Int J Clin Exp Med 2017;10(3):4313-4318
www.ijcem.com /ISSN:1940-5901/IJCEM0044043

Review Article

The association of PPARγ C1431T polymorphism with susceptibility to type 2 diabetes: a systemic review and meta-analysis

Yan Wu[1*], Yi Zhu[2*], Weijian Fan[3]

[1]Department of Endocrinology and Metabolism, Zhejiang Greentown Cardiovascular Hospital, Hangzhou, Zhejiang, P. R. China; [2]The Second Affiliated Hospital of Zhejiang University, Hangzhou, Zhejiang, P. R. China; [3]The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, Zhejiang, P. R. China. [*]Equal contributors and co-first authors.

Received November 10, 2016; Accepted February 3, 2017; Epub March 15, 2017; Published March 30, 2017

Abstract: The association between peroxisome proliferators-activated receptor γ (PPARγ) C1431T polymorphism and Type 2 diabetes mellitus (T2DM) risk is inconclusive and contradictory. Therefore, a comprehensive meta-analysis was conducted to assess the association of PPARγ C1431T polymorphism with susceptibility to T2DM. We searched the PubMed and Web of Science to select eligible studies following included criteria. Finally we identified seven publications for the further analysis. Statistical analysis was performed by using the software of Revman 5.3. The results revealed that C1431T polymorphism was significantly associated with T2DM risk in 4 models (Codominant model CT vs CC: OR = 0.87, 95% CI = 0.76-0.99, P = 0.03; Codominant model TT vs CC: OR = 0.36, 95% CI = 0.21-0.63, P = 0.0003; Recessive model TT vs CT+CC: OR = 0.35, 95% CI = 0.25-0.49, P < 0.00001; and Allele model T vs C: OR = 0.78, 95% CI = 0.62-0.99, P = 0.04) except in dominant model: CT+TT vs CC. Furthermore, we found that the significantly decreased risk of T2DM in Caucasian was associated with the Codominant model TT vs CC, Recessive model TT vs CT+CC, dominant model: CT+TT vs CC; and Allele model T vs C. And no obvious publication bias was observed using the funnel plot. Overall, the current study suggests that PPARγ C1431T polymorphism may be associated with the risk of T2DM in Caucasian.

Keywords: PPARγ, C1431T, polymorphism, type 2 diabetes, meta-analysis

Introduction

Globally, it is estimated that about 382 million adults were diagnosed with diabetes in 2013, and this number is predicted to increase to 592 million by 2035 [1]. Type 2 diabetes mellitus (T2DM), which accounts for more than 90% of diabetes cases, has been revealed to have complex interactions with environmental and genetic factors [2, 3].

The gene of PPARγ, which encodes a nuclear transcription factor involved in the expression of hundreds of genes, is located on chromosome 3p25 [4-6]. Since 1997, more and more evidences indicated that both common and rare polymorphisms of the genes of PPARγ acted as critical roles in the regulation of glucose metabolism [7-10]. Screening of the PPARγ gene of patients with type 2 diabetes for mutations has led to the identification of two polymorphisms: A c to g substitution at nucleotide 39 in the exon unique to PPARγ which results in the replacement of proline 12 with alanine (P12A) and a c to t substitution at nucleotide 1431 (c1431t) which doesn't cause an amino acid change [11, 12]. Although recent years the C1431T polymorphism in PPARγ has been widely studied with respect to T2DM, the results were still inconclusive and controversial. To the best of our knowledge, no one has performed a meta-analysis to investigate the association of this polymorphism with T2DM.

In this study, we collected all published case-control studies and prospective cohorts focused on the relationship between T2DM and PPARγ C1431T polymorphism. A meta-analysis

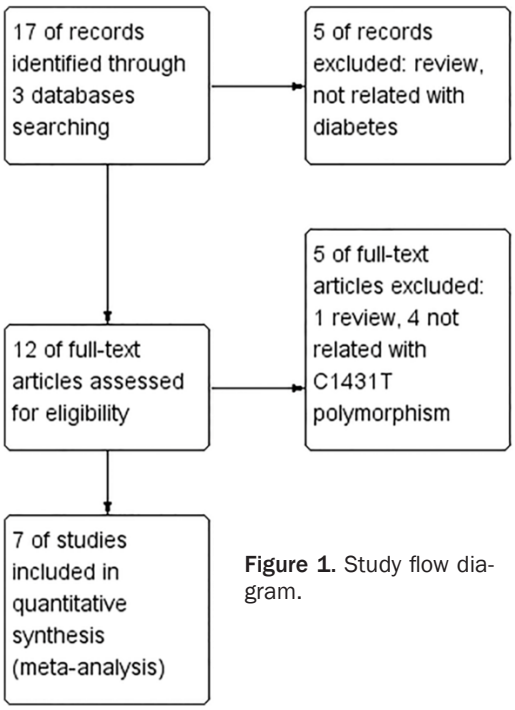


Figure 1. Study flow diagram.

was carried out and our aim was to clarify the controversial results.

Materials and methods

Search for study

A systematic search was performed by two investigators independently. Studies were mainly searched in PubMed and Web of Science from their inception to October 2016 with the following terms: 'PPARγ', 'C1431T', 'polymorphism', 'Type 2 diabetes'. The search was limited to case-control studies. Reference lists from relevant articles were also examined to find additional publications. To avoid double counting or other errors, two investigators compared their results discreetly and disagreements were resolved by consensus or by a third investigator.

Selection of study

All the included studies met the following criteria: 1. case-control study and prospective cohorts; 2. evaluation of the association between PPARγ C1431T polymorphism and T2DM risks; 3. sufficient data for analysis including genotype frequency in both cases and controls; and 4. genotype frequency in the control group was in Hardy-Weinberg equilibrium (HWE). We excluded studies without eligible data for meta-analysis.

Data extraction

Two investigators who were blinded to each other abstracted the data in a traditionalized format and reached consensus on all items. The collected data included first author, publication year, country and available genotypes. Evaluation of evidence strength was carried out according to the modified Newcastle-Ottawa Scale [13] (Supplementary Table 1).

Statistical analysis

Statistical analysis was performed by using Revman 5.3 and STATA 14.0 software. X^2 tests and I^2 statistic were used to measure the study heterogeneity between trials. Both fixed- and random-effects models were applied where appropriate, with $I^2 > 50\%$ was considered representative of significant statistical heterogeneity and the random-effects models launched, otherwise, the calculations were performed with the fixed-effects model [14, 15]. Odds ratio (OR) with 95% confidence interval (95% CI) was used to evaluate the association between polymorphism and T2DM risk with the Codominant model: CT vs CC, Codominant model: TT vs CC, Dominant model: CT+TT vs CC, Recessive model: TT vs CT+CC and Allele model: T vs C. Sensitivity analysis was used to identify sources of significant heterogeneity by removing individual studies and analyzing the effect on the overall results. Publication bias was further assessed by Funnel plot and Begg'stest [16, 17]. *P* value less than 0.05 was considered statistically significant in all statistics.

Results

Characteristics of the studies

Study flow diagram was shown in **Figure 1**. 17 studies of PPARγ C1431T polymorphism and T2DM risks were found in a primary literature search in the PubMed and Web of Science. After reviewing each publication, 10 articles were found inappropriate in the current meta-analysis given some of them were review articles, irrelevant to the current study or contained duplicated data. Seven studies with 3830

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

Author	Year	Country	Study design	Quality score	Genotyping method	No. (Cases/controls)	Genotypes case			Genotypes control			HWE *P* value
							CC	CT	TT	CC	CT	TT	
Butt et al.	2016	Pakistan	Cohorts	6	-	426/500	228	176	22	194	223	83	> 0.05
Costa et al.	2009	Italy	Case-control	5	-	211/254	171	38	2	199	44	11	> 0.05
Doney et al.	2004	United Kingdom	Cohorts	5	-	1997/983	1548	429	20	725	236	22	> 0.05
Dong et al.	2008	China	Case-control	5	PCR-RFLP	207/101	110	84	13	57	37	7	> 0.05
Evans et al.	2001	Germany	Case-control	6	PCR-RFLP	219/426	160	57	2	315	98	13	> 0.05
Haseeb et al.	2009	India	Case-control	5	PCR-RFLP	350/349	251	NA	NA	262	NA	NA	-
Tai et al.	2004	Singapore	Case-control	6	-	420/3080	274	NA	NA	1783	NA	NA	-

Table 2. Pooled ORs and 95% CIs of the meta-analysis for Allele model (T/C), codominant model (CT/CC), codominant model (TT/CC), dominant model (CT+TT/CC), and recessive model (GG/CT+CC)

Variables	No.	Allele comparison			Genetic model comparison			
		OR (95% CI)	*P* value	I^2 (%)	Model type	OR (95% CI)	*P* value	I^2 (%)
All T2DM	7	0.78 (0.62, 0.99)	0.04	74%	Codominant model: CT/CC	0.87 (0.76, 0.99)	0.03	45%
					Codominant model: TT/CC	0.36 (0.21, 0.63)	0.01	50%
					Dominant model: CT+TT/CC	0.85 (0.70, 1.03)	0.09	67%
					Recessive model: TT/CT+CC	0.35 (0.25, 0.49)	0.01	31%
Ethnicity								
Asian	4	0.75 (0.39, 1.45)	0.39	89%	Codominant model: CT/CC	0.85 (0.50, 1.47)	0.57	73%
					Codominant model: TT/CC	0.44 (0.11, 1.81)	0.25	85%
					Dominant model: CT+TT/CC	0.83 (0.59, 1.18)	0.3	81%
					Recessive model: TT/CT+CC	0.46 (0.14, 1.47)	0.19	79%
Caucasian	3	0.82 (0.71, 0.94)	0.01	0%	Codominant model: CT/CC	0.91 (0.78,1.06)	0.24	5%
					Codominant model: TT/CC	0.36 (0.21, 0.61)	0.01	0%
					Dominant model: CT+TT/CC	0.85 (0.73, 0.99)	0.04	0%
					Recessive model: TT/CT+CC	0.37 (0.22, 0.62)	0.01	0%

cases and 5693 controls shown in **Table 1** were identified appropriate for the current meta-analysis [18-24]. The genotype distribution of control population was in agreement with Hardy-Weinberg equilibrium in all seven studies.

Quantitative synthesis

We analyzed the association between PPARγ C1431T polymorphism and T2DM risk within five genetic models as mentioned in the Method. The quantitative synthesis results were presented in **Table 1**. Interestingly, the pooled results revealed a significant association between C1431T polymorphism and T2DM risk in the codominant model (CT vs CC: OR = 0.87, 95% CI = 0.76-0.99, P = 0.03) and allele model (T vs C: OR = 0.78, 95% CI = 0.62-0.99, P = 0.04). Furthermore, drastically significant difference was found between the T2DM group and control group in codominant model (TT vs CC: OR = 0.36, 95% CI = 0.21-0.63, P = 0.0003) and recessive model (TT vs CT+CC: OR = 0.35, 95% CI = 0.25-0.49, P < 0.00001). In contrast, no statistically significant association was found in the dominant model (CT+TT vs CC). Furthermore, stratified analysis of ethnicity showed that significant differences were found between the T2DM group and control group in codominant model (TT vs CC: OR = 0.36, 95% CI = 0.21-0.61, P = 0.01), recessive model (TT vs CT+CC: OR = 0.37, 95% CI = 0.22-0.62, P < 0.01), dominant model (CT+TT vs CC: OR = 0.85, 95% CI = 0.73-0.99, P < 0.01) and allele model (T vs C: OR = 0.82, 95% CI = 0.71-0.91, P = 0.01) in Caucasian group (**Table 2**). No differences was found in Asia group.

Sensitivity analysis

In order to assess the stability of the results, sensitivity analysis was performed. The sensitivity analyses did not detect any individual study which affected the results using the exclusion method step by step (Supplementary Figure 1).

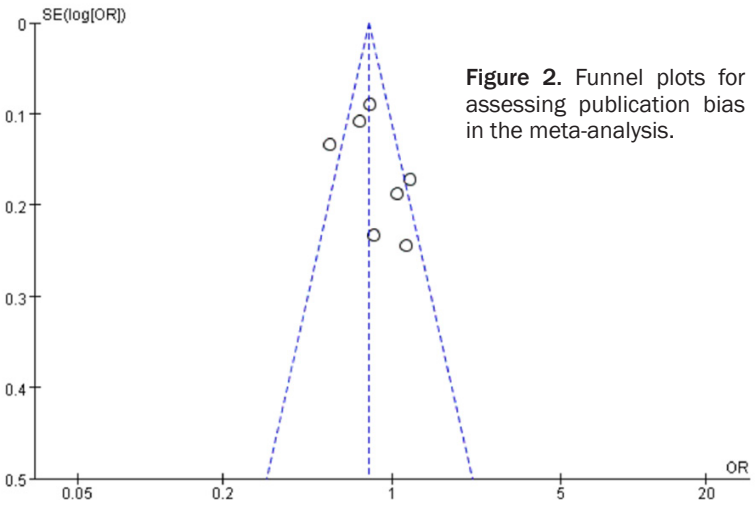


Figure 2. Funnel plots for assessing publication bias in the meta-analysis.

Publication bias

The funnel plot was performed to estimate the publication bias. The shape of the funnel plots was symmetrical, suggesting that there was no evidence of publication bias for the PPARγ C1431T polymorphism (**Figure 2**). Begg's test showed no evidence of publication bias (P = 0.293).

Discussion

PPARγ was the first gene reproducibly associated with T2DM. The association between the substitution of alanine by proline at codon 12 of PPARγ (Ala12) and the risk for T2DM has been widely studied since this polymorphism was first reported in 1997 [25]. In this meta-analysis seven studies including 3830 cases and 5693 controls were collected according to our inclusion criteria. As a result, C1431T polymorphism was found to be associated with T2DM risk in 4 models (Codominant model: CT vs CC, Codominant model: TT vs CC, Recessive model: TT vs CT+CC and Allele model: T vs C) except in dominant model: CT+TT vs CC. Stratified analysis of ethnicity showed that significant differences were found between the T2DM group and control group in codominant model (TT vs CC), recessive model (TT vs CT+CC), dominant model (CT+TT vs CC1) and allele model (T vs C) in Caucasian group. However, no difference was found in Asia group.

The association between the C1431T polymorphism and the risk of T2DM was firstly reported in 2001 and the researchers found that A12/c1431 haplotype was responsible for the T2DM risk [21]. Although not changing the coding sequence of PPARγ, the C1431T polymorphism has been associated with increased body weight and is in tight allelic disequilibrium with the Ala12 variant [26]. However, some researchers identified T allele could decrease weight and BMI and had a protection effect in T2DM [18]. In addition, it also reported that there was no association between C1431T and T2DM [22]. Our results revealed that T allele might lower the risk of T2DM mainly in Caucasian group. The controversial findings could be explained by the different genetic and environmental factors and additional studies will be required not only to detect its more prevalence rate in T2DM but also to investigate the possible biophysical mechanisms of C1431T polymorphism in coordination with other mutations.

Limitations in our analysis should also be considered. First, many other clinical factors such as age, sex or other mixed mutations in each study might lead to bias and haven't been considered in the study. Second, we restricted our included studies published in English. Last, more subgroup analysis should be carried out but no details could be extracted from the original articles.

Disclosure of conflict of interest

None.

Address correspondence to: Weijian Fan, The First Affiliated Hospital, College Of Medicine, Zhejiang University, 79 Qingchun Road, Hangzhou, Zhejiang, P. R. China. Tel: 86057186687114; E-mail: fwj0111@aliyun.com

References

[1] Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U and Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes Res Clin Pract 2014; 103: 137-149.

[2] American Diabetes Association. Classification and diagnosis of diabetes. Diabetes Care 2015; 38 Suppl: S8-S16.
[3] Stolerman ES and Florez JC. Genomics of type 2 diabetes mellitus: implications for the clinician. Nat Rev Endocrinol 2009; 5: 429-436.
[4] McIver B, Grebe SK and Eberhardt NL. The PAX8/PPAR gamma fusion oncogene as a potential therapeutic target in follicular thyroid carcinoma. Curr Drug Targets Immune Endocr Metabol Disord 2004; 4: 221-234.
[5] Chia WK, Sharifah NA, Reena RM, Zubaidah Z, Clarence-Ko CH, Rohaizak M, Naqiyah I, Srijit D, Hisham AN, Asmiati A and Rafie MK. Fluorescence in situ hybridization analysis using PAX8- and PPARG-specific probes reveals the presence of PAX8-PPARG translocation and 3p25 aneusomy in follicular thyroid neoplasms. Cancer Genet Cytogenet 2010; 196: 7-13.
[6] Bittel DC, Kibiryeva N, Dasouki M, Knoll JH and Butler MG. A 9-year-old male with a duplication of chromosome 3p25.3p26.2: clinical report and gene expression analysis. Am J Med Genet A 2006; 140: 573-579.
[7] Choi SS, Park J and Choi JH. Revisiting PPAR gamma as a target for the treatment of metabolic disorders. BMB Rep 2014; 47: 599-608.
[8] Chehaibi K, Nouira S, Mahdouani K, Hamdi S, Rouis M and Slimane MN. Effect of the PPAR gamma C161T gene variant on serum lipids in ischemic stroke patients with and without type 2 diabetes mellitus. J Mol Neurosci 2014; 54: 730-738.
[9] Zhao X, Xu K, Shi H, Cheng J, Ma J, Gao Y, Li Q, Ye X, Lu Y, Yu X, Du J, Du W, Ye Q and Zhou L. Application of the back-error propagation artificial neural network (BPANN) on genetic variants in the PPAR-gamma and RXR-alpha gene and risk of metabolic syndrome in a Chinese Han population. J Biomed Res 2014; 28: 114-122.
[10] Domenici FA, Brochado MJ, Martinelli Ade L, Zucoloto S, da Cunha SF and Vannucchi H. Peroxisome proliferator-activated receptors alpha and gamma2 polymorphisms in nonalcoholic fatty liver disease: a study in Brazilian patients. Gene 2013; 529: 326-331.
[11] Okazawa H, Mori H, Tamori Y, Araki S, Niki T, Masugi J, Kawanishi M, Kubota T, Shinoda H and Kasuga M. No coding mutations are detected in the peroxisome proliferator-activated receptor-gamma gene in Japanese patients with lipoatrophic diabetes. Diabetes 1997; 46: 1904-1906.
[12] Vigouroux C, Fajas L, Khallouf E, Meier M, Gyapay G, Lascols O, Auwerx J, Weissenbach J, Capeau J and Magre J. Human peroxisome proliferator-activated receptor-gamma2: genetic mapping, identification of a variant in the coding sequence, and exclusion as the gene responsible for lipoatrophic diabetes. Diabetes 1998; 47: 490-492.
[13] Zhao L, Roffey DM and Chen S. Association between the estrogen receptor beta (ESR2) Rs1256120 single nucleotide polymorphism and adolescent idiopathic scoliosis: a systematic review and meta-analysis. Spine (Phila Pa 1976) 2016; [Epub ahead of print].
[14] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-634.
[15] Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. Ann Intern Med 1997; 127: 820-826.
[16] Wang X, Lu X, Fang Y, Chen H, Deng X, Peng C, Li H, Shen B. Association between mir34b/c polymorphism rs4938723 and cancer risk: a meta-analysis of 11 studies including 6169 cases and 6337 controls. Med Sci Monit 2014; 20: 1977-1982.
[17] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994; 50: 1088-1101.
[18] Butt H, Shabana and Hasnain S. The C1431T polymorphism of peroxisome proliferator activated receptor gamma (PPAR gamma) is associated with low risk of diabetes in a Pakistani cohort. Diabetol Metab Syndr 2016; 8: 67.
[19] Tai ES, Corella D, Deurenberg-Yap M, Adiconis X, Chew SK, Tan CE and Ordovas JM. Differential effects of the C1431T and Pro12Ala PPAR gamma gene variants on plasma lipids and diabetes risk in an Asian population. J Lipid Res 2004; 45: 674-685.
[20] Haseeb A, Iliyas M, Chakrabarti S, Farooqui AA, Naik SR, Ghosh S, Suragani M and Ehtesham NZ. Single-nucleotide polymorphisms in peroxisome proliferator-activated receptor gamma and their association with plasma levels of resistin and the metabolic syndrome in a South Indian population. J Biosci 2009; 34: 405-414.
[21] Evans D, de Heer J, Hagemann C, Wendt D, Wolf A, Beisiegel U and Mann WA. Association between the P12A and c1431t polymorphisms in the peroxisome proliferator activated receptor gamma (PPAR gamma) gene and type 2 diabetes. Exp Clin Endocrinol Diabetes 2001; 109: 151-154.
[22] Dong CP, He L, Li JN, Ye F, He M and Wang Y. [Association of the Pro12Ala and C1431T polymorphism of the PPAR gamma2 gene and their haplotypes with obesity and type 2 diabetes]. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 2008; 25: 447-451.
[23] Doney AS, Fischer B, Cecil JE, Boylan K, McGuigan FE, Ralston SH, Morris AD and Palmer CN. Association of the Pro12Ala and

C1431T variants of PPARG and their haplotypes with susceptibility to Type 2 diabetes. Diabetologia 2004; 47: 555-558.

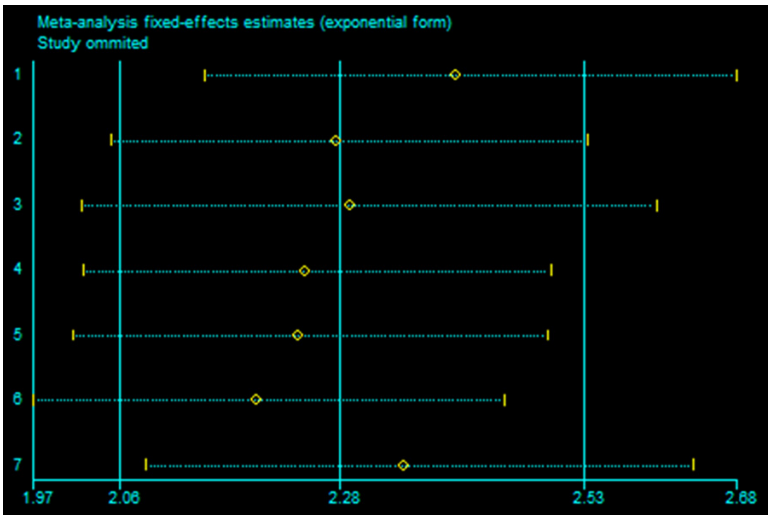
[24] Costa V, Casamassimi A, Esposito K, Villani A, Capone M, Iannella R, Schisano B, Ciotola M, Di Palo C, Corrado FC, Santangelo F, Giugliano D and Ciccodicola A. Characterization of a novel polymorphism in PPARG regulatory region associated with type 2 diabetes and diabetic retinopathy in Italy. J Biomed Biotechnol 2009; 2009: 126917.

[25] Yen CJ, Beamer BA, Negri C, Silver K, Brown KA, Yarnall DP, Burns DK, Roth J and Shuldiner AR. Molecular scanning of the human peroxisome proliferator activated receptor gamma (hPPAR gamma) gene in diabetic Caucasians: identification of a Pro12Ala PPAR gamma 2 missense mutation. Biochem Biophys Res Commun 1997; 241: 270-274.

[26] Doney A, Fischer B, Frew D, Cumming A, Flavell DM, World M, Montgomery HE, Boyle D, Morris A and Palmer CN. Haplotype analysis of the PPAR gamma Pro12Ala and C1431T variants reveals opposing associations with body weight. BMC Genet 2002; 3: 21.

Supplementary Table 1. Quality assessment of studies included in the systematic review according to the modified Newcastle-Ottawa Scale

Author	Butt et al.	Costa et al.	Doney et al.	Dong et al.	Evans et al.	Haseeb et al.	Tai et al.
Selection							
Adequacy of case definition	a★	a★	a★	a★	a★	a★	a★
Representativeness of the cases	a★	a★	a★	a★	a★	a★	a★
Selection of controls	a★	b	b	b	a★	b	a★
Definition of controls	a★	a★	a★	a★	a★	a★	a★
Comparability							
Cases and controls of homogeneous ethnic descent	a★	a★	a★	a★	a★	a★	a★
Population stratification	b	b	b	b	b	b	b
Exposure							
Ascertainment of exposure	b	b	b	b	b	b	b
Same method of ascertainment for cases and controls	a★	a★	a★	a★	a★	a★	a★
Genotyping call rate	b	b	b	b	b	b	b
Total	6★	5★	5★	5★	6★	5★	6★



Supplementary Figure 1. Sensitive analysis of studies in the meta-analysis.