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Meta-Analysis of the Association Between Urokinase-Plasminogen Activator Gene rs2227564 Polymorphism and Alzheimer's Disease

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Abstract

Objective: The association between urokinase-plasminogen activator (PLAU) gene rs2227564 polymorphism and Alzheimer's disease (AD) risk has been widely reported across different ethnic populations, with inconsistent results. Thus, we performed a meta-analysis to assess the association between PLAU rs2227564 polymorphism and AD risk. **Methods:** Fixed or random effect model was used as the pooling method to assess the basis of homogeneity test among studies. Summarized estimation of odds ratio (OR) and 95% confidence interval (CI) were calculated. Heterogeneity among studies was evaluated using Q test and I^2. Publication bias was estimated using Harbord's test. **Results:** A total of 27 studies (comprising 6100 AD cases and 5718 controls) were included in this meta-analysis. The present meta-analysis showed a significant increased effect of T allele on risk of AD in dominant model (fixed effect model [FEM] OR 1.123, 95% CI 1.025-1.231) and heterozygote comparison (CT vs CC; FEM OR 1.126, 95% CI 1.027-1.235). No publication bias was detected. **Conclusion:** This meta-analysis showed that T allele of rs2227564 polymorphism in PLAU gene could increase the effects on risk of AD, and this result needs to be confirmed by further studies.

Keywords

urokinase-plasminogen activator gene, polymorphism, Alzheimer's disease, meta-analysis

Background

Alzheimer's disease (AD) is the most common form of dementia in aging human. It is predicted that worldwide population of AD would grow to over 100 million by 2050.[1] Genetic variation has been postulated to influence the variable risk of AD observed both within and across populations. Linkage studies indicate that chromosome 10 contains several genetic risk loci for late-onset AD.[2,3] Urokinase-plasminogen activator (PLAU) gene that maps to chromosome 10q22.2 is located within this linkage peak and has been shown to block β-amyloid (Aβ) protein neurotoxicity and to enhance α-secretase cleavage of the amyloid precursor protein and Aβ degradation.[4,5] The PLAU protein is a serine protease whose action is to convert plasminogen to plasmin. Plasmin is involved in the clearance of secreted Aβ, reducing aggregated forms of Aβ and preventing Aβ neurotoxicity. Therefore, PLAU is a reasonable positional candidate for association with AD.

The rs2227564 (also called P141L) polymorphism in PLAU gene is a variant in exon 6 which causes a proline to leucine change at position 141 in the coded protein within the kringle domain of PLAU at the junction between 2 β-pleated sheets.[6,7] Additionally, this mutation (P141L) in PLAU gene was more common and was a better candidate than the other coding single-nucleotide polymorphisms (SNPs).[8] Although several articles[8-21] have investigated the genetic associations between rs2227564 polymorphism in PLAU gene and AD risk, the results were inconsistent. Single studies may be underpowered to estimate the effects of loci conferring small changes in disease risk. So large-scale studies are required to reliably confirm or refute gene–disease associations.[22,23] Therefore, we conducted a meta-analysis including 27 case–control studies comprising 6100 AD cases and 5718 controls to derive a more precise estimation of the relationship between the PLAU SNP rs2227564 and the AD risk.

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Methods

Search Strategy

A comprehensive search was conducted for available articles published in English or Chinese up to September 2012 for studies on the association between PLAU gene and AD from the following databases: (1) PubMed, (2) Embase, (3) ISI (Web of Science), (4) China National Knowledge Infrastructure (CNKI), (5) China Biology Medical literature database (CBM), and (6) Wan Fang Med Online. The search strategy used the following keywords: "AD," "plasminogen activator urina" or "PLAU" or "rs2227564" or "P141L" or "PLAU_1," and "polymorphism" or "mutation" or "variant". We also reviewed the bibliographies of relevant articles and searched the studies not captured by our database as well as those of relevant studies.

Inclusion Criteria

In the current meta-analysis, all relevant studies reporting the association of PLAU gene rs2227564 polymorphism and AD risk were considered for inclusion. The inclusion criteria were as follows: (1) evaluation of the rs2227564 polymorphism in PLAU gene and AD risk; (2) using a case–control or cohort design; (3) English or Chinese language articles were included; (4) numbers for the genotype was reported in the article or could be obtain from authors or others; (5) the most recent or largest population was selected if the studies were published with the same or overlapping data by the same authors; (6) AD in each articles were diagnosed explicitly; and (7) each subpopulation was considered as a separate study in this meta-analysis if an article reported results with different ethnicity subpopulations. Accordingly, the following exclusion criteria were also used: (1) abstracts or reviews; (2) genotype frequency not reported; and (3) repeated or overlapped publications.

Data Extraction

Two investigators independently extracted the information needed from all the studies based on the inclusion criteria. The retrieved data were as follows: name of the first author, publication date, journal, country, mean age of the patients with AD and control, selection criteria for cases, total number of cases and controls, and genotype distributions in cases and controls. If a consensus could not be established, a third investigator was invited to the discussion.

Statistical Analysis

The chi-square (χ^2) analysis was used to test for deviation from Hardy-Weinberg equilibrium (HWE) for the rs2227564 genotype distribution of PLAU gene in case groups and control groups, and $P < .05$ was considered as departure from HWE. Pooled measure was calculated as the inverse variance-weighted mean of the logarithm of odds ratio (OR) with 95% confidence interval (CI) to estimate the strength of association between rs2227564 polymorphism in PLAU gene and risk of AD for codominant model (T vs C), dominant model (TT + CT vs CC) and recessive model (TT vs CC + CT), heterozygote comparison (CT vs CC), and homozygote comparison (TT vs CC), respectively. Heterogeneity among studies was estimated using the I^2 of Higgins and Thompson.[24] The I^2 reflects the proportion of total variation attributable to between-study heterogeneity as opposed to random error or chance. We would use the DerSimonian and Laird random effect model (REM; if $I^2 > 50\%$)[25] or fixed effect model (FEM; if $I^2 < 50\%$) as the pooling method. Metaregression with restricted maximum likelihood estimation was performed to describe the potentially important covariates, including sample size (the sum of case and control numbers), age (ratio of age or median age in the case group to that in the control group), and publication year which might exert substantial impacts on between-study heterogeneity. If no significant covariates were found to be heterogeneous, the "leave-one-out" sensitive analysis[26] was carried out to evaluate the key studies with substantial impact on between-study heterogeneity. A study of influence analysis was conducted[27] to describe how robust the pooled estimator is to removal of individual studies. An individual study that has excessive influence should be removed if the point estimate of its omitted analysis lies outside the 95% CI of the combined analysis. Publication bias was assessed using Harbord's test.[28] All the statistical analyses were performed with STATA version 10.0 (Stata Corporation, College Station, Texas). Two-tailed $P \leq .05$ was accepted as statistically significant.

Results

Characteristics of Studies

According to the comprehensive search and selection based on the inclusion criteria, 14 articles (including 27 independent studies) with 6100 AD cases and 5718 controls were identified with data on association between rs2227564 polymorphisms and susceptibility to AD. All the eligible studies included in this meta-analysis were case–control designs. The characteristics of rs2227564 polymorphism genotype distributions in present meta-analysis are shown in Table 1.

Quantitative Synthesis

Results of pooled analysis are summarized in Table 2. The meta-analysis showed a significant increased effect of T allele on risk of AD in heterozygote comparison (CT vs CC; FEM OR 1.096, 95% CI 1.006-1.193), but this was only marginally significant in the codominant model (REM OR 1.048, 95% CI 0.944-1.162) and dominant model (REM OR 1.085, 95% CI 0.956-1.232). However, no significant associations were found in the recessive model (FEM OR 0.963, 95% CI 0.842-1.103) and homozygote comparison (TT vs CC; FEM OR 1.031, 95% CI 0.869-1.224). After excluding 4 studies[8,12,17,21] that deviated from HWE in cases and/or in controls, significant associations were also found between the T allele and increased AD risk considering heterozygote comparison (CT vs CC;

Table 1. The Characteristics of PLAU Gene rs2227564 Polymorphism Genotype Distributions in this Meta-Analysis.

Author	Year	Country	Diagnostic criteria	Mean age (case/control)	Genotypes CC/CT/TT				T allele frequency, %			
					Case	P_h value[a]	Control	P_h value[a]	Case	Control	*P* value	OR[b]
Finckh et al[9]	2003	Germany	NINCDS-ADRDA	NA/NA	134/64/12	.29	107/85/14	.73	21.0	27.4	.030	0.701
Finckh et al[9]	2003	Switzerland	NINCDS-ADRDA	NA/NA	31/12/0	.58	27/22/6	.75	14.0	30.9	.007	0.362
Finckh et al[9]	2003	Italy	NINCDS-ADRDA	NA/NA	69/23/2	1	18/11/1	1.00	14.4	21.7	.183	0.606
Myers et al[8]	2003	America	ADRC	75.5/78.4	116/54/16	.02	115/65/11	.68	23.1	22.8	.911	1.020
Myers et al[8]	2003	America	ADRC	82.7/75.4	180/131/17	.31	282/170/30	.53	25.2	23.9	.552	1.072
Myers et al[8]	2003	UK	ADRC	77/75.6	80/52/6	.63	79/67/5	.052	23.2	25.5	.519	0.882
Papassotiropoulos et al[10]	2004	Switzerland	NINCDS-ADRDA	NA/NA	71/49/4	.31	158/100/19	.52	23.0	24.9	.557	0.900
Papassotiropoulos et al[10]	2004	Greece	NINCDS-ADRDA	NA/NA	120/57/4	.27	65/32/2	.52	18.0	18.2	.947	0.985
Bagnoli et al[11]	2004	Italy	*DSM-IV*	72.3/84.2	171/62/5	1	151/50/6	.42	15.1	15.0	.950	1.012
Ertekin-Taner et al[12]	2005	America	NINCDS-ADRDA	75.1/79.2	67/34/12	.03	96/59/5	.35	25.7	21.6	.264	1.256
Ertekin-Taner et al[12]	2005	America	NINCDS-ADRDA	80.4/80.3	114/99/14	.25	142/71/14	.24	28.0	21.8	.032	1.393
Ertekin-Taner et al[12]	2005	America	NINCDS-ADRDA	78.3/77.8	80/74/10	.25	87/71/6	.10	28.7	25.3	.333	1.186
Ertekin-Taner et al[12]	2005	Sweden	NINCDS-ADRDA	75.3/68.8	54/46/11	.21	41/28/8	.40	30.6	28.6	.668	1.104
Ertekin-Taner et al[12]	2005	Sweden	NINCDS-ADRDA	80.2/76.6	49/37/7	1	46/39/10	.64	27.4	31.1	.439	0.839
Ertekin-Taner et al[12]	2005	UK	NINCDS-ADRDA	57.8/58.1	61/48/12	.66	80/59/11	1.00	29.8	27.0	.479	1.145
Riemenschneider et al[13]	2006	Germany	NINCDS-ADRDA	69.1/68.8	215/177/30	.47	151/98/8	.11	28.1	22.2	.016	1.370
Riemenschneider et al[13]	2006	Germany	NINCDS-ADRDA	74.8/75.1	64/37/8	.44	126/42/5	.55	24.3	15.0	.006	1.816
Riemenschneider et al[13]	2006	Australia	NINCDS-ADRDA	74.3/77.1	116/85/18	.74	223/98/17	.17	27.6	19.5	.002	1.573
Riemenschneider et al[13]	2006	Italy	NINCDS-ADRDA	67.3/64.6	77/36/7	.4	85/13/1	.44	20.8	7.6	.000	3.211
Ozturk et al[14]	2006	America	NINCDS-ADRDA	76.57/75.2	38/319/563	.43	31/211/402	.64	78.5	78.8	.855	0.984
Blomqvist et al[15]	2006	Sweden	NINCDS-ADRDA	76.2/73.2	422/330/56	.48	113/95/21	.88	27.4	29.9	.281	0.882
Pesaresi et al[16]	2007	Italy	NINCDS-ADRDA	74.5/67.9	129/57/6	1	93/27/6	.08	18.0	15.5	.413	1.196
Ji et al[17]	2007	China	NINCDS-ADRDA	76.1/62.1	61/86/10	.01	56/53/19	.33	33.8	35.5	.655	0.924
Xiang et al[18]	2008	China	NINCDS-ADRDA	77.67/75.65	25/33/9	.8	25/34/12	1.00	38.1	40.8	.636	0.890
Giedraitis et al[19]	2008	Sweden	NINCDS-ADRDA and *DSM-IV*	80.2/81.8	44/36/5	.59	227/139/34	.07	27.1	25.9	.750	1.063
Cousin et al[20]	2009	France	NINCDS-ADRDA	64.9/66.2	274/132/15	1	289/148/25	.33	19.2	21.4	.254	0.874
Zhou et al[21]	2010	China	*DSM-I*	67.2/65.5	121/84/4	.01	115/98/7	.01	22.0	25.5	.236	0.826

Abbreviations: ADRC, Alzheimer Disease Research Center; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria; *DSM-IV*, *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition); *DSM-I*, *Diagnostic and Statistical Manual of Mental Disorders* (First Edition); HWE, Hardy-Weinberg equilibrium; NA, not available; PLAU, urokinase-plasminogen activator; OR, odds ratio.

[a] Exact *P* value for HWE test.

[b] OR ratio calculated by T versus C allele.

Table 2. Pooled Measures on the Relation of PLAU Gene rs2227564 Polymorphism With AD.

Data	Inherited model	Before HETRED[a] analysis					After HETRED analysis			
		Sample size cases/controls	Pooled OR (95% CI) FEM	Pooled OR (95% CI) REM	Q value	I^2, %	Sample size cases/controls	Pooled OR (95% CI)	Q value	I^2, %
All included articles	T vs C	6100/5718	1.041 (0.978-1.109)	1.048 (0.944-1.162)	63.683	59.2	5761/5281	1.006 (0.943-1.074)	41.419	42.1
	TT + CT vs CC	6100/5718	1.086 (1.000-1.178)	1.085 (0.956-1.232)	57.758	55.0	5980/5619	1.067 (0.983-1.159)	46.738	46.5
	TT vs CC + CT	6100/5718	0.963 (0.842-1.103)	0.983 (0.806-1.200)	37.698	31.0	–	–	–	–
	TT vs CC	3846/3733	1.031 (0.869-1.224)	1.040 (0.830-1.303)	40.117	35.2	–	–	–	–
	CT vs CC	5237/5013	1.096 (1.006-1.193)	1.096 (0.968-1.241)	50.599	48.6	–	–	–	–
Excluded for DHWE	T vs C	5453/5043	1.052 (0.984-1.126)	1.059 (0.941-1.193)	60.214	63.5	5114/4606	1.012 (0.944-1.085)	38.482	48.0
	TT + CT vs CC	5453/5043	1.110 (1.016-1.212)	1.108 (0.958-1.281)	54.027	59.3	5123/4738	1.123 (1.025-1.231)	34.726	42.4
	TT vs CC + CT	5453/5043	0.960 (0.833-1.105)	0.968 (0.811-1.155)	24.934	11.8	–	–	–	–
	TT vs CC	3439/3309	1.029 (0.856-1.236)	1.036 (0.823-1.304)	30.680	28.3	–	–	–	–
	CT vs CC	4614/4356	1.126 (1.027-1.235)	1.127 (0.983-1.291)	43.845	49.8	–	–	–	–
Europe[b]	T vs C	3528/3117	1.002 (0.918-1.093)	1.015 (0.867-1.187)	46.415	65.5	3299/2845	0.951 (0.869-1.041)	23.780	41.1
	TT + CT vs CC	3528/3117	1.023 (0.920-1.138)	1.036 (0.867-1.239)	40.713	60.7	3408/3018	0.993 (0.892-1.105)	28.390	47.2
	TT vs CC + CT	3528/3117	0.914 (0.723-1.155)	0.931 (0.704-1.231)	20.460	21.8	–	–	–	–
	TT vs CC	2255/2038	0.919 (0.723-1.167)	0.947 (0.691-1.296)	24.085	33.6	–	–	–	–
	CT vs CC	3320/2911	1.038 (0.929-1.160)	1.051 (0.891-1.240)	32.187	50.3	3207/2813	1.010 (0.903-1.130)	22.950	34.6
America	T vs C	1938/1868	1.090 (0.979-1.214)	1.090 (0.979-1.214)	4.727	0.0	–	–	–	–
	TT + CT vs CC	1938/1868	1.185 (1.010-1.390)	1.185 (1.010-1.390)	4.930	0.0	–	–	–	–
	TT vs CC + CT	1938/1868	1.019 (0.852-1.220)	1.167 (0.830-1.641)	8.417	40.6	–	–	–	–
	TT vs CC	1227/1221	1.266 (0.944-1.697)	1.272 (0.941-1.720)	5.190	3.7	–	–	–	–
	CT vs CC	1306/1400	1.168 (0.988-1.380)	1.151 (0.924-1.433)	8.107	38.3	–	–	–	–
Excluded for DHWE	T vs C	1639/1517	1.085 (0.964-1.222)	1.103 (0.955-1.275)	4.091	26.7	–	–	–	–
	TT + CT vs CC	1639/1517	1.273 (1.058-1.531)	1.273 (1.058-1.531)	2.527	0.0	–	–	–	–
	TT vs CC + CT	1639/1517	0.958 (0.794-1.155)	0.958 (0.794-1.155)	1.455	0.0	–	–	–	–
	TT vs CC	1016/994	1.131 (0.814-1.571)	1.131 (0.814-1.571)	1.405	0.0	–	–	–	–
	CT vs CC	1035/1065	1.307 (1.078-1.584)	1.307 (1.078-1.584)	2.744	0.0	–	–	–	–
Asia[c]	T vs C	433/419	0.873 (0.708-1.077)	0.873 (0.708-1.077)	0.225	0.0	–	–	–	–
	TT + CT vs CC	433/419	0.938 (0.714-1.233)	0.938 (0.714-1.233)	1.922	0.0	–	–	–	–
	TT vs CC + CT	433/419	0.533 (0.308-0.921)	0.533 (0.308-0.921)	1.168	0.0	–	–	–	–
	TT vs CC	230/234	0.570 (0.319-1.017)	0.570 (0.319-1.017)	0.426	0.0	–	–	–	–
	CT vs CC	410/381	1.015 (0.765-1.345)	1.042 (0.701-1.548)	3.525	43.3	–	–	–	–

Abbreviations: AD, Alzheimer's disease; CI, confidence interval; DHWE, deviated from HWE in cases and/or in controls; FEM, fixed effect model; HWE, Hardy-Weinberg equilibrium; OR, odds ratio; PLAU, urokinase-plasminogen activator; REM, random effect model.

[a] Sensitivity analysis for reducing heterogeneity by omitting study using the STATA module when $I^2 \geq 50\%$.

[b] All articles for Europe were DHWE in cases and/or in controls.

[c] There is only 1 study left after deviated from HWE in cases and/or in controls.

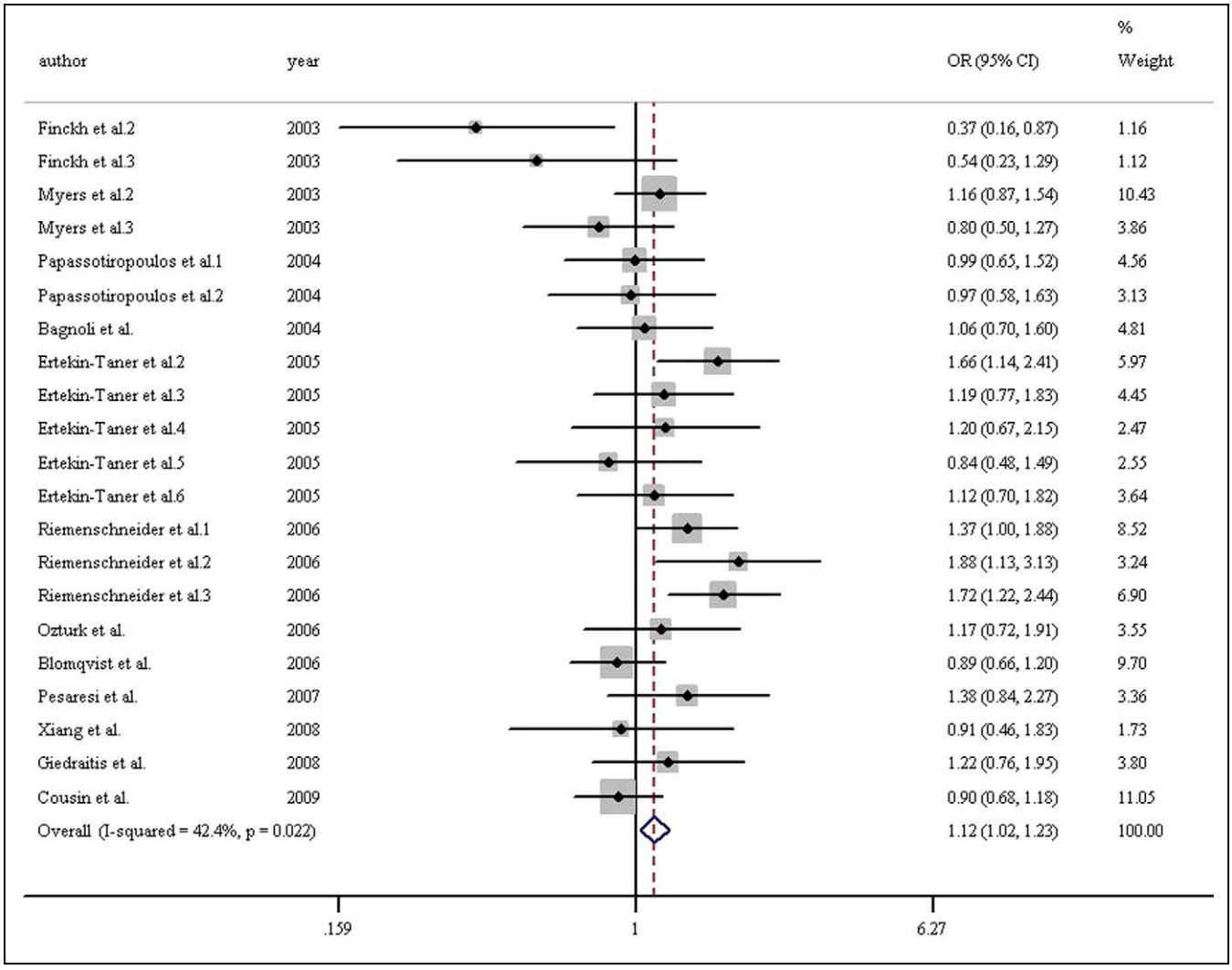

Figure 1. Forest plots of relationship between urokinase-plasminogen activator (PLAU) gene rs2227564 polymorphism and Alzheimer's disease (AD) in dominant model (TT + CT vs CC) after excluding the studies that deviated from Hardy-Weinberg equilibrium (HWE) in cases and/or control groups and sensitivity analysis. White diamond denotes the pooled odds ratio (OR). Black squares indicate the OR in each study, with square sizes inversely proportional to the standard error of the OR. Horizontal lines represent 95% confidence interval (CI).

FEM OR 1.126, 95% CI 1.027-1.235), only marginally significant in the codominant model (REM OR 1.059, 95% CI 0.941-1.193) and dominant model (REM OR 1.108, 95% CI 0.958-1.281) but not in the recessive model (FEM OR 0.960, 95% CI 0.833-1.105) and homozygote comparison (TT vs CC; FEM OR 1.029, 95% CI 0.856-1.236).

Sources of Heterogeneity and Sensitive Analysis

Before and after excluding the studies[8,12,17,21] deviating from HWE in the cases and/or controls, strong evidence of heterogeneity was demonstrated in the codominant- and dominant-inherited models for this meta-analysis. However, univariate metaregression, with the covariates of sample size (the sum of case and control numbers), age (ratio of mean age in the case group to that in the control group), and publication year for the rs2227564 polymorphism, showed that no covariates had a significant impact on between-study heterogeneity (data not shown). The key contributor of the study to between-study heterogeneity was assessed by the "leave-one-out" sensitive analysis[26] in the included studies. Low and moderate heterogeneities ($I^2 < 50\%$) were found in any inherited models following the exclusion of certain studies. However, the association of PLAU gene rs2227564 polymorphism with AD risk was significant in the dominant model (FEM OR 1.123, 95% CI 1.025-1.231) and heterozygote comparison (CT vs CC; FEM OR 1.126, 95% CI 1.027-1.235), only marginally significant in the codominant model (FEM OR 1.012, 95% CI 0.944-1.085). We also conducted a subgroup analysis with studies conducted in Europe groups, America groups, and Asia groups (detailed data are shown in Table 2). Figure 1 shows the forest plot of OR for AD in dominant model of PLAU gene rs2227564 polymorphism in all articles after excluding studies deviating from HWE in cases and/or controls and sensitivity analysis.

Influence Analysis

After exclusion of studies deviating from HWE in cases and/or controls and sensitivity analysis, there is 1 individual study[14] that should be removed, because the point estimate of its omitted analysis lies outside the 95% CI of the combined analysis in codominant model, dominant model, and heterozygote comparison. No independent study was found having excessive influence on the pooled effect in the above-mentioned inherited models after further excluding the individual study.[14]

Publication Bias

Harbord's test was used to assess the publication bias. There is no evidence showing publication bias for association between PLAU gene rs2227564 polymorphism and AD in the above-mentioned inherited models after exclusion of studies deviating from HWE in cases and/or controls and sensitivity analysis.

Discussion

Urokinase-plasminogen activator gene is a serine protease that converts plasminogen to plasmin, and plasmin also degrades plasma Aβ protein, affecting its circulating concentration that might be important in AD neuropathogenesis or diagnosis.[29,30] Since the first study that attempted to explore the association between PLAU rs2227654 polymorphism and AD risk in humans was reported in 2003,[9] many studies have tried to replicate the association. However, these results were inconsistent. Therefore, a meta-analysis should be performed to form a more precise estimation of those studies.

A total of 27 independent studies with 6100 AD cases and 5718 controls were included to assess the association between rs2227564 polymorphism and AD. To our knowledge, this is the first meta-analysis carried out to investigate the relationship between PLAU gene rs2227564 genetic polymorphism and AD. In the present meta-analysis, our pooled results showed that the PLAU rs2227564 polymorphism was significantly associated with AD risk in the dominant model, heterozygote comparison, and marginally significant in the codominant model after exclusion of studies deviating from HWE in cases and/or controls and sensitivity analysis. However, no significant associations were found in the recessive model and homozygote comparison. Evidence of heterogeneity was found for the rs2227564 polymorphism with AD risk. Between-study heterogeneity is common in meta-analysis for genetic association studies[31] and exploring the potential sources of between-study heterogeneity is the essential component of meta-analysis.[32] The between-study heterogeneity might arise from an indeterminate number of characteristics that vary among studies, such as study quality, characteristics of the subjects involved, genotyping quality, variation of the covariate, and deviation from HWE in some studies, and so on. Thus, we used metaregression to explore the causes of heterogeneity for covariates. However, sample size (the sum of case and control numbers), age (ratio of mean age in the case group to that in the control group), and publication year were not found to be the important sources of between-study heterogeneity in this meta-analysis. Thus, we used "leave-one-out" sensitive analysis,[26] which aims to reduce between-study heterogeneity and explore the potential important causes of between-study heterogeneity for both covariates and studies. The key contributor of the article to this low between-study heterogeneity assessed by the "leave-one-out" sensitive analysis was the one conducted by Finckh et al.[9] When we performed the data analysis, after the "leave-one-out" sensitive analysis, on the studies that obeyed the HWE in cases and controls, our results showed that the T allele of rs2227564 polymorphism in PLAU gene had significant effect on increased AD risk. No publication bias were found in all the inherited models after exclusion of studies deviating from HWE in cases and/or controls and sensitivity analysis.

Meta-analysis that can summarize and review previously published quantitative research has been recognized as an effective method to solve a wide variety of clinical questions. Nevertheless, some limitations have affected the objectivity of the conclusions and should be addressed. For example, lack of original information for included studies made it impracticable to stratify by other variables, such as smoking status, drinking status, family history, or other relevant diseases, which may affect AD. In spite of these limitations, our meta-analysis also showed some advantages. First, no publication biases were detected, indicating that the whole pooled results may be unbiased; second, substantial number of cases and controls were pooled from different studies, which significantly increased the statistical power of the analysis, and so on.

Conclusions

Our study suggested that the mutant genotype of TT + CT was significantly associated with AD risk from 27 case–control studies, and the T allele probably acts as an important AD risk factor. With regard to AD with multifactorial etiology, large well-designed epidemiological studies, especially considering different ethnic background, gene–gene, gene–environmental interactions, or other risk factors, should be performed in the future to clarify the possible roles of PLAU rs2227564 polymorphism in the pathogenesis of AD.

Declaration of Conflicting Interests

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