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REVIEW ARTICLE

Association between PDE4D rs966221 polymorphism and risk of ischemic stroke: a systematic review and meta-analysis

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Abstract

PDE4D polymorphism (SNP83/rs966221) was reported to be associated with the susceptibility to ischemic stroke (IS), however, the results were inconclusive. An electronic search of Embase, PubMed, CNKI and Wan Fang Date was performed to identify relevant studies published throughout April 2017. A total of 26 studies were enrolled in the analysis. No significant association between the rs9662221 polymorphism and IS was observed in the overall analysis. Nevertheless, in the subgroup analysis, our results showed a significant association between the SNP83 polymorphism and IS in CC+ CT vs. TT (OR = 1.19, 95% CI: 1.02–1.38), CT vs.TT (OR = 1.14, 95% CI: 1.01–1.29) and C vs. T (OR = 1.25, 95% CI: 1.06–1.48) in Asian population. But we did not found any association in CC vs. CT + TT (OR = 1.2, 95% CI: 0.9–1.61) and CC vs. TT (OR = 1.26, 95% CI: 0.91–1.75) in the Asian populations. Meantime, no significant correlations were observed under the five genetic model in Caucasian population ($p > 0.05$). In conclusion, our meta-analysis demonstrated that the SNP83 polymorphism in the PDE4D gene might contribute to IS susceptibility especially in Asian populations. Whereas the relationship of the polymorphism to the disease in Caucasian population was still in controversial. In future, additional well designed studies with larger sample sizes are still required to further elucidate this association.

Keywords PDE4D · Ischemic stroke · Polymorphism · SNP83 · rs9662221

Ischemic stroke (IS) is a most common cause of death and long-term disability which accounting for approximately 85% of all types strokes (Kotlęga et al. 2017). Being one of the most devastating consequences of atherosclerotic disease, ischemic stroke can be caused by any or the combination of multifactorial disease, including age, hypertension, diabetes mellitus, smoking, obesity and so on (Munshi and Kaul 2008). Of all the risk factors, genetic susceptibility to ischemic stroke was considerate to play a vital role in the development of IS since first shown in twin pedigree studies in 1992 (Bak et al. 2002), however, until now, the genetic pathogenesis of stroke remains unclear.

Phosphodiesterase 4D (PDE4D) is a member of the superfamily of cyclic nucleotide phosphodiesterases and is involved in degradation of cyclic adenosine monophosphate (cAMP) which is a key signaling molecule involved in the inflammatory responses of vascular cells (Das et al. 2016). Researches showed that inhibitors of PDE4D can increase cAMP levels and adhesion in vascular endothelial cells and decrease migration of vascular smooth muscle cells (Jorgensen et al. 2015). Thus it had been postulated to contribute to vascular diseases in the pathogenesis of atherosclerosis. Since Gretarsdottir et al. identified SNP83 (rs966221) in PDE4D as a susceptible gene for ischemic stroke in Caucasian population, a large number of studies reported the association of single nucleotide polymorphisms across this gene with the disease (Gretarsdottir et al. 2003). Xue et al. had also identified that SNP83 as a genetic risk factor for atherothrombotic strokes in a Chinese population (Xue et al. 2009). Nevertheless, results have been contradictory. Quarta et al. reported that there were no evidences of association between SNP83 and IS in a

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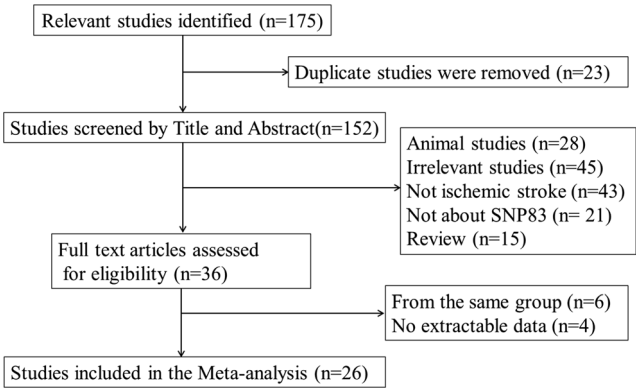

Fig. 1 The flow sheet of identification of eligible studies

genetically homogenous population from Sardinia (Quarta et al. 2009). Meantime, Matsushita et al. also reported the same results in Japanese cohort (Matsushita et al. 2009). Therefore, to confirm the association between SNP83 and the risk of IS, we performed a meta-analysis of case-control studies by pooling all eligible studies to evaluate the overall risk and influence of ethnic factors to this disease.

Materials and methods

To identify all relevant publications focus on the risk for Is and SNP83 polymorphism, we conducted a comprehensive literature search of electronic databases, including the Pubmed, Embase, China National Knowledge Infrastructure (CNKI) and Wan Fang Data. Eligible case-control studies were extracted with the last search update on April 1, 2017. The following terms were used: "ischemic infarction OR cerebrovascular disease OR stroke OR cerebrovascular disorders OR ischemic stroke" in combination with "PDE4D OR phosphodiesterase 4D OR rs966221 OR SNP83" in combination with "polymorphism OR variant OR mutation". The reference lists of retrieved studies and recent reviews were also manually searched for further relevant studies. In addition, if the

Table 1 Distribution of SNP83 genotype

Author	Year	Country	Case	Control	Case					Control				
					CC	CT	TT	C	T	CC	CT	TT	C	T
Gretarsdottir et al. (2003)	2003	America	510	349	167	249	94	583	37	98	167	84	363	335
Meschia et al. (2005)	2005	America	358	256	55	139	164	249	467	46	120	90	212	300
Woo et al. (2006)	2006	America	357	303	108	170	68	386	306	97	134	46	328	226
Song et al. (2006)	2006	America	224	211	40	93	59	173	211	45	93	48	183	189
Kuhlenbaumer et al. (2006)	2006	Germany	1181	1569	434	546	179	1414	904	595	700	254	1890	1208
Staton et al. (2006)	2006	Australia	151	164	43	68	39	154	146	61	75	28	197	131
Van Rijn et al. (2005)	2005	Netherlands	88	188	34	37	17	105	71	70	86	32	226	150
Matsushita et al. (2009)	2009	Japan	739	3729	11	167	561	189	1289	85	910	2734	1080	6378
Banerjee et al. (2008)	2008	India	176	212	46	81	49	173	179	38	110	64	186	238
Munshi et al. (2009)	2009	India	250	250	26	124	100	176	324	5	100	145	110	390
Kalita et al. (2011)	2	India	145	188	54	64	27	172	118	38	92	58	168	208
Saleheen et al. (2005)	2005	Pakistan	200	250	55	96	47	206	190	49	139	69	237	277
Wang et al. (2012)	2012	China	235	105	16	82	137	114	356	4	25	76	33	177
Cheng H et al. (2011)	2011	China	280	258	12	102	166	126	434	12	94	152	118	398
Sun Y et al. (2009)	2009	China	649	761	40	223	385	303	993	35	230	496	300	1222
Xue H et al. (2009)	2009	China	424	887	27	144	253	198	650	29	255	603	313	1461
Zhang et al. (2009)	2009	China	122	44	3	20	37	26	94	4	10	30	18	70
Xu SL et al. (2008)	2008	China	116	110	4	46	66	54	178	6	29	75	41	179
Wang et al. (2017)	2017	China	610	618	312	240	58	864	356	410	182	24	1002	230
Zhao et al. (2012)	2015	China	396	300	13	123	260	149	383	19	100	181	138	462
Shao MJ et al. (2015)	2015	China	459	462	16	139	304	171	N/A	29	133	300	191	N/A
Jianhua and Zhang (2012)	2012	China	207	216	177	26	4	380	34	165	36	15	366	66
Luo M et al. (2014)	2014	China	712	744	21	207	484	N/A	N/A	18	203	553	N/A	N/A
Lin HF et al. (2007)	2007	China	190	211	6	54	117	N/A	N/A	13	51	147	N/A	N/A
Li N et al. (2010)	2010	China	371	371	117	173	81	407	335	76	197	98	364	378
Zhao JH et al. (2012)	2012	China	682	598	210	320	152	740	624	138	310	150	586	610

genotype data for the SNP83 polymorphism was not illuminated in the original studies, we send an email to obtain full data for the meta-analysis.

Inclusion and exclusion criteria

Studies were considered eligible if they met the following criteria: (1) evaluation of the association between PDE4D SNP83 and risk of ischemia stroke; (2) the study provided sufficient information of allele or genotype frequencies; (3) the study was a case-control study; Exclusion criteria: (1) duplication of previous publications; (2) comment, review or editorial; (3) study without detailed genotype data. A study reporting the results for different subpopulations was treated as separate studies.

Data extraction

The data of the eligible studies were extracted in duplicate by two investigators (Peng Wang and Fei Yang) independently with a standard data-collection form. The following data was collected from each study if available: (1) first author's name; (2) country of origin; (3) years of publication; (4) ethnicity of the individuals (categorized as Caucasians or Asians); (5) Gender and mean age in cases and controls; (6) Hardy-Winberg equilibrium; (7) numbers of cases and controls; (8) genotyping method; (9) counts of cases and controls for each genotype. If there were multiple publications from the same group, only the one with largest study was included. The discrepancies were resolved through discussion. If the dissent still existed, the third investigators would be invited to resolve the dispute.

Quality assessment

The quality of the included studies was evaluated by using the quality scoring criteria modified from Newcastle–Ottawa scale (NOS) for genetic association studies (Zhang et al. 2017). Total score of quality assessment ranged from zero to nine stars, and six or more stars

Table 2 Characteristics of the studies in this meta-analysis

Author	Genotype Methods	Diagnostic criteria	Source of Control	HWE	NOS
Gretarsdottir et al.	PCR	CT	Hospital	0.439	8
Meschia et al.	PCR	CT&MRI	Hospital	0.587	5
Woo et al.	RaqMan	Neuroimaging	Population	0.981	5
Song et al.	DHPLC	Neuro exam	Hospital	0.997	6
Kuhlenbaumer et al.	TaqMan	CT&MRI	Population	0.048	4
Staton et al.	Not Know	CT	Population	0.549	6
Van Rijn et al.	PCR	CT&MRI	Population	0.527	6
Matsushita et al.	TaqMan	CT&MRI	Population	0.368	4
Banerjee et al.	PCR	CT&MRI	Population	0.435	4
Munshi et al.	PCR	CT&MRI	Hospital	0.009	4
Kalita et al.	PCR	MRI	Population	0.890	6
Saleheen et al.	PCR	Neuro exam	Population	0.157	5
Wang HM et al.	PCR	CT &MRI	Hospital	0.300	5
Cheng H et al.	PCR-LDR	CT &MRI	Hospital	0.598	4
Sun Y et al.	PCR	CT &MRI	Hospital	0.213	5
Xue H et al.	PCR/RFLP	CT &MRI	Hospital	0.748	7
Zhang HL et al.	PCR-LDR	CT &MRI	Hospital	0.045	4
Xu SL et al.	PCR-RFLP	CT &MRI	Hospital	0.171	5
Wang XX et al.	PCR	CT &MRI	Hospital	0.502	5
Wang JN et al.	MALDI-TOF-MS	CT &MRI	Hospital	0.308	5
Shao MJ et al.	spectroCHIP	CT &MRI	Hospital	0.009	4
Ma JH et al.	PCR	CT &MRI	Hospital	0.070	3
Luo M et al.	PCR	CT &MRI	Hospital	0.901	6
Lin HF et al.	TaqMan	Not Tell	Hospital	0.006	4
Li N et al.	PCR-RFLP	CT &MRI	Hospital	0.205	5
Zhao JH et al.	PCR	CT &MRI	Hospital	0.363	5

are rated as high quality. Disagreement was settled through discussion among the investigators.

Statistics analysis

Hardy-Weinberg equilibrium was evaluated for each study by chi-square test in the control groups and P value <0.05 was considered significant disequilibrium. The odds ratio (OR) and 95% confidence interval (95% CI) were calculated to evaluate the strength of the association between SNP83 polymorphisms and susceptibility to IS. In the overall and subgroup meta-analysis, Pooled ORs were obtained from combination of single study for the dominant model (CC + CT vs. TT), recessive model (CC vs. CT + TT), homozygote model (CC vs. TT), heterozygote model (CT vs. TT) and allelic model (C vs. T). Heterogeneity was evaluated by Q statistic (significance level of $p < 0.1$) and I^2 statistic (greater than 50% as evidence of significant inconsistency). Once, Q-test >0.10 or $I^2 < 50\%$, the fixed effect model (Mantel–Haenszelmethod) was used to calculate the pooled ORs, otherwise, the random-effect model (DerSimonian–Laird method) was employed in the study. Subgroup analysis was conducted according to

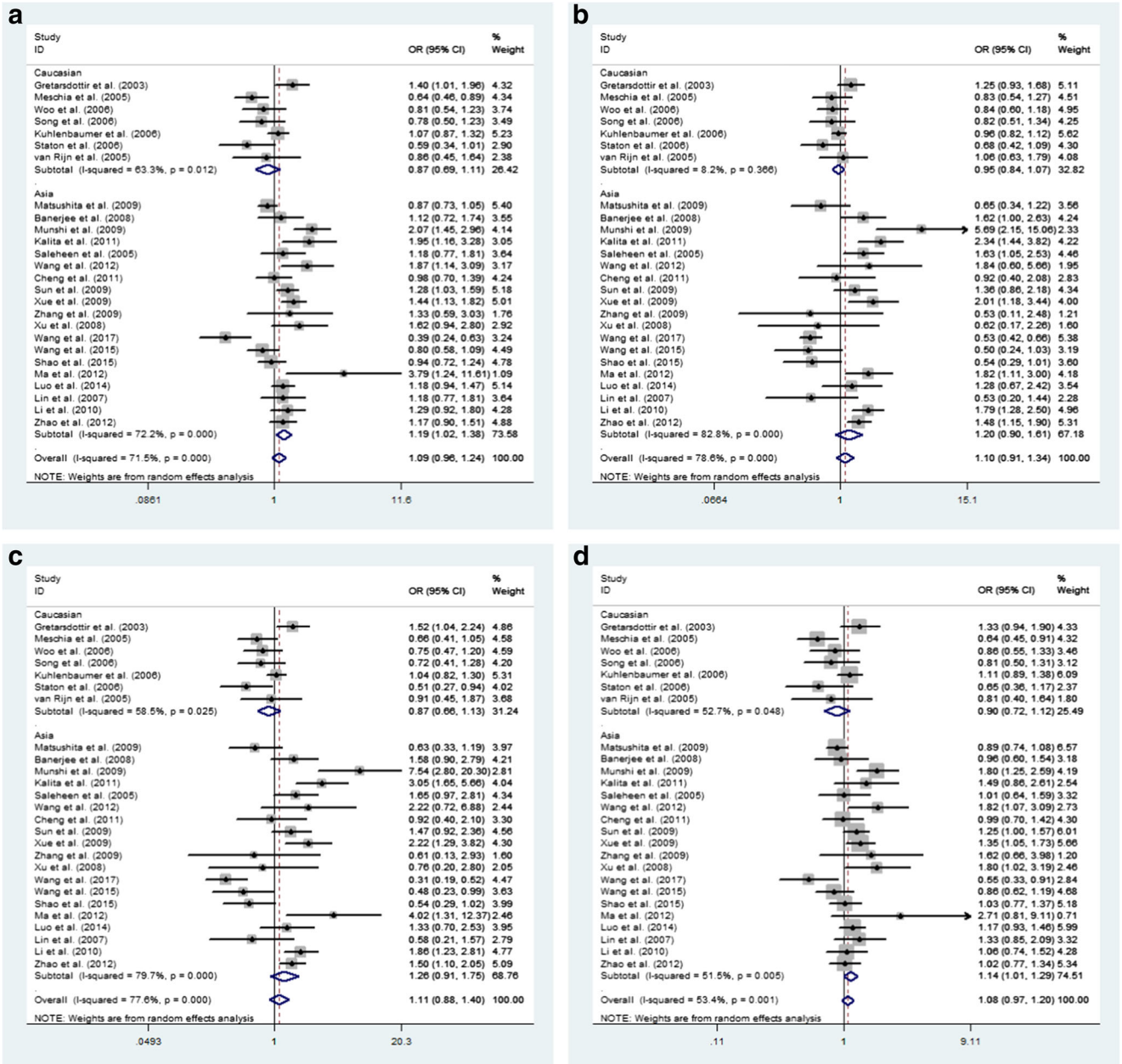

Fig. 2 Forest plots of the SNP83 polymorphism under different genetic models. A is the dominant model of CC + CT vs.TT; B is the recessive model of CC vs. CT + TT; C is the homozygote model of CC vs.TT; D is the heterozygote model of CT vs. TT; E is the allelic model of C vs. T

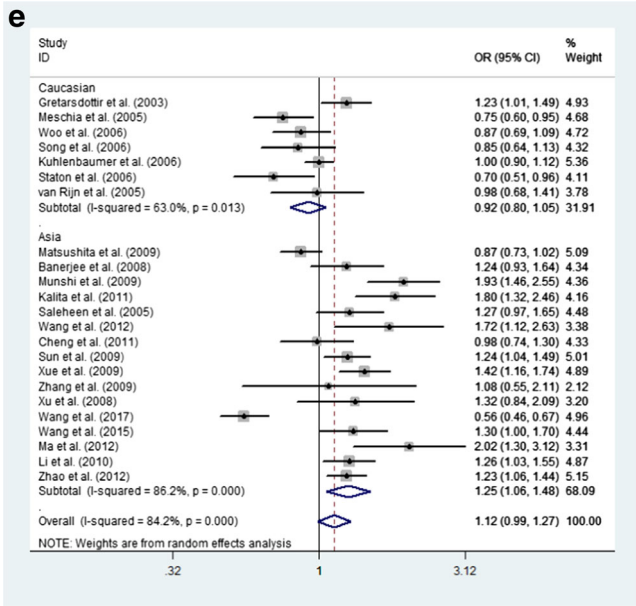

Fig. 2 (continued)

the different ethnicities in the study population. Publication bias was estimated by Begg's funnel plot. Sensitivity analyses were performed to evaluate the effect of each study on the combined ORs. All statistical analyses were performed with the software Stata 12.0 (STATA Corporation, College Station, TX, USA).

Results

Characteristics of studies

A flowchart of the literature search is presented in Fig. 1. After a preliminary online search, 175 potentially relevant articles were identified for further detailed evaluation. Among which 23 duplicated citations were removed, and 152 citations were included for further review by title and abstract screening. Finally, 36 articles were selected for full-text review and 26 cautions were enrolled in the analysis. Of all the studies, 7 were Caucasians and 19 were Chinese population. These studies were published between 2003 and 2015. Multiple genotyping methods were performed in the studies, including PCR-RFLP, TaqMan, DNA sequencing and so on.

A total of 9832 patients were from IS case group and 13,354 were enrolled in control group. The distribution of genotypes in the controls of all studies was consistent with Hardy-Weinberg equilibrium (HWE) except 6 studies. The NOS results showed that the score ranged from 3 to 8 which indicated that the methodological quality of these selected articles was generally good. The characteristics of involved articles were summarized in Tables 1 and 2.

Meta-analysis results

The heterogeneity was identified by Q-test and I-squared statistic among genetic models. As is showed in the Fig. 2, serious heterogeneity were found under dominant model (I^2 = 71.5%), recessive model (I^2 = 78.6%), homozygote model (I^2 = 77.6%), heterozygote model (I^2 = 53.4%) and allelic model (I^2 = 84.2%), thus the random model was employed in the analysis. Our results reveled that there were no significant associations between SNP83 and IS under genetic model of CC + CT vs. TT (OR = 1.09, 95% CI:0.96–1.24), CC vs. CT + TT (OR = 1.1,95% CI: 0.91–1.34), CC vs. TT (OR = 1.11, 95% CI: 0.88–1.4), CT vs. TT (OR = 1.08, 95% CI:0.97–1.20) and C vs. T (OR = 1.12, 95% CI: 0.99–1.27).

Subgroups based on ethnicity were utilized to further analyze the relationship of polymorphism with IS. In Chinese populations, IS was proved to be correlated with SNP83 polymorphism under CC+ CT vs. TT (OR = 1.19, 95% CI:1.02–1.38), CT vs. TT (OR = 1.14, 95% CI:1.01–1.29) and C vs. T (OR = 1.25, 95% CI:1.06–1.48) Nevertheless, no significant association were found in CC vs. CT + TT (OR = 1.2, 95% CI:0.9–1.61) and CC vs. TT (OR = 1.26, 95% CI:0.91–1.75). In addition, we did not observed any correlation of SNP83 polymorphism with IS in all the five genetic models(CC+ CT vs. TT: OR = 0.87, 95% CI: 0.69–1.11; CC vs. CT + TT: OR = 0.95, 95% CI:0.84–1.07; CC vs.TT:0.87, 95% CI:0.66–1.13; CT vs.TT: OR = 0.9, 95% CI:0.72–1.12; C vs. T: OR = 0.92, 95% CI:0.8–1.05) in the Caucasian populations.

Sensitivity analysis

A sensitivity analysis by sequentially removing each eligible study at a time was used to assess the influence of each individual study on the pooled OR. Our results indicated that there was not any single study influence the quality of the pooled ORs (Fig. 3).

Publication bias

Publication bias was evaluated using the Begg's funnel plot. No significant evidence of publication bias was observed in the five genetic models (CC + CT vs. TT: p = 0.853; CC vs. CT + TT: p = 0.731; CC vs. TT: p = 0.544; CT vs. TT: p = 0.812; C vs. T: p = 0.692) (Fig. 4).

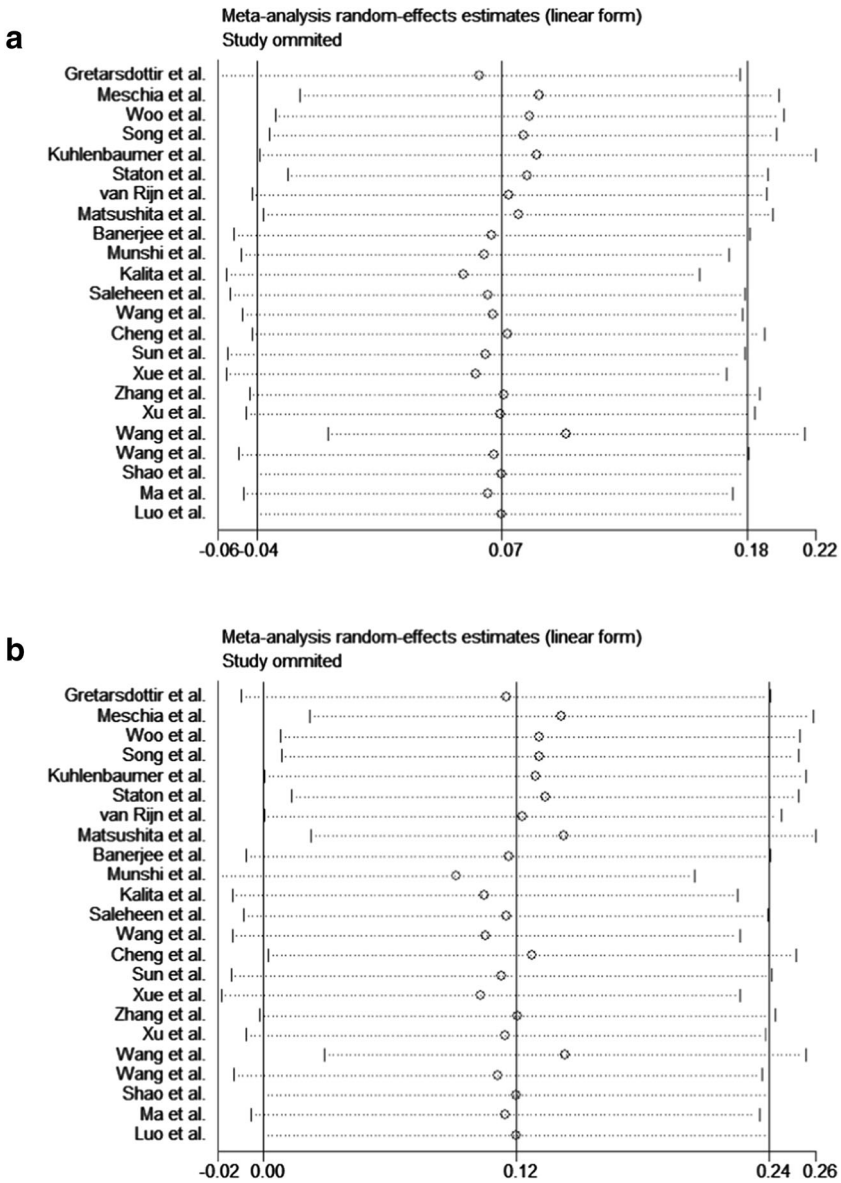

Fig. 3 Begg's funnel plot for publication bias analysis. A is the homozygote model and B is the heterozygote model

Discussion

PDE4D is a large gene spanning >1.5 Mb on chromosomal region 5q12 and has 8 splice variants, 22 exons and several hundreds of SNPs (Song et al. 2015; Song et al. 2017). It has been shown to effects on brain function, pulmonary hypertension and vascular smooth cells migration (Mika and Conti 2016). It is more of a clinical syndrome rather than a disease due to numerous clinical, genetic, and lifestyle risk factors. Work over the past few decades has shown that PDE4D are present in the brain regions such as the amygdala, prefrontal cortex, hippocampus, and nucleus accumbens (Yang et al. 2012). The distribution pattern suggests that they may serve distinct roles in the central nervous system and provide a theoretical basis for the separation of therapeutic and adverse effects of PDE4 inhibitors.

The association of specific PDE4D single-nucleotide polymorphisms (SNPs) with stroke is initially identified in an Icelandic population and further evaluated in both animal models and human beings (Liu et al. 2013). Since the first study reported the associations of PDE4D SNPs and ischemic stroke risk, an increasing amount of research has been subsequently published to study the relationship of PDE4D SNP with IS, especially SNP 83(Gretarsdottir et al. 2003). Yoon et al. retrieved 15 publications with 19,318 subjects, failed to find a linkage between SNP83 and IS in the overall population (Yoon et al. 2011). However, Yan et al. comprised of 8878 cases and 12,306 controls in a review had shown that association between SNP83 and IS in the overall population and in the Asian and Chinese populations, but not among Caucasians (Yan et al. 2014). Till now there was

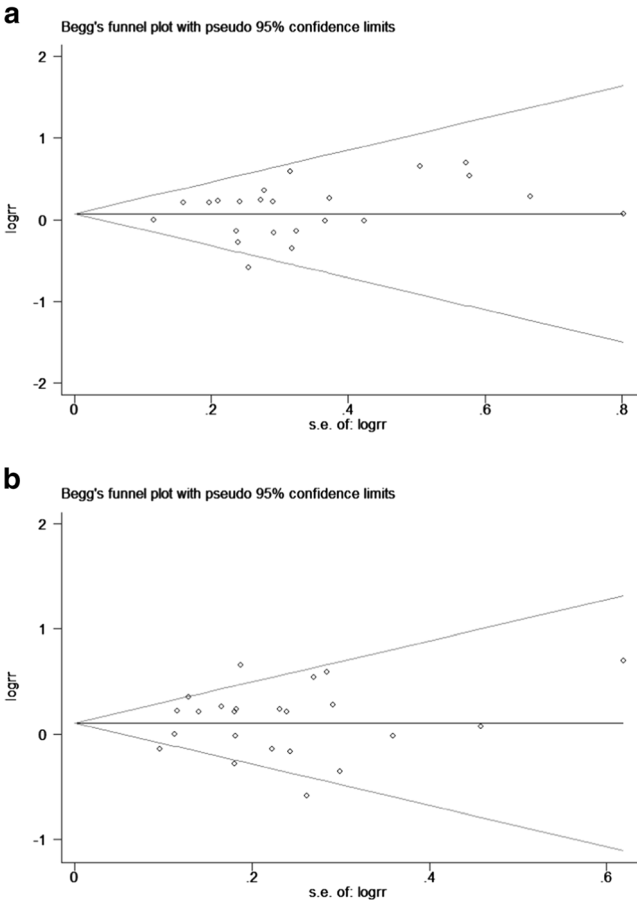

Fig. 4 Sensitivity analysis examining the association between the SNP83 polymorphism and risk of IS under homozygote model and heterozygote model

still not a consistency conclusion. In our study, we examined the association between SNP83 and ischemic stroke using case-control and population-based cohort. We had found that there were significant association of SNP83 with IS risk under the dominant model, heterozygote model and allelic model. Nevertheless, we didn't observed any correlation of the polymorphism with IS in the Caucasian. Our results were in accordance with the former meta-analysis which was done by Yan et al. (Yan et al. 2014). However, other studies had also reported with opposite conclusions, such as Matsushita et al., who failed to replicate the results in Japanese populations (Matsushita et al. 2009). Whereas, Staton et al. and Gretarsdottir et al. found that SNP83 was associated with an increased risk of ischemic stroke in Caucasians (Gretarsdottir et al. 2003; Staton et al. 2006).

Although we had got the positive results in Asian population, however, the conclusions should be treated with caution. The HWE results showed that there were 6 studies with their $p < 0.05$ which included Chinese population studies and Caucasian populations. However, in the stratified analysis by HWE, we had observed that the results were mostly unchanged. In addition, the heterogeneity was detected under five genetic models in this meta-analysis. This could be caused by various reasons, such as the small sample size, different diagnostic criteria and disunity detection methods. Meantime, most studies ($n = 19$) enrolled in our analysis were done in Asian populations and there were only 7 articles explored the PDE4D polymorphism with IS in Caucasian. This can partly explain the reasons why we cannot found any correlations of SNP83 with IS in Caucasian populations. In addition, though significant difference was observed in at least 3 genetic models, the results were still worth deliberated. Most of the studies were cross with the invalid line in the analysis of dominant model, heterozygote model and allelic model, thus the significance drawn were without enough persuasion. Besides, there was a lack of sufficient data regarding the patients' gender, environment or complicating disease such as hypertension or diabetes, which may modulate the relationship when discussing those confounding factors.

In summary, the current meta-analysis revealed that SNP83 displayed significant association with IS in Asian populations under the dominant model, heterozygote model and allelic model, which offering evidence that PDE4D may be involved in the pathogenesis of IS. Nevertheless, no correlation was observed in Caucasians. Additional, as with kinds of limitations, the relationships of SNP83 with IS susceptibility in Asian and Caucasian populations were worth further exploration. In future, well designed case-control studies with large sample sizes and stroke subtype analysis regarding the association of SNP83 with IS needed to be performed.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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