A meta-analysis of the association between angiotensin-converting enzyme insertion/deletion gene polymorphism and Henoch-Schönlein purpura nephritis risk in Asian children

Sirs,

Henoch-Schönlein purpura (HSP) is one of the most common vasculitis syndromes, and skin purpura, arthritis and gastrointestinal disease are the primary clinical performance (1). The condition is also accompanied by renal involvement, which is named Henoch-Schönlein purpura nephritis (HSPN). The angiotensin-converting enzyme (ACE) insertion/deletion (I/D) gene polymorphism, correlating with the circulating and cellular ACE concentration (2, 3), might be implicated in the etiology of HSPN and has been investigated in numerous epidemiologic studies. Interestingly, most of the studies were conducted in Asian children. This study was the first meta-analysis to investigate the relationship between ACE I/D gene polymorphism and HSPN risk in Asian children, with the intention to provide a much more reliable finding on the significance of the association.

The relevant studies about the association of ACE I/D gene polymorphism with HSPN risk in Asian children were searched from the electronic database of PubMed, Embase, Cochrane Library and CBM-disc (China Biological Medicine Database) on March 1, 2011. Cochrane Review Manager Version 5 (Cochrane Library, UK) was used to calculate the available data from each investigation. A chi-square (χ^2) test was applied to determine if genotype distribution reported conformed to Hardy-Weinberg equilibrium (HWE; $p<0.05$ was considered significant), and the study that the genotype distributions were significantly deviated from HWE was excluded from our sensitive analysis.

Eight studies (4-11) in Asian children were recruited into our meta-analysis (Table I). Two reports (6, 11) published in English and six (4, 5, 7-10) in Chinese. We calculated the frequencies of alleles in cases and controls (Table I), and found that the average frequencies of D allele and DD genotype in case group were marked elevation than those of control group (D: HSPN/control = 1.27; DD: HSPN/control = 1.64). We conducted the meta-analysis and found that D allele or DD genotype was associated with HSPN risk (p=0.002 and p=0.02, respectively; Table II). Furthermore, the II homozygous seemed to play a protective role against HSPN onset (p=0.0004, Table II). In order to draw a more stable conclusion, sensitive analysis was performed. Three reports (7, 10, 11) were included into our sensitive analysis and we found that the association of D allele or DD genotype with HSPN risk was positively significant (p=0.0004 and p=0.0002, respectively; Table II), and the II homozygous seemed to play a protective role against HSPN risk (p=0.02). The results from the sensitivity analysis were similar to those in non-sensitivity analysis. To sum up those mentioned above, the conclusions in our meta-analysis were stable.

In the included studies, there were six studies (4-7, 10, 11) reporting that ACE I/D gene polymorphism was association with HSPN risk, and other two investigations (8, 9) did not find the association between ACE I/D gene polymorphism and HSPN susceptibility. To achieve a satisfactory power, meta-analysis of multiple studies clearly has a role in offering an association with such potentials and the results from meta-analysis might be more convincing when compared with those from the separate studies. Interestingly, our results were similar to most of the included studies. When sensitivity analysis was performed, we found that the results were stable. It might be safe to draw a conclusion that ACE I/D gene polymorphism were associated with HSPN susceptibility in Asian children.

In the past years, some meta-analyses were also carried out to explore the association of ACE I/D gene polymorphism with the susceptibility of diseases in an Asian population. Some reports (12-14) found that the DD homozygous was associated with an increased risk of immunoglobulin A nephropathy in an Asian population. Zhang *et al*. (15) reported that there was an association between ACE D allele or DD genotype and the onset of asthma in Asians. Our previous studies also found that D allele or DD homozygosity might become a significant genetic molecular marker for the risk of focal segmental glomerulosclerosis (3) and minimal change nephrotic syndrome (2). ACE D allele or DD homozygote is a risk factor for disease in Asians.

In conclusion, ACE DD genotype or D allele was associated with HSPN susceptibility in Asian children, and II genotype seemed to play a positive role against HSPN onset. However, these findings should be regarded cautiously because many other factors, such as the sample of the included studies was a little small, were closely related to affect the results. Furthermore, whether ACE I/D gene polymorphism are just linked with other discrete loci involved in the occurrence and progression of HSPN is not clear at the moment. In order to explore whether there exists an exact association between ACE I/D gene polymorphism and HSPN risk in Asian children, more investigations on larger population are required to further clarify the role of the ACE I/D gene polymorphism in HSPN susceptibility.

Table I. Characteristics of the studies evaluating the effects of ACE genes on HSPN risk in Asian children.

First author, year	Ethnicity	Case			Control			P (HWE)	
		DD	ID	II	DD	ID	II	Case	Control
Lin 1999	Asian	20	18	29	21	35	44	0	0.009
Wan 2003	Asian	34	18	20	14	17	27	0	0.004
Zhou 2004	Asian	30	32	41	6	39	55	0	0.791
Gao 2004	Asian	2	9	12	10	12	22	0.867	0.006
Zhang 2004	Asian	7	16	15	10	53	37	0.464	0.152
Fan 2007	Asian	5	25	18	18	36	53	0.390	0.011
Cui 2010	Asian	13	15	4	13	56	31	0.919	0.115
Liu 2010	Asian	11	33	17	21	102	94	0.470	0.376

Table II. Meta analysis of the association of ACE I/D gene polymorphism with HSPN risk in Asian children.

Genetic contrasts	Group and subgroups	Studies	Q test *p*-value	Model seclected	OR (95% CI)	*p*-value
D *vs*. I	Asian	8	0.02	Random	1.55 (1.17, 2.06)	0.002
DD *vs*. (DI+II)	Asian	8	0.005	Random	1.99 (1.14, 3.49)	0.02
II *vs*. (DI+DD)	Asian	8	0.32	Fixed	0.64 (0.50, 0.81)	0.0004
Sensitivity analysis						
D *vs*. I	Asian	3	0.13	Fixed	1.66 (1.25, 2.20)	0.0004
DD *vs*. (DI+II)	Asian	3	0.36	Fixed	2.65 (1.58, 4.42)	0.0002
II *vs*. (DI+DD)	Asian	3	0.14	Fixed	0.60 (0.39, 0.92)	0.02

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Letters to the Editors

Acknowledgements: The authors would like to gratefully acknowledge the most helpful comments on this paper received from Professor Liang Rong, Department of Pediatric Neonatology, Baylor College of Medicine, Houston, Texas, USA.

All the authors contributed equally to this study.

Competing interests: none declared.

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