VKORC1 Haplotypes Are Associated With Arterial Vascular Diseases (Stroke, Coronary Heart Disease, and Aortic Dissection)

Yibo Wang, BS; Weili Zhang, PhD; Yuhui Zhang, MD; Yuejin Yang, MD, PhD; Lizhong Sun, MD; Shengshou Hu, MD; Jilin Chen, MD; Channa Zhang; Yi Zheng, MD; Yisong Zhen, PhD; Kai Sun, PhD; Chunyan Fu, MD; Tao Yang, BS; Jianwei Wang, BS; Jing Sun, BS; Haiying Wu, MD; Wayne C. Glasgow, PhD; Rutai Hui, MD, PhD

Background—The haplotypes in the gene vitamin K epoxide reductase complex subunit 1 (VKORC1) have been found to affect warfarin dose response through effects on the formation of reduced-form vitamin K, a cofactor for γ-carboxylation of vitamin K–dependent proteins, which is involved in the coagulation cascade and has a potential impact on atherosclerosis. We hypothesized that VKORC1-dependent effects on the coagulation cascade and atherosclerosis would contribute to susceptibility for vascular diseases.

Methods and Results—To test the hypothesis, we studied the association of polymorphisms of VKORC1 with stroke (1811 patients), coronary heart disease (740 patients), and aortic dissection (253 patients) compared with matched controls (n = 1811, 740, and 416, respectively). Five common noncoding single-nucleotide polymorphisms of VKORC1 were identified in a natural haplotype block with strong linkage disequilibrium (D = 0.9, r² = 0.9), then single-nucleotide polymorphism (SNP) +2255 in the block was selected for the association study. We found that the presence of the C allele of the +2255 locus conferred almost twice the risk of vascular disease (odds ratio [OR] 1.95, 95% confidence interval [CI] 0.58 to 2.41, P = 0.001 for stroke; OR 1.72, 95% CI 1.24 to 2.38, P = 0.01 for coronary heart disease; and OR 1.90, 95% CI 1.04 to 3.48, P = 0.05 for aortic dissection). We also observed that subjects with the CC and CT genotypes had lower levels of undercarboxylated osteocalcin (a regulator for the bone), probably vascular calcification, and lower levels of protein induced in vitamin K absence or antagonism II (PIVKA-II, a des-γ-carboxy prothrombin) than those with TT genotypes.

Conclusions—The haplotype of VKORC1 may serve as a novel genetic marker for the risk of stroke, coronary heart disease, and aortic dissection. (Circulation. 2006;113:1615-1621.)

Key Words: vitamin K epoxide reductase ■ haplotypes ■ stroke ■ coronary disease ■ aortic dissection

Stroke and coronary heart disease (CHD) are the leading causes of morbidity and mortality in China.1 Each year, more than 2.5 million Chinese have strokes, 1 million have heart attacks, and 2 million die of stroke- and CHD-related causes. Furthermore, 7 million patients have survived a stroke and are disabled (http://www.moh.gov.cn). Elucidation of the pathogenesis of these diseases and identification of subjects at risk for these events are major challenges to medical society. A high degree of comorbidity and common risk factors have been observed among myocardial infarction (MI), stroke, and aortic dissection. Most of these cases result from atherosclerotic disease that is characterized by lesions in large and medium-sized elastic and muscular arteries.2-4

Platelet adhesion and mural thrombosis are ubiquitous in the initiation and generation of lesions of atherosclerosis in animals and in humans.5,6 Platelet adhesion and thrombosis formation result from activation of the coagulation cascade, initiated by atherosclerotic plaque erosion or rupture contributing to propagation of thrombosis.7-9 Vitamin K–dependent proteins play very important roles in activation of the coagulation cascade and in maintaining blood flow and integrity of the vasculature.10-13 The biological activity of all known vitamin K–dependent proteins is...
highly dependent on correct γ-carboxylation.14 Vitamin K hydroquinone, a cofactor for γ-carboxylation, is converted to vitamin K epoxide, which in turn is recycled to vitamin K hydroquinone by vitamin K epoxide reductase.15,16

Undercarboxylation of vitamin K–dependent proteins in patients with a specific mutation in the γ-carboxylase results in bleeding disorders.17,18 Common polymorphisms in the gene vitamin K epoxide reductase complex subunit 1 (VKORC1) affect warfarin dose response and blood clotting through effects on the formation of the reduced form of vitamin K, which subsequently alters carboxylation of vitamin K–dependent hemostatic and nonhemostatic proteins.19–25 Numerous studies indicate that vitamin K–dependent proteins have additional activities that extend their roles beyond hemostatic and bone metabolism, perhaps in vascular calcification and atherosclerotic complications. Price et al26 showed that inhibition of VKORC1 by warfarin results in undercarboxylation of matrix Gla protein (MGP) and subsequent medial calcification of the arterial vessel wall. Gene-deletion studies in mice have shown that MGP is an inhibitor of calcification.27

Arterial calcification has been correlated with an increased probability of dissection and a higher incidence of future ischemic episodes in patients undergoing angioplasty.28 Intimal calcification of atherosclerotic plaques correlates with plaque burden and high risk of cardiovascular events.29 Medial calcification has been shown to be associated with diabetes mellitus and end-stage renal disease and as a prognostic marker for cardiovascular mortality in patients requiring hemodialysis.30 Despite the fact that VKORC1 mediates vitamin K–dependent γ-carboxylation, which is involved in calcification, it remains unknown whether this could translate into higher risk for arterial disease. We hypothesized that VKORC1–dependent effects on the coagulation cascade and vascular calcification would contribute to susceptibility to vascular diseases. To test the hypothesis, we investigated the association of VKORC1 polymorphisms with stroke, CHD, or aortic dissection.

**Methods**

The study was approved by both the ethics committee of Fuwai Hospital and the local ethics committee of the collaborative hospitals. All subjects who participated in the study provided written informed consent and reported themselves to be of Han nationality.

**Stroke Cohort**

The primary study population has previously been used to investigate risk factors of stroke.31,32 Briefly, case and control subjects were recruited from 7 clinical centers located in 7 provinces from the same demographic area and at the same time from November 2000 to November 2001. Only 3 subtypes of stroke—cerebral atherosclerosis, lacunar infarction, and intracerebral hemorrhage—were included. Diagnosis of stroke was based on strict neurological examination, computed tomography, or MRI according to the International Classification of Diseases, 9th revision. Controls were selected from inpatients (21.5%) with minor illness from the departments of ophthalmology, gastroenterology, otorhinolaryngology, and orthopedics and from community-based inhabitants (78.5%) free of neurological diseases, following the same exclusion criteria as case subjects. In each local community, both men and women 35 to 74 years of age in the range of selection were grouped by age (5-year range for each group), and the control subject was randomly selected from the corresponding group.

**CHD and Aortic Dissection Cohorts**

Patients for the 2 studies were consecutive patients admitted to Fuwai Hospital from December 2001 to December 2002. The second population comprised 740 unrelated patients with CHD aged from 30 to 75 years and 740 control subjects. Inclusion criteria were normal lumina of at least 1 major coronary artery. A detailed history of angina or MI was obtained. Of the patients, 57.8% had MI judged by typical ECG change (Minnesota Code 1.1 or 1.2 in ECG) and by changes in serum enzymes (troponin T, troponin I, creatine kinase-MB, aspartate aminotransferase, and glutamic pyruvic transaminase). The 740 control subjects were selected from hospital inpatients whose major coronary arteries had no more than 20% stenosis and who did not have any vascular disease.

The third study sample comprised 253 unrelated cases with aortic dissection who were 20 to 75 years old and 416 control subjects. Aortic dissection was diagnosed on the basis of symptoms, signs, ECG, cardiac enzymes, coronary angiography, magnetic resonance angiography, and/or aortic angiography.70% of the patients underwent aortography, aortic surgery, and pathological examination. One hundred sixty-three patients were excluded because of known causes of disease, including aortic disease caused by coarctation of aorta, congenital aortic valve disease, inflammation arteritis, and trauma during cardiovascular procedure or glucocorticoid treatment. The diagnosis of Marfan syndrome (11.5% in these patients with aortic dissection) was based on revised clinical criteria of the Gent nosology.33 None of the control subjects had a history or symptoms of cardiovascular disease.

**Biological Variable Determination and Clinical Data Collection**

Blood samples were collected after a 12-hour overnight fast before cardiovascular procedures. In subjects with an acute event, the drawing of blood was delayed for at least 6 weeks. The plasma and cell buffet coat were kept at −70°C. Genomic DNA was extracted, and biological variables were determined within 3 months. A complete clinical history was obtained from all subjects. In addition to neurological history and family history of hypertension, CHD, and diabetes mellitus (DM), the following vascular risk factors were also recorded: history of vascular disease, cigarette smoking, alcohol consumption, body mass index, systolic blood pressure (SBP), diastolic blood pressure (DBP), blood glucose, HDL cholesterol (HDL-C), non–HDL-C lipids, total plasma cholesterol (TC), and triglycerides (TG). Plasma biochemical parameters were assayed by an automatic analyzer (Hitachi 7060, Hitachi, Tokyo, Japan). Non–HDL-C was calculated by the Friedewald formula. Hypertension was defined as a mean of 3 independent measures of blood pressure >140/90 mm Hg or the use of antihypertensive drugs.34 DM was diagnosed when the subject had a fasting glucose level >7.8 mmol/L, >11.1 mmol/L at 2 hours after oral glucose challenge, or both. All lipids were determined in a Centers for Disease Control and Prevention (CDC)–qualified laboratory in Fuwai hospital.

**Screening for Single-Nucleotide Polymorphisms**

The entire gene region of VKORC1 and the 2-kilobase (kb) 5′ upstream promoter region and 2-kb 3′ downstream region were screened by sequencing (ABI Prism 377, Perkin-Elmer Applied Biosystems, Foster City, Calif) in 50 stroke patients and 50 control subjects. No polymorphism was found in the entire coding sequence. The alleles with frequencies <0.05 were excluded; 5 common noncoding polymorphisms were identified in the VKORC1 gene, including −1639A/G (rs9923231) in the promoter region, +1173T/C (rs9934438) in the first intron, +1542C/G (rs8050894) and +2255T/C (rs2359612) in the second intron, and +3730G/A (rs7294) in the 3′ downstream region (defined by the nucleotide position from the translational start site). These single-nucleotide polymorphisms (SNPs) are located at positions 3673, 6484, 6853, 7566, and 9841 of the VKORC1 reference sequence (GenBank
across all populations. Because the C allele of VKORC1 almost 2-fold increase in vascular disease risk within these populations. Because the C allele of VKORC1
No Evidence of Strong Population Stratification
Among the 7 highly polymorphic markers that we genotyped, no significant allele-frequency differences were detected between controls and patients within each clinic center and among these centers, which indicates that there was no obvious evidence for genetic stratification in the cohort. The serum levels of undercarboxylated osteocalcin and PIVKA-II were lower in the subjects carrying the C allele of the VKORC1 locus. The levels of both undercarboxylated osteocalcin and PIVKA-II antigen were lower in carriers of the C allele than in T allele carriers (Figure). The Spearman coefficient for the existing correlation was \( r = -0.219 \) for undercarboxylated osteocalcin and \(-0.567 \) for PIVKA-II with genotype, respectively. The differences were also significant in undercarboxylated osteocalcin and in PIVKA-II between TT and CC carriers (\( P = 0.021 \) and \( P < 0.001 \), respectively), which suggests that the C allele contributes to a higher functional efficiency of the VKORC1 complex.

Discussion
The present study is the first clinical investigation of the significance of the polymorphisms of VKORC1 in vascular disease, including stroke, CHD, and aortic dissection. We found that the variants of VKORC1 are associated with almost double the risk of stroke, CHD, and aortic dissection. Next, we examined whether the disease-associated allele was related to specific vascular risk factors, such as hypertension, diabetes, age, and sex. No significant association was observed between the +2255 allele and these risk factors, which suggests that the contribution of SNP +2255 to the risk of vascular disease is independent of those conventional vascular risk factors. We examined the population stratification effect by genotyping 7 unlinked highly polymorphic microsatellite markers in the case subjects and in control subjects, and no association was found between these markers and vascular disease.

Stroke, CHD, and aortic dissection are all vascular diseases. The pathologies of these diseases are quite different. Atherothrombotic stroke mainly results from large-artery diseases. The pathologies of these diseases are quite different. The differences were also significant in undercarboxylated osteocalcin and in PIVKA-II between TT and CC carriers (\( P = 0.021 \) and \( P < 0.001 \), respectively), which suggests that the C allele contributes to a higher functional efficiency of the VKORC1 complex.

Table 1: Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Controls (n=1811)</th>
<th>Total (n=1811)</th>
<th>Thrombosis (n=798)</th>
<th>Lacunar Stroke (n=514)</th>
<th>Hemorrhage (n=499)</th>
<th>ChD (n=740)</th>
<th>Aortic Dissection (n=416)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men, %</td>
<td>57.4</td>
<td>63.5†</td>
<td>63.7†</td>
<td>62.8†</td>
<td>63.5†</td>
<td>85.3</td>
<td>84.7</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.2 (3.3)</td>
<td>24.3 (3.5)</td>
<td>24.4 (3.5)</td>
<td>24.4 (3.3)</td>
<td>24.0 (3.5)</td>
<td>24.5 (3.2)</td>
<td>25.2 (3.1)†</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>126.8 (17.3)</td>
<td>147.0 (22.5)†</td>
<td>147.0 (23.0)†</td>
<td>142.6 (20.1)†</td>
<td>151.7 (23.2)†</td>
<td>125.8 (14.9)</td>
<td>124.5 (17.7)†</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>79.4 (9.7)</td>
<td>87.9 (12.9)†</td>
<td>86.7 (12.9)†</td>
<td>85.7 (11.7)†</td>
<td>92.0 (13.3)†</td>
<td>78.9 (9.3)</td>
<td>76.5 (10.7)†</td>
</tr>
<tr>
<td>HOM-C, mmol/L</td>
<td>1.05 (0.28)</td>
<td>0.91 (0.26)†</td>
<td>0.90 (0.27)†</td>
<td>0.93 (0.27)†</td>
<td>0.89 (0.32)†</td>
<td>1.05 (0.29)</td>
<td>1.08 (0.26)†</td>
</tr>
<tr>
<td>Non-HDL-C, mmol/L</td>
<td>2.94 (0.97)</td>
<td>2.87 (0.92)†</td>
<td>3.06 (0.96)†</td>
<td>2.92 (0.95)†</td>
<td>2.87 (0.96)†</td>
<td>2.89 (0.95)</td>
<td>3.16 (1.07)†</td>
</tr>
<tr>
<td>TC, mmol/L</td>
<td>4.97 (1.00)</td>
<td>4.74 (1.02)†</td>
<td>4.86 (1.04)†</td>
<td>4.78 (0.99)†</td>
<td>4.54 (0.99)†</td>
<td>4.78 (0.92)</td>
<td>5.08 (1.11)†</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.47 (15.10)</td>
<td>1.65 (13.90)†</td>
<td>1.70 (8.41)†</td>
<td>1.71 (12.91)†</td>
<td>1.45 (16.87)†</td>
<td>1.60 (15.45)</td>
<td>1.80 (17.82)†</td>
</tr>
<tr>
<td>TG, mmol/L</td>
<td>5.86 (1.74)</td>
<td>6.61 (2.64)†</td>
<td>6.78 (2.81)†</td>
<td>6.39 (2.60)†</td>
<td>6.58 (2.37)†</td>
<td>5.70 (1.70)</td>
<td>5.77 (2.11)†</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>31.0</td>
<td>37.8†</td>
<td>37.9†</td>
<td>34.3†</td>
<td>41.2†</td>
<td>42.6</td>
<td>35.8†</td>
</tr>
<tr>
<td>Alcohol intake, %</td>
<td>26.5</td>
<td>63.2</td>
<td>63.8</td>
<td>59.8</td>
<td>65.3</td>
<td>25.8</td>
<td>44.4</td>
</tr>
<tr>
<td>DM history, %</td>
<td>5.2</td>
<td>12.4</td>
<td>16.6</td>
<td>12.3</td>
<td>5.9</td>
<td>5.7</td>
<td>15.3</td>
</tr>
</tbody>
</table>

Table 2: Association of SNP +2255 in VKORC1 Gene With Stroke

<table>
<thead>
<tr>
<th>Genotype, n (%)</th>
<th>Frequency, %</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>59.6 (9.3)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>CT</td>
<td>36.7†</td>
<td>1.85 (1.54–2.23)†</td>
<td>1.95 (1.58–2.41)†</td>
</tr>
<tr>
<td>TT</td>
<td>3.7†</td>
<td>1.85 (1.54–2.23)†</td>
<td>1.95 (1.58–2.41)†</td>
</tr>
</tbody>
</table>

**ORs and 95% CIs were calculated with the use of multivariate logistic regression analyses. Adjusted ORs were stratified by age, sex, body mass index, blood pressure, cigarette smoking, alcohol consumption, glucose, HDL-C, non-HDL-C, TC, and TG.**

\( \chi^2 \) Test vs control, \( \text{**P}<0.05, \text{†P}<0.001} \).
microaneurysms in intracerebral arteries (whether this is the main cause is still in debate), and lacunar infarction is usually caused by lipohyalinosis or microatheromata with thrombosis of the vascular lumen (≈30 to 100 μm). Although stroke results from a number of different pathological processes, predisposing factors for each stroke subtype are surprisingly similar, such as increased age, hypertension, smoking, and DM. These are risk factors for CHD and aortic dissection as well. Some of the same factors are manifested in Marfan syndrome, which is caused primarily by mutations in the FBN1 gene. However, other factors are clearly important in the expression of Marfan syndrome; relatives who share the same mutations show dramatically different phenotypes.  

Therefore, all mechanisms that weaken the aorta’s medial layers will contribute to higher aortic wall stress. This can induce aortic dilation and aneurysm formation and eventually cause intramural hemorrhage, aortic dissection, or rupture. 

VKORC1 variation could serve as a common genetic risk factor for all vascular diseases. It involves mediation of γ-carboxylation of hemostatic and nonhemostatic proteins by control of the vitamin K cycle. Polymorphisms of VKORC1 have been shown to affect the expression and activity of VKORC1 and thus warfarin dose response and blood clotting. Vitamin K–dependent nonhemostatic proteins mediate calcification. Vessel calcification decreases vessel elasticity and increases shear stress and is associated with the increased morbidity and mortality of arterial disease.  

D’Andrea et al19 recently found that patients with the TT genotype of SNP rs9934438 require a lower dose of warfarin, due at least in part to a lower activity of VKORC1. This leads to less conversion of vitamin K epoxide back to its reduced form, which results in less carboxylation of vitamin K–dependent proteins.19 The T allele at rs9934438 is on the same haplotype as the T allele of SNP +2255 had higher levels of undercarboxylated vitamin K–dependent proteins, osteocalcin and PIVKA-II. We proposed that the VKORC1 promoter with the G allele yielded a 44% increase of activity compared with the A allele of 1639. Consistent with these results, we found that subjects with the TT genotype of +2255 had higher levels of undercarboxylated vitamin K–dependent proteins, osteocalcin and PIVKA-II. We proposed that the VKORC1 haplotype G-C-G-C-A (3673-6483-6852-7562-9042) would increase the promoter activity and higher expression of VKORC1 mRNA and protein. This would result in increased γ-carboxylation, as indicated by the decreased levels of the undercarboxylated vitamin K–dependent proteins osteocalcin and PIVKA-II and a potential need for increased warfarin dosage.

The biological activity of all known vitamin K–dependent proteins is highly dependent on correct γ-carboxylation, which affects not only procoagulatory (factor II, VII, IX, and X) but also anticoagulatory (protein C, S, and Z) clotting factors and osteocalcin in the same way as MGP.  

The greater functional activity of the C allele may also lead to higher levels of MGP and less vascular calcification. Therefore, the observed association may not be related to the effect on the γ-carboxylation of the vitamin K–dependent proteins but may be caused by another yet-unknown function of VKORC1.

One possibility is that VKORC1 haplotypes are only markers for LD, and some genes in the linkage region independent of or in conjunction with VKORC1 confer susceptibility to arterial disease. At least 6 other genes are found in the natural haplotype block over the 68,000 bases around VKORC1: ZNF668 (zinc finger protein), ZNF646, BCKDK (branched chain ketoacid dehydrogenase kinase), MYST1 (histone acetyltransferase1), PRSS8 (protease serine

### Table 3. Association of SNP +2255 in VKORC1 Gene With CHD

<table>
<thead>
<tr>
<th>Groups</th>
<th>Genotype, n (%)</th>
<th>Frequency, %</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (n=740)</td>
<td>CC 2 (0.3)</td>
<td>81 (10.9)</td>
<td>657 (88.8)</td>
<td>11.2</td>
</tr>
<tr>
<td>Cases (n=740)</td>
<td>CT 5 (0.7)</td>
<td>120 (16.2)</td>
<td>615 (83.1)</td>
<td>16.9</td>
</tr>
</tbody>
</table>

ORs and 95% CIs were computed with the use of multivariate logistic regression analyses. Adjusted ORs were stratified by age, sex, body mass index, blood pressure, cigarette smoking, alcohol consumption, glucose, HDL-C, non-HDL-C, TC, and TG.

χ² Test vs control, *P<0.01.

### Table 4. Association of SNP +2255 in VKORC1 Gene With Aortic Dissection

<table>
<thead>
<tr>
<th>Groups</th>
<th>Genotype, n (%)</th>
<th>Frequency, %</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (n=416)</td>
<td>CC 0 (0.0)</td>
<td>41 (9.9)</td>
<td>375 (90.1)</td>
<td>9.9</td>
</tr>
<tr>
<td>Cases (n=253)</td>
<td>CT 3 (1.2)</td>
<td>40 (15.8)</td>
<td>210 (83.0)</td>
<td>17.0</td>
</tr>
</tbody>
</table>

ORs and 95% CIs were computed with the use of multivariate logistic regression analyses. Adjusted ORs were stratified by age, sex, body mass index, blood pressure, cigarette smoking, alcohol consumption, glucose, HDL-C, non-HDL-C, TC, and TG.

χ² Test vs control, *P<0.05, †P<0.01.
Undercarboxylated osteocalcin and PIVKA-II antigen serum levels in carriers of different genotypes of the VKORC1 gene SNP +2255. Levels of the 2 proteins are presented as means; T bars represent SDs. PIVKA-II antigen serum levels were significantly correlated with SNP +2255 (P<0.001). Five samples in the CC group, 18 in the CT group, and 26 in the TT group were analyzed. **P<0.05, ***P<0.001 for the comparison between genotype TT and CC groups.

References


Acknowledgments

We thank Dr Thomas Eling (NIH/NIHES) for his text editing. The study was supported by the Ministry of Science and Technology of China with grant 2002BA711A05 and National 973 Basic Research Project (973 G2000056901) to Dr Rutai. The authors also acknowledge the International HapMap Consortium for the data of LD around VKORC1.

Disclosures

None.


41. Hak AE, Pols HA, van Hottem AM, Hofman A, Witteman JC. Pro- 


**CLINICAL PERSPECTIVE**

Epidemiological data indicate that coronary atherosclerosis is an important cause of morbidity and mortality worldwide. To minimize the devastating consequence of vascular disease, we must reliably distinguish those individuals who will experience an event from those who will not. The haplotypes in **VKORC1** affect warfarin dose response through effects on the formation of the reduced form of vitamin K, a cofactor for γ-carboxylation of vitamin K–dependent proteins. Vitamin K–dependent proteins play a critical role in the coagulation cascade and may potentially impact atherosclerosis. We tested the association of the single-nucleotide polymorphisms of the **VKORC1** gene and arterial vascular diseases including coronary heart disease, stroke, and aortic dissection. We observed that **VKORC1** variation is significantly associated with each of these diseases. Although the pathophysiology behind the present findings is not entirely clear, confirmation of these observations in additional studies is warranted. Additional research is necessary to elucidate the potential role of **VKORC1** and its downstream products in the pathogenesis of vascular disease.
VKORC1 Haplotypes Are Associated With Arterial Vascular Diseases (Stroke, Coronary Heart Disease, and Aortic Dissection)
Yibo Wang, Weili Zhang, Yuhui Zhang, Yuejin Yang, Lizhong Sun, Shengshou Hu, Jilin Chen, Channa Zhang, Yi Zheng, Yisong Zhen, Kai Sun, Chunyan Fu, Tao Yang, Jianwei Wang, Jing Sun, Haiying Wu, Wayne C. Glasgow and Rutai Hui

Circulation. 2006;113:1615-1621; originally published online March 20, 2006; doi: 10.1161/CIRCULATIONAHA.105.580167
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/113/12/1615

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/