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ORIGINAL ARTICLE

Correlation of *PICALM* polymorphism rs3851179 with Alzheimer's disease among Caucasian and Chinese populations: a meta-analysis and systematic review

Bin Zhu[1] · Li-Xia Li[2] · Lei Zhang[3] · Shu Yang[1] · Yue Tian[1] · Shan-Shan Guo[1] · Wei Zhang[2] · Zhi-Gang Zhao[1]

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Abstract
The rs3851179 which located at upstream of *PICALM* was reported to be associated with Alzheimer's disease (AD); however, the relationship is still undefined. To gain a more precise understanding of the association, we conducted a meta-analysis: a comprehensive survey of 16 case-control studies that evaluated the role of rs3851179 gene variants in AD patients. The overall analysis revealed a significant association between the polymorphism and AD in the allelic, homozygote, heterozygote, dominant, and recessive models ($p < 0.05$). When stratified by ethnicity, a significant association was observed between AD development in Caucasian populations and the five-genetic models; Asian populations, however, featured a significant association in only the allelic, homozygote, and recessive models. We did not observe any influence of *APOE ε4* carrier status on the incidence of AD and rs3851179 ($p > 0.05$). Our meta-analysis thus suggested that the *PICALM* rs3851179 polymorphism was associated with AD; the *APOE ε4* status did not influence the relationship. Nevertheless, considering the limitations of our meta-analysis, further large-scale studies should be conducted to gain a more comprehensive understanding.

Keywords *PICALM* · Alzheimer's disease · rs3851179 · *APOE ε4* · Polymorphism

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by the decline of memory and other cognitive functions (Mawuenyega et al. 2010; Wang et al. 2017). As a prominent global health issue, AD has become a key epidemiological factor compromising the quality of life of the elderly: a total of 46.8 million people worldwide currently live with dementia and the number is projected to increase to 131.5 million by 2050 according to the "World Alzheimer Report 2015". It was reported that nearly 5.3 million Americans have AD, of whom 5.1 million are over 65 years old (Alzheimer's Association 2015). Possibly due to the complex roots of AD pathogenesis—genetic factors, lifestyle, and environmental conditions all contribute to its onset—available treatments slow disease progression only slightly (Tosto et al. 2016).

Researchers discovered that genetic factors had contributed to the development of AD (Bettens et al. 2013; Mengel-From et al. 2013). Recent genome-wide association studies (GWS) have also identified several putative candidate genes conferring risk for AD, such as phosphatidylinositol binding clatrin assembly protein (*PICALM*), clusterin (*CLU*), and ATP binding cassette subfamily A member 7 (*ABCA7*) (Zhu et al. 2017). Most of such risk genes are involved in neural apoptosis and the production, degradation, and clearance of Aβ. Among these genes, *PICALM* has been identified to play a crucial role in AD development (Thomas et al. 2016; Zhao et al. 2015).

PICALM is located on chromosome 11q14 and extends over 112 kb. It is involved in reversing the recruitment of

✉ Wei Zhang
ttyyzw@163.com

✉ Zhi-Gang Zhao
1022zzg@sina.com

[1] Department of Pharmacy, Beijing Tiantan Hospital, Capital Medical University, Beijing 100050, China

[2] Department of Geriatrics, Beijing Tiantan Hospital, Capital Medical University, Beijing 100050, China

[3] Department of Pharmacy, Beijing Shijitan Hospital, Capital Medical University, Beijing 100050, China

clathrin and mediating endocytosis; it thus protects neurons against Aβ toxicity. A large-scale GWAS conducted by Harold et al. identified the rs3851179 (A > G) single nucleotide polymorphisms (SNPs) in *PICALM*; the study found that it was significantly associated with AD in Caucasian populations (Harold et al. 2009). A later study performed by Seshadri et al. reported similar results in Spanish populations (Seshadri et al. 2010). Liu et al. conducted two pooled meta-analyses and found the same significant association in Asian populations (Liu et al. 2013, 2017). These studies were, however, limited by their sample size and ethnic bias; the results could not define the relationship between rs3851179 and AD in either Caucasian or Asian populations.

Further confounding possible conclusions, results from recent investigations are inconsistent with those from the aforementioned studies: Shankarappa et al. and Liu et al. reported no correlation between rs3851179 susceptibility and AD in Indian and Chinese populations, respectively (Shankarappa et al. 2017; Li et al. 2011). The present study sought to further elucidate a possible correlation between rs3851179 polymorphism and AD; we performed a meta-analysis of case-control studies by pooling all eligible studies—including published theses—to explore the correlation.

Methods

Search strategy

This meta-analysis was performed according to the criteria for the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA). Two investigators independently searched PubMed, Embase, Web of Knowledge, China National Knowledge Infrastructure (CNKI), and Wan Fang Data for studies published before 20 November 2017. MeSH and title/abstract were used to find eligible case-control studies according to the following format: ("Alzheimer's disease","Alzheimer disease", "AD" or "Dementia*") AND ("phosphatidylinositol binding clatrin assembly protein", "*PICALM*", "rs3851179") AND ("polymorphism", "SNP", "mutation", "variant" or "genotype").

Inclusion and exclusion criteria

Eligible reports met the following criteria: (1) the study evaluated the association between *PICALM* rs3851179 polymorphism and risk of AD, (2) the report focused on detailed genotype frequencies among human beings of late onset sporadic AD, and (3) the investigation was a case-control study. Accordingly, the exclusion criteria were as follows: (1) comment, review, and editorial articles; (2) studies without detailed genotype data; and (3) reports with overlapping data.

Data extraction

Two investigators independently extracted relevant information from all eligible articles by using a standardized form. If available, the following data were collected from each study: primary author, year of publication, country of origin, ethnicity of subjects, source of controls, frequency of genotypes among AD patients and controls, and evidence of Hardy-Weinberg equilibrium among controls. If multiple publications conducted a study on the same population, the study with the most thorough analysis was selected. Any discrepancy was resolved through discussion among the two investigators until a consensus was reached. If dissent remained, a third investigator resolved the dispute.

Quality assessment

The quality of the literature was evaluated independently by two investigators using quality scoring criteria modified from a previous study (Zhang et al. 2017). Quality scores ranged from 0 (worst) to 10 (best). Studies scoring higher than 5 were classified as having adequate quality.

Statistics analysis

All statistical analyses were performed by using the STATA version 12.0 (STATA Corporation, College Station, TX, USA). Hardy-Weinberg equilibrium (HWE) was assessed among controls using a χ^2 test. A P value <0.05 was considered significant. The odds ratio (OR) and 95% confidence interval (95% CI) were calculated to assess the strength of associations between *PICALM* polymorphism and AD susceptibility. Pooled ORs were obtained from a combination of single studies by homozygote comparison (AA vs.GG), heterozygote comparison (AG vs. GG), dominant model (AG + GG vs. AA), recessive model (GG vs. AG + AA), and allelic model (A vs. G). Heterogeneity was evaluated by Q statistic and I^2 statistic. The fixed effect model (Mantel–Haenszel method) was used to calculate the pooled ORs (Q-test >0.10 or $I^2 < 50\%$); for all other analyses, the random-effect model (DerSimonian–Laird method) was used. The significance of the pooled ORs was assessed by a Z-test, where $P < 0.05$ indicated statistical significance. Subgroup analyses were conducted based on ethnicity and source of control. Sensitivity analyses were performed to display possible variability. Begg's and Egger's linear regression tests were applied to assess potential publication bias. We further evaluated the number of missing studies in the meta-analysis by applying the trim and fill method; we recalculated the pooled risks with the addition of the missing studies.

Results

Characteristics of the studies

A total of 189 relevant studies were identified from an initial search through databases. Thirteen duplicated publications were removed in the preliminary screening. After screening titles and abstracts, 139 irrelevant articles were further excluded. The remaining articles were subjected to full-text review by two independent investigators. Finally, 16 eligible articles were included in this meta-analysis. The flow diagram of the search process is illustrated in Fig. 1. The studies were published between 2009 and 2017. They encompassed a total of 6972 AD patients and 10,199 controls; the former was composed of 3227 Asians and 3745 Caucasians. The characteristics of the enrolled studies are summarized in Table 1. The genotype and allele distribution among AD cases and controls are summarized in Table 2. The distributions of the genotype frequencies of the controls were all consistent with the Hardy-Weinberg equilibrium (HWE) (all $P > 0.05$)).

Meta-analysis results

Heterogeneity was identified by Q-test and I-squared statistic in five genetic models. As is shown in Table 3, serious heterogeneity was found only in the heterozygote and recessive models ($I^2 = 59.8\%$, $I^2 = 57.1\%$); the random-effect model was therefore employed in the analysis. The fixed model was used in the homozygote, dominant and allelic models ($I^2 = 22.3\%$, $I^2 = 18.6\%$, $I^2 = 43.3\%$). The results revealed that there was a significant association between the *PICALM* rs3851179 polymorphism and AD in all five genetic models. The pooled ORs revealed that the allelic, homozygote, and heterozygote models showed a decreased risk of AD (OR = 0.894, 95% CI: 0.865–0.923; OR = 0.773, 95% CI: 0.720–0.829; OR = 0.878, 95% CI: 0.838–0.920; OR = 1.213, 95% CI: 1.135–1.296; and OR = 1.162, 95% CI: 1.074–1.258, respectively). The dominant (OR = 1.213, 95% CI: 1.135–1.296) and recessive models (OR = 1.162, 95% CI: 1.074–1.258) showed an increased risk of AD. Subgroup analysis based on ethnic descent showed that rs3851179 polymorphism was strongly associated with AD

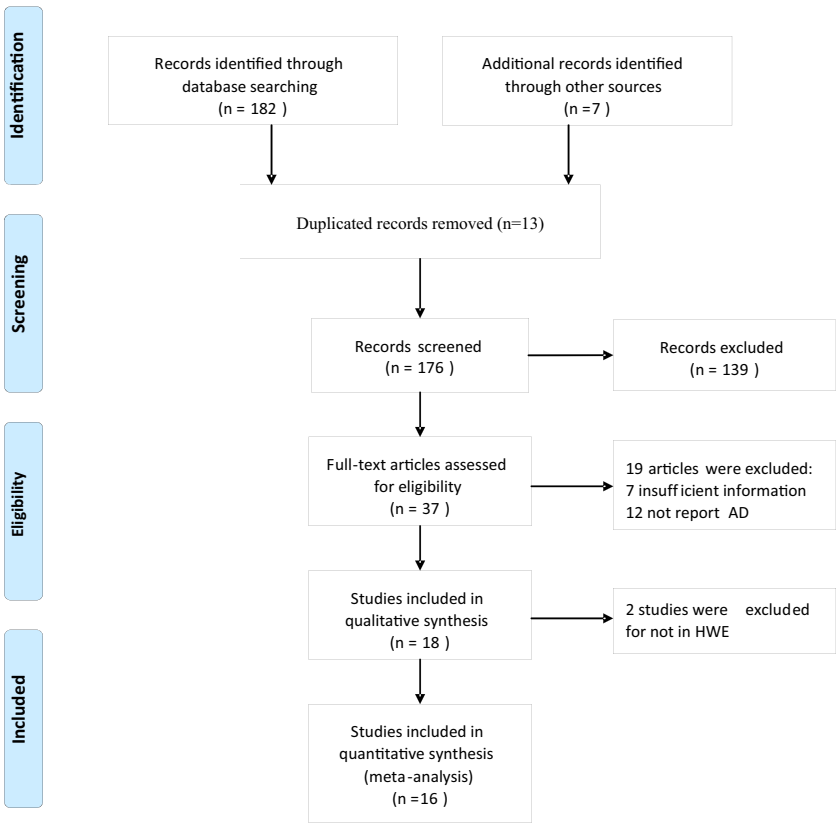

Fig. 1 Flow sheet summarizing studies identification and selection

Table 1 Characteristics of individual studies included in the meta-analysis

Author	Year	Country	Age(N)		Diagnostic criteria	Genotype methods
			AD	Control		
Shankarappa et al.(Bushlin et al. 2008)	2017	India	67.9 ± 8.7(243)	66.9 ± 8.7 (164)	HMSE	PCR- RFLP
Jin Tai Yu et al.(Yu et al. 2011)	2011	China	76.98 ± 6.58(266)	76.69 ± 5.93(343)	NINCDS-ADRDA	MALDI-TOFMS
Lu Hua Chen et al.(Chen et al. 2012)	2012	China Hong Kong	N/A(462)	N/A(350)	NINCDS-ADRDA	PCR- RFLP
Santos-Rebouças CB et al.(Santos-Rebouças et al. 2017)	2017	Brazil	77.15 ± 6.36(174)	70.7 ± 6.04(176)	NINCDS-ADRDA	TaqMan
Carrasquillo et al.(Carrasquillo et al. 2010)	2010	USA	N/A(1829)	N/A(2576)	NINCDS-ADRDA	TaqMan
Harold et al.(Harold et al. 2009)	2009	USA	N/A	N/A	NINCDS-ADRDA, DSM-IV/CERAD	Illumina Infinium™ system
Harold et al.(Harold et al. 2009)	2009	Germany	N/A	N/A	NINCDS-ADRDA, DSM-IV/CERAD	Illumina Infinium™ system
Harold et al.(Harold et al. 2009)	2009	UK	N/A	N/A	NINCDS-ADRDA, DSM-IV/CERAD	Illumina Infinium™ system
Lambert et al.(Lambert et al. 2009)	2009	France	N/A	N/A	NINCDS-ADRDA	N/A
Seshadri S et al.(Seshadri et al. 2010)	2010	Spain	78.8 ± 7.9(1140)	49.9 ± 9.2(1209)	NINCDS-ADRDA /DSM-IV	PCR- RFLP
Ohara T et al.(Ohara et al. 2012)	2012	Japan	83.2 ± 6.5(825)	60.2 ± 11.5(2934)	DSM-III	Multiplex PCR-based Invader assay
Piaceri I et al.(Piaceri et al. 2011)	2011	Italy	74.04 ± 6.1(349)	74.5 ± 6.2(359)	DSM-IV	PCR-RFLP
Hong Lei Li et al.(Li et al. 2011)	2011	China	69.4 ± 9.9(474)	68.564 ± 9.6(591)	NINCDS-ADRDA /DSM-IV-R	PCR-RFLP
Xiao Yan Liu et al.(Liu 2014)	2014	China	75.2 ± 5.0(239)	72.02 ± 5.5(207)	NINCDS-ADRDA/MMSE	MALDI-TOFMS
Juan Hui et al.(Hui 2014)	2014	China	77.35 ± 8.35(248)	70.23 ± 7.58 (340)	NINCDS-ADRDA	N/A
Hui Zhen Wang et al.(Wang et al. 2016)	2016	China(East China)	N/A(416)	N/A(426)	N/A	SNP shot assay
Ding Ding et al.(Ding 2012)	2012	China	81.2 ± 5.3(54)	80.4 ± 4.9(216)	MMSE	TaqMan
Klimkowicz-Mrowiec A et al.(Klimkowicz-Mrowiec et al. 2013)	2013	Poland	73.9 ± 5.2(253)	73.8 ± 6.9(240)	NINCDS-ADRDA	TaqMan

HMSE Hindi Mental Status Examination, *NINCDS-ADRDA* National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders- 4th Edition, *MMSE* Mini-mental State Examination

Table 2 PICALM rs3851179 genotype and allele distribution among AD cases and controls in the included studies

	AD					Control					HWE	Quality
	AA	GA	GG	A	G	AA	GA	GG	A	G		
Shankarappa et al.	47	104	92	198	288	32	79	53	143	185	0.79	4
Jin Tai Yu et al.	26	126	114	178	354	44	164	135	252	434	0.60	6
Lu Hua Chen et al.	77	210	170	364	550	56	163	122	275	407	0.90	5
Santos-Rebouças CB et al.	12	19	99	43	217	22	71	83	115	237	0.27	5
Carrasquillo et al.	198	803	815	1199	2433	349	1190	1013	1888	3216	0.99	7
Harold et al.	135	499	525	769	1549	276	1032	880	1584	2792	0.32	7
Harold et al.	76	227	252	379	731	108	384	332	600	1048	0.85	7
Harold et al.	244	1004	979	1492	2692	720	2240	1876	3680	5992	0.22	7
Lambert et al.	240	892	893	1372	2678	688	2378	2257	3754	6892	0.12	7
Seshadri S et al.	103	479	559	685	1597	140	543	527	823	1597	0.99	6
Ohara T et al.	121	394	310	636	1014	518	1434	982	2470	3398	0.89	7
Piaceri I et al.	55	154	140	264	434	61	153	145	275	443	0.06	6
Hong Lei Li et al.	55	258	161	368	580	74	321	196	469	713	0.07	6
Xiao Yan Liu et al.	23	133	83	179	299	41	100	66	181	233	0.78	6
Juan Hui et al.	34	139	75	207	308	61	186	159	289	504	0.59	5
Hui Zhen Wang et al.	55	198	162	308	522	57	214	155	328	524	0.21	6
Ding Ding et al.	9	19	23	37	65	28	100	84	156	268	0.84	7
Klimkowicz-Mrowiec A et al.	24	128	100	176	328	34	110	99	178	308	0.70	4

HWE Hardy-Weinberg equilibrium

among Caucasians in the five genetic models, while the association in Asians populations was only significant in the allelic (OR = 0.918,95% CI: 0.860–0.981), homozygote (OR = 0.822, 95% CI: 0.714–0.947), and dominant models (OR = 1.172, 95% CI: 1.030–1.333) (Table 3 and Fig. 2). We subsequently performed a comparison of the risk of *PICALM* rs3851179 polymorphism for AD development between the APOE ϵ4+ group and the APOE ϵ4- group to explore the potential effect of APOE ϵ4 status on AD development. However, we did not observe any correlation between the polymorphism and AD in either the APOE ϵ4+ group or the APOE ϵ4- group in any of the five genetic models (Table 4).

Publication bias

No significant publication bias was found in the Begg's test or Egger's test ($P > 0.05$)(Fig. 3). The trim and fill method was also employed to further determine a possible publication bias. Negligible changes in OR and 95% CI were observed between the different (Table 5).

Sensitivity analysis

We performed a sensitivity analysis to assess the influence of each individual study on the pooled OR by sequentially

Table 3 Summary of the overall and subgroup analysis results from different comparative genetic models

	I^2	OR	95%CI	P	Model
A vs. G					
Asian	4.2%	0.918	0.860–0.981	0.011	Fixed
Caucasian	61.5%	0.874	0.816–0.936	0.001	Random
Overall	43.3%	0.894	0.865–0.923	0.001	Fixed
AA vs. GG					
Asian	10.3%	0.822	0.714–0.947	0.007	Fixed
Caucasian	33.1%	0.757	0.697–0.822	0.001	Fixed
Overall	22.3%	0.773	0.720–0.829	0.001	Fixed
AG vs. GG					
Asian	30.6%	0.940	0.851–1.038	0.223	Fixed
Caucasian	72.1%	0.861	0.816–0.908	0.003	Random
Overall	59.8%	0.878	0.838–0.920	0.005	Random
AG + GG vs. AA					
Asian	20.2%	1.172	1.030–1.333	0.016	Fixed
Caucasian	23.6%	1.227	1.136–1.326	0.001	Fixed
Overall	18.6%	1.213	1.135–1.296	0.001	Fixed
GG vs. AG + AA					
Asian	22.1%	1.096	0.997–1.204	0.159	Fixed
Caucasian	70.4%	1.217	1.095–1.352	0.001	Random
Overall	57.1%	1.162	1.074–1.258	0.001	Random

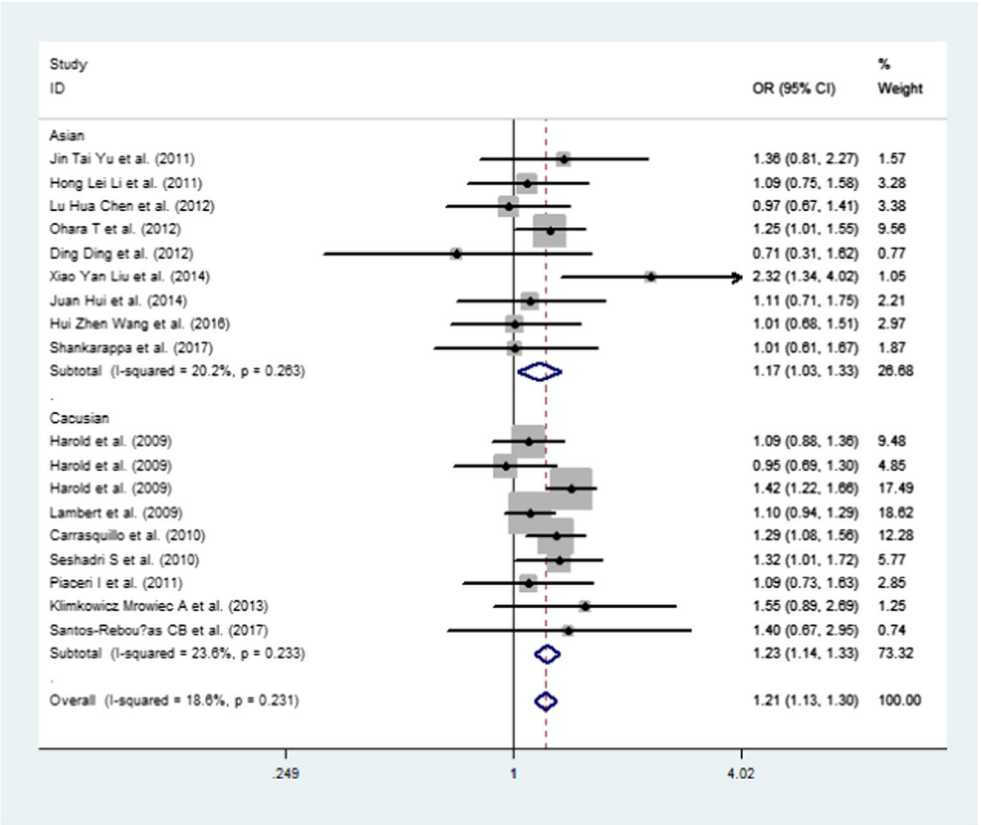

Fig. 2 Forest plot of association between PICALM rs3851179 polymorphism (AG + GG vs. AA) and AD susceptibility

removing each eligible study. The results indicated that only the removal of the study by Lambert et al. led to the loss of a significant association between *PICALM* rs3851179 polymorphism and the risk of AD in the pooled population. No other single study influenced the quality of the pooled ORs in the sensitivity analyses (Fig. 4).

Disscussion

Ubiquitously expressed in the central nervous system, especially at presynaptic and postsynaptic structures, *PICALM* has been shown to be associated with the morbidity of AD. Bushlin et al. observed that the reduction in PICALM levels in cultured embryonic hippocampal neurons resulted in dendritic dystrophy, reduced endocytosis, and disrupted secretory transport (Bushlin et al. 2008), and Kanatsu et al. reported that the reduction in PICALM levels decreased Aβ deposition, as well as brain levels of insoluble Aβ1–42 in vivo (Kanatsu et al. 2016).

Since Harold et al. first reported on the possible association of the rs3851179 polymorphism with *PICALM*, several investigations have published contradictory results. We found that rs3851179 polymorphism was associated with AD in the domain and recessive models in the overall meta-analysis; in the allelic, homozygote, and

Table 4 The influence of APOE ε4 status to PICALM rs3851179 polymorphism with AD susceptibility

Genetic model	APOE ε4+				APOE ε4-			
	I^2	OR	95%CI	P	I^2	OR	95%CI	P
A vs. G	28.8%	0.885	0.728–1.074	0.217	22.8%	0.883	0.757–1.029	0.111
AA vs. GG	27.6%	1.043	0.637–1.708	0.867	60.5%	0.657	0.364–1.185	0.163
AG vs. GG	0%	1.246	0.926–1.676	0.146	0.0%	0.868	0.685–1.100	0.241
AG + GG vs. AA	40.6%	1.087	0.686–1.724	0.722	75.6%	1.450	0.721–2.915	0.297
GG vs. AG + AA	0%	0.826	0.620–1.100	0.190	0.0%	1.205	0.961–1.510	0.106

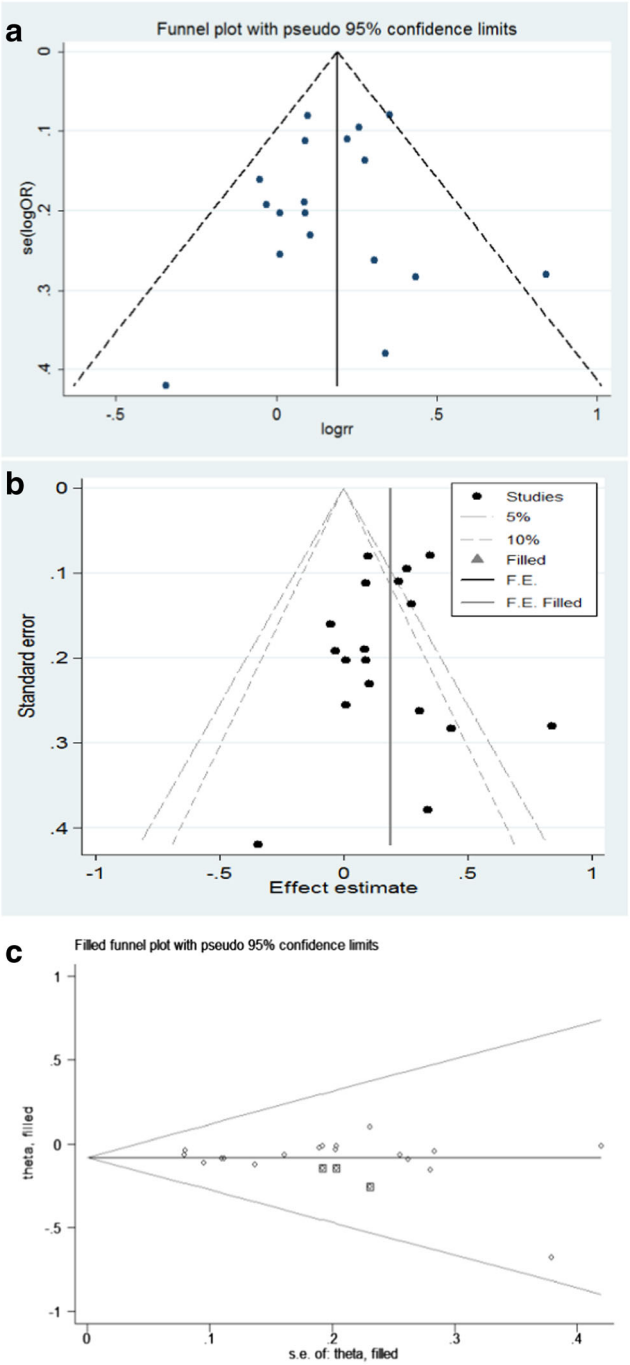

Fig. 3 The publication bias examined by Begger and Egger's test (AG + GG vs. AA); **a** The funnel plot of Egger's test; **b** Contour enhanced funnel plots of the dominant genetic model; **c** The funnel plot after using Trim and Fill method

heterozygote models, however, the polymorphism reflected a reduced risk of AD. The subgroup analysis of the Caucasian population showed a trend similar to the overall analysis in all models, while no association was found in the heterozygote and recessive models in the Asian population; the former finding agreed with those of Harold et al., while the latter was in accordance with those of Wang et al. (2016). Our results diverged from those of Liu et al., however, which showed that the polymorphism was associated with AD in the recessive model (Liu et al. 2013); the difference may be caused by the numbers of enrolled studies.

Table 5 The publication bias examined by Begger and Egger's test

Gene model	Begg's test *P* value	Egger's test *P* value	Trim and Fill	95% CI
A vs. G	0.970	0.709	0.887	0.859–0.916
AA vs. GG	0.910	0.517	0.759	0.709–0.814
AG vs. GG	0.622	0.865	0.883	0.810–0.963
AG + GG vs. AA	0.733	0.569	1.210	1.132–1.293
GG vs. AG + AA	0.91	0.546	1.197	1.103–1.300

The present study sought to further contribute to the literature by examining the difference in the *APOE ϵ4* status between AD patients and healthy controls. As one of the risk factors for AD, APOE ϵ4 can form deposits in neuritic plaques and neurofibrillary tangles; it thus augments the effect of other factors promoting disease progression (Michaelson 2014). It was reported that *APOE ϵ4* may account for approximately 50% or more of the late onset Alzheimer's disease cases in the USA. Nevertheless, we did not find any significant differences between *APOE ϵ4* carriers and non-carriers. Our results were in accordance with those reported by Tomoyuki Ohara et al., which showed no significant association between *PICALM* and *APOE ε4* carrier status ($p = 0.68$) (Ohara et al. 2012).

Compared to prior studies, our meta-analysis made use of a more comprehensive collection of references; we enrolled investigations from not only the Alzgene database, but also recently published studies and theses. The present study thus performed a thorough analysis of the relationship between the rs3851179 polymorphism and AD in the Caucasian and Asian population; our findings provide new support for the GWAS results of Harold et al. We also add to the literature by having used the obtained data to evaluate of the association of *APOE ε4* with AD and the rs3851179 polymorphism. Upon selecting eligible studies, a methodological quality assessment was conducted; all studies were of acceptable quality.

Due to potential limitations of the present meta-analysis, however, results from this study should be interpreted with caution. Specifically, there were no unified detection methods: serious heterogeneity was observed even in our subgroup analyses, possibly accounting for the negative results. Further, publication bias – though none was detected – or other confounding factors may have further distorted the meta-analysis. Our investigation into the association between *PICALM* rs3851179 polymorphisms

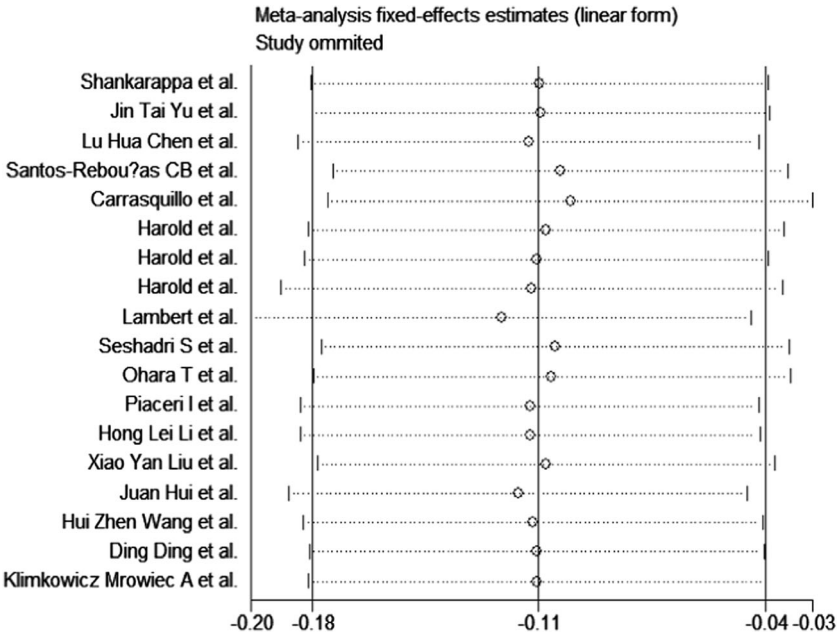

Fig. 4 Sensitivity analysis result of the association between PICALM rs3851179 polymorphism (AG + GG vs. AA) and AD susceptibility

and *APOE ε4* status featured another limitation: insufficient data precluded a comprehensive meta-analysis. Small sample sizes in each study may underlie the failure to achieve statistical significance.

Conclusion

In conclusion, the results of this meta-analysis suggest that the *PICALM* rs3851179 polymorphism is associated with the susceptibility to AD among Asians and Caucasians. However, as confounding factors may exist, our results were not consistent with several prior case-control studies. Future research should analyze larger populations with different ethnicities and prioritize data including *APOE ε4* status in order to explore the broader role that polymorphisms play in the pathogenesis of AD.

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Author's contributions BZ. and ZGZ designed this study and had full access to all of the data in the study; LXL and SYA acquisition of data, LZ, YT and SSG analysis and interpretation of data. WZ Critical revision of the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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