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A Meta-Analysis of Candidate Gene Polymorphisms and Ischemic Stroke in Six Study Populations: Association of Lymphotoxin-alpha in Non-hypertensive Patients

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Abstract

Background and Purpose—Ischemic stroke is a multifactorial disease with a strong genetic component. Pathways including lipid metabolism, systemic chronic inflammation, coagulation, blood pressure regulation, and cellular adhesion have been implicated in stroke pathophysiology, and candidate gene polymorphisms in these pathways have been proposed as genetic risk factors.

Methods—We genotyped 105 simple deletions and single nucleotide polymorphisms from 64 candidate genes in 3550 patients and 6560 controls from six case-control association studies conducted in the United States, Europe and China. Genotyping was performed using the same immobilized probe typing system and meta-analyses were based on summary logistic regressions for each study. The primary analyses were fixed-effects meta-analyses adjusting for age and sex with additive, dominant and recessive models of inheritance.

Results—Although seven polymorphisms showed a nominal additive association, none remained statistically significant after adjustment for multiple comparisons. In contrast, after stratification for hypertension, two lymphotoxin-alpha polymorphisms which are in strong linkage disequilibrium were significantly associated among non-hypertensive individuals: for LTA 252A>G (additive model), OR=1.41 with 95% CI, 1.20 to 1.65, p=0.00002; for LTA 26Thr>Asn, OR 1.19 with 95% CI, 1.06 to 1.34, p=0.003. LTA 252A>G remained significant after adjustment for multiple testing

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using either the false discover rate or by permutation testing. The two SNPs showed no association in hypertensive subjects (eg, LTA 252A>G, OR=0.93; 95%CI, 0.84 to 1.03, p=0.17).

Conclusions—These observations may indicate an important role of LTA-mediated inflammatory processes in the pathogenesis of ischemic stroke.

Indexing terms

ischemic stroke; hypertension; inflammation; genetics

Ischemic stroke is a complex multi-factorial and polygenic disorder thought to reflect interactions between an individual's genetic background and various environmental components. Previous studies have established hypertension, smoking, diabetes mellitus, body mass index and age as reliable stroke-risk predictors[1,2]. However, these conventional stroke risk factors do not fully account for the overall risk of stroke. Several physiological pathways, including lipid metabolism, blood pressure regulation, coagulation, and cellular adhesion are thought to play critical roles in stroke pathophysiology.

Among the known risk factors for ischemic stroke, hypertension contributes significantly to the onset of disease. Increased risk of stroke is not, however, limited to those with hypertension and the conventional stroke risk factors do not fully explain the risk among normotensives. Strategies to identify additional risk factors include stratification by hypertension[3,4] and using blood pressure as a matching criterion for cases and controls[5]. A key role for inflammation is suggested by observations that hypertensive patients have elevated circulating levels of markers of inflammation and that some anti-hypertensive therapies reduce both levels of pro-inflammatory markers and the risk of ischemic stroke, in addition to lowering blood pressure[6].

Both systemic and local inflammatory processes are implicated in the etiology of ischemic cerebrovascular disease and in the pathophysiology of cerebral ischemia[7]. Viral and bacterial infections are independent risk factors for ischemic stroke[8] and increased levels of systemic inflammatory markers such as C-reactive protein (CRP), leukocyte count, and fibrinogen are associated with increased risk of ischemic stroke[9]. Moreover, many stroke-related diseases such as Alzheimer's disease and atherosclerosis are initiated or worsened by systemic inflammation[10,11]. Polymorphisms in the CRP gene have been recently associated with both circulating protein levels and cardiovascular events[12], demonstrating the potential impact of genetic variation. Pro-inflammatory cytokines are believed to play a pathogenic role in these diseases, and variations in cytokine genes have also been shown to influence both predisposition and penetrance by altering the transcription profile and pattern of pro-inflammatory cytokine production[13]. For example, polymorphism in the lymphotoxin-alpha gene can enhance transcription and susceptibility to myocardial infarction[14]. At the local level, migration of inflammatory cells to the vascular wall is associated with vascular changes leading to atherosclerosis, and early atherosclerotic lesions are preceded by inflammatory cell deposition in the sub-endothelial layer of major cerebral arteries and in small brain vessels[15]. Genetic variants influencing inflammatory processes could potentially contribute to the etiology of stroke.

The complex etiology of stroke suggests that individual genetic polymorphisms have modest effects that are difficult to detect, as has been observed to date[16]. Large studies are needed to assess these polymorphisms as risk factors. Here we report a six-study meta-analysis to investigate the associations of 105 simple deletions and single nucleotide polymorphisms (SNPs) in inflammatory and cardiovascular system-related genes with susceptibility to ischemic stroke. To search for genetic risk factors contributing to ischemic stroke beyond hypertension, we stratified the study cohort on hypertension status.

Materials and Methods

Study Sample Description

As part of the Roche Stroke SNP Consortium, results of six independent studies (Table 1) were pooled for this analysis. All six study samples were comprised of individuals with proven ischemic stroke status and healthy controls. All studies were approved by the local ethics committees and all participants gave informed consent. Briefly, the study subjects were recruited as follows:

Physician's Health Study (PHS)—A nested case-control sample (319 cases, 2092 controls) was derived from the PHS cohort consisting of 22,071 predominantly Caucasian U.S. male physicians initially free of prior myocardial infarction, stroke, transient ischemic attack and cancer, who were enrolled in a placebo controlled trial of aspirin and beta-carotene for the primary prevention of cardiovascular disease and cancer[17]. DNA was isolated from baseline blood samples provided by 14,916 (68%) of the participants. Incident cases of ischemic stroke were identified during an average 13-year follow-up, and confirmed by medical record review. Controls were selected from study participants remaining free of reported cardiovascular disease, and matched to cases of any cardiovascular disease by age, smoking, and time since study entry[18].

Study of Osteoporotic Fractures (SOF)—Ambulatory women were recruited from four clinical centers in Portland, Oregon; Minneapolis, Minnesota; Baltimore, Maryland; and the Monongahela Valley, Pennsylvania[19]. The SOF cohort consists of 9615 white women of at least 65 years of age who had not had bilateral hip replacement or earlier hip fracture at the time of recruitment. The stroke subgroup included here consists of 247 who suffered adjudicated ischemic strokes and 559 controls who remained free of stroke through the mean follow-up of 5.4 years. Individuals who died during follow-up were included in both cases and controls, avoiding survivor bias.

Westphalia, Germany—Cases (n = 700) were recruited through the regional Westphalian Stroke Register in northwestern Germany[20]. Standardized patient documentation included socio-demographic characteristics, comorbidities, stroke type and severity as well as details regarding the diagnostic and therapeutic procedures and complications; 96.8% had at least one CT or MRI of the brain during hospitalization. Controls (n = 757) were recruited from the population-based Dortmund Health Study, conducted in the same region[21]. Participants in this study were randomly drawn from the city's registration office within 5-year age groups and stratified by sex. Medical histories were assessed in face to face interviews.

Pomerania, Germany—Cases (n = 277) were recruited with a standardized patient assessment form; 96.5% had at least one CT or MRI during hospitalization. Controls for this region were recruited from the population-based Study of Health in Pomerania (SHIP)[22]. Participants in SHIP were 20- to 79-year-olds randomly sampled from registration offices in the area. Face-to-face interviews with each participant included a short stroke symptom questionnaire. A random sample of 702 SHIP participants who were free of self-reported stroke and within the same age range and sex distribution as the cases, formed the control group.

Vienna Stroke Study—In the Vienna Stroke Registry, cases (n= 844) consisted of consecutive Caucasian patients submitted to one of nine stroke units within 72 hours of symptom onset of acute ischemic stroke. Patients who died on the way to the hospital or were first admitted to an intensive care unit were not included[23]. All patients underwent cranial CT or MRI and were documented according to a standardized protocol including stroke severity, risk factors and medical history (with particular reference to vascular diseases). Controls (n =

979) were voluntary participants in a health care program offered by the city of Vienna, were free of clinically manifest arterial vascular disease and reported no arterial vascular diseases in first degree relatives.

Stroke Hypertension Investigation in Genetics (SHINING)—Individuals were recruited from six geographical regions within China; 70% came from in and near Beijing. Cases (n = 1163) were individuals who had suffered a stroke within the previous 5 years, as diagnosed by brain CT/MRI. The original goal was to identify SNPs that predispose to stroke independent of blood pressure, thus randomly drawn population-based controls were initially individually matched to cases by sex, birth year ±3 yrs, geographic location, and blood pressure category (<140/90, ≥140/90 and ≤180/105, >180/105). Because some cases could not be matched, additional controls were recruited for a total of 1471 controls[5].

Genotyping

A total of 105 polymorphisms from 64 genes were selected based on reported associations in the literature, as well as on evidence of gene product involvement in cardiovascular disease and inflammatory processes. As previously described[24,25], three separate multi-locus polymerase chain reactions (PCRs) were carried out using biotinylated primer pools (Roche Molecular Systems, Inc., CA). The resulting PCR product pools were denatured and hybridized to linear arrays of immobilized, sequence-specific oligonucleotide probes. Hybridized amplicon was detected using a streptavidin-horseradish peroxidase conjugate and a chromogenic substrate. Laboratory technicians were blinded to the case-control status of each sample. Genotype assignments were made either manually and independently by two researchers or made by capturing images with a flatbed scanner and then using proprietary software developed by Roche Molecular Systems to resolve probe signals into genotypes for all polymorphisms. Discordant or ambiguous results were resolved by repeat PCR or hybridization. Twenty polymorphisms were not available for PHS and 23 polymorphisms were genotyped in only a subset of the Vienna Stroke participants; for these, genotypes were obtained for >90.5% of the individuals typed. For each of the 62 polymorphisms genotyped for all 10,110 subjects across all six studies, the final genotype database was ≥97.5% complete. For the *LTA* [MIM 153440] 252A>G and *LTA* 26Thr>Asn polymorphisms, in particular, the database contained 6090 (not available for PHS) and 10,091 genotypes (99.8% complete), respectively.

Statistical analysis

Individual level data were provided from each study site to the Coordinating Center at the Brigham and Women's Hospital in Boston. Pre-specified inclusion criteria for the meta-analyses were: age of at least 20 years and no prior history of myocardial infarction. Cases were restricted to those experiencing an ischemic stroke and controls had no previous history of stroke.

Allele and genotype frequencies were estimated by study site among cases and controls separately using SAS GENETICS. Tests for Hardy-Weinberg equilibrium (HWE), both large-sample and exact, were conducted among cases and controls for each site (Supplementary Table 1). Results for the effect of each SNP on ischemic stroke were estimated for each study separately using logistic regression. Each analysis controlled for age and sex, and assessed genetic effects under three modes of inheritance: additive, dominant, and recessive. In addition, analyses were conducted for each site using all three genotypes, using a two-degree of freedom test.

Meta-analyses were conducted based on the summary logistic regression results for each study site[26]. The primary analyses were fixed effects meta-analyses adjusting for age and sex. These meta-analyses were also conducted across Caucasians only (data not shown), since these

comprised the majority of participants for five of the six studies. Effects for each of the three modes of inheritance were estimated. PROC MIXED of SAS was used for effect estimation. Tests for heterogeneity of the genetic effect across sites were conducted using the Q-statistic[27]. For comparison, random effects models were estimated which allowed the genetic effect to vary across sites using study-specific effect estimates and PROC MIXED of SAS. To adjust for multiple comparisons, the false discovery rate (FDR)[28] was computed and stepdown permutation tests were conducted for selected comparisons[29].

Other pre-specified analyses adjusted for hypertension as well as age and sex. Across all studies, hypertensives were defined as having current or past anti-hypertensive medication, systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg. Additional smoking-adjusted analyses were limited to five studies due to the limited availability of smoking data for the Westphalian study participants. Subgroup analyses were conducted according to age, sex, presence of hypertension, or smoking (ever vs. never).

Results

A total of 3550 stroke patients and 6560 controls were genotyped with inflammation and cardiovascular SNP panels in six study sites with common methodology and genotyping software. The characteristics of all participants from six study sites are listed in Table 1. Two studies were drawn from prospective cohorts; the PHS study followed only male subjects and the SOF study followed only female subjects. The SHINING study was comprised of subjects of Han ethnicity, while the five other study populations were >99% Caucasian. There was a greater proportion of hypertension among cases than in controls, except in the SHINING study subset, for which blood pressure had been matched between the majority of cases and controls.

Table 2 lists the results obtained in the primary fixed-effects meta-analysis for all polymorphic sites under dominant, additive and recessive genetic modes of inheritance; similar results were observed under a random effects meta-analysis (data not shown). Nine SNPs were nominally significant ($P < 0.05$) under at least one mode of inheritance: *ADRB3* [MIM 109691] Trp64Arg, *CETP* [MIM 118470] (−629)C>A, *GNB3* [MIM 139130] 825C>T, *IL4* [MIM 147780] (−590) C>T, *LIPC* [MIM 151670] (−480)C>T, *LPL* [MIM 609708] Ser447Ter, *NOS3* [MIM 163729] (−690)C>T, *PON2* [MIM 602447] Ser311Cys and *TGFB1* [MIM 190180] (−509)C>T. To account for multiple hypothesis testing, the false discovery rate or permutation testing was applied and none of these SNPs remained statistically significantly associated with ischemic stroke. Among Caucasian participants only, the same *GNB3*, *LPL*, *NOS3*, *PON2* and *TGFB1* SNPs were nominally significant under at least one mode of inheritance, in addition to eight others (*APOB* [MIM 107730] 71Ile>Thr, *APOC3* [MIM 107720] 3175C>G, *CCR5* [MIM 601373] (−2459)G>A, *IL6* [MIM 147620] (−174)G>C, *IL10* [MIM 124092] (−571)C>A , *ITGA3* [MIM 192974] 873G>A, *NOS2A* [MIM 163730] 231C>T, *TNF* [MIM 191160] (−376) G>A), but none of the SNPs remained statistically significant after the false discovery rate was applied (data not shown).

The data were then stratified on age, sex, hypertension or smoking status. No statistically significant associations were observed in the age- (Supplementary Table 2A) or sex-stratified (Supplementary Table 2B) analyses, nor among those with current or past hypertension (Table 3) after adjusting for the FDR. In contrast, a large number of nominally significant associations with ischemic stroke among normotensives were observed (Table 4). The strongest associations under the additive and dominant models were for *LTA* 252A>G and *LTA* 26Thr>Asn, two SNPs in strong linkage disequilibrium, while *NOS3* 298Glu>Asp had the strongest association under the recessive model. After adjusting for FDR and permutation testing, only the *LTA* 252A>G SNP showed significant association among those without hypertension. In the additive mode, the estimated relative risk across the three *LTA* 252

genotypes was 1.41 (p=0.00002) in the fixed effects analysis and the FDR was 0.002, with p<0.01 in permutation testing. Results for the dominant model were similar (OR = 1.57, FDR = 0.005). In the random effects meta-analysis (data not shown), the *LTA* 252A>G association with stroke under the dominant model (OR = 1.56) had an FDR of 0.02. Among Caucasians only, *LTA* 252A>G was similarly associated with ischemic stroke among those without hypertension under additive and dominant models (OR = 1.28, p=0.016 and OR = 1.39, p=0.019, respectively). Minor allele frequencies among non-hypertensive controls are given in Table 4; frequencies among non-hypertensive cases were 0.37, 0.38, 0.31, 0.41, and 0.46 in SOF, Vienna, Westphalia, Pomerania, and SHINING, respectively.

The point estimates for the OR were somewhat higher for *LTA* 252A>G, a polymorphism in intron 1, than for the non-synonymous polymorphism *LTA* 26Thr>Asn, although the confidence intervals overlapped after adjusting for age and sex (Figure1, A–D). The FDR values for the Thr>Asn polymorphism were also greater than 0.05. The associations with stroke risk for both *LTA* SNPs reached statistical significance among normotensives within the individual studies of SHINING and Pomerania, whereas among hypertensives, the OR point estimates were usually just below 1 and were not statistically significant (Figure 1). This trend for increased stroke risk associated with the *LTA* SNPs among normotensives relative to hypertensives was observed across the other studies, although none of these individual associations was statistically significant. We note that the PHS cohort was genotyped only for the *LTA* 26Thr>Asn polymorphism under the expectation that this coding SNP could be functional and would be an effective "tag" for *LTA* 252, based on the very strong LD between these two polymorphisms; furthermore, in the Vienna and Westphalia studies, some samples had missing genotypes for *LTA 252*A>G. When the meta-analysis was repeated with only those samples that had been genotyped for both *LTA* SNPs, the OR estimates were virtually identical (1.572 and 1.565 among normotensives under the dominant model for *LTA* 252 and *LTA* 26, respectively; data not shown). In addition, if the *LTA* 26 result for the PHS were imputed for the missing *LTA* 252 data, the additive result for *LTA* 252 would remain highly significant (OR=1.30, p=0.0001). Alternatively, if a completely null estimate for the PHS were imputed, the overall result would remain significant (OR=1.27, p=0.0004) and would continue to pass the stringent multiple comparisons testing.

In the smoking-stratified analyses, no associations remained statistically significant after the false discovery rate was applied, although under the dominant model, *CD14* (−260)C>T was suggestively associated (OR 1.24, P = 0.001, FDR = 0.058) with ischemic stroke among never-smokers (Supplementary Table 2C). Both *LTA* SNPs were associated with a greater risk for ischemic stroke in never-smokers than ever-smokers under the dominant model and although these associations were not statistically significant after accounting for multiple testing, this trend was consistent across five studies (data not shown); the Westphalian study was excluded due to limited smoking data.

Discussion

In this meta-analysis, we evaluated the association between 105 polymorphisms in 64 inflammation and cardiovascular-related genes and ischemic stroke in 3550 case and 6560 control subjects across six different studies. Although we could not further define subtypes of ischemic stroke, key strengths of our stroke consortium are that these analyses were not subject to publication bias and all studies used common genotyping reagents. In the primary meta-analysis, modest associations with stroke became non-significant after adjustment for multiple testing using the FDR or permutation testing. Stratification on sex or age also revealed no significant associations. Notably, subjects in two of our studies were limited to one sex and the consortium encompassed subjects recruited from different regions in Europe, North America, and China. We observed similar results among Caucasian participants only, but study

population differences resulting in heterogeneity in stroke etiology could have obscured genetic associations.

Stratification on hypertension status did, however, reveal a statistically significant association for *LTA 2*52A>G that remained after adjustment for multiple testing. Across four Caucasian populations and one Chinese population, the odds ratio for *LTA 2*52G was consistently greater among normotensive than hypertensive subjects. *LTA 2*6Thr>Asn yielded similar results among study participants with genotypes at both sites, as expected, given the strong linkage disequilibrium between these two *LTA* SNPs. Although a recent Japanese study observed no association of these SNPs with any subtype of ischemic stroke[30], a smaller Hungarian study had previously reported *LTA* 252G as a risk factor for large-vessel ischemic stroke[31] and an earlier Korean study had identified the *LTA* 252AA genotype as a risk factor for cerebral infarction[32]. We were unable to analyze ischemic stroke subtypes, but there is some evidence that subtypes may differ depending upon hypertensive status[33]. Although the number of non-hypertensives cases was limited to 1068, stratification by hypertension across our six populations may have reduced heterogeneity and thus enabled us to discern the modest risk associated with LTA polymorphism.

A role for LTA in chronic inflammation has been suggested by its ability to induce expression of ICAM-1 and VCAM-1 on endothelial cells in vitro[34,35]. LTA expression results in a localized infiltrate consisting of T cells, B cells, follicular and interdigitating dendritic cells and macrophages[36]. A recent mouse model study indicated that LTA was expressed in atherosclerotic lesions whose size correlated with concentration. Moreover, loss of the adjacent gene *TNF* did not affect development of lesions in mice fed an atherogenic diet[37]. The A252G site is intronic, but has been associated with higher transcriptional activity in a luciferase assay, while the variant protein bearing the *LTA 2*6 threonine to asparagine substitution has been observed to induce greater expression of VCAM1 and SELE mRNA in vascular smooth-muscle cells. Since these two *LTA* SNPs are in almost complete LD, the variant protein level was estimated to be 1.5-fold higher than wildtype[10]. An increased level of the variant protein may contribute to the increased risk for ischemic stroke through inflammatory processes. Although the mechanism by which *LTA* polymorphisms influence inflammatory pathways is not clear, the meta-analysis presented here indicated that these *LTA* variants were associated with ischemic stroke in non-hypertensive patients.

It is believed that subjects with hypertension tend to develop chronic, low-grade systemic inflammation[38–40]. Severity of inflammation caused by genetic variation could independently modify predisposition to ischemic stroke. Recent reports on the association of *PDE4D* variants with ischemic stroke among normotensives[3,4] are consistent with the hypothesis that hypertension may obscure or mask the effect of inflammation-related genetic variants and that such genetic effects can be most readily observed in the absence of this major risk factor.

Smoking, like hypertension, can elicit an inflammatory response[41]. In our study, the effect of *LTA* variation on stroke was more discernable among never-smokers than ever-smokers. Whether pro-inflammatory risks for ischemic stroke caused by hypertension, smoking, or carrying a risk allele are additive remains to be addressed by a carefully designed study.

Summary

Our six-study analysis surveyed inflammatory and cardiovascular gene polymorphisms in examining the risk for ischemic stroke. Our results indicate that the *LTA 2*52A>G and *LTA 2*6Thr>Asn polymorphisms have significant effects on the risk for ischemic stroke in non-hypertensive subjects. We cannot rule out the possible importance of these polymorphisms in hypertensive subjects, but a much larger cohort may be needed to clarify the interaction of hypertension and inflammation in the etiology of ischemic stroke.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Design and interpretation of meta-analysis: XW, SC, VHB, HAE, CM, KB, WL, PMR, RYLZ, NRC

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Manuscript writing and approval: all

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Acknowledgments Appendix

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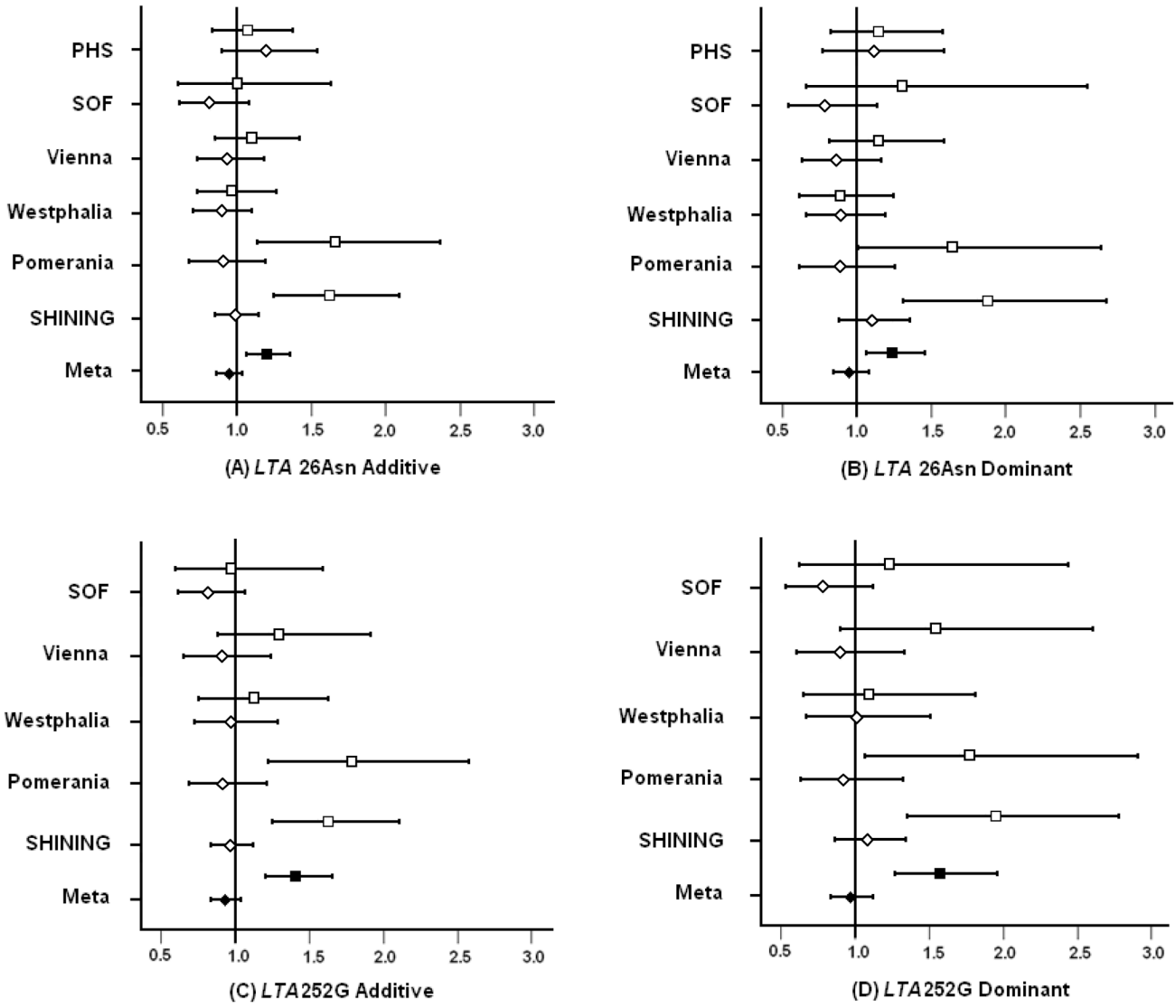

Figure 1.

Risk of ischemic stroke associated with *LTA* polymorphism. Odds ratios under additive and dominant modes of inheritance for the *LTA* 252A>G and *LTA* 26Thr>Asn polymorphisms among normotensive (square) and hypertensive (diamond) subjects are plotted for each study (open squares/diamonds) and the fixed effects meta-analysis (filled squares/diamonds). Horizontal lines extend across the 95% confidence limits.

Table 1

Characteristics of the Study Subjects. Summary of population characteristics for each of the six studies used in the meta-analysis. All cases were diagnosed by CT/MRI.

	PHS[17,18]			SOF[19]			Vienna[23]		
Subjects (n)	319 cases, 2092 controls			247 cases, 559 controls			844 cases, 979 controls		
Study Type	prospective			prospective			cross-sectional		
Recruitment Period	1982; follow-up through 1995			1986 – 1988; follow-up through 1998			1998 – 2001		
Population	Caucasians from USA			Caucasians from USA			Caucasians from Vienna, Austria		
	Cases	Controls	p‡	Cases	Controls	p‡	Cases	Controls	p‡
Age* (yrs)	61.1±8.3	58.8±8.5	<.0001	73.9±5.9	70.4±4.5	<.0001	66.1±14.4	48.8±13.0	<.0001
Sex (% male)	100	100		0	0		50.6	53.4	0.23
Hypertension (% yes)	48.6	26.8	<.0001	79.8	62.1	<.0001	72.2	34.2	<.0001
Diabetes (%yes)	10.7	2.7	<.0001	19.3	4.3	<.0001	32.8	2.5	<.0001
Smoking (% ever)	60.7	56.6	0.15	29.8	37.5	0.15	54.9	41.7	<.0001
BMI*,† (kg/m^2)	25.6±3.3	25.0±3.0	0.002	26.9±4.6	26.8±4.9	0.83	26.7±4.6	25.3±3.9	<.0001
SBP*,† (mm Hg)	133.6±12.8	127.4±11.9	<.0001	151.9±23.1	140.4±17.5	<.0001	NA	132.3±20.7	
DBP*,† (mm Hg)	82.1±7.0	79.0±7.2	<.0001	78.2±11.6	76.9±8.9	0.13	NA	82.7±11.7	

	Westphalia[20,21]			Pomerania[22]			SHINING[5]		
Subjects (n)	700 cases, 757 controls			277 cases, 702 controls			1163 cases, 1471 controls		
Study Type	cross-sectional			cross-sectional			cross-sectional		
Recruitment Period	2000 – 2003			1996 – 2001			1997–2000		
Population	Caucasians from northwestern Germany			Caucasians from northeastern Germany			Chinese primarily from Beijing, China		
	Cases	Controls	p‡	Cases	Controls	p‡	Cases§	Controls§	p‡
Age* (yrs)	61.0±16.9	58.7±9.9	0.002	62.8±13.2	62.7±11.8	0.88	59.3±10.7	61.1 ±10.7	<.0001
Sex (% male)	56.3	46.6	<.0001	55.1	50.8	0.23	60.3	60.1	0.93
Hypertension (% yes)	68.0	41.0	<.0001	66.8	52.9	<.0001	69.6	77.1	<.0001
Diabetes (%yes)	21	8.9	<.0001	30.1	14.5	<.0001	15.3	8.5	<.0001

	PHS[17,18]		SOF[19]			Vienna[23]		
Smoking (% ever)	NA	54.1	87.6	58.3	<.0001	39.7	32.3	<.0001
BMI[*,†] **(kg/m^2)**	NA	NA	NA	NA		24.4±3.0	25.0±3.3	<.0001
SBP[*,†] **(mm Hg)**	NA	145.9±21.4	NA	148.7±21.3		145.4±23.2	143.2±23.7	0.018
DBP[*,†] **(mm Hg)**	NA	89.1±12.2	NA	86.1±11.1		87.0±12.8	86.1±13.0	0.087

[*] Continuous variables are given as mean ±SD.

[†] BMI = Body mass index, SBP = Systolic blood pressure prior to stroke, DBP =Diastolic blood pressure prior to stroke.

[‡] Using chi-square test for categorical variables, t-test for continuous variables.

[§] Partially matched by age and BP group during recruitment

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Table 2

f ischemic stroke: all SNPs under three modes of inheritance.

SNP Name	n*	Additive			Dominant			Recessive			
		Sites†	OR (LCL,UCL)‡	p‡	Het p§	OR (LCL,UCL)‡	p‡	Het p§	Sites//	OR (LCL,UCL)‡	p‡	Het p§
ADD1 460Gly>Trp	9936	6	1.02 (0.95,1.10)	0.638	0.960	1.04 (0.95,1.15)	0.403	0.876	6	0.98 (0.84,1.14)	0.762	0.692
ADRB2 16Gly>Arg	10082	6	0.94 (0.89,1.01)	0.080	0.271	0.95 (0.86,1.05)	0.303	0.437	6	0.90 (0.80,1.01)	0.064	0.502
ADRB2 27Gln>Glu	10087	6	1.04 (0.97,1.11)	0.323	0.121	1.04 (0.94,1.15)	0.461	0.177	6	1.06 (0.93,1.22)	0.381	0.222
ADRB2 164Thr>Ile	8535	6	1.33 (0.88,2.02)	0.175	0.308	1.29 (0.85,1.98)	0.236	0.324		Too few variant homozygotes observed		
ADRB3 64Trp>Arg	10093	6	0.91 (0.82,1.02)	0.090	0.679	0.89 (0.79,1.00)	0.046	0.803	6	1.13 (0.75,1.69)	0.570	0.265
AGTR1 1166A>C	9942	6	1.04 (0.96,1.13)	0.346	0.068	1.03 (0.93,1.14)	0.546	0.015	6	1.11 (0.92,1.35)	0.284	0.734
AGT 235Met>Thr	9939	6	1.00 (0.94,1.07)	0.973	0.371	0.97 (0.87,1.08)	0.586	0.279	6	1.03 (0.93,1.15)	0.581	0.344
ACE IVS16 Del>Ins	9862	6	0.99 (0.93,1.06)	0.841	0.069	1.02 (0.91,1.13)	0.758	0.473	6	0.97 (0.88,1.07)	0.556	0.029
APOA4 347Thr>Ser	10091	6	0.94 (0.85,1.03)	0.193	0.672	0.96 (0.86,1.07)	0.446	0.551	5	0.76 (0.57,1.03)	0.074	0.512
APOA4 360Gln>His	10088	6	0.95 (0.82,1.11)	0.545	0.297	0.97 (0.83,1.14)	0.730	0.288	5	0.81 (0.32,2.03)	0.653	0.999
APOB 71Thr>Ile	10091	6	1.04 (0.97,1.12)	0.259	0.807	1.02 (0.93,1.12)	0.675	0.416	6	1.18 (1.00,1.41)	0.056	0.849
APOB 3500Arg>Gln	10093	3	6.11 (0.45,82.6)	0.173	0.999	6.11 (0.45,82.6)	0.173	0.999		No variant homozygotes observed		
APOC3 (−641)C>A	10064	6	1.03 (0.97,1.10)	0.303	0.864	1.04 (0.95,1.15)	0.377	0.595	6	1.05 (0.93,1.18)	0.434	0.834
APOC3 (−482)C>T	10089	6	1.06 (0.99,1.13)	0.096	0.266	1.06 (0.97,1.16)	0.226	0.137	6	1.12 (0.97,1.28)	0.114	0.728
APOC3 (−455)T>C	10087	6	1.04 (0.97,1.11)	0.244	0.775	1.04 (0.95,1.15)	0.372	0.544	6	1.06 (0.94,1.20)	0.311	0.871
APOC3 1100C>T	10089	6	1.02 (0.96,1.09)	0.517	0.313	1.03 (0.93,1.13)	0.609	0.244	6	1.04 (0.92,1.18)	0.562	0.111
APOC3 3175C>G	10091	6	1.01 (0.93,1.10)	0.776	0.124	1.05 (0.95,1.16)	0.351	0.153	6	0.84 (0.66,1.08)	0.173	0.389
APOC3 3206T>G	10073	6	1.04 (0.97,1.11)	0.274	0.372	1.09 (0.97,1.21)	0.137	0.606	6	1.02 (0.91,1.13)	0.780	0.405
APOE 112Cys>Arg	10050	6	1.04 (0.94,1.14)	0.447	0.341	1.03 (0.92,1.14)	0.624	0.469	6	1.25 (0.88,1.78)	0.206	0.223
APOE 158Arg>Cys	10055	6	0.96 (0.85,1.07)	0.424	0.171	0.97 (0.86,1.09)	0.570	0.221	6	0.71 (0.41,1.23)	0.223	0.531
CD14 (−260)C>T	8536	6	1.03 (0.96,1.11)	0.397	0.474	1.02 (0.90,1.14)	0.801	0.274	6	1.06 (0.95,1.19)	0.285	0.952
CCL11 (−1328)G>A	6123	5	0.96 (0.85,1.08)	0.476	0.202	0.97 (0.84,1.11)	0.602	0.083	5	0.88 (0.58,1.33)	0.536	0.707
CCL11 23Ala>Thr	8536	6	1.08 (0.99,1.19)	0.099	0.856	1.09 (0.98,1.21)	0.113	0.985	6	1.16 (0.86,1.57)	0.341	0.224
CXCL12 (+800)G>A	6032	5	0.97 (0.88,1.06)	0.454	0.599	0.96 (0.86,1.07)	0.446	0.748	5	0.99 (0.76,1.27)	0.911	0.079
CCR2 62Val>Ile	8532	6	1.08 (0.98,1.19)	0.118	0.661	1.07 (0.96,1.20)	0.241	0.670	6	1.28 (0.96,1.69)	0.090	0.717

SNP Name	n*	Additive			Dominant			Recessive			
		Sites†	OR (LCL,UCL)‡	p‡	Het p§	OR (LCL,UCL)‡	p‡	Het p§	Sites//	OR (LCL,UCL)‡	p‡	Het p§
CCR3 39Pro>Leu	8542	5	0.86 (0.37,2.02)	0.730	0.565	0.86 (0.37,2.02)	0.730	0.565		No variant homozygotes observed		
CCR5 (−2459)A>G	8541	6	1.01 (0.94,1.08)	0.850	0.040	1.00 (0.89,1.12)	0.960	0.045	6	1.02 (0.91,1.15)	0.701	0.095
CCR5 580Ins>Del32	8523	5	0.94 (0.81,1.08)	0.372	0.264	0.94 (0.81,1.10)	0.461	0.174	5	0.82 (0.44,1.51)	0.517	0.706
CETP (−631)C>A	10088	6	1.00 (0.87,1.15)	0.977	0.616	1.02 (0.88,1.19)	0.792	0.718	5	0.92 (0.46,1.83)	0.800	0.565
CETP (−629)C>A	10076	6	0.95 (0.90,1.01)	0.129	0.203	0.90 (0.81,1.00)	0.046	0.595	6	0.98 (0.88,1.08)	0.653	0.134
CETP 405Ile>Val	10086	6	0.99 (0.92,1.05)	0.661	0.748	0.99 (0.91,1.09)	0.895	0.635	6	0.96 (0.84,1.09)	0.498	0.791
CETP 442Asp>Gly	10089	5	1.28 (0.87,1.89)	0.207	1.000	1.41 (0.93,2.13)	0.108	1.000		Too few variant homozygotes observed		
F2 20210G>A	9902	5	1.01 (0.74,1.39)	0.941	0.108	1.02 (0.74,1.40)	0.928	0.099		Too few variant homozygotes observed		
F5 506Arg>Gln	9941	6	0.96 (0.77,1.20)	0.712	0.867	0.96 (0.76,1.20)	0.698	0.848		Too few variant homozygotes observed		
F7 (−323) Del>Ins10	9941	6	0.99 (0.89,1.11)	0.909	0.057	1.00 (0.89,1.12)	0.984	0.072	6	1.05 (0.67,1.64)	0.832	0.908
F7 353Arg>Gln	9938	6	0.96 (0.86,1.08)	0.510	0.193	0.97 (0.86,1.10)	0.638	0.163	6	0.83 (0.53,1.31)	0.427	0.736
C3 102Arg>Gly	6083	5	0.99 (0.87,1.13)	0.891	0.488	0.96 (0.83,1.12)	0.609	0.429	5	1.18 (0.80,1.76)	0.408	0.798
C5 802Val>Ile	6117	5	1.02 (0.95,1.10)	0.604	0.087	1.07 (0.94,1.21)	0.328	0.162	5	0.99 (0.88,1.12)	0.897	0.328
CSF2 117Ile>Thr	6127	5	1.00 (0.92,1.09)	0.961	0.610	1.03 (0.91,1.17)	0.601	0.285	5	0.96 (0.83,1.12)	0.626	0.535
CTLA4 (−318)C>T	6119	5	0.91 (0.80,1.02)	0.100	0.688	0.91 (0.79,1.03)	0.135	0.544	5	0.81 (0.51,1.30)	0.387	0.197
CTLA4 17Thr>Ala	6128	5	1.02 (0.94,1.11)	0.580	0.139	0.99 (0.87,1.13)	0.862	0.154	5	1.07 (0.94,1.21)	0.301	0.251
FGB (−455)G>A	9933	6	1.01 (0.93,1.09)	0.905	0.877	1.01 (0.92,1.11)	0.866	0.646	6	1.01 (0.81,1.25)	0.963	0.503
GC 416Glu>Asp	6121	5	1.02 (0.94,1.10)	0.719	0.224	0.97 (0.85,1.12)	0.718	0.306	5	1.05 (0.93,1.19)	0.395	0.336
GC 420Thr>Lys	6122	5	1.02 (0.94,1.11)	0.598	0.436	1.01 (0.89,1.14)	0.928	0.382	5	1.06 (0.92,1.21)	0.437	0.443
GNB3 825C>T	9941	6	1.08 (1.01,1.15)	0.031	0.759	1.06 (0.96,1.16)	0.243	0.864	6	1.19 (1.05,1.36)	0.009	0.134
ITGA2 873G>A	9941	6	1.04 (0.97,1.11)	0.268	0.157	1.04 (0.95,1.14)	0.367	0.327	6	1.06 (0.93,1.21)	0.356	0.163

SNP Name	n*	Additive			Dominant			Recessive			
		Sites†	OR (LCL,UCL)‡	p‡	Het p§	OR (LCL,UCL)‡	p‡	Het p§	Sites‖	OR (LCL,UCL)‡	p‡	Het p§
ITGB3 33Leu>Pro	9937	6	0.98 (0.88,1.08)	0.648	0.349	0.97 (0.87,1.10)	0.662	0.423	5	1.00 (0.70,1.44)	0.993	0.375
ICAM1 56Lys>Met	8531	6	1.04 (0.84,1.29)	0.717	0.928	1.05 (0.84,1.31)	0.690	0.940	3	0.98 (0.26,3.70)	0.980	0.907
ICAM1 241Gly>Arg	10088	6	1.09 (0.97,1.23)	0.139	0.466	1.09 (0.95,1.24)	0.208	0.398	6	1.31 (0.86,1.99)	0.203	0.916
IL1A (−889)C>T	8508	6	0.93 (0.85,1.02)	0.110	0.778	0.91 (0.82,1.01)	0.083	0.834	6	0.95 (0.76,1.19)	0.659	0.686
IL1B (−1418)C>T	6094	5	1.05 (0.97,1.13)	0.240	0.506	1.06 (0.95,1.19)	0.288	0.473	5	1.06 (0.92,1.23)	0.407	0.541
IL1B 4336C>T	8534	6	0.95 (0.86,1.05)	0.331	0.415	0.92 (0.82,1.04)	0.188	0.286	6	1.07 (0.81,1.41)	0.642	0.595
IL4 (−590)C>T	8541	6	1.05 (0.97,1.15)	0.237	0.015	1.19 (1.05,1.35)	0.007	0.101	6	0.92 (0.8,1.07)	0.275	0.081
IL4R 75Ile>Val	8538	6	1.00 (0.93,1.07)	0.987	0.910	1.02 (0.91,1.14)	0.722	0.790	6	0.98 (0.87,1.10)	0.720	0.915
IL4R 503Ser>Pro	6130	5	1.00 (0.89,1.12)	0.945	0.286	1.00 (0.88,1.14)	0.979	0.536	5	1.00 (0.63,1.59)	0.997	0.168
IL4R 576Gln>Arg	8525	6	1.04 (0.95,1.13)	0.437	0.058	1.06 (0.96,1.18)	0.247	0.088	6	0.92 (0.70,1.21)	0.546	0.273
IL5RA (−82)G>A	8528	6	1.02 (0.94,1.11)	0.608	0.182	1.02 (0.92,1.12)	0.754	0.275	6	1.08 (0.87,1.34)	0.482	0.114
IL6 (−572)G>C	6124	5	0.92 (0.82,1.02)	0.103	0.061	0.84 (0.70,1.00)	0.052	0.113	4	0.95 (0.81,1.10)	0.480	1.000
IL6 (−174)G>C	8543	6	1.08 (0.99,1.18)	0.095	0.687	1.08 (0.95,1.23)	0.232	0.248	5	1.14 (0.97,1.34)	0.121	0.718
IL9 113Thr>Met	8544	6	1.04 (0.92,1.18)	0.559	0.543	1.10 (0.95,1.26)	0.209	0.772	5	0.73 (0.44,1.19)	0.205	0.131
IL10 (−571)C>A	8538	6	0.96 (0.89,1.04)	0.307	0.012	0.96 (0.86,1.07)	0.463	0.028	6	0.94 (0.82,1.08)	0.375	0.190
IL13 4045C>T	5366	4	1.01 (0.92,1.11)	0.894	0.751	0.99 (0.89,1.12)	0.917	0.854	4	1.07 (0.85,1.35)	0.561	0.380
LTC4S (−444)A>C	6044	5	0.99 (0.90,1.09)	0.797	0.241	1.01 (0.91,1.13)	0.874	0.193	5	0.88 (0.69,1.13)	0.308	0.940
LIPC (−480)C>T	10092	6	0.93 (0.87,1.00)	0.048	0.468	0.94 (0.86,1.03)	0.182	0.636	6	0.85 (0.71,1.00)	0.051	0.091
LPA 93C>T	10082	6	0.96 (0.88,1.04)	0.309	0.524	0.97 (0.88,1.06)	0.475	0.588	6	0.89 (0.66,1.19)	0.424	0.155
LPA 121G>A	10080	6	0.95 (0.88,1.03)	0.206	0.404	0.94 (0.85,1.03)	0.194	0.647	6	0.97 (0.81,1.15)	0.680	0.127
LPL (−93)T>G	10091	6	1.12 (0.84,1.49)	0.433	0.460	1.13 (0.83,1.54)	0.444	0.450	3	1.64 (0.42,6.36)	0.473	0.861
LPL 9Asp>Asn	10091	6	1.15 (0.80,1.65)	0.464	0.610	1.15 (0.80,1.66)	0.443	0.611		Too few variant homozygotes observed		
LPL 291Asn>Ser	10090	6	1.24 (0.94,1.64)	0.133	0.887	1.29 (0.97,1.72)	0.080	0.925		Too few variant homozygotes observed		
LPL 447Ser>Term	10088	6	0.89 (0.80,0.99)	0.033	0.455	0.88 (0.79,0.99)	0.033	0.542	6	0.89 (0.57,1.40)	0.623	0.244
LDLR NcoI +/−	10086	6	1.01 (0.94,1.08)	0.882	0.869	0.99 (0.91,1.09)	0.860	0.862	6	1.05 (0.91,1.21)	0.540	0.472
LTA 252A>G	6090	5	1.02 (0.94,1.10)	0.682	0.404	1.07 (0.96,1.20)	0.226	0.561	5	0.93 (0.80,1.09)	0.381	0.294
LTA 26Thr>Asn	10091	6	1.01 (0.95,1.08)	0.742	0.387	1.02 (0.93,1.11)	0.715	0.274	6	1.01 (0.88,1.16)	0.872	0.344

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SNP Name	n*	Additive Sites†	Additive OR (LCL,UCL)‡	Additive p‡	Additive Het p§	Dominant OR (LCL,UCL)‡	Dominant p‡	Dominant Het p§	Recessive Sites#	Recessive OR (LCL,UCL)‡	Recessive p‡	Recessive Het p§
MS4A2 237Glu>Gly	8517	6	1.08 (0.95,1.23)	0.256	0.479	1.10 (0.95,1.27)	0.220	0.480	3	1.03 (0.65,1.64)	0.891	0.999
MTHFR 677C>T	9943	6	1.03 (0.96,1.10)	0.383	0.389	1.05 (0.95,1.15)	0.360	0.514	6	1.03 (0.91,1.16)	0.629	0.165
NPPA 664G>A	9940	6	0.96 (0.83,1.11)	0.555	0.016	0.94 (0.81,1.10)	0.448	0.022	5	1.54 (0.73,3.26)	0.257	0.689
NPPA 2238T>C	9939	6	1.03 (0.92,1.15)	0.612	0.781	1.05 (0.93,1.18)	0.452	0.924	6	0.89 (0.59,1.33)	0.560	0.453
NOS2A 231C>T	6131	5	0.91 (0.82,1.01)	0.062	0.659	0.91 (0.81,1.02)	0.111	0.439	5	0.81 (0.60,1.09)	0.166	0.516
NOS3 (−922)A>G	10093	6	1.02 (0.95,1.10)	0.575	0.676	1.03 (0.93,1.14)	0.562	0.358	6	1.03 (0.88,1.20)	0.714	0.129
NOS3 (−690)C>T	9936	6	1.15 (1.00,1.32)	0.047	0.479	1.16 (1.00,1.34)	0.052	0.562	5	1.30 (0.70,2.41)	0.408	0.726
NOS3 298Glu>Asp	10094	6	1.05 (0.97,1.13)	0.224	0.176	1.05 (0.95,1.15)	0.327	0.145	6	1.10 (0.92,1.31)	0.293	0.569
PON1 55Leu>Met	10090	6	0.97 (0.91,1.05)	0.467	0.510	0.97 (0.88,1.08)	0.584	0.495	6	0.95 (0.81,1.12)	0.554	0.157
PON1 192Gln>Arg	10088	6	1.05 (0.98,1.13)	0.155	0.774	1.07 (0.97,1.18)	0.167	0.463	6	1.05 (0.93,1.20)	0.412	0.268
PON2 311Ser>Cys	10092	6	1.09 (1.01,1.18)	0.025	0.793	1.09 (1.00,1.20)	0.060	0.628	6	1.22 (0.99,1.49)	0.063	0.460
PPARG 12Pro>Ala	10093	6	1.05 (0.95,1.16)	0.362	0.702	1.07 (0.96,1.20)	0.220	0.425	6	0.88 (0.59,1.32)	0.532	0.490
SCGB1A1 (+38)G>A	8538	6	0.99 (0.92,1.06)	0.797	0.103	0.98 (0.89,1.09)	0.701	0.431	6	1.01 (0.88,1.16)	0.884	0.040
SELE 128Ser>Arg	10094	6	1.00 (0.89,1.13)	0.965	0.666	1.01 (0.89,1.15)	0.903	0.642	6	1.05 (0.61,1.81)	0.850	0.673
SELE 554Leu>Phe	9904	6	0.91 (0.76,1.08)	0.266	0.004	0.92 (0.77,1.10)	0.362	0.005	5	0.37 (0.07,1.88)	0.228	0.998
SELP 330Ser>Asn	8539	6	1.04 (0.95,1.13)	0.424	0.296	1.03 (0.93,1.14)	0.565	0.483	6	1.12 (0.88,1.43)	0.365	0.506
SELP 640Val>Leu	8537	6	1.09 (0.95,1.25)	0.229	0.037	1.10 (0.94,1.28)	0.226	0.028	5	1.22 (0.71,2.12)	0.471	0.876
SERPINE1 (−675)Del>InsG	9931	6	0.99 (0.93,1.06)	0.769	0.541	1.04 (0.95,1.15)	0.387	0.525	6	0.92 (0.82,1.03)	0.126	0.669
SERPINE1 11053T>G	9940	6	0.99 (0.93,1.05)	0.699	0.266	1.02 (0.92,1.12)	0.766	0.257	6	0.95 (0.84,1.06)	0.324	0.413
SCNN1A 493Trp>Arg	9940	6	0.99 (0.76,1.27)	0.907	0.004	0.97 (0.75,1.26)	0.817	0.002	4	1.73 (0.10,28.9)	0.705	1.000

SNP Name	n*	Additive			Dominant			Recessive			
		Sites†	OR (LCL,UCL)‡	p‡	Het p§	OR (LCL,UCL)‡	p‡	Het p§	Sites#	OR (LCL,UCL)‡	p‡	Het p§
SCNN1A 663Ala>Thr	9932	6	1.00 (0.93,1.07)	0.958	0.958	1.00 (0.91,1.10)	1.000	0.921	6	1.00 (0.87,1.14)	0.939	0.275
MMP3 (−1171) Ins>DelA	9932	6	0.97 (0.91,1.04)	0.384	0.074	0.95 (0.85,1.05)	0.279	0.126	6	0.98 (0.87,1.11)	0.801	0.273
TCF7 (−1459)A>T	6118	5	0.96 (0.86,1.07)	0.438	0.033	0.97 (0.86,1.10)	0.674	0.037	5	0.75 (0.50,1.14)	0.174	0.610
TCF7 19Pro>Thr	6117	5	1.05 (0.88,1.25)	0.614	0.404	1.04 (0.86,1.25)	0.724	0.498	4	1.40 (0.65,3.02)	0.388	0.570
TGFB1 (−509)C>T	8486	6	0.92 (0.86,0.99)	0.028	0.750	0.89 (0.8,0.98)	0.023	0.148	6	0.92 (0.81,1.06)	0.252	0.658
TNF (−376)G>A	9941	6	0.72 (0.50,1.04)	0.077	0.371	0.72 (0.5,1.04)	0.081	0.363		Too few variant homozygotes observed		
TNF (−308)G>A	10096	6	1.04 (0.95,1.15)	0.395	0.253	1.04 (0.93,1.16)	0.479	0.326	6	1.14 (0.83,1.59)	0.420	0.506
TNF (−244)G>A	9938	5	1.51 (0.38,6.01)	0.562	0.944	1.51 (0.38,6.01)	0.562	0.944		Too few variant homozygotes observed		
TNF (−238)G>A	10050	6	1.02 (0.88,1.18)	0.815	0.231	1.02 (0.87,1.19)	0.797	0.280	6	1.04 (0.38,2.82)	0.946	0.694
VCAM1 (−1594)T>C	8525	6	0.98 (0.89,1.07)	0.595	0.891	0.99 (0.89,1.10)	0.805	0.871	6	0.86 (0.64,1.16)	0.325	0.967
VDR 1Thr>Met	6104	5	1.07 (0.99,1.16)	0.078	0.424	1.12 (1.00,1.25)	0.057	0.867	5	1.07 (0.93,1.23)	0.367	0.237
VDR 45082G>A	6120	5	1.01 (0.92,1.12)	0.798	0.504	1.00 (0.88,1.14)	0.974	0.173	5	1.06 (0.87,1.31)	0.558	0.508

s.

or analysis under additive and dominant modes.

nfidence limit, p= corresponding p-value

or analysis under recessive mode.

Table 3

Nominally significant (P<0.05) fixed-effects meta-analysis results among those with current or past hypertension

SNP	Mode*	# Studies	OR†	Lower CL†	Upper CL†	p	FDR‡
LPA 121G>A	ADD	6	0.886	0.801	0.979	0.017	0.915
TGFB1 (−509)C>T	ADD	6	0.894	0.812	0.983	0.021	0.915
CTLA4 (−318)C>T	ADD	5	0.851	0.730	0.993	0.040	0.915
TGFB1 (−509)C>T	DOM	6	0.845	0.737	0.969	0.016	0.968
LPA 121G>A	DOM	6	0.872	0.768	0.992	0.037	0.968
APOC3 3175C>G	REC	6	0.708	0.514	0.975	0.034	0.824
SERPINE1 (−675)Del>InsG	REC	6	0.851	0.731	0.991	0.038	0.824
LTA 252A>G	REC	5	0.806	0.657	0.989	0.039	0.824
ITGA2 873G>A	REC	6	1.202	1.003	1.442	0.047	0.824

*ADD = additive, DOM = dominant, REC = recessive mode of inheritance

†Odds ratio (OR) and confidence limits (CL)

‡False discovery rate

ong normotensives (1068 cases, 3390 controls) under three modes of

s, 212 ctrl)*		Vienna (232 cs, 632 ctrl)			Westphalia (224 cs, 444 ctrl)			Pomerania (92 cs, 330 ctrl)			SHINING (307 cs, 250 ctrl)			Meta*			
P	MAF‡	OR†	P	MAF‡	OR†	P	MAF‡	OR†	P	MAF‡	OR†	P	MAF‡	OR†	P	FDR†	Het§
913	0.33	1.30	0.182	0.32	1.11	0.604	0.32	**1.77**	**0.003**	0.29	**1.62**	**<0.001**	0.36	**1.41**	**<0.0001**	**0.002**	*
970	0.33	1.10	0.475	0.32	0.96	0.771	0.33	**1.63**	**0.008**	0.29	**1.60**	**<0.001**	0.35	**1.19**	**0.003**	**0.161**	**0.03**
508	0.49	0.93	0.518	0.47	**0.69**	**0.003**	0.55	0.98	0.884	0.50	0.97	0.826	0.65	**0.86**	**0.007**	**0.244**	*
371	0.09	0.99	0.976	0.09	**0.45**	**0.003**	0.08	0.78	0.47	0.08	not polymorphic		0.00	**0.71**	**0.009**	**0.244**	*
518	0.12	0.91	0.759	0.11	1.02	0.947	0.11	0.92	0.777	0.11	1.52	0.637	0.004	**1.31**	**0.013**	**0.255**	*
788	0.11	**1.94**	**0.024**	0.07	1.03	0.922	0.10	**1.91**	**0.023**	0.08	not polymorphic		0.00	**1.45**	**0.017**	**0.255**	*
963	0.17	0.96	0.797	0.18	1.22	0.203	0.19	**1.56**	**0.022**	0.20	1.16	0.241	0.51	**1.17**	**0.017**	**0.255**	*
034	0.26	1.15	0.508	0.23	0.78	0.249	0.26	1.02	0.915	0.22	0.93	0.548	0.63	**0.84**	**0.020**	**0.255**	*
917	0.40	1.13	0.309	0.46	0.91	0.436	0.45	**0.64**	**0.011**	0.43	0.94	0.670	0.81	**0.87**	**0.021**	**0.255**	**0.03**
706	0.24	1.27	0.096	0.23	1.21	0.195	0.23	1.11	0.608	0.24	1.15	0.366	0.19	**1.15**	**0.038**	**0.389**	*
894	0.05	0.74	0.485	0.06	0.54	0.189	0.06	1.30	0.499	0.05	**0.76**	**0.039**	0.72	**0.79**	**0.041**	**0.389**	*
493	0.32	1.25	0.089	0.28	**1.32**	**0.036**	0.28	0.93	0.682	0.33	0.84	0.333	0.14	**1.13**	**0.046**	**0.389**	*
542	0.33	1.53	0.116	0.32	1.09	0.746	0.32	**1.77**	**0.025**	0.29	**1.94**	**<0.001**	0.36	**1.57**	**<0.0001**	**0.005**	*
461	0.33	1.13	0.462	0.32	0.88	0.454	0.33	**1.63**	**0.045**	0.29	**1.87**	**0.001**	0.35	**1.24**	**0.007**	**0.253**	**0.06**
235	0.17	0.97	0.860	0.18	1.40	0.066	0.19	1.57	0.059	0.20	1.35	0.161	0.51	**1.25**	**0.008**	**0.253**	*
315	0.12	0.98	0.936	0.11	1.01	0.983	0.11	0.96	0.896	0.11	1.52	0.637	0.004	**1.36**	**0.011**	**0.253**	*
982	0.09	1.01	0.954	0.09	**0.38**	**0.001**	0.08	0.79	0.494	0.08	not polymorphic		0.00	**0.71**	**0.011**	**0.253**	**0.08**
682	0.14	0.86	0.570	0.18	1.00	0.993	0.15	1.35	0.245	0.15	**4.44**	**0.002**	0.80	**1.30**	**0.015**	**0.275**	**0.07**
920	0.11	**2.14**	**0.017**	0.07	0.96	0.888	0.10	**1.84**	**0.038**	0.08	not polymorphic		0.00	**1.46**	**0.022**	**0.353**	*
042	0.26	1.24	0.388	0.23	0.78	0.356	0.26	0.86	0.569	0.22	1.06	0.821	0.63	**0.80**	**0.028**	**0.363**	*
720	0.24	1.31	0.116	0.23	1.38	0.073	0.23	1.12	0.646	0.24	1.27	0.184	0.19	**1.19**	**0.031**	**0.363**	*
704	0.40	1.17	0.406	0.46	0.90	0.580	0.45	**0.57**	**0.023**	0.43	1.26	0.609	0.81	**0.82**	**0.033**	**0.363**	**0.05**
241	0.49	0.949	0.778	0.47	0.74	0.149	0.55	0.93	0.794	0.50	0.73	0.249	0.65	**0.83**	**0.046**	**0.413**	*
648	0.13	1.23	0.327	0.11	**1.54**	**0.025**	0.14	1.09	0.754	0.12	0.92	0.700	0.11	**1.20**	**0.048**	**0.413**	*
205	0.31	1.52	0.125	0.29	1.63	0.084	0.31	**2.49**	**0.013**	0.27	0.58	0.423	0.11	**1.56**	**0.001**	**0.102**	*

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s, 212 ctrl)*		Vienna (232 cs, 632 ctrl)		Westphalia (224 cs, 444 ctrl)				Pomerania (92 cs, 330 ctrl)			SHINING (307 cs, 250 ctrl)			Meta*			
P	MAF‡	OR†	P	MAF‡	OR†	P	MAF‡	OR†	P	MAF‡	OR†	P	MAF‡	OR†	P	FDR†	Het§
272	0.33	1.15	0.744	0.32	1.29	0.548	0.32	**2.90**	**0.005**	0.29	**1.72**	**0.029**	0.36	**1.55**	**0.007**	**0.360**	*
926	0.49	0.85	0.420	0.47	**0.48**	**0.001**	0.55	1.01	0.98	0.50	1.09	0.635	0.65	**0.80**	**0.020**	**0.536**	**0.06**
164	0.30	1.03	0.928	0.31	**1.75**	**0.045**	0.31	1.21	0.661	0.28	1.42	0.112	0.44	**1.31**	**0.028**	**0.569**	*
254	0.33	1.10	0.737	0.32	1.20	0.533	0.33	**2.50**	**0.013**	0.29	**1.80**	**0.017**	0.35	**1.31**	**0.032**	**0.569**	*
305	0.32	0.88	0.676	0.28	1.51	0.154	0.28	1.14	0.721	0.33	1.09	0.897	0.14	**1.33**	**0.039**	**0.592**	*

sion results for each study site.Cs = cases, ctrl = controls.

llele based upon the PHASE population.

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