Genome-Wide Linkage Study of Retinal Vessel Diameters in the Beaver Dam Eye Study

Chao Xing, Barbara E.K. Klein, Ronald Klein, Gyungah Jun, Kristine E. Lee, Sudha K. Iyengar

Abstract—Retinal vessels can be observed noninvasively and provide a window to microvascular systems elsewhere in the body. Generalized retinal arteriolar narrowing can represent structural changes resulting from persistent high blood pressure. However, data from recent studies also suggest that generalized retinal arteriolar narrowing might precede hypertension and contribute to its pathogenesis. To determine whether vessel diameters in the eye are genetically determined, we conducted a genome-wide linkage scan on retinal vessel diameters (central retinal artery equivalent and central retinal vein equivalent) using data from the Beaver Dam Eye Study. There were 7 regions on 5 chromosomes (3q28, 5q35, 7q21, 7q32, 11q14, 11q24, and 17q11) showing linkage signals at the nominal multipoint significance level of 0.01 for either covariate-unadjusted or -adjusted central retinal artery equivalent; there were 7 regions on 6 chromosomes (1p36, 6p25, 6q14, 8q21, 11p15, 13q34, and 14q21) showing linkage signals at the nominal multipoint significance level of 0.01 for either covariate-unadjusted or -adjusted central retinal vein equivalent. The linkage results for retinal vessel diameters indicate genetic contributions that remain significant even after adjusting for hypertension and other covariates. In summary, we provide evidence demonstrating that genetic factors independent of hypertension affect retinal vessel diameters. (Hypertension. 2006;47:797-802.)

Key Words: genetics ■ arterioles ■ veins ■ microcirculation ■ retinal vessels

The retinal vessels can be observed noninvasively and are thought to characterize microvascular systems elsewhere in the body. It is believed that the retinal vessels, as an end point of the arteriolar system, are particularly susceptible to changes in blood pressure.1 There have been several studies showing an association between past and present hypertension and narrowing of retinal arterioles.2–5 Data from general population-based cohort studies have shown that generalized retinal arteriolar narrowing precedes hypertension and may contribute to its pathogenesis.6,7 Moreover, independent of blood pressure, generalized retinal arteriolar narrowing was shown to be a predictor of stroke,8 cardiovascular disease mortality,9 and coronary heart disease.10 Recently, Lee et al11 investigated the familial aggregation of retinal vessel diameters and showed that it was more highly correlated between relatives than between unrelated individuals, suggesting the involvement of genetic components. To our knowledge, however, there have been no genetic linkage or association studies investigating the genetic influence on retinal vessel diameters.

In the present study, we performed a genome-wide linkage scan on retinal vessel diameters using data from the Beaver Dam Eye Study. Our specific aims were: (1) to study the underlying genetic factors influencing retinal vessel diameters, and (2) to study the differences between retinal vessel diameters (venules and arterioles) in terms of the genetic background. Given the association between retinal arteriolar narrowing and hypertension, stroke, and cardiovascular disease, understanding the genetic determinants of retinal vessel diameters may provide additional insights into the pathogenesis of these complex diseases.

Methods

Family Ascertainment

The Beaver Dam Eye Study, as described in detail in previous reports,12,13 is a population-based cohort study of age-related eye diseases. At the time of census 4926 subjects between 43 and 86 years of age, living in the city or township of Beaver Dam, Wis, participated in the baseline examination from 1988 to 1990. Informed consent was obtained from the participants following a protocol approved by the Institutional Review Board of the University of Wisconsin. Ninety-nine percent of the participants were European Americans. Familial relationships among participants were identified based on information collected at the baseline examination and confirmed during follow-ups and/or by phone contact of ≥1 family members. Pedigrees containing ≥2 eligible participants, between which there was first-, second-, or third-degree relationships, were then constructed. A total of 602 pedigrees composed of 2783 eligible participants were constructed, of which 1762 persons from 486 families consisting of 812 sibling pairs had the measured retinal vessel diameter data available and, therefore, served as the subjects of the linkage study. The retinal vessel diameters of the other 1021 individuals were missing because: (1) their retinal vessel
diameters were not measured, (2) they did not have measurable vessels, or (3) they did not have a direct relative with data; however, their retinal vessel diameters could be treated as missing at random, because there was no significant difference in terms of other phenotypes, such as blood pressure, height, and weight, and so forth (data now shown) between the 1762 individuals and the 1021 individuals.

Phenotypic Evaluation

Stereoscopic 30° color fundus retinal photographs, centered on the optic disc, were taken on both eyes of participants after dilation. The photographs for the right eyes were then converted to digital images by a high-resolution scanner (Nikon LS2000; Nikon Inc). A grader identified the arterioles and venules and then used a semiautomated procedure to measure the vessel diameters (3.8 μm per pixel) in the area between circles with a 0.5 and 1.0 standard disc diameter, which was a defined unit of measurement (1850 μm) established by the Early Treatment Diabetic Retinopathy Study, from the optic disc margin. The measurements for the arterioles were combined into a central retinal artery equivalent (CRAE), and the measurements for the venules were combined into a central retinal vein equivalent (CRVE), which were robust to variability of vessel number, independent of image scale, and easy to implement, using the formulae by Knudtson et al.

As part of the baseline examination, blood pressure, height, and weight were measured. Information on medical history and lifestyle, including the use of antihypertensive medication, diabetes status, control of hyperglycemia, smoking, alcohol drinking, and sedentary lifestyle, was collected by a questionnaire. Blood specimens were obtained, on which a number of biochemical assays were performed.

Genotyping

For the genome scan, a total of 385 microsatellite markers on 22 autosomes, with an average marker distance of 9.14 cM, were typed by the Center for Inherited Disease Research (http://www.cidr.jhmi.edu/) using a modified version of the Weber panel 8 marker set. The genetic map and intermarker distances were from the Center for Inherited Disease Research database. Inconsistencies in the segregation of the genotypes within families were checked using the MARKERINFO program. Genotypes of markers showing Mendelian inconsistencies that could not be resolved during the relationship testing phase were set to missing for certain individuals. In total, 3.8% of the data were treated as missing. Before any linkage analysis, all of the family relationships were confirmed using the RELTEST program. Allele frequencies for each marker were established by maximum likelihood estimation using the FREQ program. The above programs are included in Statistical Analysis for Genetic Epidemiology (S.A.G.E.) software suite version 5.0.

Statistical Analysis

For each phenotype (trait or covariate), we compared sex-specific differences by performing \( \chi^2 \) goodness-of-fit tests. We then screened the covariates by regressing the CRAE or CRVE on the covariates using stepwise regression, as implemented in the SAS procedure.
REG. Covariates considered included sex, age (years), systolic blood pressure (SBP; mm Hg), diastolic blood pressure (DBP; mm Hg), blood pressure treatment (never, past, or current), dichotomized hypertension status conditional on blood pressure and treatment (yes or no; hypertension was defined as SBP ≥140 mm Hg, DBP ≥90 mm Hg, or use of antihypertensive medication), height (inches), weight (pounds), body mass index (kg/m²), diabetes status (yes or no), smoking (never, past, or current), alcohol drinking (never, past, or current), sedentary lifestyle (yes or no), total serum cholesterol (mg/dL), and serum high-density lipoprotein cholesterol (HDL; mg/dL). Sex, age, and age² were always retained in the model, as were other covariates that were significant at the level of 0.05.

The robustness of the power of the t test, which was used in the model-free quantitative trait linkage method of this article, in the presence of nonnormality, is not well guaranteed as the robustness of the type I error. Therefore, we performed commingling analyses for the covariate-adjusted traits using the program SEGREG implemented in S.A.G.E., during the process of which a Box-Cox power transformation was performed to simultaneously obtain normal and homoscedastic residuals.

We estimated the narrow sense of heritability of traits using the program FCOR in S.A.G.E. Three sets of CRVE and CRAE were considered for the heritability estimation: (1) no covariates adjustment, (2) adjustment for significant covariates, and (3) Box-Cox power transformation after covariate adjustment.

Given the quantitative and complex characteristics of traits, we performed the model-free linkage analyses by using the Haseman–Elston regression as implemented in the program SBPAL. Specifically, we used a weighted combination of the squared sibling-pair trait difference and the squared sibling-pair mean-corrected trait sum as the dependent variable and regressed it on the estimated proportion of alleles shared identical by descent between sibling pairs. Single-point and multipoint identical by descent-sharing estimates were calculated by the program GENIBD. Both programs are included in S.A.G.E. software. All of the multipoint results that were nominally significant (P≤0.01) were verified by comparing the nominal P values to those obtained from the null permutation distribution, using a sample of ≥100 000 replicate permutations of the allele-sharing data.

Results

Phenotype Distribution

Among the 1762 individuals with the measured retinal vessel diameter data available, there were more women (941) than men (821; P = 0.005), and women were significantly older than men (P<0.01). There was no difference between men and women in CRAE, whereas CRVE was significantly narrower in women (P<0.01). DBP was significantly lower in women (P<0.01), whereas there was no difference in SBP between men and women. Both total serum cholesterol and HDL were higher in women (P<0.01). More men had alcohol drinking and smoking habits than women (P<0.01 and P = 0.002, respectively). There was no difference between men and women in terms of body mass index, diabetes status, and sedentary lifestyle (Table I, available at http://www.hypertensionaha.org). At the level of 0.05, sex, age, age², smoking, and HDL were significant for both CRVE and CRAE; in addition, DBP was significant for CRAE. SBP and the use of antihypertension medication did not remain in the model after adjustment for the other covariates.

Box-Cox Transformation and Heritability Estimation

The commingling analyses found that the most parsimonious model for covariate-adjusted CRAE was the 2-mean dominant model and for covariate-adjusted CRVE, the 3-mean decreasing model. Specifically, the Box-Cox transformation of power (λ) equal to 2.5 for CRAE and equal to 1.8 for CRVE gave the best indication of genetic involvement under dominant and incompletely dominant models, respectively.

The estimated heritability for unadjusted, covariate-adjusted, and covariate-adjusted and power-transformed CRAE (±SE) was 0.60 (±0.13), 0.51 (±0.13), and 0.51 (±0.13), respectively. Similarly, the estimated heritability for unadjusted, covariate-adjusted, and covariate-adjusted and power-transformed CRVE (±SE) was 0.46 (±0.13), 0.48 (±0.13) and 0.49 (±0.13), respectively. All of the estimates were accompanied with small P values (<2.0×10⁻³). The results were not statistically different from those by Lee et al (P>0.4) and strongly indicated involvement of genetic effects on CRAE and CRVE.

Linkage Genome Scan

The linkage scan results for covariate-unadjusteded traits and covariate-adjusted and power-transformed traits (data not shown) had similar trends in terms of linkage signal, although the signals usually slightly decreased after Box-Cox power transformation compared with the untransformed data. The Figure is illustrative of the linkage signal for CRAE on chromosome 3, which increased after covariate adjustment and then decreased after power transformation. Therefore, only the covariate-adjusted genome scan is presented (supplement Figures I and II, available online).

There were 7 regions on 5 chromosomes showing linkage signals at the nominal multipoint significance level of 0.01 for either covariate-unadjusted or -adjusted CRAE (Table I). The strongest evidence for linkage was detected on chromo-

<table>
<thead>
<tr>
<th>Genomic Region (cM)</th>
<th>Closest Marker</th>
<th>Trait</th>
<th>P_adj</th>
<th>P_em</th>
<th>P_s</th>
</tr>
</thead>
<tbody>
<tr>
<td>1p36 (2)</td>
<td>D1S2660</td>
<td>CRAE</td>
<td>2.0×10⁻²</td>
<td>...</td>
<td>3.7×10⁻²</td>
</tr>
<tr>
<td>3q28 (212)</td>
<td>D3S2418</td>
<td>CRVE</td>
<td>6.5×10⁻³</td>
<td>1.6×10⁻²</td>
<td>8.4×10⁻⁴</td>
</tr>
<tr>
<td>5q35 (184)</td>
<td>D5S211</td>
<td>CRAE</td>
<td>6.2×10⁻³</td>
<td>2.1×10⁻²</td>
<td>6.4×10⁻²</td>
</tr>
<tr>
<td>6p25 (9)</td>
<td>F13A1</td>
<td>CRVE</td>
<td>4.1×10⁻²</td>
<td>...</td>
<td>3.9×10⁻²</td>
</tr>
<tr>
<td>6q14 (89)</td>
<td>D6S1031</td>
<td>CRVE</td>
<td>6.4×10⁻³</td>
<td>1.8×10⁻²</td>
<td>9.1×10⁻²</td>
</tr>
<tr>
<td>7q21 (91)</td>
<td>D7S2204</td>
<td>CRVE</td>
<td>2.2×10⁻²</td>
<td>3.8×10⁻³</td>
<td>1.4×10⁻³</td>
</tr>
<tr>
<td>8q21 (88)</td>
<td>D8S2324</td>
<td>CRVE</td>
<td>5.8×10⁻⁴</td>
<td>2.9×10⁻³</td>
<td>5.2×10⁻³</td>
</tr>
<tr>
<td>11p15 (6)</td>
<td>D11S1999</td>
<td>CRAE</td>
<td>1.1×10⁻²</td>
<td>...</td>
<td>4.4×10⁻²</td>
</tr>
<tr>
<td>11q14 (78)</td>
<td>D11S2002</td>
<td>CRAE</td>
<td>2.3×10⁻³</td>
<td>9.0×10⁻³</td>
<td>5.2×10⁻²</td>
</tr>
<tr>
<td>11q24 (122)</td>
<td>D11S912</td>
<td>CRAE</td>
<td>5.6×10⁻⁴</td>
<td>3.8×10⁻³</td>
<td>3.1×10⁻²</td>
</tr>
<tr>
<td>13q34 (96)</td>
<td>D13S285</td>
<td>CRVE</td>
<td>2.4×10⁻²</td>
<td>...</td>
<td>1.8×10⁻²</td>
</tr>
<tr>
<td>14q21 (32)</td>
<td>D14S306</td>
<td>CRVE</td>
<td>3.5×10⁻³</td>
<td>1.5×10⁻²</td>
<td>4.6×10⁻³</td>
</tr>
<tr>
<td>17q11 (50)</td>
<td>D17S975</td>
<td>CRAE</td>
<td>3.8×10⁻³</td>
<td>6.5×10⁻³</td>
<td>1.2×10⁻²</td>
</tr>
</tbody>
</table>

Results were reported as either any of the traits, unadjusted and covariate-adjusted CRAE and CRVE, with a multipoint P<0.01, or as both of the traits, covariate-adjusted CRAE and CRVE, with a multipoint P<0.05. P_adj indicates asymptotic multipoint P value; P_em empirical multipoint P value; P_s single-point P value.
some 3q28 close to marker D3S2418 with a multipoint \( P \) value of \( 8.7 \times 10^{-3} \) (empirical multipoint \( P \) value \( 1.2 \times 10^{-4} \); single point \( P \) value \( 9.2 \times 10^{-4} \)) for covariate-adjusted CRAE. Compared with the signals for covariate-unadjusted CRAE, the signals on chromosomes 3q28, 5q35, 7q21, 7q32, 11q14, and 11q24 increased, whereas the signal on chromosome 18q11 remained unchanged.

There were 7 regions on 6 chromosomes showing linkage signals at the nominal multipoint significance level of 0.01 for either covariate-unadjusted or -adjusted CRVE (Table 1). The strongest evidence for linkage was detected on chromosome 8q21 close to marker D8S2324 with a multipoint \( P \) value of \( 5.8 \times 10^{-4} \) (empirical multipoint \( P \) value \( 2.9 \times 10^{-3} \); single point \( P \) value \( 5.2 \times 10^{-3} \)) for covariate-adjusted CRVE. The signal covered a relatively broad region and the 1-lod drop spanned \( \approx 20 \) cM. Compared with the signals for covariate-unadjusted CRVE, the signals on chromosomes 1p36, 6p25, 7q21, 7q32, 11q14, and 11q24 increased, whereas the signal on chromosome 18q111 remained unchanged.

There were 7 regions on 6 chromosomes showing linkage signals at the nominal multipoint significance level of 0.01 for either covariate-unadjusted or -adjusted CRVE (Table 1). The strongest evidence for linkage was detected on chromosome 8q21 close to marker D8S2324 with a multipoint \( P \) value of \( 5.8 \times 10^{-4} \) (empirical multipoint \( P \) value \( 2.9 \times 10^{-3} \); single point \( P \) value \( 5.2 \times 10^{-3} \)) for covariate-adjusted CRVE. The signal covered a relatively broad region and the 1-lod drop spanned \( \approx 20 \) cM. Compared with the signals for covariate-unadjusted CRVE, the signals on chromosomes 1p36, 6p25, 7q21, 7q32, 11q14, and 11q24 increased, whereas the signal on chromosome 18q11 remained unchanged.

CRVE and CRAE as measurements of retinal venule and arteriole diameters, respectively, not only had their own specific linkage signals, but also shared some common regions suggestive of linkage. These regions were located on chromosomes 1p36, 6p25, and 7q21, where both CRVE and CRAE showed multipoint linkage signals at the significance level of 0.05.

### Table 2. A List of Potential Candidate Genes Located in the Linkage Regions of CRAE and CRVE

<table>
<thead>
<tr>
<th>Genomic Region</th>
<th>Linked Trait</th>
<th>Candidate Gene</th>
<th>Function, Pathway Involved or Susceptibility Related</th>
<th>Within 1-Lod Drop Region of Linkage Peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>1p36</td>
<td>CRAE, CRVE</td>
<td>Tie1</td>
<td>eNOS-related pathway(^{29})</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eph-B2</td>
<td>Growth factor receptor</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eph-A2</td>
<td>Growth factor receptor</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eph-A8</td>
<td>Growth factor receptor</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ID3</td>
<td>VEGF-related pathway</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ECE-1</td>
<td>Essential hypertension(^{32})</td>
<td>Yes</td>
</tr>
<tr>
<td>3q28</td>
<td>CRAE</td>
<td>Eph-B3</td>
<td>Growth factor receptor</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FGF12</td>
<td>Growth factor</td>
<td>Yes</td>
</tr>
<tr>
<td>5q35</td>
<td>CRAE</td>
<td>VEGFR3</td>
<td>Growth factor receptor</td>
<td>Yes</td>
</tr>
<tr>
<td>6p25</td>
<td>CRAE, CRVE</td>
<td>End-1</td>
<td>eNOS-related pathway(^{29})</td>
<td>Yes</td>
</tr>
<tr>
<td>7q21</td>
<td>CRAE, CRVE</td>
<td>Eph-B4</td>
<td>Growth factor receptor</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HGF</td>
<td>eNOS-related pathway(^{27})</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epo</td>
<td>eNOS-related pathway(^{28})</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CYP3A5</td>
<td>Essential hypertension(^{33})</td>
<td>No</td>
</tr>
<tr>
<td>7q32</td>
<td>CRAE</td>
<td>Eph-A1</td>
<td>Growth factor receptor</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MET</td>
<td>eNOS-related pathway(^{27})</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leptin</td>
<td>eNOS-related pathway(^{28})</td>
<td>Yes</td>
</tr>
<tr>
<td>8q21</td>
<td>CRVE</td>
<td>Ang1</td>
<td>eNOS-related pathway(^{29})</td>
<td>Yes</td>
</tr>
<tr>
<td>11q14</td>
<td>CRAE</td>
<td>VEGFB</td>
<td>eNOS-related pathway(^{29})</td>
<td>Yes</td>
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<tr>
<td></td>
<td></td>
<td>Fzd-4</td>
<td>Norrin receptor</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pcp</td>
<td>Essential hypertension(^{28})</td>
<td>Yes</td>
</tr>
<tr>
<td>11q24</td>
<td>CRAE</td>
<td>MMP3</td>
<td>CHD susceptibility(^{38})</td>
<td>No</td>
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<tr>
<td>13q34</td>
<td>CRVE</td>
<td>Ephrin-B2</td>
<td>Growth factor</td>
<td>Yes</td>
</tr>
<tr>
<td>14q21</td>
<td>CRVE</td>
<td>HIF1</td>
<td>eNOS-related pathway(^{31,35})</td>
<td>No</td>
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<tr>
<td>17q11</td>
<td>CRAE</td>
<td>NOS2A</td>
<td>Essential hypertension(^{36,37})</td>
<td>Yes</td>
</tr>
</tbody>
</table>

VEGF indicates vascular endothelial growth factor; eNOS, endothelial NO synthase; CHD, coronary heart disease.
several genes of angiogenesis factors physiologically involved in endothelial NO synthase–related pathways.\textsuperscript{25–31} There is also the possibility that the vessel diameters are genetically determined by vasculogenesis factors during vascular development, and many candidate genes, for example, fibroblast growth factor 12 at 3q28, involved in this process are present in the linkage regions. Linkage regions for hypertension-adjusted retinal vessel diameters in this study overlapped with the regions of essential hypertension,\textsuperscript{32–37} which suggested generalized retinal arteriolar narrowing preceding hypertension and contributing to the pathogenesis of hypertension. There was also a candidate for coronary heart disease susceptibility at 11q24,\textsuperscript{38} which was shown to be independently associated with reduced retinal arteriolar diameter.\textsuperscript{10}

For long time it had been believed that the differences between arteries and veins reflected only physiological influences, such as blood pressure, oxygenation, and shear forces, and the developing capillary networks were treated as a uniform structure. The remarkable work of Wang et al\textsuperscript{39} showed that arterial and venous endothelial cells are molecularly distinct from the earliest stages of angiogenesis and that reciprocal interactions between prespecified arterial and venous endothelial cells are necessary for angiogenesis. Therefore, the differences between arteries and veins are likely to be genetically determined in part, and the reciprocal signaling between these 2 types of vessels is crucial for the morphogenesis of capillary beds. In the present study, the linkage signals for CRAE and CRVE overlapped in some regions (1p36, 6p25, and 7q21), suggesting common genetic factors contributing to vessel diameters. Moreover, the signals were distinct in some regions (3q28, 5q35, 6q14, 7q32, 11p15, 11q14, 11q24, 14q21, and 17q11), suggesting genetically different determinants between CRAE and CRVE, the interaction between which is likely to be essential for developing both arteries and veins.

Linkage results must be replicated to be credible. However, this is the first report on the genetics of retinal vessel diameters, and the closest report to the current study is that of Wang et al,\textsuperscript{40} who detected a linkage signal at 13q33.3 when scanning for a macrovascular end point, carotid artery intima-media thickness, a subclinical measure of atherosclerosis. Given that generalized vessel narrowing may reflect intimal thickening, medial hyperplasia and hyalinization, and sclerosis of retinal vessels,\textsuperscript{41} the linkage signal in the same region for CRVE can be viewed as an independent replication. Although these results strongly suggest the existence of genetic contribution for retinal vessel diameters and related traits in this region, additional replications of our findings in different populations are needed.

Perspectives

This genome-wide linkage scan of retinal vessel diameters suggests a genetic contribution to retinal vessel characteristics and that the differences between arterioles and venules could, in part, be genetically determined. We were able to locate many potential candidate genes in the linked regions that are either associated with endothelial dysfunction or involved in the process of vasculogenesis. The majority of these genes are fairly well described in the literature; however, other attractive candidates not previously implicated in these pathways may also play a role. It may evoke additional fine mapping, candidate gene association studies, and interaction analyses on a larger scale, which will help to identify genes influencing retinal vessel development, in particular, in terms of diameters. Understanding the genetic determinants of retinal vessel diameters, as a window to microvascular systems elsewhere in the body, may provide insight into the pathogenesis of complex diseases, such as hypertension and cardiovascular disease.

Acknowledgments

This study was supported, in part, by U10-EY06594, EY10605, and EY015810 from the National Eye Institute and Resource Grant RR03655 from the National Center for Research Resources. Genotyping services were provided by the Center for Inherited Disease Research (CIDR). CIDR is fully funded through a federal contract from the National Institutes of Health to the Johns Hopkins University, contract number N01-HG-65403.

References


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Hypertension. 2006;47:797-802; originally published online February 27, 2006;
doi: 10.1161/01.HYP.0000208330.68355.72
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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