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Polymorphisms Associated with Both Noncardioembolic Stroke and Coronary Heart Disease: Vienna Stroke Registry

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Key Words
Single nucleotide polymorphisms · Coronary heart disease · Stroke · Risk factors · Genetics

Abstract
Noncardioembolic stroke and coronary heart disease (CHD) may share genetic predispositions. We tested the hypothesis that genetic variants which are associated with risk of CHD would also be associated with risk of noncardioembolic stroke in 562 cases from the Vienna Stroke Registry and 815 controls. We selected 6 gene variants that had been consistently associated with risk of CHD in 3 studies, including the Atherosclerosis Risk in Communities study, and found that 4 of these gene variants were also associated with risk of noncardioembolic stroke. The odds ratios for noncardioembolic stroke were 1.31 (90% CI 1.07–1.60) for rs3900940 in *MYH15*, 1.24 (90% CI 1.01–1.5) for rs20455 in *KIF6*, 1.21 (90% CI 0.99–1.49) for rs1010 in *VAMP8*, and 1.20 (90% CI 0.95–1.50) for rs10757274 on chromosome 9p21.

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Introduction

Stroke and coronary heart disease (CHD) share several common risk factors [1]. In particular, noncardioembolic stroke and CHD both involve atherosclerosis and thrombosis; thus, gene variants associated with CHD may also be associated with noncardioembolic stroke.

For this study, we investigated whether gene variants associated with CHD are also associated with noncardioembolic stroke. We selected 6 single nucleotide polymorphisms (SNPs) that had previously been reported to be associated with CHD in at least 3 studies: the Atherosclerosis Risk in Communities (ARIC) and 2 additional studies. These included 5 SNPs that we have previously described: rs3900940 in *MYH15*, rs20455 in *KIF6*, rs1010 in *VAMP8*, rs2298566 in *SNX19*, and rs7439293 in *PALLD* [2], as well as the rs10757274 SNP on chromosome 9p21 described by McPherson et al. [3]. We asked whether carriers of the CHD risk alleles of these 6 SNPs, compared with noncarriers, had increased risk of noncardioembolic stroke in a case-control study consisting of 562 noncardioembolic stroke patients of Vienna Stroke Registry (VSR) [4] and 815 healthy controls from the city of Vienna [5].

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Subjects and Methods

Study Population

The stroke cases in VSR are consecutive Caucasian patients admitted to stroke units in Vienna within 72 h of onset of acute ischemic stroke between October 1998 and June 2001 [4]. Only patients with noncardioembolic stroke (defined as ischemic stroke that was not of cardioembolic origin) were included as cases in this study since cardioembolic stroke involves distinct disease mechanisms, such as atrial fibrillation or heart valve disease, which are not common mechanisms of noncardioembolic stroke or CHD [6, 7]. In addition, there is evidence that some genetic variants may be associated with specific stroke subtypes [8, 9]. Controls were unrelated Caucasian participants in a health care program in Vienna, 45 years old or older, free of arterial vascular disease, and reported no arterial vascular diseases in first-degree relatives [5]. Genotypes were determined as described previously [10]. This study complied with the Declaration of Helsinki and was approved by the Ethics Committee of Medical University Vienna. All subjects gave written informed consent.

Statistics

Differences in traditional risk factors between cases and controls were assessed by the Wilcoxon rank-sum test for continuous variables or by the χ^2 test for discrete variables. Odds ratios (OR) for the risk of noncardioembolic stroke for carriers of the CHD risk allele, compared with noncarriers, were estimated from logistic regression models and were adjusted for age (at the index stroke event for cases, at enrollment for controls), sex, current smoker (vs. not), diabetes (defined by a physician's diagnosis or the use of either insulin or oral hypoglycemic medications), hypertension (defined by systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, a physician's diagnosis of hypertension, or the use of anti-hypertensive medications), dyslipidemia [defined by a total cholesterol ≥240 mg/dl (6.2 mmol/l), LDL-C ≥160 mg/dl (4.1 mmol/l), HDL-C <40 mg/dl (1.0 mmol/l), or the use of lipid lowering medications], and body mass index (BMI). Since this study tested whether the allele associated with increased CHD risk was also associated with increased risk of noncardioembolic stroke, and we would not have considered any association of the opposite direction (e.g. between noncardioembolic stroke and the CHD nonrisk allele) to be significant, we used one-sided p values and 90% CI to assess the significance of the genetic associations. To account for multiple hypothesis testing, the false discovery rate *q* values were estimated by the method of Benjamini and Hochberg [11] using the p values for carriers of the risk allele from the age- and sex-adjusted model (model 1, table 1). The *q* value of a given SNP represents the expected proportion of false-positives among the set of SNPs with equal or lower *q* values. We used Quanto 1.1 (http://hydra.usc.edu/gxe) to calculate the effect sizes of noncardioembolic stroke risk (for carriers of the risk alleles, compared with noncarriers) that would be detectable with 90% power assuming a one-sided test and a significance level of 0.05.

To explore whether population stratification may have confounded our results, we used a Bayesian clustering approach with the Structure software [12] and the genotypes of 130 SNPs (minor allele frequencies ranged from 0.95 to 49.8%) to evaluate models that assumed 1, 2, 3, or 4 distinct ancestral populations among our study population. We found that a model assuming 2 ancestral populations resulted in the highest estimated log likelihood. Using the 2 ancestral population model, we estimated the fraction of the 2 ancestral populations in each individual subject. To adjust the risk estimates for population stratification, we included the fraction of the ancestral population as a covariate in logistic regression models.

Results

The clinical characteristics of the cases and controls are presented in table 2. We tested the hypothesis that 6 SNPs that had previously been associated with risk of CHD in at least 3 studies [2, 3] were also associated with risk of noncardioembolic stroke in the Vienna Stroke Registry. Specifically, we tested if carriers of the CHD risk alleles of these 6 SNPs were also at increased risk of noncardioembolic stroke. The genotype distribution of these 6 SNPs did not deviate from Hardy-Weinberg equilibrium ($p > 0.17$).

We found that for 2 of these SNPs, carriers of the CHD risk allele, compared with noncarriers, had increased risk of noncardioembolic stroke after adjusting for age and sex: the ORs were 1.31 (CI 1.07–1.60) for the *MYH15* SNP and 1.24 (CI 1.01–1.52) for the *KIF6* SNP (table 1). To account for multiple testing (6 SNPs were tested), we estimated the false discovery rate [11]. We found that for the group of 4 SNPs with the lowest p values, the false discovery rate was 15% (table 1), that is, we expect that on average, 15% of these 4 SNPs (i.e. less than 1 SNP) would be false-positives. In addition to the *MYH15* and *KIF6* SNPs, this group of 4 SNPs included 1 in *VAMP8* and 1 on chromosome 9p21: the ORs for noncardioembolic stroke were 1.21 (CI 0.99–1.49) for the *VAMP8* SNP and 1.20 (CI 0.95–1.50) for the 9p21 SNP (table 1). Although our prespecified analysis was a comparison of carriers versus noncarriers, on examination of the homozygous and heterozygous carriers separately, we found that for the 9p21 SNP only the homozygous carriers (OR = 1.59) and not the heterozygous (OR = 1.05) carriers were at increased risk of stroke. These ORs for noncardioembolic stroke for carriers of these 4 SNPs decreased somewhat after adjustment for additional risk factors (smoking, hypertension, diabetes, dyslipidemia, and BMI) with the exception of the OR for the *VAMP8* carriers which increased (model 2, table 1). To investigate whether the associations between stroke and these SNPs could have been confounded by myocardial infarction among the stroke cases, we repeated the analysis for association of the 6 CHD-associated SNPs with noncardioembolic stroke after excluding all cases with a history of myocardial infarction (n = 40). We found that excluding cases with a history of myocar-

Table 1. Adjusted association of 6 SNPs with noncardioembolic stroke in VSR

SNP ID	Case[a]	Control[a]	Model 1			Model 2	
			OR and 90% CI	p	q[b]	OR and 90% CI	p
MYH15 rs3900940							
CC + CT	281 (55.6)	390 (49.8)	1.31 (1.07–1.60)	0.01	0.06	1.25 (1.00–1.56)	0.05
CC	56 (11.1)	72 (9.2)	1.50 (1.06–2.11)	0.03		1.19 (0.80–1.75)	0.24
CT	225 (44.5)	318 (40.6)	1.27 (1.03–1.56)	0.03		1.26 (1.00–1.59)	0.05
TT	225 (44.5)	394 (50.3)	ref.			ref.	
KIF6 rs20455							
GG + GA	327 (64.8)	475 (60.7)	1.24 (1.01–1.52)	0.05	0.12	1.23 (0.98–1.54)	0.07
GG	73 (14.5)	102 (13.0)	1.24 (0.91–1.69)	0.13		1.30 (0.93–1.83)	0.10
GA	254 (50.3)	373 (47.7)	1.24 (1.00–1.53)	0.05		1.20 (0.95–1.53)	0.10
AA	178 (35.3)	307 (39.3)	ref.			ref.	
VAMP8 rs1010							
CC + CT	326 (64.4)	483 (61.6)	1.21 (0.99–1.49)	0.06	0.12	1.33 (1.06–1.67)	0.02
CC	77 (15.2)	112 (14.3)	1.27 (0.93–1.72)	0.10		1.37 (0.98–1.91)	0.06
CT	249 (49.2)	371 (47.3)	1.20 (0.96–1.49)	0.09		1.32 (1.04–1.68)	0.03
TT	180 (35.6)	301 (38.4)	ref.			ref.	
9p21 rs10757274							
GG + GA	386 (76.7)	568 (72.4)	1.20 (0.95–1.50)	0.10	0.15	1.14 (0.89–1.46)	0.20
GG	139 (27.6)	154 (19.6)	1.59 (1.20–2.11)	0.004		1.45 (1.06–1.98)	0.03
GA	247 (49.1)	414 (52.8)	1.05 (0.82–1.34)	0.38		1.02 (0.78–1.33)	0.45
AA	117 (23.3)	216 (27.6)	ref.			ref.	
SNX19 rs2298566							
CC + AC	473 (94.5)	744 (94.9)	0.93 (0.61–1.43)	0.61	0.73	0.88 (0.55–1.40)	0.68
CC	294 (58.1)	456 (58.2)	0.97 (0.63–1.50)	0.55		0.95 (0.59–1.53)	0.57
AC	179 (35.4)	288 (36.7)	0.87 (0.56–1.37)	0.69		0.77 (0.48–1.26)	0.81
AA	33 (6.5)	40 (5.1)	ref.			ref.	
PALLD rs7439293							
AA + GA	425 (84.3)	667 (85.4)	0.89 (0.68–1.17)	0.76	0.76	0.92 (0.67–1.25)	0.68
AA	201 (39.9)	290 (37.1)	0.94 (0.70–1.27)	0.63		1.02 (0.73–1.42)	0.46
GA	224 (44.4)	377 (48.3)	0.85 (0.63–1.14)	0.83		0.84 (0.60–1.16)	0.81
GG	79 (15.7)	114 (14.6)	ref.			ref.	

Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, smoking, hypertension, diabetes, dyslipidemia, and BMI. Values in parentheses indicate percentages or 95% CI.

[a] Individuals with missing genotype or traditional risk factor information were excluded.

[b] False discovery rate q value.

dial infarction from the analysis did not appreciably change the fully adjusted ORs for the 9p21 homozygotes (1.45, CI 1.05–1.99), *MYH15* carriers (1.24, CI 0.99–1.55), or *VAMP8* carriers (1.28, CI 1.01–1.61). However, it did reduce the OR for *KIF6* carriers to 1.15 (CI 0.91–1.45).

Since population stratification can confound analyses of case-control studies, we estimated the fraction of ancestral populations due to admixture in each subject and further adjusted the risk estimates of each SNP by the ancestry composition of the subjects. This adjustment did not appreciably change the risk estimates (the largest change was a decrease of 0.01 in the OR for 9p21 homozygotes).

Discussion

We tested the hypothesis that SNPs associated with CHD were associated with noncardioembolic stroke in VSR. When limiting the false discovery rate to 15%, we

Table 2. Characteristics of noncardioembolic stroke cases and healthy controls

Characteristics	Cases (n = 562)	Controls (n = 815)	p
Age, years	66.0 ± 14	58.8 ± 8.5	<0.0001
Male	326 (58.0)	397 (48.7)	0.0007
Smoking	172 (32.0)	147 (18.7)	<0.0001
Hypertension	400 (71.2)	403 (49.5)	<0.0001
Diabetes	191 (34.0)	36 (4.4)	<0.0001
Dyslipidemia	347 (61.7)	464 (56.9)	0.07
BMI	26.8 ± 4.9	26.0 ± 3.8	0.004

Age and BMI are presented as means ± SD. Figures in parentheses are percentages.

found that carriers of the CHD risk allele for 4 of the 6 SNPs we tested also had increased risk of noncardioembolic stroke. Three of these 4 SNPs were in the genes *MYH15* (rs3900940), *KIF6* (rs20455), *VAMP8* (rs1010), and the remaining SNP was on chromosome 9p21 (rs10757274).

Many genetic associations of stroke, a common complex disease, have been reported, but few have been consistently replicated. Pruissen et al. [13] discussed several reasons for the failure to replicate results from the initial association studies, these include small sample sizes, inappropriate (either inadequate or overly conservative) correction for multiple testing, population stratification, phenotype heterogeneity, and different study designs. This study has addressed several of these issues: it used a sample size of 562 cases and 814 controls, corrected for multiple testing using the false discovery rate method, adjusted for potential population stratification, and used only the noncardioembolic stroke as the end point.

The *MYH15* rs3900940 SNP that showed an association with noncardioembolic stroke in the current study also showed a consistent association with incident ischemic stroke in ARIC and in the Cardiovascular Health Study (CHS). The hazard ratios for carrying each of the risk alleles among white participants were 1.18 in ARIC (p = 0.08, appendix 1 in Morrison et al. [14]) and 1.15 in CHS (p = 0.033, table 1 in Luke et al. [15]). *MYH15* encodes myosin heavy polypeptide 15, and the rs3900940 SNP, corresponding to an amino acid change at Thr1125Ala, is located in the coiled-coil rod domain of the MYH15 protein. The Thr1125 residue has been shown to be phosphorylated [16, 17]. Since the Ala1125 residue can not be phosphorylated, this substitution may affect the function of the MYH15 protein that is regulated by phosphorylation.

The *VAMP8* rs1010 SNP has also been tested in ARIC and CHS for association with incident ischemic stroke. The risk estimate for the C allele in white participants of ARIC was consistent with results in the current study: the hazard ratio was 1.16 for each C allele (p = 0.10, appendix 1 in Morrison et al. [14]). However, the *VAMP8* SNP was not associated with incident ischemic stroke in CHS (p = 0.63, online table in Luke et al. [15]).

The SNP rs10757274 on chromosome 9p21 had been reported both to be associated [18] as well as not to be associated [19, 20] with ischemic stroke. Another chromosome 9p21 SNP, rs10757278, which is associated with myocardial infarction and is in linkage disequilibrium with rs10757274 ($r^2 = 0.89$), was reported to be associated with a combined end point of large artery atherosclerotic and cardiogenic stroke [21] but not to be associated with ischemic stroke [22]. Most recently, several 9p21 SNPs were tested for association with ischemic stroke and its subtypes, cardioembolic stroke, atherosclerotic stroke, and small vessel stroke. A number of these were found to be associated only with the atherosclerotic stroke subtype [23]. Our result showed rs10757274 to be associated with noncardioembolic stroke, but since the case definition we used was different from those in the previous reports, our result does not resolve the apparent contradicting observations in the current literature.

The rs20455 SNP in *KIF6* was not associated with incident ischemic stroke in ARIC [14] or in CHS [15]. The association of this SNP with noncardioembolic stroke in this study could have been confounded by the presence of CHD in some of the stroke cases. This notion is consistent with the observation that the OR for noncardioembolic stroke was attenuated when cases with a history of myocardial infarction were excluded from the analysis.

We did not find an association of the *PALLD* or *SNX19* SNP with noncardioembolic stroke in this study. This study provided 90% power to detect an association between carrier status and noncardioembolic stroke if the risk ratio in the population was 1.70 for the *PALLD* SNP or 2.50 for the *SNX19* SNP. Thus, these 2 SNPs may not be associated with noncardioembolic stroke, or this study did not provide sufficient power to detect the associations with lower risk ratios.

Potential limitations of this study include the case-control study design; these results may have been affected by survival bias and do not account for effects on stroke risk due to various drug treatments prior to the index event of cases or to the enrollment date of the controls.

This study included only Caucasian subjects; therefore, these SNPs should be tested in other populations.

In conclusion, we found that carriers of the CHD risk allele of 4 SNPs also had increased risk of noncardioembolic stroke in VSR, and these SNPs merit further testing in additional stroke studies.

Appendix

Two-Sided Statistical Test. A statistical test in which the null hypothesis is rejected for values of the test statistics falling into either tail of its sampling distribution.

One-Sided Statistical Test. A statistical test in which the null hypothesis is rejected only for values of the test statistics falling into 1 specified tail of its sampling distribution.

Multiple Testing. A statistical problem that occurs when one simultaneously considers multiple comparisons or tests multiple hypotheses. This is a problem because the probability of rejecting 1 or more null hypotheses incorrectly by chance is increased.

False Discovery Rate. A statistical method used to estimate the proportion of hypotheses that are falsely declared significant when multiple hypotheses are tested. The false discovery rate is also the expected proportion of rejected null hypotheses that are incorrectly rejected (false-positives).

q Value. The minimum false discovery rate at which a test may be declared significant.

Population Stratification. This manifests in genetic studies as the presence of differences in allele frequencies among subpopulations within a population, possibly due to subpopulations of different ancestry or due to admixed populations where individuals may have mixed ancestry. When population stratification exists and disease prevalence varies by subpopulations or by ancestry composition, spurious associations between disease and a genetic marker may occur. Specifically, any allele that is more frequent among the subpopulation having the higher prevalence of disease will be associated with disease status.

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