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Association between PPARG Pro12Ala polymorphism and diabetic nephropathy risk; an updated meta-analysis of 27 studies

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Abstract

Diabetic nephropathy (DN) is one major complication of hyperglycemia in diabetes patients. The relationship between peroxisome proliferator-activated receptors gamma (PPARG) gene rs1801282 (Pro12Ala) polymorphism and the risk of DN has been investigated previously. However, the results were conflicting. In this study, we assessed whether PPARG gene rs1801282 polymorphism is associated with the risk of DN by meta-analysis. We searched in PubMed, Science Direct and Google Scholar databases using a combination of terms of 'Diabetic nephropathy', 'peroxisome proliferator activated receptor gamma', 'PPARG', 'Pro12Ala polymorphism' and rs1801282" between January 2001 and July 2017. Twenty-seven original studies involving 5443 cases and 7262 controls were analysed. Studies conducted in several countries in Europe and North America were assigned to the Caucasian ethnic group and countries in South, East and South East Asia were assigned to an Asian ethnic group. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. The heterogeneity of the included studies was examined with Cochran Q and I^2 statistics. Begg's rank correlation test and Egger's linear regression test were used to assess the publication bias. Our meta-analysis indicated that the PPARG Ala12 allele carriers reduced the DN risk in study populations ($P < 0.001$, OR = 0.760, 95% CI = 0.677-0.853). Although there is moderate heterogeneity between studies ($P_{heterogeneity} < 0.007$, Q= 47.0, $df = 26$, I-squared = 44.7%), publication bias was not seen. However, subgroup analyses showed that in Asian populations, a significant association was not found between the PPARG Pro12Ala and DN risk ($P = 0.133$, OR = 0.796, 95% CI = 0.591-1.072). The PPARG Pro12Ala polymorphism is a genetic risk factor for DN in Caucasian populations and no conclusion of a causal relationship can be drawn from the available data.

Keywords: PPAR-gamma, Pro12Ala, Diabetic Nephropathy, Meta-analysis, Asians, Caucasians

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Introduction

Diabetic nephropathy (DN) is a progressive kidney disease and is characterized clinically by the increased blood pressure, occurrence of albuminuria and a gradual loss of kidney function (1). The morphological changes associated with early phase DN comprise diffuse thickening of the glomerular capillary basement membrane together with the nodular glomerulosclerosis (2). Although the pathophysiology of DN is mainly occurring due to hyperglycemia, it is believed to involve a combination of genetic and environmental factors. Crucially, DN is not clinically detectable until significant kidney damage has developed, highlighting the need to identify early-stage biomarkers. Current therapies for DN target renin-angiotensin, complement and coagulation cascade, and peroxisome proliferator-activated receptor (PPAR) pathways to achieve tight glycemic control and systemic blood pressure (3).

PPARs are ligand activated transcription factors that occur in three related forms (PPAR-alpha, PPAR-beta/delta, and PPAR-gamma) (4). Gene expression studies suggested that 3 PPAR forms are differentially expressed in the kidney (5,6). PPAR-gamma (PPARG) mRNA is mainly localized in renal medullary collecting duct with lower expression in renal glomeruli and renal microvasculature (7). PPARG is involved in renal hemodynamic and water and sodium transport. Further, numerous studies have demonstrated the renoprotective actions of PPARG, such as improved insulin resistance, decreased blood glucose, reduced levels of circulating non-esterified fatty acid and insulin-desensitizing cytokines, increased plasma adiponectin level and lowered blood pressure (8-12). PPARG gene spans more than 100 kb of genomic DNA on 3q25, and harboring a most studied missense

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Implication for health policy/practice/research/ medical education

This study helps in identifying the exact role of PPARG Pro12Ala polymorphism to predict susceptibility of diabetic nephropathy in different ethnicities.

mutation resulting in the alanine substitution for proline at codon 12 (Pro12Ala) of the PPARG gene (rs1801282) (13). Although the mechanisms by which the PPARG Pro12Ala polymorphism contributes to DN is not yet elucidated completely, several studies have investigated the association between PPARG Pro12Ala polymorphism and DN risk. The aim of our meta-analysis was to quantitatively summarize the association of PPARG gene Pro12Ala polymorphisms with DN.

Materials and Methods

Literature search

A comprehensive search in PubMed, Science Direct and Google Scholar was conducted to identify published studies related to PPARG gene and DN. The keywords such as 'Diabetic nephropathy', 'peroxisome proliferator activated receptor gamma', 'PPARG', 'Pro12Ala polymorphism' and rs1801282 were used in various combinations. The search was done without any restrictions to identify all relevant papers and the last quest was updated on 25th July 2017. After initial screening, full text of all relevant papers were obtained and further filtered to fit in the following inclusion criteria; 1) prospective cohort or case-control studies, 2) all the studies had a similar purpose of investigating the association of Po12Ala polymorphism with DN, 3) enough information to calculate odds ratio (OR). The studies not providing enough information were excluded from the meta-analysis.

Data extraction

Genotype data for the target polymorphism was carefully extracted independently by two of the authors. The following data were considered; first author, year of publication, country of study, ethnicity of the study population, number of genotyped DN and control subjects and number of Pro/Pro carriers and Ala carriers (Pro/Ala and Ala/Ala). The data extracted were tabulated. This meta-analysis was performed as per the guidelines issued in the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (14) and evaluated the association of Pro12Ala polymorphism with DN risk.

Statistical analysis

The strength of association between PPARG Pro12Ala polymorphism and DN risk was assessed by calculating the crude ORs and corresponding 95% confidence interval (CI) limits. We choose OR as the effect size to find DN risk associated with rare genotypes (Pro/Ala and Ala/Ala). Heterogeneity between studies was evaluated by using the Cochran's Q test (15) and inconsistency value I^2 (16). Both fixed and random effect models were used for analysis and high-resolution forest plots were prepared to depict OR and 95% CI. To test the potential publication bias using Begg's funnel plot and Egger's test were used. Publication Bias was presented using the funnel plot of precision by log of OR. All meta-analyses were conducted using Comprehensive Meta-Analysis (CMA) software package version 2.

Results

Based on the inclusion and exclusion criteria, twenty-seven studies (5443 cases and 7262 controls) published from 2001 to 2017 were identified to be eligible studies. There were thirteen studies on Asians, fourteen studies on Caucasian. All of the studies were case-control and published in English. Characteristics of the studies used in this meta-analysis are presented in (Table 1). Overall, the combined results presented in Figure 1A, indicated that PPARG Pro12Ala polymorphism significantly associated with the reduced risk of DN in both fixed effect ($P<0.001$, OR = 0.760, 95% CI = 0.677–0.853) and random effect ($P<0.001$, OR = 0.733, 95% CI = 0.620-0.863) models. The heterogeneity test showed a mild to moderate heterogeneity between studies ($P_{heterogeneity}<0.007$, Q= 47.0, $df=26$, I-squared = 44.7%). The funnel plot did not show asymmetry by visual inspection suggesting no publication bias (Figure 1B). Further, the Egger's ($P=0.117$) or Begg's test ($P=0.269$) was not significant, thus excluding the presence of publication bias.

The sub-group analysis by ethnicity was executed to assess the potential ethnic differences. The results from the Caucasian studies were similar to the overall population studies and provided supporting evidence for the reduced risk of DN in both fixed effect ($P<0.001$, OR = 0.747, 95% CI = 0.646–0.864) and random effect ($P=0.001$, OR = 0.705, 95% CI = 0.576-0.862) models (Figure 2A). There was heterogeneity among the results of individual studies, however this was not statistically significant ($P_{heterogeneity}=0.070$, Q = 21.35, $df=13$, I-squared = 38.5%). Although the funnel plot did not show asymmetry by visual inspection (Figure 3A), the existence of publication bias was paradoxically indicated by Egger's ($P=0.007$) or Begg's ($P=0.071$) tests (Tables 2 and 3). The summary OR under a random-effects model for Asian populations did not indicate a significantly altered DN risk with 12Ala carriers ($P=0.133$, OR = 0.796, 95% CI = 0.591–1.072) (Figure 2B). Significant heterogeneity across studies was observed ($P_{heterogeneity}=0.012$, Q= 25.7, $df=12$, I-squared = 53.4%). The Funnel plots' shape did not reveal obvious evidence of asymmetry (Figure 3B), and the P values of Egger's ($P=0.939$) or Begg's ($P=0.393$) tests suggest that publication bias was not evident.

Discussion

Good glycemic control is achieved by stable equilibrium between dietary intake and gluconeogenesis and tissue uptake or utilization through storage as glycogen or

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

Study reference	Country/Ethnicity	Total samples	DN		Control	
			Pro/Pro	Ala/-	Pro/Pro	Ala/-
Mori et al, 2001 (32)	Japan/ Asian	1632	580	28	982	42
Herrmann et al, 2002 (33)	Germany/ Caucasian	400	154	43	144	59
Caramori et al, 2003 (23)	Brazil/Caucasian	256	93	11	109	43
Wu, 2004 (34)	China/ Asian	328	194	26	102	6
Maeda et al, 2004 (35)	Japan/ Asian	140	46	15	55	24
Stefanski et al, 2006 (36)	Poland/ Caucasian	214	41	14	113	46
Pollex et al, 2007 (37)	Canada/Caucasian	159	94	3	55	7
Erdogan et al, 2007 (25)	Turkey/Asian	91	43	0	47	1
Lee et al, 2008 (38)	Korea/Asian	367	171	15	159	22
Jorsal et al, 2008 (39)	Denmark/Caucasian	843	312	116	290	125
Wei et al, 2008 (40)	China/ Asian	181	68	14	89	10
Li et al, 2008 (24)	China/ Asian	259	150	15	77	17
Wu et al, 2009 (41)	Taiwan/ Asian	389	157	18	197	17
De Cosmo et al, 2009 (42)	Italy/Caucasian	1119	86	7	856	170
Liu et al, 2010 (43)	China/ Asian	760	499	33	199	29
Lapice et al, 2010 (44)	Italy/Caucasian	750	53	2	606	89
Zhu et al, 2011 (45)	China/ Asian	78	39	2	33	4
De Cosmo et al, 2011a (46)	Italy/Caucasian	841	221	40	499	81
De Cosmo et al, 2011b (46)	Italy/Caucasian	623	224	30	316	53
De Cosmo et al, 2011c (46)	Italy/Caucasian	714	207	25	422	60
Zhang et al, 2012 (26)	India/Asian	396	113	28	206	49
Bhaskar et al, 2013 (47)	India/Asian	121	37	17	36	31
Ahmed et al, 2013 (48)	Egypt/Caucasian	51	32	5	9	5
Yang et al, 2014 (49)	UK/Caucasian	267	125	26	90	26
Lapice et al, 2015 (50)	Italy/Caucasian	294	180	32	70	12
Chao et al, 2016 (51)	China/ Asian	959	733	47	158	21
Avzaletdinova et al, 2016 (52)	Russia/Caucasian	473	140	39	205	89

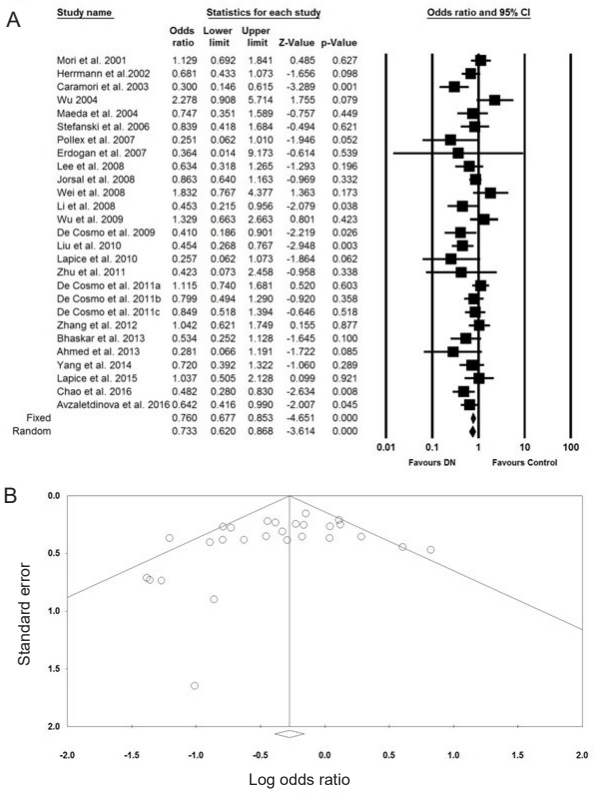

Figure 1. The association between PPARG rs1801282 and DN risk (A. Forest plot, B. Egger's funnel plot).

fat and oxidation. Hyperglycemia, advanced glycation products, and activation of cytokines are some of the causative factors of DN. The PPARs are nuclear receptors that play key roles in the regulation of lipid metabolism, inflammation, cellular growth, and differentiation (17). Studies using potent synthetic PPAR agonists and the generation of global and tissue-specific PPAR knockout mice elucidated the critical functions of these receptors in glucose, cholesterol, and fatty acid metabolism (18,19). *In vitro* and *in vivo* studies revealed that the 12Ala allele of Pro12Ala polymorphism in the PPARG gene is related to a diminished affinity of PPARG2 for the peroxisome proliferator response element sequence in target gene promoters (20) and decrease their expression level. Further, 12Ala allele increased insulin-sensitizing effect in the liver and skeletal muscles (21,22).

Several studies analyzed PPARG Pro12Ala polymorphism in Caucasian and Asian populations. PPARG Ala12 allele conferred protection against DN in Brazilian patients with type 2 diabetes (23). In contrast, no association between this allele and DN risk was observed in Han Chinese (24) and Turkish populations (25). Previous meta-analysis showed reduced risk of DN with Ala12 allele in Caucasians but not in Asians studies (26-29). In line with the earlier reports, this meta-analysis with 5443 DN cases and 7262 controls indicated that the PPARG Ala12 allele carriers

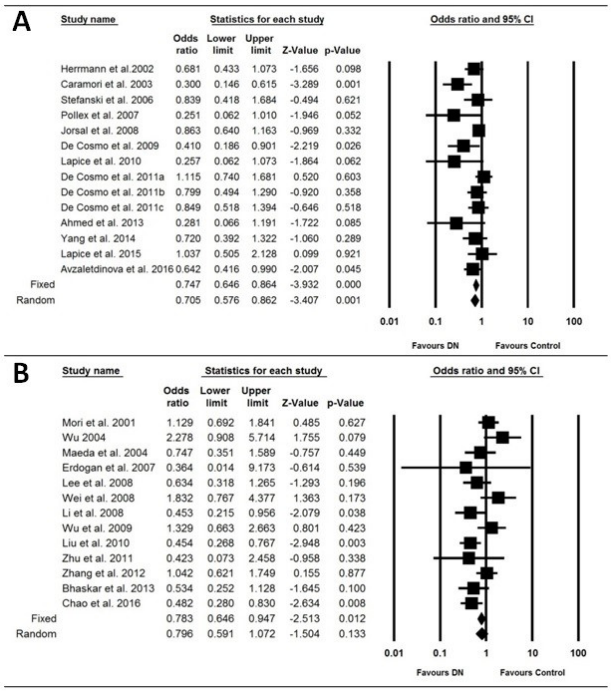

Figure 2. Forest plot of meta-analysis for the association between PPARG rs1801282 and DN risk (A. Caucasians, B. Asians). For each study fixed and random-effects summary OR estimates, 95% confidence intervals (CI), and study weights are provided.

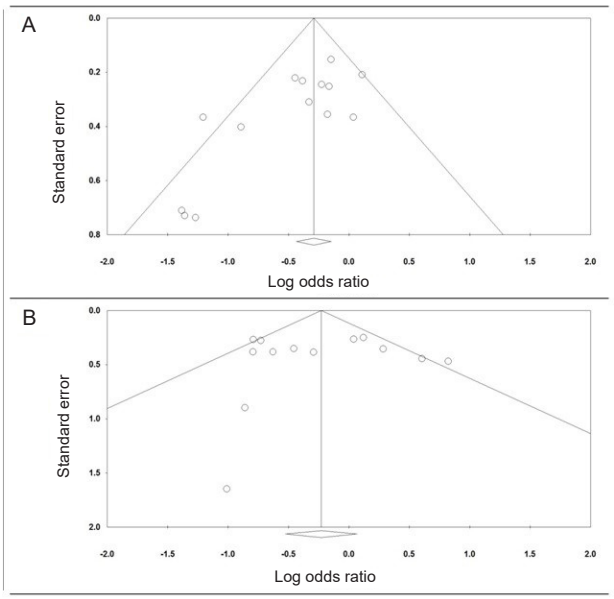

Figure 3. Egger's funnel plot of publication bias (A. Caucasians, B. Asians). Each study's effect estimate (OR) was plotted on a logarithmic scale against the precision of the respective study.

reduced the DN risk in study populations. Although there is moderate heterogeneity between studies, publication bias was not seen. A similar story was revealed in a stratified analysis in Caucasians, in which PPARG Ala12 allele carriers reduced risk of DN. However, it should be noted that in Asian populations, a significant association was not found between the PPARG Pro12Ala and DN risk. These marked differences in Asian and Caucasian studies may be due to the variations in the Ala12 allele frequencies and prevalence of DN in these populations. The genotypes and alleles of the PPARG Pro12Ala polymorphism show ethnic and regional differences. The minor allele frequency of this polymorphism (Ala12) is 12% among Caucasians, 10% in the United States, 3% in African-Americans, 8% among Samoans, and 4% in the Japanese population (30). Lower prevalence of DN and higher frequency of Ala12 allele was found in Caucasian populations compared to the Asian populations. One of our recent studies suggested that the PPARG Pro12Ala polymorphism does not modify the progression of kidney failure in DN patients (31).

DN has a multifactorial etiology resulting from the interaction of genetic and environmental factors, and it is likely that gene-to-gene and gene-to-environment interactions are important components of DN development. Inaccurate phenotyping and lack of original

Table 2. Measures of publication bias in Asians and Caucasians populations

Publication bias test	All populations	Asian populations	Caucasian populations
Classic fail-safe 'N'			
Observed studies P value	<0.001	0.020	<0.001
Observed studies Z value	-5.108	-2.321	-4.857
Number of missing studies to bring *P*> alpha	157	6	72
Orwin's fail-safe 'N'			
OR	0.760	0.783	0.747
Begg and Mazumdar rank correlation test			
Kendall' tau	-0.151	0.179	-0.363
One-tailed	0.135	0.197	0.035
Two-tailed	0.269	0.393	0.071
Egger's regression test			
Intercept value	-1.041	0.097	-2.105
't' value	1.623	0.078	3.238
One-tailed	0.059	0.469	0.004
Two-tailed	0.117	0.939	0. 007
df	25	11	12

Table 3. Summary of previous meta-analysis conducted for diabetic nephropathy and PPAR pro12Ala polymorphisms

Meta-analysis	Race	No. of studies	Heterogeneity	Publication Bias	Inference on association between PPAR Pro12Ala and DN
De Cosmo et al, 2011 (46)	Asians Caucasians	2 7	Yes*	Yes*	Ala12 carrier showed reduced risk
Yu et al, 2012 (53)	Asians Caucasians	2 3	Yes Yes	No*	High frequency of Pro12Pro genotype was found in Asian DN patients.
Zhang et al, 2012 (26)	Asians Caucasians	9 9	Yes No	No No	Significant Association was detected in Caucasian but not in Asian DN patients.
Wang et al, 2013 (27)	Asians Caucasians	9 9	Yes No	No*	Significant Association was detected in Caucasian but not in Asian DN patients.
Zhou et al, 2014 (54)	Caucasians	8	No	No	Pro12Pro genotype susceptibility to DN was found in Caucasians.
Liu et al, 2014 (55)	Asians	10	Yes	No	Pro12Pro genotype was not susceptible to DN risk in Asians.
Ding et al, 2015 (28)	Asians Caucasians	11 9	Yes*	No*	Ala12 carriers showed decreased DN risk in Caucasians but not in Asians.
Li et al, 2015 (29)	Asians Caucasians	6 10	No*	No*	Ala12 carriers showed decreased DN risk in Caucasians but not in Asians.

DN; diabetic nephropathy.
*Both Asian and Caucasian studies are pooled.

data limited further analysis on common confounders such as sex, duration of diabetes, glycemic status and lipid profiles.

Conclusion

In conclusion, although we observed decreased risk associated with the PPARG Pro12Ala polymorphism, the association was only present in Caucasian populations, not in Asian populations. Therefore, no causal relationship can be drawn from the available data.

Authors' Contribution

Study Conceived; PG and BVKSL. Data collected; SL and HV. Data analyzed; SK and BVKSL. Wrote the paper; PG and BVKSL.

Conflicts of interest

There are no conflicts of interests.

Ethical considerations

The authors of this manuscript declare that they all have followed the ethical requirements for this communication. Also, Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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