Genetics of Arterial and Venous Thrombosis: Clinical Aspects and a Look to the Future

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Harvard Medical School
Director, Center for Cardiovascular Disease Prevention
Brigham and Women’s Hospital
Boston, Massachusetts
Will genetics play a major role in patient focused thrombosis care?

Will pharmacogenetics matter for cardiovascular disease?
Applications Of Genomic Medicine

- New Drug Targets
- Understanding Biologic Pathways
- Prediction of Risk
- Personalized Medicine
- Modification of Guidelines
Strategies for Genetic Analysis

Families
Linkage Studies

Simple inheritance
Single gene
Rare variants
Small Population Attributable Risk

Populations
Association Studies

Complex inheritance
Multiple Genes
Common variants
Large Population Attributable Risk
Patterns of Inheritance, Allele Frequency, and Relative Risks in Genetic Studies

- Allele Frequency
- Relative Risk

<table>
<thead>
<tr>
<th>Allele Frequency</th>
<th>Relative Risk</th>
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<tbody>
<tr>
<td>Rare</td>
<td>10</td>
</tr>
<tr>
<td>Common</td>
<td>1</td>
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</table>

The chart illustrates the relationship between allele frequency and relative risk, showing a decrease in risk as allele frequency increases from rare to common.
Patterns of Inheritance, Allele Frequency, and Relative Risks in Genetic Studies

- **Medelian Inheritance**
  - rare SNP (<< 1 %)
  - strong effect
  - low population attributable risk

![Graph showing the relationship between Allele Frequency and Relative Risk]
Patterns of Inheritance, Allele Frequency, and Relative Risks in Genetic Studies

Complex Inheritance
- common SNP (>1 %)
- weak effect
- high population attributable risk

Medelian Inheritance
- rare SNP (<<< 1 %)
- strong effect
- low population attributable risk
Patterns of Inheritance, Allele Frequency, and Relative Risks in Genetic Studies

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**Examples:** apo E, MTHFR, CRP

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**Examples:** LDL-R, tangiers ABCA1
Patterns of Inheritance, Allele Frequency, and Relative Risks in Genetic Studies

**Complex Inheritance**
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- weak effect
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Examples: LDL-R, tangiers ABCA1
Starting Premises: The Genetic Differences Between Venous and Arterial Thrombosis

• For venous thromboembolism, we already know that genetics play a major role by increasing risk (factor v Leiden, G20210A prothrombin mutation) and in assisting with therapy (warfarin metabolism).
• For arterial thrombosis, a disorder with major environmental causes, the utility of genetic information is currently less certain.
• Other than age and smoking, will any single risk factor for CHD will have an overwhelming effect on outcome?
• Will any single gene or haplotype have a large effect on risk in the population?
• Will any specific genetic risk score be better than “positive family history”? 
Risk Factors for Venous Thromboembolism

Virchow’s Triad 1856
- Vessel Wall Trauma
- Hypercoagulability
- Stasis

Recent Surgery
- Malignancy
- Oral Contraception
- Pregnancy
- Immobilization
- Platelet Disorders

Anti-thrombin III
- Protein C
- Protein S
- tPA/PAI-1
- Homocysteine
- Lupus-anticoagulant

APC-R Factor V Leiden
- Prothrombin mutation
G1691A Mutation in Coagulation Factor V and Risks of Future Arterial and Venous Thrombosis

![Bar chart showing the risk of developing future arterial and venous thrombosis for heterozygous and referent individuals.](chart.png)

- Heterozygous, n = 1408
- Referent
- Future MI: P=0.9
- Future CVA: P=0.4
- Future MI or CVA: P=0.7
- Future DVT/PE: P=0.02

Frequency of Factor V Leiden among 4047 US Men and Women, According to Self-Reported Ethnic Group

<table>
<thead>
<tr>
<th>Ethnic Group</th>
<th>N</th>
<th>Carrier Frequency</th>
<th>Allele Frequency</th>
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<tbody>
<tr>
<td></td>
<td>%</td>
<td>95 % CI</td>
<td>%</td>
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<tr>
<td>Caucasian-American</td>
<td>2468</td>
<td>5.27</td>
<td>4.42 - 6.22</td>
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<tr>
<td>Hispanic-American</td>
<td>407</td>
<td>2.21</td>
<td>1.01 - 4.16</td>
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<tr>
<td>African-American</td>
<td>650</td>
<td>1.23</td>
<td>0.53 - 2.41</td>
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<tr>
<td>Asian-American</td>
<td>442</td>
<td>0.45</td>
<td>0.05 - 1.63</td>
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<tr>
<td>Native-American</td>
<td>80</td>
<td>1.25</td>
<td>0.03 - 6.77</td>
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</table>

Overall US Population Carrier Estimate = 4.3 percent

JAMA 1997;277:1305-7
<table>
<thead>
<tr>
<th>Diagnostic Tests for Thrombophilia</th>
<th>Genetic Basis</th>
<th>Acquired Basis</th>
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<tbody>
<tr>
<td><strong>APC resistance</strong></td>
<td>HR$_2$ Haplotype</td>
<td>Pregnancy, OC use, lupus, warfarin, increased factor VIII levels, stroke, autoantibodies against APC</td>
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<tr>
<td></td>
<td>Factor V Leiden</td>
<td></td>
</tr>
<tr>
<td><strong>Prothrombin</strong></td>
<td>G20210A</td>
<td>None</td>
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<tr>
<td><strong>Hyperhomocystinemia</strong></td>
<td>Mutations in MTHFR, renal failure cystathionine β-synthase</td>
<td>Folate, B12, B6 intake,</td>
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<tr>
<td><strong>Elevated factor VIII</strong></td>
<td>Unknown</td>
<td>Exertion, pregnancy, OC use, stress, age, acute-phase response</td>
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<tr>
<td><strong>Reduced protein C</strong></td>
<td>161 mutations</td>
<td>Liver disease, childhood, warfarin, vitamin K deficiency, autoantibodies against APC, DIC</td>
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<tr>
<td><strong>Reduced protein S</strong></td>
<td>131 mutations</td>
<td>Liver disease, childhood, warfarin, vitamin K deficiency, DIC, nephrosis, pregnancy, use of OC, autoantibodies against protein S</td>
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<tr>
<td><strong>Reduced AT-III</strong></td>
<td>127 mutations</td>
<td>Liver disease, heparin use, DIC, nephrosis</td>
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<tr>
<td><strong>Dysfibrinogenemia</strong></td>
<td>20 mutations</td>
<td>DIC, liver disease, recent birth</td>
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Prevalence of Genetic Disorders in Familial Thrombosis

<table>
<thead>
<tr>
<th>Genetic Defect</th>
<th>Estimated Prevalence (%)</th>
<th>Known Mutations (N)</th>
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<tr>
<td>Dysfibrinogenemia</td>
<td>1.0</td>
<td>&gt; 11</td>
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<tr>
<td>AT-III Deficiency</td>
<td>4.2</td>
<td>&gt; 79</td>
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<tr>
<td>Protein C</td>
<td>4.9</td>
<td>&gt; 160</td>
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<tr>
<td>Protein S</td>
<td>5.1</td>
<td>&gt; 13</td>
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<tr>
<td>APC-R</td>
<td>30 - 50</td>
<td>&gt; 1 (Factor V Leiden)</td>
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</table>

Bertina et al, Thrombosis and Haemostasis 1995;74:449-453
PREVENT: Primary Endpoint: Recurrent VTE

Hazard Ratio, 0.36 (95% CI, 0.19 to 0.67); \( P < .001 \)

Cumulative Event Rate

Placebo
(7.2/100 person-years)

Low-Intensity Warfarin
(2.6/100 person-years)

Years of Follow-Up

0 1 2 3 4

PREVENT: Recurrent VTE by Clinically Important Subgroups

<table>
<thead>
<tr>
<th>Number of prior VTE *</th>
<th>Hazard Ratio (95% CI)</th>
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<tr>
<td>&gt;2</td>
<td>0.43 (0.20-0.90)</td>
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<td>1</td>
<td>0.25 (0.08-0.74)</td>
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</table>

<table>
<thead>
<tr>
<th>Factor V Leiden or prothrombin mutation *</th>
<th>Hazard Ratio (95% CI)</th>
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<tbody>
<tr>
<td>Present</td>
<td>0.25 (0.0-0.87)</td>
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<td>Absent</td>
<td>0.42 (0.2-0.86)</td>
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<table>
<thead>
<tr>
<th>Gender</th>
<th>Hazard Ratio (95% CI)</th>
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<tbody>
<tr>
<td>Male</td>
<td>0.47 (0.23-0.96)</td>
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<tr>
<td>Female</td>
<td>0.20 (0.06-0.67)</td>
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</table>

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Hazard Ratio (95% CI)</th>
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<tr>
<td>30-44</td>
<td>0.45 (0.14-1.51)</td>
</tr>
<tr>
<td>45-64</td>
<td>0.24 (0.09-0.65)</td>
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<tr>
<td>65-89</td>
<td>0.57 (0.19-1.70)</td>
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<table>
<thead>
<tr>
<th>Time after randomization</th>
<th>Hazard Ratio (95% CI)</th>
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<tbody>
<tr>
<td>≤1 year</td>
<td>0.27 (0.11-0.66)</td>
</tr>
<tr>
<td>&gt;1 year</td>
<td>0.49 (0.21-1.16)</td>
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</table>

* Prespecified subgroup

Effects of Randomized Vitamin E Supplementation on the Occurrence of Venous Thromboembolism: Potential Effect Modification by Genetic Risk Factors

Glynn RJ, Ridker PM, Goldhaber SZ, Zee YL, Buring JE. Circulation 2007;116
Association of Genetic Variations With Nonfatal Venous Thrombosis in Postmenopausal Women

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Lucia A. Hindorff, PhD
Susan R. Heckbert, MD, PhD
Rozenn N. Lemaitre, PhD, MPH
Kristin D. Marcianite, PhD
Kenneth Rice, PhD
Thomas Lumley, PhD
Joshua C. Bis, MS
Kerri L. Wiggins, MS, RD
Frits R. Rosendaal, MD, PhD
Bruce M. Psaty, MD, PhD

**Context** Although the roles of clotting proteins and enzymes that activate or inhibit fibrin production and lysis are well characterized, the underlying contribution of genetic variation in these constituents to risk of venous thrombosis (VT) has not been fully investigated.

**Objective** To describe the association of common genetic variation in 24 coagulation, anticoagulation, fibrinolysis, and antifibrinolysis candidate genes with risk of incident nonfatal VT in postmenopausal women.

**Design, Setting, and Participants** Population-based case-control study conducted in a large integrated health care system in Washington State. Participants were perimenopausal and postmenopausal women aged 30 to 89 years who sustained a first VT event between January 1995 and December 2002 (n=349) and 1680 controls matched on age, hypertension status, and calendar year (n=1680).

**Main Outcome Measure** Risk of venous thrombosis associated with global variation within a gene as measured by common haplotypes and with individual haplotypes and single nucleotide polymorphisms (SNPs). Significance of the associations was assessed by a .20 threshold of the false-discovery rate q value, which accounts for multiple testing.

**Results** Only the tissue factor pathway inhibitor gene demonstrated global association with risk (q = .23). Five significant SNP associations were identified across 3 of the candidate genes (factors V, XI, and protein C) in SNP analyses. Two associations have been previously reported. Another 22 variants across 15 genes had P values less than .05 but q values between .20 and .35. Five of these confirm previously reported associations (fibrinogen genes and protein C). 2 were inconsistent with earlier reports (thrombomodulin and plasminogen activator inhibitor 1), and 15 were new discoveries.

**Conclusions** After accounting for multiple testing, 5 SNPs associated with VT risk were identified, 3 of which have not been previously reported. Replication of these novel associations in other populations is necessary to corroborate these findings and identify which genetic factors may influence VT risk in postmenopausal women.

JAMA 2007;297:489-498

www.jama.com
Genome Wide Association Study: Women's Genome Health Study
Venous Thromboembolism

A) F5 Locus (rs6025)
B) IKBKB Locus (rs17875571)
C) ABO Locus (rs887289)

FV Leiden
IKBKB
ABO

Pare, Chasman, Ridker 2009
VTE GWAS: CHARGE Consortium 2012  
(Tang, Smith, Folsom)

- Longitudinal Investigation of Thromboembolism Etiology (LITE)
- Atherosclerosis Risk in Communities Study (ARIC)
- Cardiovascular Health Study (CHS)
- Heart and Vascular Health Study (HVH)
- Rotterdam Study
- Women’s Genome Health Study (WGHS)
- Mayo Clinic VTE Study
- Marseille Thrombosis Association VTE Study
- French Case-Control Study of Early Onset VTE

- 45,116 participants, 1,562 incident VTE
- Genome wide results: F5, ABO, F11, FGG
- Possible association SUSD1 OTUD7A
 Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls

The Wellcome Trust Case Control Consortium*

There is increasing evidence that genome-wide association (GWA) studies represent a powerful approach to the identification of genes involved in common human diseases. We describe a joint GWA study (using the Affymetrix GeneChip 500K Mapping Array Set) undertaken in the British population, which has examined $\sim$2,000 individuals for each of 7 major diseases and a shared set of $\sim$3,000 controls. Case-control comparisons identified 24 independent association signals at $P < 5 \times 10^{-7}$: 1 in bipolar disorder, 1 in coronary artery disease, 9 in Crohn's disease, 3 in rheumatoid arthritis, 7 in type 1 diabetes and 3 in type 2 diabetes. On the basis of prior findings and replication studies thus-far completed, almost all of these signals reflect genuine susceptibility effects. We observed association at many previously identified loci, and found compelling evidence that some loci confer risk for more than one of the diseases studied. Across all diseases, we identified a large number of further signals (including 58 loci with single-point $P$ values between $10^{-5}$ and $5 \times 10^{-7}$) likely to yield additional susceptibility loci. The importance of appropriately large samples was confirmed by the modest effect sizes observed at most loci identified. This study thus represents a thorough validation of the GWA approach. It has also demonstrated that careful use of a shared control group represents a safe and effective approach to GWA analyses of multiple disease phenotypes; has generated a genome-wide genotype database for future studies of common diseases in the British population; and shown that, provided individuals with non-European ancestry are excluded, the extent of population stratification in the British population is generally modest. Our findings offer new avenues for exploring the pathophysiology of these important disorders. We anticipate that our data, results and software, which will be widely available to other investigators, will provide a powerful resource for human genetics research.
Signal-Intensity Plots Between SNPs and CAD in Genome Wide Association Analysis

A  WTCCC Study

B  German MI Family Study

Samani et al WTCCC and Cardiogenetics Consortium NEJM 2007;357 (July 18)
Relationship of 9p21 to CAD  
HR = 0.80 (0.77-0.82)  
Twenty percent lower risk among carriers

### Study Details

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
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<tbody>
<tr>
<td>Abdullahi et al, 2008</td>
<td>0.56 (0.46-0.69)</td>
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<td>Anderson et al, 2008</td>
<td>0.81 (0.66-0.99)</td>
</tr>
<tr>
<td>Asselme et al, 2008</td>
<td></td>
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<tr>
<td>Older</td>
<td>0.77 (0.60-0.99)</td>
</tr>
<tr>
<td>Younger</td>
<td>0.98 (0.63-1.44)</td>
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<td>Brocchent et al, 2008</td>
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<tr>
<td>Germany</td>
<td>0.79 (0.63-1.00)</td>
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<tr>
<td>Italy</td>
<td>0.79 (0.64-0.97)</td>
</tr>
<tr>
<td>Sweden</td>
<td>0.74 (0.60-0.91)</td>
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<tr>
<td>United Kingdom</td>
<td>0.78 (0.72-0.85)</td>
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<td>Deighan et al, 2008</td>
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<td>Helgadottir et al, 2007</td>
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<td>Korea</td>
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<td>CCHS</td>
<td>0.82 (0.72-0.93)</td>
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<tr>
<td>DHS</td>
<td>0.56 (0.35-0.90)</td>
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<tr>
<td>OHS-1</td>
<td>0.58 (0.30-0.90)</td>
</tr>
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<td>OHS-2</td>
<td>0.76 (0.50-1.14)</td>
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<td>OHS-3</td>
<td>0.87 (0.61-1.27)</td>
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<tr>
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<td>Paynter et al, 2009</td>
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<td>Germany</td>
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<td>Samani et al, 2009</td>
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<td>AMF-PAS</td>
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<td>ECTM</td>
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<td>MORGAM</td>
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<td>AtheroGene</td>
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<tr>
<td>GenMIF II</td>
<td>0.90 (0.70-1.15)</td>
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<tr>
<td>ILDE</td>
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<td>MONICA/KORA</td>
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<tr>
<td>PopGen</td>
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<tr>
<td>Prime</td>
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<td>UK MI</td>
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<td>Talmud et al, 2008</td>
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<td>Zhang et al, 2008</td>
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<tr>
<td>Zhou et al, 2008</td>
<td>0.60 (0.37-1.02)</td>
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</tbody>
</table>

**Overall (random effects)**  
0.60 (0.77-0.82)  
Test for heterogeneity: P = 0.00, R^2 = 0.04
Introducing three new genetic tests from deCODE

New deCODE AF™
Genetic risk test for atrial fibrillation

deCODE AF™ is aimed at improving the prevention and treatment of ischemic stroke related to atrial fibrillation (AF).
- Detects 2 common single-letter gene variants that are associated with an increased risk for atrial fibrillation. deCODE AF™ helps physicians identify patients who may benefit from extended cardiac monitoring and anticoagulation therapy.

New deCODE T2™
Genetic risk test for diabetes

deCODE T2™ is a test for a well-validated genetic risk factor for type 2 diabetes—a gene called TCF7L2.
- Detects a variant in the TCF7L2 gene that can help identify individuals who have an above-average risk of developing active diabetes.1-3
- Pharmacogenetic evidence suggests that patients with variation in TCF7L2 may not respond well to sulfonylurea treatment.4-6

New deCODE MI™
Genetic risk test for myocardial infarction

deCODE MI™ helps to identify a common variant on chromosome 9p21 that confers increased risk of myocardial infarction (MI).
- More than 20% of the general population carry 2 copies of the variant, corresponding to a more than 60% increase in risk of heart attack compared to those without the variant.5

To order or learn more about deCODE genetics, go to www.decodediagnostics.com, deCODE AF™, deCODE T2™ and deCODE MI™ are performed in the deCODE CLIA-certified laboratory.

References
## Association of 9p21 SNP with CVD outcomes


<table>
<thead>
<tr>
<th></th>
<th>AA (n=5793)</th>
<th>AG (n=10952)</th>
<th>GG (n=5384)</th>
<th>Additive Model</th>
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<tbody>
<tr>
<td><strong>Total CVD</strong></td>
<td>1.0</td>
<td>1.22</td>
<td>1.33</td>
<td>1.15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.01 – 1.46)</td>
<td>(1.08 – 1.65)</td>
<td>(1.04 – 1.28)</td>
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<tr>
<td><strong>CHD</strong></td>
<td>1.0</td>
<td>1.25</td>
<td>1.33</td>
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<td></td>
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<td>(0.99 – 1.58)</td>
<td>(1.03 – 1.73)</td>
<td>(1.01 – 1.31)</td>
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<tr>
<td><strong>MI</strong></td>
<td>1.0</td>
<td>1.30</td>
<td>1.31</td>
<td>1.14</td>
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<td></td>
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<td>(0.91 – 1.86)</td>
<td>(0.87 – 1.97)</td>
<td>(0.93 – 1.38)</td>
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<tr>
<td><strong>Stroke</strong></td>
<td>1.0</td>
<td>1.30</td>
<td>1.55</td>
<td>1.24</td>
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<tr>
<td></td>
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<td>(0.94 – 1.81)</td>
<td>(1.08 – 2.23)</td>
<td>(1.04 – 1.48)</td>
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Effect of Genotype on 10-Year CVD Risk

Reynolds Covariates Plus Genotype

<table>
<thead>
<tr>
<th>Reynolds Covariates</th>
<th>&lt;5%</th>
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<th>10% to &lt;20%</th>
<th>≥20%</th>
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<tbody>
<tr>
<td>&lt;5% N K-M Estimate</td>
<td>18527</td>
<td>188</td>
<td>-</td>
<td>-</td>
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<tr>
<td></td>
<td>1.5%</td>
<td>2.7%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5% to &lt;10% N K-M Estimate</td>
<td>183</td>
<td>1960</td>
<td>75</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>1.4%</td>
<td>7.7%</td>
<td>8.3%</td>
<td>-</td>
</tr>
<tr>
<td>10% to &lt;20% N K-M Estimate</td>
<td></td>
<td>85</td>
<td>761</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>10.6%</td>
<td>15.2%</td>
<td>21.4%</td>
</tr>
<tr>
<td>≥20% N K-M Estimate</td>
<td>-</td>
<td>-</td>
<td>23</td>
<td>296</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-</td>
<td>31.5%</td>
<td>30.4%</td>
</tr>
</tbody>
</table>

Of 585 women reclassified (2.6%), only 214 (1.1%) were reclassified correctly

NRI = -0.2 %
P = 0.6

No improvement in discrimination, calibration, or reclassification

Polymorphisms Associated with Cholesterol and Risk of Cardiovascular Events: Malmo Diet and Cancer Study

Polymorphisms Associated with Cholesterol and Risk of Cardiovascular Events: Malmo Diet and Cancer Study

23 Loci Associated With Coronary Artery Disease

Association Between a Literature-Based Genetic Risk Score and Cardiovascular Events in Women

Nina P. Paynter, PhD
Daniel I. Chasman, PhD
Guillaume Paré, MD, MS
Julie E. Buring, ScD
Nancy R. Cook, ScD
Joseph P. Miletich, MD, PhD
Paul M Ridker, MD, MPH

Context While multiple genetic markers associated with cardiovascular disease have been identified by genome-wide association studies, their aggregate effect on risk beyond traditional factors is uncertain, particularly among women.

Objective To test the predictive ability of a literature-based genetic risk score for cardiovascular disease.

Design, Setting, and Participants Prospective cohort of 19,313 initially healthy white women in the Women’s Genome Health Study followed up over a median of 12.3 years (interquartile range, 11.6-12.8 years). Genetic risk scores were constructed from the National Human Genome Research Institute’s catalog of genome-wide association study results published between 2005 and June 2009.

Main Outcome Measure Incident myocardial infarction, stroke, arterial revascularization, and cardiovascular death.

Results A total of 101 single nucleotide polymorphisms reported to be associated with cardiovascular disease or at least 1 intermediate cardiovascular disease phenotype at a published P value of less than 10^{-7} were identified and risk alleles were added to create a genetic risk score. During follow-up, 777 cardiovascular disease events occurred (199 myo-
Will Panels of Previously Validated SNPs Improve CVD Risk Prediction?

101 SNP GRS

12 SNP GRS

Paynter et al; JAMA 2010;303:631-637
Why about a simple question: did your parents have CVD?

- Remains associated with CVD after adjustment for other risk factors
- Shows modest improvement in prediction

Paynter et al; JAMA 2010;303:631-637
“Addition of parental information may help clinicians and patients with primary prevention of cardiovascular disease, when treatment decisions may be difficult in patients at intermediate risk based on levels of single or multiple risk factors”
Reynolds Risk Score
Calculating Heart and Stroke Risk for Women and Men

If you are healthy and without diabetes, the Reynolds Risk Score is designed to predict your risk of having a future heart attack, stroke, or other major heart disease in the next 10 years.

In addition to your age, blood pressure, cholesterol levels and whether you currently smoke, the Reynolds Risk Score uses information from two other risk factors, a blood test called hsCRP (a measure of inflammation) and whether or not either of your parents had a heart attack before they reached age 60 (a measure of genetic risk). To calculate your risk, fill in the information below with your most recent values. Click here for help filling the information.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>68</td>
<td>Years (Maximum age must be 80)</td>
</tr>
<tr>
<td>Do you currently smoke?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Systolic Blood Pressure (SBP)</td>
<td>132 mm/Hg</td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>230 mg/DL</td>
<td></td>
</tr>
<tr>
<td>HDL or “Good” Cholesterol</td>
<td>45 mg/DL</td>
<td></td>
</tr>
<tr>
<td>High Sensitivity C-Reactive Protein (hsCRP)</td>
<td>4.5 mg/L</td>
<td></td>
</tr>
<tr>
<td>Did your Mother or Father have a heart attack before age 60?</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

As shown in the graph below, at Age 68, your chance of having a heart attack, stroke, or other heart disease event at some point in the next 10-years is 29 percent. This risk is approximately 3 times higher than that of a Man the same age who has optimal levels of all modifiable risk factors.

<table>
<thead>
<tr>
<th>current Age</th>
<th>Age 78</th>
<th>Print</th>
<th>Age 68</th>
</tr>
</thead>
<tbody>
<tr>
<td>Your 10-year risk (age 68)</td>
<td>[Red]</td>
<td>[29%]</td>
<td></td>
</tr>
<tr>
<td>Your 10-year risk (age 68) if,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• your blood pressure was 120</td>
<td>[Orange]</td>
<td>[23%]</td>
<td></td>
</tr>
<tr>
<td>• your cholesterol was 160</td>
<td>[Orange]</td>
<td>[18%]</td>
<td></td>
</tr>
<tr>
<td>• your hsCRP was 0.5</td>
<td>[Orange]</td>
<td>[24%]</td>
<td></td>
</tr>
<tr>
<td>• all the above were optimal</td>
<td>[Green]</td>
<td>[11%]</td>
<td></td>
</tr>
</tbody>
</table>

The graph above also compares your risk to that of a Man of age 68 who has optimal levels for all modifiable risk factors, and shows what your risk would be if you improved your individual risk factors. For young Man, risk may appear to be low over the next 10-years, yet can be very high over a lifetime. Thus, to see what your risk would be as you get older if your risk factors remain the same, click on the buttons above.
Genetic Loci Associated With Plasma Concentration of Low-Density Lipoprotein Cholesterol, High-Density Lipoprotein Cholesterol, Triglycerides, Apolipoprotein A1, and Apolipoprotein B Among 6382 White Women in Genome-Wide Analysis With Replication

Daniel I. Chasman, PhD*; Guillaume Paré, MD, MS*; Robert Y.L. Zee, PhD, MPH; Alex N. Parker, PhD; Nancy R. Cook, ScD; Julie E. Buring, ScD; David J. Kwiatkowski, MD, PhD; Lynda M. Rose, MS; Joshua D. Smith, BS; Paul T. Williams, PhD; Mark J. Rieder, PhD; Jerome I. Rotter, MD; Deborah A. Nickerson, PhD; Ronald M. Krauss, MD; Joseph P. Miletich, MD; Paul M Ridker, MD, MPH

Background—Genome-wide genetic association analysis represents an opportunity for a comprehensive survey of the genes governing lipid metabolism, potentially revealing new insights or even therapeutic strategies for cardiovascular disease and related metabolic disorders.

Methods and Results—We have performed large-scale, genome-wide genetic analysis among 6382 white women with replication in 2 cohorts of 970 additional white men and women for associations between common single-nucleotide polymorphisms and low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, apolipoprotein (Apo) A1, and ApoB. Genome-wide associations ($P<5 \times 10^{-8}$) were found at the PCSK9 gene, the APOB gene, the LPL gene, the APOA1-APOA5 locus, the LIPC gene, the CETP gene, the LDLR gene, and the APOE locus. In addition, genome-wide associations with triglycerides at the GCKR gene confirm and extend emerging links between glucose and lipid metabolism. Still other genome-wide associations at the 1p13.3 locus are consistent with emerging biological properties for a region of the genome, possibly related to the SORT1 gene. Below genome-wide significance, our study provides confirmatory evidence for associations at 5 novel loci with low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, or triglycerides reported recently in separate genome-wide association studies. The total proportion of variance explained by common variation at the genome-wide candidate loci ranges from 4.3% for triglycerides to 12.6% for ApoB.

Conclusion—Genome-wide associations at the GCKR gene and near the SORT1 gene, as well as confirmatory associations at 5 additional novel loci, suggest emerging biological pathways for lipid metabolism among white women. (Circ Cardiovasc Genet. 2008;1:21-30.)
Association with plasma LDL cholesterol

- log₁₀(P-value)

Genes:
- SORT1
- PCSK9
- APOB
- ABCG8
- HMGCR
- APOA5
- ABO
- HNF1A
- APOE
- LDLR

Chromosomes:
- Chromosome 1 to X
Women’s Genome Health Study
Apolipoprotein B

Association with plasma ApoB

- log_{10}(P-value)

SNP genome coordinate

chrom.: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 X

SORT1  APOB  PCSK9  GCKR  ABCG8  APOE  APOA5  LDLR  TRIB1
Association with plasma HDL cholesterol

Women’s Genome Health Study
HDL Cholesterol
Women’s Genome Health Study
Apolipoprotein A1

Association with plasma ApoA1

-log_{10}(P-value)

SNP genome coordinate
Women’s Genome Health Study
Triglyceride

Association with plasma triglyceride
Women’s Genome Health Study
C-Reactive Protein

Association with plasma C–reactive protein

- \(\log_{10}(P\text{-value})\)

SNP genome coordinate

chrom.: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 X

CRP, LEPR, GCKR, IL6R, HNF1A, APOE, Gene Desert
Genetic Determinants of Statin-Induced Low-Density Lipoprotein Cholesterol Reduction

The Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) Trial

Daniel I. Chasman, PhD; Franco Giuliani, PhD; Jean MacFadyen, BA; Bryan J. Barratt, PhD; Fredrik Nyberg, MD, PhD, MPH; Paul M Ridker, MD, MPH

Background—In statin trials, each 20 mg/dL reduction in cholesterol results in a 10–15% reduction of annual incidence rates for vascular events. However, interindividual variation in low-density lipoprotein cholesterol (LDL-C) response to statins is wide and may partially be determined on a genetic basis.

Methods and Results—A genome-wide association study of LDL-C response was performed among a total of 6989 men and women of European ancestry who were randomly allocated to either a simvastatin 20- or a daily placebo. Single nucleotide polymorphisms at 11 loci were associated with a greater than 10% difference in log transformation of LDL-C response to simvastatin, including ABCG2, LPA, APOE, PCSK9 genome wide, SLCO1B1 LDLR as candidates.

“Inherited polymorphisms that predominantly relate to statin pharmacokinetics of LDL particles by the LDL receptor are common in the general population and influence individual patient response to statin therapy.”

(ABCG2, LPA, APOE, PCSK9 genome wide, SLCO1B1 LDLR as candidates)

Cholesterol levels. In candidate analysis, SNPs in SLCO1B1 and LDLR were confirmed as associated with LDL-C lowering, and a significant interaction was observed between SNPs in PCSK9 and LDLR.

Conclusions—Inherited polymorphisms that predominantly relate to statin pharmacokinetics and endocytosis of LDL particles by the LDL receptor are common in the general population and influence individual patient response to statin therapy. (Circ Cardiovasc Genet. 2012;5:257-264.)

Key Words: cardiovascular disease ■ cholesterol ■ risk factors ■ statins ■ genome-wide association study
Pharmacogenetic Determinants of Statin-Induced Reductions in C-Reactive Protein

Audrey Y. Chu, PhD; Franco Guilianini, PhD; Bryan J. Barratt, PhD; Fredrik Nyberg, MD, MPH, PhD; Daniel I. Chasman, PhD*; Paul M Ridker, MD, MPH*

Background—In randomized trials, statins reduce plasma levels of C-reactive protein (CRP) and low-density lipoprotein cholesterol (LDL-C), and the magnitude of event reduction relates to on-treatment levels of both. However, whether different mechanisms underlie statin-induced CRP and LDL-C reduction is unknown.

Methods and Results—We performed a study to evaluate potential genetic determinants of CRP response using genome-wide genetic data from a total of 6766 participants of European ancestry randomly allocated to 20 mg/d of rosuvastatin or placebo in the JUPITER trial. Among 3386 rosuvastatin-allocated individuals, both CRP and LDL-C reduction or with CRP reduction among 3380 placebo-allocated JUPITER participants.

Conclusions—The genetic determinants of rosuvastatin-induced CRP reduction differ from, and are largely independent of, the major pharmacogenetic determinants of rosuvastatin-induced LDL-C reduction. This supports the hypothesis that differing pathways may mediate the anti-inflammatory and lipid-lowering properties of statin therapy. (Circ Cardiovasc Genet. 2012;5:58-65.)

Key Words: C-reactive protein ■ cholesterol ■ genetics ■ inflammation ■ statins

“The genetic determinants of rosuvastatin-induced CRP reduction differ from, and are largely independent of, the major pharmacogenetic determinants of rosuvastatin-induced LDL-C reduction. This supports the hypothesis that differing pathways may mediate the anti-inflammatory and lipid-lowering properties of statin therapy.”
JUPITER
LDL reduction, hsCRP reduction, or both?

JUPITER GWAS:

The genetic determinants of rosuvastatin-induced LDL-C reduction do not predict rosuvastatin-induced CRP reduction

The genetic determinants of rosuvastatin-induced CRP reduction do not predict rosuvastatin-induced LDL-C reduction

Chasman et al, 2012 Circulation Cardiovascular Genetics
Chu et al, 2012 Circulation Cardiovascular Genetics
IL-6 and Risk of Future MI in Apparently Healthy Men

Quartile of IL-6 (range, pg/dL)

- Quartile 1: ≤1.04
- Quartile 2: 1.04-1.46
- Quartile 3: 1.47-2.28
- Quartile 4: ≥2.28

Relative Risk of MI

- Quartile 1: P=0.3
- Quartile 2: P=0.03
- Quartile 3: P=0.01

P Trend = 0.001

Ridker et al Circulation 2000;101:1767-1772
Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies

IL6R Genetics Consortium and Emerging Risk Factors Collaboration

Summary

Background Persistent inflammation has been proposed to contribute to various stages in the pathogenesis of cardiovascular disease. Interleukin-6 receptor (IL6R) signalling propagates downstream inflammation cascades. To assess whether this pathway is causally relevant to coronary heart disease, we studied a functional genetic variant known to affect IL6R signalling.
A

No PCSK9<sup>46L</sup> Allele (N=9223)

Frequency (%)

No PCSK9<sup>46L</sup> Allele (N=301)

3.2 % nonsense mutation

B

15 % Decrease in LDL
47 % Reduction in CHD Risk

Coronary Heart Disease (%)

P=0.003

PCSK9<sup>46L</sup>

No

Yes

Cohen NEJM 2006;354:1264-72
PCSK9, Long-Term LDL Reduction, and Vascular Event Rates – Black Subjects

A

No Nonsense Mutation (N=3278)

50th Percentile

PCSK9^{142X} or PCSK9^{679X} (N=85)

2.6 % nonsense mutation

B

28 % Decrease in LDL
88 % Reduction in CHD Risk

Coronary Heart Disease (%)

PCSK9^{142X} or PCSK9^{679X}

P=0.008

Cohen NEJM 2006;354:1264-72
Estimated Cumulative Risk of Myopathy Associated with Taking 80 mg of Simvastatin Daily, According to SLCO1B1 rs4149056 Genotype
CYP2C19 & Clinical Outcomes
1477 Patients w/ ACS and planned PCI Rx’d w/ clopidogrel


Carriers ~30% of the population
Will genetics play a major role in patient focused thrombosis care?

Will pharmacogenetics matter for cardiovascular disease?
“It’s a baby. Federal regulations prohibit our mentioning its race, age, or gender.”
By DENNIS HEVESI

Richard LaMotta, who turned his childhood passion for dunking cookies in milk into the Chipwich — two chocolate chip cookies embracing a chunk of vanilla ice cream dotted with chocolate chips — died Tuesday at his home in Chappaqua, N.Y. He was 67.

The cause was a heart attack, his daughter Kayla said.

By BRUCE WEBER

K. Dun Gifford, who started an influential nonprofit organization to combat obesity and promote healthy eating around the world, and whose well-connected life put him in celebrated company and at the scenes of many news-making events, died on Sunday in Exeter, N.H. He was 71 and lived in Cambridge, Mass.

The cause was a heart attack, his son Dun Jr. said.
“You’re fifty years old. I’d like to get that down a bit.”