Meta-Analysis of Associations Between the Peroxisome Proliferator-Activated Receptor- γ Pro12Ala Polymorphism and Susceptibility to Nonalcoholic Fatty Liver Disease, Rheumatoid Arthritis, and Psoriatic Arthritis

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Introduction: The purpose of this study was to examine whether a Proline (Pro)-to-Alanine (Ala) exchange at codon 12 (Pro12Ala) polymorphism of the peroxisome proliferator-activated receptor-gamma (PPAR γ) is associated with susceptibility to nonalcoholic fatty liver disease (NAFLD), rheumatoid arthritis (RA), and psoriatic arthritis (PsA). **Methods:** A meta-analysis was conducted on the association between the PPAR γ Pro12Ala polymorphism and NAFLD, RA, and PsA. **Results:** Nine studies, including five on NAFLD, two on RA, and two on PsA, were available for the meta-analysis consisting of 8082 cases and 3790 controls. The meta-analysis revealed no association between the Ala allele of the PPAR γ Pro12Ala polymorphism and NAFLD (odds ratios [OR]=0.936, 95% confidence interval [CI]=0.672–1.302, $p=0.693$). However, stratification by ethnicity indicated an association between the Ala allele and NAFLD in East Asians (OR=0.700, 95% CI=0.496–0.987, $p=0.042$), but not in Europeans (OR=1.128, 95% CI=0.863–1.475, $p=0.378$). Analysis using the dominant model showed the same Ala allele pattern in East Asians and Europeans (OR=0.688, 95% CI=0.484–0.978, $p=0.037$; OR=1.051, 95% CI=0.782–1.413, $p=0.742$), demonstrating a significant association between the Ala allele and NAFLD in East Asians. The meta-analysis revealed no association between the Ala allele and RA in East Asians (OR=0.467, 95% CI=0.188–1.161, $p=0.101$), and no association was found between the Ala allele and PsA in Europeans (OR=0.869, 95% CI=0.465–1.627, $p=0.662$). **Conclusions:** Our meta-analysis demonstrates that the PPAR γ Pro12Ala polymorphism is associated with susceptibility to NAFLD in East Asians, but not in European populations.

Introduction

NONALCOHOLIC FATTY LIVER DISEASE (NAFLD) is a common disorder characterized by an increase in hepatic fat content occurring in individuals with minimal or no alcohol consumption, and who have no other cause for liver disease (Brunt, 2010). Rheumatoid arthritis (RA) is a chronic inflammatory disease of predominantly synovial joints that causes significant morbidity and shortens life expectancy (McInnes and Schett, 2011). Psoriatic arthritis (PsA) is an inflammatory arthritis that occurs in 10–40% of patients with psoriasis. Although the etiology of these diseases is not fully understood, interactions between a susceptible genetic background and environmental factors have been suggested (Choi *et al.*, 2006).

Peroxisome proliferator-activated receptor- γ (PPAR γ) is a nuclear receptor that regulates proinflammatory genes, insulin sensitivity, and lipid metabolism (Beaven and Tontonoz, 2006). PPAR γ increases the expression of lipoprotein

lipase, an enzyme that serves to partition fat to adipocytes, limiting fatty acid flux to the liver (Hui *et al.*, 2008). The PPAR γ gene, which is located on chromosome 3, has been known to be linked to NAFLD (Gavrilova *et al.*, 2003). The C/G polymorphism (rs1801282), a Pro-to-Ala exchange that leads to the substitution of proline (Pro) with alanine (Ala) at codon 12, was found to be associated with reductions in both DNA binding and transcriptional activity, and as a consequence, the encoded Ala-allele form has a heavily reduced function (Deeb *et al.*, 1998). This Pro12Ala variant has been associated with increased insulin sensitivity and a lower body mass and protection from type 2 diabetes (Knouff and Auwerx, 2004; Tonjes and Stumvoll, 2007).

The PPAR γ Pro12Ala polymorphism has been studied in the context of NAFLD, RA, and PsA. However, published results on the genetic associations of the PPAR γ Pro12Ala polymorphism are controversial and inconclusive (Butt *et al.*, 2006; El-Sohemy *et al.*, 2006; Terauchi, 2007; Pan *et al.*, 2009;

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Dongiovanni *et al.*, 2010; Rey *et al.*, 2010; Cao *et al.*, 2012; Bowes *et al.*, 2012; Yang *et al.*, 2012). This may be due to small sample sizes, low statistical power, and/or clinical heterogeneity. To overcome the limitations of individual studies, resolve inconsistencies, and reduce the likelihood that random errors are responsible for false-positive or false-negative associations, we employed a meta-analysis to further characterize the association (Nath *et al.*, 2005; Lee *et al.*, 2005, 2006) and to investigate whether the PPAR γ Pro12Ala polymorphism contributes to susceptibility to NAFLD, RA, and PsA.

Materials and Methods

Identification of eligible studies and data extraction

A search of the literature for studies that examined the association between the PPAR γ Pro12Ala polymorphism and NAFLD, RA, PsA was conducted. We utilized the MEDLINE and EMBASE citation indices to identify articles published through December 2012 in which the PPAR γ Pro12Ala polymorphism was identified in NAFLD patients and controls. In addition, all references mentioned in the identified articles were reviewed to identify studies not indexed by the electronic databases. The following keywords and subject terms were used in the search: “peroxisome proliferator-activated receptor- γ ,” “PPAR γ ,” “fatty liver,” “rheumatoid arthritis,” and “psoriatic arthritis.” Studies were included in the analysis if (1) they were case-control studies, (2) contained genotype data, (3) included sufficient data to calculate odds ratios (ORs), and (4) the study included patients diagnosed with NAFLD, RA, and PsA based on the diagnostic criteria. No language restriction was applied. We excluded the following: (1) studies that included overlapping data; (2) studies in which the number of genotypes could not be ascertained; (3) studies in which family members were studied because their analysis was based on linkage considerations; and (4) studies in which the genotype distribution in controls was not consistent with the Hardy-Weinberg equilibrium (HWE), as deviation from the HWE among controls suggests the possibility of bias during control selection or genotyping errors. Data regarding the methods and results of meta-analysis were extracted from the original studies by two independent reviewers. Discrepancy between the reviewers was resolved by consensus or a third reviewer. The following information was extracted from each identified study: author, year of publication, ethnicity of the study population, demographics, numbers of cases and controls, and the frequencies of the genotypes and alleles of the PPAR γ Pro12Ala polymorphism.

Evaluation of publication bias

The chi-square test was used to determine if the observed genotype frequencies in controls conformed to HWE. Funnel plots are often used to detect publication bias, but require a range of studies of varying sizes and subjective judgments. Therefore, we evaluated publication bias using the Egger's linear regression test (Egger *et al.*, 1997). The Egger's linear regression test measures funnel plot asymmetry on a natural logarithmic scale of ORs.

Evaluation of statistical associations

We performed meta-analyses using (1) allelic contrast (Ala/Ala vs. Pro/Pro), (2) dominant (Ala/Ala + Ala/Pro vs.

Pro/Pro), and (3) overdominant (Ala/Ala + Pro/Pro vs. Ala/Pro) models. We could not perform a meta-analysis of recessive and additive models because the frequency of the Ala/Ala genotype was very low. Point estimates of risks, ORs, and 95% confidence intervals (CI) were estimated for each study. In addition, within- and between-study variations and heterogeneities were assessed using Cochran's Q-statistic. The Cochran's Q-statistic test assesses the null hypothesis that all studies evaluated the same effect. The effect of heterogeneity was quantified using I^2 with a range between 0% and 100%, representing the proportion of between-study variability attributable to heterogeneity rather than to 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-effects model assumes that a genetic factor has a similar effect on disease susceptibility across all studies investigated and that observed variations among studies are caused by chance alone (Egger *et al.* 1997). The random-effects model assumes that different studies show substantial diversity and assesses both the within-study sampling error and between-study variance (DerSimonian and Laird, 1986). When study groups are homogeneous, the two models are similar. If the study groups lack homogeneity, the random-effects model usually provides wider CIs than the fixed-effects model. The random-effects model is most appropriate in the presence of significant between-study heterogeneity (DerSimonian and Laird, 1986). Statistical manipulations were undertaken using the Comprehensive Meta-Analysis program (Biosta, Englewood, NJ). The power of each study was computed as the probability of detecting an association between the PPAR γ Pro12Ala polymorphism and diseases using a significance level of 0.05 and assuming an OR of 1.5 (small effect size). Power analysis was performed using the statistical program G*Power (www.psych.uni-duesseldorf.de/aap/projects/gpower).

Results

Studies included in the meta-analysis

Forty-five studies were identified by electronic and manual searches, 15 of which were selected for full-text review based on title and abstract details (Butt *et al.*, 2006; El-Soheymy *et al.*, 2006; Terauchi, 2007; Hui *et al.*, 2008; Pan *et al.*, 2009; Dongiovanni *et al.*, 2010; Gupta *et al.*, 2010; Rey *et al.*, 2010; Zhou *et al.*, 2010; Cao *et al.*, 2012; Bowes *et al.*, 2012; Gawrieh *et al.*, 2012; Yang *et al.*, 2012; Bhatt *et al.*, 2013; Jalil *et al.*, 2013). Six studies were excluded because one contained no data (Gawrieh *et al.*, 2012), two had other polymorphism data (Hui *et al.*, 2008; Zhou *et al.*, 2010), and three had a genotype distribution in controls that was not in HWE (Gupta *et al.*, 2010; Bhatt *et al.*, 2013; Jalil *et al.*, 2013). Thus, a total of nine studies met our inclusion criteria (Butt *et al.*, 2006; El-Soheymy *et al.*, 2006; Terauchi, 2007; Pan *et al.*, 2009; Dongiovanni *et al.*, 2010; Rey *et al.*, 2010; Cao *et al.*, 2012; Bowes *et al.*, 2012; Yang *et al.*, 2012) (Fig. 1). These studies comprised five on NAFLD, two on RA, and two on PsA. They consisted of four European and five East Asian studies. In total, the studies included 8082 cases and 3790 controls. Selected details of the individual studies are summarized in Table 1. The statistical powers of these five studies ranged from 40.5% to 100%. Four of the studies had a statistical power exceeding 80% (Table 1).

FIG. 1. Study flowchart.

TABLE 1. DETAILS OF THE INDIVIDUAL STUDIES INCLUDED IN THE META-ANALYSIS

Author	Country	Ethnicity	Disease	Numbers		Case			Control			Association p ^a	Power (%) ^b
				Case	Control	Pro/ Pro	Pro/ Ala	Ala/ Ala	Pro/ Pro	Pro/ Ala	Ala/ Ala		
Cao, 2012	China	East Asian	NAFLD	169	699	159	10	0	656	43	0	0.910	83.7
Yang, 2012	China	East Asian	NAFLD	436	467	406	30	0	409	58	0	0.007	85.1
Rey, 2010	Germany	European	NAFLD	263	363	206	48	9	280	77	6	0.878	70.6
Dongiovanni, 2010	Italy	European	NAFLD	202	346	166	33	3	295	50	1	0.217	64.8
Qing, 2007	China	East Asian	NAFLD	155	141	142	13	0	130	11	0	0.857	40.5
Pan, 2009	China	East Asian	RA	421	207	411	10	0	190	17	0	0.002	70.7
El-Sohenmy, 2006	China	East Asian	RA	473	400	450	23	0	374	25	1	0.241	84.0
Bowes, 2012	United Kingdom	European	PsA	5712	932	4416	1216	80	747	174	11	0.058	100
Butt, 2006	Canada	European	PsA	251	235	208	41	2	177	51	7	0.017	59.7

^aAllelic association.^bAssuming an odds ratio of 1.5 (small effect size) at a level of significance of 0.05.

HWE, Hardy–Weinberg equilibrium; NAFLD, nonalcoholic fatty liver disease; RA, rheumatoid arthritis; PsA, psoriatic arthritis.

TABLE 2. PREVALENCE OF THE ALA ALLELE OF THE PPAR γ Pro12Ala POLYMORPHISM

Population	No. of studies	Numbers		Ala allele (%)	
		Case	Control	Case	Control
European	4	6428	1876	11.9	10.7
East Asian	5	1654	1914	2.6	4.1
Overall	9	8082	3790	10.1	17.4

Frequencies of the Ala allele of the PPAR γ Pro12Ala polymorphism in different ethnic groups

The mean frequency of the Ala allele of the PPAR γ Pro12Ala polymorphism was 7.36% among all normal controls, and East Asians had a lower Ala allele prevalence than Europeans (4.1% vs. 10.7%,) (Table 2).

Meta-analysis of the association between the PPAR γ Pro12Ala polymorphism and NAFLD

A meta-analysis of all NAFLD patients and of each ethnic group was performed. The meta-analysis revealed no association between the Ala allele and NAFLD (OR=0.936, 95% CI=0.672–1.302, $p=0.693$) (Table 3). However, stratification by ethnicity indicated a significant association between the Ala allele of the PPAR γ Pro12Ala polymorphism and NAFLD in East Asians (OR=0.700, 95% CI=0.496–0.987, $p=0.042$), but not in Europeans (OR=1.128, 95% CI=0.863–1.475, $p=0.378$) (Table 3). Analysis using the dominant model showed the same Ala allele pattern in East Asians and Europeans (OR=0.688, 95% CI=0.484–0.978, $p=0.037$; OR=1.051, 95% CI=0.782–1.413, $p=0.742$), demonstrating a significant association between the Ala allele and NAFLD in East Asians (Table 3 and Fig. 2). Meta-analysis revealed no association between the Ala/Ala+Pro/Pro genotype of the PPAR γ Pro12Ala polymorphism and NAFLD (OR=1.210, 95% CI=0.960–1.525, $p=0.107$) (Table 3). However, stratification by ethnicity indicated an

association between the Ala/Ala+Pro/Pro genotype and NAFLD in East Asians (OR=1.453, 95% CI=1.023–2.065, $p=0.037$), but not in Europeans (OR=1.051, 95% CI=0.773–1.430, $p=0.750$) (Table 3 and Fig. 3).

Meta-analysis of the association between the PPAR γ Pro12Ala polymorphism and RA, PsA

The meta-analysis revealed no association between the Ala allele and RA in East Asians (OR=0.467, 95% CI=0.188–1.161, $p=0.101$) (Table 3). Analysis using the dominant and the overdominant models showed the same Ala allele pattern in East Asians (OR=0.465, 95% CI=0.176–1.230, $p=0.123$; OR=2.109, 95% CI=0.766–5.808, $p=0.149$) (Table 3 and Figs. 2 and 3). The meta-analysis revealed no association between the Ala allele and PsA in Europeans (OR=0.869, 95% CI=0.465–1.627, $p=0.662$) (Table 3). Analysis using the dominant and the overdominant models showed no association between the PPAR γ Pro12Ala polymorphism and PsA in Europeans (OR=0.895, 95% CI=0.484–1.654, $p=0.723$; OR=1.050, 95% CI=0.639–1.724, $p=0.848$) (Table 3 and Figs. 2 and 3).

Heterogeneity and publication bias

Between-study heterogeneity was found during meta-analyses of RA, PsA, and in the meta-analysis of the Ala allele over all groups in NAFLD (Table 3). However, the heterogeneity was resolved by an ethnicity-specific meta-analysis in NAFLD (Table 3). Publication bias causes a disproportionate number of positive studies and poses a problem for meta-analyses. Evidence of publication bias was not found in the meta-analyses of the PPAR γ Pro12Ala polymorphism (Egger's regression test p -values > 0.1).

Discussion

In this meta-analysis, we combined evidence of the associations between the PPAR γ Pro12Ala polymorphism and susceptibility to NAFLD, RA, and PsA. Meta-analysis revealed

TABLE 3. META-ANALYSIS OF THE ASSOCIATION BETWEEN THE PPAR γ Pro12Ala POLYMORPHISM AND NAFLD, RA, AND PsA

Polymorphism	Population	Disease	No. of studies	Test of association			Test of heterogeneity		
				OR	95% CI	p-value	Model	p-value	I ²
Ala vs. Pro allele	Overall	NAFLD	5	0.936	0.672–1.302	0.693	R	0.074	53.1
	European	NAFLD	2	1.128	0.863–1.475	0.378	F	0.380	0
	East Asian	NAFLD	3	0.700	0.496–0.987	0.042	F	0.206	36.7
	East Asian	RA	2	0.467	0.188–1.161	0.101	R	0.060	71.7
	European	PsA	2	0.869	0.465–1.627	0.662	R	0.004	88.1
Ala/Ala + Ala/Pro vs. Pro/Pro (Dominant)	Overall	NAFLD	5	0.882	0.703–1.105	0.275	F	0.110	46.9
	European	NAFLD	2	1.051	0.782–1.413	0.742	F	0.337	0
	East Asian	NAFLD	3	0.688	0.484–0.978	0.037	F	0.186	40.4
	East Asian	RA	2	0.465	0.176–1.230	0.323	R	0.048	74.3
	European	PsA	2	0.895	0.484–1.654	0.723	R	0.009	85.2
Ala/Ala + Pro/Pro vs. Ala/Pro (Overdominant)	Overall	NAFLD	5	1.210	0.960–1.525	0.107	F	0.178	36.4
	European	NAFLD	2	1.051	0.773–1.430	0.750	F	0.297	7.96
	East Asian	NAFLD	3	1.453	1.023–2.065	0.037	F	0.186	40.4
	East Asian	RA	2	2.109	0.766–5.808	0.149	R	0.040	76.2
	European	PsA	2	1.050	0.639–1.724	0.848	R	0.039	76.4

OR, odds ratio; CI, confidence interval; F, fixed-effects model; R, random-effects model.

FIG. 2. Odds ratios (Ors) and 95% confidence intervals (CIs) of individual studies and pooled data for the association between the Pro12Ala polymorphism of peroxisome proliferator-activated receptor-gamma (PPAR γ) and nonalcoholic fatty liver disease (NAFLD) (A), rheumatoid arthritis (RA) (B), and psoriatic arthritis (PsA) (C) under dominant model in Europeans and East Asians.

no association between the Ala allele and NAFLD. However, stratification by ethnicity indicated a significant association between the Ala allele of the PPAR γ Pro12Ala polymorphism and NAFLD in East Asians, but not in Europeans. European populations demonstrated a higher frequency of the Ala allele, while East Asians showed a lower frequency of the Ala allele. The differences in the Ala allele among ethnic groups may indicate an ethnic difference in the association between the PPAR γ Pro12Ala polymorphism and susceptibility to NAFLD between Europeans and East Asians. However, the meta-analysis revealed no association between the PPAR γ Pro12Ala polymorphism and RA and PsA.

PPAR γ increases the expression of genes that promote fatty acid storage, whereas it represses genes that induce lipolysis in adipocytes. In patients with NSFLD, hepatic

expression of PPAR γ is involved in insulin sensitivity, triglyceride clearance, and hepatic steatosis (Lee *et al.*, 2006). An association between positivity for the Ala variant and insulin resistance, type 2 diabetes, and obesity has been reported (Knouff and Auwerx, 2004, Tonjes and Stumvoll, 2007). This association may be explained by the lower activity of the Ala variant in adipose tissue, favoring insulin resistance and, potentially, the flux of FFAs to the liver and NAFLD (Deeb *et al.*, 1998). Our meta-analysis suggested a protective role for the Ala allele of the PPAR γ Pro12Ala polymorphism in NAFLD risk. It has been reported that oxidative stress resulting from overproduction of reactive oxidant species (ROS) in over-nutrition conditions contributes to the development and progression of NAFLD (Dimitrova-Shumkovska *et al.*, 2010). Carriers of the PPAR γ Ala allele showed increased resistance to

FIG. 3. ORs and 95% CIs of individual studies and pooled data for the association between the Pro12Ala polymorphism of PPAR γ and NAFLD (A), RA (B), and PsA (C) under overdominant model in Europeans and East Asians.

oxidative stress (Thamer *et al.*, 2002). The enhanced oxidative stress tolerance of the Ala carriers may imply that the Pro/Pro genotype increases the production of free radicals and ROS (Luo *et al.*, 2008).

The results of this meta-analysis differ from those of a previous meta-analysis on the relationship between the PPAR γ Pro12Ala polymorphism and NAFLD risk by Dongiovanni and Valenti (2013). Compared with the Dongiovanni *et al.* study, the present study included two new studies (Terauchi, 2007; Cao *et al.*, 2012), but excluded two studies as they were not consistent with HWE, and only studies providing genotype data were included (Gupta *et al.*, 2010; Gawrieh *et al.*, 2012). In addition, an ethnicity-specific meta-analysis was conducted for Europeans and East Asians in our meta-analysis. In contrast with the results of the previous study, this meta-analysis revealed an association between the PPAR γ Pro12Ala polymorphism and NAFLD in an East Asian population.

The present study has some limitations that should be considered. First, heterogeneity and confounding factors may

have distorted the analysis. Second, other PPAR γ polymorphisms capable of affecting the PPAR γ activity could also be associated with NAFLD. However, the limited amount of data available prevented further meta-analysis. Third, there are varying levels of disease severity, and the NAFLD severity level was unclear. Further research is required to examine whether an association exists between the PPAR γ Pro12Ala polymorphism and the activity or clinical features of the disease. Fourth, we included data from European and East Asian patients in our meta-analysis, and thus, our ethnicity-associated results are applicable only to these ethnic groups. Fifth, the number of studies included in this meta-analysis was small, especially in subgroup by ethnicity, and RA and PsA. There were two European studies and three East Asian studies in the subgroup analysis by ethnicity and for each, two studies in RA and PSA. The study numbers may not be sufficient to provide a conclusive result.

In conclusion, this meta-analysis of the PPAR γ Pro12Ala polymorphism demonstrated that the PPAR γ Pro12Ala polymorphism is associated with susceptibility to NAFLD in

East Asians, but not in Europeans. Accordingly, our findings support the notion that the PPAR γ Pro12Ala polymorphism plays a role in the pathogenesis of NAFLD. However, meta-analysis did not find an association between the PPAR γ Pro12Ala polymorphism and RA, PsA. Since the frequency of the PPAR γ Pro12Ala polymorphism is different among various ethnic groups, large-scale studies in populations with different ethnicities are needed to explore the relationships between the polymorphisms of the PPAR gene and the pathogenesis of NAFLD, RA, and PsA.

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Author Disclosure Statement

The authors have no financial or nonfinancial conflicts of interest to declare.

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