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ORIGINAL ARTICLE

Association of the *CYP3A5* polymorphism (6986G > A) with blood pressure and hypertension

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The cytochrome P450 family 3 subfamily A polypeptide 5 (*CYP3A5*) gene has been implicated in the regulation of blood pressure (BP) and thus, may serve as a potential risk factor for the development of hypertension. However, current results regarding the association between *CYP3A5* single nucleotide polymorphisms and BP/hypertension have been inconsistent. In this study, we performed a meta-analysis to evaluate the association between the *CYP3A5* rs776746 (6986G > A) polymorphism and BP/hypertension. Ten studies (representing 2799 cases and 6794 controls) were included to determine the association of this single nucleotide polymorphism with hypertension, and 12 studies (9076 subjects) were included to determine the association of this single nucleotide polymorphism with BP. Overall, no associations were observed between the rs776746 polymorphism and BP/hypertension. In subgroup analysis, *CYP3A5*1* carriers had lower systolic BP, compared with non-carriers in white populations (mean difference = −1.322, 95% confidence interval −2.401 to −0.242 mm Hg, *P* = 0.016). This meta-analysis suggested a modestly significant association between the *CYP3A5* rs776746 polymorphism and systolic BP in white populations. Given the limited sample size, additional studies are necessary to investigate the role of *CYP3A5* in the regulation of BP and the pathogenesis of hypertension.
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Keywords: blood pressure; cytochrome P450 3A5; meta-analysis

INTRODUCTION

Hypertension affects nearly one-third of the adult population worldwide and is associated with stroke and cardiovascular disease, which are major contributors to the global health burden.[1] Although lifestyle factors (for example, excess sodium intake and lack of physical activity) can contribute to elevated blood pressure (BP) and increased hypertension risks,[2] genetic factors have also been implicated in the pathogenesis of these diseases.[3–5] Genome-wide association studies have identified many genetic variants that may be associated with hypertension.[6] These exciting new results elucidating hypertension's underlying molecular mechanisms have greatly expanded our knowledge and provided new insights into the etiology of hypertension.[7]

The cytochrome P450 family 3 subfamily A polypeptide 5 (*CYP3A5*) gene encodes a member of the cytochrome P450 super family of enzymes. The *CYP3A5* gene is part of a cluster of cytochrome P450 genes on chromosome 7q21.1.[8] Cytochrome P450 proteins are monooxygenases that have an important role in the metabolism of both endogenous substances (for example, hormones) and exogenous substances (for example, drugs).[9,10] Cytochrome P450 proteins are expressed in an organ-specific manner, with CYP3A5 predominantly expressed in the kidney.[11] As a glucocorticoid 6β-hydroxylase, the CYP3A5 enzyme converts cortisol or corticosterone to 6β-corticosterone, which may lead to increased sodium and water retention.[12,13] The *CYP3A5* gene has a common polymorphism (6986G > A, rs776746) in the third intron. The G allele generates an aberrant RNA splicing site and results in a premature stop codon, which causes truncation of the *CYP3A5* protein.[14] In genetic epidemiology studies, *CYP3A5*1* refers to the A allele (functional allele) and *CYP3A5*3* refers to the G allele (nonfunctional allele).

Recently, several studies have suggested a possible relationship between *CYP3A5* gene polymorphisms and BP/hypertension. However, their conclusions have been inconsistent. This inconsistency could be due to many factors, including insufficient statistical power, varying recruitment procedures of the study population and differences in the genetic and environmental backgrounds. In this study, we performed a meta-analysis to assess the association between the *CYP3A5* rs776746 polymorphism and BP/hypertension.

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METHODS

Literature and search strategy

We searched literature databases, including PubMed (1950 to 2010), the ISI Web of Science (1975 to 2010) and Embase (1966 to 2010). The search strategy to identify all possible studies involved the use of the following key words: 'cytochrome P-450 3A5' (or '*CYP3A5*') and 'blood pressure' (or 'hypertension'). The reference lists of retrieved articles were then manually searched. If more than one article was published using the same case series, only the study with largest sample size was included. The literature search was updated on 5 December 2010.

Inclusion criteria and data extraction

The studies included in the meta-analysis necessarily met all of the following inclusion criteria: (1) evaluating the association of the *CYP3A5* polymorphism with hypertension or BP; (2) a case–control design; (3) sufficient data for calculation of effect size (odds ratio (OR) or mean difference) with a corresponding confidence interval (CI); and (4) subjects without serious diseases. The following information was extracted from each study: (1) the name of the first author; (2) the year of publication; (3) the ethnicity of the study population; (4) the gender ratio and mean age (or age range) of the study population; (5) the number of subjects with the *CYP3A5* polymorphism in hypertension cases and controls; and (6) the mean and s.d. of BP among carriers and non-carriers with *CYP3A5**1. The articles were independently assessed for compliance with the inclusion/exclusion criteria, and all disagreements were resolved to give a consistent decision for each article.

Statistical analysis

The association of the *CYP3A5* polymorphism with hypertension was estimated by calculating the pooled OR and the 95% CI. The association with BP was estimated by calculating the pooled mean differences and the 95% CI. The significance of the pooled effect size was determined by a *Z*-test ($P<0.05$ was considered statistically significant). A *Q*-test was performed to evaluate whether the variation was due to heterogeneity or by chance. A random (DerSimonian–Laird method[15])- or fixed (Mantel–Haenszel method[16])-effects model was used to calculate the pooled effect estimates in the presence ($P<=0.10$) or absence ($p>0.10$) of heterogeneity, respectively. Begg's funnel plot, a scatter plot of effect against a measure of study size, was generated as a visual aid to detect bias or systematic heterogeneity.[17] Publication bias was assessed by Egger's test[18]($P<0.05$ was considered statistically significant). Subgroup analysis by ethnicity was also performed. To evaluate the stability of the results, sensitivity analysis was performed by removing one study at a time. Data analysis was performed using STATA version 11 (StataCorp LP, College Station, TX, USA) as described previously.[19–23]

RESULTS

Characteristics of the studies

The literature search identified a total of 52 potentially relevant papers. Of these, 35 were excluded because of obvious irrelevance ascertained by reading the titles and abstracts. Some studies were excluded, because the subjects were pregnant women,[24] renal transplant patients,[25] coronary angioplasty patients[26] or coronary artery disease patients (INVEST-GENES cohort).[27] The subjects of two papers[28,29] were from the same cohort; therefore, only one paper was included.[29] One paper was excluded, because its study population contained only one *CYP3A5*3/*3* allele carrier.[30] Therefore, 12 papers met the inclusion criteria and were included in the meta-analysis.[27,29,31–40] Individuals carrying at least one *CYP3A5**1 allele were combined as *CYP3A5**1 carriers in one group (high expression), and individuals without a *CYP3A5**1 allele were combined as *CYP3A5**1 non-carriers in the other group (low expression). The characteristics of the included studies are listed in Tables 1 and 2.

Meta-analysis for determining the association with hypertension

Ten sub-studies with 2799 cases and 6794 controls were included to determine the association with hypertension.[27,33–35,38] Overall, there was evidence of heterogeneity between studies (P=0.064, I-squared=44.2%). Under a random-effects model, the meta-analysis result showed no association between the *CYP3A5* rs776746 polymorphism and hypertension (OR=1.123, 95% CI 0.906 to 1.394, P=0.290). In the subgroup analysis of groups stratified by ethnicity, the heterogeneity was not significant in the white subgroup ($p>0.10$), but it remained in black populations ($P<0.10$). The subgroup meta-analysis results showed that there was no association between the *CYP3A5* rs776746 polymorphism and hypertension in either white (OR=1.016, 95% CI 0.880 to 1.172, P=0.831) or black populations (OR=1.278, 95% CI 0.554 to 2.948, P=0.566; Figure 1 and Table 3). Sensitivity analysis was performed by excluding a single study at a time and similar results were obtained (data not shown).

Meta-analysis to determine the association with BP

Twelve sub-studies with 9076 subjects were included to determine the association with BP.[27,29,31,32,35–40] As shown in Figures 2 and 3, there was evidence of heterogeneity between studies (systolic BP (SBP):

Table 1 Characteristics of studies for association between *CYP3A5* polymorphism and hypertension

				Cases			*Controls*		
Study	*Ethnicity*	*No. (M/F)*	*Age, year, mean ± s.d. or range*	*CYP3A5*1 carriers*[a]	*CYP3A5*1 non-carriers*[b]	*Subtotal*	*CYP3A5*1 carriers*[a]	*CYP3A5*1 non-carriers*[b]	*Subtotal*
Ho[33]	White (IU)	271 (139/132)	NA	9	54	63	20	116	136
	Black (IU)			26	4	30	40	2	42
	White (UCSD)	412 (319/93)	NA	17	88	105	18	116	134
	Black (UCSD)			101	10	111	49	13	62
Kivisto[34]	White	373 (NA/NA)	⩾75	42	187	229	13	131	144
Kreutz[25]	White (men)	6777 (3344/3433)	49.0 ± 12.6	124	830	954	313	2077	2390
	White (women)		46.9 ± 11.8	69	491	560	395	2478	2873
Lieb[38]	White	1084 (554/530)	25–74	36	325	361	84	639	723
Langaee[27]	White (HG)	Cases: 187 (105/82)	Cases: 51.9 ± 7.6	30	157	187	18	148	166
		Controls: 166 (75/91)	Controls: 47.7 ± 8.2						
	Black (HG)	Cases: 199 (58/141)	Cases: 50.4 ± 8.2	119	80	199	69	55	124
		Controls: 124 (58/66)	Controls: 45.1 ± 7.3						

Abbreviations: HG, hypertension genes study; IU, study conducted at Indiana University; NA, not available; UCSD, study conducted at University of California, San Diego.
[a]*CYP3A5*1* carriers are individuals who carry one or two *CYP3A5*1* alleles.
[b]*CYP3A5*1* non-carriers are individuals who do not carry *CYP3A5*1* allele.

Table 2 Characteristics of studies for association between *CYP3A5* polymorphism and blood pressure

			*CYP3A5*1 carriers*[a]						*CYP3A5*1 non-carriers*[b]				
			Age, year, mean ± s.d.	*SBP, mmHg*		*DBP, mmHg*			*Age, year, mean ± s.d.*	*SBP, mmHg*		*DBP, mmHg*	
Study	*Ethnicity*	*No. (M/F)*		*Mean*	*s.d.*	*Mean*	*s.d.*	*No. (M/F)*		*Mean*	*s.d.*	*Mean*	*s.d.*
Givens[31]	Black	18 (8/10)	24.8 ± 9.5	128.8	10.9	69.8	8.2	7 (2/5)	25.0 ± 8.5	116.7	11	63.3	6.5
Fromm[32]	White	19 (19/0)	25.3 ± 3.3	126	10	76	8	96 (96/0)	25.7 ± 2.7	132	11	79	8
Kreutz[35]	White (men)	437 (437/0)	49.6 ± 12.9	131.6	16.9	76.2	9.1	2907 (2907/0)	48.1 ± 11.0	132.2	17.8	76.1	9.4
	White (women)	464 (0/464)	46.5 ± 11.8	120.0	17.4	69.4	8.7	2969 (0/2969)	47.0 ± 11.9	121.9	19.1	70.4	8.7
Bochud[29]	Black	261 (115/146)	46.8 ± 11.3	132.1	18.1	85.0	11.5	114 (51/63)	45.3 ± 12.2	130.5	16.3	83.7	11.3
Kim[37]	Asian	16 (NA/NA)	22.9 ± 2.2	122.5	3.1	74.0	4.1	24 (NA/NA)	23.2 ± 2.3	122.2	3.2	75.1	4.6
Lieb[38]	White	120 (53/67)	45.7 ± 13.2	131.0	16.1	80.4	10.7	964 (501/463)	49.2 ± 13.3	131.3	15.5	80.1	9.3
Marunde[36]	Black	90 (90/0)	23.6 ± 10.4	112.2	10.8	70.9	10.6	16 (16/0)	23.4 ± 9.5	113.5	6.8	75.1	6.7
Jin[39]	Mixed	13 (5/8)	34.1 ± 10.7	119.6	12.0	70.8	9.6	14 (5/9)	23.7 ± 5.3	114.5	7.0	67.2	5.5
Langaee[27]	White (HG)	22 (NA/NA)	NA	116.6	12.2	73.8	6.0	143 (NA/NA)	NA	117.2	12.2	75.3	8.3
	Black (HG)	118 (NA/NA)	NA	118.3	9.0	76.6	6.3	6 (NA/NA)	NA	118.6	9.4	77.6	5.3
Zhang[40]	Asian	135 (135/0)	46.3 ± 11.5	135.6	18.6	82.7	13.1	103 (103/0)	45.5 ± 12.1	133.5	16.4	80.1	11.6

Abbreviations: DBP, diastolic blood pressure; HG, hypertension genes study; NA, not available; SBP, systolic blood pressure.
[a]*CYP3A5*1* carriers are individuals who carry one or two *CYP3A5*1* alleles.
[b]*CYP3A5*1* non-carriers are individuals who do not carry *CYP3A5*1* allele.

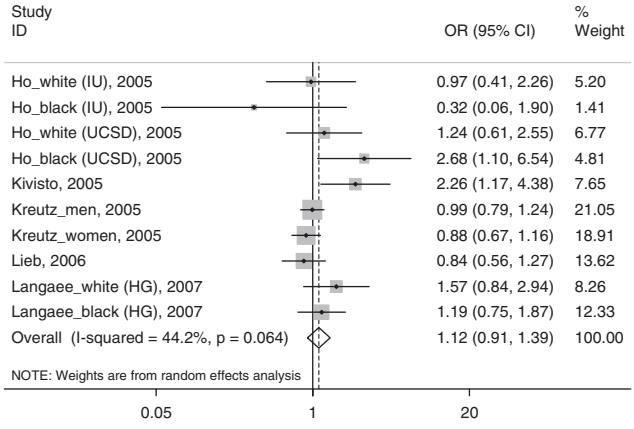

Figure 1 Forest plot of the meta-analysis of the association between the cytochrome P450 family 3 subfamily A polypeptide 5 (*CYP3A5*) polymorphism (*CYP3A5*1* carriers *vs.* *CYP3A5*1* non-carriers) and hypertension risk. A full color version of this figure is available at the *Hypertension Research* journal online.

P=0.056, I-squared=43.0%; diastolic BP (DBP): *P*=0.029, I-squared=48.8%). Overall, the meta-analysis results showed no association between the *CYP3A5* rs776746 polymorphism with either SBP or DBP (for SBP: mean difference=−0.242, 95% CI −1.576 to 1.093, *P*=0.722; for DBP: mean difference=−0.207, 95% CI −1.173 to 0.759, *P*=0.675). After stratification by ethnicity, the heterogeneity was not significant in white populations (*P*>0.10). The subgroup meta-analysis showed that, in white populations, *CYP3A5*1* carriers had significantly lower SBP compared with non-carriers (mean difference=−1.322, 95% CI −2.401 to −0.242 mm Hg, *P*=0.016; Figure 4 and Table 3). The stability of these results was also confirmed by sensitivity analysis (data not shown).

Publication bias

Begg's funnel plots were generated to assess potential publication bias (figures not shown). No publication bias was detected (Egger's test, *P*=0.243, 0.179 and 0.516 for the associations with hypertension, SBP and DBP, respectively).

Table 3 Subgroup analysis of the association of *CYP3A5* polymorphism (*CYP3A5*1* carriers *vs.* *CYP3A5*1* non-carriers) with hypertension and blood pressure by ethnicity

Group	*No. of studies*	*Statistical method*	*Effect size (95% CI)*	P-*value*
Hypertension[a]				
White	7	Fixed	1.016 (0.880, 1.172)	0.831
Black	3	Random	1.278 (0.554, 2.948)	0.566
All	10	Random	1.123 (0.906, 1.394)	0.290
SBP[b]				
White	5	Fixed	−1.322 (−2.401, −0.242)	0.016
Black	4	Random	1.700 (−2.430, 5.830)	0.420
Asian	2	Fixed	0.598 (−1.216, 2.413)	0.518
Mixed	1	—	5.100 (−2.383, 12.583)	0.182
All	12	Random	−0.242 (−1.576, 1.093)	0.722
DBP[b]				
White	5	Fixed	−0.521 (−1.099, 0.056)	0.077
Black	4	Random	0.260 (−3.380, 3.901)	0.889
Asian	2	Random	0.663 (−2.959, 4.285)	0.720
Mixed	1	—	3.600 (−2.361, 9.561)	0.237
All	12	Random	−0.207 (−1.173, 0.759)	0.675

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; SBP, systolic blood pressure.
[a]Odds ratio with (95% CI) was used to indicate the pooled effect size (95% CI).
[b]Weighted mean differences (95% CI) was used to indicate the pooled effect size (95% CI).

DISCUSSION

In this study, we performed a meta-analysis to investigate the association between the *CYP3A5* rs776746 polymorphism and BP/hypertension. Overall, no significant association was observed either for BP or hypertension. However, significant heterogeneity was found in the studies. In meta-analyses, it is well accepted that potential heterogeneity

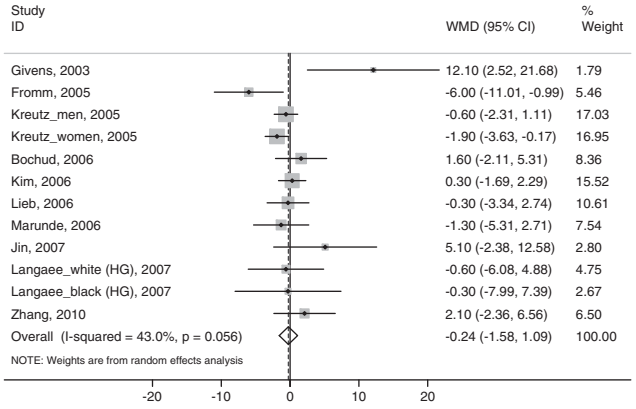

Figure 2 Forest plot of the meta-analysis of the association between the cytochrome P450 family 3 subfamily A polypeptide 5 (*CYP3A5*) polymorphism (*CYP3A5*1* carriers *vs. CYP3A5*1* non-carriers) and systolic blood pressure. A full color version of this figure is available at the *Hypertension Research* journal online.

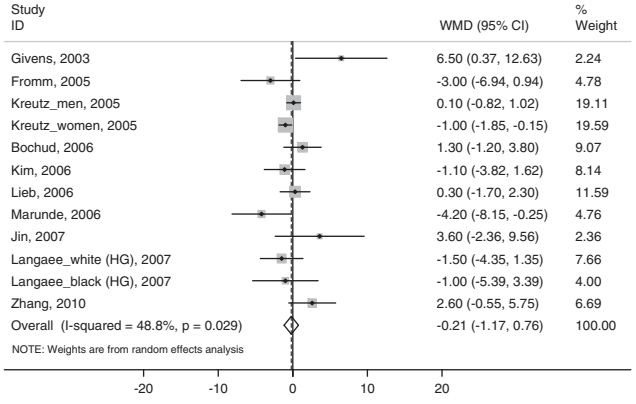

Figure 3 Forest plot of the meta-analysis of the association between the cytochrome P450 family 3 subfamily A polypeptide 5 (*CYP3A5*) polymorphism (*CYP3A5*1* carriers *vs. CYP3A5*1* non-carriers) and diastolic blood pressure. A full color version of this figure is available at the *Hypertension Research* journal online.

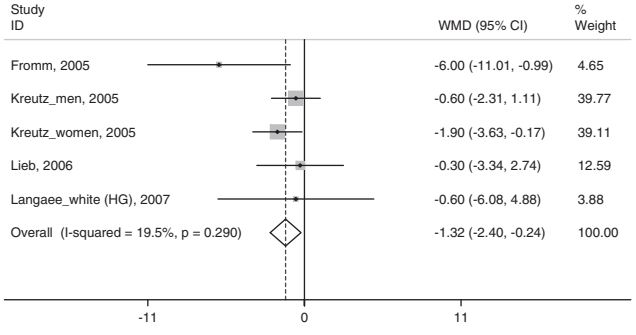

Figure 4 Forest plot of the meta-analysis of the association between the cytochrome P450 family 3 subfamily A polypeptide 5 (*CYP3A5*) polymorphism (*CYP3A5*1* carriers *vs. CYP3A5*1* non-carriers) and systolic blood pressure in white populations. A full color version of this figure is available at the *Hypertension Research* journal online.

between studies may interfere with the conclusions. Given the large interethnic differences in allele frequencies,[41] a subgroup analysis based on ethnicity was performed. Except for hypertension risks in blacks, heterogeneity was not significant within each ethnic group. We found a significant association between the *CYP3A5* rs776746 polymorphism and SBP in whites. The sensitivity analysis results confirmed these conclusions.

Currently, data on the association of *CYP3A5* polymorphisms with BP or hypertension are relatively limited. Givens *et al.*[31] first reported that the *CYP3A5*1* allele was associated with increased SBP, but not DBP in 25 African Americans. Since then, several studies have been performed to investigate the association in different ethnic populations; however, the results have been inconsistent. For example, a large population-based study (n=6777, age range: 28–75 years) by Kreutz *et al.*[35] showed that the *CYP3A5*1* allele was associated with lower SBP only in women. In a study of an elderly Finnish Caucasian population (n=373, age: ⩾75 years), *CYP3A5*1* carriers had a significantly greater hypertension risk.[34] In a Japanese population, the *CYP3A5*1* allele was associated with DBP, but not SBP, and further analysis showed that the significant association was observed only among **3/*3* carriers with high salt intake. This indicated that the *CYP3A5* rs776746 polymorphism might be a risk factor for salt sensitivity.[40]

The underlying biological mechanism by which *CYP3A5* exerts its effects on the pathogenesis of hypertension is still not known. As a potential intermediate phenotype, cortisol may have an important role in the regulation of BP levels and the development of hypertension.[42] Some previous studies suggest that excessive intrarenal conversion of cortisol to 6β-hydroxycoricosterone through increased renal CYP3A activity could enhance post-renal proximal tubular sodium reabsorption and thus result in elevated BP levels.[12,13] However, CYP3A could also protect the expression of corticosterone-induced active sodium transport in kidney cells by mineralocorticoid receptor-mediated mechanisms, which could then lead to decreased BP.[43] This may be the underlying mechanism by which the *CYP3A5*1* allele resulted in a lower SBP.

The current meta-analysis has advantages over individual studies; however, it does have some limitations. First, it was based primarily on unadjusted effect estimates and confidence intervals. Second, the methods for measuring BP were not uniform for the included studies (office BP *vs.* ambulatory BP monitoring). Third, there may also be an age effect, because in some populations, the *CYP3A5* genotype was associated with a different profile of BP increases with age. Fourth, the effect of gene–gene and gene–environment interactions (salt intake is an example of the latter) was not addressed in this meta-analysis. Finally, if the various populations are considered separately, the results of the subgroup analysis should be interpreted with caution because of limited statistical power. We anticipate that these issues will be addressed in future studies.

In summary, our meta-analysis suggested a modestly significant association between the *CYP3A5*1* genotype and a lower SBP in white populations. Given the strong interethnic differences in *CYP3A5**1 allele frequency, it is possible that the effects of *CYP3A5* may vary depending on the genetic context and physiological background. As the *CYP3A5* gene has been implicated in BP regulation, additional epidemiological, biological and clinical studies are required to further investigate the role of *CYP3A5* in the pathogenesis of hypertension.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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1 Lawes CM, Vander Hoorn S, Rodgers A. Global burden of blood-pressure-related disease, 2001. *Lancet* 2008; **371**: 1513–1518.
2 Whelton PK, He J, Appel LJ, Cutler JA, Havas S, Kotchen TA, Roccella EJ, Stout R, Vallbona C, Winston MC, Karimbakas J. Primary prevention of hypertension: clinical and public health advisory from The National High Blood Pressure Education Program. *JAMA* 2002; **288**: 1882–1888.
3 Binder A. A review of the genetics of essential hypertension. *Curr Opin Cardiol* 2007; **22**: 176–184.
4 Franceschini N, Reiner AP, Heiss G. Recent findings in the genetics of blood pressure and hypertension traits. *Am J Hypertens* 2011; **24**: 392–400.
5 Tanira MO, Al Balushi KA. Genetic variations related to hypertension: a review. *J Hum Hypertens* 2005; **19**: 7–19.
6 Ehret GB. Genome-wide association studies: contribution of genomics to understanding blood pressure and essential hypertension. *Curr Hypertens Rep* 2010; **12**: 17–25.
7 Wang C. Genetic association studies: hypertension and beyond. *Hypertension Res* 2011; **34**: 294–295.
8 Gellner K, Eiselt R, Hustert E, Arnold H, Koch I, Haberl M, Deglmann CJ, Burk O, Buntefuss D, Escher S, Bishop C, Koebe HG, Brinkmann U, Klenk HP, Kleine K, Meyer UA, Wojnowski L. Genomic organization of the human CYP3A locus: identification of a new, inducible CYP3A gene. *Pharmacogenetics* 2001; **11**: 111–121.
9 Eichelbaum M, Burk O. CYP3A genetics in drug metabolism. *Nat Med* 2001; **7**: 285–287.
10 Daly AK. Significance of the minor cytochrome P450 3A isoforms. *Clin Pharmacokinet* 2006; **45**: 13–31.
11 Haehner BD, Gorski JC, Vandenbranden M, Wrighton SA, Janardan SK, Watkins PB, Hall SD. Bimodal distribution of renal cytochrome P450 3A activity in humans. *Mol Pharmacol* 1996; **50**: 52–59.
12 Watlington CO, Kramer LB, Schuetz EG, Zilai J, Grogan WM, Guzelian P, Gizek F, Schoolwerth AC. Corticosterone 6 beta-hydroxylation correlates with blood pressure in spontaneously hypertensive rats. *Am J Physiol* 1992; **262**: F927–F931.
13 Ghosh SS, Basu AK, Ghosh S, Hagley R, Kramer L, Schuetz J, Grogan WM, Guzelian P, Watlington CO. Renal and hepatic family 3A cytochromes P450 (CYP3A) in spontaneously hypertensive rats. *Biochem Pharmacol* 1995; **50**: 49–54.
14 Kuehl P, Zhang J, Lin Y, Lamba J, Assem M, Schuetz J, Watkins PB, Daly A, Wrighton SA, Hall SD, Maurel P, Relling M, Brimer C, Yasuda K, Venkataramanan R, Strom S, Thummel K, Boguski MS, Schuetz E. Sequence diversity in CYP3A promoters and characterization of the genetic basis of polymorphic CYP3A5 expression. *Nat Genet* 2001; **27**: 383–391.
15 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**: 177–188.
16 Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959; **22**: 719–748.
17 Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; **50**: 1088–1101.
18 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**: 629–634.
19 Liu L, Zhuang W, Wang C, Chen Z, Wu XT, Zhou Y. Interleukin-8 -251 A/T gene polymorphism and gastric cancer susceptibility: a meta-analysis of epidemiological studies. *Cytokine* 2010; **50**: 328–334.
20 Sun L, Xi B, Yu L, Gao XC, Shi DJ, Yan YK, Xu DJ, Han Q, Wang C. Association of glutathione S-transferases polymorphisms (GSTM1 and GSTT1) with senile cataract: a meta-analysis. *Invest Ophthalmol Vis Sci* 2010; **51**: 6381–6386.
21 Wang R, Zhong B, Liu Y, Wang C. Association between alpha-adducin gene polymorphism (Gly460Trp) and genetic predisposition to salt sensitivity: a meta-analysis. *J Appl Genet* 2010; **51**: 87–94.
22 Wang R, Zhou D, Xi B, Ge X, Zhu P, Wang B, Zhou M, Huang Y, Liu J, Yu Y, Wang C. ENPP1/PC-1 Gene K121Q polymorphism is associated with obesity in european adult populations: evidence from a meta-analysis involving 24 324 subjects. *Biomed Environ Sci* 2011; **24**: 200–206.
23 Zhang S, Wang C, Xi B, Li X. Association between the tumour necrosis factor-alpha-308G/A polymorphism and chronic obstructive pulmonary disease: an update. *Respirology* 2011; **16**: 107–115.
24 Coto E, Tavira B, Marin R, Ortega F, Lopez-Larrea C, Ruiz-Ortega M, Ortiz A, Diaz M, Corao AI, Alonso B, Alvarez V. Functional polymorphisms in the CYP3A4, CYP3A5, and CYP21A2 genes in the risk for hypertension in pregnancy. *Biochem Biophys Res Commun* 2010; **397**: 576–579.
25 Kreutz R, Zurcher H, Kain S, Martus P, Offermann G, Beige J. The effect of variable CYP3A5 expression on cyclosporine dosing, blood pressure and long-term graft survival in renal transplant patients. *Pharmacogenetics* 2004; **14**: 665–671.
26 Suh JW, Koo BK, Zhang SY, Park KW, Cho JY, Jang IJ, Lee DS, Sohn DW, Lee MM, Kim HS. Increased risk of atherothrombotic events associated with cytochrome P450 3A5 polymorphism in patients taking clopidogrel. *CMAJ* 2006; **174**: 1715–1722.
27 Langaee TY, Gong Y, Yarandi HN, Katz DA, Cooper-DeHoff RM, Pepine CJ, Johnson JA. Association of CYP3A5 polymorphisms with hypertension and antihypertensive response to verapamil. *Clin Pharmacol Ther* 2007; **81**: 386–391.
28 Eap CB, Bochud M, Elston RC, Bovet P, Maillard MP, Nussberger J, Schild L, Shamlaye C, Burnier M. CYP3A5 and ABCB1 genes influence blood pressure and response to treatment, and their effect is modified by salt. *Hypertension* 2007; **49**: 1007–1014.
29 Bochud M, Eap CB, Elston RC, Bovet P, Maillard M, Schild L, Shamlaye C, Burnier M. Association of CYP3A5 genotypes with blood pressure and renal function in African families. *J Hypertens* 2006; **24**: 923–929.
30 Neville KA, Ayaji OE, Holland CL, Skaar TC, Hall SD. Association between CYP3A5 and blood pressure in nigerian males. *Clin Pharmacol Ther* 2005; **77**: P55–P55 (doi:10.1016/j.clpt.2004.1012.1099).
31 Givens RC, Lin YS, Dowling AL, Thummel KE, Lamba JK, Schuetz EG, Stewart PW, Watkins PB. CYP3A5 genotype predicts renal CYP3A activity and blood pressure in healthy adults. *J Appl Physiol* 2003; **95**: 1297–1300.
32 Fromm MF, Schmidt BM, Pahl A, Jacobi J, Schmieder RE. CYP3A5 genotype is associated with elevated blood pressure. *Pharmacogenet Genomics* 2005; **15**: 737–741.
33 Ho H, Pinto A, Hall SD, Flockhart DA, Li L, Skaar TC, Cadman P, O'Connor DT, Wagner U, Fineberg NS, Weinberger MH. Association between the CYP3A5 genotype and blood pressure. *Hypertension* 2005; **45**: 294–298.
34 Kivisto KT, Niemi M, Schaeffeler E, Pitkala K, Tilvis R, Fromm MF, Schwab M, Lang F, Eichelbaum M, Strandberg T. CYP3A5 genotype is associated with diagnosis of hypertension in elderly patients: data from the DEBATE Study. *Am J Pharmacogenomics* 2005; **5**: 191–195.
35 Kreutz R, Zuurman M, Kain S, Bolbrinker J, de Jong PE, Navis G. The role of the cytochrome P450 3A5 enzyme for blood pressure regulation in the general Caucasian population. *Pharmacogenet Genomics* 2005; **15**: 831–837.
36 Marunde R, Jin Y, Ayaji O, Neville K, Phillips S, Skaar TC, Hall SD. CYP3A5 genotypes and blood pressure in healthy Nigerian males. *Clin Pharmacol Ther* 2006; **79**: P67–P67 (doi:10.1016/j.clpt.2005.1012.1242).
37 Kim KA, Park PW, Lee OJ, Choi SH, Min BH, Shin KH, Chun BG, Shin JG, Park JY. Effect of CYP3A5*3 genotype on the pharmacokinetics and pharmacodynamics of amlodipine in healthy Korean subjects. *Clin Pharmacol Ther* 2006; **80**: 646–656.
38 Lieb W, Bolbrinker J, Doring A, Hense HW, Erdmann J, Schunkert H, Kreutz R. No association of the CYP3A5*1 allele with blood pressure and left ventricular mass and geometry: the KORA/MONICA Augsburg echocardiographic substudy. *Clin Sci (Lond)* 2006; **111**: 365–372.
39 Jin Y, Wang YH, Miao J, Li L, Kovacs RJ, Marunde R, Hamman MA, Philips S, Hilligoss J, Hall SD. Cytochrome P450 3A5 genotype is associated with verapamil response in healthy subjects. *Clin Pharmacol Ther* 2007; **82**: 579–585.
40 Zhang L, Miyaki K, Wang W, Muramatsu M. CYP3A5 polymorphism and sensitivity of blood pressure to dietary salt in Japanese men. *J Hum Hypertens* 2010; **24**: 345–350.
41 Xie HG, Wood AJ, Kim RB, Stein CM, Wilkinson GR. Genetic variability in CYP3A5 and its possible consequences. *Pharmacogenomics* 2004; **5**: 243–272.
42 Litchfield WR, Hunt SC, Jeunemaitre X, Fisher ND, Hopkins PN, Williams RR, Corvol P, Williams GH. Increased urinary free cortisol: a potential intermediate phenotype of essential hypertension. *Hypertension* 1998; **31**: 569–574.
43 Morris DJ, Latif SA, Rokaw MD, Watlington CO, Johnson JP. A second enzyme protecting mineralocorticoid receptors from glucocorticoid occupancy. *Am J Physiol* 1998; **274**: C1245–C1252.