Genetic Variation of the Androgen Receptor and Risk of Myocardial Infarction and Ischemic Stroke in Women

Kathryn M. Rexrode, MD, MPH; Paul M. Ridker, MD, MPH; Hillary H. Hegener, BS; Julie E. Buring, ScD; JoAnn E. Manson, MD, DrPH; Robert Y.L. Zee, PhD

Background and Purpose—Androgen receptors (AR) are expressed in endothelial cells and vascular smooth-muscle cells. Genetic variation of the AR gene, principally fewer cysteine, adenine, guanine (CAG) repeats in the amino-terminal domain, has been associated with higher testosterone levels in women, as well as the cysteine, adenine, guanine (CAG) microsatellite in exon 1, of the AR gene were evaluated among 300 white postmenopausal women who developed CVD (158 myocardial infarctions and 142 ischemic strokes) and an equal number of matched controls within the Women’s Health Study.

Methods—Six haplotype block-tagging single nucleotide polymorphisms (rs962458, rs6152, rs1204038, rs2361634, rs1337080, rs1337082), as well as the cysteine, adenine, guanine (CAG) microsatellite in exon 1, of the AR gene were assessed in logistic regression analysis. The median CAG repeat length was 21. In conditional logistic regression, there was no association between the number of alleles with CAG repeat length ≥21 (or ≥22) and risk of CVD, myocardial infarctions or ischemic stroke.

Results—Genotype distributions were similar between cases and controls, and genotypes were not significantly related to risk of CVD, myocardial infarctions or ischemic stroke in conditional logistic regression models. Seven common haplotypes were observed, but distributions did not differ between cases and controls nor were significant associations observed in logistic regression analysis. The median CAG repeat length was 21. In conditional logistic regression, there was no association between the number of alleles with CAG repeat length ≥21 (or ≥22) and risk of CVD, myocardial infarctions or ischemic stroke.

Conclusions—No association between AR genetic variation, as measured by haplotype-tagging single nucleotide polymorphisms and CAG repeat number, and risk of CVD was observed in women. (Stroke. 2008;39:1590-1592.)

Key Words: cardiac emboli ■ cerebral infarct ■ genetics ■ women & minorities ■ androgens

Androgen receptors (ARs) are expressed in vascular endothelial and smooth-muscle cells. Genetic variation of the AR gene, principally fewer cysteine, adenine, guanine [CAG] repeats in the amino-terminal domain, has been associated with higher testosterone levels in women, as well as lower HDL levels, impaired endothelial vasodilation, and increased odds of coronary heart disease in men. However, to the best of our knowledge, associations between AR genetic variation and cardiovascular disease (CVD) have not been evaluated in women. We examined 6 haplotype-tagging single nucleotide polymorphisms (htSNPs) and the CAG repeat microsatellite in exon 1 in a nested case-control study within the Women’s Health Study (WHS).

Materials and Methods

Study Design
A nested case-control study was performed within the WHS, a randomized trial of aspirin and vitamin E among 39,876 female health professionals. Before randomization, 28,345 participants provided an EDTA-anticoagulated blood sample. Participants were free of known CVD and cancer at study entry. Yearly questionnaires ascertained newly developed CVD, and medical records were used to confirm events. Before February 2004, 855 cases of first myocardial infarction or ischemic stroke occurred, with 458 meeting all our inclusion criteria (white postmenopausal women with data on smoking and hormone therapy). For 158, bloods were unavailable, leaving 300 cases for the present analysis. Compared to cases without blood, cases with blood available had similar BMI and hormone therapy use rates, but were slightly younger and less likely to smoke. For each case, a WHS control, who met these criteria but remained free from CVD until the case event, was matched by age, smoking status and use of postmenopausal hormone therapy.

The study was approved by the Brigham and Women’s Hospital Institutional Review Board for Human Subjects Research and all subjects provided signed informed consent.

Genotype Data
As previously described, six htSNPs of the AR gene (rs962458, rs6152, rs1204038, rs2361634, rs1337080, rs1337082) were selected based on data from a multiethnic sample (http://www.uscnorris.com/MECGenetics/AR.htm). Genotyping was performed according to standardized methods (see supplemental data, available online at http://stroke.ahajournals.org). Genotypes were scored by 2 independent observers, blinded to case-control status. Discordant results
Statistical Analysis
Genotype and allele frequencies were compared by Fisher exact test. Haplotype frequencies were estimated and haplotype distributions were compared using PHASEv2.1.1. Binary categories of CAG repeat length were created based on the median (21 repeats) as well as those in other reports (22 and 23 repeats). The distribution of the number of alleles (0, 1, or 2) with CAG repeat above the threshold for cases and controls was compared using Fischer exact test.

The relationship between genotype, haplotype and CAG repeat category and clinical outcomes was examined by conditional logistic regression analysis, conditional on matching factors, with additional adjustment for age. Log-additive models are presented, but results were similar for dominant and recessive models.

Results
Genetic data were available for 300 postmenopausal white women who developed CVD, including 158 myocardial infarction (MI) and 142 ischemic strokes, and their matched controls (supplemental Table I).

Genotype distribution did not differ between cases and controls for any of the 6 polymorphisms (Table 1). No associations were found for any of the genotypes in conditional logistic regression (Table 2). Analysis by haplotype blocks yielded similarly null findings (data not shown).

The median number of CAG repeats was 21 (interquartile range 19 to 23) in cases, and 21 (interquartile range 20 to 23) in controls. The number of alleles with CAG repeat above the threshold for cases and controls did not differ between cases and controls for CVD, MI or ischemic stroke (Table 3).

Discussion
No association with MI, ischemic stroke or total CVD for 6 htSNPs and their associated haplotypes in the AR gene was observed in conditional logistic regression models (Table 2). Analysis by haplotype blocks yielded similarly null findings (data not shown).

The median number of CAG repeats was 21 (interquartile range 19 to 23) in cases, and 21 (interquartile range 20 to 23) in controls. The number of alleles with CAG repeat ≥21 did not differ between cases and controls for CVD, MI or ischemic stroke (Table 3). Results were similar for cutpoints of ≥22 or ≥23 repeats. In conditional logistic regression there was no significant association between repeat length and any of the end points, nor was any association observed when CAG repeat was modeled as a log-transformed continuous term.
found. Furthermore, no significant association between the number of longer CAG repeats in the amino-terminal domain of the AR gene and the odds of CVD, MI or ischemic stroke was observed. To the best of our knowledge, the present investigation represents the first study to evaluate the AR gene locus and risk of CVD in women.

Data on the AR gene and CVD are limited. AR gene expression in the coronary artery media has been inversely correlated with coronary plaque area in men. In 1 case-control study, men in the lowest CAG repeat quartile were more likely to have significant coronary heart disease than those in the highest quartile. In contrast, no association between the number of CAG repeats and MI was observed in another case-control study in men, although those with fewer CAG repeats did have lower HDL levels.

Limitations of the present study include generalizability and potential biases. We examined only white postmenopausal women and results may not be generalizable to other groups. Additionally, heterozygote estimation for genes on the X chromosome is imprecise in women because only one allele is active in each cell; this would result in misclassification and bias results toward the null. We had >80% power to detect a risk ratio of >1.40 for CVD for a minor allele frequency of 0.50 and a risk ratio of 2.1 for a minor allele frequency of 0.05, assuming an additive model.

In conclusion, no association was observed between the number of CAG repeats in the amino-terminal domain of the AR gene and the odds of CVD, MI or ischemic stroke. In the Women’s Health Study, men in the lowest CAG repeat quartile were more likely to have significant coronary heart disease than those in the highest quartile. In contrast, no association between the number of CAG repeats and MI was observed in another case-control study in men, although those with fewer CAG repeats did have lower HDL levels.

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Disclosures
None.

References
4. Terry KL, De Vivo I, Titus-Ernstoff L, Shih MC, Cramer DW. Androgen receptor haplotypes of the AR gene and risk of CVD in this cohort of postmenopausal women. Limited power for MI and stroke may justify further examination in other populations.

<table>
<thead>
<tr>
<th>CAG Repeat No.</th>
<th>0 alleles</th>
<th>1 allele</th>
<th>2 alleles</th>
<th>P Value*</th>
<th>Odds Ratio** (95% CI)</th>
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<tbody>
<tr>
<td>CVD cases</td>
<td>20.1</td>
<td>40.6</td>
<td>39.3</td>
<td>0.40</td>
<td>0.75 (0.56–1.00)</td>
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<tr>
<td>CVD controls</td>
<td>16.8</td>
<td>38.1</td>
<td>45.1</td>
<td></td>
<td></td>
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<tr>
<td>MI cases</td>
<td>18.9</td>
<td>44.9</td>
<td>36.2</td>
<td>0.44</td>
<td>0.83 (0.57–1.20)</td>
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<tr>
<td>MI controls</td>
<td>19.5</td>
<td>37.5</td>
<td>43.0</td>
<td></td>
<td></td>
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<tr>
<td>IS cases</td>
<td>21.5</td>
<td>35.5</td>
<td>43.0</td>
<td>0.33</td>
<td>0.65 (0.41–1.04)</td>
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<tr>
<td>IS controls</td>
<td>13.8</td>
<td>38.8</td>
<td>47.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD controls</td>
<td>35.9</td>
<td>42.3</td>
<td>21.8</td>
<td>0.74</td>
<td>0.86 (0.65–1.15)</td>
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<tr>
<td>MI cases</td>
<td>34.7</td>
<td>45.7</td>
<td>19.7</td>
<td>0.43</td>
<td>0.82 (0.55–1.22)</td>
</tr>
<tr>
<td>MI controls</td>
<td>39.1</td>
<td>37.5</td>
<td>23.4</td>
<td></td>
<td></td>
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<tr>
<td>IS cases</td>
<td>37.4</td>
<td>38.3</td>
<td>24.3</td>
<td>0.93</td>
<td>0.91 (0.61–1.38)</td>
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<tr>
<td>IS controls</td>
<td>35.3</td>
<td>40.5</td>
<td>24.1</td>
<td></td>
<td></td>
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</tbody>
</table>

* Fisher exact test.
** Conditional logistic regression controlled for age.

Table 3. Association of CAG Repeat No. With CVD, MI and IS
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