

North American Thrombosis Forum September 29, 2007

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

Paul M Ridker, MD

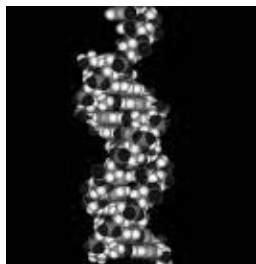
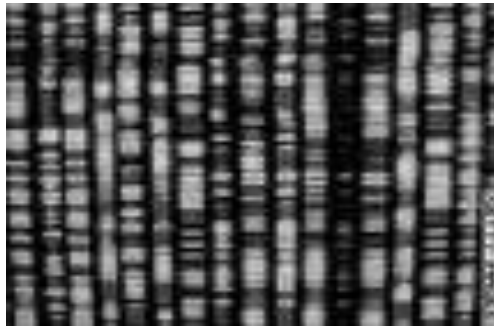
Eugene Braunwald Professor of Medicine

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

Starting Premises : The Differences Between Venous and Arterial Thrombosis

- For venous thromboembolism, we already know that genetics plays a major role by increasing risk (factor v Leiden, G20210A prothrombin mutation) and in assisting with therapy (warfarin metabolism).
- For arterial thrombosis, the utility of genetic information is currently less certain.
- Other than age, no single risk factor for CHD will have an overwhelming effect on outcome
- No single gene or haplotype will have a large effect on risk in the population
- CHD is not a Mendelian disease
- Genetic risk scores may impact upon risk detection
- Unclear if any specific genetic risk score will be better than “positive family history”

Adapted From Eric Boerwinkle

JAMA 2007;297:1551-61

Nonvalidation of Reported Genetic Risk Factors for Acute Coronary Syndrome in a Large-Scale Replication Study

Thomas M. Morgan, MD
 Harlan M. Krumholz, MD, MS
 Richard P. Lifton, MD, PhD
 John A. Spertus, MD, MPH

COMPPELLING EVIDENCE FROM twin and epidemiological studies suggests a genetic basis for atherosclerotic heart disease and acute coronary syndromes (ACS), including unstable angina, non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI).^{1,2} To date, numerous candidate genes have been implicated, mainly by case-control studies, as potential cardiovascular risk factors, but few, if any, have been established definitively.^{3,5} Factors undermining the validity of previous reports include inappropriately small sample sizes, multiple subgroup comparisons, and publication bias.⁴ Before use in clinical care, potential genetic risk factors would ideally be replicated en masse in large, well-characterized patient populations.⁶ To

Context Given the numerous, yet inconsistent, reports of genetic variants being associated with acute coronary syndromes (ACS), there is a need for comprehensive validation of ACS susceptibility genotypes.

Objective To perform an extensive validation of putative genetic risk factors for ACS.
Design, Setting, and Participants Through a systematic literature search of articles published before March 10, 2005, we identified genetic variants previously reported as significant susceptibility factors for atherosclerosis or ACS. Restricting our analysis to white patients to reduce confounding from racial admixture, we identified 811 patients who presented from March 2001 through June 2003 with ACS at 2 Kansas City, Mo, university-affiliated hospitals. During 2005-2006, we genotyped the 811 patients along with 650 age- and sex-matched controls for 85 variants in 70 genes and attempted to replicate previously reported associations. We further explored possible associations without prior assumption of specific risk models and used the Sign test to search for weak associations.

Main Outcome Measures Compare each prespecified gene variant associated with ACS risk among cases and controls. A surplus of associations would imply that some are associated with ACS.

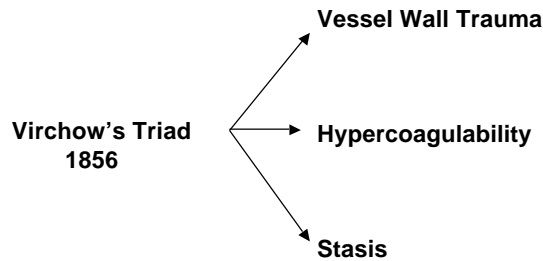
Results Of 85 variants tested, only 1 putative risk genotype (-455 promoter variant in β -fibrinogen) was nominally statistically significant ($P=.03$). Only 4 additional genes were positive in model-free analysis. Neither number of associations was more frequent than expected by chance, given the number of comparisons. Finally, only 41 of 84 predefined risk variants were even marginally more frequent in cases than in controls (with 1 tie), representing a 48.8% "win rate" (95% confidence interval, 38.1%-59.5%) for the collective risk genotypes ($P=.91$, Sign test).

Conclusions Our null results provide no support for the hypothesis that any of the 85 genetic variants tested is a susceptibility factor for ACS. These results emphasize the need for robust replication of putative genetic risk factors before their introduction into clinical care.

JAMA. 2007;297:1551-1561

www.jama.com

Risk Factors for Venous Thromboembolism

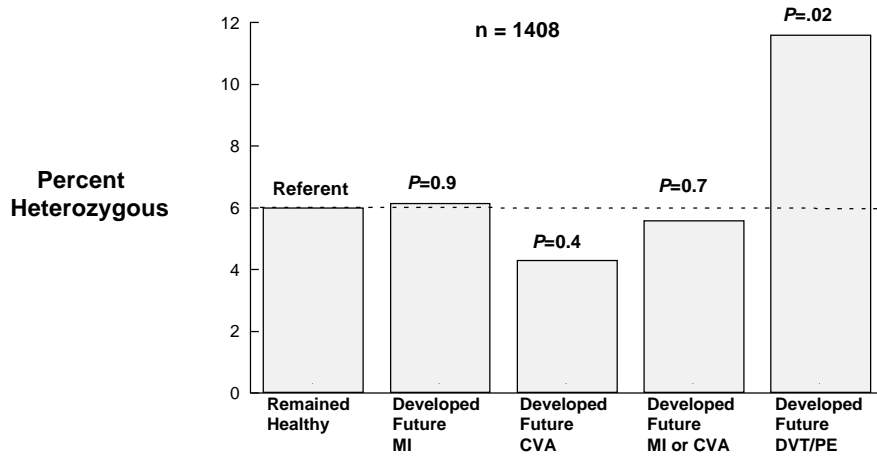


Recent Surgery
 Malignancy
 Oral Contraception
 Pregnancy
 Immobilization
 Platelet Disorders

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

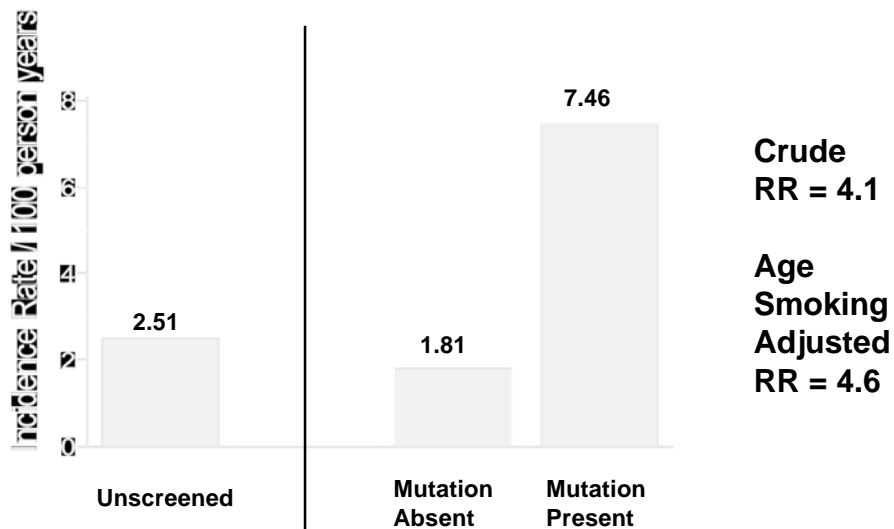
APC-R Factor V Leiden
 Prothrombin mutation

G1691A Mutation in Coagulation Factor V and Risks of Future Arterial and Venous Thrombosis



Ridker PM et al. *N Engl J Med.* 1995;332:912-917.

Factor V Leiden and Risks of Recurrent Idiopathic Venous Thrombosis



Ridker PM, Miletich JP, Stampfer MJ, Goldhaber SZ, Lindpaintner K, Hennekens CH. *Circulation* 1995; 92:2800-2802

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

Ethnic Group	N	Carrier Frequency		Allele Frequency	
		%	95 % CI	%	95 % CI
Caucasian-American	2468	5.27	4.42 - 6.22	2.67	2.24 - 3.16
Hispanic-American	407	2.21	1.01 - 4.16	1.11	0.51 - 2.09
African-American	650	1.23	0.53 - 2.41	0.69	0.32 - 1.31
Asian-American	442	0.45	0.05 - 1.63	0.23	0.03 - 0.81
Native-American	80	1.25	0.03 - 6.77	0.63	0.02 - 3.43

Overall US Population Carrier Estimate = 4.3 percent

Ridker PM, Miletich JP, Hennekens CH, Buring JE. *JAMA* 1997;277:1305-7

Diagnostic Tests for Thrombophilia - Seligsohn U, Lubetsky A. *N Engl J Med.* 2001;344:1222-1231.

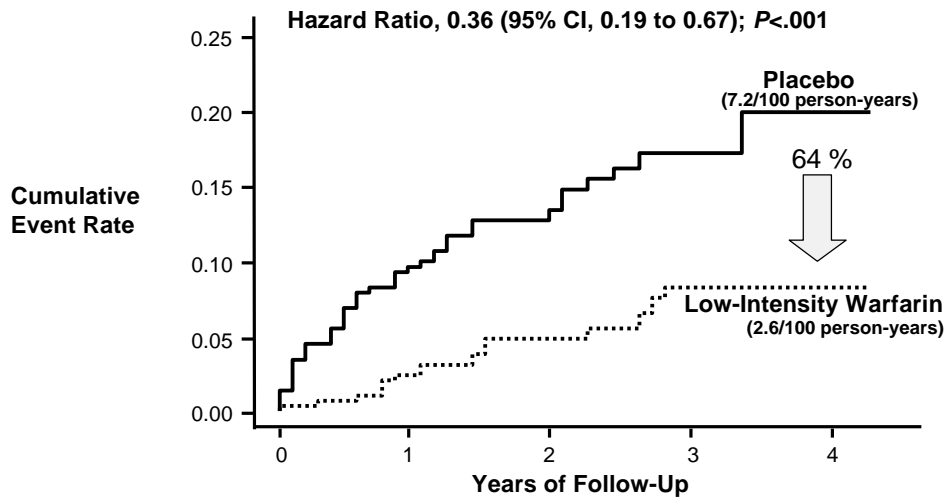
	Genetic Basis	Acquired Basis
APC resistance	HR ₂ Haplotype Factor V Leiden	Pregnancy, OC use, lupus, warfarin, increased factor VIII levels, stroke, autoantibodies against APC
Prothrombin	G20210A	None
Hyperhomocystinemia	Mutations in MTHFR, renal failure cystathionine β-synthase	Folate, B12, B6 intake,
Elevated factor VIII	Unknown	Exertion, pregnancy, OC use, stress, age, acute-phase response
Reduced protein C	161 mutations	Liver disease, childhood, warfarin, vitamin K deficiency, autoantibodies against APC, DIC
Reduced protein S	131 mutations	Liver disease, childhood, warfarin, vitamin K deficiency, DIC, nephrosis, pregnancy, use of OC, autoantibodies against protein S
Reduced AT-III	127 mutations	Liver disease, heparin use, DIC, nephrosis
Dysfibrinogenemia	20 mutations	DIC, liver disease, recent birth

Prevalence of Genetic Disorders in Familial Thrombosis

Genetic Defect	Estimated Prevalence (%)	Known Mutations (N)
Dysfibrinogenemia	1.0	> 11
AT-III Deficiency	4.2	> 79
Protein C	4.9	> 160
Protein S	5.1	> 13
APC-R	30 - 50	> 1

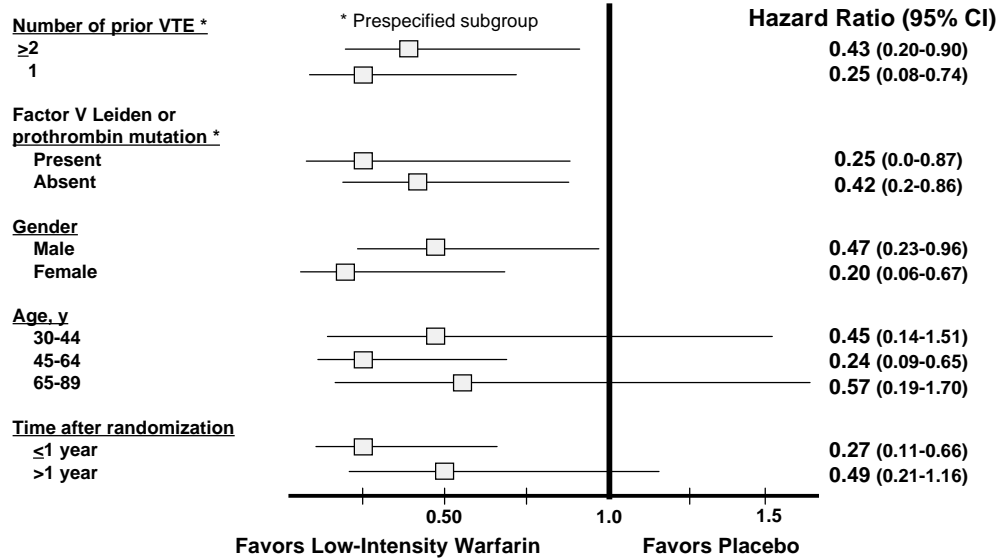
Bertina et al, Thrombosis and Haemostasis 1995;74:449-453

PREVENT: Primary Endpoint: Recurrent VTE



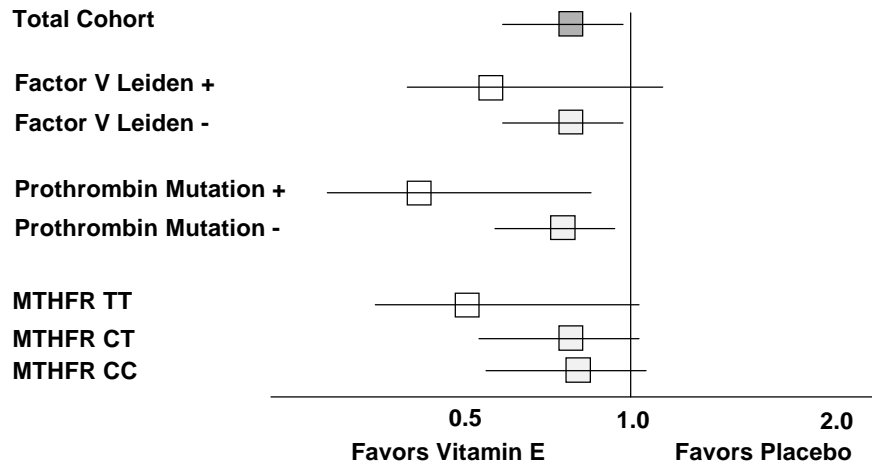
Ridker PM for the PREVENT Investigators. *N Engl J Med.* 2003;348:1425-1434.

PREVENT: Recurrent VTE by Clinically Important Subgroups



Ridker PM for the PREVENT Investigators. *N Engl J Med.* 2003;348:1425-1434.

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 (in press)

Association of Genetic Variations With Nonfatal Venous Thrombosis in Postmenopausal Women

Nicholas L. Smith, PhD, MPH

Lucia A. Hindorff, PhD

Susan R. Heckbert, MD, PhD

Rozenn N. Lemaitre, PhD, MPH

Kristin D. Marciano, 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

DEEP VEIN THROMBOSIS AND pulmonary embolism are significant contributors to morbidity and mortality in adult women and occur at annual rates of 3 to 5 per 1000 person-years among women older than 55 years.^{1,2} Despite improved prophylaxis in high-risk patients, the incidence of venous thrombosis (VT) has not decreased.¹

Causes of VT primarily involve modifications in the coagulation, anticoagulation, fibrinolysis, and antifibrinolysis pathways regulating hemostasis.

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*=.13). 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

Factors of Risk in the Development of Coronary Heart Disease—Six-Year Follow-up Experience

The Framingham Study

WILLIAM B. KANNEL, M.D., THOMAS R. DAWBER, M.D., F.A.C.P.,

ABRAHAM KAGAN, M.D., F.A.C.P., NICHOLAS REVOTSKIE, M.D.,

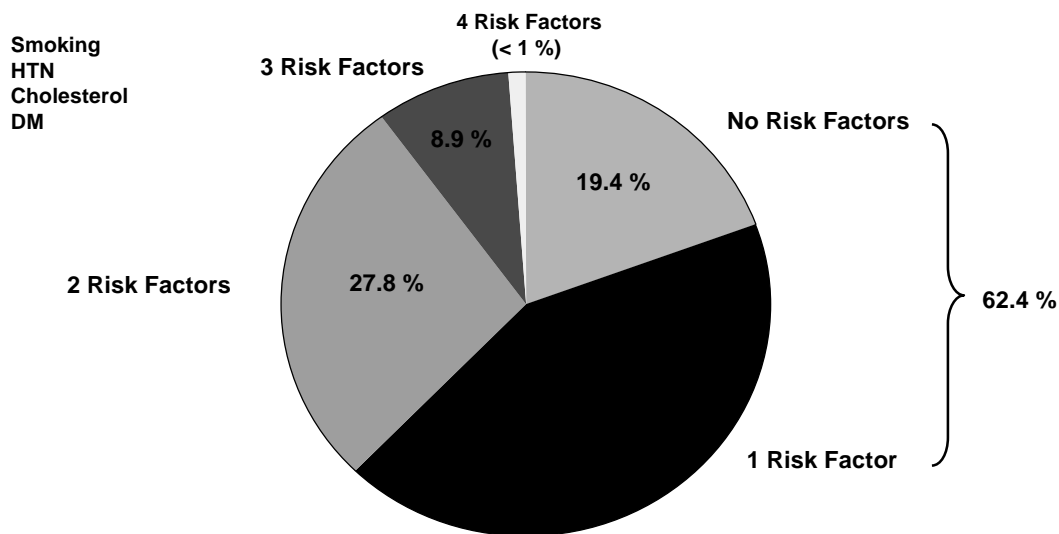
AND JOSEPH STOKES, III, M.D.

Framingham, Massachusetts

INCREASINGLY RELIABLE ESTIMATES of the prevalence and incidence of coronary heart disease (CHD) emphasize the importance of this disease as a contemporary health hazard. Cardiovascular disease is now the leading cause of death, with coronary heart disease accounting for two-thirds of all heart disease deaths. While advances in the diagnosis and therapeutic management of CHD have been made in the past

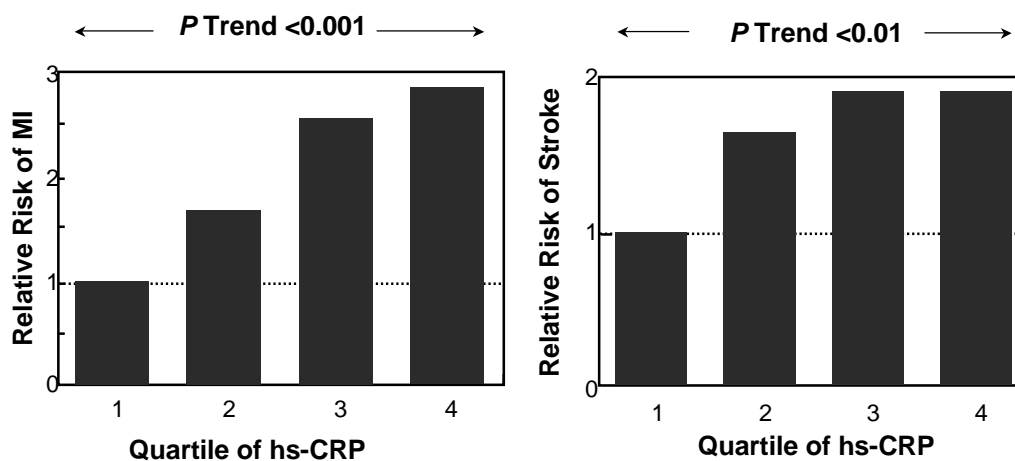
Since it has been established that coronary atherosclerosis is present for many years prior to the development of symptomatic CHD, it seems evident that efforts at prevention must begin many years before the appearance of clinical CHD. A knowledge of the epidemiology of the disease is highly desirable if a program of prevention is to be developed. From a study of the characteristics of persons who develop coronary heart

Prevalence of Conventional Risk Factors in Patients with Coronary Heart Disease (N = 87,869)



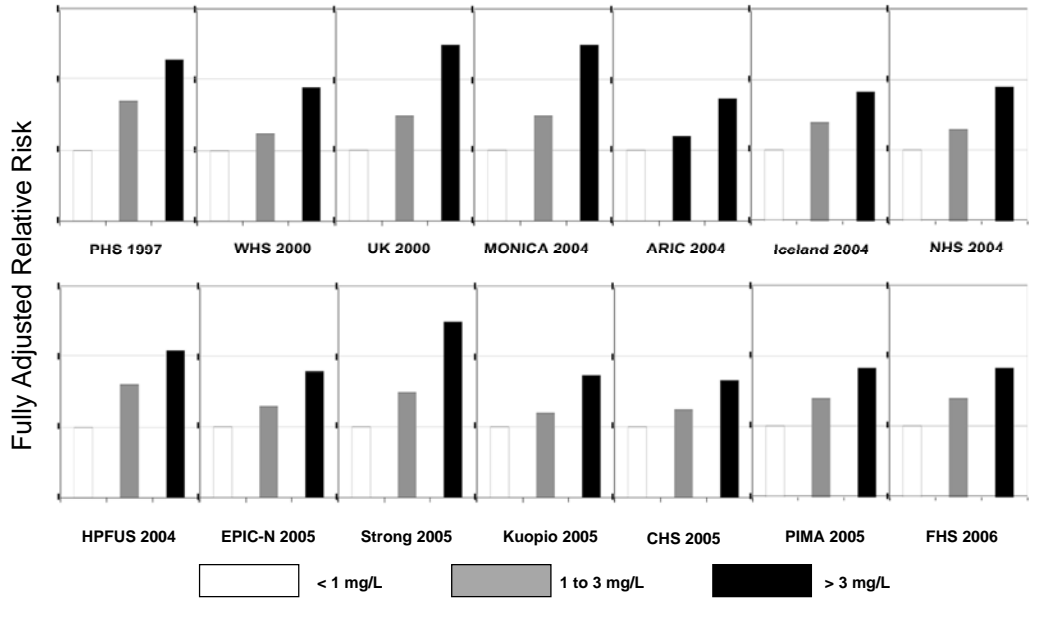
Khot U et al, JAMA 2003;290:898-904

hs-CRP and Risk of Future MI and CVA in Apparently Healthy Men

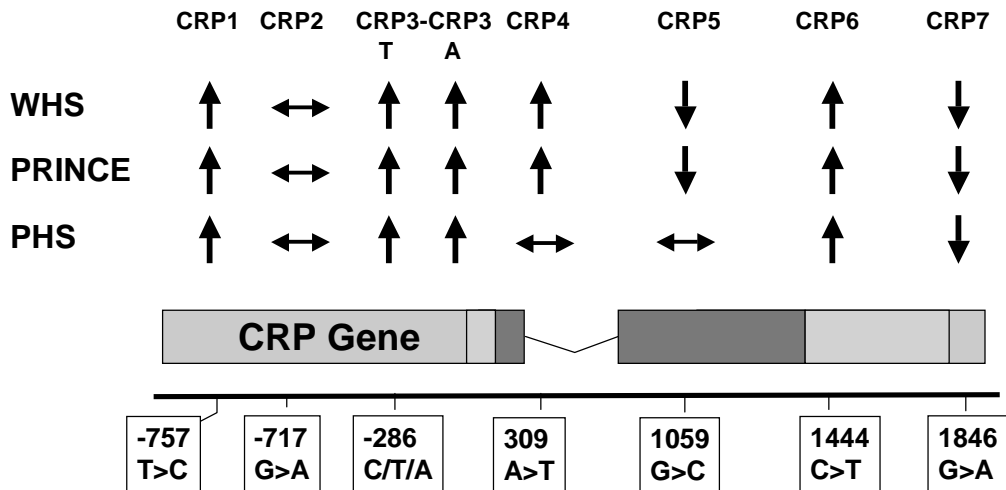


Ridker et al N Engl J Med 1997;336:973-979.

hsCRP Adds Prognostic Information Beyond Traditional Risk Factors in All Major Cohorts Evaluated

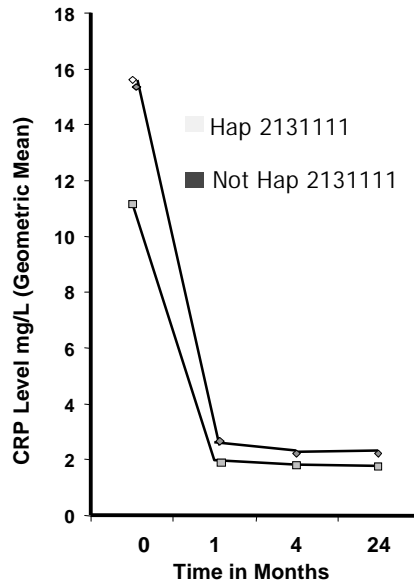
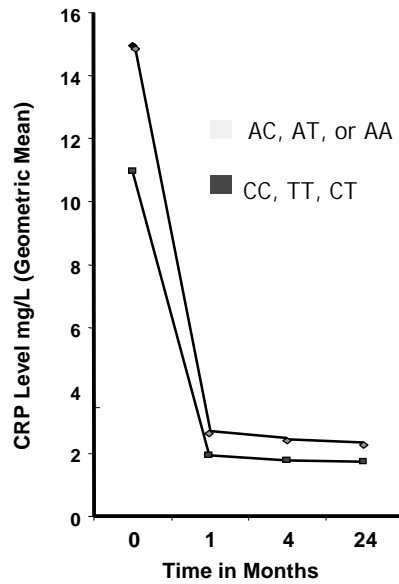


Association of Common CRP SNPs with Plasma CRP Levels

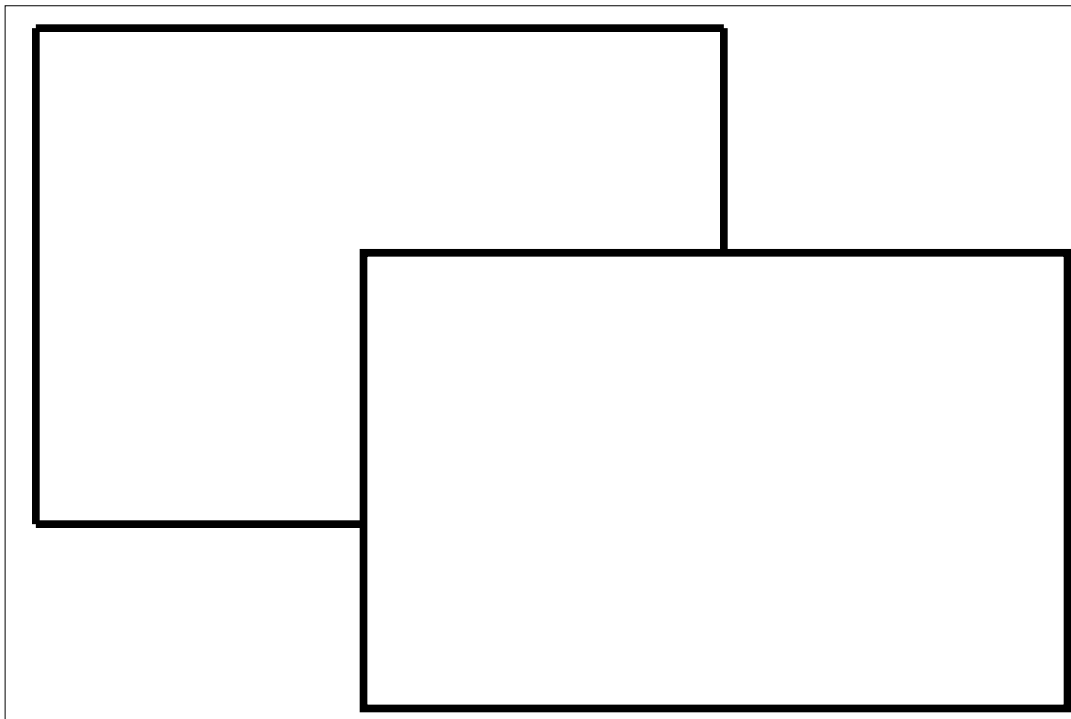


Miller DT et al, Ann Hum Gen 2005;69:623-38

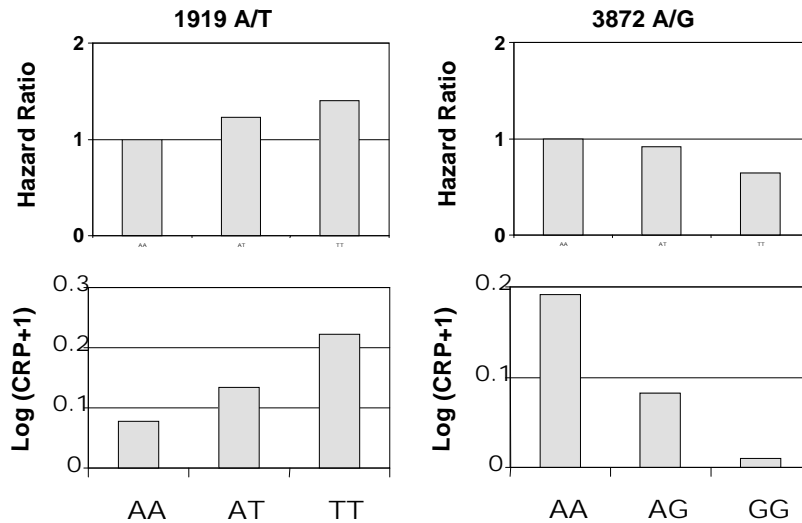
CRP Levels During and After Acute Ischemia According to SNP -286C>T>A and Associated Haplotypes



Suk-Danik et al, Ann Hum Genet 2006;70:1-12



Association of Polymorphisms in the CRP Gene with Circulation CRP Levels and CV Mortality



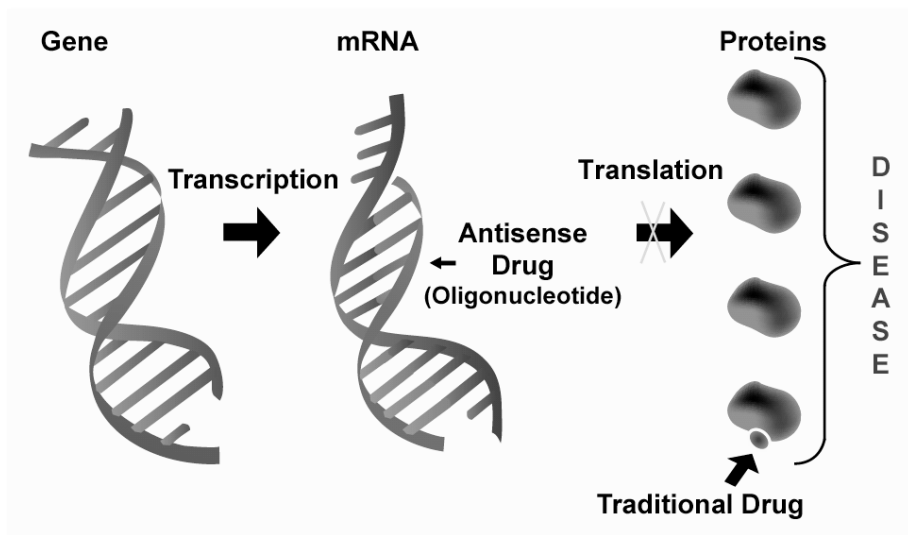
Lange et al, JAMA 2006;196:2703-11

Genetics of CRP - 2007

- Heritability estimates suggest that 25 to 60 percent of of the variance in basal CRP levels can be attributed to genetic effects.
- Part of this effect is due to common SNPs in the CRP gene itself, and part due to genes in CRP regulatory pathways (IL-6, IL-1B).
- In several studies, CRP SNPs have themselves been associated with increased or decreased event rates, data supporting a causal role for CRP in atherothrombosis.
- Findings have been replicated in multiple studies worldwide, including in Asia.



Antisense Technology as a New Approach for Drug Discovery



Courtesy of Stanley Crooke

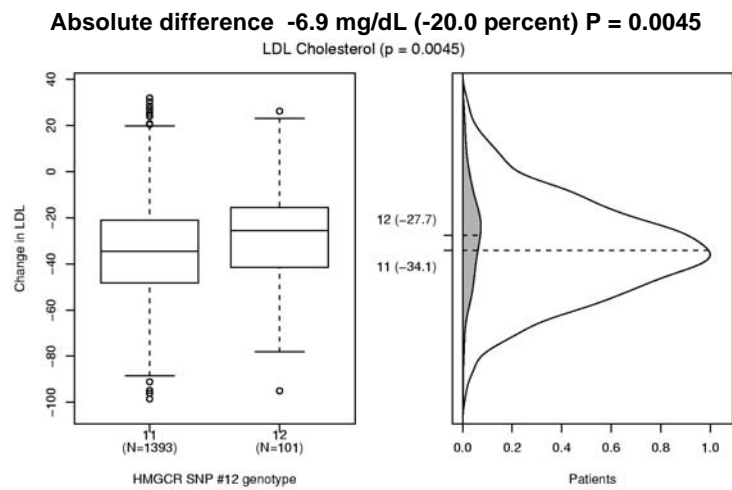
Chasman et al,
JAMA 2004;291:2821-27

Candidate Genes for Statin Efficacy and Cholesterol Reduction

Gene Symbol	N SNPs	Encoded Protein
ABCG5	2	ATP Binding Cassette, Subfamily G, Member 5
ABCG8	15	ATP Binding Cassette, Subfamily G, Member 8
APOB	22	Apolipoprotein B
APOE	19	Apolipoprotein E
CETP	17	Cholesteryl Ester Transfer Protein
CYP3A4	1	Cytochrome P450, Subfamily IIIA, Polypeptide 4
CYP3A5	6	Cytochrome P450, Subfamily IIIA, Polypeptide 5
FDFT1	11	Farnesyl diphosphate Farnesyltransferase 1, Squalene Synthase
HMGCR	33	3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase
LDLR	22	Low Density Lipoprotein Receptor

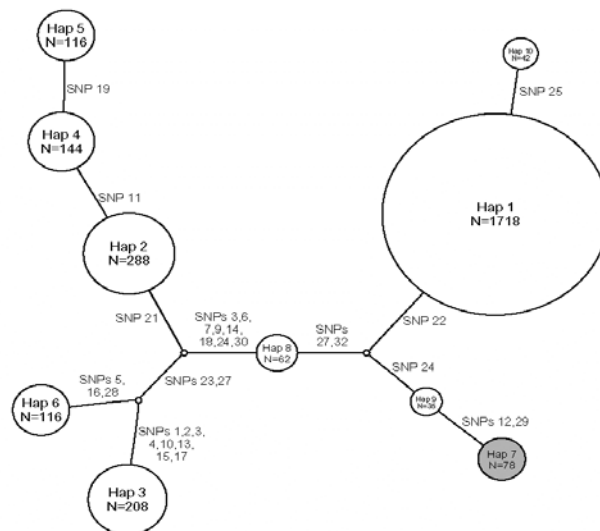
Chasman et al, JAMA 2004;291:2821-6

HMGR SNP 12 and LDL-C reduction with pravastatin therapy (PRINCE)



Chasman et al, JAMA 2004;291:2821-6

Proposed Evolutionary History of the HMGCoA Reductase Gene: Cladistic (haplotype-based) analysis



Chasman et al, JAMA 2004;291:2821-6

Example of Genetic Replication: Candidate Gene Approach
 Kinesin Family Member 6 (KIF 6) rs20455 trp6719arg
 Risk of First or Recurrent Myocardial Infarction

Study	Risk Allele Allele (%)	Hazard Ratio	CI	P
ARIC	0.36	1.09	1.00-1.19	0.05
CARE	0.36	1.50	1.05-2.15	0.03
WOSCOPS	0.34	1.55	1.14-2.09	0.005
WHS	0.36	1.27	1.09-1.50	0.007

Genetic Variation and Disease Incidence : Recent Examples

- Klein et al. Complement factor H polymorphism in age-related macular degeneration. *Science* 2005;308:385-9
- Herbert et al. A common genetic variant is associated with adult and childhood obesity. *Science* 2006;312:279-83
- Smyth et al. A genome-wide association study on nonsynonymous SNPs identifies a type 1 diabetes locus in the interferon-induced helicase (IFIH1) region. *Nature Genetics* 2006;38:617-19.
- Arking et al. A common genetic variant in the NOS1 regulator NOS1AP modulates cardiac repolarization. *Nature Genetics* 2006;38:644-51.
- Cohen et al. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med* 2006;354:1264-72.

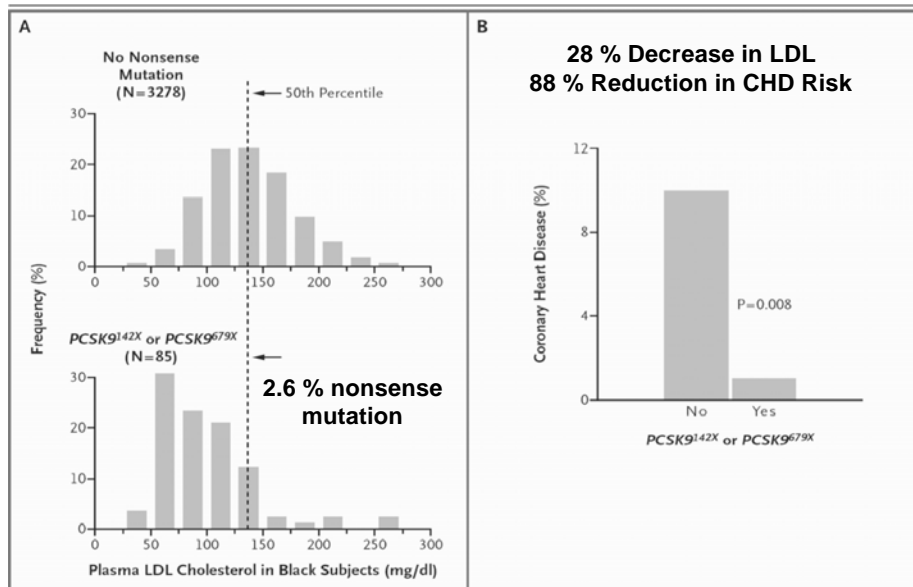
PCSK9, Long-Term LDL Reduction, and Vascular Event Rates – White Subjects

15 % Decrease in LDL
47 % Reduction in CHD Risk

3.2 % nonsense
mutation

Cohen NEJM 2006;354:1264-72

PCSK9, Long-Term LDL Reduction, and Vascular Event Rates – Black Subjects



Cohen NEJM 2006;354:1264-72

ARTICLES

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 ~2,000 individuals for each of 7 major diseases and a shared set of ~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 5×10^{-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.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

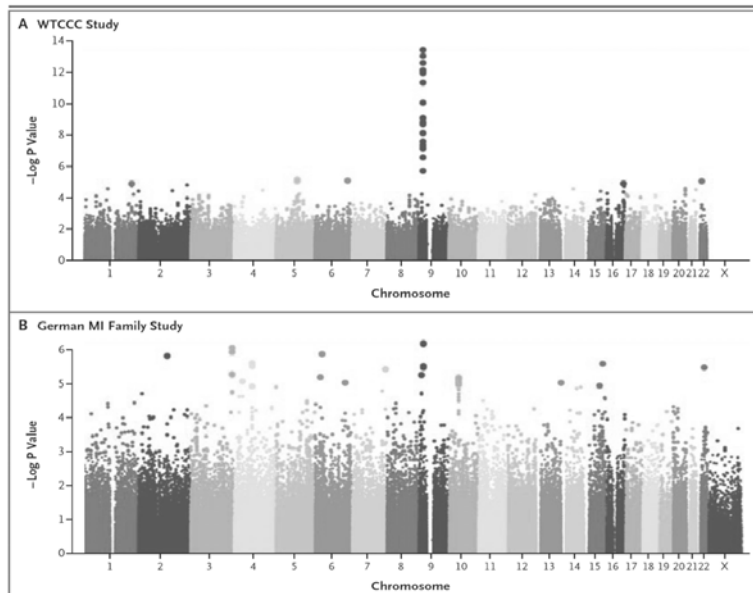
AUGUST 2, 2007

VOL. 357 NO. 5

Genomewide Association Analysis of Coronary Artery Disease

Nilesh J. Samani, F.Med.Sci., Jeanette Erdmann, Ph.D., Alistair S. Hall, F.R.C.P., Christian Hengstenberg, M.D., Massimo Mangino, Ph.D., Bjoern Mayer, M.D., Richard J. Dixon, Ph.D., Thomas Meitinger, M.D., Peter Braund, M.Sc., H.-Erich Wichmann, M.D., Jennifer H. Barrett, Ph.D., Inke R. König, Ph.D., Suzanne E. Stevens, M.Sc., Silke Szymczak, M.Sc., David-Alexandre Tregouet, Ph.D., Mark M. Iles, Ph.D., Friedrich Pahlke, M.Sc., Helen Pollard, M.Sc., Wolfgang Lieb, M.D., Francois Cambien, M.D., Marcus Fischer, M.D., Willem Ouwehand, F.R.C.Path., Stefan Blankenberg, M.D., Anthony J. Balmforth, Ph.D., Andrea Baessler, M.D., Stephen G. Ball, F.R.C.P., Tim M. Strom, M.D., Ingrid Brænne, M.Sc., Christian Gieger, Ph.D., Panos Deloukas, Ph.D., Martin D. Tobin, M.F.P.H.M., Andreas Ziegler, Ph.D., John R. Thompson, Ph.D., and Heribert Schunkert, M.D., for the WTCCC and the Cardiogenics Consortium*

Signal-Intensity Plots Between SNPs and CAD in Genome Wide Association Analysis



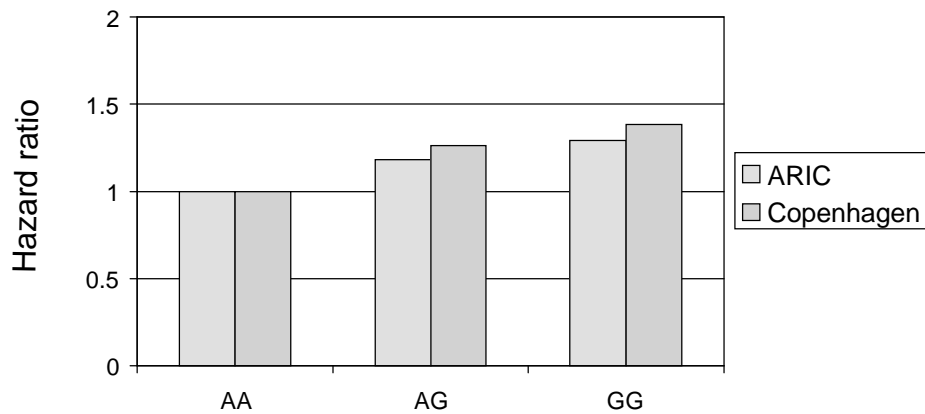
Samani et al WTCCC and Cardiogenetics Consortium NEJM 2007;357 (July 18)

Table 2. Loci from the WTCCC Study with Significant Associations with Coronary Artery Disease That Were Replicated in the German MI Family Study.*

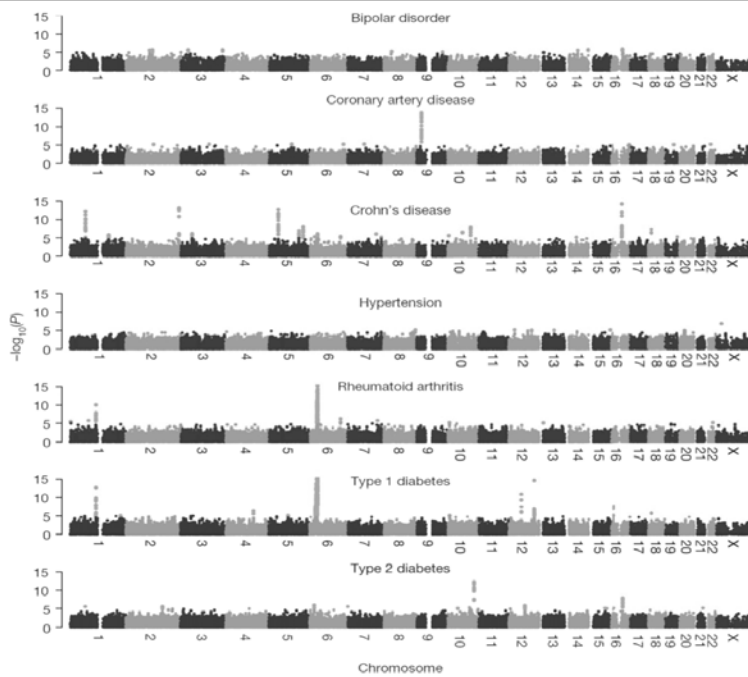
Chromosome	Lead SNP	Minor Allele in Controls	Risk Allele	Data	Frequency of Minor Allele		Odds Ratio for Risk Allele (95% CI)	Population Attributable Fraction	P Value
					Case Subjects	Controls			
2	rs2943634	A	C	WTCCC	0.30	0.34	1.22 (1.11–1.33)		1.19×10^{-5}
				German	0.32	0.37	1.20 (1.06–1.35)		0.004
				Adjusted German			1.08 (0.90–1.31)	0.10	0.03
6	rs6922269	A	A	WTCCC	0.29	0.25	1.23 (1.13–1.35)		6.33×10^{-6}
				German	0.30	0.26	1.24 (1.09–1.41)		0.001
				Adjusted German			1.23 (1.01–1.50)	0.11	0.009
9	rs1333049	C	C	WTCCC	0.55	0.47	1.37 (1.26–1.48)		1.80×10^{-14}
				German	0.54	0.48	1.33 (1.18–1.51)		6.80×10^{-6}
				Adjusted German			1.28 (1.07–1.53)	0.22	6.12×10^{-5}

Samani et al WTCCC and Cardiogenetics Consortium NEJM 2007;357 (July 18)

A Common Allele (rs10757274) on Chromosome 9 Associated With
 Coronary Heart Disease
 Ottawa Heart Study, ARIC, Copenhagen City, Dallas Heart, deCODE
 Iceland



McPherson et al / Helgadottir et al, Science May 3, 2007



Welcome Trust Case Control Consortium Nature June 2007

Women's Genome Health Study

Tying Diseases to DNA in Thousands of Women

By RON WINSLOW
And ANTONIO REGALADO

STARTING from the disease and working back to the DNA, a team of academic, government and industry researchers hopes to discover the genetic causes of breast cancer, heart disease and a host of other common disorders affecting women.

The novel collaboration, which involves Brigham and Women's Hospital in Boston, the National Institutes of Health and the biotechnology giant Amgen Inc., will analyze DNA collected more than a decade ago from 28,000 participants in the Women's Health Study, combing it for differences between those who have developed serious illness and those who have remained healthy. Researchers believe the results will eventually enable physicians to better predict a woman's risk for disease and to tailor more effective treatments.

The project is part of a new gold rush sweeping medical research aimed at uncovering the genetic underpinnings of common diseases using new DNA-reading technologies. The joint involvement of corporate, government and academic players underscores the increased interest in translating existing genetics research into practical medical knowledge. But it also raises thorny questions about how to patent and commercialize discoveries stemming from publicly funded research efforts.

DNA Deals

A new, faster approach to genetic research is attracting funding. A look at recent partnerships:

- **October 2006:** National Institutes of Health sponsors gene hunts in six diseases with \$26 million donated by companies, including Pfizer and Affymetrix
- **August 2006:** Genentech buys exclusive rights from Quebec's Genizon BioSciences to DNA data on Crohn's disease, a bowel disorder
- **March 2006:** Muscular Dystrophy Association gives \$650,000 to Translational Genomics Institute to study Lou Gehrig's disease
- **December 2005:** Pfizer enters four-year agreement with Perlegen Sciences to study DNA collected as part of drug trials

Source: WSJ research

The comprehensive gene map created by the Human Genome Project provided a one-size-fits-all map of human genes. But each person's DNA varies slightly, which accounts for each person's unique appearance—and unique susceptibility to disease. The scientists' goal now is to link those DNA variations to who gets sick and who doesn't.

The Women's Health study is one of several federally funded research projects for which participants provided blood samples years ago that now constitute a potentially rich resource to match genetic variations with disease on a large scale, a new approach called a "whole-genome association study."

Because huge amounts of data are involved—the new initiative will look at 317,000 different variations from each person's DNA—the cost of scanning the genes significantly exceeds what the NIH and academic institutions can afford. That has prompted academic scientists to seek support from private industry.

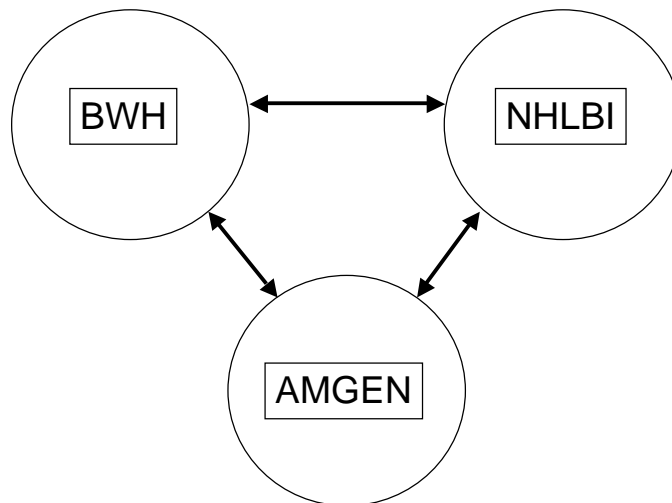
"We're entering a time where scientific projects are becoming larger and more complex," says Paul Ridker, director of the Center for Cardiovascular Disease Prevention at Brigham and Harvard Medical School and the principal investigator for the study. "To unlock the genetic information we can use to improve the health of our patients and our understanding of what causes disease is going to require very large projects and expertise from many kinds of individuals."

Previously, scientists have discovered the genetic causes of scores of rare, inherited disorders, including cystic fibrosis. But for most common diseases, the genetic risk factors still aren't known. Indeed, scientists expect that for

Please Turn to Page B2, Column 6

WSJ, October 24, 2006

Women's Genome Health Study : The Scientific Opportunity and Collaborative Structure



Moving Toward The Women's Genome Health Study

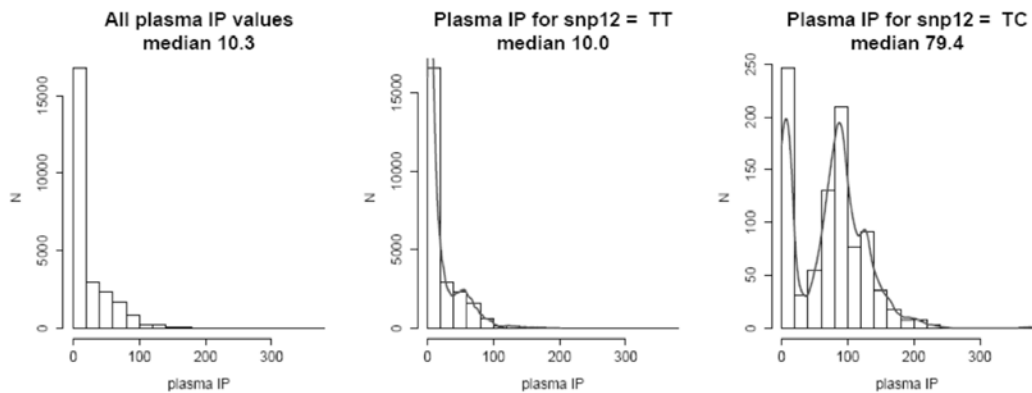
What are the core genetic determinants of myocardial infarction, stroke, venous thrombosis, type 2 diabetes, and hypertension?

What are the core genetic determinants of plasma LDL, HDL, TG, hsCRP, Apo A-I, Apo B100, sICAM, Lp(a), homocysteine, fibrinogen, creatinine, and HbA1c?

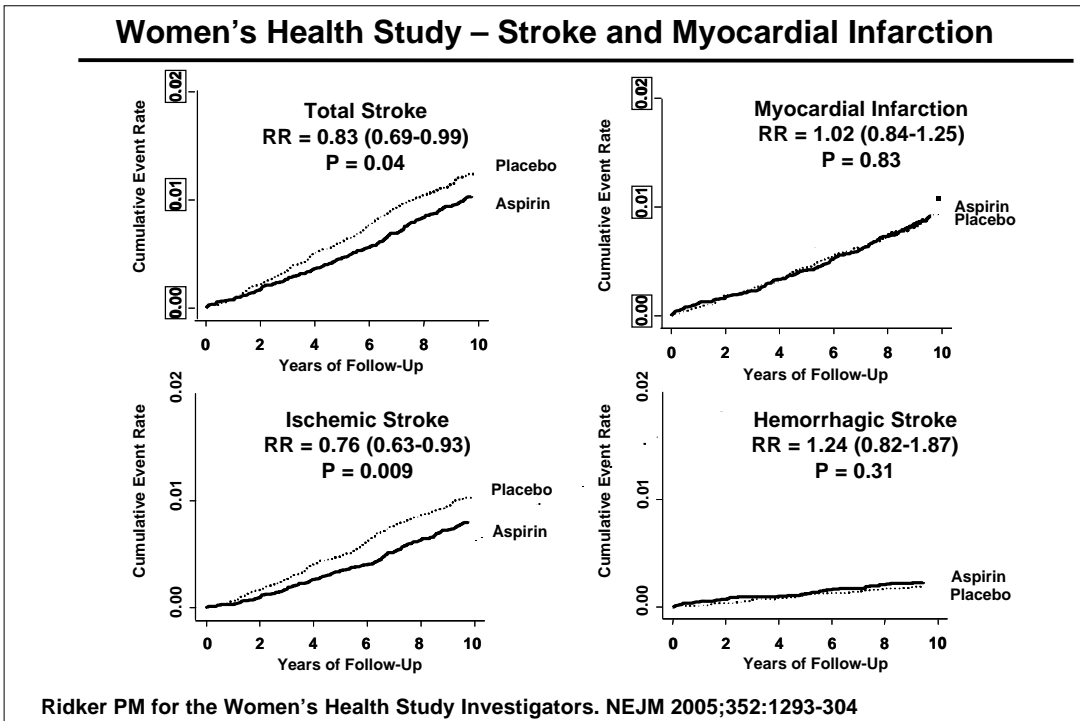
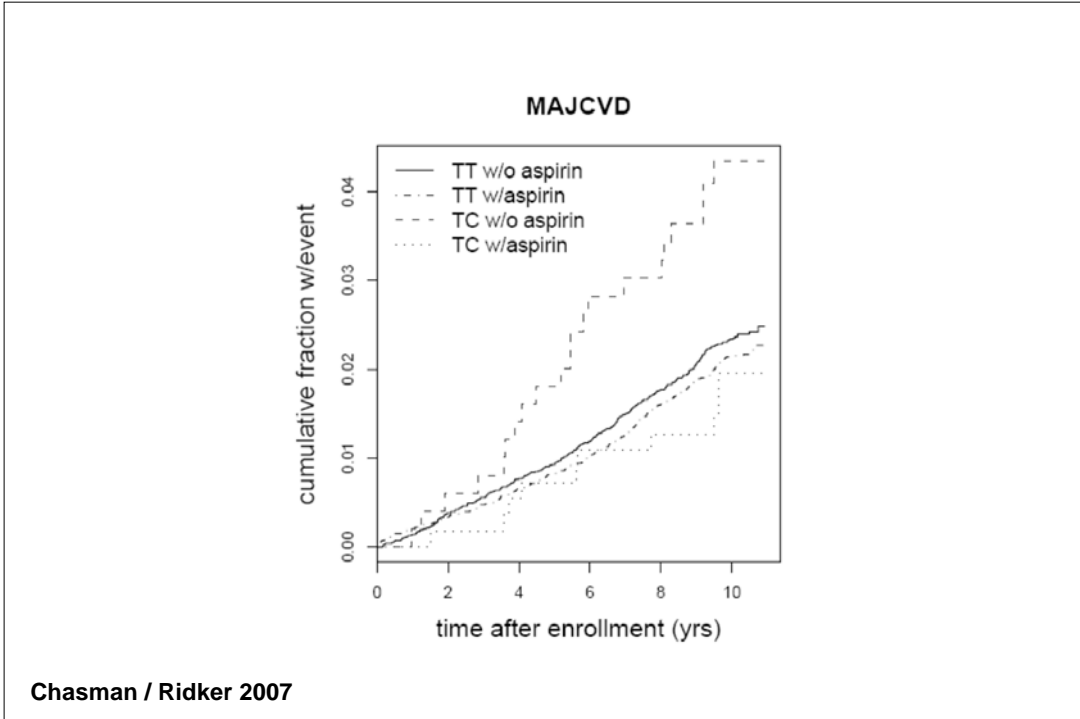
What are the core gene-environment interactions that determine vascular risk?

Can we develop third generation risk prediction scores?

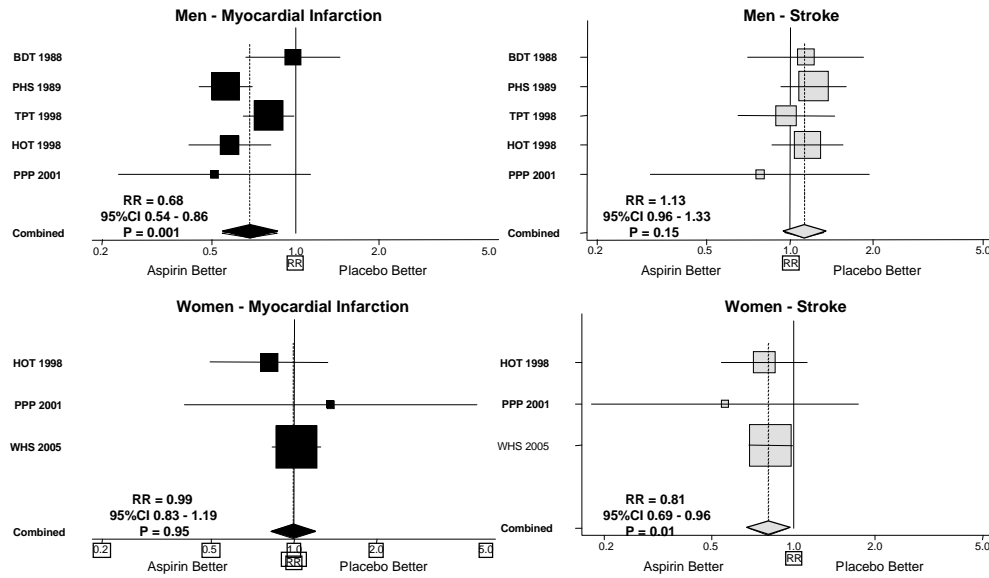
Will Genome Wide Analyses of Cardiovascular Risk Work ? (Confidential Example)



Chasman / Ridker 2007



Meta-Analysis: Low-Dose Aspirin in Primary Prevention



Ridker PM for the Women's Health Study Investigators. NEJM 2005;352:1293-304


Low-Dose Aspirin In Primary Prevention - Meta-analysis

	Myocardial Infarction	Stroke
All Participants (N=95,456)	0.76 (0.62-0.95)	0.97 (0.83-1.13)
Men (N=44,114)	0.68 (0.54-0.86)	1.13 (0.96-1.33)
Women (N=51,342)	0.99 (0.83-1.19)	0.81 (0.69-0.96)
	P = 0.01	P = 0.005

Ridker PM for the Women's Health Study Investigators. NEJM 2005;352:1293-304

REYNOLDS RISK SCORE

Calculating Heart & Stroke Risk for Women



How Do I Improve My Risk Factors?
There are many excellent websites that provide information on risk reduction including sites sponsored by the American Heart Association and the American College of Cardiology. Excellent sites with information specific to women include www.goRedforWomen.com, www.ChooseToLive.com, www.womenshealth.gov. For specific information on C-reactive protein, patient-friendly information can be obtained at crzhealth.com.

Advice for Prevention in Women

If you are a healthy woman 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.

Age Years

Do you currently smoke? Yes No

Systolic Blood Pressure (SBP) mm/Hg

Total Cholesterol mg/DL

HDL or "Good" Cholesterol mg/DL

High Sensitivity C-Reactive Protein (hsCRP) mg/L

Did your Mother or Father have a heart attack before age 60? Yes No

As shown in the graph below, at Age 72, your chance of having a heart attack, stroke, or other heart disease event at some point in the next 10-years is **37 percent**.

current Age	Age 72	Age 82	Print	Age 72
Your 10-year risk (age 72) 37%				
Your 10-year risk (age 72) if:				
• you didn't smoke 19%				
• your blood pressure were optimal 25%				
• your cholesterol were optimal 18%				
• your hsCRP were optimal 27%				
• all the above were optimal 4%				

The graph above also compares your risk to that of a woman of age 72 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 women, 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.

The Reynolds Risk Score
Calculating Heart and Stroke
Risk for Women

www.ReynoldsRiskScore.org

JAMA 2007;297:611-619

