J.H. Brandsma, M. Pina Concas, J. Derringer, N.A. Furlotte, T.E. Galesloot, G. Girotto, R. Gupta, L.M. Hall, S.E. Harris, E. Hofer, M. Horikoshi, J.E. Huffman, K. Kaasik, I.P. Kalafati, R. Karlsson, A. Kong, J. Lahti, S.J. Van Der Lee, C. Deleeuw, P.A. Lind, K.O. Lindgren, T. Liu, M. Mangino, J. Marten, E. Mihailov, M.B. Miller, P.J. Van Der Most, C. Oldmeadow, A. Payton, N. Pervjakova, W.J. Peyrot, Y. Qian, O. Raitakari, R. Rueedi, E. Salvi, B. Schmidt, K.E. Schraut, J. Shi, A.V. Smith, R.A. Poot, B. Pourcain St, A. Teumer, G. Thorleifsson, N. Verweij, D. Vuckovic, J. Wellmann, H.J. Westra, J. Yang, W. Zhao, Z. Zhu, B.Z. Alizadeh, N. Amin, A. Bakshi, S.E. Baumeister, G. Biino, K. Bønnelykke, P.A. Boyle, H. Campbell, F.P. Cappuccio, G. Davies, J.E. De Neve, P. Deloukas, I. Demuth, J. Ding, P. Eibich, L. Eisele, N. Eklund, D.M. Evans, J.D. Faul, M.F. Feitosa, A.J. Forstner, I. Gandin, B. Gunnarsson, B.V. Halldórsson, T.B. Harris, E.G. Holliday, A.C. Heath, L.J. Hocking, G. Homuth, M.A. Horan, J.J. Hottenga, P.L. De Jager, P.K. Joshi, A. Jugessur, M.A. Kaakinen, M. Kähönen, S. Kanoni, L. Keltigangas-Järvinen, L.A.L.M. Kiemeney, I. Kolcic, S. Koskinen, A.T. Kraja, M. Kroh, Z. Kutalik, A. Latvala, L.J. Launer, M.P. Lebreton, D.F. Levinson, P. Lichtenstein, P. Lichtner, D.C.M. Liewald, A. Loukola, P.A. Madden, R. Mägi, T. Mäki-Opas, R.E. Marioni, P. Marques-Vidal, G.A. Meddens, G. Mcmahon, C. Meisinger, T. Meitinger, Y. Milaneschi, L. Milani, G.W. Montgomery, R. Myhre, C.P. Nelson, D.R. Nyholt, W.E.R. Ollier, A. Palotie, L. Paternoster, N.L. Pedersen, K.E. Petrovic, D.J. Porteous, K. Raïkkönen, S.M. Ring, A. Robino, O. Rostapshova, I. Rudan, A. Rustichini, V. Salomaa, A.R. Sanders, A.P. Sarin, H. Schmidt, R.J. Scott, B.H. Smith, J.A. Smith, J.A. Staessen, E. Steinhagen-Thiessen, K. Strauch, A. Terracciano, M.D. Tobin, S. Ulivi, S. Vaccargiu, L. Quaye, F.J.A. Van Rooij, C. Venturini, A.A.E. Vinkhuyzen, U. Völker, H. Völzke, J.M. Vonk, D. Vozzi, J. Waage, E.B. Ware, G. Willemsen, J.R. Attia, D.A. Bennett, K. Berger, L. Bertram, H. Bisgaard, D.I. Boomsma, I.B. Borecki, U. Bültmann, C.F. Chabris, F. Cucca, D. Cusi, I.J. Deary, G.V. Dedoussis, C.M. Van Duijn, J.G. Eriksson, B. Franke, L. Franke, P. Gasparini, P.V. Gejman, C. Gieger, H.J. Grabe, J. Gratten, P.J.F. Groenen, V. Gudnason,

P. Van Der Harst, C. Hayward, D.A. Hinds, W. Hoffmann, E. Hyppönen, W. G. Iacono, B. Jacobsson, M.R. Järvelin, K.H. Jöckel, J. Kaprio, S.L.R. Kardia, T. Lehtimäki, S.F. Lehrer, P.K.E. Magnusson, N.G. Martin, M. Mcgue, A. Metspalu, N. Pendleton, B.W.J.H. Penninx, M. Perola, N. Pirastu, M. Pirastu, O. Polasek, D. Posthuma, C. Power, M.A. Province, N.J. Samani, D. Schlessinger, R. Schmidt, T.I.A. Sørensen, T.D. Spector, K. Stefansson, U. Thorsteinsdottir, A.R. Thurik, N. J. Timpson, H. Tiemeier, J.Y. Tung, A.G. Uitterlinden, V. Vitart, P. Vollenweider, D.R. Weir, J.F. Wilson, A.F. Wright, D.C. Conley, R.F. Krueger, G. Davey Smith, A. Hofman, D.I. Laibson, S.E. Medland, M.N. Meyer, J. Yang, M. Johannesson, P. M. Visscher, T. Esko, P.D. Koellinger, D. Cesarini, D.J. Benjamin, Genome-wide association study identifies 74 loci associated with educational attainment, Nature 533 (2016) 539–542, https://doi.org/10.1038/nature17671.

[64] R.E. Marioni, S.E. Harris, Q. Zhang, A.F. McRae, S.P. Hagenaars, W.D. Hill, G. Davies, C.W. Ritchie, C.R. Gale, J.M. Starr, A.M. Goate, D.J. Porteous, J. Yang, K.L. Evans, I.J. Deary, N.R. Wray, P.M. Visscher, GWAS on family history of Alzheimer's disease, Transl. Psychiatry 8 (2018) 0–6, https://doi.org/10.1038/s41398-018-0150-6.

[65] J. Prox, C. Bernreuther, H. Altmeppen, J. Grende, M. Glatze, R. D'Hooge, S. Stroobants, T. Ahmed, D. Balschun, M. Willem, S. Lammich, D. Isbrandt, M. Schweizer, K. Horré, B. De Strooper, P. Saftig, Postnatal disruption of the disintegrin/metalloproteinase ADAM10 in brain causes epileptic seizures, learning deficits, altered spine morphology, and defective synaptic functions, J. Neurosci. 33 (2013) 12915–12928, https://doi.org/10.1523/JNEUROSCI.5910-12.2013.

[66] P.-H. Kuhn, A.V. Colombo, B. Schusser, D. Dreymueller, S. Wetzel, U. Schepers, J. Herber, A. Ludwig, E. Kremmer, D. Montag, U. Müller, M. Schweizer, P. Saftig, S. Bräse, S.F. Lichtenthaler, Systematic substrate identification indicates a central role for the metalloprotease ADAM10 in axon targeting and synapse function, Elife 5 (2016) 1–29, https://doi.org/10.7554/elife.12748.

[67] E. Montagna, M.M. Dorostkar, J. Herms, The role of APP in structural spine plasticity, Front. Mol. Neurosci. 10 (2017) 1–7, https://doi.org/10.3389/fnmol.2017.00136.

[68] E. Pasciuto, T. Ahmed, T. Wahle, F. Gardoni, L. D'Andrea, L. Pacini, S. Jacquemont, T. Tassone, D. Balschun, C.G. Dotti, Z. Callaerts-Vegh, R. D'Hooge, U.C. Müller, M. Di Luca, B. De Strooper, C. Bagni, Dysregulated ADAM10-mediated processing of APP during a critical time window leads to synaptic deficits in fragile X syndrome, Neuron 87 (2015) 382–398, https://doi.org/10.1016/j.neuron.2015.06.032.

[69] M. Malinverno, M. Carta, R. Epis, E. Marcello, C. Verpelli, F. Cattabeni, C. Sala, C. Mulle, M. Di Luca, F. Gardoni, Synaptic localization and activity of ADAM10 regulate excitatory synapses through N-cadherin cleavage, J. Neurosci. 30 (2010) 16343–16355, https://doi.org/10.1523/JNEUROSCI.1984-10.2010.

[70] A.M. Gomez, L. Traunmüller, P. Scheiffele, Neurexins: molecular codes for shaping neuronal synapses, Nat. Rev. Neurosci. 22 (2021) 137–151, https://doi.org/10.1038/s41583-020-00415-7.

[71] J.H. Trotter, J. Hao, S. Maxeiner, T. Tsetsenis, Z. Liu, X. Zhuang, T.C. Südhof, Synaptic neurexin-1 assembles into dynamically regulated active zone nanoclusters, J. Cell Biol. 218 (2019) 2677–2698, https://doi.org/10.1083/JCB.201812076.

[72] K. Suzuki, Y. Hayashi, S. Nakahara, H. Kumazaki, J. Prox, K. Horiuchi, M. Zeng, S. Tanimura, Y. Nishiyama, S. Osawa, A. Sehara-Fujisawa, P. Saftig, S. Yokoshima, T. Fukuyama, N. Matsuki, R. Koyama, T. Tomita, T. Iwatsubo, Activity-dependent proteolytic cleavage of neuroligin-1, Neuron 76 (2012) 410–422, https://doi.org/10.1016/j.neuron.2012.10.003.

[73] G. Gunner, L. Cheadle, K.M. Johnson, P. Ayata, A. Badimon, E. Mondo, M. A. Nagy, L. Liu, S.M. Bemiller, K.W. Kim, S.A. Lira, B.T. Lamb, A.R. Tapper, R. M. Ransohoff, M.E. Greenberg, A. Schaefer, D.P. Schafer, Sensory lesioning induces microglial synapse elimination via ADAM10 and fractalkine signaling, Nat. Neurosci. 22 (2019) 1075–1088, https://doi.org/10.1038/s41593-019-0419-y.

[74] E. Marcello, C. Saraceno, S. Musardo, H. Vara, A.G. De La Fuente, S. Pelucchi, D. Di Marino, B. Borroni, A. Tramontano, I. Pérez-Otaño, A. Padovani, M. Giustetto, F. Gardoni, M. Di Luca, Endocytosis of synaptic ADAM10 in neuronal plasticity and Alzheimer's disease, J. Clin. Investig. 123 (2013) 2523–2538, https://doi.org/10.1172/JCI65401.

[75] E. Marcello, F. Gardoni, D. Mauceri, S. Romorini, A. Jeromin, R. Epis, B. Borroni, F. Cattabeni, C. Sala, A. Padovani, M. Di Luca, Synapse-associated protein-97 mediates α-secretase ADAM10 trafficking and promotes its activity, J. Neurosci. 27 (2007) 1682–1691, https://doi.org/10.1523/JNEUROSCI.3439-06.2007.

[76] E.M. Hwang, S.K. Kim, J.H. Sohn, J.Y. Lee, Y. Kim, Y.S. Kim, I. Mook-Jung, Furin is an endogenous regulator of α-secretase associated APP processing, Biochem. Biophys. Res. Commun. 349 (2006) 654–659, https://doi.org/10.1016/j.bbrc.2006.08.077.

[77] E. Eschenbrenner, S. Jouannet, D. Clay, J. Chaker, C. Boucheix, C. Brou, M. G. Tomlinson, S. Charrin, E. Rubinstein, TspanC8 tetraspanins differentially regulate ADAM10 endocytosis and half-life, Life Sci. Alliance 3 (2020) 1–19, https://doi.org/10.26508/lsa.201900444.

[78] J. Schwartzentruber, S. Cooper, J.Z. Liu, I. Barrio-Hernandez, E. Bello, N. Kumasaka, A.M.H. Young, R.J.M. Franklin, T. Johnson, K. Estrada, D. J. Gaffney, P. Beltrao, A. Bassett, Genome-wide meta-analysis, fine-mapping and integrative prioritization implicate new Alzheimer's disease risk genes, Nat. Genet. 53 (2021) 392–402, https://doi.org/10.1038/s41588-020-00776-w.

[79] G. Dallérac, J. Zapata, N. Rouach, Versatile control of synaptic circuits by astrocytes: where, when and how, Nat. Rev. Neurosci. 19 (2018) 729–743, https://doi.org/10.1038/s41583-018-0080-6.

[80] F.Y. Liew, J.P. Girard, H.R. Turnquist, Interleukin-33 in health and disease, Nat. Rev. Immunol. 16 (2016) 676–689, https://doi.org/10.1038/nri.2016.95.

[81] S. Yasuoka, J. Kawanokuchi, B. Parajuli, S. Jin, Y. Doi, M. Noda, Y. Sonobe, H. Takeuchi, T. Mizuno, A. Suzumura, Production and functions of IL-33 in the central nervous system, Brain Res. (2011), https://doi.org/10.1016/j.brainres.2011.02.045.

[82] Y. Wang, W.Y. Fu, K. Cheung, K.W. Hung, C. Chen, H. Geng, W.H. Yung, J.Y. Qu, A.K.Y. Fu, N.Y. Ip, Astrocyte-secreted IL-33 mediates homeostatic synaptic plasticity in the adult hippocampus, Proc. Natl. Acad. Sci. USA 118 (2021) 1–12, https://doi.org/10.1073/pnas.2020810118.

[83] P.T. Nguyen, L.C. Dorman, S. Pan, I.D. Vainchtein, R.T. Han, H. Nakao-Inoue, S. E. Taloma, J.J. Barron, A.B. Molofsky, M.A. Kheirbek, A.V. Molofsky, Microglial remodeling of the extracellular matrix promotes synapse plasticity, Cell 182 (388–403) (2020), e15, https://doi.org/10.1016/j.cell.2020.05.050.

[84] T. Nishizaki, IL-33 acts to express schaffer collateral/CA1 LTP and regulate learning and memory by targeting MyD88, Neural Plast. (2017) (2017), https://doi.org/10.1155/2017/2531453.

[85] I.D. Vainchtein, G. Chin, F.S. Cho, K.W. Kelley, J.G. Miller, E.C. Chien, S. A. Liddelow, P.T. Nguyen, H. Nakao-Inoue, L.C. Dorman, O. Akil, S. Joshita, B. A. Barres, J.T. Paz, A.B. Molofsky, A.V. Molofsky, Astrocyte-derived interleukin-33 promotes microglial synapse engulfment and neural circuit development, Science (80) (2018), https://doi.org/10.1126/science.aal3589.

[86] J. Chapuis, D. Hot, F. Hansmannel, O. Kerdraon, S. Ferreira, C. Hubans, C. A. Maurage, L. Huot, F. Bensemain, G. Laumet, A.M. Ayral, N. Fievet, J.J. Hauw, S.T. Dekosky, Y. Lemoine, T. Iwatsubo, F. Wavrant-Devrièze, J.F. Dartigues, C. Tzourio, L. Buée, F. Pasquier, C. Berr, D. Mann, C. Lendon, A. Alpérovitch, M. I. Kamboh, P. Amouyel, J.C. Lambert, Transcriptomic and genetic studies identify IL-33 as a candidate gene for Alzheimer's disease, Mol. Psychiatry 14 (2009) 1004–1016, https://doi.org/10.1038/mp.2009.10.

[87] C.-S. Liang, K.-P. Su, C.-L. Tsai, J.-T. Lee, C.-S. Chu, T.-C. Yeh, M.-W. Su, G.-Y. Lin, Y.-K. Lin, H.-T. Chu, C.-K. Tsai, F.-C. Yang, The role of interleukin-33 in patients with mild cognitive impairment and Alzheimer's disease, Alzheimers Res. Ther. 12 (2020) 86, https://doi.org/10.1186/s13195-020-00652-z.

[88] A.K.Y. Fu, K.W. Hung, M.Y.F. Yuen, X. Zhou, D.S.Y. Mak, I.C.W. Chan, T. H. Cheung, B. Zhang, W.Y. Fu, F.Y. Liew, N.Y. Ip, IL-33 ameliorates Alzheimer's disease-like pathology and cognitive decline, Proc. Natl. Acad. Sci. USA 113 (2016) E2705–E2713, https://doi.org/10.1073/pnas.1604032113.

[89] Y. Jiang, X. Zhou, H.Y. Wong, L. Ouyang, F.C.F. Ip, V.M.N. Chau, S.-F. Lau, W. Wu, D.Y.K. Wong, H. Seo, W.-Y. Fu, N.C.H. Lai, Y. Chen, Y. Chen, E.P.S. Tong, M.W. Weiner, P. Aisen, R. Petersen, C.R. Jack, W. Jagust, J.Q. Trojanowski, A. W. Toga, L. Beckett, R.C. Green, A.J. Saykin, J. Morris, L.M. Shaw, Z. Khachaturian, G. Sorensen, L. Kuller, M. Raichle, S. Paul, P. Davies, H. Fillit, F. Hefti, D. Holtzman, M.M. Mesulam, W. Potter, P. Snyder, A. Schwartz, T. Montine, R.G. Thomas, M. Donohue, S. Walter, D. Gessert, T. Sather, G. Jiminez, D. Harvey, M. Bernstein, P. Thompson, N. Schuff, B. Borowski, J. Gunter, M. Senjem, P. Vemuri, D. Jones, K. Kantarci, C. Ward, R.A. Koeppe, N. Foster, E.M. Reiman, K. Chen, C. Mathis, S. Landau, N.J. Cairns, E. Householder, L. Taylor-Reinwald, V. Lee, M. Korecka, M. Figurski, K. Crawford, S. Neu, T.M. Foroud, S.G. Potkin, L. Shen, K. Faber, S. Kim, K. Nho, L. Thal, N. Buckholtz, M. Albert, R. Frank, J. Hsiao, J. Kaye, J. Quinn, B. Lind, R. Carter, S. Dolen, L.S. Schneider, S. Pawluczyk, M. Beccera, L. Teodoro, B.M. Spann, J. Brewer, H. Vanderswag, A. Fleisher, J.L. Heidebrink, J.L. Lord, S.S. Mason, C. S. Albers, D. Knopman, K. Johnson, R.S. Doody, J. Villanueva-Meyer, M. Chowdhury, S. Rountree, M. Dang, Y. Stern, L.S. Honig, K.L. Bell, B. Ances, M. Carroll, S. Leon, M.A. Mintun, S. Schneider, A. Oliver, D. Marson, R. Griffith, D. Clark, D. Geldmacher, J. Brockington, E. Roberson, H. Grossman, E. Mitsis, L. de Toledo-Morrell, R.C. Shah, R. Duara, D. Varon, M.T. Greig, P. Roberts, C. Onyike, D. D'Agostino, S. Kielb, J.E. Galvin, B. Cerbone, C.A. Michel, H. Rusinek, M.J. de Leon, L. Glodzik, S. De Santi, P.M. Doraiswamy, J.R. Petrella, T.Z. Wong, S.E. Arnold, J.H. Karlawish, D. Wolk, C.D. Smith, G. Jicha, P. Hardy, P. Sinha, E. Oates, G. Conrad, O.L. Lopez, M. Oakley, D.M. Simpson, A. P. Porsteinsson, B.S. Goldstein, K. Martin, K.M. Makino, M.S. Ismail, C. Brand, R. A. Mulnard, G. Thai, C. McAdams-Ortiz, K. Womack, D. Mathews, M. Quiceno, R. Diaz-Arrastia, R. King, M. Weiner, K. Martin-Cook, M. DeVous, A.I. Levey, J. J. Lah, J.S. Cellar, J.M. Burns, H.S. Anderson, R.H. Swerdlow, L. Apostolova, K. Tingus, E. Woo, D.H.S. Silverman, P.H. Lu, G. Bartzokis, N.R. Graff-Radford, F. Parfitt, T. Kendall, H. Johnson, M.R. Farlow, A.M. Hake, B.R. Matthews, S. Herring, C. Hunt, C.H. van Dyck, R.E. Carson, M.G. MacAvoy, H. Chertkow, H. Bergman, C. Hosein, G.-Y.R. Hsiung, H. Feldman, B. Mudge, M. Assaly, C. Bernick, D. Munic, A. Kertesz, J. Rogers, D. Trost, D. Kerwin, K. Lipowski, C.-K. Wu, N. Johnson, C. Sadowsky, W. Martinez, T. Villena, R.S. Turner, K. Johnson, B. Reynolds, R.A. Sperling, K.A. Johnson, G. Marshall, M. Frey, B. Lane, A. Rosen, J. Tinklenberg, M.N. Sabbagh, C.M. Belden, S.A. Jacobson, S. A. Sirrel, N. Kowall, R. Killiany, A.E. Budson, A. Norbash, P.L. Johnson, J. Allard, A. Lerner, P. Ogrocki, L. Hudson, E. Fletcher, O. Carmichael, J. Olichney, C. DeCarli, S. Kittur, M. Borrie, T.-Y. Lee, R. Bartha, S. Johnson, S. Asthana, C. M. Carlsson, A. Preda, D. Nguyen, P. Tariot, S. Reeder, V. Bates, H. Capote, M. Rainka, D.W. Scharre, M. Kataki, A. Adeli, E.A. Zimmerman, D. Celmins, A. D. Brown, G.D. Pearlson, K. Blank, K. Anderson, R.B. Santulli, T.J. Kitzmiller, E. S. Schwartz, K.M. Sink, J.D. Williamson, P. Garg, F. Watkins, B.R. Ott, H. Querfurth, G. Tremont, S. Salloway, P. Malloy, S. Correia, H.J. Rosen, B. L. Miller, J. Mintzer, K. Spicer, D. Bachman, S. Pasternak, I. Rachinsky, D. Drost, N. Pomara, R. Hernando, A. Sarrael, S.K. Schultz, L.L.B. Ponto, H. Shim, K. E. Smith, N. Relkin, G. Chaing, L. Raudin, A. Smith, K. Fargher, B.A. Raj, T. Neylan, J. Grafman, M. Davis, R. Morrison, J. Hayes, S. Finley, K. Friedl, D. Fleischman, K. Arfanakis, O. James, D. Massoglia, J.J. Fruehling, S. Harding, E.

R. Peskind, E.C. Petrie, G. Li, J.A. Yesavage, J.L. Taylor, A.J. Furst, V.C.T. Mok, T.C.Y. Kwok, K.Y. Mok, M. Shoai, B. Lehallier, P.M. Losada, E. O'Brien, T. Porter, S.M. Laws, J. Hardy, T. Wyss-Coray, C.L. Masters, A.K.Y. Fu, N.Y. Ip, An IL1RL1 genetic variant lowers soluble ST2 levels and the risk effects of APOE-ε4 in female patients with Alzheimer's disease, Nat. Aging 2 (2022) 616–634, https://doi.org/10.1038/s43587-022-00241-9.

[90] X. Zhou, A.K.Y. Fu, N.Y. Ip, APOE signaling in neurodegenerative diseases: an integrative approach targeting APOE coding and noncoding variants for disease intervention, Curr. Opin. Neurobiol. 69 (2021) 58–67, https://doi.org/10.1016/j.conb.2021.02.001.

[91] Y. Yamazaki, N. Zhao, T.R. Caulfield, C.-C. Liu, G. Bu, Apolipoprotein E and Alzheimer disease: pathobiology and targeting strategies, Nat. Rev. Neurol. 15 (2019) 501–518, https://doi.org/10.1038/s41582-019-0228-7.

[92] R.M. Koffie, T. Hashimoto, H.C. Tai, K.R. Kay, A. Serrano-Pozo, D. Joyner, S. Hou, K.J. Kopeikina, M.P. Frosch, V.M. Lee, D.M. Holtzman, B.T. Hyman, T.L. Spires-Jones, Apolipoprotein E4 effects in Alzheimer's disease are mediated by synaptotoxic oligomeric amyloid-β, Brain 135 (2012) 2155–2168, https://doi.org/10.1093/brain/aws127.

[93] C.T. Lewandowski, J. Maldonado Weng, M.J. LaDu, Alzheimer's disease pathology in APOE transgenic mouse models: the Who, What, When, Where, Why, and How, Neurobiol. Dis. 139 (2020), 104811, https://doi.org/10.1016/j.nbd.2020.104811.

[94] J. Kim, H. Yoon, J. Basak, J. Kim, Apolipoprotein E in synaptic plasticity and alzheimer's disease: potential cellular and molecular mechanisms, Mol. Cells 37 (2014) 833–840, https://doi.org/10.14348/molcells.2014.0248.

[95] Y.T. Lin, J. Seo, F. Gao, H.M. Feldman, H.L. Wen, J. Penney, H.P. Cam, E. Gjoneska, W.K. Raja, J. Cheng, R. Rueda, O. Kritskiy, F. Abdurrob, Z. Peng, B. Milo, C.J. Yu, S. Elmsaouri, D. Dey, T. Ko, B.A. Yankner, L.H. Tsai, A.P.O.E.4 Causes Widespread, Molecular and cellular alterations associated with Alzheimer's disease phenotypes in human iPSC-derived brain cell types, e7, Neuron 98 (2018) 1141–1154, https://doi.org/10.1016/j.neuron.2018.05.008.

[96] K. Meyer, H.M. Feldman, T. Lu, D. Drake, E.T. Lim, K.H. Ling, N.A. Bishop, Y. Pan, J. Seo, Y.T. Lin, S.C. Su, G.M. Church, L.H. Tsai, B.A. Yankner, REST and neural gene network dysregulation in iPSC models of Alzheimer's disease, e9, Cell Rep. 26 (2019) 1112–1127, https://doi.org/10.1016/j.celrep.2019.01.023.

[97] Y.W.A. Huang, B. Zhou, A.M. Nabet, M. Wernig, T.C. Südhof, Differential signaling mediated by ApoE2, ApoE3, and ApoE4 in human neurons parallels Alzheimer's disease risk, J. Neurosci. 39 (2019) 7408–7427, https://doi.org/10.1523/JNEUROSCI.2994-18.2019.

[98] J. Zhao, Y. Fu, Y. Yamazaki, Y. Ren, M.D. Davis, C.C. Liu, W. Lu, X. Wang, K. Chen, Y. Cherukuri, L. Jia, Y.A. Martens, L. Job, F. Shue, T.T. Nguyen, S.G. Younkin, N.R. Graff-Radford, Z.K. Wszolek, D.A. Brafman, Y.W. Asmann, N. Ertekin-Taner, T. Kanekiyo, G. Bu, APOE4 exacerbates synapse loss and neurodegeneration in Alzheimer's disease patient iPSC-derived cerebral organoids, Nat. Commun. 11 (2020), https://doi.org/10.1038/s41467-020-19264-0.

[99] S.B. Dumanis, A.M. Dibattista, M. Miessau, C.E.H. Moussa, G.W. Rebeck, APOE genotype affects the pre-synaptic compartment of glutamatergic nerve terminals, J. Neurochem. 124 (2013) 4–14, https://doi.org/10.1111/j.1471-4159.2012.07908.x.

[100] Y. Chen, M.S. Durakoglugil, X. Xian, J. Herz, ApoE4 reduces glutamate receptor function and synaptic plasticity by selectively impairing ApoE receptor recycling, Proc. Natl. Acad. Sci. USA 107 (2010) 12011–12016, https://doi.org/10.1073/pnas.0914984107.

[101] F. Qiao, X.P. Gao, L. Yuan, H.Y. Cai, J.S. Qi, Apolipoprotein E4 impairs in vivo hippocampal long-term synaptic plasticity by reducing the phosphorylation of CaMKIIα and CREB, J. Alzheimer's Dis. 41 (2014) 1165–1176, https://doi.org/10.3233/JAD-140375.

[102] X. Li, J. Zhang, D. Li, C. He, K. He, T. Xue, L. Wan, C. Zhang, Q. Liu, Astrocytic ApoE reprograms neuronal cholesterol metabolism and histone-acetylation-mediated memory, e8, Neuron 109 (2021) 957–970, https://doi.org/10.1016/j.neuron.2021.01.005.

[103] S. Ramakrishna, V. Jhaveri, S.C. Konings, S. Nawalpuri, S. Chakraborty, B. Holst, B. Schmid, G.K. Gouras, K.K. Freude, R.S. Muddashetty, APOE4 affects basal and NMDAR-mediated protein synthesis in neurons by perturbing calcium homeostasis, J. Neurosci. 41 (2021) 8686–8709, https://doi.org/10.1523/jneurosci.0435-21.2021.

[104] W.S. Chung, P.B. Verghese, C. Chakraborty, J. Joung, B.T. Hyman, J.D. Ulrich, D.M. Holtzman, B.A. Barres, Novel allele-dependent role for APOE in controlling the rate of synapse pruning by astrocytes, Proc. Natl. Acad. Sci. USA 113 (2016) 10186–10191, https://doi.org/10.1073/pnas.1609896113.

[105] C.J. Bohlen, B.A. Friedman, B. Dejanovic, M. Sheng, Microglia in brain development, homeostasis, and neurodegeneration, Annu. Rev. Genet. 53 (2019) 263–288, https://doi.org/10.1146/annurev-genet-112618-043515.

[106] L. Shi, X. Du, H. Zhou, C. Tao, Y. Liu, F. Meng, G. Wu, Y. Xiong, C. Xia, Y. Wang, G. Bi, J.N. Zhou, Cumulative effects of the ApoE genotype and gender on the synaptic proteome and oxidative stress in the mouse brain, Int. J. Neuropsychopharmacol. 17 (2014) 1863–1879, https://doi.org/10.1017/S1461145714000601.

[107] R.A. Sweet, M.L. MacDonald, C.M. Kirkwood, Y. Ding, T. Schempf, J. Jones-Laughner, J. Kofler, M.D. Ikonomovic, O.L. Lopez, M.E. Garver, N.F. Fitz, R. Koldamova, N.A. Yates, Apolipoprotein E*4 (APOE*4) genotype is associated with altered levels of glutamate signaling proteins and synaptic coexpression networks in the prefrontal cortex in mild to moderate Alzheimer disease, Mol. Cell. Proteom. 15 (2016) 2252–2262, https://doi.org/10.1074/mcp.M115.056580.

[108] L.I. Sinclair, S. Love, Effect of APOE genotype on synaptic proteins in earlier adult life, J. Alzheimer's Dis. 59 (2017) 1123–1137, https://doi.org/10.3233/JAD-170316.

[109] C. Wang, M. Xiong, M. Gratuze, X. Bao, Y. Shi, P.S. Andhey, M. Manis, C. Schroeder, Z. Yin, C. Madore, O. Butovsky, M. Artyomov, J.D. Ulrich, D.M. Holtzman, Selective removal of astrocytic APOE4 strongly protects against tau-mediated neurodegeneration and decreases synaptic phagocytosis by microglia, e7, Neuron 109 (2021) 1657–1674, https://doi.org/10.1016/j.neuron.2021.03.024.

[110] E.M. Foster, A. Dangla-Valls, S. Lovestone, E.M. Ribe, N.J. Buckley, Clusterin in Alzheimer's disease: mechanisms, genetics, and lessons from other pathologies, Front. Neurosci. 13 (2019) 1–27, https://doi.org/10.3389/fnins.2019.00164.

[111] P. Yuste-Checa, A. Bracher, F.U. Hartl, The chaperone Clusterin in neurodegeneration–friend or foe, BioEssays 44 (2022) 2100287, https://doi.org/10.1002/bies.202100287.

[112] F. Chen, D.B. Swartzlander, A. Ghosh, J.D. Fryer, B. Wang, H. Zheng, Clusterin secreted from astrocyte promotes excitatory synaptic transmission and ameliorates Alzheimer's disease neuropathology, Mol. Neurodegener. 16 (2021) 1–16, https://doi.org/10.1186/s13024-021-00426-7.

[113] T.K. Ulland, M. Colonna, TREM2 — a key player in microglial biology and Alzheimer disease, Nat. Rev. Neurol. (2018), https://doi.org/10.1038/s41582-018-0072-1.

[114] A. Deczkowska, A. Weiner, I. Amit, The physiology, pathology, and potential therapeutic applications of the TREM2 signaling pathway, Cell 181 (2020) 1207–1217, https://doi.org/10.1016/j.cell.2020.05.003.

[115] A. Deczkowska, H. Keren-Shaul, A. Weiner, M. Colonna, M. Schwartz, I. Amit, Disease-associated microglia: a universal immune sensor of neurodegeneration, Cell 173 (2018) 1073–1081, https://doi.org/10.1016/j.cell.2018.05.003.

[116] L. Sheng, M. Chen, K. Cai, Y. Song, D. Yu, H. Zhang, G. Xu, Microglial Trem2 induces synaptic impairment at early stage and prevents amyloidosis at late stage in APP/PS1 mice, FASEB J. 33 (2019) 10425–10442, https://doi.org/10.1096/fj.201900527R.

[117] F. Filipello, R. Morini, I. Corradini, V. Zerbi, A. Canzi, B. Michalski, M. Erreni, M. Markicevic, C. Starvaggi-Cucuzza, K. Otero, L. Piccio, F. Cignarella, F. Perrucci, M. Tamborini, M. Genua, L. Rajendran, E. Menna, S. Vetrano, M. Fahnestock, R.C. Paolicelli, M. Matteoli, The microglial innate immune receptor TREM2 is required for synapse elimination and normal brain connectivity, e8, Immunity 48 (2018) 979–991, https://doi.org/10.1016/j.immuni.2018.04.016.

[118] C.Y.D. Lee, A. Daggett, X. Gu, L.L. Jiang, P. Langfelder, X. Li, N. Wang, Y. Zhao, C.S. Park, Y. Cooper, I. Ferando, I. Mody, G. Coppola, H. Xu, X.W. Yang, Elevated TREM2 gene dosage reprograms microglia responsivity and ameliorates pathological phenotypes in Alzheimer's disease models, e5, Neuron 97 (2018) 1032–1048, https://doi.org/10.1016/j.neuron.2018.02.002.

[119] R. Guerreiro, A. Wojtas, J. Bras, M. Carrasquillo, E. Rogaeva, E. Majounie, C. Cruchaga, C. Sassi, J.S.K. Kauwe, S. Younkin, L. Hazrati, J. Collinge, J. Pocock, T. Lashley, J. Williams, J.-C. Lambert, P. Amouyel, A. Goate, R. Rademakers, K. Morgan, J. Powell, P. George-Hyslop St., A. Singleton, J. Hardy, TREM2 variants in Alzheimer's disease, N. Engl. J. Med. 368 (2013) 117–127, https://doi.org/10.1056/nejmoa1211851.

[120] S. Ren, W. Yao, M.D. Tambini, T. Yin, K.A. Norris, L. D'adamio, Microglia TREM2R47H alzheimer-linked variant enhances excitatory transmission and reduces LTP via increased TNF-α levels, Elife 9 (2020) 1–18, https://doi.org/10.7554/eLife.57513.

[121] S. Ren, L. Breuillaud, W. Yao, T. Yin, K.A. Norris, S.P. Zehntner, L. D'Adamio, TNF-α–mediated reduction in inhibitory neurotransmission precedes sporadic Alzheimer's disease pathology in young Trem2 rats, J. Biol. Chem. 296 (2021), 100089, https://doi.org/10.1074/jbc.RA120.016395.

[122] E. Taoufik, G. Kouroupi, O. Zygogianni, R. Matsas, Synaptic dysfunction in neurodegenerative and neurodevelopmental diseases: an overview of induced pluripotent stem-cell-based disease models, Open Biol. 8 (2018), https://doi.org/10.1098/rsob.180138.