ADD1 460W Allele Associated With Cardiovascular Disease in Hypertensive Individuals

Alanna C. Morrison, Molly S. Bray, Aaron R. Folsom, Eric Boerwinkle

Abstract—High blood pressure is a predictor of cardiovascular disease. Hence, genes contributing to essential hypertension may play a role in the etiology of cardiovascular disease. For this reason, we examined the association between the α-adducin (ADD1) G460W and G-protein β3 subunit (GNB3) 825C→T polymorphisms and the prevalence of peripheral arterial disease (PAD) and incidence of coronary heart disease (CHD) in non-Hispanic whites from the Atherosclerosis Risk in Communities (ARIC) Study. PAD prevalence was defined by an ankle-brachial index, ie, the ratio of ankle systolic blood pressure to brachial artery systolic blood pressure, of ≥0.90 for men and ≥0.85 for women. CHD incidence was determined by following the ARIC cohort for a median of 5.3 years for potential coronary events. Stratified random samples of the ARIC cohort (n = 703 and n = 684) were used, respectively, as the comparison groups for the PAD (n = 144) and incident CHD (n = 408) cases. The GNB3 825T allele and the ADD1 460W allele were not significantly associated with prevalence of PAD or incidence of CHD. However, a test of the interaction between hypertension status and the ADD1 G460W polymorphism indicated that further evaluation of the ADD1 polymorphism in only hypertensive individuals was warranted. The ADD1 460W allele was significantly associated with PAD (odds ratio [OR]: 2.61, 95% CI, 1.27–5.37, P = 0.01) and CHD (hazard rate ratio [HRR]: 2.30, 95% CI, 1.20–4.42, P = 0.01) in hypertensive individuals after adjustment for multiple cardiovascular disease risk factors. An interaction with hypertension in the association between the ADD1 G460W polymorphism and cardiovascular disease merits further testing in additional populations. (Hypertension. 2002;39:1053-1057.)

Key Words: genetics ■ risk factors ■ polymorphism ■ hypertension, essential ■ cardiovascular diseases

Coronary heart disease (CHD) is the leading cause of mortality among men and women in the United States.1 Numerous epidemiological studies have focused on the identification of risk factors contributing to increased CHD risk. Hypertension is considered to be one of the most important risk factors for cardiovascular disease, especially in the presence of other contributing factors such as hypercholesterolemia, smoking, and diabetes.2 Numerous epidemiological studies have also worked to establish predictive, noninvasive measures of future cardiovascular events. Several studies suggest that ankle-brachial index (ABI), a noninvasive measure of peripheral arterial disease (PAD), is highly predictive of subsequent cardiovascular mortality and morbidity in patients with hypertension.3,4 The established relationship between hypertension and cardiovascular disease indicates that they may share at least some genes in common. For example, polymorphisms of the α-adducin (ADD1) and G-protein β3 subunit (GNB3) genes have received considerable attention as candidate genes for essential hypertension.5–12 GNB3 has also been shown to play a role in coronary artery vasoconstriction.13,14 These genes may play a role in the etiology of PAD and CHD through their effects on blood pressure levels or through separate pathways.

The effect of the ADD1 and GNB3 polymorphisms on cellular ion transport and their hypothesized importance in predisposing certain individuals to hypertension prompted us to evaluate their association with PAD and CHD in white participants from the large prospective Atherosclerosis Risk in Communities (ARIC) Study. Our objective was to consider both of these subclinical and clinical indicators of cardiovascular disease and to gain insight into whether any observed association was independent of established cardiovascular risk factors.

Methods

Atherosclerosis Risk in Communities (ARIC) Study

Study participants were selected from the ARIC Study, a prospective investigation of atherosclerosis and its clinical sequelae involving 15,792 individuals aged 45 to 64 years at recruitment (1986 to 1989). Subjects were selected by probability sampling from four communities: Forsyth County, NC; Jackson, Miss (African-Americans only); northwestern suburbs of Minneapolis, Minn; and Washington County, Md. The initial clinical exams included a home interview to

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1053
ascertain cardiovascular risk factors, socioeconomic factors, and family medical history, a clinical examination, and blood drawing for laboratory determinations including extraction of DNA. Medical events were identified by an annual questionnaire, 3-year cycles of exams, and hospital and death certificate surveillance. Appropriate institutional review boards approved the ARIC study, and all participants provided their written informed consent. A detailed description of the ARIC study design and methods is published elsewhere.15

Prevalent Peripheral Arterial Disease

Ankle-brachial index (ABI) is defined as the ratio of ankle systolic blood pressure to brachial artery systolic blood pressure. Measurements were obtained by trained, certified sonographers using a standardized protocol and equipment, and a detailed description of measurement procedures has been described elsewhere.16 Briefly, ankle systolic blood pressure was measured in one leg selected at random with the participant in a prone position. Brachial systolic blood pressure was measured with the participant in the supine position. The mean of 2 measurements in the arm and ankle were used to calculate the ABI. Peripheral arterial disease (PAD) cases (n=144) were identified from the ARIC cohort by an ABI ≤0.9 for men and an ABI ≤0.85 for women. Participants were excluded from analysis if they had a positive or unknown history of prevalent stroke or coronary heart disease or history of transient ischemic attack (TIA)/stroke symptoms at the initial clinic visit, or ethnic background other than white. Following these exclusions, a comparison group for the PAD cases was selected randomly from the remaining cohort of 10,401 participants, stratified on the basis of ultrasound examination of carotid arteries, age, and gender. The resulting comparison group for the PAD cases included 703 individuals.

Incident Coronary Heart Disease

Incidence of coronary heart disease (CHD) was determined by contacting participants annually to identify hospitalizations during the previous year and by surveying discharge lists from local hospitals and death certificates from state vital statistics offices for potential cardiovascular events.17 Hospital records were obtained, abstracted, and classified by computer algorithm and physician review. Details on quality assurance for ascertaining and classification of CHD events have been published elsewhere.17 CHD cases (n=408) were defined as a definite or probable myocardial infarction (MI), a silent MI between examinations by ECG, a definite CHD death, or a coronary revascularization. Participants were excluded from analyses if they had a positive or unknown history of prevalent stroke or coronary heart disease or a history of transient ischemic attack (TIA)/stroke symptoms at the initial clinic visit, or ethnic background other than white. The remaining 10,401 participants were followed for incident CHD for a median of 5.3 years between the baseline examination and December 31, 1993. The comparison group for the CHD cases was selected randomly from the ARIC cohort, stratified on the basis of ultrasound examination of carotid arteries, age, and gender. As a result, the comparison group for the CHD cases included 684 individuals. A case-cohort design was employed to account for individuals selected as part of the cohort random sample who were also identified as incident CHD cases.

Examination and Laboratory Measures

Seated blood pressure was measured 3 times with a random-zero sphygmomanometer and the last 2 measurements were averaged. Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or current use of antihypertensive medication. Questionnaires and in-person interviews were used to assess use of antihypertensive medication. Diabetes was defined by a fasting glucose level ≥126 mg/dL, a nonfasting glucose level ≥200 mg/dL, and/or a history of or treatment for diabetes. Cigarette-smoking status was analyzed by comparing current smokers to individuals who had formerly or never smoked. Body mass index (BMI, kg/m²) was calculated from height and weight measurements. Plasma total cholesterol was measured by an enzymatic method,18 and low-density lipoprotein (LDL)-cholesterol was calculated.19 High-density lipoprotein (HDL)-cholesterol was measured after dextran-magnesium precipitation of non-HDL lipoproteins.20

Genotype Determination

Genotyping of the ADD1 G460W and GNB3 825C>T polymorphisms was performed using the TaqMan assay (Applied Biosystems). Oligonucleotide sequences for polymerase chain reaction (PCR) primers and TaqMan probes are available on request from the authors and have been described previously.21 Allele detection and genotype calling were performed using the ABI 7700 and the Sequence Detection System software (Applied Biosystems).

Statistical Analysis

Allele frequencies were estimated by gene counting. Agreement of the ADD1 G460W and GNB3 825C>T genotype frequencies with Hardy-Weinberg equilibrium expectations were tested using a χ² goodness-of-fit test. The proportions, means, and standard errors (SE) of established cardiovascular risk factors were reported as weighted results for the PAD cases, CHD cases, and the noncase comparison groups. Multivariable logistic regression models were used to assess the relationship between PAD case status and the ADD1 460W or GNB3 825T alleles. The SUDAAN software package (Research Triangle Institute) was used to adjust for sampling strategy in the logistic regression models.22 Cox proportional hazards models were used to estimate the ratios of hazards rates of incident CHD between those with or without the ADD1 460W or GNB3 825T alleles. The method of Barlow23 was used to adjust for the sampling strategy in the Cox proportional hazards modeling. For incident CHD cases, the follow-up time interval was defined as the time between the initial clinical visit and the date of the first CHD event. For the cohort random sample, follow-up continued until December 31, 1993, the date of death, or the date of last contact if lost to follow-up, whichever came first. The established cardiovascular risk factors evaluated as potential confounders in the logistic regression and Cox proportional hazards models included age, gender, BMI, HDL- and LDL-cholesterol, as well as diabetes, hypertension, and smoking status. Odds ratios and hazard rate ratios were calculated assuming a codominant effect of the 460W and 825T alleles. Covariates were assessed for statistical significance in the models by the Wald χ² statistic.

Results

Group-specific proportions, means, and standard errors for multiple established cardiovascular risk factors are presented in Table 1. Mean values for all variables shown, except BMI, differed significantly between PAD cases and the noncases. The PAD cases had a significantly greater frequency of hypertensives, diabetics, and smokers compared with the noncases. Incident CHD cases differed significantly from the noncases for all variables shown, except total cholesterol levels. The frequency of males, hypertensives, and diabetics was significantly greater among CHD cases compared with the noncases. Allele and genotype frequencies for the ADD1 G460W and GNB3 825C>T polymorphisms are presented in Table 2 and were in accordance with Hardy-Weinberg equilibrium expectations. The frequency of the ADD1 460W allele was greater in the PAD and CHD case groups than in their respective comparison groups. This observation was consistent among hypertensive and normotensive individuals. Additionally, the frequency of the ADD1 460W allele was slightly increased among the hypertensive PAD (0.26) and CHD (0.22) cases compared with normotensive individuals in these case groups (0.23 and 0.20, respectively). The frequency of the GNB3
825T allele was greater in the PAD case group than in the noncases, but was less frequent in the CHD case group than in the noncases. These observations were consistent among hypertensive and normotensive individuals. None of the genotype or allele frequency differences reached statistical significance.

Results from the multivariable logistic regression models examining the association of the ADD1 460W allele and the GNB3 825T allele with PAD prevalence are presented in Table 3. Adjusting for multiple cardiovascular risk factors, the ADD1 460W allele was not observed to be significantly associated with increased PAD prevalence (P=0.09). Similarly, the 825T allele of the GNB3 gene was not found to be significantly associated with PAD after adjustment for established cardiovascular risk factors (P=0.35). Results from the Cox proportional hazards models used to estimate and compare the hazard rate ratios (HRR) of incident CHD between individuals with or without the variant alleles of ADD1 and GNB3 are also presented in Table 3. The ADD1 460W allele was not a significant predictor of incident CHD (P=0.09), adjusting for multiple cardiovascular risk factors in the analysis model. The GNB3 825T allele was not significantly associated with incident CHD in a similar analysis model (P=0.25).

Based on the above results and given the hypothesized complex relationship among genetic variation, hypertension, and cardiovascular disease, variables representing the interaction between hypertension status and the ADD1 or GNB3

### Table 1. Characteristics of the Case and Comparison Groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Prevalent Peripheral Arterial Disease Cases <em>(n=144)</em></th>
<th>Noncases* <em>(n=703)</em></th>
<th>Incident Coronary Heart Disease Cases † <em>(n=408)</em></th>
<th>Noncases† <em>(n=684)</em></th>
<th>P*</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at visit 1, y</td>
<td>Mean: 56.8 SE: 0.5</td>
<td>Mean: 54.3 SE: 0.1</td>
<td>Mean: 55.9 SE: 0.7</td>
<td>Mean: 54.1 SE: 0.2</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>Mean: 26.8 SE: 0.4</td>
<td>Mean: 26.2 SE: 0.2</td>
<td>Mean: 28.3 SE: 0.6</td>
<td>Mean: 25.9 SE: 0.2</td>
<td>0.24</td>
<td>0.01</td>
</tr>
<tr>
<td>HDL-cholesterol levels, mg/dL</td>
<td>Mean: 47.1 SE: 1.2</td>
<td>Mean: 52.7 SE: 0.8</td>
<td>Mean: 42.0 SE: 1.9</td>
<td>Mean: 53.8 SE: 0.9</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LDL-cholesterol levels, mg/dL</td>
<td>Mean: 145.4 SE: 3.8</td>
<td>Mean: 136.8 SE: 1.9</td>
<td>Mean: 149.2 SE: 4.2</td>
<td>Mean: 134.9 SE: 2.0</td>
<td>0.04</td>
<td>0.01</td>
</tr>
<tr>
<td>Total cholesterol levels, mg/dL</td>
<td>Mean: 223.5 SE: 4.1</td>
<td>Mean: 214.5 SE: 2.0</td>
<td>Mean: 221.7 SE: 4.6</td>
<td>Mean: 213.2 SE: 2.0</td>
<td>0.05</td>
<td>0.09</td>
</tr>
<tr>
<td>% Males</td>
<td>52%</td>
<td>45%</td>
<td>69%</td>
<td>44%</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>44%</td>
<td>24%</td>
<td>48%</td>
<td>21%</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diabetic</td>
<td>17%</td>
<td>9%</td>
<td>28%</td>
<td>7%</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Smoker</td>
<td>53%</td>
<td>24%</td>
<td>33%</td>
<td>24%</td>
<td>0.19</td>
<td>0.19</td>
</tr>
</tbody>
</table>

*Comparison of PAD cases and the PAD noncases; †comparison of CHD cases and the CHD noncases.

### Table 2. Allele and Genotype Frequencies in Case and Comparison Groups

<table>
<thead>
<tr>
<th>Allele/Genotype</th>
<th>Peripheral Arterial Disease Cases*</th>
<th>Noncases*</th>
<th>Coronary Heart Disease Cases†</th>
<th>Noncases†</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADD1 genotype frequency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W460W</td>
<td>n: 10</td>
<td>%: 7</td>
<td>n: 12</td>
<td>%: 4</td>
</tr>
<tr>
<td>G460W</td>
<td>n: 49</td>
<td>%: 34</td>
<td>n: 142</td>
<td>%: 29</td>
</tr>
<tr>
<td>G460G</td>
<td>n: 85</td>
<td>%: 59</td>
<td>n: 252</td>
<td>%: 67</td>
</tr>
<tr>
<td>ADD1 allele frequency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>460W</td>
<td>n: 69</td>
<td>%: 24</td>
<td>n: 166</td>
<td>%: 20</td>
</tr>
<tr>
<td>460G</td>
<td>n: 219</td>
<td>%: 76</td>
<td>n: 646</td>
<td>%: 80</td>
</tr>
<tr>
<td>GNB3 genotype frequency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>825T&gt;T</td>
<td>n: 15</td>
<td>%: 11</td>
<td>n: 31</td>
<td>%: 6</td>
</tr>
<tr>
<td>825C&gt;T</td>
<td>n: 56</td>
<td>%: 43</td>
<td>n: 149</td>
<td>%: 38</td>
</tr>
<tr>
<td>825C&gt;C</td>
<td>n: 61</td>
<td>%: 46</td>
<td>n: 193</td>
<td>%: 56</td>
</tr>
<tr>
<td>GNB3 allele frequency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>825T</td>
<td>n: 86</td>
<td>%: 33</td>
<td>n: 211</td>
<td>%: 28</td>
</tr>
<tr>
<td>825C</td>
<td>n: 178</td>
<td>%: 67</td>
<td>n: 535</td>
<td>%: 72</td>
</tr>
</tbody>
</table>

*Comparison of genotype frequency between PAD cases and the PAD noncases; ADD1 P=0.25, GNB3 P=0.48; †comparison of genotype frequency between CHD cases and the CHD noncases: ADD1 P=0.89, GNB3 P=0.66.
polygenetic polymorphisms were included in the respective analysis models for PAD and CHD. The interaction between hypertension status and the \textit{GNB3} 825C>T polymorphism was not significant in analyses of PAD or CHD. Evaluation of the interaction between hypertension status and the \textit{ADD1} 460W polymorphism was significant in the analysis of PAD (\(P=0.04\)) and was suggestive in the analysis of CHD (\(P=0.07\)). Given these observations, the association between the 460W polymorphism and prevalence of PAD and incidence of CHD was further investigated in only hypertensive individuals. Table 4 details the relationship between PAD and CHD case status and the \textit{ADD1} 460W allele in white hypertensive individuals. After adjusting for multiple cardiovascular risk factors the \textit{ADD1} 460W allele was a significant predictor of increased PAD prevalence in white hypertensives (OR: 2.61, 95% CI, 1.27–5.37, \(P=0.01\)). Similarly, an analysis model adjusting for multiple cardiovascular risk factors revealed a statistically significant association between the \textit{ADD1} 460W allele and increased incidence of CHD in white hypertensive individuals (HRR: 2.30, 95% CI, 1.20–4.42, \(P=0.01\)).

All multivariable logistic regression and Cox proportional hazards models were investigated for potential interactions between the \textit{ADD1} or \textit{GNB3} polymorphisms, respectively, and gender. These interaction terms were not significant in the analysis models (data not shown).

### Discussion

We have investigated the association between variants of the \textit{ADD1} and \textit{GNB3} genes and PAD and CHD in white individuals selected from the large prospective ARIC study. This investigation was motivated by the hypothesis that genetic polymorphisms shown to be associated with essential hypertension may influence cardiovascular risk by means of a common pathophysiological pathway. The 825T allele of the \textit{GNB3} gene was not significantly associated with PAD or CHD in this sample of middle-aged white Americans, whereas the 460W allele of the \textit{ADD1} gene was found to be significantly associated with increased prevalence of PAD and incidence of CHD among hypertensive individuals.

Based on previous reports suggesting that patients with PAD are at increased risk for CHD\(^1,24,25\) and that the 2 conditions share similar risk factors,\(^{26,27}\) we expected a similar magnitude of association for the relationships between each of the gene variants and both vascular endpoints. Indeed, the \textit{ADD1} 460W allele appears predictive of both PAD and CHD case status. The magnitude of the observed association was consistent in analyses of both prevalent PAD and incident CHD in the total sample (OR: 1.40 and HRR: 1.32, respectively) as well as in analyses of only hypertensives (OR: 2.61 and HRR: 2.30, respectively). These results suggest that polymorphic variation in the \textit{ADD1} gene may play an important role in both subclinical and clinical evidence of cardiovascular disease. Observation of increased prevalence of PAD and incidence of CHD among hypertensive individuals with the \textit{ADD1} 460W does not conclusively indicate that the atherogenicity of polymorphic variation in \textit{ADD1} may be solely attributed to a direct effect on blood pressure levels. Indeed, blood pressure levels were not significantly different across \textit{ADD1} genotypes within the sample of hypertensive white individuals (data not shown). Genetic variation in \textit{ADD1} likely has multiple effects, some of which in turn may influence potential pathophysiological pathways, contributing to increased cardiovascular risk in a hypertensive background. One such potential pathophysiological pathway may involve salt sensitivity. Independent of blood pressure, salt sensitivity has been associated with an increased risk of cardiovascular events.\(^{28}\) Although the relationship between polymorphic variation in \textit{ADD1} and salt sensitivity remains controversial,\(^{29,30}\) impaired renal sodium handling and salt sensitivity should be considered important physiological mechanisms potentially contributing to cardiovascular risk.

It is important to note that in comparison to the large number of studies investigating the effect of specific genes on the occurrence of essential hypertension or coronary heart disease, relatively few studies have explored the relationship between specific candidate gene polymorphisms and increased PAD risk. Of the few published studies investigating the role of genetic variation on the onset and occurrence of PAD, the majority have involved genes influencing lipid and lipoprotein synthesis and metabolism. To the best of our knowledge, no study has directly investigated the relationship between hypertension candidate genes and the risk of PAD. Similarly, studies investigating the relationship between the \textit{ADD1} G460W polymorphism and CHD have not been previously published.

### Perspectives

The G460W polymorphism of the \textit{ADD1} gene was significantly associated with increased risk of cardiovascular dis-
ease in white hypertensive participants of the ARIC Study. This association did not appear to be mediated by established cardiovascular risk factors. An interaction with hypertension in the association between the ADD1 G460W polymorphism and cardiovascular disease merits further testing in additional populations. Further characterization of whether the ADD1 gene contributes to increased PAD and CHD risk will be useful for the potential early identification of hypertensive individuals at increased risk for these important complications and for developing a better understanding of the etiology and pathophysiology of these diseases.

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