Polymorphisms in the Advanced Glycosylation End Product–Specific Receptor Gene and Risk of Incident Myocardial Infarction or Ischemic Stroke

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Background and Purpose—Recent findings of an association between polymorphisms of advanced glycosylation end product–specific receptor (AGER) and risk of diabetic vasculopathy have generated great interest. However, to date, no genetic–epidemiological data are available on risk of atherothrombotic events among nondiabetic populations.

Methods—Using DNA samples collected at baseline in a prospective cohort of 14 916 initially healthy American men, we evaluated 3 AGER genetic variants: −429T>C, −374T>A, and Gly82Ser, among 600 white individuals who subsequently developed atherothrombotic event (incident myocardial infarction or ischemic stroke) and among 600 age- and smoking-matched white individuals who remained free of reported vascular disease during follow-up (controls).

Results—Genotype distributions for the polymorphisms tested were in Hardy–Weinberg equilibrium. Haplotype-based conditional logistic regression, adjusting for other potential confounders, showed that haplotype C-T-Gly (myocardial infarction: odds ratio [OR], 0.60; 95% CI, 0.41 to 0.90; $P=0.01$) and haplotype T-A-Gly (ischemic stroke: OR, 0.63; 95% CI, 0.40 to 0.99; $P=0.05$), compared with the reference haplotype T-T-Gly, were associated with reduced risk of atherothrombosis. Prespecified analysis limited to those without baseline history of diabetes showed similar significant findings.

Conclusions—We found an association of specific AGER promoter gene haplotypes with reduced risk of incident myocardial infarction and ischemic stroke that was independent of the presence of diabetes. **(*Stroke*. 2006;37:1686-1690.)**

Key Words: genetics ■ polymorphism ■ risk factors

Recent data from human and animal studies have shown an upregulated expression of advanced glycosylation end product–specific receptor (AGER; alias RAGE) in human atherosclerotic plaques[1] and in retina, messangial, and aortic vessels,[2,3] suggesting an important role of AGER in the pathogenesis of atherothrombotic diseases.

AGER, a member of the immunoglobulin superfamily of cell surface molecules, is a receptor for various molecules, including the amyloidogenic form of serum amyloid A, amyloid-β protein, members of the S100/calgranulin superfamily, amphoterin, and AGE products.[4] The gene for AGER (LocusID 177; chromosome 6p21.3) consists of a 1.7-kb 5′ flanking region and 11 exons. Variants in the AGER gene, in particular a −429T>C (dbSNP rs1800625), a −374T>A (dbSNP rs1800624), and a Gly82Ser (dbSNP rs2070600) polymorphism, have been associated with diabetic atherosclerosis, resulting in increased risk of mortality and morbidity.[5] Furthermore, recent findings of an association between a −374T>A polymorphism and reduced risk of angiographic coronary artery disease have generated great interest.[7]

Despite these observations, no genetic–epidemiological studies have investigated the role of common AGER gene polymorphisms (−429T>C, −374T>A, and Gly82Ser) as risk markers for atherothrombotic events such as incident myocardial infarction (MI) or ischemic stroke. We therefore examined the role of these polymorphisms, or haplotypes thereof, as risk determinants in a large, prospective cohort of apparently healthy men.

Methods

Study Design

We used a nested case-control design within the Physicians' Health Study cohort, a randomized, double-blinded, placebo-controlled trial of aspirin and beta carotene initiated in 1982 among 22 071 male, predominantly white (>94%), US physicians, 40 to 84 years of age at study entry.[8] Before randomization, 14 916 participants provided an EDTA-anticoagulated blood sample that was stored for genetic

Received January 31, 2006; final revision received May 2, 2006; accepted May 4, 2006.

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Stroke **is available at http://www.strokeaha.org** **DOI: 10.1161/01.STR.0000226994.93914.6c**

analysis. All participants were free of previous MI, stroke, transient ischemic attacks, and cancer at study entry. History of cardiovascular risk factors, such as hypertension, diabetes, or hyperlipidemia, was defined by self-report of diagnosis at entry into the study. For all reported incident vascular events occurring after study enrollment, hospital records, death certificates, and autopsy reports were requested and reviewed by an end points committee using standardized diagnostic criteria.

The diagnosis of MI[8] was confirmed by evidence of symptoms in the presence of either diagnostic elevations of cardiac enzymes or diagnostic changes on electrocardiograms. In the case of fatal events, the diagnosis of MI was also accepted based on autopsy findings. Stroke was defined by the presence of a new focal neurological deficit, with symptoms and signs persisting for >24 hours, and was ascertained from blinded review of medical records, autopsy results, and the judgment of a board-certified neurologist, on the basis of clinical reports, computed tomographic (CT), or MRI scanning (>90% of CT or MRI available on stroke cases).[9]

For each case (MI or ischemic stroke), a control matched by age, smoking history, and length of follow-up were chosen among those subjects who remained free of vascular diseases. The present association study consisted of white men only (341 MI pairs and 259 ischemic stroke pairs). Among the ischemic stroke cases, 33% were embolic, 29% thrombotic, and 38% nondifferentiable embolic–thrombotic. The study was approved by the Brigham and Women's Hospital institutional review board for human subject research.

Genotype Determination

Genotype determination was performed using an Applied Biosystems (ABI) fluorescence-based assay-on-demand or assay-by-design allelic discrimination method (Applied Biosystems).[10] Each 10-μL amplification reaction volume contained 1× TaqMan Universal Master Mix (Applied Biosystems) and 10 ng of template DNA. Amplification reactions were performed on an ABI 7900HT Sequence Detection System according to manufacturer specifications.

To confirm genotype assignment, scoring was performed by 2 independent observers. Discordant results (<1% of all scoring) were resolved by a joint reading and, where necessary, a repeat genotyping. Results were scored blinded as to case-control status.

Statistical Analysis

Allele and genotype frequencies among cases and controls were compared with values predicted by Hardy–Weinberg equilibrium using the χ^2 test. Odds ratios (ORs) of MI or ischemic stroke associated with each genotype with 95% CIs were calculated separately by conditional logistic regression analysis conditional on age, smoking status, and length of follow-up because randomization and further controlling for randomized treatment assignment, history of hypertension (≥140/90 mm Hg), presence or absence of diabetes, and body mass index (BMI), assuming additive, dominant, or recessive mode of inheritance. Prespecified analysis was also performed limited to those without baseline diabetes status. Pairwise linkage disequilibrium (LD) was examined as described by Devlin and Risch.[11] Haplotype estimation and inference was determined using PHASE v2.1.1.[12] Haplotype distributions between cases and controls were examined by likelihood ratio test. In addition, the relationship between haplotypes and incident MI or ischemic stroke was examined using a haplotype-based logistic regression analysis with baseline parameterization,[13] adjusting for age, BMI, hypertension, diabetes, and randomized treatment assignment. Further, haplotype-based conditional logistic regression analysis excluding participants with baseline diabetes was performed. A global test statistic, comparing the model with genetic data with the model without genetic data using the likelihood-ratio test, was performed to check the overall association of haplotypes with the clinical outcome. All analyses were performed using SAS v9.1 package (SAS Institute Inc.). For each OR, we calculated 95% CIs. A 2-tailed P value of 0.05 was considered a statistically significant result.

TABLE 1. Baseline Characteristics of Study Participants Who Subsequently Developed Any Arterial Event (cases) and Those Who Remained Free of Vascular Disease During Follow-Up (controls)

	Controls (n=600)	Cases (n=600)	P
Age (y)	60.8±0.3	61.0±0.3	m.v.
Smoking status (%)			m.v.
Never	41.7	41.7	
Past	41.5	41.5	
Current	16.8	16.8	
BMI, kg/m^2	24.9±0.1	25.4±0.1	0.002
Blood pressure, mm Hg			
Systolic	28.6±0.5	132.7±0.6	<0.0001
Diastolic	79.6±0.3	81.8±0.3	<0.0001
*History of hyperlipidemia, %	14.9	22.8	<0.001
History of hypertension, %	29.0	47.2	<0.0001
History of diabetes, %	2.8	8.9	<0.0001
Aspirin use, %	46.3	44.8	0.60
Alcohol use, %			0.35
Daily	30.8	26.6	
Weekly	43.8	44.3	
Monthly	9.9	11.2	
Rarely/never	15.5	17.9	
Family history of premature coronary artery disease, %	8.9	10.9	0.30

Mean±SE unless otherwise stated.
m.v. indicates matching variable.
t test for continuous variables and χ^2 test for categorical variables.
*Cholesterol values were recorded categorically without lipid fractions.

Results

Baseline characteristics of the study population are shown in Table 1. As expected in a prospective cohort study, the case subjects had a higher prevalence of traditional atherosclerotic risk factors at baseline than did the control subjects. Similar baseline characteristics were observed between the MI and the ischemic stroke group (data not shown). The observed genotype distributions were in Hardy–Weinberg equilibrium in the control group. Using a standard marker-by-marker χ^2 analysis, genotype distribution was significantly different for −429T>C between MI cases and the matched controls (additive P=0.05; recessive P=0.03; Table 2), −374T>A between ischemic stroke cases and the matched controls (recessive P=0.04; Table 2), and Gly82Ser between ischemic stroke cases and the matched controls (additive P=0.02; Table 2). Results from the conditional logistic regression analysis showed: (1) an association of −492T>C polymorphism with reduced risk of MI (adjusted: additive OR, 0.71, 95% CI, 0.52 to 0.96, P=0.03; recessive OR, 0.31, 95% CI, 0.11 to 0.84, P=0.02; Table 3), and (2) an association of −374T>A polymorphism with increased risk of MI (adjusted: dominant OR, 1.45; 95% CI, 1.02 to 2.06; P=0.04; Table 3), and with reduced risk of ischemic stroke (adjusted: recessive OR, 0.27; 95% CI, 0.09 to 0.85; P=0.02). Additional adjustment for alcohol use and hyperlipidemia status again yielded virtually identical results (data not shown).

TABLE 2. Genotype and Allele Distribution

	MI			Ischemic Stroke		
	Controls, n=341	Cases, n=341	*P* Add Dom Rec	Controls, n=259	Cases, n=259	*P* Add Dom Rec
Genotype, % rs1800625 (−429T>C)						
TT	67.6	72.5	0.05	71.1	66.5	0.52
TC	27.4	25.7	0.18	25.7	30.2	0.29
CC	5.0	1.8	0.03	3.2	3.3	1.00
Allele						
T	0.81	0.85		0.84	0.82	
C	0.19	0.15	0.04	0.16	0.18	0.34
Genotype, % rs1800624 (−374T>A)						
TT	58.1	51.6	0.25	54.5	61.6	0.06
TA	34.6	39.9	0.11	38.8	35.7	0.11
AA	7.3	8.5	0.67	6.7	2.7	0.04
Allele						
T	0.75	0.72		0.74	0.79	
A	0.25	0.28	0.11	0.26	0.21	0.036
Genotype, % rs2070600 (Gly82Ser)						
GlyGly	91.1	92.1	0.68	95.7	91.5	0.02
GlySer	8.9	7.9	0.68	3.5	8.5	0.07
SerSer	...		...	0.8	0.0	0.50
Allele						
Gly	0.96	0.96		0.97	0.96	
Ser	0.04	0.04	0.66	0.03	0.04	0.14

Genotype distributions were in Hardy–Weinberg equilibrium.

P values (exact test) for the differences between cases and matched controls in genotype distribution.

Additive (Add) indicates major homozygotes vs heterozygotes vs minor homozygotes; dominant (Dom), major homozygotes vs heterozygotes/minor homozygotes; Recessive (Rec), major homozygotes/heterozygotes vs minor homozygotes.

The polymorphisms tested were in LD among one another (Table 4). Overall haplotype distributions were similar between cases and controls (Table 5). Results from the haplotype-based conditional logistic regression analysis showed that compared with the reference haplotype T-T-Gly, haplotype C-T-Gly (MI OR, 0.60, 95% CI, 0.41 to 0.90, $P=0.01$; global test statistic χ^2 3 $df=9.11$, $P=0.028$), and haplotype T-A-Gly (ischemic stroke OR, 0.63, 95% CI, 0.40 to 0.99, $P=0.05$; global test statistic χ^2 3 $df=4.61$, $P=0.20$) were associated with reduced risk of atherothrombosis (Table 6). Because the 3 most common haplotypes (Table 6) contained the Gly allele, the haplotype-based analysis was rerun excluding the Gly82Ser variant, and similar significant findings were observed. Furthermore, similar findings were obtained in analyses limited to nondiabetic participants in the MI group but not in the ischemic stroke group (Table 6). This could be because of the small sample size leading to loss of power.

TABLE 3. Conditional Logistic Regression Analysis

	MI			Ischemic Stroke		
Adjusted	OR	95% CI	*P*	OR	95% CI	*P*
rs1800625 (−429T>C)						
Additive mode	0.71	0.52–0.96	0.03	1.02	0.70–1.48	0.93
Dominant mode	0.73	0.51–1.04	0.08	1.09	0.71–1.67	0.70
Recessive mode	0.31	0.11–0.84	0.02	0.58	0.17–2.01	0.39
rs1800624 (−374T>A)						
Additive mode	1.23	0.94–1.61	0.13	0.75	0.54–1.06	0.10
Dominant mode	1.45	1.02–2.06	0.04	0.81	0.55–1.21	0.31
Recessive mode	0.98	0.55–1.76	0.95	0.27	0.09–0.85	0.02
rs2070600 (Gly82Ser)						
Additive mode	0.83	0.47–1.47	0.52	1.62	0.76–3.44	0.21
Dominant mode	0.83	0.47–1.47	0.52	1.88	0.81–4.40	0.14
Recessive mode	...	...	...	...	...	...

Adjusted indicates further controlling for randomized treatment group, BMI, history of hypertension, and presence or absence of diabetes; additive, major homozygotes vs heterozygotes vs minor homozygotes; dominant, major homozygotes vs heterozygotes/minor homozygotes; recessive, major homozygotes/heterozygotes vs minor homozygotes.

Discussion

The present study represents a nested case-control, genetic–epidemiological investigation examining possible associa-

TABLE 4. Pairwise LD Analysis

	r		
	−429T>C	−374T>A	Gly82Ser
D′			
−429T>C	...	0.26	0.09
−374T>A	1.00	...	0.11
Gly82Ser	1.00	0.90	...

D′ indicates Lewontin's normalized value; *r*, correlation coefficient.

TABLE 5. Haplotype Frequency by Study Group

	MI Controls	MI Cases	*P*	*P**	Ischemic Stroke Controls	Ischemic Stroke Cases	*P*	*P**
Haplotype				0.35				0.17
T-T-Gly	0.522	0.530	0.77		0.555	0.567	0.69	
T-A-Gly	0.246	0.284	0.11		0.258	0.205	0.04	
C-T-Gly	0.187	0.146	0.04		0.161	0.184	0.32	
T-T-Ser	0.044	0.040	0.66		0.023	0.043	0.06	

Haplotype with frequency ≥1% shown.
Confidence level for haplotype estimation and inference ≥95%.
**P* for global likelihood ratio test.
P for χ^2 test of haplotype–trait association on each individual haplotype between cases and controls.

tions of AGER gene haplotypes with risk of atherothrombotic events. Overall, we found an association of haplotype carrying the −429T>C variant with reduced risk of incident MI and of haplotype carrying the −374T>A variant with reduced risk of incident ischemic stroke.

Vascular disease is a major cause of death and disability in the Western world, and inflammatory-immune reactions have been implicated in the pathogenesis of atherothrombotic disorders. AGER, a multiligand receptor, mediates cellular dysfunction in several inflammatory-immune disorders, tumors, neurodegenerative conditions such as Alzheimer disease, renal disease, and in diabetes-associated atherosclerosis.[4,14] Further, −429T>C and −374T>A gene variants have also been associated with diabetic nephropathy in type II diabetic patients and with proteinuria and cardiovascular disease in type I diabetic patients, respectively.[5] In addition, −429T>C and −374T>A gene variants have been shown to have a 2-fold and 3-fold increase in transcriptional activity, respectively.[6] As for Gly82Ser variant, its location in V-domain of the extracellular segment of the receptor in exon 3 has been demonstrated to exhibit differential receptor-binding affinity for AGER ligands.[15]

Using a single-marker approach, Falcone et al recently reported an association of the −374T>A polymorphism with reduced risk of coronary artery disease, assuming a recessive mode of inheritance, in a small cross-sectional Italian study population.[7] However, these authors did not evaluate other polymorphisms in AGER gene and therefore provide no haplotype-based analysis. Because common, complex diseases exhibit an unknown mode of inheritance, an alternative approach is to assess the possible/appropriate genetic model using marker-by-marker χ^2 analyses and test only those for which a genetic model has been determined.

Together, our findings that haplotypes carrying either the −429T>C or the −374T>A variant are associated with reduced risk of MI and ischemic stroke, respectively, provide additional evidence of a protective role for AGER promoter gene polymorphisms in atherothrombosis. The pathophysiological consequences of the altered transcriptional activity or receptor-binding affinity associated with these gene variants remain elusive. As noted previously,[16,17] our results also suggest the importance of including a haplotype-based approach for assessment of genetic association investigations. Of note, we found no correlation between the T-A-Gly haplotype with baseline BMI (MI $r=-0.04$, $P=0.42$; ischemic stroke $r=0.04$, $P=0.50$), systolic blood pressure (MI $r=-0.05$, $P=0.36$; ischemic stroke $r=0.04$, $P=0.55$), and diastolic blood pressure (MI $r=-0.03$, $P=0.55$; ischemic stroke $r=0.02$, $P=0.80$) in the respective control groups. Similar null findings were also observed for the C-T-Gly haplotype with baseline BMI (MI $r=0.01$, $P=0.88$; ischemic

TABLE 6. Conditional Logistic Regression With Haplotype-Based Parameterization: T-T-G as the Reference Haplotype

Arterial Event	OR	95% CI	*P*	*χ^2 3 *df P*	Arterial Event Without Baseline Diabetes	OR	95% CI	*P*	*χ^2 3 *df P*
Adjusted									
MI				9.11, 0.03					7.05, 0.07
T-T-Gly	Reference	...	...			Reference	...	...	
T-A-Gly	1.05	0.76–1.45	0.77			1.00	0.72–1.39	0.99	
C-T-Gly	0.60	0.41–0.90	0.01			0.62	0.41–0.93	0.02	
T-T-Ser	0.69	0.36–1.33	0.27			0.70	0.36–1.37	0.30	
Ischemic stroke				4.61, 0.20					4.29, 0.23
T-T-Gly	Reference	...	...			Reference	...	...	
T-A-Gly	0.63	0.40–0.99	0.05			0.63	0.39–1.02	0.06	
C-T-Gly	0.75	0.45–1.23	0.25			0.85	0.49–1.48	0.57	
T-T-Ser	1.07	0.42–2.70	0.89			1.25	0.46–3.45	0.66	

Adjusted indicates further controlling for randomized treatment group, BMI, history of hypertension, and presence or absence of diabetes.
Confidence level for haplotype estimation and inference ≥95%.
*χ^2 and *P* values for global likelihood–ratio test comparing model with haplotypes to model without.

stroke $r=-0.05$, $P=0.43$), systolic blood pressure (MI $r=-0.05$, $P=0.35$; ischemic stroke $r=-0.01$, $P=0.91$), and diastolic blood pressure (MI $r=-0.07$, $P=0.19$; ischemic stroke $r=0.06$, $P=0.37$). Because the baseline hyperlipidemia status was collected as a binary variable, the correlation of this baseline variable with these 2 haplotypes cannot be examined in the present investigation.

The fact that we used a closed cohort in which the determination of case status was based solely on the subsequent development of disease rather than on any arbitrary selection criteria designed by the investigators greatly reduced the possibility of bias and confounding. Nonetheless, our study population consists entirely of white males, so the data cannot be generalized to other ethnic groups/women and other populations. It is also important to recognize that association studies like the present one only examine the possible association between phenotype and the actually tested polymorphism(s); such studies cannot exclude the possibility that the polymorphisms/haplotypes tested are in LD with a yet-to-be-identified susceptibility gene(s)/polymorphism(s) that is responsible for the observed significant associations. Further investigation of these AGER polymorphisms combined with a gene-based approach with tagging single-nucleotide polymorphisms is warranted to evaluate the possible involvement of AGER gene variation in atherothrombotic events. Because data are not available on baseline plasma AGER levels, the impact of this intermediate phenotype cannot be examined within the context of the present investigation. Further, we have limited information on ischemic stroke subtype classification, and small sample size for our available subtypes (namely embolic, thrombotic, or nondifferentiable), the potential association of these AGER polymorphisms/haplotypes with subtypes of ischemic stroke, and noncardioembolic infarction cannot be evaluated in the present investigation.

In conclusion, these data from a cohort of apparently healthy white US men provide evidence of an association between specific AGER haplotypes tested and reduced risk of atherothrombotic events. If corroborated in other studies, our data suggest a possible protective effect of the AGER gene in atherothrombosis.

Sources of Funding

This work was supported by grants from the National Heart, Lung, and Blood Institute (HL-58755, HL-63293, and DK-064841 [to J.R.R.]), the Doris Duke Charitable Foundation, the American Heart Association, and the Donald W. Reynolds Foundation, Las Vegas, Nev.

Disclosures

None.

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Stroke. 2006;37:1686-1690; originally published online May 25, 2006;
doi: 10.1161/01.STR.0000226994.93914.6c
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628