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The association of angiotensin-converting enzyme gene insertion/deletion polymorphisms with OSA: a meta-analysis

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ABSTRACT: Obstructive sleep apnoea (OSA) is an independent risk factor for hypertension. Increased angiotensin-converting enzyme (ACE) activity may be a possible promoting mechanism with different ACE insertion/deletion (I/D) genotypes influencing this activity. Studies investigating the association of ACE I/D polymorphisms with OSA have shown conflicting results. We aimed to undertake a meta-analysis of existing studies exploring the association of ACE I/D polymorphisms with the risk of OSA and hypertension.

10 studies were included in a random effects meta-analysis, comprising 1,227 OSA subjects and 1,227 controls.

The effect size was measured using the odds ratio. The risk of having OSA in carriers of the D allele was 0.92 (95% CI 0.69–1.23). There was statistically significant heterogeneity across the studies (I^2=42%, p=0.08 and I^2=74%, p<0.0001 for genotype and allele frequency, respectively). The association of D allele frequency with the risk of OSA remained nonsignificant after stratification based on ethnicity, source of population sample, and the presence of hypertension. Subgroup analysis failed to show any influence of genotype and allele frequency on OSA severity.

This meta-analysis revealed no association between the ACE I/D polymorphisms and OSA susceptibility.

KEYWORDS: Angiotensin-converting enzyme polymorphism, meta-analysis, obstructive sleep apnoea

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Obstructive sleep apnoea (OSA) is characterised by recurrent collapse of the upper airway during sleep, resulting in intermittent hypoxia and sleep fragmentation that can lead to excessive daytime sleepiness. Untreated OSA is an independent risk factor for hypertension [1–3]. The exact mechanisms linking OSA and hypertension are not clear. One possibility is that OSA-related hypoxia and arousal might lead to sympathetic hyperactivity and activation of the renin–angiotensin–aldosterone system [4].

The angiotensin-converting enzyme (ACE) regulates blood pressure by hydrolysing angiotensin I into angiotensin II and inactivating bradykinin and angiotensin I–VII [5]. The importance of ACE in the regulation of blood pressure is demonstrated by the beneficial effect of ACE inhibitors on hypertension [6]. The insertion/deletion (I/D) polymorphism of ACE has been shown to account for 47% of the observed variance in serum ACE levels. The DD genotype carriers have the highest serum ACE concentrations and II genotype carriers have the lowest serum ACE concentrations [7]. The DD genotype has been associated with hypertension; the association being stronger in Asians and females [8]. However, recent meta-analyses have failed to confirm an association between ACE polymorphisms and hypertension [9–11].

In one study, increased serum ACE activity was measured in patients with OSA when compared with controls, independently of hypertension [12]. However, the distribution of the DD, II and ID genotypes did not differ from those in the controls [12]. Many studies have investigated the potential association between OSA and the ACE I/D polymorphism. The results are conflicting, as there is significant heterogeneity amongst the recruited subjects, sample sizes, ethnicities and definitions of OSA [2, 3, 6, 12, 13]. For example, a higher frequency of the I allele has been reported in Chinese hypertensive patients with moderate-to-severe OSA, in contrast to a higher frequency of the D allele in hypertensive Caucasian patients with mild-to-moderate OSA [14–16]. In an effort

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to clarify the association between ACE I/D polymorphisms and OSA, we undertook a meta-analysis on all studies published within this area from January 2000 to December 2010.

MATERIALS AND METHODS

Data extraction

Data extraction was carried out by one researcher (P. Lee) (fig. 1) and the accuracy was checked independently (R.L. Riha). First, we performed a literature search using the computerised bibliographic databases PubMed and EMBASE using the terms ''sleep apnoea AND angiotensin converting enzyme''. No limitation on any type of study in the literature was imposed. Unpublished dissertations were accessed *via* the same search strategy in the UMI Dissertation Abstract database. We also conducted a web-based search through a variety of commercial internet search engines (*e.g.* Google® and Yahoo®) using the same technique. Additional publications were drawn from reference lists of articles obtained, including studies and reviews. Secondly, we manually reviewed all articles that included empirical data related to ACE genotype in association with OSA. Thirdly, we excluded each potential reference for sample overlap. Reviews and other publications, *e.g.* editorials and letters, were excluded unless they contained original data. Finally, the remaining references were subjected to inclusion and exclusion criteria. Studies were considered for inclusion if the population had OSA and ACE genotyping had been performed; OSA was defined as an apnoea/hypopnoea index (AHI) $\geqslant$5 events·h^{-1}, categorised as mild-to-moderate (AHI 5–30 events·h^{-1}) and severe (AHI >30 events·h^{-1}). Exclusion criteria were: 1) paediatric OSA (there is evidence that paediatric OSA may have a different aetiopathogenesis and clinical characteristics compared with adult OSA); 2) lack of baseline data; and 3) lack of control subjects. Figure 1 provides a summary of the search strategy employed.

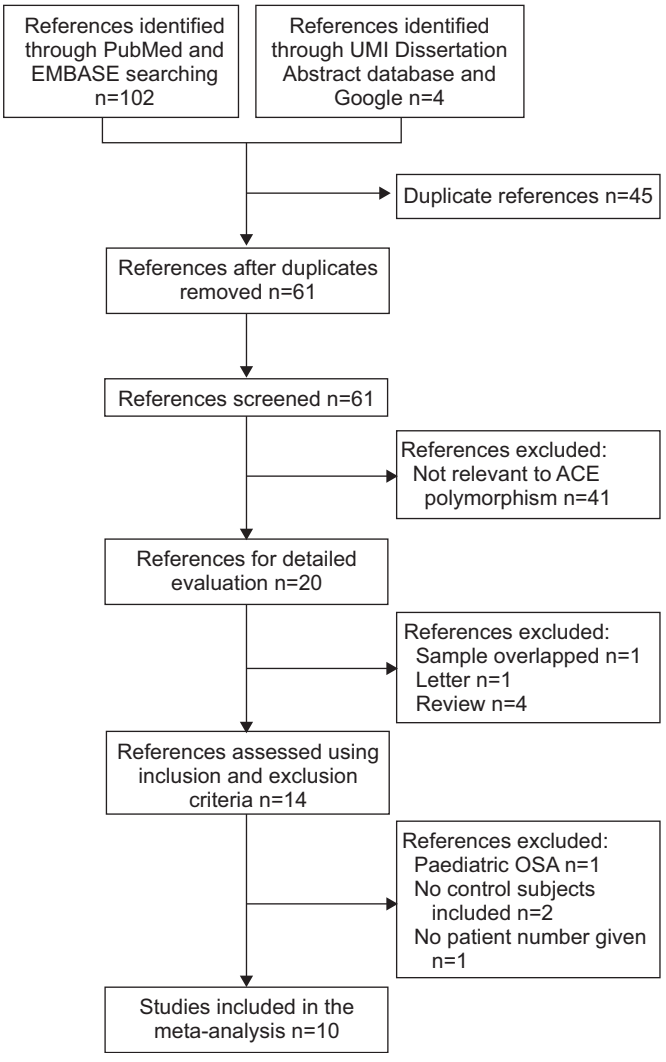

FIGURE 1. Flow diagram of literature search strategy. ACE: angiotensin-converting enzyme; OSA: obstructive sleep apnoea.

Sample coding

Included studies were reviewed with special emphasis on extracting information about the following variables: source of the OSA sample (community *versus* clinical); number of cases and controls (defined as those without OSA); ethnicity; mean age of study subjects; sex ratio; comorbidities of study participants; body mass index; AHI; proportion of study subjects with the I allele; and the geographic setting of the study. We extracted or derived a contingency table that summarised the association of the ACE I allele with the risk of having OSA. The outcome was the odds ratio of having OSA.

Statistical analysis

Analysis was performed using SPSS version 16 (SPSS Inc., Chicago, IL, USA) and Review Manager 5.0 (The Cochrane Collaboration, Copenhagen, Denmark). We used a random effects model for the meta-analysis. We assessed the association of the D or I alleles on OSA using the dominant (DD+DI *versus* II) model. For subgroup analysis, we stratified studies by ethnicity, source of OSA sample (clinic referral *versus* community), OSA severity (mild-to-moderate *versus* severe) and hypertension. Homogeneity across the included studies was tested using the Q-statistic and inconsistency quantified using the I^2 statistic. When only a few studies are included in a meta-analysis the Q-test has ''low power'' for detecting heterogeneity, therefore, $p<0.1$ is taken as the threshold for statistical significance. The I^2 statistic is represented by a value of 0–100%, with a value directly proportional to degree of inconsistency. This latter statistic quantifies heterogeneity not explained by sampling variability in the included studies [17]. A funnel plot was used to assess publication bias.

RESULTS

Characteristics of the studies

In total, 14 studies (published in English, Polish and Chinese; not all shown) were evaluated for eligibility for the analysis and 10 studies fulfilling the criteria were included; seven of the 10 references were in English and three were in Chinese. The characteristics of these 10 studies are shown in table 1. Six studies [2, 6, 12, 13, 18, 20] were conducted in a Caucasian population and four [14–16, 20] were exclusively conducted in Chinese subjects. Two studies [6, 18] identified OSA patients by screening a community population and eight [2, 12–16, 19, 20] identified OSA patients through referrals to a sleep lab. Five studies [2, 6, 14, 15, 20] reported coexistent hypertension in OSA patients. The study by ZHANG *et al.* [14] in 2000 exclusively recruited hypertensive OSA patients. Six studies

TABLE 1 Characteristics of studies included in the meta-analysis

First author [ref.]	Year	Sample	Control subjects					OSA subjects						
			Subjects n	Age yrs	Males	Ethnicity	BMI kg·m^{-2}	Subjects n	Age yrs	Males	Ethnicity	HT	BMI kg·m^{-2}	Phenotype AHI events·h^{-1}
Barceló [12]	2001	R	32	49±1	100	Caucasian 96.7	25.6±0.6	44	50±1	100	Caucasian 96.7	NM	32.8±0.6	54.5±2.5
Benjamin [2]	2008	R	52	43.59	57.7	Caucasian 100	32.3±5.2	26	47.5±11.2	80.8	Caucasian 100	46.2	38.4±8.0	Defined as 4% oxygen dip ⩾10
Boström [18]	2007	C	108	NM	42.8	Caucasian 96.7	NM	230	NM	50.2	Caucasian 96.7	53.9	NM	OSA defined as AHI ⩾10
Li [15]	2004	R	30	45.2	86.7	Asian 100	26.9	60	42.9±8.2	93.3	Asian 100	50	29.3±3.9	59.3±29.0
Lin [6]	2004	C	626	NM	NM	Caucasian 96.7	NM	474	NM	54	Caucasian 96.7	56.4	NM	OSA defined as AHI ⩾5
Ogus [19]	2010	R	79	60.1±10	45.6	Caucasian 96.7	NM	97	51.3±9.9	90.7	Caucasian 100	NM	30.6±5.8	24.24±18.34
Xiao [20]	1998	R	50	30.9±6.6	60	Asian 100	NM	50	50.9±10.5	90	Asian 100	50	29.6±6.7	39±23.3
Yakut [13]	2010	R	37	49.9±10.4	70.2	Caucasian 96.7	28.5±4.6	64	50.4±11.2	82.8	Caucasian 100	NM	30.6±4.3	OSA defined as AHI ⩾5
Zhang [14]	2000	R	113	54.0±12.4	64.6	Asian 100	26.2±4.4	61	54.4±11.3	85.2	Asian 100	100	28.5±2.9	31.3±17.3
Zhang [16]	2004	R	100	40.1±2.1	100	Asian 100	26.2±2.0	121	43.2±2.3	100	Asian 100	NM	28.8±1.4	OSA/HS defined as AHI ⩾5

Data presented as mean±SEM or %, unless otherwise stated. OSA: obstructive sleep apnoea; BMI: body mass index; HT: hypertension, as defined by the authors: AHI: apnoea/hypopnoea index; R: OSA subjects referred from clinic; C: OSA subjects derived from a screened community; NM: not mentioned; OSA/HS: OSA/hypopnoea syndrome.

[2, 12, 15, 16, 19, 20] included subjects free of comorbidities other than hypertension, whereas comorbidities were not addressed in four of the studies [6, 16, 18, 13].

Association between OSA and ACE I/D genotype

The funnel plot showed there was no evidence for significant publication bias for the 10 studies overall (fig. 2). The majority of the studies found no association of the ACE I/D genotype with OSA in either Caucasian [2, 6, 12, 13, 18, 19] or Chinese populations [16, 20]. The study conducted by Zhang *et al.* [14] reported the presence of the D allele as lowering the risk of having OSA in a Chinese hypertensive population (fig. 3).

The present meta-analysis combined information on the genotype of 1,227 OSA subjects and 1,227 control subjects, with 934 OSA subjects and 939 control subjects being carriers of the D allele. We found a nonsignificant decrease in OSA risk with the D allele (OR 0.92, 95% CI 0.69–1.23) (fig. 3). However, there was significant heterogeneity across the studies (I^2=42%, p=0.08). After performing stratified analysis for Caucasians (OR 1.09, 95% CI 0.86–1.37) and Asians (OR 0.67, 95% CI 0.35–1.29) separately, the association remained nonsignificant.

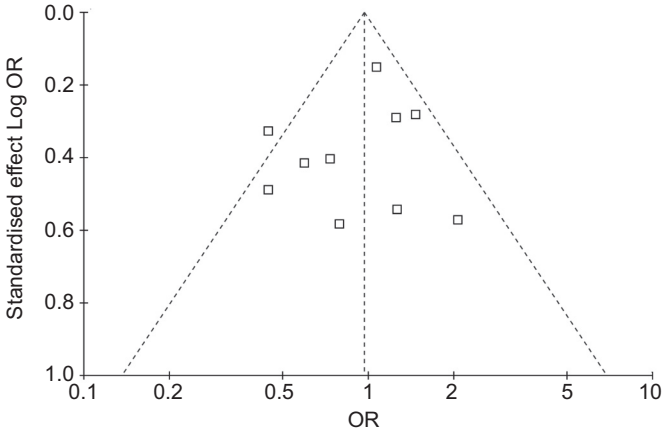

FIGURE 2. A funnel plot showing publication bias with odds ratio (OR) and standardised effect size.

After further stratifying studies as either community based (OR 1.10, 95% CI 0.85–1.44) [6, 18] or clinic referral based (OR 0.82, 95% CI 0.55–1.24) [2, 6, 12–14, 16, 19, 20], the association of ACE I/D genotype with OSA remained nonsignificant. There was significant heterogeneity across the clinic-referral based studies (I^2=47%, p=0.07), which was not seen among community-based studies (I^2=0, p=0.64). Combining the information taken from two studies of 180 hypertensive OSA subjects and 115 hypertensive controls, and 134 OSA subjects and 89 hypertensive controls, we found a nonsignificant decrease in OSA risk with the D allele (OR 0.78, 95% CI 0.34–1.78) [14, 18].

Four studies reported genotype against OSA severity [6, 14, 18, 19]. There was no significant association in OSA severity with the D allele (OR 0.75, 95% CI 0.49–1.16).

Association between OSA and ACE gene D allele frequency

One study reported the D allele to be associated with a decreased risk for OSA in a Caucasian population [19]. In a Chinese population three studies [14, 15, 20] showed the D allele to decrease OSA risk and one study showed the D allele to increase OSA [16] (fig. 4). We found a nonsignificant decrease in OSA risk with D allele frequency (OR 0.92, 95% CI 0.71 to 1.20) (fig. 3). There was a high degree of heterogeneity across the studies (I^2=74%, p<0.0001). After performing stratified analysis for Caucasian (OR 1.09, 95% CI 0.85–1.39) and Chinese populations (OR 0.67, 95% CI 0.36–1.26) separately, the association

	Carrier		Total		Weight %	OR (95% CI)
	n	N	n	N		
Caucasian population						
Barceló [12]	37	23	44	32	5.4	2.07 (0.68–6.32)
Benjamin [2]	20	42	26	52	5.2	0.79 (0.25–2.49)
Boström [18]	189	85	230	108	13.2	1.25 (0.70–2.21)
Lin [6]	382	498	474	626	20.9	1.07 (0.79–1.44)
Ogus [19]	78	67	97	79	8.9	0.74 (0.33–1.63)
Yakut [13]	54	30	64	37	5.8	1.26 (0.43–3.65)
Sum (I^2=0%, p=0.73)	760	745	935	934	59.4	1.09 (0.86–1.37)
Asian population						
Li [15]	33	22	60	30	6.8	0.44 (0.17–1.16)
Xiao [20]	28	34	50	50	8.6	0.60 (0.27–1.35)
Zhang [14]	31	79	61	113	11.6	0.44 (0.23–0.85)
Zhang [16]	82	59	121	100	13.6	1.46 (0.35–1.29)
Sum (I^2=69%, p=0.02)	174	194	292	293	40.6	0.67 (0.35–1.29)
Overall (I^2=42%, p=0.08)	934	939	1227	1227	100	0.92 (0.69–1.23)

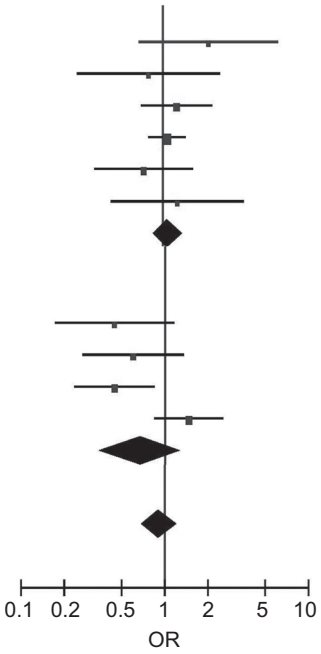

FIGURE 3. Association of angiotensin-converting enzyme insertion/deletion genotypes under a dominant model where the random effect model was use. n: number of obstructive sleep apnoea subjects; N: number of control subjects. Heterogeneity overall (I^2=42%, p=0.08) and in the Asian population (I^2=69%, p=0.02) was significant.

	Carrier		Total		Weight %	OR (95% CI)
	n	N	n	N		
Caucasian population						
Barceló [12]	50	33	88	64	7.9	1.24 (0.65–2.36)
Benjamin [2]	32	57	52	104	7.6	1.32 (0.67–2.60)
Boström [18]	268	107	460	216	12.3	1.42 (1.03–1.97)
Lin [6]	514	678	948	1252	14.3	1.00 (0.85–1.19)
Ogus [19]	105	104	194	158	10.8	0.61 (0.40–0.94)
Yakut [13]	81	41	128	74	8.7	1.39 (0.77–2.48)
Sum (I^2=55%, p=0.05)	1050	1020	1870	1868	61.6	1.09 (0.85–1.390
Asian population						
Li [15]	54	41	120	60	7.9	0.38 (0.20–0.73)
Xiao [20]	28	42	100	100	8.6	0.54 (0.30–0.97)
Zhang [14]	42	107	122	226	10.4	0.58 (0.37–0.92)
Zhang [16]	118	78	242	200	11.5	1.49 (1.02–2.18)
Sum (I^2=84%, p=0.0003)	242	268	584	586	38.4	0.67 (0.36–1.26)
Overall (I^2=74%, p<0.0001)	1292	1288	2454	2454	100.0	0.92 (0.71–1.20)

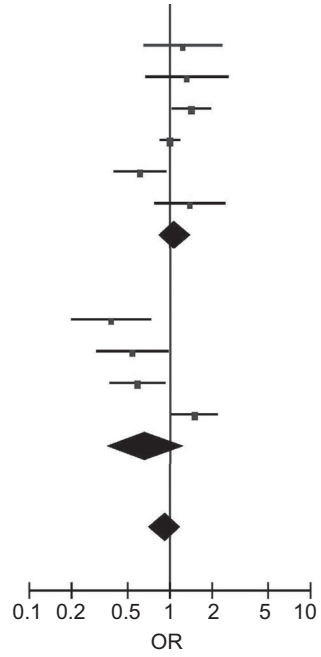

FIGURE 4. Association of angiotensin-converting enzyme D allele frequency where the random effect model was used. n: number of obstructive sleep apnoea subjects; N: number of control subjects. Heterogeneity overall (I^2=74%, p<0.0001), and for Caucasian (I^2=55%, p=0.05) and Asian populations (I^2=84%, p=0.0003) was significant.

remained nonsignificant and heterogeneity remained significant (Caucasians: I^2=55%, p=0.05; Chinese: I^2=84%, p=0.0003).

Studies were further stratified as community based (OR 1.16, 95% CI 0.83–1.63) [6, 18] or clinic referral based (OR 0.84, 95% CI 0.58–1.22) [2, 6, 13, 14, 16, 19, 20], with the association remaining nonsignificant. There was a high degree of heterogeneity across the clinic-referral based studies (I^2=74%, p=0.0003) and community-based studies (I^2=71%, p=0.06). In studies of hypertensive subjects with and without OSA and controls no significant association of OSA risk with D allele frequency was observed (OR 1.00, 95% CI 0.46–2.20) [14, 18]. The risk of having OSA overall, was not associated with the D allele (OR 0.87, 95% CI 0.69–1.09).

Four studies reported D allele frequency against OSA severity [6, 14, 18, 19]. In 238 severe OSA subjects and 624 mild-to-moderate OSA subjects with D allele frequencies of 242 and 686, respectively, there was a nonsignificant decrease in OSA risk with the D allele (OR 0.87, CI 95% 0.69–1.09).

DISCUSSION

The aim of this study was to clarify the role of the ACE I/D polymorphism and its association with OSA using meta-analysis in a series of case–control, population-based studies. Our meta-analysis combined genotype information from 10 studies representing 2,454 subjects (1,227 OSA subjects and 1,227 controls) and failed to demonstrate an association between ACE I/D polymorphisms with OSA susceptibility. The analysis further explored and excluded any influence of ethnicity, source of OSA sample, and the presence of hypertension. A subgroup analysis revealed that genotype and allele frequency did not influence OSA severity.

Our findings, showing the lack of an association of the ACE I/D genotype with OSA susceptibility, echo the negative results of the recent meta-analyses on the association of ACE I/D genotype with blood pressure [9–11, 21]. Although the D allele is associated with increased serum ACE activity, the majority of the evidence indicates that the effect of the D allele on blood pressure is small and additional environmental or genetic factors are most likely required to determine blood pressure [5, 10, 11]. OSA subjects may have higher serum ACE activity than control subjects, but it is unlikely that ACE I/D polymorphisms increase susceptibility to OSA *per se*.

Limitations of the study are those inherent to the publications available for analysis and related to the populations studied, their ethnicity and any confounding comorbidities and other covariates, including environmental factors that have neither been considered nor controlled for. Heterogeneity across trials is significant despite an attempt at stratification of the studies by source of referral and ethnicity. The most likely contributors to heterogeneity in this meta-analysis are related to the disparate phenotype definitions of OSA/hypopnoea syndrome (OSA/HS) (table 1), the small sample sizes, the low-order magnitude of the genetic effects of the ACE gene polymorphisms in OSA/HS and gene–environment interactions that can never be fully accounted for.

Notwithstanding these limitations, the present meta-analysis has failed to demonstrate an association between ACE I/D polymorphisms and OSA susceptibility, irrespective of ethnicity, population sample or the presence and/or absence of comorbid hypertension.

SUPPORT STATEMENT

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STATEMENT OF INTEREST

None declared.

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REFERENCES

1 Marin JM, Carrizo SJ, Vicente E, *et al.* Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* 2005; 365: 1046–1053.
2 Benjamin JA, Moller M, Ebden P, *et al.* Serum angiotensin converting enzyme and the obstructive sleep apnea hypopnea syndrome. *J Clin Sleep Med* 2008; 4: 325–331.
3 Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, *et al.* Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. *Lancet* 2002; 359: 204–210.
4 Lavie L, Lavie P. Molecular mechanisms of cardiovascular disease in OSAHS: the oxidative stress link. *Eur Respir J* 2009; 33: 1467–1484.
5 Sayed-Tabatabaei FA, Oostra BA, Isaacs A, *et al.* ACE polymorphisms. *Circ Res* 2006; 98: 1123–1133.
6 Lin L, Finn L, Zhang J, *et al.* Angiotensin-converting enzyme, sleep-disordered breathing, and hypertension. *Am J Respir Crit Care Med* 2004; 170: 1349–1353.
7 Rigat B, Hubert C, Alhenc-Gelas F, *et al.* An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. *J Clin Invest* 1990; 86: 1343–1346.
8 Agachan B, Isbir T, Yilmaz H, *et al.* Angiotensin converting enzyme I/D, angiotensinogen T174M-M235T and angiotensin II type 1 receptor A1166C gene polymorphisms in Turkish hypertensive patients. *Exp Mol Med* 2003; 35: 545–459.
9 Agarwal A, Williams GH, Fisher ND. Genetics of human hypertension. *Trends Endocrinol Metab* 2005; 16: 127–133.
10 Staessen JA, Wang JG, Ginocchio G, *et al.* The deletion/insertion polymorphism of the angiotensin converting enzyme gene and cardiovascular-renal risk. *J Hypertens* 1997; 15: 1579–1592.
11 Agerholm-Larsen B, Nordestgaard BG, Tybjaerg-Hansen A. *ACE* gene polymorphism in cardiovascular disease: meta-analyses of small and large studies in whites. *Arterioscler Thromb Vasc Biol* 2000; 20: 484–492.
12 Barceló A, Elorza MA, Barbé F, *et al.* Angiotensin converting enzyme in patients with sleep apnoea syndrome: plasma activity and gene polymorphisms. *Eur Respir J* 2001; 17: 728–732.
13 Yakut T, Karkucak M, Ursavas A, *et al.* Lack of association of ACE gene I/D polymorphism with obstructive sleep apnea syndrome in Turkish patients. *Genet Mol Res* 2010; 9: 734–738.
14 Zhang J, Zhao B, Gesongluobu, *et al.* Angiotensin-converting enzyme gene insertion/deletion (I/D) polymorphism in hypertensive patients with different degrees of obstructive sleep apnea. *Hypertens Res* 2000; 23: 407–411.
15 Li Y, Zhang W, Wang T, *et al.* [Study on the polymorphism of angiotensin converting enzyme genes and serum angiotensin II

level in patients with obstructive sleep apnea hypopnea syndrome accompanied hypertension]. *Lin Chuang Er Bi Yan Hou Ke Za Zhi* 2004; 18: 456–459.

16 Zhang LQ, Yao WZ, He QY, *et al.* [Association of polymorphisms in the angiotensin system genes with obstructive sleep apnea-hypopnea syndrome]. *Zhonghua Jie He He Hu Xi Za Zhi* 2004; 27: 507–510.

17 Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. Oxford, The Cochrane Collaboration, 2011.

18 Boström KB, Hedner J, Melander O, *et al.* Interaction between the angiotensin-converting enzyme gene insertion/deletion polymorphism and obstructive sleep apnoea as a mechanism for hypertension. *J Hypertens* 2007; 25: 779–783.

19 Ogus C, Ket S, Bilgen T, *et al.* Insertion/deletion polymorphism and serum activity of the angiotensin-converting enzyme in Turkish patients with obstructive sleep apnea syndrome. *Biochem Genet* 2010; 48: 516–523.

20 Xiao Y, Huang X, Qiu C. [Angiotension I converting enzyme gene polymorphism in Chinese patients with obstructive sleep apnea syndrome]. *Zhonghua Jie He He Hu Xi Za Zhi* 1998; 21: 489–491.

21 Thakre TP, Mamtani MR, Kulkarni. H Lack of association of the APOE epsilon 4 allele with the risk of obstructive sleep apnea: meta-analysis and meta-regression. *Sleep* 2009; 32: 1507–1511.