Peroxisome Proliferator–Activated Receptor γ Polymorphism Pro12Ala Is Associated With Nephropathy in Type 2 Diabetes

Evidence from meta-analysis of 18 studies

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OBJECTIVE—Insulin resistance plays a part in diabetic nephropathy (DN). The association between the peroxisome proliferator–activated receptor γ Pro to Ala alteration at codon 12 (Pro12Ala) polymorphism and the risk of insulin resistance has been confirmed. The association between the polymorphism and DN risk has also been widely studied recently, but no consensus was available up to now.

RESEARCH DESIGN AND METHODS—A systematic search of electronic databases (MEDLINE, Embase, and China National Knowledge Infrastructure) and reference lists of relevant articles was carried out, and then 18 case-control studies involving 3,361 DN cases and 5,825 control subjects were identified.

RESULTS—In the overall analysis, the Ala12 variant was observed to be significantly associated with decreased DN risk (odds ratio 0.76 [95% CI 0.61–0.93]). Some evidence of heterogeneity among the included studies was detected, which could be explained by the difference of ethnicity and stage of DN. Subgroup analyses stratified by ethnicity and stage of DN were performed, and results indicated the Pro12Ala polymorphism was associated with the risk of DN in Caucasians but no similar association was observed in Asians. Additionally, we observed that Ala12 was associated with decreased risk of albuminuria. With only a few of subjects were available, we failed to detect statistically significant association between the polymorphism and end-stage renal disease (ESRD).

CONCLUSIONS—Our results indicated that the Ala12 variant is a significantly protective factor for DN. Future research should focus on the effect of Pro12Ala polymorphism on ESRD and gathering data of Africans.

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Diabetic nephropathy (DN) is a common complication of diabetes and currently represents an important issue of public health because DN is the leading cause of end-stage renal disease (ESRD) in the United States as well as many other parts of the world (1,2). A recent epidemiological study has revealed that albuminuria is present in 49.6% of type 2 diabetic (T2DM) patients, aged >30 years, in China (3). Predictive markers to identify high-risk population are urgently needed for early detection and preventive care. Genetic susceptibility of disease has been a research focus in the scientific community. The peroxisome proliferator–activated receptor γ gene (PPARγ) locates on chromosome 3. As the most extensively studied and clinically validated gene for therapeutic utility in T2DM, PPARγ can be upregulated by thiazolidinediones and anthocyanins to improve insulin sensitivity and glucose uptake in human adipocytes and animal models of diabetes (4). A screening of the PPARγ gene for sequence variants has identified several genetic variants, among which the most common polymorphism is the CG change in exon B, resulting in Pro to Ala alteration at codon 12 (Pro12Ala). The Pro12Ala polymorphism is associated with reductions both in DNA binding and transcriptional activity in vitro, and Ala12 carriers show significant improvement in insulin sensitivity (5), which may be responsible for the development of DN.

Some studies suggested that there was an association between PPARγ Pro12Ala polymorphism and the risk of DN in patients with T2DM (T2DM-DN) (6,7); however, some others suggested there was no significant association (8,9). At present, the relationship was still precarious and remained inconclusive. A recent meta-analysis strongly suggested that the Pro12 variant was an allele that increased risk of developing albuminuria in T2DM subjects, whereas in this study, nine genetic association studies were identified without considering the difference of ethnicity, and the authors admitted publication bias existed (10). Thus, we performed the present quantitative synthesis of 18 suitable studies, containing data from our study, to derive a more precise estimation of the association between Pro12Ala polymorphism and DN.

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RESEARCH DESIGN AND METHODS

Search strategy, inclusion criteria, and information extracted

Two investigators (H.Z. and S.Z.) carried out the comprehensive literature searches independently using the electronic databases MEDLINE, Embase, and China National Knowledge Infrastructure without date and language restrictions. We used any possible combinations of relevant keywords of PPARγ (e.g., PPAR, PPARG, PPARgamma, Pro12Ala, and P12A) polymorphism and each term designating T2DM-DN (e.g., type 2 diabetes, nephropathy, albuminuria, proteinuria, and ESRD). Reference lists from relevant meta-analyses, systematic reviews, and clinical guidelines were also examined. The last quest was updated on 5 October 2011. When more than one study of the same population was included in several publications, only the most recent or complete study was used in this meta-analysis. Studies included in our meta-analysis had to meet the following inclusion criteria: *1*) prospective cohort or case-control studies, *2*) studies investigating the association of Pro12Ala polymorphism with T2DM-DN as the outcome, and *3*) the control group with subjects who had T2DM but were free of diabetic kidney disease.

Information was carefully extracted from all eligible publications independently by two of the authors (Y.T. and H.H.). Discrepancies were adjudicated by the third reviewer (H.C.) until consensus was achieved on every item. The following data were considered: author name, year and country of the study, ethnicity, genotyping method, and numbers of genotyped cases and control subjects. Different ethnic descents were categorized as Caucasian and Asian.

Subjects and genotyping of data

A total of 255 T2D subjects were selected from phase 2 of the Chennai Urban Rural Epidemiology Study. The 255 individuals without microalbuminuria or proteinuria were randomly selected from all self-reported diabetic subjects (n = 1,529). The identified subjects had a 2-h plasma glucose value ≥200 mg/dL. Subjects with DN (n = 141) were selected from Dr. Mohan's Diabetes Specialities Centre, a tertiary center for diabetes in Chennai, India. In all subjects, albumin excretion rate, measured by immuneturbidmetric assay, was at least 300 μg/mg in at least two out of three fasting urine collections over a period of 3 months. The 141 proteinuric patients with albumin-to-creatinine ratio ≥300 μg/mg were defined as case subjects. The clinical and biochemical characteristics of the data from our study had been described previously (11).

The polymorphism was genotyped by PCR–restriction fragment length polymorphism, and 10% of them were subjected to direct sequencing in order to confirm the quality of genotyping. The sequences of primers to genotype the Pro12Ala polymorphism of PPARG were 5′-GCCAATTCAAGCCCAGTC-3′ and 5′-GATATGTTTGCAGACAGTGTATC-AGTGAAGGAATCGCTTTCCG-3′ (12).

Statistical analyses

The effect measures of choice were odds radio (OR) for dichotomous variables and standardized mean difference (SMD) for continuous parameters with their corresponding 95% CIs. SMD was used because of the significant differences in the dimensions. The departure of frequencies from those expected under Hardy-Weinberg equilibrium was assessed by χ^2 goodness-of-fit tests in control subjects. We evaluated the heterogeneity using the Q test (13). A P value <0.05 was considered significant for the heterogeneity. We also calculated the quantity I^2 that represented the percentage of total variation across studies. As a guide, values of I^2 <25% may be considered low, and values >75% may be considered high (14). The fixed-effects model was used when there was no heterogeneity among the included studies; otherwise, the random-effects model was used. In the absence of heterogeneity, the two methods provide identical results, because the fixed effects model, using the Mantel-Haenszel method, assumes that studies are sampled from populations with the same effect size, whereas the random-effects model using the DerSimonian and Laird method assumes that studies are taken from populations with different effect sizes, calculating the study weights both from interstudy and between-study variances, and considering the extent of variation or heterogeneity. The Begg and Mazumdar adjusted rank correlation test (15) and Egger linear regression test (16) were used to provide diagnosis of the potential publication bias. The Begg adjusted rank correlation test, a direct statistical analog of the visual funnel graph, tests for publication bias by determining if there is a significant correlation between the effect estimates and their variances and carries out this test by first standardizing the effect estimates to stabilize the variances and second by performing an adjusted rank correlation test based on Kendall τ. The Egger test detects funnel plot asymmetry by determining whether the intercept deviates significantly from zero in a regression of the standardized effect estimates against their precision. Sensitivity analyses were also performed to assess the stability of the results, namely, a single study in the meta-analysis was deleted each time to manifest the influence of the individual dataset to the pooled OR (17). All meta-analyses were conducted using Review Manage, version 5.1 (The Cochrane Collaboration, Oxford, U.K.), whereas publication bias and sensitive tests were conducted using STATA software (version 11.0; Stata, College Station, TX). All tests were two-sided.

RESULTS

Eligible studies

Out of 486 potentially relevant articles retrieved from electronic databases and reference lists, 17 case-control studies met the inclusion criteria (6–10,18–27). An additional one set of data from our study was included. A flow diagram of search and selection is shown in Supplementary Fig. 1. Fourteen datasets had albuminuria evaluated, two ESRD, and three unrestricted DN (Supplementary Table 3). A total of 3,361 T2MD-DN and 5,825 T2MD subjects without DN were included. Additionally, there were five (7,19,21,24,25) and four studies (7,19,21,27) available to identify the effect of Pro12Ala polymorphism on the levels of serum creatinine (SCr) or albumin excretion rate (AER) in T2DM patients, respectively. The eligible data sets were obtained from 11 English-language and 4 Chinese-language articles. Of these data sets, nine focus on a Caucasian (five for Italian and four for others), and the other nine focus on an Asian population (five for Chinese and four for others). Given the low frequency of Ala allele, even in some studies, Ala homozygous individuals are absent, and only the dominant model was investigated, comparing Ala carriers to Pro/Pro. We also assessed the deviation of Hardy-Weinberg equilibrium in control subjects, and the results demonstrated that all the genotype distributions in the control groups had high goodness-of-fit. The methods used for measuring SCr or AER in both case and control arms were the same. The other detailed characteristics of included

studies were summarized in Supplementary Table 1.

Data from our study

In the case of T2DM subjects without complications, the mean duration of diabetes was 6.6 years. No significant impact of the Pro12Ala polymorphism on the risk of proteinuria was observed, as ORs (95% CI) were 0.98 (0.58–1.67), 3.64 (0.32–40.6), and 1.04 (0.62–1.75) for Pro/Ala versus Pro/Pro, Ala/Ala versus Pro/Pro, and Ala carriers versus Pro/Pro, respectively. The details are summarized in Supplementary Table 2.

Quantitative synthesis

T2MD-ND susceptibility. The results of aggregated ORs and heterogeneity test were shown in Table 1. Overall, the Pro12Ala polymorphism was found to be significantly associated with decreased T2MD-DN risk (OR 0.76 [95% CI 0.61–0.93]) (Fig. 1). Both the Cochran Q test and estimate of I^2 revealed significant heterogeneity among the constituent studies ($P_h = 0.03$; $I^2 = 42\%$).

To avoid the influence of heterogeneity among the included studies, subgroup analyses were distinctively carried out for each stage of DN and ethnic group. In the analysis stratified by stage of DN, the significantly decreased risk of albuminuria (e.g., microalbuminuria and macroalbuminuria) was observed (OR 0.72 [95% CI 0.58–0.89] for albuminuria; 0.38 [0.25–0.57] for microalbuminuria; and 0.64 [0.49–0.82] for macroalbuminuria), but there was no statistically significant association between Pro12Ala polymorphism and ESRD. Furthermore, in the analysis stratified by ethnicity, significant association was detected between the polymorphism and DN risk in Caucasian (0.68 [0.51–0.90]) but not in Asian populations (0.85 [0.62–1.17]). Significant heterogeneity was eliminated in most of the subgroup analyses but the Asian groups ($P_h = 0.05$; $I^2 = 48$). The details are also listed in Table 1.

To test the stability of the pooled results, one-way sensitivity analyses of the pooled ORs and 95% CIs were performed. The integrated ORs were calculated by means of the random-effects model. When omitting each dataset in the overall meta-analysis, the pooled ORs were always persistent (Fig. 2). Begg and Egger tests were used to provide diagnosis of the potential publication bias, and no evidence of publication bias was found in the overall analysis ($P_{Begg} = 0.150$; $P_{Egger} = 0.085$) (Table 1 and Fig. 3). Evidence also suggested no publication bias in the subanalyses mentioned above, but one for the association between PPARγ Pro12Ala and albuminuria ($P_{Begg} = 0.063$; $P_{Egger} = 0.036$). However, after getting rid of one dataset each by Caramori (24), De Cosmo (7), Pollex (21), or Li (19), the existing bias disappeared ($P_{Begg} = 0.100$, $P_{Egger} = 0.053$; $P_{Begg} = 0.100$, $P_{Egger} = 0.060$; $P_{Begg} = 0.100$, $P_{Egger} = 0.089$; and $P_{Begg} = 0.100$, $P_{Egger} = 0.056$, respectively), whereas the significant ORs were persistent. The persistent result indicated that the emerging publication bias did not decrease the reliability of the result.

SCr and AER assessment. We observed that levels of SCr were significantly associated with the Pro12Ala polymorphism of PPARγ in T2DM subjects (Supplementary Fig. 2, *bottom*). Overall, the SMD for SCr was statistically significant (SMD = −0.12; 95% CI −0.23 to −0.01; $z = 2.13$, $P_z = 0.03$). There was no significant heterogeneity among the trials ($P_h = 0.52$; $I^2 = 0\%$). We also failed to detect reliable evidence for publication bias (Supplementary Fig. 3, *bottom*).

The effects of the polymorphism on the level of AER were all significant in the four included trials (Supplementary Fig. 2, *top*). The synthetic SMD for AER was significant (SMD = −3.04; 95% CI −4.90 to −1.18; $z = 3.20$, $P_z = 0.001$). However, the heterogeneity among eligible studies ($P_h < 0.001$; $I^2 = 99\%$) was significant. It is noteworthy that a significant decline in AER was detected in the individuals with 12Ala, whereas no evidence of publication bias was observed (Supplementary Fig. 3, *top*).

CONCLUSIONS—Genetic epidemiologic studies of single nucleotide polymorphism, if large and unbiased, can provide evidence of the association between candidate gene and disease risk. This Human Genome Epidemiology association review is an updated meta-analysis of the relationship between the PPARγ Pro12Ala polymorphism and susceptibility of DN in T2DM patients. The overall meta-analysis, based on 18 case-control studies involving 3,361 case subjects and 5,825 control subjects, indicates that the polymorphism is associated with the risk of T2DM-DN. Considering the significant heterogeneity among the identified studies, subgroup analyses are also performed, stratified by ethnicity of population and stage of nephropathy. In selected subgroup of Caucasians but not Asians, we observe a significant association between Ala allele and the risk of T2DM-DN. In the other subanalysis, we also observe that the Pro12Ala is associated with decreased albuminuria risk (i.e., microalbuminuria and macroalbuminuria), whereas there is no relationship between the polymorphism and ESRD risk. The levels of SCr

Table 1—*Stratified analyses of Ala carrier versus Pro/Pro and nephropathy susceptibility of T2DM patients*

Study group	*N*	Sample size (case/control)	Heterogeneity P_h	Heterogeneity I^2 (%)	Pooled OR (95% CI)	*z* test	Begg test (*P*)	Egger test (*P*)
Overall nephropathy	18	3,361/5,825	**0.03**	42	**0.76 (0.61–0.93)***	$z = 2.61$; $P_z = 0.009$	0.150	0.085
Nephropathy stage								
Albuminuria	14	2,988/4,738	0.08	37	**0.72 (0.58–0.89)**	$z = 2.98$; $P_z = 0.003$	0.063	**0.036**
Albuminuria stage								
Microalbuminuria	5	617/1,388	0.98	0	**0.38 (0.25–0.57)**	$z = 4.56$; $P_z < 0.001$	1.000	0.461
Macroalbuminuria	6	825/1,054	0.27	22	**0.64 (0.49–0.82)**	$z = 3.41$; $P_z < 0.001$	0.707	0.275
ESRD	2	105/282	0.42	0	0.93 (0.56–1.56)	$z = 0.26$; $P_z = 0.79$	1.000	NA
Ethnicities								
Caucasian	9	1,336/3,677	0.12	38	**0.68 (0.51–0.90)**	$z = 2.67$; $P_z = 0.008$	0.180	0.076
Asian	9	2,025/2,148	0.05	48	0.85 (0.62–1.17)*	$z = 1.00$; $P_z = 0.32$	0.917	0.853

The boldface values indicate significant association. *N*, number of included studies; P_h, *P* values for heterogeneity of Q test. *Random-effects model.

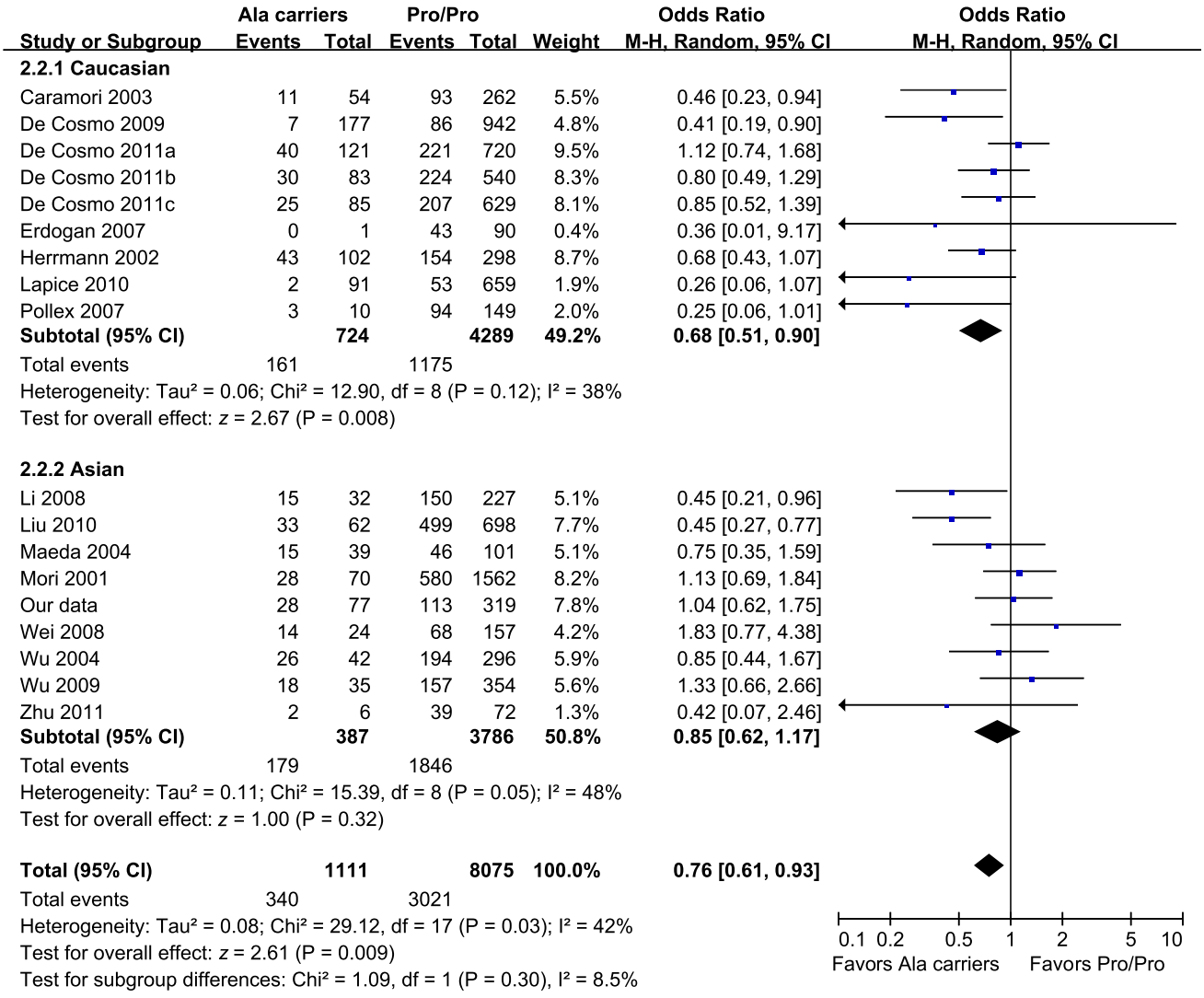

Figure 1—*Forest plots of the meta-analysis for Pro12Ala polymorphism of PPARγ associated with nephropathy in T2DM patients.*

and AER are the essential diagnostic elements for nephropathy. So we also make two additional analyses to investigate the effect of the Pro12Ala polymorphism on the SCr and AER. As expected, we do see an association of the Pro12 allele with higher SCr and AER levels.

Ethnicity difference and stage of disease may be responsible for the significant heterogeneity among the studies included in the overall analysis, so subgroup analyses stratified by ethnicity and stage of DN are addressed. In the Caucasian subgroup, the Ala carriers are associated with significantly decreased T2DM-DN risk. The absence of a statistical effect in the Asian subgroup might be explained by the low frequency of Ala12 allele in Asian populations, the distinction between various races varies from ~4% in Asian to ~28% in Caucasian populations (28). The much lower frequency of the Ala carriers in the Asian population requires a larger sample to detect statistically significant association. There may also be false positives in the Caucasian subgroup due to the control subjects not having the same allele frequency as the cases because the cases and control subjects by chance come from different populations (the Brazilians and Turks are both mixed race, although they mostly consist of Caucasians). Additionally, gene–gene and gene–environmental interactions should also contribute to the different results (29). The ethnic difference may be also induced by curative activities, such as drug use or age at the first diagnosis, although these have to be further confirmed by large population studies.

The first reason that we fail to detect an association between the polymorphism and ESRD risk in our patients with T2DM might be related to the fact that ESRD is more complex than albuminuria, which is determined by plenty of pathophysiological factors. In addition, patients with T2DM usually die of other complications, such as cardiovascular risk, before developing ESRD (30,31); therefore, no significant association between the polymorphism and ESRD is introduced. Additionally, as only a few of the ESRD subjects are available, the reliability of this result remains suspicious.

PPARγ has been implicated in almost all of the pathological processes contributing to atherosclerosis, including endothelial dysfunction, leukocyte chemotaxis, foam cell formation, and plaque evolution, destabilization, and rupture (32). However, the mechanisms by which the variations of PPARγ gene actually protect against DN remain incompletely

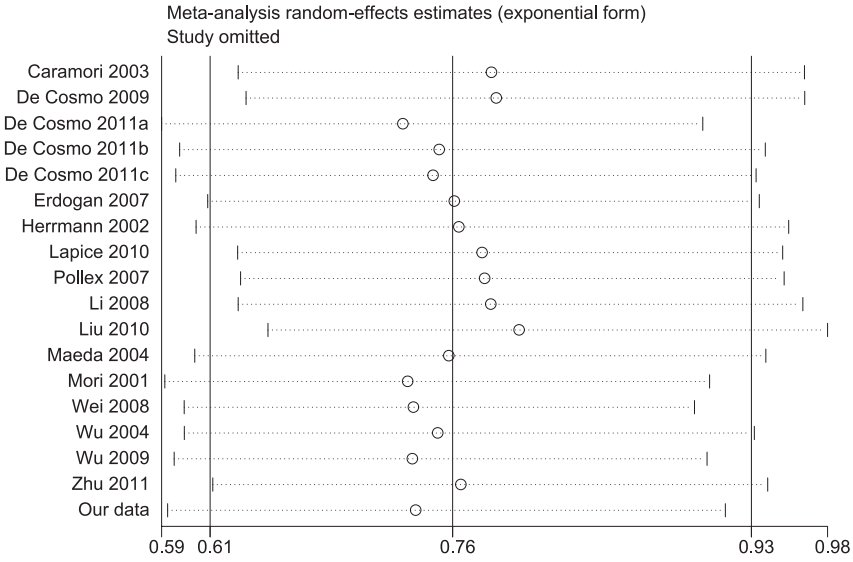

Figure 2—*One-way sensitivity analysis of the pooled ORs and 95% CI for the overall analysis, omitting each dataset in the meta-analysis. Random-effects model was used.*

understood. Various mouse models of PPARγ deficiency have been generated to dissect the function of PPARγ. The study of these models has confirmed that PPARγ plays a key role in regulating insulin sensitivity (33,34), which has been proved to be closely associated with glomerular filtration rate and albuminuria (35). The AMP-activated protein kinase signaling pathway may play a critical role in mediating the insulin-sensitizing action of PPARγ (36). Other studies also identify that thiazolidinedione-induced adiponectin may sensitize the insulin action through the AMP-activated protein kinase-dependent pathway in adipose tissue, skeletal muscle, and liver (37,38). Additionally, a recent study addressed by Cabezas et al. (39) revealed that PPARγ and its agonists positively control megalin expression; this regulation could have an important impact on several megalin-mediated physiological processes and pathophysiologies such as chronic kidney disease associated with diabetes and hypertension.

The stability of the meta-analysis was verified by one-way sensitivity analysis, which pooled ORs by omitting each dataset

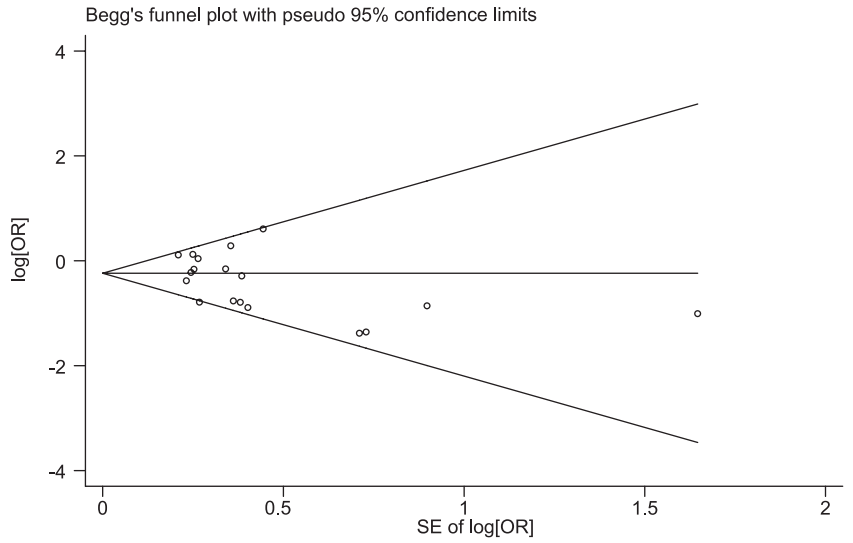

Figure 3—*Begg funnel plot analysis to detect potential publication bias. Each point represents a separate study for the indicated association. The SE is plotted against a logarithmic scale of the OR [log(OR)].*

included. It may indicate that the included patients effectively maintained the most important inherent nature of population in genetic structure and that largely improved the predictability and reliability of the meta-analysis. Moreover, to confirm the reliability of our results, we minimized the possible publication bias by performing searches comprehensively and designing this study precisely. Additionally, Begg and Egger tests were used to test the potential publication bias, and no significant evidence was observed in the overall analysis.

However, some limitations of our study should be acknowledged. First, the number of ESRD patients is relatively small for exploring the reliable result with enough statistical power in the subgroup analyses; second, our results are based on unadjusted estimates, whereas a more precise analysis should be conducted if other covariates (i.e., age, sex, and so on) are available. Despite these limitations, our meta-analyses suggest that the PPARγ 12Ala allele significantly decreases the T2DM-DN risk and the level of SCr and AER. More well-designed studies with larger sample sizes and more details on individuals are needed to provide more precise evidence to further confirm our meta-analysis.

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H.Z., S.Z., Y.T., H.H., and J.W. performed data searching and screening. S.Z. and H.C. designed the research. H.Z., S.Z., Y.T., and H.H. analyzed data. V.M. and R.V. provided the data from our study. H.Z., S.Z., and H.C. wrote the manuscript. H.Z., S.Z., Y.T., H.H., V.M., R.V., J.W., and H.C. reviewed the manuscript. J.C. revised the manuscript according to the suggestions from the editor and reviewers. H.C. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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