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The Role of PICALM in Alzheimer's Disease

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Abstract Alzheimer's disease (AD) is a highly heritable disease (with heritability up to 76 %) with a complex genetic profile of susceptibility, among which large genome-wide association studies (GWASs) pointed to the phosphatidylinositol-binding clathrin assembly protein (PICALM) gene as a susceptibility locus for late-onset Alzheimer's disease (LOAD) incidence. Here, we summarize the known functions of PICALM and discuss its genetic polymorphisms and their potential physiological effects associated with LOAD. Compelling data indicated that PICALM affects AD risk primarily by modulating production, transportation, and clearance of β-amyloid (Aβ) peptide, but other Aβ-independent pathways are discussed, including tauopathy, synaptic dysfunction, disorganized lipid metabolism, immune disorder, and disrupted iron homeostasis. Finally, given the potential involvement of PICALM in facilitating AD occurrence in multiple ways, it might be possible that targeting PICALM might provide promising and novel avenues for AD therapy.

Keywords PICALM · Polymorphism · Alzheimer's disease · Genetics · Mechanism · Amyloid beta

Introduction

As the most common cause of senile dementia, Alzheimer's disease (AD) has been increasingly known as a prominently global health issue. AD has been classified into two major forms: the early-onset type (<65 years of age) and late-onset type (LOAD; >65 years of age). Its etiology and trajectory can be characterized as a complex interaction effect between environmental and genetic factors [1–4]. For the genetic realm specifically, mutations in multiple loci have been associated with risk of developing AD of two forms. Rare but usually highly penetrant mutations of genes encoding amyloid precursor protein (APP) [5], presenilin 1 (PSEN1) [6], and presenilin 2 (PSEN2) [7] have been established as the susceptibility genes for rare, Mendelian form of the disease, while apolipoprotein allele epsilon 4 (*APOE4*) is convincingly considered a risk gene for a more common form of the disease (namely LOAD) [8, 9]. However, it has been estimated that the contribution from *APOE4* may account for just less than 20 % of LOAD risk [10]. Also, with 65 % sensitivity and 68 % specificity, the diagnostic implication of *APOE4* for LOAD is to some extent constrained [11]. In this context, an array of large genome-wide association studies (GWASs) according to the AlzGene database (http://www.alzgene.org/geneoverview.asp?geneid=636) have been conducted, pinpointing several novel susceptibility loci, which altogether contribute to the genetic mapping of etiology of AD along with *APOE4* despite that "genetic dark matter" still exists [12].

Among them, the gene encoding phosphatidylinositol-binding clathrin assembly protein (PICALM; source: HGNC Symbol; Acc: 15514) [13] has been considered to be one of the numerous reproducible risk genes for LOAD [14], despite with disputable results when it comes to concrete single nucleotide polymorphism (SNP) locus. A large, two-stage meta-analysis has showed that the population attributable fraction [15] of one specific SNP at PILACM (rs10792832) is estimated as 5.3 %, just next to the *APOE4* (27.3 %) and *BIN1* (8.1 %) [16]. Also, rs3851179, which is the initial SNP at *PICALM* identified to be associated with AD risk, has been listed in top results (http://www.alzgene.org/TopResults.asp, April 2011) despite as a protective locus in Caucasian

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ethnicity (odd ratio (OR)=0.879, 95 % confidence interval (CI)=0.86–0.9, p value=2.85E−20). Accordingly, we can make a preliminary postulation that PICALM may play a certain role in AD. It is thus worthy to gain better knowledge of PICALM for further advance in treatment and prevention of the disease.

In this manuscript, we will review PICALM from perspectives of biochemical properties and genetics. Special emphasis will be put on discussing potential pathways of PICALM involved in AD. Finally, we will probe into the therapeutic significance of PICALM for AD.

Biochemical Properties of PICALM

PICALM which contains 112 kb is located on chromosome 11q14 (ENSG00000073921, chromosome 11: 85,668,727–85,780,924 reverse strand) (Fig. 1), encoding a protein also known as clathrin assembly lymphoid myeloid leukemia protein [17]. There are at least 14 transcripts which contain an open reading frame (ORF) of *PICALM* according to Ensembl Genome (http://www.ensembl.org) and Vega Genome database (http://vega.sanger.ac.uk), despite disparity in total number of spliced variants exists.

PICALM has been reported to be expressed ubiquitously in multiple vertebrate species, tissues, and cells [18]. In central nervous system [19], presence of PICALM has been identified in neurons, astrocytes, and oligodendrocytes [20–23]. However, a recent study employing immunolabling technology found that PICALM predominately exists in endothelial cells of vascular walls, with weak labeling in neurons and glial cells [24]. Otherwise, it was found in APP/PS1 mice that the expression of PICALM colocalized with APP in neurons [25]. Further elucidation of the distribution characteristics of the protein especially under Alzheimer's pathological conditions may help us investigate its roles in AD pathogenesis.

PICALM was initially implicated to be involved in acute myeloid leukemia and acute lymphoblastic leukemia by creating a *PICALM/AF10* fusion gene through a rare translocation (t(10;11)(p13;q14)) [26, 27]. In addition to potential roles in growth, haematopoiesis and iron metabolism [18, 28, 29], the gene product (PICALM) play a major role in clathrin-mediated endocytosis (CME) [20], a process which is further associated with modulation of protein component of the plasma membrane, management of the distribution of the receptors, removal of apoptotic cells, promotion of sustained neurotransmission [30] as well as the APP metabolism [31, 32], which may be pivotal in AD pathological formation.

CME is virtually a receptor-mediated endocytosis (RME) which transports ligands binding the receptor from extracellular matrix to the cytoplasmic environment [22]. The cargo list is not homogeneous (such as proteins, lipids, growth factors, and neurotransmitters) [33]. There is a basic procedure in CME (Fig. 2): after receiving the signal derived from binding of target ligand to specific receptor on cell membrane, clathrin triskelions and adaptor protein 2 (AP-2) assemble to bind to the C-terminal region of PICALM on the cytoplasmic side of membrane while the N-terminal region of PICALM binds to phosphatidylinositol-4,5-bisphosphate (PIP2), which is located in the plasma membrane. The binding then leads to the formation of clathrin coating which consists of polyhedral lattices of clathrin network and eventually the deformation of membrane (invagination). Afterward, the newly formed clathrin-coated vesicles (CCVs) segregate from the cell

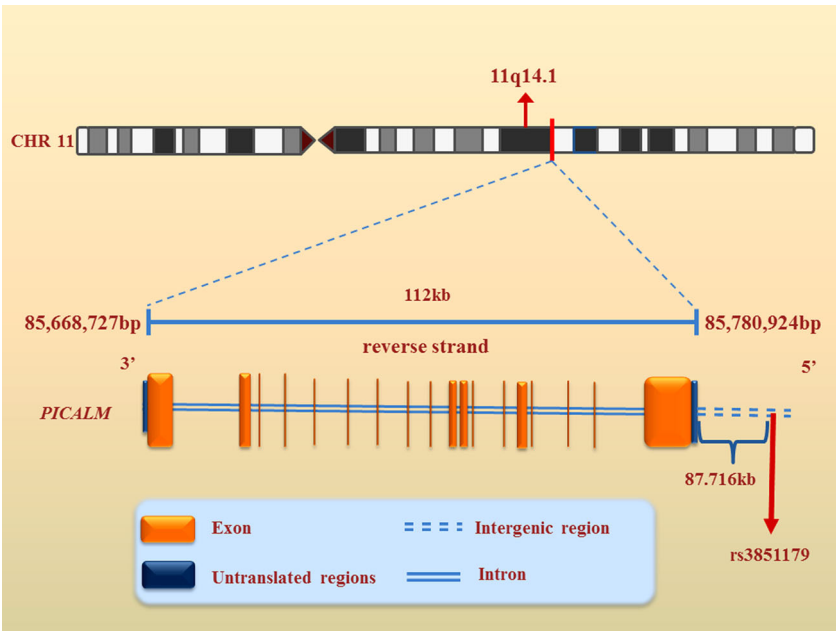

Fig. 1 Schematic of *PICALM*. *PICALM* structure spans 112 kb (85,668,727–85,780,924 bp) on chromosome 11q14 (hg19) and encodes 20 exons (represented by *orange boxes*). The most replicated SNP (*rs3851179*) associated with AD risk at 87.716 kb to 5′ terminal of *PICALM* is highlighted on this figure, which is depicted based on data from NCBI Gene database (http://www.ncbi.nlm.nih.gov/) and UCSC Genome Bioinformatics (http://genome.ucsc.edu)

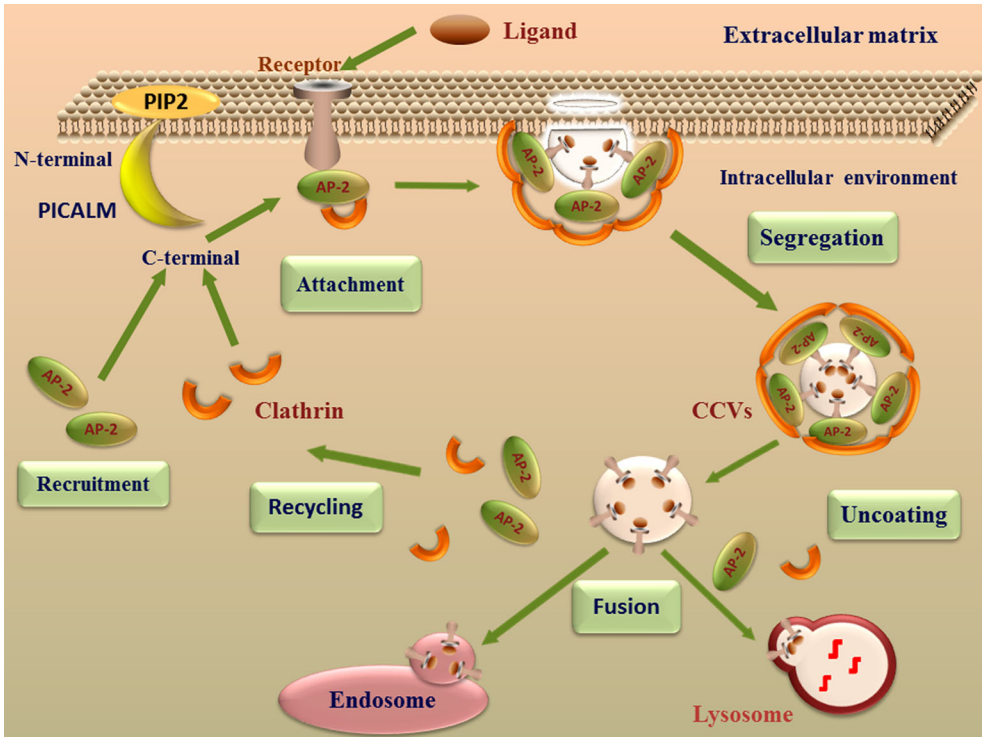

Fig. 2 Basic procedure in CME. After receiving the signal derived from binding of target ligand to specific receptor on cell membrane, clathrin triskelions and adaptor protein 2 (*AP-2*) assemble to bind to the C-terminal region of PICALM on the cytoplasmic side of the membrane while the N-terminal region of PICALM binds to phosphatidylinositol-4,5-bisphosphate (*PIP2*), which is located in the plasma membrane, leading to the formation of clathrin coating which consists of polyhedral lattices of clathrin network and eventually the deformation of membrane (invagination); then the newly formed clathrin-coated vesicles (*CCVs*) segregate from the cell membrane and enter into the cell plasma after which the clathrin cage disintegrates, which is called uncoating (a prerequisite for the vesicle to fuse with other membranes), rendering the coat components free to return to cell membrane and available for another round of CME, and fusion with either endosomes or lysosomes occurs subsequently, through which the internalized target ligands are modified or degraded

membrane and enter into the cell plasma, after which the clathrin cage disintegrates (the process is called uncoating, which is a prerequisite for the vesicle to fuse with other membranes), rendering the coat components free to return to cell membrane and available for another round of CME, and fusion with either endosomes or lysosomes occurs subsequently, through which the internalized target ligands are modified or degraded [34].

Additionally, CCVs are also involved in intracellular movement of macromolecules. These processes are employed by synaptic vesicles (SV) and facilitate a rapid communication pathway between neurons [35]. Also, PICALM has been implicated in modulating the size of CCVs and endosomes [36], which has been found aberrant in the context of AD [37]. Obviously, a better knowledge of effects of PICALM on physiological processes may promote our understanding its roles in AD pathogenesis.

Genetics of PICALM Gene in AD

In 2009, Harold et al. first reported in a large (recruiting over 16,000 individuals) two-stage GWAS of AD that a specific SNP (rs3851179), at 5′ to the *PICALM* gene, is significantly associated with AD risk in both stages (p value=1.9×10^{-8}, 1.3×10^{-9}, respectively; OR=0.86) [38]. Moreover, numerous case–control GWASs have been subsequently published, unambiguously verifying the association between various *PICALM* loci and LOAD risk in the Caucasian population [39–44] (Table 1). However, inconformity of the replication results occurred when the initial SNP (rs3851179) was investigated in Asian population (Table 2). For example, in Han Chinese population with a sample size of 1,065 [45], 609 [13], 2,486 [46], and 2,292 [47], respectively, researchers failed to identify the association between rs3851179 and AD risk either from allele frequency or genotypic association analysis. Among others, Chen reported that the association between LOAD and rs3851179 can only be observed in APOE epsilon4 (−) subgroup [48], which is against the proposition that *APOE4* and *PICALM* (rs3851179) synergistically confer risk to AD [49, 50]. On the other hand, Liu attributed these replication failures to two basic reasons: (1) the genetic heterogeneity among different populations [51] and (2) the limited sample size compared with that in Caucasian descent [52]. Consistent with which Liu observed no obvious genetic heterogeneity of rs3851179 polymorphism between

Table 1 Association between *PICALM* and AD in Caucasian populations

SNPs	Case/control	OR (95 % CI)	*p* value	Population type	References
rs17159904	549/544	–	0.04243	Caribbean Hispanic ancestry	[39]
rs541458			0.36300		
rs543293			0.72240		
rs7941541			0.73180		
rs3851179			0.32050		
rs3851179	349/359	0.98 (0.79–1.22)	0.85	Italy	[40]
rs541458	561/521	0.85 (0.71–1.01)	6.8×10^{-2}	Finland	[41]
	1,460/1,257	0.78 (0.69–0.88)	5.1×10^{-5}	Italy	
	723/819	0.81 (0.69–0.95)	1.1×10^{-2}	Spain	
	2,816/2,706	0.80 (0.74–0.88)	4.6×10^{-7}	Meta-analysis of three populations above	
rs3851179	342/277	1.387 (1.091–1.764)	7.4×10^{-4}	Caucasian, African American, and others	[42]
rs541458	1,322/1,338	0.890 (0.832–0.953)	0.087	Caucasian Americans	[43]
rs3851179	1,328/1,337	0.889 (0.833–0.949)	0.071		
rs541458	7,288/14,509	0.876 (0.838–0.915)	3.48×10^{-9}	Caucasian Americans	
rs3851179	7,294/14,508	0.880 (0.844–0.918)	3.35×10^{-9}		
rs10501602	1,291/958	0.7217	0.0102	Caucasian Americans	[44]
rs10792820		–	–		
rs694011		–	–		
rs609903		–	–		

SNP single nucleotide polymorphism, *OR* odds ratio, *CI* confidence interval

Caucasian and Asian population and reported significant association with LOAD via pooled analysis and meta-analysis approach [52]. Also, this polymorphism was also investigated in a Japanese population with a result indicating a weak association (p=0.02) [53].

Otherwise, it has been suggested that spurious association may derived from the intervention of *APOE4* status with a robust association with AD [54], suggesting that we are supposed to adjust *APOE4* status in the GWA studies of AD. However, it is still inconclusive whether there exits an

Table 2 Association between *PICALM* and AD in Asia populations

SNPs	Case/control size	Allele, genotype, or models	OR (95 % CI)	*p* value	Population type	References
rs3851179	266/343	Dom	0.85 (0.60–1.19)	0.33	Han Chinese	[13]
		Rec	0.79 (0.46–1.35)	0.39		
		Add	0.86 (0.67–1.11)	0.26		
rs3851179	474/591	AA	0.954 (0.632–1.440)	0.822	Han Chinese	[45]
		AG	0.987 (0.758–1.296)	0.948		
		GG	–	–		
		AA+AG	0.984 (0.760–1.275)	0.905		
		GG	–	–		
rs3851179	1,197/1,275	–	–	0.69	Han Chinese	[46]
rs149406961	1,133/1,159	–	–	0.001	Han Chinese	[47]
rs592297			1.364 (1.020–1.824)	0.037		
rs76710109		Dom	0.625 (0.424e0.922)	0.216		
		Add	0.728(0.549e0.966)	0.336		
rs3851179	550/407	G	0.98 (0.80–1.20)	0.840	Southern Chinese population	[50]
	76/56	AA	0.94 (0.70–1.26)	0.679		
rs541458	439/338	C	0.97 (0.79–1.18)	0.747		
	112/92	CC	1.02 (0.75–1.41)	0.882		
rs3851179	825/2,934	–	1.23 (1.03–1.47)	0.02	Japanese population	[51]

SNP single nucleotide polymorphism, *OR* odds ratio, *CI* confidence interval, *Dom* dominant model, *Rec* recessive model, *Add* additive model

interaction between *PICALM* and *APOE4* status in influencing the risk of AD [53, 13, 48, 50]. Nevertheless, given that many common contributing genes (including *PICALM*) confer large effects in aggregate but small effects singly, more comprehensive analysis and studies with larger sample size are therefore needed to elucidate the genuine association between PICALM gene and AD risk in disparate ancestries. Similarly, it is worthy to note that the effects of concomitant presence of different alleles (such as *PICALM* and *APOE4* [50], *PICALM* and *BIN1* [55]) or SNPs, which is called multilocus genotype patterns (MLGPs), on the prediction effect of AD-related phenotype as well as reduction of sample sizes needed to detect therapeutic efficacy [56] may be more significant than single locus alone [57–59]. These MLGPs maybe naturally derived from epistatic genetic effect or being located in a haplotype block, providing an alternative analytical approach for LOAD genetic risk as well as an avenue for preclinical diagnosis of AD.

Moreover, in addition to genetic heterogeneity and sample size, the ascertainment bias derived from classification method has also been implicated in influencing the effect size of case–control genetic study [60]. Similarly, a confounding factor inherent in the case–control GWASs design and derived from the potential interference of normal individuals with a long clinical silent prodromal phase has been proposed [61]. To address this confound, one approach is to use the endophenotype based on the neuroimaging data. Despite some contradictory [62], *PICALM* has been found to be significantly associated with hippocampal volume [63, 64] and entorhinal cortex thickness (ECT) [61, 64], both of which is unequivocally affected by AD-related neurodegeneration. Additionally, *PICALM* has also been linked to the earlier age at onset (AAO), which is a specific clinical phenotype of AD [65, 66].

To verify the potential mechanisms underpinning the GWAS-validated association between *PICALM* and LOAD risk and to translate them into meaningful clinical predictors or therapies, great amounts of studies have focused on investigating association between *PICALM* and phenotypes relevant to AD such as specific anatomical changes [61, 63, 64], rate of cognitive decline [67–71], or progression of the disease (such as AAO) (Table 3). For example, it has been found that a higher *PICALM* rs3851179 A allele frequency was consistently but weakly associated with better cognitive functioning in nondemented old men [68, 72] while Sweet et al. reported an association between *PICALM* and an earlier age at midpoint of cognitive decline [70]. Still, some disagreements exist [67, 69, 73].

On the other hand, two novel SNP loci at *PICALM*, rs561655 (p value$=1\times10^{-7}$), which is within a putative transcription factor binding site, and rs592297 (p value$=2\times10^{-7}$), which is a synonymous SNP in exon 5 that may influence a predicted exon splicing enhancer (ESE) sequence, had been highlighted [74]. The association with LOAD risk for rs561655 has been confirmed subsequently [75, 76]. In addition, a recent study aiming to examine the coding sequence of *PICALM* reported that rs592297 is in robust linkage disequilibrium (LD) with rs3851179 and deserved further investigation for its functional significance in AD [77].

Potential Pathways Underpinning Roles of PICALM in AD

Potential pathways underpinning roles of PICALM in AD can be roughly sorted into two classifications: amyloid-β (Aβ)-dependent (Fig. 3) and (Aβ)-independent way (Fig. 4). The latter includes tauopathy, synaptic dysfunction, disorganized lipid metabolism, immune disorder, and disrupted iron homeostasis. Even

Table 3 Associations between *PICALM* and phenotypes relevant to AD

SNPs	Phenotype	Data source	p value	References
rs17148741	HV	African American	9.4×10^{-5}	[63]
rs3851179	HV ECT	USA and Canada	0.04 0.01	[64]
ENSG00000073921	ECT	Finland, Italy, Greece, UK, Poland, and France	6.7×10^{-6}	[61]
rs2888903 rs7941541	AAO of AD	Patients with DS	0.011 0.016	[65]
rs10751134			0.040	
rs3851179	AAO of AD	ADC cohorts	0.0086	[66]
rs3851179	Cognitive function	Danish birth cohort study	0.016	[68]
rs541458	Earlier age at midpoint of cognitive decline	Caucasian	–	[70]

HV hippocampal volume, *ECT* entorhinal cortex thickness, *AAO* age at onset, *AD* Alzheimer's disease, DS Down syndrome, ADC Alzheimer's Disease Center

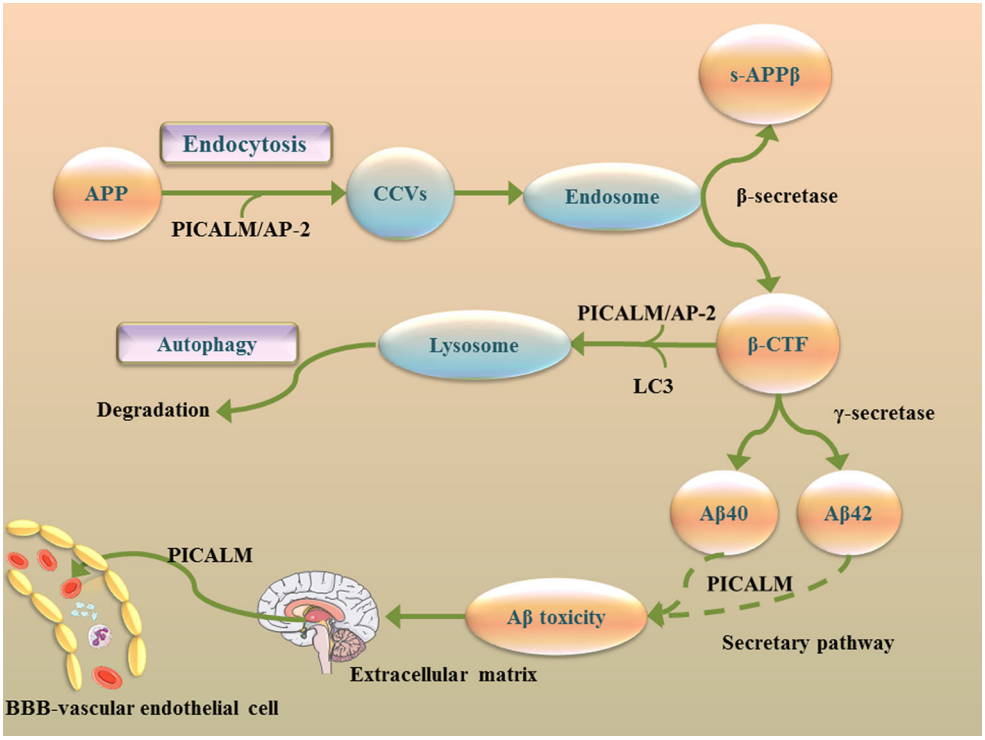

Fig. 3 Aβ-dependent role of PICALM in AD. PICALM may facilitate not only the production of Aβ peptide via endocytosis mechanism but also its clearance via promoting autophagic process of APP-CTF and facilitating extracellular Aβ to cross the vascular endothelial cells of the blood–brain barrier (*BBB*)

though the concrete molecule mechanism by which PICALM acts in AD is still an enigma, the identifications of association between PICALM and molecular pathways contributing to etiology of AD have been suggestive of promising research targets and potential intervention approaches.

Aβ Dependent Role of PICALM in AD

Role of PICALM in Amyloidogenesis

According to the amyloid cascade hypothesis, senile plaque (SP), which is composed of aggregated Aβ peptides has been

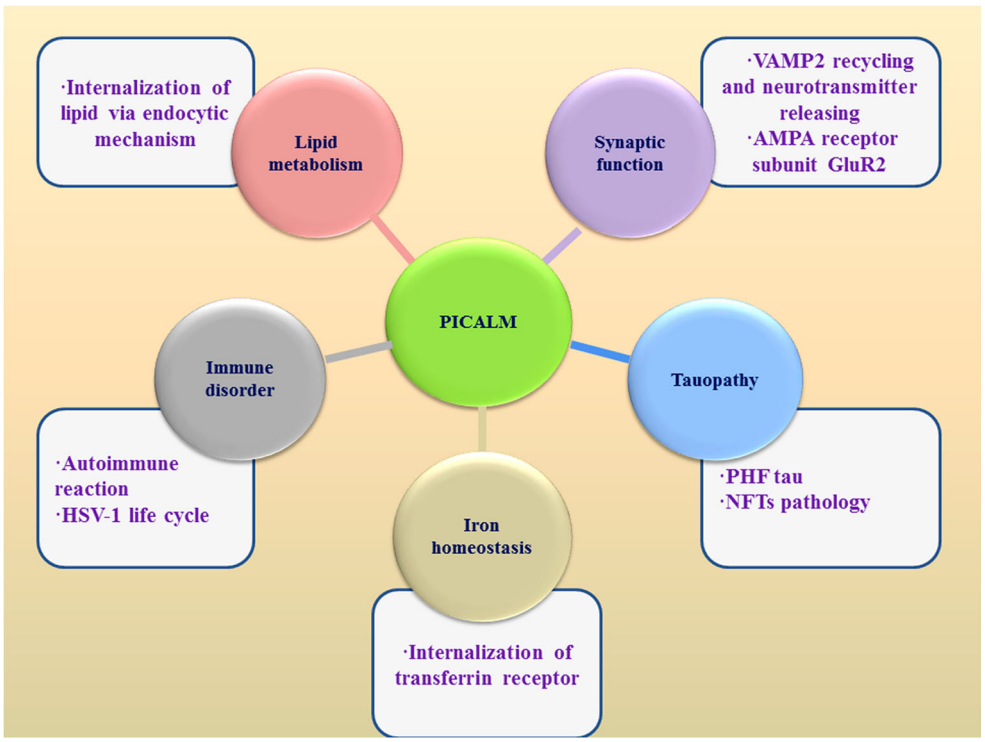

Fig. 4 Aβ-independent role of PICALM in AD. PICALM may contribute to AD risk by influencing lipid metabolism, synaptic function, immune disorder, and iron homeostasis

considered to be a special biomarker of AD. Kok et al. suggested that *PICALM* (T-allele) is marginally associated with lower coverage of SP [78] while Chibnik et al. found no association between *PICALM* (rs7110631) and deposition of SP [67]. On the other hand, increasing studies suggestive of the mismatch between total amyloid deposition and degree of AD [79] or cognitive deficits [80] and the clinical failure of SP treatment for patient's cognitive ability [81] have to some degree moved the focus from SP to the soluble oligomeric Aβ, which has been indicated to play a key role in synaptic alteration, abnormal tau phosphorylation, glial activation, and neuronal loss in AD pathogenesis [82]. Moreover, PICALM has been reported to contribute to amyloid plaque load by its influence on Aβ metabolism in cell culture models and APP/PS1 mice [25].

Aβ peptides are generated via sequential proteolysis of APP, a transmembrane protein primarily found in neurons [83], by BACE1/β-secretase and presenilin/γ-secretase complexes during the course of its trafficking along the secretory pathway, before which APP needs to be internalized through endocytosis mechanism [84], which was mediated by PICALM. In accordance with this theory, inhibition of endocytosis [85] or PICALM expression [25] has been found to result in the reduced APP internalization and diminished Aβ release. Also, endocytosis has been reported to be blocked by degradation of PICALM and AP-2 by calpain and caspase protease, levels of which rise in the context of AD [86, 87]. Therefore, PICALM may function as a modulator for APP uptake, trafficking and processing. Both the internalization and intracellular transportation of APP have been identified to be modulated by several key APs such as PICALM and AP-2 which synergistically act for bridging as well as targeting.

Apart from affecting the trafficking of APP and thus generation of Aβ peptide [25], PICALM has also been reported in yeast to be a protective modifier of Aβ toxicity itself [88]. Treusch et al. also found that Aβ can disturb the distribution of clathrin and the endocytosis process, which can be partially reversed by YAP1802 (yeast ortholog of mammalian PICALM) but not the secretory pathway [88]. Nonetheless, another subsequent yeast model in which Aβ in fusion with GFP directly enters the secretory pathway made an opposite conclusion, suggesting that Aβ toxicity depends upon concrete form of Aβ as well as the presence of PICALM [89]. Moreover, D'Angelo et al. found that Aβ toxicity is detected only when it enters the secretory pathway and disturbance of intracellular trafficking pathway diminishes the toxicity triggered by Aβ chimeric proteins [89], in consistency with the notion that PICALM can promote the Aβ toxicity through modulating its intracellular transportation during the secretory stage.

Furthermore, Ando et al. detected neither PICALM immune reactivity relevant to the Aβ deposition in the core of SP nor Aβ immune reactivity in PICALM immunoprecipitates in a postmortem examination of human LOAD brain sample, suggesting that PICALM may not directly impart influence on aggregated or oligomeric Aβ peptide [90]. On the other hand, one possible explanation of the contradictory conclusions about the role of PICALM in Aβ toxicity is that there is another process in which PICALM facilitates the inhibition of Aβ toxicity or generation. In accordance with this hypothesis, Treusch et al. suggested that Aβ toxicity is observed only when a huge amount of this peptide is produced [88]. Therefore, we can deduce that PICALM may play a role in the restraining Aβ production, which will be reviewed subsequently.

Role of PICALM in Clearance of Aβ Peptide

Autophagy (namely "self-eating") is defined as a degradation process by lysosome in which lipids, proteins, and organelles get degraded, facilitating the homeostasis in cell and metabolic balance between synthesis, degradation, and subsequent turnover of cytoplasmic substances [91]. Autophagy has been implicated in the regulation of the levels of Aβ peptides [92, 93]. Recently, Tian et al. had proposed that the clearance of Aβ peptides results from the degradation of the APP-cleaved C-terminal fragment (especially APP-βCTF) via autophagy [93] and more recently reported that PICALM/AP-2 complex played a pivotal role in the recognizing and shipping of APP-CTF from the endocytic pathway to the LC3-marked autophagic degradation process [94]. In other words, PICALM is involved in inhibiting production of Aβ peptides through promoting the transportation of APP-CTF from the plasma membrane into the process which allows the fusion of autophagosomes and endosomes, ultimately leading to the degradation of APP-CTF in lysosomes and indirectly precluding the generation of Aβ peptides [95]. These findings obviously link the PICALM to the protective role in ameliorating neurotoxicity triggered by Aβ peptides and may explain the conflicting results shown above (Fig. 3).

On the other hand, the transportation of Aβ peptides across the blood–brain barrier (BBB) and into the bloodstream is the major pathway for removal of extracellular Aβ peptides in brain parenchyma. The distribution of PICALM has been found to be primarily restricted to the endothelial cells [24], suggesting a potential role of PICALM to participate in the elimination of Aβ through BBB (Fig. 3) In line with this theory, it has been suggested that rs541458 at *PICALM* was associated with descending level of Aβ42 (two-tailed p value=0.002) in cerebrospinal fluid (CSF) [96]. However, contradictory result about the association between *PICALM* and Aβ42 in CSF exists [97].

Aβ-Independent Role of PICALM in AD

PICALM and Tauopathy in AD

Apart from the Aβ peptide, another typical pathological biomarker of AD is neurofibrillary tangles (NFTs), which consist of hyper-phosphorylated tau (p-tau) protein and further contribute to formation of intracellular aggregates of paired helical filament (PHF) tau proteins. Both total tau (t-tau) and p-tau levels are associated with neuronal degeneration and reported to rise in the context of AD [98].

Despite the substantial importance of tauopathy in AD, a number of studies have failed to identify the association between *PICALM* and CSF t-tau protein level [96], CSF p-tau at threonine 181 (p-tau181) [97], as well as NTFs in brain [67, 78]. Also, a qualitative review including 17 studies summarized that *PICALM* exhibits consistency in affecting level of Aβ but not tau. However, it was suggested that CSF profile combining Aβ1–42 and p-tau181 was linked to rs541458 (OR=0.68, 95 % CI=0.47–0.98) rather than rs3851179 [99]. Further, a recent study employing Western blotting analysis indicated the association between PICALM and NFTs pathology in individuals with LOAD, EOAD, and DS [90]. Also, it was found that PHF tau proteins coimmunoprecipitated with PICALM [90]. All these results are suggestive of the involvement of PICALM in tauopathy of AD.

PICALM and Synaptic Function in AD

Biological synapse is the communication hub in the neural network and performs its function by delivering the chemical signal called neurotransmitter. In the presynaptic terminal, neurotransmitter release via exocytosis starts with the integration of SV to the presynaptic membrane [100]. In addition, soluble *N*-ethyl-maleimide-sensitive fusion protein attachment protein receptor (SNARE) proteins (such as VAMP2, the most abundant SV protein) provide the majority of the energy and specificity needed in the SV fusion [101], following which the retrieval of SV components (such as VAMP2) is achieved via CME [102], which is mediated by PICALM [20].

It has been demonstrated that the expression level of PICALM can affect the amount of VAMP2 at the plasma membrane by regulating endocytosis [103]. Moreover, Miller et al. suggested that PICALM/SNARE interaction is the prerequisite for recycling of SNARE between the plasma membrane and endosomes [104]. We can therefore infer that PICALM may be associated with the synaptic function via mediating the retrieval of VAMP2 which facilitates SV fusion and thus the neurotransmitter release. Furthermore, Aβ has been implicated in affecting the neurotransmitter release by disturbing the complex formed by VAMP2 and synaptophysin [105], bolstering the conflicting role of PICALM versus Aβ peptide. It is therefore possible that PICALM acts as a protector for AD pathology in this specific manner.

In addition to affecting SNAREs at the presynaptic membrane, PICALM has also been found to modulate the abundance of alpha-amino-3-hydroxy-5-methyl-4-isoaxolepropionate (AMPA) receptor subunit GluR2 at the postsynaptic membrane by influencing its endocytic trafficking [106]. Interestingly, GluR2 levels on the surface of the postsynaptic terminal are closely associated with the intensity of synaptic transmission [107]. Also, dysfunction of AMPA receptor has been suggested as a culprit for AD incidence [108]. All these results strengthened the association between PICALM and synaptic function in triggering onset of AD.

PICALM and Lipid Metabolism in AD

Aberrant concentration of lipid molecules in AD tissues has been previously reported [109–111] and lipoproteins apolipoprotein E (ApoE) and apolipoprotein J (ApoJ) were associated with AD via genetic and proteomic studies [112]. Additionally, researchers showed that statins (lipid-lowering drugs such as simvastatin) may confer protection to AD risk [113–115] despite contentious argument [116]. Based on these findings which provide strong evidences linking AD and high-density lipoproteins and related proteins in plasma, it is therefore of great importance to understand the etiology of AD from the perspective of PICALM's potential role in lipid metabolism.

Given that PICALM played a key role in CME (or RME) and lipid is on the cargo list of trafficking, we can therefore postulate that PICALM may be involved in affecting the lipid metabolism and thus the AD risk by modulating its internalization and transportation. To our knowledge, there seems to be however little evidence-based studies suggestive of this association [117, 118] and given the complicated picture of the genetic influence (of *PICALM* and *ABCA7* [119]) on cholesterol transport, more in-depth studies warrant to validate and bolster the association among PICALM, AD risk, and lipid metabolism.

PICALM and Immune Disorder in AD

Virus infection hypothesis posits that virus infections contribute to the etiology of AD onset [120]. Particularly, compelling pieces of evidence have been strongly suggestive of the association between herpes simplex virus 1 (HSV-1) and AD [121–125].

Licastro et al. and Carter et al. proposed that the presence of susceptibility genes associated with AD (such as *PICALM*) leads to some vulnerability of HSV-1 invasion to CNS by affecting immune defense ability and viral invasiveness, and thus results in subsequent neuropathological insults, such as neuronal loss, inflammation, and amyloid deposition [126, 127], suggesting the causative interaction among genes,

pathogens, and the immune system in etiology of sporadic AD. Similarly, PICALM has been linked also to HSV-1 life cycle, suggesting that PICALM binds to receptors used by HSV-1 for cellular entry, intracellular trafficking, and nuclear egress [128]. On the other hand, it has been suggested that the amino acid stretches (namely vatches) in proteins expressed by HSV-1 are homologous to PICALM and other risk loci and pathogens relevant to AD [129]. Accordingly, immune response triggered by HSV-1 infection may target their human counterparts, leading to protein knockdown and neurons killing [129].

As an environmental risk factor, roles of HSV-1 and other pathogens in AD etiology are increasingly coming into the spotlight. However, the specific role and therapeutic significance of PICALM in the virus infection hypothesis still warrants more investigations.

PICALM and Iron Homeostasis in AD

Mounting pieces of evidence have indicated the robust association between iron homeostasis and AD. For example, Crespo et al. hypothesize that the aberrant level of systemic iron status observed in AD patients owe much to an iron homeostasis dysregulation and the intracellular iron accumulation result in increased oxidative damage which would contribute to AD [130]. In accordance with this hypothesis, it has been found that huperzine A (an anti-AD drug in China) inhibits the rising level of iron in CNS, as well as the expression of transferrin-receptor 1 and the transferrin-bound iron uptake in cultured neurons [131]. On the other hand, mitochondrial ferritin has been implicated in the protective mechanism of AD [132, 133]. Moreover, anemia [134] and iron level in diet [135] have also been linked to AD prevalence. Taken all together, we can make a preliminary conclusion that maintenance in iron homeostasis plays a significant role in prevention of AD.

However, it seems that little literatures have been focused on the investigation of roles of PICALM in iron homeostasis in the context of AD. Scotland et al. found that PICALM function as a modulator of transferrin-receptor (TfR) internalization and PICALM-deficient cells exhibit characteristics associated with iron deficiency and extremely sensitive to iron chelation [136]. It is imperative to know the specific mechanism by which PICALM functions in iron homeostasis and contributes to AD.

PICALM as a Therapeutic Target for AD

All in all, the potential pathways underpinning roles of PICALM in AD etiology suggested by studies shown above have provided several avenues for further investigations and intervention of the disease. Among them, the focus should be put on the Aβ-dependent pathways because of its direct influence on Aβ pathology, which is the most proved culprit of AD onset till now. However, it seems that PICALM can simultaneously promote production [25, 88, 89] and elimination [93, 94] of Aβ peptide (or its neurotoxicity) via APP internalization and transportation with however subsequently disparate processing (enzymolysis in endosomes and degradation in lysosomes). Still, we may target PICALM as a potential modulator of tauopathy in the pursuit of therapeutic strategies for AD [90].

Also, it has been suggested that the level of full-length PICALM was substantially decreased while that of its abnormally cleaved fragments increases in AD brains [90], suggesting the possibility that impaired PICALM may contribute to the dysfunction of endocytosis and therefore a series of relevant physiological processes and eventually the onset of AD. If it was the case, we could hypothesize that restoration of normal PICALM may act as a protector for AD progression. Before we achieve transition from experimental data to clinical efficacy, however, more accurate and detailed mechanisms by which PICALM contribute to AD etiology should be further explored.

Concluding Remarks

PICALM gene is a novel and replicable contributor to AD risk despite its transcript sorts warrant further expansion and confirmation. Moreover, although the association between *PICALM* and AD risk have been well replicated and bolstered in Caucasian populations, the results get contentious when it comes to other populations such as Asian group. It is possible that larger sample size, matching for significant confounding factors like *APOE4* status and employment of more precise phenotype of the disease (such as neuroimaging data) may improve the strength of association in case–control studies. On the other hand, multi-locus genotype pattern (MLGPs) provided a novel and promising strategy for future studies and maybe preclinical diagnosis of AD. Even though there is discrepancy in the distribution pattern (endothelial cells or neurons) of PICALM in the CNS, investigation about roles of PICALM in affecting production and clearance of intracellular and extracellular Aβ peptide (especially the oligomers) should be the priority in the future. Other potential pathways, such as tauopathy, synaptic function, lipid metabolism, immune disorder, and iron homeostasis, should also need more investigations before translating into efficacy for clinical practice. We believe that figuring out the way in which PICALM is involved in AD pathogenesis will facilitate our understanding of the mechanism of the disease. Finally, given that LOAD is a complex multifactorial neurodegenerative disease, we

sincerely hope that these new findings of PICALM will open up novel avenues for further studies on therapeutic intervention.

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Conflict of Interest The authors declare no conflicts of interest.

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