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STATE OF THE ART REVIEW

Association of AGT M235T gene polymorphism with HSP/HSPN risk

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Abstract

To evaluate the association between angiotensinogen (AGT) gene polymorphism and the risk of Henoch–Schönlein purpura (HSP)/Henoch–Schönlein purpura nephritis (HSPN) we searched the eligible studies through Pub Med, Embase, Cochrane, and China National Knowledge Infrastructure (CNKI) databases according to predefined criteria. A random-effects model was used to calculate the combined odds ratios (ORs) and its corresponding 95% confidence interval (CI). Five studies were recruited for the analysis of the association between AGT M235T gene polymorphism and HSP/HSPN risk. M allele was associated with lower risk of HSP in adult ($p = 0.050$), TT genotype was associated with the susceptibility to HSP in adult ($p = 0.039$). AGT M235T gene polymorphism was not associated with HSP risk in children. No marked association was observed between AGT M235T gene polymorphism and HSPN risk. No evidence of publication bias was observed. In conclusion, M allele might be a protective factor against the HSP risk in adult, TT genotype might be a risk factor for the susceptibility to HSP in adult. However, further larger studies should be performed in the future.

Keywords

AGT M235T, gene polymorphism, HSP, HSPN, meta-analysis

History

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Introduction

Henoch–Schönlein purpura (HSP) is the most common form of small vessel vasculitis in children.[1] Major clinical manifestations include arthritis, non-thrombocytopenic purpura, abdominal pain and renal disease. Although HSP is a self-limited condition that lasts an average of four weeks in most cases,[1] a number of HSP cases will progress to be complicated with nephritis. The long-term prognosis of HSP is largely determined by the severity and duration of renal involvement.[2,3] To date, no effective approach to prevent Henoch–Schönlein purpura nephritis (HSPN) has been found. Hence, to search for a sensitive biomarker for the onset of HSP/HSPN seems imperative. Genetic factors might be associated with the onset of HSP/HSPN.

The renin–angiotensin system (RAS) mediates the regulation of sodium homeostasis, blood pressure, and inflammation.[4] HSP usually occurs due to vasculitis of the small blood vessels, and endothelial cell activation.[5] The RAS also plays a role in the modulation of vascular tone and possibly vascular structure either directly or via various factors such as endothelin and nitric oxide.[6] Hence, RAS might be involved in the pathogenesis of HSP. Furthermore, angiotensin II promoted the renal tubular and mesangial cell proliferation.[6] The local RAS in the kidney also regulates renal cell growth and induces TGF-β production.[7] In this sense, RAS is involved in the pathogenesis of renal diseases, including HSPN. Angiotensin II is the main mediator of action of RAS, angiotensinogen (AGT) is involved in the production of angiotensin II.[8] Functional polymorphism of AGT was associated with the AGT status. Therefore, we speculated that AGT gene polymorphism might predict the risk of HSP/HSPN through its influence on the level of AGT.

Currently, a number of studies have shown the association between AGT M235T gene polymorphism and HSP/HSPN risk.[9–13] However, the results were inconsistent across these studies. An in-depth understanding of this issue may have important clinical implications provided the possibility that AGT M235T gene polymorphism might predict the susceptibility to HSP/HSPN. Meta-analysis is a good way to summarize the available evidence to provide a more robust result. Several previous meta-analyses[14,15] reported the association between ACE I/D gene polymorphism and HSP risk. However, the meta-analysis regarding the association between AGT M235T gene polymorphism and HSP/HSPN risk was rare.

With the accumulating evidence, we, therefore, performed this meta-analysis to investigate the association between AGT M235T gene polymorphism and the risk of HSP/HSPN with the aim of providing a much more reliable finding on the significance of this association.

Methods

Search strategy

We searched the published papers that reported the association between AGT M235T gene polymorphism and the

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risk of HSP/HSPN through May 2014 by using Pub Med, Embase, Cochrane and China National Knowledge Infrastructure (CNKI) databases. No restriction was imposed on search languages. The used search terms were as follows: (1) Henoch–Schönlein purpura, HSP; Henoch–Schönlein purpura nephritis, HSPN; and (2) angiotensinogen, AGT M235T, gene, polymorphism. We also reviewed the reference lists of retrieved reviews and articles. If the same data were enrolled in more than one study, we chose the study with the most complete analysis.

Inclusion and exclusion criteria

Inclusion criteria: (1) case-control study; and (2) the outcome of interest was HSP/HSPN; and (3) a minimum of two comparison groups (HSP group versus Healthy group or HSPN group versus HSP without nephropathy group); and (4) odds ratio (OR) with 95% confidence intervals (CIs) available (data to calculate them).

Exclusion criteria: (1) case reports, editorials and reviews; (2) association between other genes and HSP/HSPN risk; and (3) multiple publications of the same data.

Data extraction and synthesis

We extracted study characteristics from each study. Data were recorded as follows: first author's last year, publication year, ethnicity of study population, number of cases and controls for AGT M235T genotype. Frequencies of M allele were calculated for case and control groups, from the corresponding genotype distribution. Two authors independently performed the data extraction and quality assessment with any disagreements resolved by discussion.

Statistical analysis

OR was used to measure the association between AGT M235T M/T gene polymorphism and HSP/HSPN risk across studies. Heterogeneity of ORs among studies was tested by using the Q statistic. The I^2 statistic, a quantitative measure of inconsistency across studies, was also computed. The combined ORs were calculated using a random-effects model. In addition, 95% confidence intervals (CIs) were also calculated. In order to avoid excessive comparisons, the OR was calculated using three methods: method 1, allele comparison (M allele vs. T allele); method 2, comparing MM homozygous with the other two combinations (MM vs. MT + TT); and method 3, comparing TT genotype with the other two combinations (TT vs. MT + MM). A chi-square test using a web-based program was used to determine whether genotype distribution of the control population reported conformed to Hardy–Weinberg equilibrium (HWE) (HWE; significance level at $p < 0.05$). Subgroup analysis was conducted in adult and children with HSP/HSPN. Potential publication bias was assessed by Begg's test and Egger's test ($p < 0.05$ was considered significant). All analyses were conducted using STATA version 12.0 (Stata Corp, College Station, TX). p Value < 0.05 was considered statistically significant, except where otherwise specified.

Results

Literature search

We initially extracted 76 relevant publications from the Pub Med, Embase, Cochrane and China National Knowledge Infrastructure (CNKI) databases. Of these, 70 studies were excluded according to the inclusion and exclusion criteria, five articles[4,6–22] were included in our meta-analysis (Figure 1). The retrieved data were recorded as follows: first author's surname, publication year, ethnicity, the number of cases and controls.

Characteristics for included studies

Five studies[9–13] were identified for the analysis of the association between AGT M235T gene polymorphism and the risk of HSP/HSPN (Table 1). They were all conducted in Asians. These studies were published between 2006 and 2013. A total of 676 HSP patients and 702 healthy controls were included. Meanwhile, a total of 334 HSPN patients and 342 HSP subjects without renal involvement were recruited. The genotype distributions of the control groups in all the studies were in HWE. The average frequency of the M allele was 35.9% in adult HSP patients and 47.9% in controls. For children, the average frequency of M allele was 58.4% in the HSP patients group and 69.6% for controls. The ratio of HSP/controls for average frequency of M allele in adult was obviously lower compared with that in children (Adult: cases/controls = 0.75; Children: cases/controls = 0.84). The average frequency of the M allele was 30.2% in adult HSPN and 39.6% in controls. For children, the average frequency of M allele was 54.7% in the HSPN and 62.4% for controls. The ratio of HSPN/controls for average frequency of M allele in adult was obviously lower compared with that in children (Adult: cases/controls = 0.76; Children: cases/controls = 0.88).

Association of AGT M2357 gene polymorphism with HSP/HSPN

AGT M235T gene polymorphism was not associated with the risk of HSP/HSPN in overall populations and children (Table 2). No significant association was observed between AGT M235T gene polymorphism and HSPN risk in adult (Table 2). M allele was associated with lower risk of HSP in adult ($p = 0.050$, Table 2, Figure 2), TT genotype was associated with the susceptibility to HSP in adult ($p = 0.039$, Table 2, Figure 3).

Publication bias

The funnel plot showed no marked asymmetry (Figure 4). The Begg rank correlation test and Egger linear regression test indicated no significant publication bias across studies (M vs. T: Begg $p = 0.327$, Egger $p = 0.250$; MM vs. MT + TT: Begg $p = 0.999$, Egger $p = 0.927$; TT vs. MT + MM: Begg $p = 0.624$, Egger $p = 0.366$).

Discussion

Increasing attention has been paid to the association between AGT M235T gene polymorphism and the risk of HSP/HSPN.

Figure 1. Flow chart of study selection.

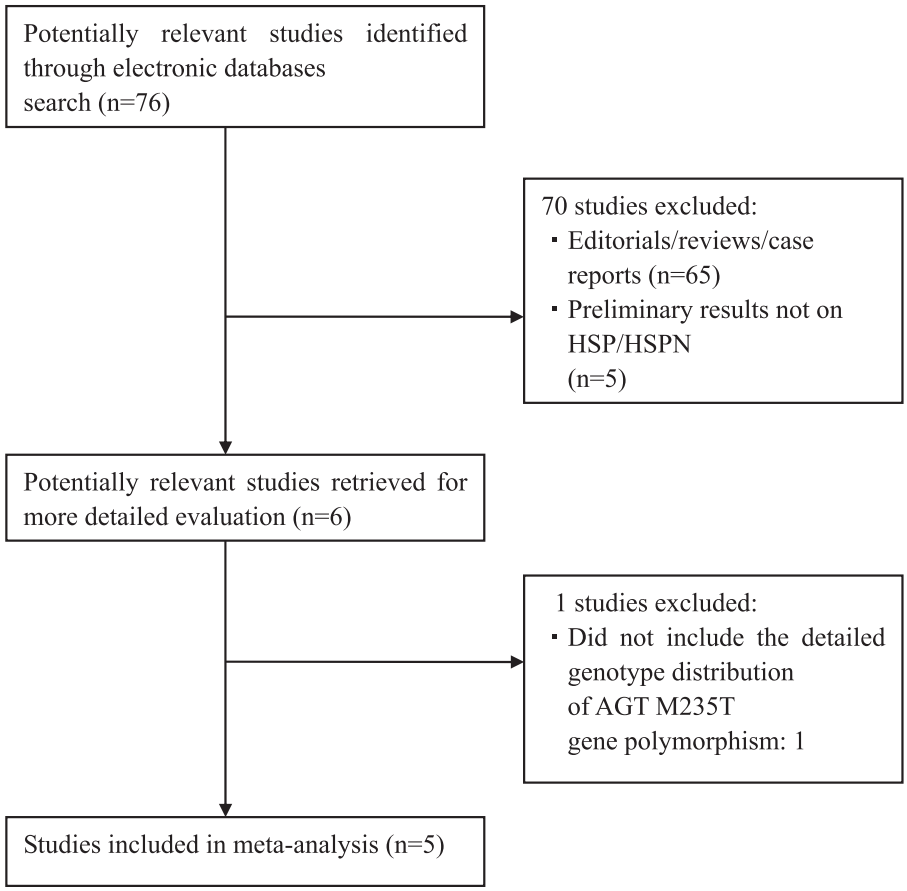


Table 1. Characteristics of studies evaluating the effects of AGT M235T gene polymorphism on HSP/HSPN risk.

		Case				Control				M allele (%)		HWE
Author, year	Ethnicity	MM	MT	TT	Total	MM	MT	TT	Total	Case	Control	P
HSP/Healthy												
Ozkaya et al., 2006	Asian	37	60	17	114	86	65	13	164	58.9	72.1	0.989
Wu et al., 2009	Asian	13	84	40	137	5	54	2	61	40.1	52.5	0.464
Liu et al., 2010	Asian	104	35	2	141	141	69	8	218	86.2	80.5	0.675
An et al., 2012	Asian	23	58	64	145	41	83	48	172	35.9	47.9	0.909
Nalbantoglu et al., 2013	Asian	37	59	43	139	18	50	19	87	47.8	49.4	0.378
HSPN/HSP without nephropathy												
Ozkaya et al., 2006	Asian	11	22	11	44	26	38	6	70	70.7	62.9	0.313
Wu et al., 2009	Asian	12	65	30	107	1	19	10	30	41.6	35	0.099
Liu et al., 2010	Asian	42	17	2	61	62	18	0	80	86.2	80.5	0.675
An et al., 2012	Asian	8	19	31	58	15	39	33	87	30.2	39.6	0.839
Nalbantoglu et al., 2013	Asian	22	24	18	64	15	35	25	75	51.1	48.9	0.911

HWE: Hardy-Weinberg equilibrium, AGT: angiotensinogen, HSP: Henoch–Schönlein purpura, HSPN: Henoch–Schönlein purpura nephritis.

Our meta-analysis showed that M allele was associated with lower risk of HSP in adult, TT genotype was associated with the susceptibility to HSP in adult. AGT M235T gene polymorphism was not associated with HSP risk in children. No marked association was observed between AGT M235T gene polymorphism and HSPN risk. Notably, only one study regarding adult HSP was included, which made our conclusion less robust. Nevertheless, our findings still have implication that TT genotype might be a genetic marker for the onset of HSP in adult.

The age differences might affect the association between AGT M235T gene polymorphism and HSP/HSPN risk. In our study, the ratio of HSP/controls for average frequency of M allele was 0.75 and 0.84 in adult and children, respectively.

The ratio of HSPN/controls for average frequency of M allele was 0.76 and 0.88 in adult and children, respectively. Notably, the ratio in adult is lower than that in children, which is consistent with our findings that M allele conferred protection against HSP risk in adult, TT genotype might be a risk factor for the susceptibility to HSP in adult. However, there was only one study included for the meta-analysis in adult, which made it difficult to draw a robust conclusion for adult. More studies regarding adult are needed.

Several mechanisms may account for the association between AGT M235T gene polymorphism and HSP/HSPN

Table 2. Meta-analysis of the association of AGT M235T gene polymorphism with HSP/HSPN risk.

Study	Ethnicity	Studies	*Q* test *p*-Value	Model selected	OR (95% CI)	*p*-Value
HSP/Healthy						
M versus T	Overall	5	0.255	Random	0.884 (0.761–1.026)	0.104
	Adult	1	–	Random	0.748 (0.559–1.000)	0.050
	Children	4	0.311	Random	0.924 (0.790–1.080)	0.321
MM versus (MT + TT)	Overall	5	0.128	Random	0.904 (0.656–1.245)	0.535
	Adult	1	–	Random	0.665 (0.381–1.161)	0.151
	Children	4	0.134	Random	0.974 (0.675–1.404)	0.888
TT versus (MT + MM)	Overall	5	0.064	Random	1.674 (0.983–2.849)	0.058
	Adult	1	–	Random	1.582 (1.024–2.443)	0.039
	Children	4	0.031	Random	1.741 (0.747–4.061)	0.199
HSPN/HSP without nephropathy						
M versus T	Overall	5	0.446	Random	0.952 (0.785–1.155)	0.619
	Adult	1	–	Random	0.761 (0.476–1.217)	0.254
	Children	4	0.447	Random	0.997 (0.807–1.231)	0.975
MM versus (MT + TT)	Overall	5	0.313	Random	1.005 (0.682–1.481)	0.980
	Adult	1	–	Random	0.800 (0.319–2.008)	0.635
	Children	4	0.212	Random	1.069 (0.653–1.749)	0.791
TT versus (MT + MM)	Overall	5	0.211	Random	1.265 (0.785–2.037)	0.334
	Adult	1	–	Random	1.409 (0.779–2.548)	0.256
	Children	4	0.138	Random	1.272 (0.628–2.573)	0.504

OR: odds ratio, CI: confidence interval, AGT: angiotensinogen, HSP: Henoch–Schönlein purpura, HSPN: Henoch–Schönlein purpura nephritis.

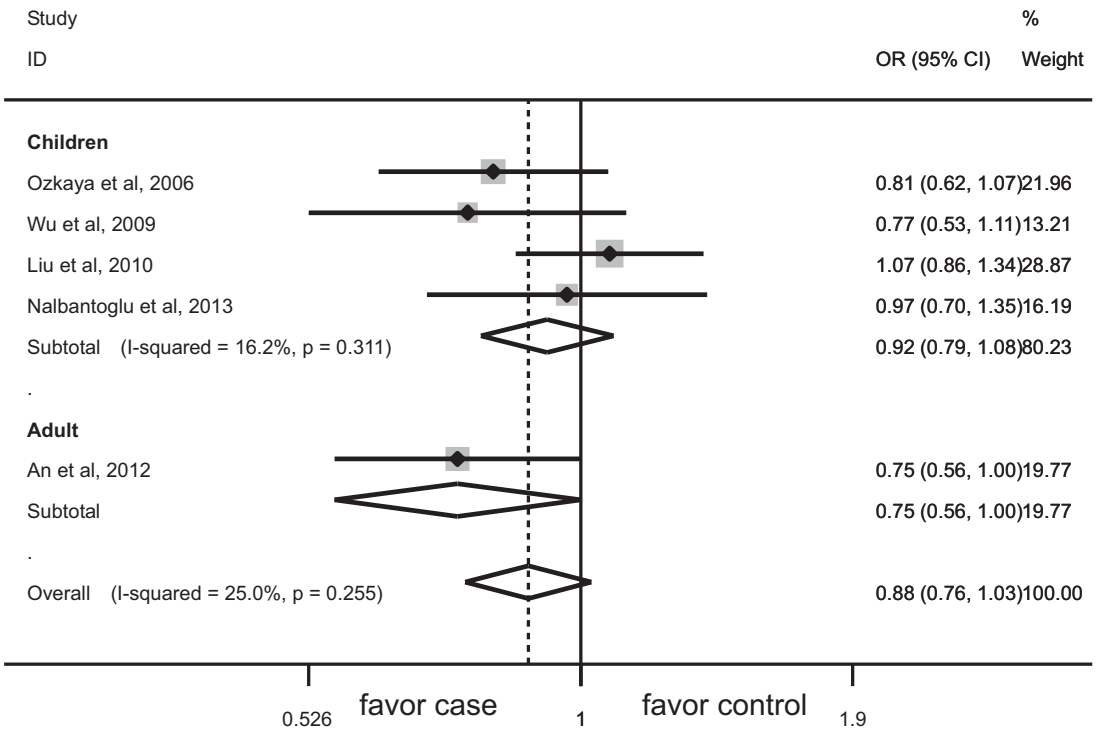


Figure 2. Association between M allele and HSP risk.

risk. First, the RAS is involved in the progress of several immune-inflammatory diseases.[16] Over-activation of the RAS is involved in the initiation of inflammation.[16] HSP is a leukocytoclastic vasculitis and is due to a complex series of inflammatory and immunologic processes. The interaction between leukocytes and vascular endothelial cells contributes to the pathogenesis of leukocytoclastic vasculitis.[17] Furthermore, RAS dysregulation results in renal organ damage.[18] The RAS is one of the pathophysiologic factors for the development of nephropathies.[19] In this sense, RAS is involved in the development of HSP/HSPN. Second, angiotensin II is main biologically product of RAS, AGT interacted with renin to produce angiotensin I, which was then catalyzed to form angiotensin II. Hence, AGT might be associated with the pathogenesis of HSP/HSPN. Finally, gene polymorphism of AGT might affect the AGT concentration. For example, AGT M235T gene polymorphism was closely associated with plasma AGT level, M235T TT genotype carriers have been shown to have 10–20% more plasma AGT level than in M235T MM genotype carriers.[20] The above-mentioned

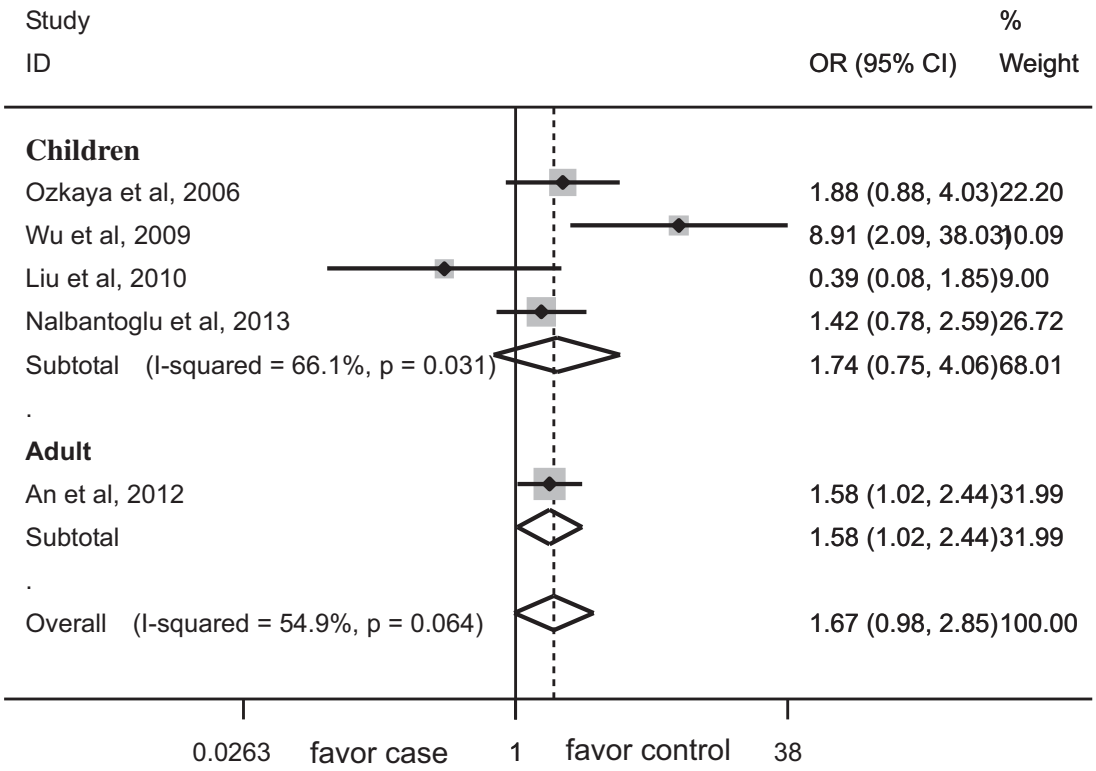
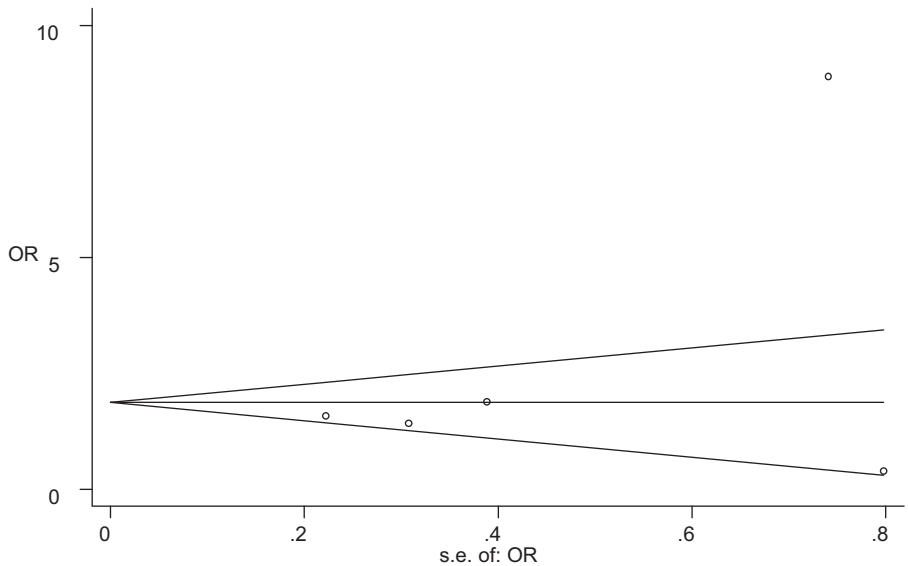


Figure 3. Association between TT genotype and HSP risk.

Figure 4. Publication bias for the analysis of association of AGT M235T gene polymorphism with HSP risk.



evidence indicated that AGT M235T gene polymorphism might be associated with the risk of HSP/HSPN.

Our findings were partially consistent with the above-mentioned mechanisms. However, AGT M235T gene polymorphism was not associated with HSPN risk, which might be due to the facts that AGT regulated the function of RAS indirectly. In addition, the renal damage of HSPN is comparatively mild. The mild renal damage might not be associated with AGT M235T gene polymorphism.

In the past, there were a number of meta-analyses and studies investigating the association between AGT M235T gene polymorphism and immune-related and renal diseases. A meta-analysis by Ding et al.[21] reported that AGT M235T gene polymorphism was not associated with diabetic nephropathy. Zhou et al.[22] reported that no marked association between AGT M235T gene polymorphism and ESRD was observed in overall populations. Mao et al.[23] reported that AGT M235T gene polymorphism was not associated with the risk of IgA nephropathy. Arfa et al.[24] reported that AGT M235T gene polymorphism was not associated with the development of hypertension. Eroglu et al.[25] reported that there were no differences in the frequencies of the AGT M235T gene polymorphism between Turkish patients with type 2 DM with and without nephropathy. Takakura et al.[26]

reported that TT genotype of the AGT M235T gene polymorphism was positively related to visceral obesity and hyperinsulinemia in obese Japanese women. Zulian et al.[27] reported that AGT M235T gene polymorphism was associated with polycystic ovary syndrome. These previous findings strongly suggest that AGT M235T gene polymorphism might not be associated with renal damage.

Although our study has obvious strengths, such as that the participants were all form Asia, the genotype distribution of control groups were all in HWE, the control group of HSPN cases are all HSP without nephropathy, several limitations should be considered in our meta-analysis. First, the heterogeneities across studies might affect the results, although no evidence of marked publication bias was noted. Second, studies included were only from Asia, which made it difficult to extrapolate our conclusions to other populations. More studies in other regions, such as Europe, should be performed in the future. Finally, the limited number of participants decreases the statistical power.

Taken together, this meta-analysis suggests M allele was associated with lower risk of HSP in adult, TT genotype was associated with the susceptibility to HSP in adult. However, more studies are needed to validate our findings.

Declaration of interest

There is no conflict of interest for all authors. This study was supported by Grants from the National Basic Research Program of China 973 Program (Nos. 2012CB517602 and 2013CB530604), the National Natural Science Foundation of China (Nos. 81170635 and 81270785) and the Research and innovation Project for College Graduates of Jiangsu Province, China (grant number CXLX13_556).

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