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Angiotensin-converting enzyme insertion/deletion polymorphism and susceptibility to Henoch–Schönlein purpura: a meta-analysis

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Abstract

Objective: Meta-analysis was performed in the current study to evaluate the relationship of the angiotensin-converting enzyme insertion/deletion polymorphism with the risk of the incidence of Henoch–Schönlein purpura.

Methods: The electronic databases, including Embase, PubMed and Google scholar, were systemically retrieved to search for related articles. Meanwhile, statistical analysis was performed using the odds ratio and the corresponding 95% confidence interval.

Results: A total of six articles enrolling 504 patients and 706 healthy controls was enrolled into the current meta-analysis. Results of the meta-analysis suggested that the angiotensin-converting enzyme D allele was markedly correlated with the risk of the incidence of Henoch–Schönlein purpura among the general population (deletion (D) vs. insertion (I): odds ratio (OR) 1.42, 95% confidence interval (CI) 1.05–1.93; DD vs. II: OR 2.23, 95% CI 1.06–4.70; DI vs. II: OR 1.36, 95% CI 1.00–1.85; dominant model: OR 1.56, 95% CI 1.00–2.42; recessive model: OR 1.83, 95% CI 1.06–3.16). Moreover, such a polymorphism was found to correlate with the susceptibility to Henoch–Schönlein purpura when studies were stratified according to the sample size of over 200. In addition, such a polymorphism was recognised to be remarkably associated with the susceptibility to Henoch–Schönlein purpura in the Caucasian population, which was not found in the Asian population.

Conclusions: The results of the current meta-analysis indicate that the angiotensin-converting enzyme D allele might be a risk factor against the risk of Henoch–Schönlein purpura, especially in Caucasians.

Keywords

ACE, I/D polymorphism, angiotensin-converting enzyme

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Introduction

Henoch–Schönlein purpura (HSP), the most frequently occurring paediatric systemic vasculitis, has the morbidity of 10–20/100,000. Among them, over 90% of HSP cases are found at the age of onset of less than 10 years.[1] The clinical manifestations of HSP have been extensively recognised, such as palpable non-thrombocytopenic purpura, arthritis and visceral involvement (such as the gastrointestinal tract and the kidney). Generally, HSP is self-limited, which is associated with a favourable long-term prognosis, regardless of the serious involvement of the gastrointestinal tract or the kidney. Currently, the pathogenesis of HSP remains incompletely illustrated. Nonetheless, the interaction between multiple genes and environmental factors is identified to be an important factor in 50% of HSP cases. Importantly, such interaction is proposed to be critical in the development of HSP.[2]

Sodium homeostasis, blood pressure and inflammation in the human body are regulated under the mediation of the renin–angiotensin system (RAS).[3] Typically, HSP is

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induced by the presence of small vasculitis and activation of endothelial cells.[4] In the meantime, RAS has a certain effect on directly regulating the vascular tone and vascular structure; alternatively, such an effect is achieved through different factors, such as endothelin and nitric oxide.[5] On this account, RAS potentially participates in the aetiology of HSP. ACE is a critical circulatory enzyme of RAS, which is extensively expressed in various tissues, such as the kidney, heart, lung, vascular endothelium and testes.

Located on the human chromosome 17q23, the ACE gene has been identified to be associated with plenty of polymorphisms. Typically, the intron 16 insertion/deletion (I/D, rs4646994) polymorphism of ACE is featured by the insertion or deletion of a 287 bp Alu repetitive sequence.[6] Moreover, the homozygous D allele is associated with the highest level of plasma ACE, while the heterozygous allele (ID) is associated with the medium level, and the homozygous I allele is associated with the lowest level.[7] In addition, the ACE I/D polymorphism was reported in a previous meta-analysis to be potentially related to the risk of the incidence of vascular autoimmune diseases such as Kawasaki disease.[8]

Many epidemiological studies have been carried out in the past 10 years to evaluate the relationship of the ACE I/D polymorphism with the susceptibility to HSP. Nonetheless, the results remain a source of controversy, which may be ascribed to the insufficient statistical power as a result of a small sample size as well as the eco-geographical heterogeneities. Notably, such drawbacks of a single study may be solved through carrying out a meta-analysis. On this account, a meta-analysis was carried out in this study based on the accumulating evidence, aiming to investigate the association between the ACE I/D gene polymorphism and the risk of HSP, with the aim of providing a much more reliable finding on the significance of this association.

Subjects and methods

Identification of studies

In this work, the meta-analysis was performed according to the statement guidelines of preferred reporting items for systematic reviews and meta-analysis (PRISMA).The electronic databases, including Google Scholar, PubMed, Embase, CNKI and Wangfang, were systemically retrieved for studies regarding the association of HSP with the ACE I/D polymorphism from database construction to August 2018 without language restrictions, using the search terms of angiotensin-converting enzyme(or ACE), Henoch–Schönlein purpura (or HSP) and I/D polymorphism. Moreover, the cited references in related studies were also searched to identify the potentially related studies. The latest version of duplicate reports or studies reporting results from the same study population was adopted. In addition, the reference lists of major textbooks, review articles and the included papers were manually retrieved, so as to search for the potentially eligible papers.

Inclusion and exclusion

The study inclusion criteria were as follows: (a) studies that adopted a case–control design; (b) those assessing the relationship between the ACE I/D polymorphism and the risk of HSP; (c) those with the sample size of 40 or greater; and (d) those with sufficient data to calculate the odds ratio (OR) with the corresponding 95% confidence interval (CI). Moreover, the study exclusion criteria are shown below: (a) duplicate reports; (b) comments, reviews and editorials; (c) family-based studies; and (d) those with insufficient genotype data.

Data extraction

Related data, including: (a) authors, (b) publication year, (c) country, (d) ethnicity of the objects of study, (e) sample size, (f) allele and genotype distribution and (g) evidence of Hardy–Weinberg equilibrium (HWE) in controls, were extracted from all eligible studies by two investigators independently, and any disagreement between them was settled by mutual discussion. Moreover, the authors were contacted to collect more information when needed.

Statistical analysis

The strength of the relationship of the ACE I/D polymorphism with susceptibility to HSP was evaluated by ORs and their 95% CIs. In particular, the genetic models below were employed in this meta-analysis, including D versus I, the homozygote comparison (DD vs. II), the heterozygote comparison (DI vs. II), the dominant model (DD+DI vs. II) and the recessive model (II+DI vs. DD). The inconsistency index I^2 was calculated to evaluate the heterogeneity-induced variation; in the case of I^2 greater than 50%, the ORs and 95% CIs were calculated using the random effects model; otherwise, the fixed effects model was utilised. Moreover, a sensitivity test was also carried out, which was achieved through removing one study each time to see its influence on the pooled results. Meanwhile, publication bias was also tested using Begg's funnel plot and Egger's funnel plot. A difference of $P<0.05$ was deemed to be of statistical significance. The STATA software (version 12.0; Stata Corporation, College Station, TX, USA) was used for all statistical analyses.

Results

Study characteristics

A total of 163 potentially related studies was preliminarily retrieved from the electronic databases (Google Scholar,

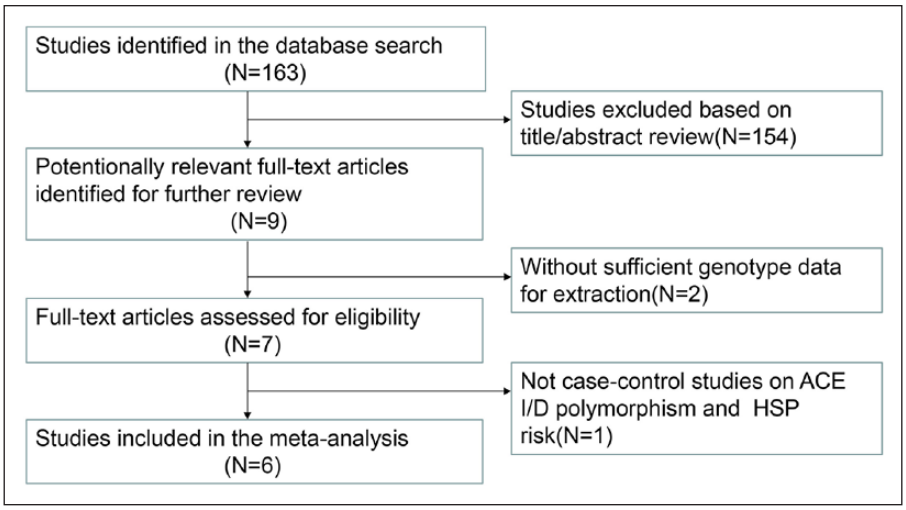

Figure 1. The flowchart of the included studies in the meta-analysis.

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

Study included	Year	Area	Race	Cases/ controls	Allele for cases	Allele for controls	Genotypes for cases	Genotypes for controls	HWE test
					D I	D I	DD ID II	DD ID II	
Yoshioka	1998	Japan	Asians	40/79	49 31	101 57	17 15 8	33 35 11	0.73
Zhou	2004	China	Asians	103/100	92 114	51 149	30 32 41	6 39 55	0.79
Ozkaya	2006	Turkey	Caucasians	114/164	124 104	155 173	18 88 8	19 117 28	0.00
Liu	2010	China	Asians	61/217	121 159	144 290	11 33 17	21 102 94	0.38
Nalbantoglu	2013	Turkey	Caucasians	139/72	180 98	68 76	61 58 20	16 36 20	0.98
Mohammadian	2017	Iran	Asians	47/74	50 44	88 60	17 16 14	30 28 16	0.06

HWE: Hardy–Weinberg equilibrium.

PubMed, Embase, CNKI and Wangfang), which were then screened by the titles as well as abstract and full-text reading. Finally, a total of six eligible studies was enrolled into the current meta-analysis.[9–14] The study selection flow chart is presented in Figure 1. When stratified by ethnicity, two articles were carried out among the Caucasian population and four in the Asian population. Meanwhile, the genotype distribution among the control subjects of the enrolled studies was in agreement with HWE, except for the study by Mohammadian et al.[14] Moreover, the enrolled studies were published from 1998 to 2017, and their main characteristics are displayed in Table 1.

Main results

Table 2 displays the major findings from the current meta-analysis on the association of the ACE I/D polymorphism with susceptibility to HSP. Data from all the enrolled studies were pooled, and the results suggested that the ACE D allele is markedly correlated with the susceptibility to HSP (D vs. I: OR 1.42, 95% CI 1.05–1.93; Figure 2: DD vs. II: OR 2.23, 95% CI 1.06–4.70; DI vs. II: OR 1.36, 95% CI 1.00–1.85; dominant model: OR 1.56, 95% CI 1.00–2.42; recessive model: OR 1.83, 95% CI 1.06–3.16). Besides, studies were further divided into two groups according to the sample size of over 200 or 200 or less for subgroup analysis, and the results indicated that the ACE I/D polymorphism is remarkably correlated with the susceptibility to HSP in the sample size of over 200 subgroup (D vs. I: OR 1.69, 95% CI 1.41–2.02; DD vs. II: OR 4.04, 95% CI 2.57–6.36; DI vs. II: OR 1.62, 95% CI 1.15–2.29; dominant model: OR 2.11, 95% CI 1.52–2.92; recessive model: OR 2.56, 95% CI 1.44–4.52), which could not be observed in that of the 200 or less subgroup (D vs. I: OR 0.83, 95% CI 0.57–1.21; DD vs. II: OR 0.67, 95% CI 0.33–1.36; DI vs. II: OR 0.63, 95% CI 0.31–1.28; dominant model: OR 0.65, 95% CI 0.34–1.23; recessive model: OR 0.92, 95% CI 0.54–1.58). In addition, studies were also stratified according to ethnicity for subgroup analysis, and the results found a significant correlation of the ACE I/D polymorphism with the susceptibility to HSP in the Caucasian population (D vs. I: OR 1.63, 95% CI 1.07–2.49; DD vs. II: OR 3.60, 95% CI 1.89–6.84; DI vs. II: OR 2.04, 95% CI 1.18–3.53; dominant model: OR 2.48, 95% CI 1.46–4.23;

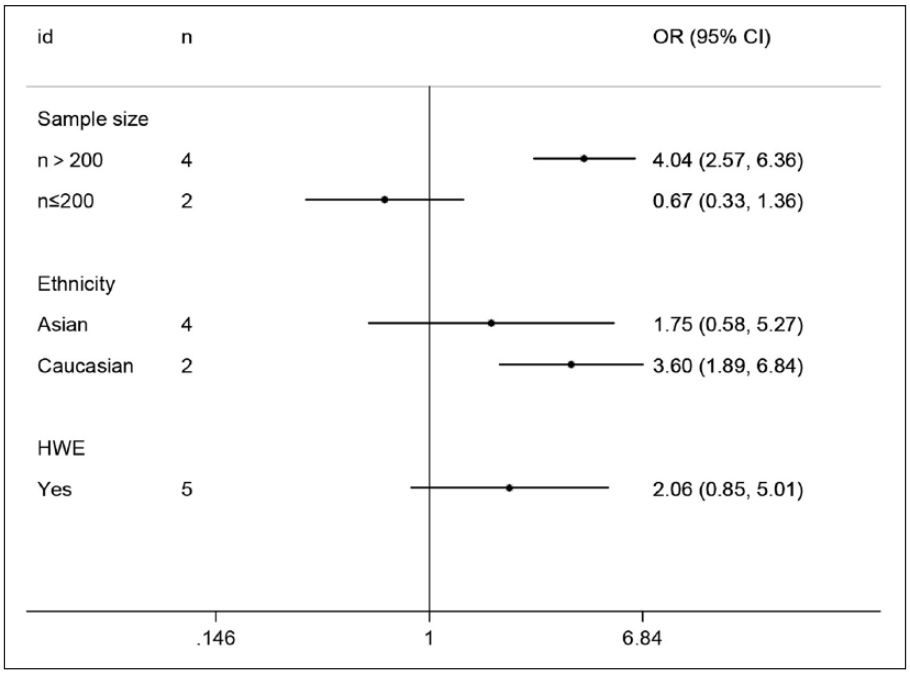

Figure 2. Forest plot for meta-analysis of the association between the angiotensin-converting enzyme I/D polymorphism and Henoch–Schönlein purpura risk under DD versus II.

Table 2. Summary of different comparative results.

Variables	*N*	D vs. I	DD vs. II	OR (95% CI)	Dominant model	Recessive model
				DI vs. II		
Total	6	1.42 (1.05–1.93)	2.23 (1.06–4.70)	1.36 (1.00–1.85)	1.56 (1.00–2.42)	1.83 (1.06–3.16)
Sample size						
>200	4	1.69 (1.41–2.02)	4.04 (2.57–6.36)	1.62 (1.15–2.29)	2.11 (1.52–2.92)	2.56 (1.44–4.52)
⩽200	2	0.83 (0.57–1.21)	0.67 (0.33–1.36)	0.63 (0.31–1.28)	0.65 (0.34–1.23)	0.92 (0.54–1.58)
Ethnicity						
Asian	4	1.30 (0.81–2.07)	1.75 (0.58–5.27)	1.12 (0.77–1.62)	1.22 (0.68–2.19)	1.78 (0.76–4.16)
Caucasian	2	1.63 (1.07–2.49)	3.60 (1.89–6.84)	2.04 (1.18–3.53)	2.48 (1.46–4.23)	1.05 (1.29–3.27)
HWE						
Yes	5	1.43 (0.97–2.11)	2.06 (0.85–5.01)	1.20 (0.86–1.68)	1.41 (0.86–2.29)	1.94 (1.00–3.79)
No	1	/	/	/	/	/

N: number; CI: confidence interval; OR: odds ratio.

recessive model: OR 1.05, 95% CI 1.29–3.27), but not in the Asian population (D vs. I: OR 1.30, 95% CI 0.81–2.07; DD vs. II: OR 1.75, 95% CI 0.58–5.27; DI vs. II: OR 1.12, 95% CI 0.77–1.62; dominant model: OR 1.22, 95% CI 0.68–2.19; recessive model: OR 1.78, 95% CI 0.76–4.16).

Heterogeneity analysis and publication bias

Sensitivity analysis was carried out by eliminating one non-HWE study each time to observe the influence on the final result. In particular, an unchanged final result suggested that the meta-analysis result was statistically significant (Table 2). On the other hand, the publication bias among the enrolled studies was assessed through Begg's funnel plot and Egger's funnel plot, and no evidence of obvious asymmetry was observed from the shape of the funnel plot, revealing no obvious evidence of publication bias for the ACE I/D polymorphism (Figures 3 and 4).

Discussion

HSP, the most frequently occurring vasculitis syndrome, is associated with the major clinical manifestations of skin purpura, arthritis as well as gastrointestinal tract disease.[15] The ACE I/D polymorphism is correlated with the ACE

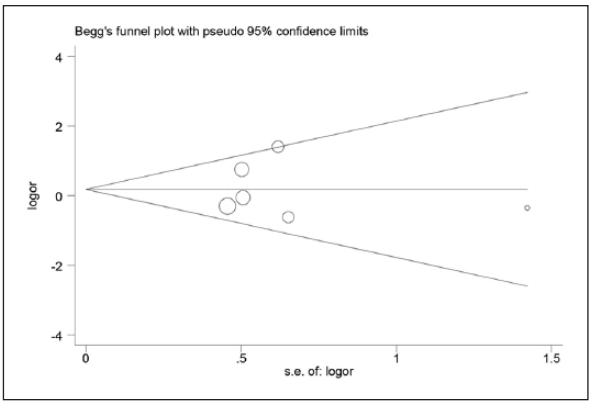

Figure 3. Begg's funnel plot analysis to detect potential publication bias for thr IL-18 –607C>A polymorphism.

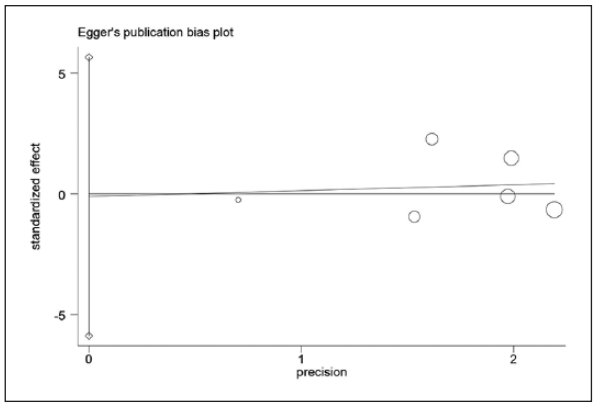

Figure 4. Egger's funnel plot analysis to detect potential publication bias for the IL-18 –137G>C polymorphism.

contents in the circulation and cells, which may be potentially involved in the pathogenesis of HSP. It has been widely examined in a number of epidemiological studies. Nonetheless, the results from different studies remain a source of controversy. Thus, intensively understanding such a problem is of great clinical significance, which may potentially suggest that the ACE I/D polymorphism can predict the risk of HSP. On this account, the current meta-analysis was carried out to evaluate better the association of the ACE I/D polymorphism with susceptibility to HSP.

A total of six eligible case–control studies involving 504 patients and 706 control subjects were enrolled into the current meta-analysis to assess systemically the relationship of the ACE I/D polymorphism with susceptibility to HSP. The pooled findings of this meta-analysis indicated that the ACE D allele is associated with increased HSP risk. In the stratified analysis by sample size, pooled results showed a significant association with a sample size greater than 200 but not with a sample size of 200 or less, indicating there was no small-study bias in this meta-analysis. In term of stratified analyses by race, our findings indicate that the ACE I/D polymorphism had a significant association with HSP risk in Caucasians, but not in Asians. Such heterogeneities might result from the differences in genetic background and environmental exposure. Moreover, the deviation of allelic distributions from HWE may contribute to between-study heterogeneity, the subgroup analysis by limiting this meta-analysis to those papers that are consistent with HWE revealed that our data were believable.

The precise underlying mechanism of HSP has not yet been fully illustrated. It is widely accepted that RAS plays a key role in the development of HSP. Typically, ACE is important in the conversion of RAS and angiotensin II, which can enhance the content of vascular smooth muscle cells and influences the proliferation of smooth muscle cells, adhesion and aggregation of monocytes and platelets. The ACE I/D polymorphism is located in an intron of the ACE gene, and the ACE I/D polymorphism accounts for approximately one-half of the variance in ACE plasma levels.[16] Moreover, the homozygous D allele is associated with the highest level of plasma ACE.[7] Taken together, our findings suggesting that ACE may be a risk factor for the development of HSP are biologically plausible. A previous meta-analysis showed that the M allele of the angiotensinogen (AGT) M235T polymorphism in the RAS gene was associated with the risk of HSP.[17] Gene–gene interactions are very important for the pathogenesis of HSP, and single genetic changes may present only a modest effect. Because the complete genotype information was unavailable, we could not perform gene–gene interaction analysis.

There are some limitations in the current study. First, only two out of the eligible studies were performed among Caucasians, which could not provide enough statistical power to detect the possible effects of the ACE I/D polymorphism in Caucasians. Second, only published literature was included in this study, while some potentially relevant studies that were not published were excluded, probably resulting in publication bias. Third, the influence of interactions between genes, as well as environmental factors, had not been examined in the current meta-analysis.

In conclusion, the present meta-analysis suggests that the ACE D allele might increase the risk of HSP, especially in the Caucasian population. In addition, understanding the combination of genetic factors together with environmental exposures will increase our understanding of the aetiology of HSP.

Declaration of conflicting interests

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