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PPARγ Pro12Ala and His447His polymorphisms and susceptibility to Alzheimer's disease: a meta-analysis

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ABSTRACT. We investigated whether Pro12Ala (C→G) and His447His (C→T) polymorphisms of the peroxisome proliferator-activated receptor gamma (PPARγ) gene are associated with susceptibility to Alzheimer's disease (AD). We conducted a meta-analysis of the associations between the PPARγ Pro12Ala and His447His polymorphisms and AD in subjects. The meta-analysis was performed according to the apolipoprotein E (APOE) ε4 allele status. A total of eight studies were considered in our meta-analysis, comprising 2948 patients with AD and 3753 controls. Meta-analysis showed no association between AD and the PPARγ Pro12Ala G allele in any of the study subjects [odds ratio (OR) = 1.013, 95% confidence interval (95%CI) = 0.906-1.132, P = 0.821] or in the European and Asian populations (OR = 0.997, 95%CI = 0.890-1.118, P = 0.965; OR = 1.409, 95%CI = 0.832-2.387, P = 0.202, respectively). We tested whether the APOE ε4 allele affects the association between the PPARγ Pro12Ala polymorphism and AD. Meta-analysis showed no association between AD and the PPARγ G allele in any of the study subjects with or without the APOE ε4 allele. Meta-analysis showed no association between AD and the PPARγ His447His T allele in the European population (OR for

T allele = 0.912, 95%CI = 0.732-1.136, P = 0.409). This meta-analysis has shown that there is a lack of association between the PPARγ Pro12Ala and His447His polymorphisms and AD risk.

Key words: Alzheimer's disease; Polymorphism; Meta-analysis; PPARγ; Apolipoprotein E

INTRODUCTION

Alzheimer's disease (AD) is a complex, progressive, and irreversible neurodegenerative disease. AD is the most common form of dementia, a general term used for memory loss and other cognitive impairments that interfere with daily life. Although the etiology of AD is not fully understood, interactions between a susceptible genetic background and environmental factors are thought to play a role (Bertram and Tanzi, 2012).

Peroxisome proliferator-activated receptor gamma (PPARγ) is a nuclear receptor that regulates adipocyte differentiation, insulin sensitivity, and lipid metabolism (Beaven and Tontonoz, 2006). PPARγ acts as a ligand-inducible transcription factor that suppresses microglial inflammatory responses and inhibits amyloid beta (Aβ) generation by promoting cholesterol efflux from glial cells (Wang et al., 2010). The locus of the gene encoding PPARγ (*PPARG*) is 3p25, and several single nucleotide polymorphisms have been identified. Of these polymorphisms, the Pro12Ala (C→G, rs1801282) and His447His (C→T, rs3856806) polymorphisms of the *PPARG* gene have been most commonly studied. The C/G polymorphism in the *PPARG* gene is responsible for a Pro to Ala transition in codon 12. The associated reductions in DNA binding and transcriptional activity lead to significantly reduced function of the Ala-allele nuclear receptor (Deeb et al., 1998). The Pro12Ala variant has been associated with increased insulin sensitivity, lower body mass, and protection from type 2 diabetes (Knouff and Auwerx, 2004; Tönjes and Stumvoll, 2007). Although the functional significance of the PPARγ His447His polymorphism is unclear, both the PPARγ Pro12Ala and His447His polymorphisms have been associated with type 2 diabetes and coronary artery disease (Knouff and Auwerx, 2004; Tönjes and Stumvoll, 2007).

The PPARγ Pro12Ala and His447His polymorphisms have been studied in the context of AD (Sauder et al., 2005; Koivisto et al., 2006; Hamilton et al., 2007; Scacchi et al., 2007; Helisalmi et al., 2008; Yao et al., 2009; Combarros et al., 2011; Shibata et al., 2013). However, published results on the genetic associations of these PPARγ polymorphisms are controversial and inconclusive. Individual studies based on small sample sizes have insufficient statistical power to detect positive associations and are incapable of demonstrating the absence of an association. To overcome the limitations of individual studies, resolve inconsistencies, and reduce the likelihood of random errors causing false-positive or false-negative associations (Lee et al., 2007, 2010, 2011), we performed a meta-analysis to determine whether the PPARγ Pro12Ala and His447His polymorphisms are associated with susceptibility to AD.

MATERIAL AND METHODS

Identification of eligible studies and data extraction

Using the MEDLINE and EMBASE citation databases, we performed a literature

search to identify articles that were published before August 2014, and examined associations between the PPARγ Pro12Ala and His447His polymorphisms and AD. Combinations of key words such as "peroxisome proliferator-activated receptor-γ", "PPARγ", "polymorphism", and "Alzheimer's disease" were entered as Medical Subject Heading terms and text words. References in the identified studies were used to identify additional studies not indexed by the electronic databases. Inclusion criteria were as follows: 1) case-control study design, 2) original data, and 3) genotype data to calculate odds ratios (ORs). No language restriction was applied. Exclusion criteria were as follows: 1) overlapping data, 2) inability to ascertain the number of null- and wild-type genotypes, and 3) family members studied because the analysis was based on linkage considerations. Data were extracted from the original studies by two independent reviewers. Discrepancies between the reviewers were resolved by reaching an agreement or by consulting a third reviewer. The following information was extracted from each selected study: author, year of publication, ethnicity of the study population, demographics, and numbers of cases and controls for each of the PPARγ Pro12Ala or His447His polymorphisms. Allele frequencies were calculated from the corresponding genotype distributions.

Evaluation of statistical associations

Meta-analyses were performed using: 1) allelic contrast, 2) homozygote contrast, 3) recessive models, and 4) dominant models. Subgroup analyses were performed based on ethnicity. Point estimates of risks, ORs, and 95% confidence intervals (95%CIs) were estimated for each study. Cochran's Q-statistic was used for assessing within- and between-study variation or heterogeneity. The heterogeneity test assessed the null hypothesis that all studies were evaluating the same effect. I^2 values were used to quantify heterogeneity. I^2 values ranged from 0 to 100% and represented the proportion of between-study variability attributable to heterogeneity rather than chance (Higgins and Thompson, 2002). I^2 values of 25, 50, and 75% were nominally assigned as low, moderate, and high estimates, respectively. The fixed-effect model assumed that a genetic factor had the same effect on AD susceptibility across all studies investigated, and that variations between studies were caused by chance alone. The random-effect model assumed that different studies had substantial diversity and assessed both within-study sampling error and between-study variance. For homogeneous study groups, the two models were similar, but for non-homogeneous study groups, the random-effect model generated wider CIs than the fixed-effect model. The random-effect model was used to allow significant heterogeneity between studies (DerSimonian and Laird, 1986). Statistical manipulations were made with a comprehensive meta-analysis program (Biostat, Englewood, NJ, USA). Study power was computed as the probability of detecting an association between the PPARγ polymorphisms and AD at a significance level of 0.05, assuming a small effect size OR. Power analysis was performed using the G*Power statistical program (http://www.psycho.uni-duesseldorf.de/aap/projects/gpower).

Evaluation of publication bias

The chi-square test was used to determine whether the observed genotype frequencies conformed to Hardy-Weinberg equilibrium (HWE). While funnel plots are often used to detect publication bias, funnel plotting requires a range of studies of varying sizes and involves subjective judgments. Therefore, we evaluated publication bias using the Egger linear regres-

sion test (Egger et al., 1997), which measures funnel plot asymmetry using a natural logarithm scale of ORs. When asymmetry was indicated, we used the "trim and fill" method to adjust summary estimates for observed bias (Duval and Tweedie, 2000). This method removes small studies until symmetry in the funnel plot is achieved by recalculating the center of the funnel before removed studies are replaced with their missing mirror-image counterparts. A revised summary estimate is then calculated using all original studies and hypothetical "filled" studies (Duval and Tweedie, 2000).

RESULTS

Studies included in the meta-analysis

We identified 36 studies by electronic and manual searching, of which nine were selected for a full-text review based on the title and abstract. After full-text review, one study was excluded, because the study was a review. A total of eight studies met all the inclusion criteria and were considered in our meta-analysis, comprising 2948 patients with AD and 3753 controls (Sauder et al., 2005; Koivisto et al., 2006; Hamilton et al., 2007; Scacchi et al., 2007; Helisalmi et al., 2008; Yao et al., 2009; Combarros et al., 2011; Shibata et al., 2013). Eight studies (seven European, one Asian) with 3501 cases and 4622 controls considered the PPARγ Pro12Ala polymorphism, and three studies (three European) with 553 cases and 869 controls considered the PPARγ His447His polymorphism. Ethnicity-specific meta-analysis was conducted on the populations. Selected characteristics of the relationships found between the PPARγ Pro12Ala or His447His polymorphisms and AD are summarized in Table 1. The statistical power of the studies ranged from 41.7 to 99.3%, and three of the studies had statistical power exceeding 80% (Liu et al., 2012).

Table 1. Characteristics of studies in the meta-analysis.

Study (Ref.)	Country	Ethnicity	Numbers		Case			Control			Association P value	Power (%)[a]
			AD	Control	CC	CG	GG	CC	CG	GG		
PPARγ Pro12Ala polymorphism												
Shibata et al. (2013)	Estonia	European	171	136	154	16	1	128	7	1	0.245	41.7
Combarros et al. (2011)	Spain	European	351	438	292	49	10	376	56	6	0.148	80.2
Yao et al. (2009)	China	Asian	362	370	328	34	0	345	25	0	0.202	77.2
Helisalmi et al. (2008)	Finland	European	513	671	364	144	5	470	181	20	0.336	93.0
Hamilton et al. (2007)	UK	European	919	1077	715	189	15	825	233	19	0.523	99.3
Scacchi et al. (2007)	Italy	European	260	276	212	47	1	234	39	3	0.463	63.8
Koivisto et al. (2006)	Finland	European	125	461	93	30	2	330	122	9	0.532	67.7
Sauder et al. (2005)	Germany	European	247	324	186	58	3	252	67	5	0.585	66.6
					CC	CT	TT	CC	CT	TT		
PPARγ rs3856806 polymorphism												
Shibata et al. (2013)	Estonia	European	171	136	123	40	8	87	45	4	0.317	41.7
Hamilton et al. (2007)	UK	European	257	272	210	42	5	210	59	3	0.343	63.3
Koivisto et al. (2006)	Finland	European	125	461	78	43	4	295	154	12	0.699	67.7

Ref. = reference; AD = Alzheimer's disease. [a]Assuming a small effect size at a significance level of 0.05.

Meta-analysis of the PPARγ Pro12Ala polymorphism and AD

Meta-analysis showed no association between AD and the PPARγ G allele in any

of the study subjects (OR = 1.013, 95%CI = 0.906-1.132, P = 0.821; Table 2 and Figure 1). Stratification by ethnicity indicated no association between the PPARγ G allele and AD in the European or Asian populations (OR = 0.997, 95%CI = 0.890-1.118, P = 0.965; OR = 1.409, 95%CI = 0.832-2.387, P = 0.202, respectively; Table 2). Analysis using the dominant model showed the same pattern for the PPARγ G allele (Table 2). We tested whether an association between the PPARγ Pro12Ala polymorphism and AD was apolipoprotein E (APOE) ε4 allele-dependent. Meta-analysis showed no association between AD and the PPARγ G allele in any of the study subjects with the APOE ε4 allele (OR = 0.889, 95%CI = 0.672-1.176, P = 0.411; Table 3 and Figure 2). Stratification by ethnicity indicated no association between the PPARγ G allele and AD in the European or Asian populations with the APOE ε4 allele (Table 3). In addition, no association was found between AD and the PPARγ G allele in the overall, European, or Asian groups lacking the APOE ε4 allele (Table 3). Analysis using the dominant, recessive, and homozygote models showed the same pattern for the PPARγ G allele (Table 3).

Table 2. Analysis of the association between PPARγ polymorphisms and Alzheimer's disease.

Polymorphism	Population	No. of studies	Numbers		Test of association			Test of heterogeneity		
			Case	Control	OR	95%CI	P value	Model	P value	I^2
PPARγ Pro12Ala G *vs* C	Overall	8	2.948	3.753	1.013	0.906-1.132	0.821	F	0.371	7.70
	European	7	2.586	3.383	0.997	0.890-1.118	0.965	F	0.423	0.07
	Asian	1	362	370	1.409	0.832-2.387	0.202	NA	NA	NA
GG *vs* GC + CC (Recessive)	Overall	7	2.586	3.383	0.821	0.533-1.264	1.370	F	0.283	19.2
	European	7	2.586	3.383	0.821	0.533-1.264	1.370	F	0.283	19.2
	Asian	0	0	0	NA	NA	NA	NA	NA	NA
GG + GC *vs* CC (Dominant)	Overall	8	2.948	3.753	1.037	0.917-1.173	0.559	F	0.489	0
	European	7	2.586	3.383	1.019	0.898-1.156	0.768	F	0.544	0
	Asian	1	362	370	1.430	0.825-2.450	0.192	NA	NA	NA
GG *vs* CC	Overall	7	2.586	3.383	0.823	0.533-1.268	0.377	F	0.288	18.6
	European	7	2.586	3.383	0.823	0.533-1.268	0.377	F	0.288	18.6
	Asian	0	0	0	NA	NA	NA	NA	NA	NA
PPARγ rs3856806 T *vs* C	European	3	553	869	0.912	0.732-1.136	0.409	F	0.504	0
TT *vs* TC + CC (Recessive)	European	3	553	869	1.490	0.722-3.074	0.280	F	0.915	0
TT + TC *vs* CC (Dominant)	European	3	553	869	0.842	0.647-1.095	0.200	F	0.335	8.56
TT *vs* CC	European	3	553	869	1.409	0.680-2.920	0.356	F	0.956	0

OR = odds ratio; 95%CI = 95% confidence interval; F = fixed model; NA = not available.

Meta-analysis of the PPARγ His447His polymorphism and AD

Meta-analysis of the combined European study subjects showed no association between AD and the PPARγ T allele (OR = 0.912, 95%CI = 0.732-1.136, P = 0.409; Table 3 and Figure 1). Similarly, no association was found between AD and the PPARγ His447His polymorphism using recessive, dominant, or homozygote contrast models (Table 3).

Heterogeneity and publication bias

The distribution of the PPARγ Pro12Ala polymorphism in normal controls was not consistent with HWE in one study. Deviation from HWE among controls implies potential bias during control selection or genotyping errors. However, excluding the study did not significantly affect our results. No between-study heterogeneity was found in analyses of the PPARγ polymorphisms in the combined or European study populations.

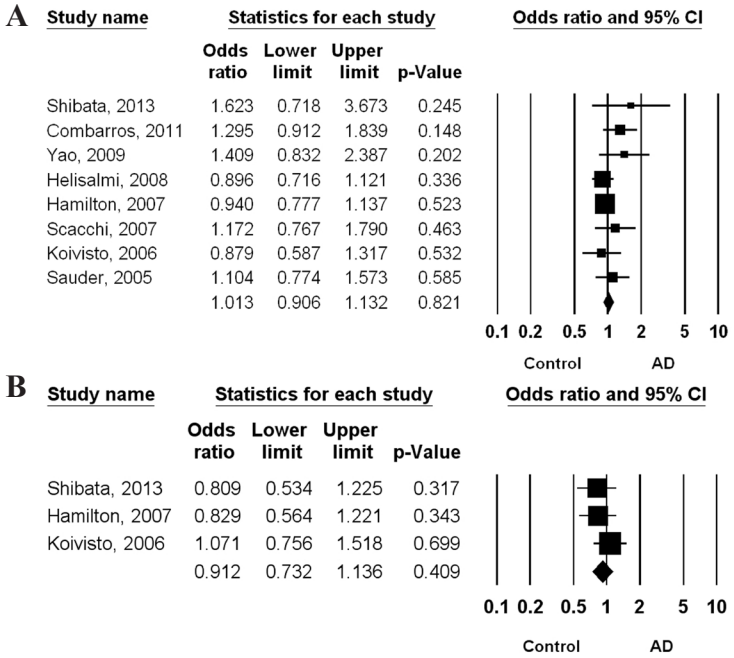

Figure 1. Odds ratios and 95% confidence intervals (CI) of studies and pooled data for the allelic association between Alzheimer's disease (AD) and the PPARγ Pro12Ala (**A**) and His447His (**B**) polymorphisms in all subjects.

Table 3. Analysis of the association between the PPARγ Pro12Ala polymorphism and Alzheimer's disease in subjects with the APOE ε4 allele or without the APOE ε4 allele.

Polymorphism	Population	No. of studies	Numbers		Test of association			Test of heterogeneity		
			Case	Control	OR	95%CI	P value	Model	P value	I^2
APOE ε4 allele (+)										
PPARγ Pro12Ala G *vs* C	Overall	3	864	372	0.889	0.672-1.176	0.411	F	0.479	0
	European	2	713	314	0.871	0.651-1.164	0.351	F	0.273	16.6
	Asian	1	151	58	1.160	0.412-3.268	0.778	NA	NA	NA
GG *vs* GC + CC (Recessive)	Overall	2	713	314	1.466	0.458-4.694	0.519	F	0.153	51.1
	European	2	713	314	1.466	0.458-4.694	0.519	F	0.153	51.1
	Asian	0	0	0	NA	NA	NA	NA	NA	NA
GG + GC *vs* CC (Dominant)	Overall	3	864	372	0.815	0.599-1.110	0.195	F	0.237	30.5
	European	2	713	314	0.789	0.571-1.089	0.149	F	0.122	58.2
	Asian	1	151	58	1.169	0.405-3.377	0.773	NA	NA	NA
GG *vs* CC	Overall	2	713	314	1.474	0.459-4.730	0.514	F	0.191	41.4
	European	2	713	314	1.474	0.459-4.730	0.514	F	0.191	41.4
	Asian	0	0	0	NA	NA	NA	NA	NA	NA
APOE ε4 allele (-)										
PPARγ Pro12Ala G *vs* C	Overall	3	705	1386	1.099	0.879-1.374	0.406	F	0.587	0
	European	2	494	1274	1.061	0.836-1.346	0.628	F	0.553	0
	Asian	1	211	312	1.424	0.750-2.701	0.280	NA	NA	NA
GG *vs* GC + CC (Recessive)	Overall	2	494	1274	0.656	0.029-17.71	0.791	R	0.017	85.5
	European	2	494	1274	0.656	0.029-17.71	0.791	R	0.017	85.5
	Asian	0	0	0	NA	NA	NA	NA	NA	NA
GG+ GC *vs* CC (Dominant)	Overall	3	705	1386	1.169	0.917-1.41	0.207	F	0.783	0
	European	2	494	1274	1.130	0.870-1.468	0.359	F	0.884	0
	Asian	1	211	312	1.445	0.751-2.778	0.270	NA	NA	NA
GG *vs* CC	Overall	2	494	1274	0.674	0.032-14.28	0.800	R	0.015	82.9
	European	2	494	1274	0.674	0.032-14.28	0.800	R	0.015	82.9
	Asian	0	0	0	NA	NA	NA	NA	NA	NA

OR = odds ratio; 95%CI = 95% confidence interval; F = fixed model; R = random model; NA = not available.

Funnel plots to detect publication bias were difficult to correlate because of the small number of studies in the meta-analysis. Egger regression tests showed evidence of publication bias in the meta-analysis of the PPARγ Pro12Ala polymorphism (Egger regression test P value = 0.025; Figure 3). Publication bias results in a disproportionate number of positive studies and poses a problem for meta-analyses. However, the adjusted OR calculated using the "trim and fill" technique remained insignificant (OR = 0.965, 95%CI = 0.839-1.110).

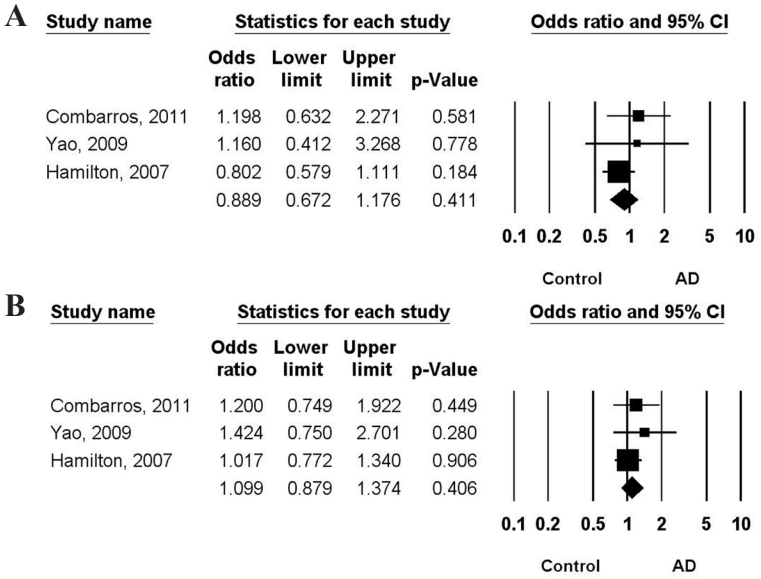

Figure 2. Odds ratios and 95% confidence intervals (CI) of studies and pooled data for the allelic association between the PPARγ Pro12Ala polymorphisms and Alzheimer's disease (AD) in subjects with (**A**) or without (**B**) the APOE ε4 allele.

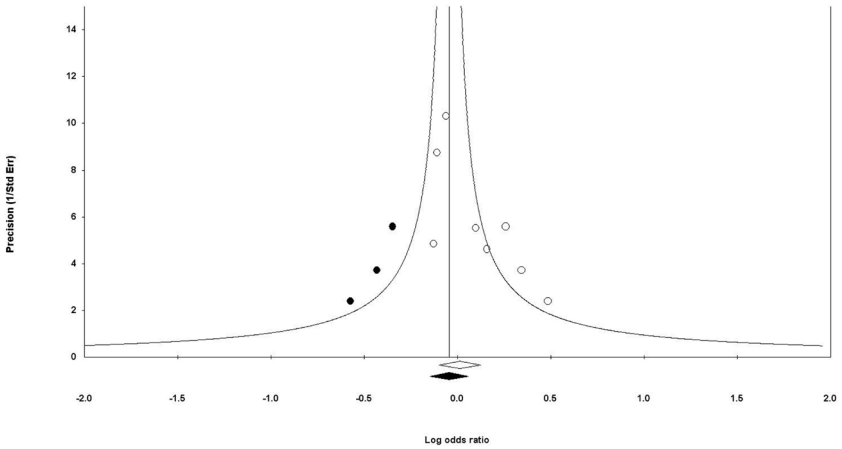

Figure 3. Funnel plot of studies examining the family-based association between the PPARγ Pro12Ala G allele and Alzheimer's disease (Egger regression P value = 0.025). The filled circles represent studies that showed publication bias. The diamonds at the bottom of the figure show summary effect estimates before (open) and after (filled) adjustment for publication bias.

DISCUSSION

The *PPARG* gene has been studied in connection with AD. The PPAR family consists of the PPARα, PPARγ, and PPARδ nuclear receptors, which mediate the transcriptional response to insulin, inducing glucose uptake, increased fatty acid oxidation, lipogenesis, and lipid storage (Lee et al., 2007). PPARγ regulates genes involved in inflammation and lipid metabolism by inhibiting NF-κB in microglia and promoting cholesterol efflux from cells (Wang et al., 2010). PPARγ plays a major role in modulating Aβ production by inflammatory processes (Wang et al., 2010). The N-terminal mutation from proline to alanine (Pro12Ala) occurs in the extra domain of the PPARγ 2 transcript. This PPARγ splice isoform includes 30 additional amino acids (Zhu et al., 1995), which are responsible for an increase in PPARγ transcriptional activity in adipose tissue. The functionality of the PPARγ Pro12Ala variant is significantly reduced (Deeb et al., 1998). In this meta-analysis, we combined data from published studies to evaluate genetic associations between AD and the PPARγ Pro12Ala and His447His polymorphisms. We found no association between the PPARγ Pro12Ala and His447His polymorphisms in the European or Asian populations. None of the genetic models we used detected an association between the PPARγ polymorphisms and AD susceptibility. However, an important cautionary note is that our investigation of Asians was underpowered because only one of the studies included was conducted on Asians.

The APOE ε4 allele is the primary genetic determinant of AD risk (Bertram and Tanzi, 2012). Thus, we examined whether the presence of an APOE ε4 allele influenced the association between the PPARγ Pro12Ala polymorphism and AD susceptibility. We found no APOE ε4 allele-dependent association between AD risk and the PPARγ Pro12Ala polymorphism. The results of our meta-analysis of the PPARγ Pro12Ala polymorphism are not consistent with functional studies of this polymorphism (Kishikawa et al., 2006). In general, disagreements between epidemiological and functional studies of AD are not entirely unexpected because it is a complex disease involving multiple genes, genetic backgrounds, and environmental factors. In our analysis, the discrepancy might arise from mixed clinical subtypes or different neurological lesions in the study populations, but examination of these possibilities requires further studies.

Our study has several limitations. First, publication bias and heterogeneity may have distorted the meta-analysis. In particular, publication bias was found among the studies used in the PPARγ Pro12Ala polymorphism meta-analysis. Publication bias may prevent our conclusion on the absence of an association between the PPARγ Pro12Ala polymorphism and AD. Although the adjusted OR calculated by the "trim and fill" method remains insignificant, the possibility of bias cannot be eliminated owing to the small number of studies used in the analysis. Second, our ethnicity-specific analysis included only data from European and Asian patients. Therefore, these results are applicable only to these groups. Furthermore, there was one Asian study on the PPARγ Pro12Ala polymorphism and three European studies on the PPARγ His447His polymorphism in the subgroup analysis by ethnicity. The study numbers in the ethnicity-specific meta-analysis may not be sufficient to provide a conclusive result. Third, it would have been interesting to evaluate the association between the PPARγ polymorphisms and the PPARγ activity or clinical features of AD, but this was not possible because of the limited data in this study.

In conclusion, this meta-analysis using published data demonstrates no association between the PPARγ Pro12Ala and His447His polymorphisms with AD risk in any study popu-

lation. These data do not support the claims that the PPARγ polymorphisms play an important role in susceptibility to AD. Further studies are needed to clarify the roles of these PPARγ alleles in different ethnic groups.

Conflicts of interest

The authors declare no conflict of interest.

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