Genetic Associations with Hypertension: Meta-Analyses of Six Candidate Genetic Variants

Cheng Zhang,^{1,*} Lingyan Wang,^{2,*} Qi Liao,¹ Lina Zhang,¹ Leiting Xu,¹ Cheng Chen,³ Huadan Ye,¹
Xuting Xu,¹ Meng Ye,³ and Shiwei Duan¹

Aims: The aim of this study was to perform combined analyses of six genetic variants for the risk of hypertension. **Methods:** After a comprehensive literature search for genetic variants involved with the association study of hypertension, we harvested a total of five genes (six variants) for the current meta-analyses. These genes consisted of *CYP4A11* (T8590C), *RGS2* (1891-1892del TC and G638A), *HTR2A* (T102C), *GNAS* (T393C), and *HSD3B1* (T→C Leu338). **Results:** A total of 20 studies among 13,816 cases and 19,248 controls were retrieved for the meta-analyses of six genetic variants. It was shown that the *RGS2* 1891-1892del TC (OR=1.10, 95% CI=1.02–1.19, $p=0.02$) polymorphism and the *CYP4A11* T8590C (OR=1.19, 95% CI=1.00–1.41, $p=0.05$) polymorphism were significantly associated with increased risk of hypertension. No association was found between the other four variants and the risk of hypertension. **Conclusion:** This meta-analysis revealed that the *RGS2* 1891-1892del TC polymorphism and *CYP4A11* T8590C polymorphism were associated with hypertension risk. However, *HSD3B1* T→C Leu338, *HTR2A* T102C, *GNAS* T393C, and *RGS2* G638A polymorphisms were not associated with hypertension risk.

Introduction

HYPERTENSION HAS BEEN IDENTIFIED as the leading risk factor for mortality and is ranked third among the causes of disability-adjusted life years (Ezzati *et al.*, 2002; Chobanian *et al.*, 2003). In 2000, an estimated 26.4% (972 million) of the world's adult population was recorded as hypertensive. This number is projected to increase by 60% to a total of 1.56 billion by 2025 (Kearney *et al.*, 2005). It is now recognized that small vessel disease plays a role in the pathogenesis of hypertension (Rizzoni *et al.*, 1994).

Hypertension is a complex disease influenced by genes, environmental factors, and their interactions (Harrison *et al.*, 2008). Twin and family studies have suggested that approximately 20%–60% of blood pressure variation could be attributed to genetics (Kurtz and Spence, 1993). Up to now, many candidate genes have been reported to be implicated in the regulation of blood pressure and the susceptibility of hypertension (Halushka *et al.*, 1999; Kohara *et al.*, 2008; Sober *et al.*, 2009). In addition, several genome-wide association studies also identified many susceptibility loci, which were associated with blood pressure and hypertension (Levy *et al.*, 2009; Newton-Cheh *et al.*, 2009).

HSD3B1 is exclusively expressed as 3 β -HSD in the placenta and peripheral tissues, including in the mammary gland,

prostate, and skin. *HSD3B1* is the susceptibility gene for hypertension. In humans, a genetic variation in *HSD3B1* can lead to an elevation in plasma aldosterone with a resultant increase in the intravascular volume and blood pressure (Rheume *et al.*, 1991; Simard *et al.*, 1996). *HTR2A* encodes the 5HT_{2a} receptor, which is expressed in the peripheral vasculature and has been implicated in hypertension due to its vasoconstrictive effect (Hoyer *et al.*, 1994). *GNAS* encodes the G α s subunit of the stimulatory G protein, which is expressed in a tissue-specific manner. The TT genotype of the 393T>C polymorphism of the *GNAS1* gene, which is associated with higher G α s expression levels in different tissues, for example, heart tissue, is also associated with an increased pulse rate during opiate withdrawal (Frey *et al.*, 2005). *CYP4A11* acts mainly as an enzyme that converts arachidonic acid (AA) to 20-hydroxyeicosatetraenoic acid (20-HETE), and has a crucial role in the modulation of cardiovascular homeostasis (Zordoky and El-Kadi, 2010). The relationship between the polymorphisms of the *CYP4A11* gene and hypertension as well as cerebral infarction has been established (Muthalif *et al.*, 1998; Gainer *et al.*, 2005). *RGS2* interacts with the G-subunits of heterotrimeric G proteins, accelerating the rate of GTP hydrolysis and finalizing the intracellular signaling. It may be the most potent GTPase-activating protein for Gq α mediating

¹Zhejiang Provincial Key Laboratory of Pathophysiology, School of Medicine, Ningbo University, Ningbo, Zhejiang, China.

²Bank of Blood Products, Ningbo No. 2 Hospital, Ningbo, Zhejiang, China.

³The Affiliated Hospital, Ningbo University, Ningbo, Zhejiang, China.

*These two authors are cofirst authors of this work.

the action of a wide variety of key neurotransmitters and hormones that are active in the cardiovascular system (Ross and Wilkie, 2000; Tang *et al.*, 2003). From a theoretical standpoint, genetic alterations of *RGS2* may contribute to the development of hypertension in humans.

Associations between single-nucleotide polymorphisms (SNPs) of the above five genes and hypertension have been reported in different ethnic groups (Abe *et al.*, 2002; Yamamoto *et al.*, 2006; Fu *et al.*, 2008; Shimodaira *et al.*, 2010; Kamide *et al.*, 2011). Since the allelic frequencies of genes often differ substantially in different ethnic groups, meta-analysis may help compare the genetic associations in different populations. In the present study, we evaluate the combined contribution of the SNPs in these genes to hypertension susceptibility in different populations using a meta-analysis approach.

Materials and Methods

Publication search and selection criteria

Articles were identified by a search of the following electronic databases: PubMed (www.ncbi.nlm.nih.gov/pubmed),

Embase (www.elsevier.com/online-tools/embase), Web of Science (thomsonreuters.com/products_services/science/science_products/a-z/web_of_science), Wanfang data base (www.wanfangdata.com.cn), and China National Knowledge Infrastructure (CNKI; www.cnki.net). The search terms used the keywords and Medical Subject headings: "hypertension," "polymorphism," "allele," "genotype," and "SNP" published from 2001 to 2012. The publications eligible for the present meta-analyses should be case-control studies on hypertension, addressing the following polymorphisms: T8590C in *CYP4A11*, 1891-1892del TC and G638A in *RGS2*, T102C in *HTR2A*, T393C in *GNAS*, or T→C Leu338 in *HSD3B1* gene. The flow diagram of our meta-analyses is shown in Figure 1.

Data extraction

We carefully extracted information from the eligible articles. We read the articles and identified the SNPs that were analyzed in at least three articles and never had a meta-analysis concerning hypertension. The following data were extracted from each article: the PMID, the first author's name, year of publication, ethnic group, number of

FIG. 1. Flow diagram of meta-analyses.

genotypes, genotyping, and total number of cases and controls.

Statistical analysis

All statistical analyses were performed using the REVMAN software (version 5.0; Cochrane Collaboration, Oxford, United Kingdom). In our meta-analysis, we used Cochran's Q and the inconsistency index (I^2) statistic to measure heterogeneity (Lau *et al.*, 1997). Substantial heterogeneity was defined when I^2 is greater than or equal to 50%. The OR with 95% CI was used to estimate the strength of association between genetic variants and hypertension. The combined ORs and the corresponding 95% CIs were based on either the fixed-effect ($I^2 < 50\%$) or random-effect model ($I^2 \geq 50\%$) (Mantel and Haenszel, 1959; DerSimonian and Laird, 1986; DerSimonian and Kacker, 2007). The Z-test was used to

determine the pooled OR. A $p < 0.05$ was considered as significant.

Results

As shown in Figure 1, our initial search for the genetic studies of hypertension retrieved 2697 articles from PubMed, Embase, Web of Science, CNKI, and Wanfang from 2001 to 2012. Among them, 1785 studies have addressed genes reported in previous meta-analyses and thus they were excluded in further analysis. A total of 892 articles were again filtered out because they did not meet the criteria that the chosen articles must accumulate at least three independent genotypic datasets for the same genetic variants so that this study would be statistically significant. At last, 20 case-control studies of 6 SNPs from 20 articles were included in the current meta-analyses (Table 1).

FIG. 2. Forest plot for the six polymorphisms associated with the risk of hypertension.

No evidence of statistical heterogeneity was observed for four SNPs (Fig. 2), including T→C Leu 338 of *HSD3B1* ($I^2=22\%$), T102C of *HTR2A* ($I^2=41\%$), T393C of *GNAS* ($I^2=0\%$), and G638A of *RGS2* ($I^2=0\%$). No visual bias was shown in the meta-analyses of these four SNPs (Fig. 3). Meta-analysis of *GNAS* T393C polymorphism included three studies (Abe *et al.*, 2002; Chen *et al.*, 2003; Yamamoto *et al.*, 2004) among 1933 hypertension cases and 4003 controls. As shown in Figure 2, our result indicated that 1891-1892del TC of the *RGS2* gene was significantly associated with hypertension risk in the Japanese, Chinese, and Xinjiang Kazakh populations (the overall OR=1.10, 95% CI=1.02–1.19, $p=0.02$). Meta-analysis of T8590C of *CYP4A11* among 1871 hypertension cases and 1978 controls (Gainer *et al.*, 2005; Mayer *et al.*, 2005, 2006; Fu *et al.*, 2008; Sugimoto *et al.*, 2008) indicated that the *CYP4A11* T8590C polymorphism was significantly associated with hypertension risk in the Tennessee, Augsburg, Japanese, and German populations (Fig. 2, the overall OR=1.19, 95% CI=1.00–1.41, $p=0.05$). For the other four SNPs, our meta-analyses were unable to find significant associations of them with hypertension.

Discussion

The present meta-analyses encompassed 13,816 hypertension cases and 19,248 controls for the association analyses of

five genes. The meta-analysis of *RGS2* 1891-1892del TC indicates a significant contribution of this polymorphism to the risk of hypertension. In addition, our results conclude that the *CYP4A11* T8590C polymorphism is moderately associated with hypertension risk, which is in accordance with previous observations (Gainer *et al.*, 2005; Mayer *et al.*, 2005, 2006; Fu *et al.*, 2008; Sugimoto *et al.*, 2008). Under a moderate risk of hypertension (OR=1.2), power analysis showed that there was a lack of power for T→C Leu338 of *HSD3B1* (51.3%). This may partly explain why we cannot observe a positive association for T→C Leu338 of the *HSD3B1* gene.

Signaling by G-protein-coupled neurotransmitter receptors governs both blood pressure and electrolyte and fluid balance by the kidney (Takahashi and Smithies, 1999; Lifton *et al.*, 2001). The regulator of G protein signaling (RGS) proteins is important in regulating signaling cascades initiated by G-protein-coupled receptors (GPCRs) activation (De Vries *et al.*, 2000). RGS proteins facilitate the intrinsic inactivation of guanosine triphosphatase activity of G-protein α -subunits, and thereby serve as effector channel blockers. *RGS2* is unique among the RGS proteins in its apparent selectivity toward Gpa, which mediates the action of mouse physiological vasoconstrictors, including norepinephrine, angiotensin II, endothelin-1, and thrombin. *RGS2* also attenuates Gi- and Gs-mediated pathways (Ingi *et al.*, 1998; Sinnarajah *et al.*,

FIG. 3. Funnel plot for the six genetic variants involved in the meta-analyses.

TABLE 1. CHARACTERISTICS OF THE SIX GENETIC VARIANTS ASSOCIATED WITH HYPERTENSION

Gene	SNP	Year	Author	Ethnic group	Genotype (case/control)			Allele (case/control)	
HSD3B1	T→C Leu338	2002	Rosmond <i>et al.</i>	Swedish	TT	TC	CC	T	C
		2004	Speirs <i>et al.</i>	Australian	4/26	20/68	15/21	28/120	50/110
		2010	Shimodaira <i>et al.</i>	Japanese	20/60	71/109	32/61	111/229	135/231
					122/129	114/133	39/24	358/391	192/181
HTR2A	T102C				CC	CT	TT	C	T
		2001	Lioltisa <i>et al.</i>	British	124/87	172/174	46/58	420/348	264/290
		2004	Yu <i>et al.</i>	Chinese	34/31	68/67	96/66	136/129	260/199
		2006	Yamamoto <i>et al.</i>	Japanese	298/467	517/899	287/500	1113/1833	1091/1899
GNAS	T393C				TT	TC	CC	T	C
		2002	Abe <i>et al.</i>	Japanese	297/532	486/904	184/404	1080/1968	854/1712
		2003	Chen <i>et al.</i>	Japanese	238/500	342/776	119/333	818/1776	580/1442
		2004	Yamamoto <i>et al.</i>	Japanese	87/187	126/254	54/113	300/628	234/480
CYP4A11	T8590C				TT	CT	CC	T	C
		2005	Gainer <i>et al.</i>	American	126/152	64/41	5/4	316/345	74/49
		2005	Mayer <i>et al.</i>	German	481/574	149/164	19/10	1111/1312	187/184
		2006	Mayer <i>et al.</i>	German	152/250	68/79	8/3	372/579	84/85
		2008	Fu <i>et al.</i>	Japanese	179/133	122/64	3/10	480/330	128/84
		2008	Sugimoto <i>et al.</i>	Japanese	325/326	157/153	13/15	807/805	183/183
					II	ID	DD	I	D
RGS2	1891-1892del TC	2005	Yang <i>et al.</i>	Japanese	257/420	391/513	123/169	905/1353	637/851
		2008	Zhao <i>et al.</i>	Chinese	690/758	1229/1168	474/411	2609/2684	2177/1990
		2010	Li <i>et al.</i>	Xinjiang Kazak	177/227	214/215	53/47	568/669	320/309
		2011	Kamide <i>et al.</i>	Japanese	300/646	410/862	124/272	1010/2154	658/1404
RGS2	G638A				GG	GA	AA	G	A
		2005	Yang <i>et al.</i>	Japanese	174/220	389/554	208/328	737/994	805/1210
		2008	Kohara <i>et al.</i>	Japanese	603/663	1520/1837	1104/1224	2726/3163	3728/4285
		2009	Ruixing <i>et al.</i>	Chinese	46/165	118/446	93/254	210/776	304/954
		2011	Kamide <i>et al.</i>	Japanese	174/369	413/890	243/519	761/1628	899/1928

SNP, single-nucleotide polymorphism.

2001), suggesting that it can affect blood pressure via other physiologically important agonists such as serotonin, dopamine, and bradykinin.

The mechanisms by which the common SNP 1891-1892TC I/D of the *RGS2* gene might contribute to hypertension are unknown. The 1891-1892TC I/D is located in an intronic region (Riddle *et al.*, 2006). Although functions of introns are largely unknown, introns contain several short sequences important for efficient splicing by the spliceosome (Trapnell *et al.*, 2009). Further investigation is critically needed to determine whether 1891-1892TC I/D could change *RGS2* function. In addition, 1891-1892TC I/D may be a mere genetic marker and it may be in linkage disequilibrium with other functional polymorphisms that play important roles in the pathogenesis of hypertension. Therefore, a greater density of genotyping around the *RGS2* or 1891-1892TC I/D site is needed.

CYP4A11 converts AA to 20-HETE, which acts in either a prohypertensive or antihypertensive manner depending on whether it is expressed at renovascular or tubular sites in the kidney, respectively. In the renal tubule, 20-HETE blocks sodium transport and acts primarily as a natriuretic, antihypertensive substance. In the renal vasculature, 20-HETE has vasoconstricting and prohypertensive effects (McGiff and Quilley, 2001; Roman, 2002). Both animal and human studies (Carroll and McGiff, 2000; McGiff and Quilley, 2001; Laffer *et al.*, 2003a, 2003b) indicate that the *CYP4A11* gene is a candidate gene of hypertension. A variant of the human *CYP4A11* (T8590C) encodes for a monooxygenase with a reduced 20-HETE synthase activity. The association of the

T8590C variant with hypertension supports its role as a polygenic determinant of blood pressure control in humans. The results obtained from the large population database further suggest that the relevance of the variant may vary according to hypertension comorbidity (Gainer *et al.*, 2005).

CYP4A11 T8590C is a risk factor of hypertension in the Tennessee, Augsburg, Japanese, and German populations. However, the effects of the *CYP4A11* T8590C polymorphism on the four ethnic groups are different, due to the hereditary, environmental, climatical, and dietetical diversities. The hypertension meta-analysis of the *CYP4A11* T8590C polymorphism in the Japanese population shows OR of 1.05 (0.68, 1.62) and 1.00 (0.72, 1.37), suggesting that the risk in the Japanese population is relatively small, compared to the Augsburg population (OR=1.21, 95% CI=0.89–1.64), the Tennessee population (OR=1.52, 95% CI=0.95–2.41), and the German population (OR=1.61, 95% CI=0.93–2.80, Fig. 2).

There are some limitations in our study and the results should be interpreted with caution. First, such a result could be owing to a small number of studies that may lead to insufficient statistical power to find a slight effect or a fluctuated risk estimate. Second, the inconsistent conclusion of this analysis may be related to case selection, regional difference, diet and lifestyle of cases, genetic background, and other factors. Third, the positive results reported in the studies may lead to publication bias and heterogeneity in the results of different populations.

In conclusion, we identified significant associations between two SNPs (1891-1892del TC of the *RGS2* gene and T8590C of

the *CYP4A11* gene) and hypertension. Meta-analysis among 10,150 samples confirmed that the *RGS2* 1891-1892del TC is a risk factor of hypertension in the Japanese, Chinese, and Xinjiang Kazakh populations. Another meta-analysis among 3849 samples suggested that *CYP4A11* T8590C is a risk factor of hypertension in the Tennessee, Augsburg, Japanese, and German populations.

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Author Disclosure Statement

No competing financial interests exist.

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Address correspondence to:

Shiwei Duan, PhD

Zhejiang Provincial Key Laboratory of Pathophysiology

School of Medicine

Ningbo University

Ningbo

Zhejiang 315211

China

E-mail: duanshiwei@nbu.edu.cn

Meng Ye, MD

The Affiliated Hospital

Ningbo University

Ningbo

Zhejiang 315000

China

E-mail: yemeng@nbu.edu.cn