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Triplication of *Synaptojanin 1* in Alzheimer's Disease Pathology in Down Syndrome

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Abstract

Down Syndrome (DS), caused by triplication of human chromosome 21 (Hsa21) is the most common form of intellectual disability worldwide. Recent progress in healthcare has resulted in a dramatic increase in the lifespan of individuals with DS. Unfortunately, most will develop Alzheimer's disease like dementia (DS-AD) as they age. Understanding similarities and differences between DS-AD and the other forms of the disease - *i.e.,* late-onset AD (LOAD) and autosomal dominant AD (ADAD) - will provide important clues for the treatment of DS-AD. In addition to the *APP* gene that codes the precursor of the main component of amyloid plaques found in the brain of AD patients, other genes on Hsa21 are likely to contribute to disease initiation and progression. This review focuses on *SYNJ1,* coding the phosphoinositide phosphatase synaptojanin 1 (*SYNJ1*). First, we highlight the function of *SYNJ1* in the brain. We then summarize the involvement of *SYNJ1* in the different forms of AD at the genetic, transcriptomic, proteomic and neuropathology levels in humans. We further examine whether results in humans correlate with what has been described in murine and cellular models of the disease and report possible mechanistic links between *SYNJ1* and the progression of the disease. Finally, we propose a set of questions that would further strengthen and clarify the role of *SYNJ1* in the different forms of AD.

Keywords

Synaptojanin 1; Down syndrome; Alzheimer's disease; late-onset; autosomal dominant; genetic association; neuropathology; disease models; *APP*; growth factor receptor-bound protein 2 (Grb2)

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

1. INTRODUCTION

Down Syndrome (DS), caused by triplication of human chromosome 21 (Hsa21) is the most common form of intellectual disability worldwide. As they age, the vast majority of individuals with DS will go on to develop an Alzheimer's disease like dementia (DS-AD) [1]. AD is characterized by the presence in the brain of extracellular amyloid plaques and intracellular neurofibrillary tangles [2]. The main components of amyloid plaques are amyloid β (Aβ) peptides derived from the proteolytic cleavage of the amyloid precursor protein (APP). As the *APP* gene is located on Hsa21, it is straightforward to hypothesize that its triplication would play a role in the development of DS-AD. Indeed, individuals with *APP* microduplications go on to develop DS-AD [3] and those with partial trisomies without an extra copy of the *APP* gene do not [4, 5]. However, evidence indicates that Hsa21 genes other than *APP* may also be important for the development of DS-AD [6].

In this review, we focus on the potential role of the triplication of the Hsa21 gene *SYNJ1*, coding the phosphoinositide phosphatase synaptojanin 1 (*SYNJ1*) on the development of AD and DS-AD.

2. *SYNJ1* FUNCTION

Synaptojanin 1 (*SYNJ1*) is a member of the inositol-5-phosphatase family that is highly enriched at the nerve terminal [7]. It is coded by the *SYNJ1* gene on human chromosome 21q22.2 [8]. There are two naturally occurring synaptojanin 1 isoforms. The 145-kDa isoform was first discovered in 1994 as a phosphoprotein that interacts with growth factor receptor-bound protein 2 (Grb2) and participates with dynamin in synaptic vesicle endocytosis and recycling [9, 10]. Meanwhile, the 170-kDa isoform was later identified as a longer form of the protein, composed of two open reading frames instead of one [11]. Interestingly, while both isoforms are ubiquitously expressed, the 145-kDa isoform is highly enriched in the human brain - specifically localized on coated endocytic intermediates in nerve terminals - while the 170-kDa isoform is widely distributed throughout the body in non-neuronal cells [7, 11, 12].

SYNJ1 consists of three functional domains: a suppressor of actin1 (Sac1) homologous domain at its N-terminus, a 5'-phosphatase domain, and a proline-rich domain (PRD) at its C-terminus [7]. Both isoforms have this structure, although the 170-kDa isoform has a second C-terminal PRD due to the additional open reading frame [11] (Fig. 1A).

SYNJ1's PRD enables it to bind to the Scr homology 3 (SH3) domain of a variety of proteins involved in membrane trafficking and/or cellular signaling, such as Grb2, syndapin I, and BAR proteins like amphiphysin and endophilin [7, 9, 13–16] (Fig. 1A). Further, the additional C-terminal tail of the 170-kDa isoform contains binding sites for clathrin, clathrin adaptor protein complex 2 (AP2), and accessory factor Eps15 [12, 17] (Fig. 1A). Cyclin-dependent kinase 5 (Cdk5), a proline-directed serine/threonine protein kinase, is of particular interest as it plays key functions in neuronal migration, neurite outgrowth, synaptic plasticity and homeostasis, circadian clocks [18], and AD pathogenesis [18, 19]. Cdk5 regulates *SYNJ1* at synapses through phosphorylation, specifically inhibiting

its interaction with endophilin and consequently its activity (working antagonistically to calcineurin) [20].

Owing to its different functional domains and enrichment in nerve terminals, *SYNJ1* has thus been implicated in the clathrin-dependent endocytosis of synaptic vesicles (SV) and in actin cytoskeleton function [9, 12, 21] (Fig. 1B). An early study demonstrated that *SYNJ1*-deficient mice exhibited neurological defects and died shortly after birth. These mice also display an accumulation of clathrin-coated vesicles in their brains, strongly suggesting that *SYNJ1* regulates clathrin coat shedding through the dephosphorylation of phosphoinositides [22]. Further supporting *SYNJ1*'s involvement in SV endocytosis, mutations in the single synaptojanin (*unc-26*) gene of *C. elegans* also resulted in an accumulation of clathrin-coated vesicles, though additional defects were observed as well, including a depletion of SV, an accumulation of endocytic pits, a buildup of endosome-like compartments, and cytoskeletal tethering defects [23]. Likewise, the deletion of synaptojanin-like genes in yeast resulted in multiple phenotypes, such as a mislocalization of phosphatidylinositol (4,5)-bisphosphate (PtdIns(4,5)P_2) and defects in actin function/organization [24, 25]. Taken together, *SYNJ1* mediates SV endocytic membrane trafficking in a variety of crucial ways.

Notably, endophilin - an adaptor coordinating membrane curvature acquisition with fission and uncoating of clathrin-coated vesicles - and amphiphysin - proposed to coordinate membrane curvature acquisition with fission - have been identified as important interactors with distinct binding sites on the PRD of *SYNJ1*. Specifically, endophilin is required to recruit and stabilize *SYNJ1* to clathrin-coated pit necks for SV uncoating after fission, while amphiphysin likely participates in *SYNJ1* targeting as it does for dynamin [26–28]. A later study demonstrated *SYNJ1*'s role in the progression of recycling vesicles to the functional SV pool, as rapid degradation of PtdIns(4,5)P_2 by its 5'-phosphatase domain is critical for efficient SV regeneration and the recovery of normal presynaptic function after prolonged stimulation [29].

SYNJ1's PRD is not the only domain involved in SV endocytosis. As a later study has demonstrated, the dual action of both phosphatase domains is necessary for normal SV internalization and re-availability [30]. *SYNJ1*'s Sac1-homologous domain particularly controls endocytosis during weak synaptic activity, as its 3- and 4-phosphatase function participates in the polymerization/depolymerization of actin cytoskeleton [30, 31]. A study conducted on mice with a *SYNJ1* Sac1 domain mutation revealed an abnormal accumulation of clathrin-coated intermediates as well, further supporting the theory of a functional partnership between both of *SYNJ1*'s phosphatase domains in clathrin-coat dynamics [32]. One notable exception is the discovery that *SYNJ1*, along with endophilin, mediates neck formation of endocytic pits during ultrafast endocytosis- a process that involves the 5'-phosphatase domain exclusively, not the Sac1-like domain [33].

Most research thus far has focused on *SYNJ1*'s presynaptic role in SV endocytosis. However, there is evidence that *SYNJ1* has a postsynaptic function as well, specifically in the regulation of glutamate AMPA receptor trafficking (Fig. 1B). A study using *SYNJ1* knockout mice found enlarged miniature excitatory postsynaptic current (mEPSC) amplitudes in comparison to wild-type (WT) mice, which were attributed to an increase in

surface-exposed AMPA receptors. This strongly suggests that *SYNJ1* is a key component in the internalization of AMPA receptors and thus a vital regulator of postsynaptic AMPA responses [34]. A likely explanation for this is *SYNJ1*'s observed role in PtdIns(4,5)P_2 metabolism, as increased levels of PtdIns(4,5)P_2 have been shown to lead to actin dysfunction and alterations in synaptic structure that could consequently affect AMPA receptor responses [34, 35].

Furthermore, *SYNJ1*'s role in the autophagy pathway is an area of recent interest (Fig. 1B). One study was conducted on *drosophila* with a Parkinson's disease-causing mutation that nullifies solely *SYNJ1*'s Sac1-like domain, resulting in neurodegeneration and an accumulation of Atg18a - a binding protein of PtdIns(3)P and PtdIns(3,5)P_2 -, indicating that the intact function of *SYNJ1*'s Sac1 domain is required for successful autophagosome maturation at presynaptic terminals [36]. Likewise, mutations of the *SYNJ1/unc-26* allele in *C. elegans* resulted in mislocalization of ATG-9, a transmembrane protein of the core autophagy machinery, as well as in defects in activity-induced synaptic autophagy and sustained neurotransmission [37]. In addition, it has been reported that heterozygous deletion of *SYNJ1* in mice leads to the enhancement of autophagy markers LC3 and p62, along with hyperactive basal autophagosome formation in astrocytes. Both results further support *SYNJ1* as a crucial mediator of neuronal autophagy [38, 39]. Interestingly, one study analyzing the zebrafish cone photoreceptor inner segments found through mutational analysis of *SYNJ1* enzymatic domains that the 5'-phosphatase domain activity, but not the Sac1 domain, was required to rescue both aberrant late endosomes and autophagosomes [40, 41]. Thus, both phosphatase domains likely work in cooperation to regulate the autophagy pathway, falling in line with the previously discussed dual-action model of *SYNJ1* [30].

3. *SYNJ1* IN ALZHEIMER'S DISEASE: GENETIC ASSOCIATION STUDIES

Most genetic association studies of Alzheimer's disease have been conducted in general (neurotypical) populations, and publications on the *SYNJ1* gene in DS are sparse. Thus, we will first discuss the genetic association of *SYNJ1* in the general populations and then discuss that in high-risk populations, including DS and Autosomal Dominant Alzheimer's Disease (ADAD) (Table 1).

3.1. Late Onset Alzheimer's Disease (LOAD)

The recent large meta-analysis study by Bellenguez and colleagues failed to show any significant allelic association between variants in the *SYNJ1* gene and AD-related traits [42]. This study examined a total of 788,989 individuals (111,326 AD cases and 677,663 controls) and showed no significant association. Similarly, the earlier large-scale meta-analysis studies by Kunkle *et al.* [43] and Jansen and colleagues [44, 45] did not show a significant association between variants in the *SYNJ1* gene and AD-related traits. These studies had sufficient statistical power to detect allelic association when variants were rare (*i.e.,* minimum allele frequency ≥1%). However, when the effect sizes of the identified variants are weak to modest, studies have limited power to detect genetic modifiers that interact with other genetic variants. For example, in the study by Kunkle *et al.* the identified variants had effect sizes ranging from 0.88 to 2.01, with the exception of *APOE*, which

had an effect size of 3.32 [43]. Given the fact that identified genetic variants in the general population have weak to modest effects, their interactions with variants in *SYNJ1* would be difficult to detect. This becomes a study design issue, where it would be more powerful to examine the role of the *SYNJ1* gene in high-risk cohorts where primary genetic factors have strong effects. To further strengthen statistical power to identify and characterize genetic contributions, it is ideal to examine intermediate endophenotypes (*e.g.,* protein levels, metabolites, memory performance, or age at onset of AD) that are closer to the actions of the gene [46, 47]. For example, Gieger *et al.* have shown that multiple endophenotypes that characterize multiple omic layers representing physiological states can shed light on complex biological processes [48].

3.2. High Risk Down Syndrome (DS)

Studies of the *SYNJ1* gene for AD in adults with DS can be particularly insightful to understand the biology the biology given that the gene with extra allelic dosage is located on 21q22.11, thereby allowing the dosage effect beyond having two copies of rare homozygous variants on AD-related phenotypes. To date, however, most genetic association studies of adults with DS have been focusing on candidate genes that were identified from the general population due to the small sample size of studies on adults with DS leading to limited statistical power to detect risk variants without strong effects. Thus, there are currently no published studies examining the overall effects of genetic variants in *SYNJ1* on the risk to develop DS-AD. There are, however published studies investigating *SYNJ1* RNA and protein levels in DS-AD (see Section 4.2). Measuring these gene-associated biomarkers in high-risk cohorts can enhance power, but the costs of these assays have been prohibitive thus far. As next-generation sequencing and biomarker assays have become more affordable, large scale genetic studies and associated biomarker measurements [49] are currently underway in adults with DS.

3.3. High Risk Autosomal Dominant Alzheimer's Disease (ADAD)

Individuals with ADAD, along with DS, can shed light on the role of *SYNJ1* in the neurodegenerative processes leading to AD as the effect sizes of their primary genetic risk factors are substantial [50]. The three genes that have been implicated in ADAD are the amyloid precursor protein (*APP*) gene on 21q21.3, presenilin 1 (*PSEN1*) on 14q24.2, and presenilin 2 (*PSEN2*) on 1q42.13. *PSEN1* and *PSEN2* encode for the presenilin 1 and presenilin 2 proteins, as part of the γ-secretase complex, and are responsible for cleaving APP into Aβ peptides. As with individuals with DS, those with autosomal dominant genes tend to have early onset of cognitive decline and high prevalence of AD and suffer from the burden of high levels of Aβ peptides. Carriers of these genes can provide insight into genetic modifiers where these genes can alter the phenotypes in the presence of high amyloid β peptides. To explore this possibility, we examined a collection of Puerto Rican *PSEN1*-G206A mutation carrier families [51]. We identified SNP variants in the *SYNJ1* gene that were associated with delayed age at onset in families with early onset familial AD. This finding was further extended to late-onset familial AD. Specifically, we showed that 3- and 4-SNP haplotypes were associated with delayed age at onset of AD by 8–10 years. Subsequently, the haplotypes that were associated with a delay in age at onset of AD

were also associated with enhanced memory performance, further supporting the biological plausibility.

4. *SYNJ1* IN ALZHEIMER'S DISEASE: EXPRESSION IN HUMAN BRAINS AND NEUROPATHOLOGY

Another way to assess the relevance of *SYNJ1* to the etiopathology of AD is to investigate whether levels of *SYNJ1* transcripts and *SYNJ1* protein vary as a function of the occurrence and progression of AD neuropathology, cognitive impairment, or both (Table 1).

4.1. Late Onset Alzheimer's Disease (LOAD)

Multiple large-scale transcriptomic studies in the general population have reported that *SYNJ1* is expressed above the significance threshold in all brain regions [52, 53]. Using a combination of datasets publicly available through the AD Knowledge Portal investigating differential RNA expression between LOAD cases and controls, adjusting for potential confounders including sex (accession code syn9702085) [54–56], we have observed that RNA expression of *SYNJ1* in LOAD cases is decreased in the temporal cortex (Log2FC = −0.34833, $P_{FDR\ corrected}$ = 1.73E-6), parahippocampal gyrus (Log2FC = −0.42654, $P_{FDR\ corrected}$ = 7.55E-9), inferior frontal gyrus (Log2FC = −0.2749, $P_{FDR\ corrected}$ = 0.0007), and superior temporal gyrus (Log2FC = −0.2544, $P_{FDR\ corrected}$=0.002) regions, compared to controls. While *SYNJ1* was not significantly differentially expressed in other investigated brain regions, expression in LOAD brains additionally trended downwards for all other regions except the cerebellum. We note that there were no significant differences in *SYNJ1* expression between *APOE4* carriers and non-carriers across all investigated brain regions. Together, these findings suggest that *SYNJ1* may be broadly downregulated in LOAD brains. However, these observations must be mitigated by the fact that *SYNJ1* is a synaptic protein and that differentiating between overall synaptic loss and specific *SYNJ1* downregulation at autopsy at very advanced stages of LOAD may be difficult.

Proteomic studies of the brain tissues in the general neurotypical population show conflicting evidence with respect to *SYNJ1* levels in LOAD. Higginbotham *et al.* have examined differential protein expression between LOAD cases and age- and gender-matched controls in the dorsolateral prefrontal cortex (DLPFC) and have consistently observed higher levels of the *SYNJ1* protein in DLPFC tissues of LOAD cases compared with those from controls ($P_{nominal}$ = 3.3E-3), mixed AD/Parkinson's disease (PD) cases ($P_{nominal}$ = 0.0464), and PD cases ($P_{nominal}$ = 4.9E-4) [57]. A similar trend of elevated *SYNJ1* in DLPFC tissues of AD cases (compared with controls, $P_{nominal}$=6.5E-3, asymptomatic AD, $P_{nominal}$ = 0.0297) has also been observed in the replication stage of this study [57]. In a separate meta-analysis of tissues across four different cohorts [58] (AD Knowledge Portal, accession code syn2580853), however, we have observed that *SYNJ1* protein levels are significantly lower in DLPFC tissues (P_{FDR} = 1.3E-7) of LOAD cases compared to controls. In meta-analyses, there are no significant differences in *SYNJ1* levels in anterior prefrontal cortex and temporal cortex. These conflicting results may in part, be explained by additional evidence stemming from studies specifically focusing on *SYNJ1* in LOAD brains, although

differences in extraction protocols and disease characterization (*e.g.,* Braak stage *vs.* clinical dementia rating (CDR)) hinder proper data homogenization.

Using immunohistochemistry, *SYNJ1* was found to be increased in hippocampal neurons of LOAD brains compared to controls [59]. *SYNJ1* accumulates in plaque-associated dystrophic neurites and in some neurofibrillary tangles in LOAD brains [59]. Interestingly, *SYNJ1* also accumulates in Hirano bodies [59], intracellular rod-like aggregates enriched in actin and actin-binding proteins [60]. Whether this association is biologically relevant to *SYNJ1*'s function in the maintenance of the actin network (see Section 2) remains to be investigated.

At advanced stages of the disease, *SYNJ1* mRNA levels are increased in the cortex of LOAD patients compared to controls and correlate with the amount of phosphorylated tau [59]. In contrast, at advanced stages of the disease, *SYNJ1* protein levels are decreased in the total homogenate and in the detergent (SDS or RIPA)-soluble fraction of LOAD cases compared to controls [59, 61]. However, *SYNJ1* protein levels are increased in the detergent-insoluble fraction of LOAD cases compared to controls and correlate with the amount of phosphorylated tau in this fraction [59]. Moreover, *SYNJ1* co-precipitates with paired helical filament (PHF)-tau after sarkosyl fractionation [59]. This intriguing association of tau and *SYNJ1* will require further investigation.

The most potent genetic risk factor for LOAD is the ε4 allele of the *APOE* gene (*APOE4*) [42, 62] and experimental evidence supports the existence of a relationship between *SYNJ1* levels and carrying the *APOE4* allele. At advanced stages of the disease, *SYNJ1* staining is increased in the hippocampus of LOAD cases carrying one or two *APOE4* alleles compared to those without an *APOE4* allele [59]. *SYNJ1* mRNA levels are increased in cases carrying an *APOE4* allele compared to cases carrying no *APOE4* allele in a control-aged cohort (CDR 0) and in cases with mild AD (CDR 0.5–1) [63]. *SYNJ1* mRNA levels are also increased in *APOE4* carriers compared to non-*APOE4* carriers within a cohort of late-stage LOAD cases (Braak V-VI) [59]. However, such a difference is not observed in the control group of this latter study. *SYNJ1* protein levels are also increased in cases carrying an *APOE4* allele compared to cases carrying no *APOE4* allele in a control-aged cohort (CDR 0) and in cases with mild AD (CDR 0.5–1) [63]. However, *SYNJ1* protein levels were similar between *APOE4* carriers and non-carriers at advanced stages (CDR 3) [63]. In addition, although *SYNJ1* protein levels are overall decreased in the detergent-soluble fraction of late stage LOAD cases (Braak V-VI) compared to controls [59], a finer dissection revealed differences between *APOE4* carriers and non-carriers LOAD cases. Indeed, within the LOAD cohort, *SYNJ1* protein levels are increased in cases carrying one or two *APOE4* allele(s) compared to cases carrying no *APOE4* allele in the detergent-soluble fraction [59].

Altogether, the levels of *SYNJ1* transcripts and *SYNJ1* protein seem intimately linked with LOAD. However, the stage of the disease, whether cognition- or neuropathology-based, as well as the protocols used to extract and quantify transcripts and proteins, profoundly affect the reported results. Nevertheless, the increase in *SYNJ1* levels in *APOE4* carriers as well as the accumulation of *SYNJ1* with phosphorylated Tau and Hirano bodies, strongly support that *SYNJ1* plays a robust role in LOAD disease progression.

4.2. High Risk Down Syndrome (DS)

Sharma *et al.* conducted a bioinformatic integrative study to identify the genes that may be associated with AD in DS by integrating the results from the bioinformatic search of Alzheimer's in DS, and genes identified from the differential gene expression study of the dorsal frontal cortex (DFC) and cerebral cortex in the Down Syndrome Developmental Brain Transcriptome database [64]. Their exploratory analysis supports that *SYNJ1* contributes to the pathogenesis of AD in DS, however, experimental evidence is needed for confirmation.

SYNJ1 protein levels are increased in the brain of individuals with DS compared to disomic controls at the gestational stage, in childhood and in young adults [61, 65, 66]. Recent single cell RNA sequencing data support that this increase is heightened in inhibitory neurons and microglia [67]. Interestingly, in older individuals with DS-AD, there is a very large increase in *SYNJ1* levels compared to age-matched disomic controls, and the difference between DS and disomic individuals is much greater than at a younger age [59, 61]. Moreover, in older individuals with DS-AD, levels of *SYNJ1* inversely correlate with levels of synaptophysin, a synaptic marker and an indicator of synaptic health [51]. Taken together, these results strongly suggest that elevated levels of *SYNJ1* observed in populations at high risk for developing AD could directly affect synaptic structure, function, or both.

4.3. High Risk Autosomal Dominant Alzheimer's Disease (ADAD)

Little is known on the levels of *SYNJ1* in ADAD brains, mostly because ADAD represents only about 1% of all AD cases and such brains are therefore rare. A recent study has investigated *SYNJ1* levels in two ADAD brains, an *APP*-V717I mutation carrier with *APOE3/3* genotype and a *PSEN1*-R35E/E120D with *APOE4/3* genotype. Although it is impossible to draw definitive conclusions with such a small sample size, results obtained on *SYNJ1* mRNA levels and *SYNJ1* solubility are comparable overall between ADAD and LOAD brains [59]. Importantly, *SYNJ1* co-precipitates with paired helical filament (PHF)-tau after sarkosyl fractionation in an ADAD brain, similar to what is observed in LOAD brains [59]. It would be extremely interesting to carry out a systematic study of *SYNJ1* levels in ADAD brains with different *APP*, *PSEN1* and *PSEN2* mutations.

5. *SYNJ1* IN ALZHEIMER'S DISEASE: CELLULAR AND MURINE MODELS

An important tool to support our understanding of disease mechanisms and progress towards potential therapies is disease modeling, whether in animal or cellular model systems (Table 2).

5.1. Late Onset Alzheimer's Disease (LOAD)

Although defining an accurate model to study LOAD is still a matter of intense debate in the field, we have decided to focus here on ApoE4 models, as carrying an *APOE4* allele is the most potent genetic risk factor to develop LOAD [42, 62], as stated previously.

SYNJ1 mRNA levels and *SYNJ1* protein levels are increased in the cortex and hippocampus of human *APOE4/4* knock-in (KI) mouse models, compared to *APOE3/3* KI mouse models [63], in good accordance with what was observed in human *APOE4* carrier brains. This

increase in *SYNJ1* levels is functionally relevant as genetically decreasing *SYNJ1* levels in *ApoE4* KI mice rescues the cognitive deficits exhibited by these mice [63].

Interestingly, levels of *SYNJ1* were comparable in *APOE4/4* KI and in *ApoE* null (knock-out) mice, but much lower in *APOE3/3* KI mice [63]. In addition, in primary cultures of hippocampal *ApoE* null neurons, incubation with conditioned media derived from *APOE3/3* astrocytes, but not *APOE4/4* or *ApoE* null astrocytes, leads to a reduction of *SYNJ1* levels *via* accelerated degradation of *SYNJ1* mRNA [63]. Altogether, these results suggest that APOE4 displays a loss-of-function effect towards *SYNJ1* and cannot promote *SYNJ1* mRNA degradation and subsequent decreased *SYNJ1* levels [63].

As mRNA stability can be regulated by micro-RNA (miRNA) binding to 3′-UTR regions of mRNA, the same group further tested whether *SYNJ1* expression may be differentially regulated by ApoE isoforms through modulation of miR-195 [68]. miR-195 levels are reduced in the cortex of human *APOE4* carriers with mild cognitive impairment (MCI) and early AD (CDR 0.5–1) compared to non-*APOE4* carriers. However, no such difference was observed in a cohort of normal aging (CDR 0) or at advanced stages (CDR 3). miR-195 levels are also reduced in *ApoE4/4* KI mouse brains compared to *ApoE3/3* KI mice. In addition, in primary cultures of hippocampal *ApoE* null neurons, incubation with conditioned media derived from *APOE4/4* astrocytes leads to lower miR-195 levels compared to conditioned media from *APOE3/3* astrocytes. Over-expressing miR-195 significantly reduces *SYNJ1* protein levels in *ApoE* null neurons, as well as in *ApoE3/3* and *ApoE4/4* neurons, supporting that upregulation of miR-195 can modulate *SYNJ1* expression levels. In addition, viral delivery of miR-195 in the hippocampus of *APOE4/4* KI mice with or without a transgenic AD background rescues cognitive deficits and reduces tau hyper-phosphorylation. A reduction in Aβ42 oligomers and amyloid plaque burden was also observed, specifically in the transgenic AD background [68].

The same authors also used human induced pluripotent stem cells (iPSCs)-derived neurons and astrocytes co-cultures from an *APOE4/4* LOAD patient or an *APOE3/3* control. Over-expressing miR-195 significantly reduces the enlargement of lysosomes observed in human *APOE4/4* neurons and reduces phosphorylated tau levels in these cells [68]. Using an elegant combination of $SYNJ1^{+/+}$ and $SYNJ1^{-/-}$ neurons co-cultured with *APOE4/4* iPSC-derived astrocytes, they showed that lysosomal size was reduced in $SYNJ1^{-/-}$ neurons compared to $SYNJ1^{+/+}$ neurons. Furthermore, over-expressing miR-195 did not have an additional effect on lysosomal size in $SYNJ1^{-/-}$ neurons, strongly suggesting that miR-195 acts through the control of *SYNJ1* levels on lysosomal homeostasis [68]. Altogether, the authors provide solid evidence for a mechanistic link between APOE4 and *SYNJ1* levels. Specifically, they propose that carrying an *APOE4* allele results in having less miR-195, causing a defect in the degradation of *SYNJ1* mRNA and ultimately leading to increased *SYNJ1* levels.

In the context of LOAD, it is interesting to focus on a transgenic mouse model overexpressing murine *SYNJ1*, Tg(*SYNJ1*) [69]. We have reported that these mice express about 75% more *SYNJ1* than their littermate controls (wild-type (WT)) at older ages (19 months old) [51] which closely recapitulates the overexpression levels (+73%) described in

APOE4 carriers with early AD (CDR 0.5–1) [63]. This increase is, however, milder than the overexpression levels in individuals with DS-AD (+155% compared with age-matched disomic controls) [61]. These mice were initially generated in the Antonarakis lab on the FVB background using mouse BAC RPCI-23 402J16 [69]. Of note, this BAC also contains two additional complete genes, the mouse orthologs of C21orf59 and C21orf66 [69], and contributing effects from these genes cannot be excluded. Three- to four-month-old Tg(*SYNJ1*) mice with a mixed FVB/C57BL/6 background exhibit a milder *SYNJ1* increase (~ 40%). They do not show deficits in the Morris water maze paradigm but perform slightly worse than control animals in the reverse platform test variation of this paradigm. They also show no differences in basal neurotransmission and synaptic plasticity [69]. Interestingly, it has been reported that Early Endosome Antigen 1 (EEA1)-positive early endosomes are enlarged in the prefrontal cortex of Tg(*SYNJ1*) compared to WT littermates [70]. The enlargement of early endosomes is one of the earliest cellular phenotypes of AD pathogenesis, preceding even amyloid deposition [71]. Endosomal abnormalities are accelerated in the brains of *APOE4* carriers and can be observed in the brains of individuals with DS from the youngest age [71]. Nine-month-old Tg(*SYNJ1*) mice with a C57BL/6 background perform similarly to their WT littermates in the radial arm water maze (RAWM) and fear conditioning (FC) paradigms [51]. However, at nineteen-month old, when *SYNJ1* increase is ~ 75%, Tg(*SYNJ1*) mice show a significantly higher number of errors in the RAWM compared with WT mice, as well as a specific decrease in freezing in contextual but not in cued conditioning compared with WT mice, suggesting hippocampal but not amygdala impairment [51]. We also reported that age-dependent cognitive deficits were significantly more pronounced in Tg(*SYNJ1*) than in WT littermates [51]. These cognitive deficits are not due to obvious synaptic loss, as levels of pre-and post-synaptic proteins are similar in transgenic and WT animals. However, using *in vivo* electrophysiology, we found that elevated levels of *SYNJ1* trigger acute hyperexcitability as well as dramatic defects in the spatial reproducibility of place fields in the hippocampus of older Tg(*SYNJ1*) animals [51]. Taken together, these results indicate that having higher levels of *SYNJ1* increases cognitive deficits over time, by impacting hippocampal synaptic function.

5.2. High Risk Down Syndrome (DS)

SYNJ1 levels are increased by ~40% in Ts65Dn mice, one of the most used models of DS. This is accompanied by a decrease in PtdIns(4,5)P_2, one of the lipids that can be targeted by *SYNJ1*. In addition, genetically restoring *SYNJ1* copy number is sufficient to increase PtdIns(4,5)P_2 levels to control conditions [69].

Lymphoblastoid cell lines (LCLs) and fibroblasts derived from individuals with DS show increased levels of *SYNJ1* as well as enlarged endosomes [70]. An elegant study using LCLs from individuals with partial trisomies highlighted that the segment of Hsa21 containing *SYNJ1* was sufficient to induce the enlargement of early endosomes [70]. Furthermore, overexpressing *SYNJ1* in SH-SY5Y neuroblastoma cell lines is sufficient to recapitulate endosomal enlargement and decreasing *SYNJ1* levels in DS fibroblasts by a shRNA approach leads to a decrease in the percentage of larger endosomes [70].

A recent study used human iPSCs-derived neurons from two individuals with DS and compared them with their euploid isogenic controls [72]. DS neurons showed higher levels of *SYNJ1*, as well as higher secreted Aβ peptides, higher phosphorylated tau, impaired lysosomal transport and increased synaptic vesicle release. Restoring *SYNJ1* copy number to disomy did not rescue Aβ peptide secretion or tau phosphorylation, in contrast to restoring *APP* copy number [72]. Of note, this study did not report the effect of restoring *SYNJ1* copy number to disomy on the lysosomal and synaptic vesicle phenotypes.

5.3. High Risk Autosomal Dominant Alzheimer's Disease (ADAD)

Overexpressing the inositol 5-phosphatase domain of synaptojanin 1 resulted in enhanced levels of Aβ42 peptide, likely through the reduction of PtdIns(4,5)P_2 levels [73]. Landman and colleagues highlighted that such PtdIns(4,5)P_2 reduction and Aβ42 increase was recapitulated in cells expressing *PSEN1* or *PSEN2* ADAD mutations compared to control cells [73].

Two independent studies have reported that genetically decreasing *SYNJ1* levels in ADAD mouse models alleviate learning and memory deficits [74, 75]. One group proposed that *SYNJ1* reduction is protective against the effect of Aβ oligomers on PtdIns(4,5)P_2 decrease, long-term potentiation (LTP) impairment and synaptic toxicity [74, 76], while the other proposed that *SYNJ1* reduction leads to increased Aβ uptake and degradation [75].

CONCLUSION AND PERSPECTIVES

As we highlighted previously [51] and further illustrate in this review, *SYNJ1* is important for all forms of AD, whether LOAD, DS-AD, or ADAD. Of note, we did not develop select aspects of AD, DS and *SYNJ1* biology in this manuscript as they have been the focus of recent reviews (*e.g.,* the endo-lysosomal pathway in DS and AD [77, 78] or the dysregulation of phosphoinositides in AD [79]).

We have reported intronic variants in *SYNJ1* that are associated with ADAD [51] and have recently discovered two *SYNJ1* mutations associated with the age of onset of ADAD (J.H.L., unpublished). Very little is currently known about the association of *SYNJ1* with DS-AD. However, we expect that large efforts such as the ABC-DS project [49] will generate a valuable set of data on the genome, proteome, and metabolome along with imaging that can be used to further investigate this question. Altogether, it would be interesting to investigate the functional effects of current and future *SYNJ1* variants to delineate: (i) the nature of the pathways affected by these variants, *e.g.,* endolysosomal pathway, autophagy, synaptic vesicle release, amyloid or tau pathology, and (ii) whether possible *SYNJ1* variants in DS-AD show structural or functional similarities with variants in ADAD. Future understanding of the functional relevance of *SYNJ1* variants combined with advances in structure and modeling [80] will be key vectors in delineating potential therapeutic strategies targeting *SYNJ1* in DS and AD.

Although we focus on DS and AD in this review, it is important to note that *SYNJ1* mutations have been associated with other disorders, such as bipolar disorder [81], epilepsy [82] and Parkinson's disease [83–87], as recently reviewed [88]. It would also be

informative to investigate whether current and future *SYNJ1* variants in DS-AD and ADAD show structural or functional similarities with mutations described in these disorders.

Below, we highlight a few additional unanswered questions.

- **i.** Late Onset Alzheimer's Disease (LOAD) and High Risk Autosomal dominant Alzheimer's Disease (ADAD)
  - **a.** n human LOAD, is the association of *SYNJ1* with Hirano bodies linked to its function in the dynamics of actin?
  - **b.** In human ADAD, are there differences in *SYNJ1* expression and solubility as a function of the ADAD-causing mutation?
  - **c.** Are the beneficial effects of genetically decreasing*SYNJ1* on cognitive deficits observed in models of ADAD and LOAD mediated at least in part by lowering hippocampal hyperactivity?
- **ii.** High Risk Down Syndrome (DS)
  - **a.** In human DS, *SYNJ1* levels are much higher in older individuals than in younger individuals. What is driving this rise in *SYNJ1* levels?
  - **b.** In human iPSCs-derived neurons from individuals with DS, would restoring *SYNJ1* copy number to disomy rescue the lysosomal and synaptic vesicle phenotypes?
  - **c.** Are there differences in *SYNJ1* expression and *SYNJ1* levels in iPSCs-derived neurons isolated from: (1) a young *vs.* an older individual with DS, (2) an older individual with DS without or with DS-AD?

Finally, most studies performed thus far have focused individually on *SYNJ1* and other Hsa21 genes. However, moving forward, it would be interesting to test potential functional interactions between *SYNJ1* and other Hsa21 genes in the context of DS-AD. As also proposed by others [69, 70], some candidates of interest include *ITSN1*, coding Intersectin 1, *DYRK1A*, coding Dual Specificity Tyrosine Phosphorylation Regulated Kinase 1A (DYRK1A) and *RCAN1* (also called *DSCR1*), coding Regulator Of Calcineurin 1 (RCAN1). Intersectin1 binds to *SYNJ1* [89] and overexpressing its homolog dap160 alters the subcellular distribution of synaptojanin in *drosophila* models [90]. DYRK1A can phosphorylate *SYNJ1* and modulate its activity [91–93]. RCAN regulates calcineurin, which mediates the dephosphorylation of *SYNJ1* [20] and overexpressing its homolog nla regulates synaptojanin activity in *drosophila* models [90].

In conclusion, although *SYNJ1* has been thoroughly investigated in the normal and diseased brain over the years, additional evidence and key mechanistic pathways remain to be identified to offer concrete therapeutic avenues targeting *SYNJ1* in neurodegenerative disorders.

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LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
ADAD	Autosomal Dominant Alzheimer's Disease
AMPA	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
APP	Amyloid Precursor Protein
BAC	Bacterial Artificial Chromosome
BAR	Bin/Amphiphysin/RVS
Cdk5	Cyclin-dependent Kinase 5
CDR	Clinical Dementia Rating
DS	Down Syndrome
EEA1	Early Endosome Antigen 1
FC	Fear Conditioning
Grb2	Growth Factor Receptor-bound Protein 2
Hsa21	Human Chromosome 21
iPSCs	Induced Pluripotent Stem Cells
KI	Knock-in
LCLs	Lymphoblastoid Cell Lines
LOAD	Late Onset Alzheimer's Disease

LTP	Long-term Potentiation
MCI	Mild Cognitive Impairment
mEPSC	Miniature Excitatory Postsynaptic Current
miR	microRNA
PHF	Paired Helical Filament
PRD	Proline-rich Domain
PtdIns(4,5)P2	Phosphatidylinositol (4,5)-bisphosphate
RAWM	Radial Arm Water Maze
Sac1	Suppressor of Actin 1
SH3	Scr Homology 3
SNP	Single Nucleotide Polymorphism
SV	Synaptic Vesicles
SYNJ1	Synaptojanin 1
WT	Wild-type

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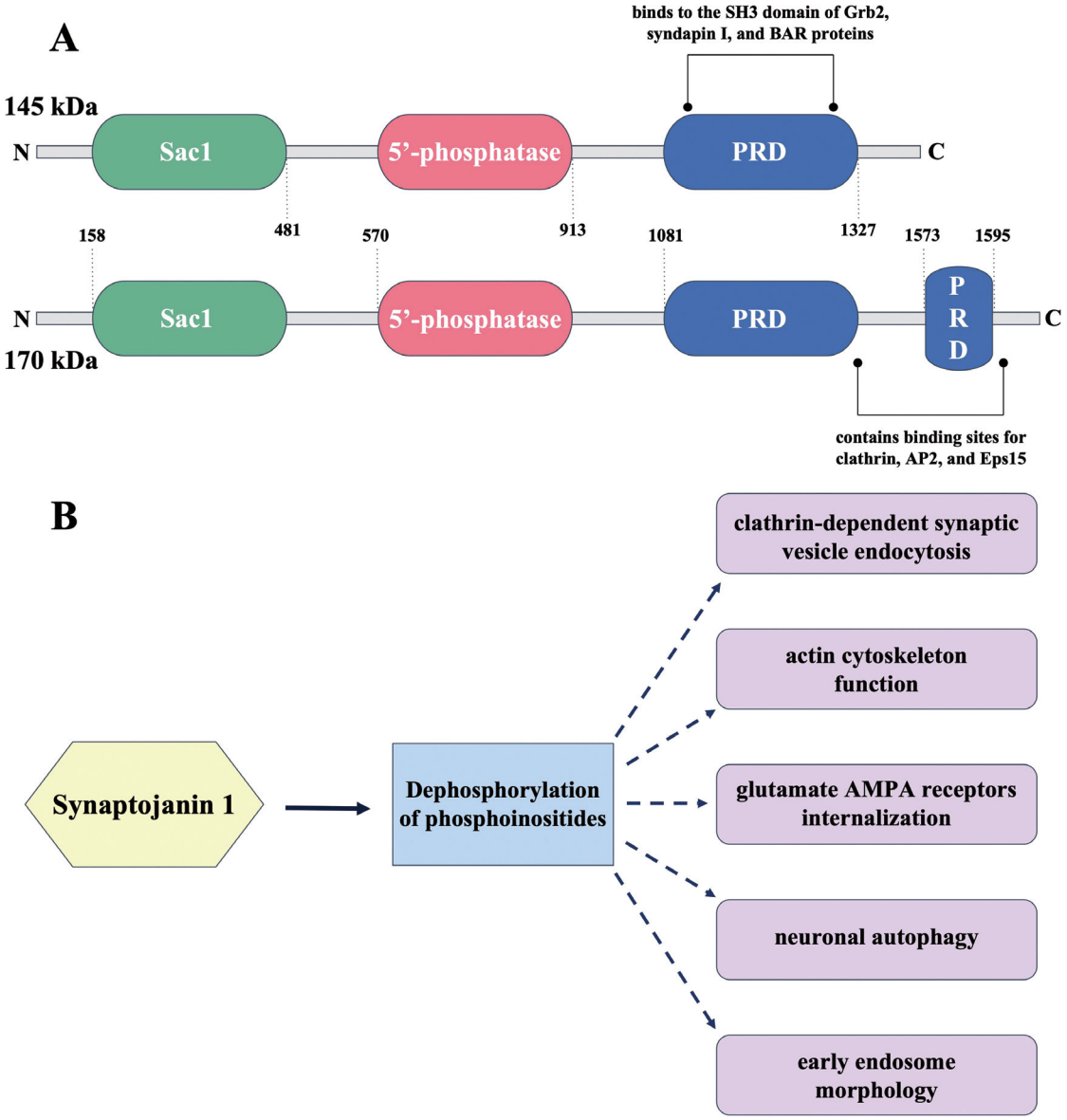

Fig. (1).

Structure and function of Synaptojanin 1 (*SYNJ1*). **A.** Schematic representation of the structure of the two isoforms of *SYNJ1*, including functional domains and known interactors. **B.** Representation of the multiple functions of *SYNJ1*, through its effect on the dephosphorylation of phosphoinositides. PRD, proline-rich domain, BAR, Bin/Amphiphysin/RVS.

Table 1.

SYNJ1 in human Alzheimer's disease: genetic association, neuropathology and expression in human brains.

Populations	Genetic Association of *SYNJ1*	Human Brains		
	-	**Neuropathology**	***SYNJ1* RNA**	***SYNJ1* Protein**
Late Onset AD (LOAD)	Not detected [42–46]	Accumulation in plaque-associated dystrophic neurites, in Hirano bodies and in some neurofibrillary tangles [60] Co-precipitation with (PHF)-tau [60]	Transcriptomics: decreased in LOAD (AD Knowledge Portal) [55–57] Increased in LOAD, correlate with levels of phosphorylated tau [60]	Proteomics: increased [58] or decreased (AD Knowledge Portal) [59] in LOAD Increased in detergent-insoluble fraction in LOAD, correlate with levels of phosphorylated tau [60] Decreased in total homogenate and detergent-soluble fraction in LOAD [60, 62]. Within the LOAD cohort, *APOE4* carriers have higher *SYNJ1* levels than non-carriers [60]
			Increased [64] or unchanged [60] in *APOE4* carriers in a control cohort	Increased in *APOE4* carriers in a control cohort [64]
			Increased in *APOE4* carriers with early LOAD (CDR 0.5–1) [64] and late-stage LOAD (Braak V-VI) [60] miR-195 levels reduced in *APOE4* carriers with MCI and early LOAD (CDR 0.5–1), but unchanged in normal aging (CDR 0) or at advanced stages (CDR 3) [69]	Increased in cases with early LOAD (CDR 0.5–1), unchanged at advanced stages (CDR 3) [64]
High Risk Down Syndrome (DS)	Unexplored	Inverse correlation with synaptophysin levels among older individuals with DS-AD [52]	Increased in DS *vs.* disomic controls [68]	Increased in DS *vs.* disomic controls [60, 62, 66, 67]
High Risk Autosomal Dominant AD (ADAD)	Yes, early- and late-onset [52]	Co-precipitation with (PHF)-tau [60]	Similar to LOAD (small sample size) [60]	Similar to LOAD (small sample size) [60]

Abbreviations: PHF, paired helical filaments, CDR, clinical dementia rating, miR, microRNA, MCI, mild cognitive impairment.

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Table 2.

SYNJ1 in cellular and murine models of Alzheimer's disease.

Populations	Cellular and Murine Models		
	Model and Treatment	**Phenotype**	**Proposed Mechanism**
Late Onset AD (LOAD)	Human *APOE4/4* knock-in (KI) mouse models	*SYNJ1* levels unchanged, compared to *ApoE* null (knock-out) mice [64] *SYNJ1* mRNA levels and *SYNJ1* protein levels increased, compared to *APOE3/3* KI mouse models [64] miR-195 levels reduced, compared to *APOE3/3* KI mice [69]	Genetically decreasing *SYNJ1* levels in *ApoE4* KI mice rescues the cognitive deficits exhibited by these mice [64]
	Primary cultures of hippocampal *ApoE* null neurons	Incubation with conditioned media derived from *APOE3/3* astrocytes, but not *ApoE4/4* or *ApoE* null astrocytes, leads to a reduction of *SYNJ1* levels [64]	Accelerated degradation of *SYNJ1* mRNA [64]
		Incubation with conditioned media derived from *ApoE4/4* astrocytes leads to lower miR-195 levels, compared to *APOE3/3* astrocytes [69]	Upregulation of miR-195 can modulate *SYNJ1* expression, supported by the fact that overexpressing miR-195 reduces *SYNJ1* protein levels in *ApoE* null, *APOE3/3* and *ApoE4/4* neurons [69]
	Human *ApoE4/4* knock-in (KI) mouse models with or without a transgenic AD background, viral delivery of miR-195 in the hippocampus	Rescue of cognitive deficits and reduction of tau hyper-phosphorylation [69]. Reduction in Aβ42 oligomers and amyloid plaque burden in the transgenic AD background [69]	
	Human iPSCs-derived neurons and astrocytes co-cultures from an *ApoE4/4* LOAD patient or an *APOE3/3* control.	Enlargement of lysosomes in human *ApoE4/4* neurons [69]	Over-expression of miR-195 reduces lysosomal enlargement and reduces phosphorylated tau levels in human *ApoE4/4* neurons [69]
	$SYNJ1^{+/+}$ and $SYNJ1^{-/-}$ neurons co-cultured with *ApoE4/4* iPSC-derived astrocytes	Reduction of lysosomal size in $SYNJ1^{-/-}$ neurons compared to $SYNJ1^{+/+}$ neurons [69]	miR-195 acts through the control of *SYNJ1* levels on lysosomal homeostasis, supported by no additional effect of over-expression of miR-195 on lysosomal size in $SYNJ1^{-/-}$ neurons [69]
	Tg(*SYNJ1*) [70], compared to WT littermates	Increased levels of *SYNJ1* [52,70]	
		Early endosomes enlargement [71]	
		3-4-month-old: no deficit in the Morris water maze, deficit in the reverse platform test [70]	No differences in basal neurotransmission and synaptic plasticity [70]
		9-month-old: no deficit in the radial arm water maze (RAWM) and fear conditioning (FC) paradigms [52]	
		19-month-old: deficit in the RAWM and decreased freezing in contextual FC [52]	Unchanged levels of pre-and post-synaptic proteins, but acute hyperexcitability and defect in the spatial reproducibility of hippocampal place fields [52]

Populations	Cellular and Murine Models		
	Model and Treatment	**Phenotype**	**Proposed Mechanism**
High risk Down Syndrome (Ds)	Ts65Dn mouse model	Increased levels of *SYNJ1*, PtdIns(4,5)P_2 reduction [70]	Restoring *SYNJ1* copy number rescues PtdIns(4,5)P_2 levels [70]
	Lymphoblastoid cell lines derived from individuals with DS	Increased levels of *SYNJ1*, enlarged early endosomes [71]	The Hsa21 segment containing *SYNJ1* is sufficient to induce early endosomal enlargement [71]
	Fibroblasts derived from individuals with DS	Increased levels of *SYNJ1*, enlarged early endosomes [71]	Decreasing *SYNJ1* levels reduces the percentage of larger endosomes [71]
	Overexpression of *SYNJ1* in SH-SY5Y neuroblastoma cell lines	Enlarged early endosomes [71]	
	Human iPSCs-derived neurons from individuals with DS and their euploid isogenic controls [73]	Increased levels of *SYNJ1*, higher secreted Aβ peptides, higher phosphorylated tau, impaired lysosomal transport, increased synaptic vesicle release [73]	Restoring *SYNJ1* copy number to disomy did not rescue Aβ peptide secretion or tau phosphorylation, but restoring *APP* copy number did [73]
High risk Autosomal Dominant AD (ADAD)	*PSEN1* and *PSEN2* ADAD cells	PtdIns(4,5)P_2 reduction, Aβ42 increase [74]	Similarities with the overexpression of the inositol 5-phosphatase domain of *SYNJ1* [74]
	Genetic decrease of *SYNJ1* in ADAD mouse models	Improvement of learning and memory deficits [75, 76]	Protection against the effect of Aβ oligomers on PtdIns(4,5)P_2 decrease, long-term potentiation (LTP) impairment and synaptic toxicity [75, 77] Increased Aβ uptake and degradation [76]

Abbreviations: miR, microRNA, iPSCs, induced pluripotent stem ceils, WT, wild-type.

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