α-Adducin Polymorphism, Atherosclerosis, and Cardiovascular and Cerebrovascular Risk

Marie Josee E. van Rijn, MSc; Michiel J. Bos, MSc; Mojgan Yazdanpanah, MD, PhD; Aaron Isaacs, DSc; Alejandro Arias-Vásquez, DSc; Peter J. Koudstaal, MD, PhD; Albert Hofman, MD, PhD; Jacqueline C. Witteman, PhD; Cornelia M. van Duijn, PhD; Monique M.B. Breteler, MD, PhD

Background and Purpose—Carriers of the 460Trp allele of the α-adducin gene (ADD1) show higher rates of sodium reabsorption compared with homozygous carriers of the Gly460 allele and were found to have an increased risk of hypertension and cardiovascular disease. We studied the association between the Gly460Trp polymorphism and atherosclerosis, cardiovascular disease, and cerebrovascular disease.

Methods—Intima-media thickness of the common carotid artery, as well as incident stroke and myocardial infarction, were studied within 6471 subjects of the Rotterdam Study. Within 1018 subjects of the Rotterdam Scan Study, prevalent silent brain infarcts and cerebral white matter lesions were studied. Subjects were grouped into 460Trp carriers (variant carriers) and homozygous carriers of the Gly460 allele (reference).

Results—Intima-media thickness of the common carotid artery was 0.80 mm in variant carriers compared with 0.79 mm in the reference group (P=0.04). Variant carriers had an increased risk of any stroke (hazard ratio [HR], 1.22; 95% CI, 1.02 to 1.45), ischemic stroke (HR, 1.29; 95% CI, 1.02 to 1.63), hemorrhagic stroke (HR, 1.07; 95% CI, 0.59 to 1.92), and of myocardial infarction (HR, 1.33; 95% CI, 1.05 to 1.69). For any ischemic stroke, there was a significant interaction between the Gly460Trp polymorphism and hypertension. Variant carriers more often had a silent brain infarct (odds ratio, 1.36; 95% CI, 0.98 to 1.88) and had more subcortical white matter lesions than the reference group (1.45 vs 1.24 mL; P=0.22).

Conclusions—The Gly460Trp polymorphism is associated with atherosclerosis, cardiovascular disease, and cerebrovascular disease, especially in hypertensive subjects. (Stroke. 2006;37:2930-2934.)

Key Words: α-adducin ▪ atherosclerosis ▪ cardiovascular disease ▪ cerebrovascular disease ▪ polymorphism

Hypertension is a major risk factor for atherosclerosis, cardiovascular disease, and cerebrovascular disease.1–4 Recently, it was found that not only hypertension and stroke but also hypertension and myocardial infarction (MI) cluster within families.5,6 This suggests that overlapping genetic factors, alone or in conjunction with environmental factors, influence susceptibility to hypertension, stroke, and MI.

Adducin is a cytoskeletal protein consisting of an α- and a β-subunit. It favors the binding of actin to spectrin and may affect ion transport through the actin cytoskeleton and modulation of Na+/K+ pump activity.7,8 Carriers of the 460Trp allele (variant allele) of the α-adducin gene (ADD1), located on chromosome 4p16.3, show a higher Na+/K+ pump activity and therefore, higher rates of renal tubular sodium reabsorption compared with homozygous carriers of the Gly460 allele (wild-type allele).9,10 The Gly460Trp polymorphism has been associated with blood pressure levels and the risk of hypertension in many, but not all, populations.11 Furthermore, this polymorphism has been associated with salt sensitivity,12 which reportedly is a risk factor for cardiovascular events.13 Indeed, carriers of the 460Trp allele were found to have an increased risk of cardiovascular disease, although findings have not been consistent.11,14 So far, no association has been found between ADD1 and ischemic stroke.15,16 We studied the Gly460Trp polymorphism in relation to atherosclerosis, MI, and cerebrovascular disease. Also, we studied the interaction between hypertension and the Gly460Trp polymorphism with respect to all of the aforementioned outcomes.

Subjects and Methods

Study Populations

The Rotterdam Study is an ongoing prospective, population-based cohort study on chronic and disabling diseases in the elderly. Baseline examinations were done between 1990 and 1993. A total of 7983 subjects (age ≥55 years) participated in this study. In 6471

Received March 23, 2006; final revision received June 9, 2006; accepted July 18, 2006.


Correspondence to Prof M.M.B. Breteler, Department of Epidemiology and Biostatistics, Erasmus Medical Center, PO Box 1738, 3000 DR Rotterdam, The Netherlands. E-mail m.breteler@erasusmc.nl

© 2006 American Heart Association, Inc.

Stroke is available at http://www.strokeaha.org DOI: 10.1161/01.STR.0000248760.67039.2b

2930
(81.1%) participants, the Gly460Trp polymorphism was successfully genotyped. The Rotterdam Scan Study was designed to study the etiology and natural history of age-related brain changes in the elderly. Baseline examinations, which included brain MRI scanning, were performed in 1995 and 1996 in 1077 participants (aged 60 to 90 years). In 1018 (94.5%) participants, the Gly460Trp polymorphism was successfully genotyped. The medical ethic committee of Erasmus Medical Center, Rotterdam, approved both studies, and all participants gave written, informed consent and permission to retrieve information from treating physicians.

**Measurements**

Body mass index (BMI) was calculated from height and weight. Blood pressure was measured twice with a random-zero sphygmomanometer. The average of 2 measurements was used for analyses. Hypertension was defined as a systolic blood pressure of 160 mm Hg or higher or a diastolic blood pressure of 100 mm Hg or higher (grade 2 and 3 of the 1999 World Health Organization criteria) or use of blood pressure–lowering medication. Information on smoking habits was obtained during a home interview.

We collected nonfasting blood samples from all participants. We defined diabetes mellitus as a random glucose level ≥11.1 mmol/L or use of oral antidiabetic agents or insulin. Total serum cholesterol and HDL cholesterol were determined by means of an automated enzymatic method.

**Measurements of Atherosclerosis**

Intima-media thickness of the common carotid artery (CCA IMT) was assessed by duplex scan ultrasonography for an average distance of 10 mm. We used the average of the measurements of 3 still images of both the left and right arteries. CCA IMT was determined as the mean of the mean IMT of near- and far-wall measurements of both the left and right arteries. From a reproducibility study, it could be calculated that the intraclass correlation coefficient between 2 visits was 0.74. These measurements were done in 5643 participants. For 5083 participants, genotypic information was available.

**Stroke and MI**

Stroke and MI were assessed as part of the Rotterdam Study. A prevalent stroke or MI was determined during the baseline interview and verified by checking medical records. Incident stroke and MI were determined by continuously monitoring subjects for major events. Research physicians reviewed information on all possible strokes and transient ischemic attacks with an experienced stroke neurologist (P.J.K.) to verify all diagnoses. Subarachnoid hemorrhages and retinal strokes were excluded. A stroke was classified ischemic when a patient had typical symptoms and a CT or MRI scan, that was made within 4 weeks after the stroke occurred, ruled out other diagnoses, or when indirect evidence (deficit limited to 1 limb or completely resolved within 72 hours, or atrial fibrillation in the absence of anticoagulants) pointed to an ischemic nature of the stroke. A stroke was classified hemorrhagic when a relevant hemorrhage was shown on CT or MRI scan, or when the subject lost consciousness permanently or died within hours after the onset of focal signs. If a stroke did not match any of these criteria, it was classified unspecified. During follow-up, 637 first-ever strokes occurred. Genotype data were available for 498 of these individuals. Information on MIs was obtained from general practitioners. Two research physicians independently coded all reported events according to the International Classification of Diseases, 10th edition. In case of disagreement, consensus was reached. Finally, a medical expert in cardiovascular disease, whose judgment was considered final, reviewed all events. All available information, which included ECG, cardiac enzyme levels, and the clinical judgment of the treating specialist, was used. Incident MI was defined as the occurrence of a fatal or nonfatal MI (International Classification of Diseases, 10th edition, code I21) after the baseline examination. Follow-up started at baseline and lasted until January 1, 2002, for stroke and until January 1, 2003, for MI. Of all participants, 2.6% were lost to follow-up. For these subjects, the follow-up time was computed until the last date of contact. We ascertained 371 incident MI cases. For 272 cases, genotypic data were available.

**Silent Brain Infarcts and White Matter Lesions**

The presence of silent brain infarcts (SBIs) was assessed in the Rotterdam Scan Study. Infarcts were defined as focal hyperintensities on T2-weighted images, 3 to 20 mm in size. SBIs were defined as evidence for 1 or more infarcts on MRI, without a history of a (corresponding) stroke or transient ischemic attack. We observed SBIs in 217 participants. Genotypic data were available for 119 cases.

White matter lesions (WMLs) were scored as present if visible as hyperintensities on proton-density and T2-weighted images, without a prominent hypointensity on T1-weighted scans and, according to their location, as periventricular or subcortical. Periventricular WMLs were rated semiquantitatively (range, 0 to 9). A total volume of subcortical WMLs was approximated on the basis of the number and size of lesions (volume range, 0 to 29.5 mL).

**Genotyping**

Genotyping was performed with TaqMan allelic discrimination assays-by-design (Applied Biosystems). The forward primer sequence was 5′-GAGAAGACAGATGGCTGAACCT-3′, and the reverse primer sequence was 5′-GTCTTCGACTTGAGACTGCTT-3′. The minor groove binding probes were 5′-VIC-CATTTCTGCCTTCCTC-3′ and 5′-FAM-ATTTCTGCCATTCCTC-3′. We used the reverse-strand design. The assays used 5 ng of genomic DNA and 5-μL reaction volumes. The amplification and extension protocol was as follows: an initial activation step of 10 minutes at 95°C preceded 40 cycles of denaturation at 95°C for 15 seconds and annealing and extension at 50°C for 60 seconds. Allele-specific fluorescence was then analyzed on an ABI Prism 7900HT sequence detection system with SDS v 2.1 (Applied Biosystems). Based on the analysis of blind duplicates, there was a 98% concordance in genotyping.

**Statistical Analyses**

Hardy-Weinberg equilibrium proportions were tested with the GENEPOP package. Baseline characteristics were compared by univariate ANOVA or χ² statistics. Univariate ANOVAs were used to assess the relation between the Gly460Trp polymorphism and CCA IMT and WMLs. Cox proportional-hazards regression analysis was used to assess the association between the Gly460Trp polymorphism and stroke and MI. For the analyses on incident stroke, we excluded prevalent strokes; for the analyses on incident MI, we excluded prevalent MI at baseline from the analyses. We performed a binary logistic-regression analysis to study the relation between the Gly460Trp polymorphism and SBIs. All analyses were adjusted for age and sex and additionally for hypertension, BMI, total cholesterol, diabetes mellitus, and smoking and performed with SPSS version 11.0.

**Results**

Genotype frequencies were in Hardy-Weinberg equilibrium in both study populations. Table 1 shows the baseline characteristics stratified by ADD1 genotype. No significant differences were observed between the genotype groups with the exception of smoking. Within the Rotterdam Study, there were significantly more smokers among the variant carriers, compared with wild-type homozygotes. After adjusting for age and sex, no association between the Gly460Trp polymorphism and blood pressure or hypertension was found in either of the 2 study populations (not shown).

The Figure shows that overall, adjusted for age and sex, variant carriers had an increase in mean CCA IMT (0.80 mm) compared with wild-type homozygotes (0.79 mm, P = 0.04). This finding did not remain significant after additional
adjustment for smoking and other cardiovascular risk factors. Within hypertensive subjects, mean CCA IMT was 0.85 mm in variant carriers, compared with 0.83 mm in wild-type homozygotes (P=0.03). After additional adjustment for smoking and other cardiovascular risk factors, this finding remained significant. No significant differences were observed within normotensive subjects. The interaction term hypertension × ADD1 was not a significant predictor of CCA IMT (P=0.07) in the model including age, sex, hypertension, and ADD1.

We classified 291 stroke cases as ischemic, 47 as hemorrhagic, and 160 as unspecified. Table 2 shows the hazard ratio (HR) for incident stroke and MI, by genotype, adjusted for age and sex. Variant carriers were found to have an increased risk of any stroke (hazard ratio [HR], 1.22; 95% CI, 1.02 to 1.45), ischemic stroke (HR, 1.29; 95% CI, 1.05 to 1.63), and MI (HR, 1.33; 95% CI, 1.05 to 1.69), compared with wild-type homozygotes. Findings remained significant after additional adjustment for smoking and other cardiovascular risk factors. No significant association was found between the Gly460Trp polymorphism and hemorrhagic stroke.

Table 3 shows that for variant carriers, after adjusting for age and sex, we observed an increased risk for the prevalence of SBI (odds ratio, 1.36; 95% CI, 0.98 to 1.88). There was no difference in mean periventricular WML grade between variant carriers and wild-type homozygotes (Table 3). There was an increase in mean subcortical WML volume for variant carriers (1.45 ± 0.14 mL) compared with wild-type homozygotes (1.24 ± 0.10 mL), but this difference was not significant (P=0.22).

Within the Rotterdam Study, we investigated the interaction between hypertension and the Gly460Trp polymorphism in relation to atherosclerosis (see the Figure), stroke, and MI. Table 4 shows the interaction between hypertension and the Gly460Trp polymorphism in relation to stroke and MI. We found an increased risk for variant carriers with hypertension for any stroke (HR, 2.18; 95% CI, 1.70 to 2.79), ischemic stroke (HR, 2.32; 95% CI, 1.68 to 3.21), hemorrhagic stroke (HR, 2.48; 95% CI, 1.13 to 5.42), and MI (HR, 1.81; 95% CI, 1.26 to 2.62), compared with wild-type homozygotes without hypertension, adjusted for age and sex. Adjusting for smoking and other cardiovascular risk factors did not alter these results. The interaction term hypertension × ADD1 was a significant predictor of any stroke (P=0.04) in the model including age, sex, hypertension and ADD1 and in the full model including age, sex, hypertension, ADD1, BMI, total cholesterol, diabetes mellitus, and smoking (P=0.04). This interaction term was also significant for ischemic stroke, in the model including age, sex, ADD1, and hypertension.

---

TABLE 2. The Rotterdam Study: Risk of Incident Stroke and MI in Relation to the ADD1 Polymorphism

<table>
<thead>
<tr>
<th>ADD1 Gly460Trp</th>
<th>n</th>
<th>HR (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADD1 Gly460Trp</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG GT/TT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any incident stroke</td>
<td>498</td>
<td>1 (Reference)</td>
<td>1.22 (1.02–1.45)*</td>
</tr>
<tr>
<td>Incident ischemic stroke</td>
<td>291</td>
<td>1 (Reference)</td>
<td>1.29 (1.02–1.63)*</td>
</tr>
<tr>
<td>Incident hemorrhagic stroke</td>
<td>47</td>
<td>1 (Reference)</td>
<td>1.07 (0.59–1.92)</td>
</tr>
<tr>
<td>Incident MI</td>
<td>272</td>
<td>1 (Reference)</td>
<td>1.33 (1.05–1.69)*</td>
</tr>
</tbody>
</table>

n indicates the absolute No. of cases. All HRs were adjusted for age and sex. For incident stroke, all prevalent strokes were excluded; for incident MI, all prevalent MIs were excluded.

*P<0.05 compared with the GG genotype.
families. This suggests that overlapping genetic factors as well as hypertension and MI, coaggregate strongly within stroke.22,26 Also, it has been reported that variant carriers have an increased left ventricular mass29 and are at increased risk of coronary heart disease.14 Recently, it was found that hypertension and stroke, as well as hypertension and MI, coaggregate strongly within families.5,6 This suggests that overlapping genetic factors influence the susceptibility to hypertension, stroke, and MI. We did not observe an association between the Gly460Trp polymorphism and hemorrhagic stroke. This may be due to small numbers. Also, this may be the result of survival bias.

This is especially important, as case fatality is higher in patients with hemorrhagic stroke compared with ischemic stroke.30,31 Especially in hemorrhagic stroke patients with high blood pressure on admission, the prognosis was found to be poor.32 Consistent with the association between stroke and SBIs and WMLs22,26 and the association between the Gly460Trp polymorphism and stroke in our study, we observed an association between the Gly460Trp polymorphism and SBIs and subcortical WMLs. The lack of statistical significance may have been due to a lack of power.

We found a significant interaction between the Gly460Trp polymorphism and hypertension with respect to any and ischemic stroke, suggesting that hypertension is an effect modifier in the development of these diseases. This does not mean that the effect of ADD1 on these outcomes may be solely attributed to an effect on blood pressure. We did not observe a relation between the Gly460Trp polymorphism and blood pressure or hypertension. Also, after adjusting for hypertension or blood pressure, the associations between the Gly460Trp polymorphism and IMT, stroke, and MI remained significant, suggesting that hypertension and blood pressure are not part of the intermediate pathway. A potential pathway could be salt sensitivity, which was found to be a risk factor for cardiovascular events, independent of blood pressure.13

In the Rotterdam Study, we found an increased mean CCA IMT and a higher risk for any stroke, ischemic stroke, and MI for carriers of the 460Trp allele. Consistent with these findings, we found in the Rotterdam Scan Study that variant carriers had an increased risk of SBI and an increase in mean subcortical WML volume, but these findings were not significant. We found a significant interaction between the Gly460Trp polymorphism and hypertension in relation to any stroke and ischemic stroke. To the best of our knowledge, this is the first study to find an association between the Gly460Trp polymorphism and CCA IMT, ischemic stroke, and MI. The strengths of our study are the size of our study populations and the fact that we were able to study the effect of ADD1 in relation to clinical stroke, SBIs, and WMLs. SBIs and WMLs have previously been found to be risk factors for stroke.22,26

An early marker of ischemic stroke, CCA IMT27 was increased in variant carriers in this study, especially in hypertensive subjects. Also, we observed significant associations between the Gly460Trp polymorphism and any and ischemic stroke and MI. Hypertension has been found to be a strong risk factor for all of these outcomes.1–3,13,28 Also, it has been reported that variant carriers have an increased left ventricular mass29 and are at increased risk of coronary heart disease.14 Recently, it was found that hypertension and stroke, as well as hypertension and MI, coaggregate strongly within families.5,6 This suggests that overlapping genetic factors influence the susceptibility to hypertension, stroke, and MI.

We did not observe an association between the Gly460Trp polymorphism and hemorrhagic stroke. This may be due to small numbers. Also, this may be the result of survival bias. This is especially important, as case fatality is higher in patients with hemorrhagic stroke compared with ischemic stroke.30,31 Especially in hemorrhagic stroke patients with high blood pressure on admission, the prognosis was found to be poor.32 Consistent with the association between stroke and SBIs and WMLs22,26 and the association between the Gly460Trp polymorphism and stroke in our study, we observed an association between the Gly460Trp polymorphism and SBIs and subcortical WMLs. The lack of statistical significance may have been due to a lack of power.

We found a significant interaction between the Gly460Trp polymorphism and hypertension with respect to any and ischemic stroke, suggesting that hypertension is an effect modifier in the development of these diseases. This does not mean that the effect of ADD1 on these outcomes may be solely attributed to an effect on blood pressure. We did not observe a relation between the Gly460Trp polymorphism and blood pressure or hypertension. Also, after adjusting for hypertension or blood pressure, the associations between the Gly460Trp polymorphism and IMT, stroke, and MI remained significant, suggesting that hypertension and blood pressure are not part of the intermediate pathway. A potential pathway could be salt sensitivity, which was found to be a risk factor for cardiovascular events, independent of blood pressure.13

It has previously been reported that there is an interaction between the 460Trp allele and diuretic therapy. Hypertensive subjects carrying the variant allele and treated with diuretics were at lower risk of stroke and MI compared with other antihypertensive therapies. We found that in hypertensive subjects carrying the variant allele of the Gly460Trp polymorphism, the risk of stroke was significantly increased. Therefore, it is of great importance to optimize treatment of hypertension for these patients. When selecting antihypertensive medication, the genetic profile of a patient may need to be taken into account in the future.

\[
\text{(P=0.05) but was only borderline in the full model (P=0.06). No interaction was found between hypertension and SBIs or WML.}
\]

**Discussion**

In the Rotterdam Study, we found an increased mean CCA IMT and a higher risk for any stroke, ischemic stroke, and MI for carriers of the 460Trp allele. Consistent with these findings, we found in the Rotterdam Scan Study that variant carriers had an increased risk of SBI and an increase in mean subcortical WML volume, but these findings were not significant. We found a significant interaction between the Gly460Trp polymorphism and hypertension in relation to any stroke and ischemic stroke. To the best of our knowledge, this is the first study to find an association between the Gly460Trp polymorphism and CCA IMT, ischemic stroke, and MI. The strengths of our study are the size of our study populations and the fact that we were able to study the effect of ADD1 in relation to clinical stroke, SBIs, and WMLs. SBIs and WMLs have previously been found to be risk factors for stroke.22,26

An early marker of ischemic stroke, CCA IMT27 was increased in variant carriers in this study, especially in hypertensive subjects. Also, we observed significant associations between the Gly460Trp polymorphism and any and ischemic stroke and MI. Hypertension has been found to be a strong risk factor for all of these outcomes.1–3,13,28 Also, it has been reported that variant carriers have an increased left ventricular mass29 and are at increased risk of coronary heart disease.14 Recently, it was found that hypertension and stroke, as well as hypertension and MI, coaggregate strongly within families.5,6 This suggests that overlapping genetic factors influence the susceptibility to hypertension, stroke, and MI.

We did not observe an association between the Gly460Trp polymorphism and hemorrhagic stroke. This may be due to small numbers. Also, this may be the result of survival bias. This is especially important, as case fatality is higher in patients with hemorrhagic stroke compared with ischemic stroke.30,31 Especially in hemorrhagic stroke patients with high blood pressure on admission, the prognosis was found to be poor.32 Consistent with the association between stroke and SBIs and WMLs22,26 and the association between the Gly460Trp polymorphism and stroke in our study, we observed an association between the Gly460Trp polymorphism and SBIs and subcortical WMLs. The lack of statistical significance may have been due to a lack of power.

We found a significant interaction between the Gly460Trp polymorphism and hypertension with respect to any and ischemic stroke, suggesting that hypertension is an effect modifier in the development of these diseases. This does not mean that the effect of ADD1 on these outcomes may be solely attributed to an effect on blood pressure. We did not observe a relation between the Gly460Trp polymorphism and blood pressure or hypertension. Also, after adjusting for hypertension or blood pressure, the associations between the Gly460Trp polymorphism and IMT, stroke, and MI remained significant, suggesting that hypertension and blood pressure are not part of the intermediate pathway. A potential pathway could be salt sensitivity, which was found to be a risk factor for cardiovascular events, independent of blood pressure.13

It has previously been reported that there is an interaction between the 460Trp allele and diuretic therapy.15 Hypertensive subjects carrying the variant allele and treated with diuretics were at lower risk of stroke and MI compared with other antihypertensive therapies. We found that in hypertensive subjects carrying the variant allele of the Gly460Trp polymorphism, the risk of stroke was significantly increased. Therefore, it is of great importance to optimize treatment of hypertension for these patients. When selecting antihypertensive medication, the genetic profile of a patient may need to be taken into account in the future.

**Table 3. Rotterdam Scan Study: Association of the ADD1 Polymorphism With SBIs and WMLs**

<table>
<thead>
<tr>
<th>ADD1 Gly460Trp</th>
<th>SBIs</th>
<th>Periventricular WMLs</th>
<th>Deep Subcortical WMLs</th>
</tr>
</thead>
<tbody>
<tr>
<td>GG</td>
<td>n</td>
<td>OR (95% CI)</td>
<td>Mean ± SE</td>
</tr>
<tr>
<td>GT/TT</td>
<td>85</td>
<td>1.36 (0.98–1.88)</td>
<td>369</td>
</tr>
</tbody>
</table>

**Table 4. The Rotterdam Study: Interaction Between Hypertension and the ADD1 Polymorphism in Relation to Incident Stroke and MI**

<table>
<thead>
<tr>
<th>Hypertension (HT), ADD1</th>
<th>Any Stroke</th>
<th>Ischemic Stroke</th>
<th>Hemorrhagic Stroke</th>
<th>MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HT−, GG</td>
<td>n</td>
<td>HR (95% CI)</td>
<td>n</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>GT/TT</td>
<td>154</td>
<td>1 (Reference)</td>
<td>91</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>GT/TT</td>
<td>94</td>
<td>1.02 (0.79–1.31)</td>
<td>57</td>
<td>1.03 (0.74–1.43)</td>
</tr>
<tr>
<td>GT/TT</td>
<td>130</td>
<td>1.46 (1.15–1.84)*</td>
<td>69</td>
<td>1.42 (1.03–1.94)*</td>
</tr>
<tr>
<td>GT/TT</td>
<td>104</td>
<td>2.18 (1.70–2.79)†</td>
<td>62</td>
<td>2.32 (1.68–3.21)†</td>
</tr>
</tbody>
</table>

**P for interaction**

0.04

0.05

0.3

0.6

All HRs were adjusted for age and sex.

*P=0.05, †P=0.001 compared with the reference group HT−, GG.
Sources of Funding

The Rotterdam Study is supported by the Erasmus Medical Center and Erasmus University Rotterdam; the Netherlands Organization for Scientific Research (NWO); the Netherlands Organization for Health Research and Development (ZonMW); the Research Institute for Diseases in the Elderly (RIJE); the Ministry of Education, Culture and Science; the Ministry of Health, Welfare and Sports; the European Commission (DG XII); and the Municipality of Rotterdam.

Disclosures

None.

References


α-Adducin Polymorphism, Atherosclerosis, and Cardiovascular and Cerebrovascular Risk
Marie Josee E. van Rijn, Michiel J. Bos, Mojgan Yazdanpanah, Aaron Isaacs, Alejandro Arias-Vásquez, Peter J. Koudstaal, Albert Hofman, Jacqueline C. Witteman, Cornelia M. van Duijn and Monique M. B. Breteler

Stroke. 2006;37:2930-2934; originally published online November 2, 2006;
doi: 10.1161/01.STR.0000248760.67039.2b
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/37/12/2930