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Genética Médica, la Clínica entre Genes, Genomas y Herencia.

Epidemiología

Roberto Elosua
Grupo de Epidemiología y Genética Cardiovascular. IMIM-Hospital del Mar

4º Curso de Genética Humana de la Sociedad Española de Genética
4 y 5 de Febrero de 2010

Epidemiología

Estudio de la distribución y determinantes de la enfermedad en poblaciones humanas:

- Magnitud del problema
- Factores asociados y estudio de la relación causal

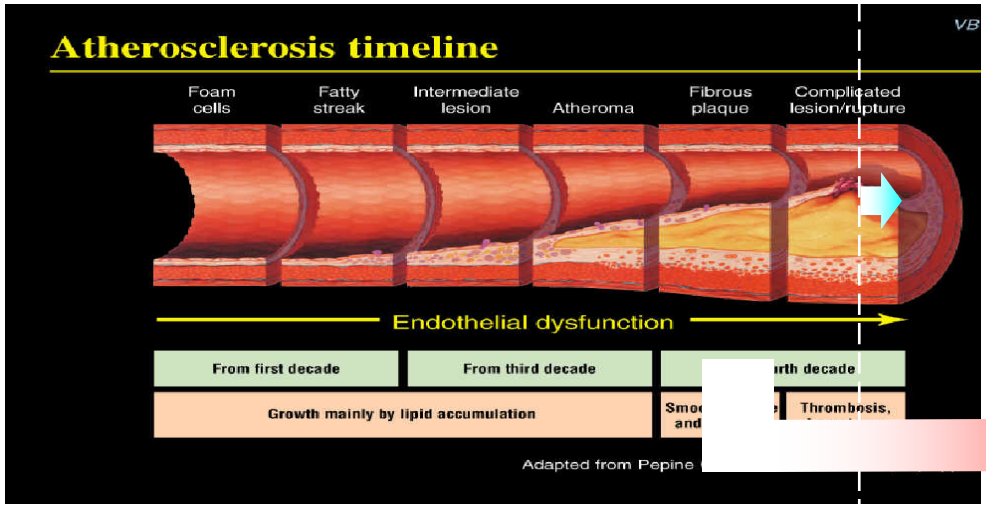
Epidemiología Genética

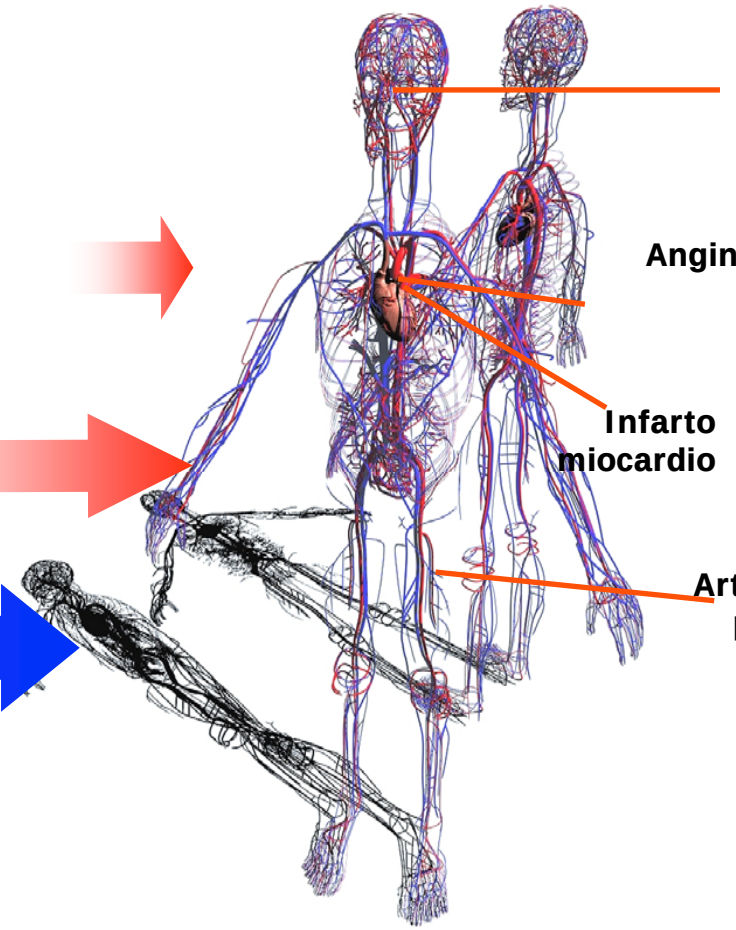
Estudio del papel de los factores genéticos en la susceptibilidad para presentar una enfermedad, y de su relación con los factores ambientales.

Una disciplina que tiene como objetivo determinar la etiología, distribución y prevención:

- de la enfermedad en familiares y
- de enfermedades con una base genética en la población.

Enfermedad Cardiovascular
Ateroesclerosis: un proceso crónico y generalizado





Ictus

Angina

SCA

Infarto miocardio

Arteriopatía periférica

Asintomático

Edad

Muerte súbita

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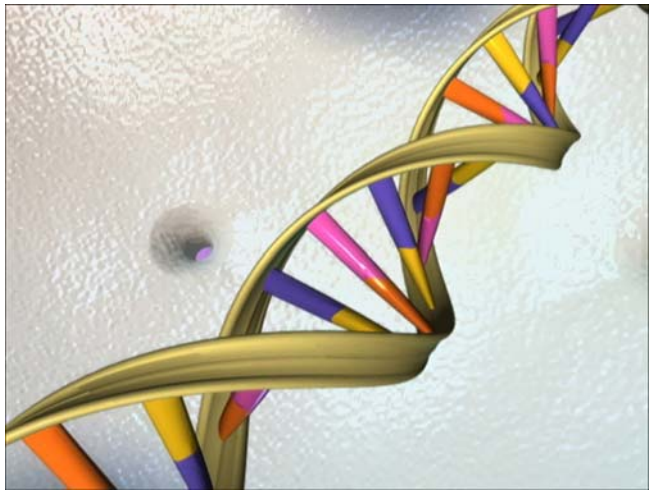
Enfermedades cardiovasculares:

- de las poblaciones a los genes

- de los genes a las poblaciones



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Enfermedades monogénicas

Definir si existe un componente genético en la enfermedad en estudio.

Establecer la arquitectura genética de la enfermedad (genes, variantes genéticas).

Evaluación del impacto de la información genética en el diagnóstico, la prevención y el tratamiento de la enfermedad.

Enf complejas

Enfermedades cardiovasculares:

- de las poblaciones a los genes

- de los genes a las poblaciones

Heredabilidad (h^2)

- **Proporción de la variancia del fenotipo de la población que es atribuible a la variabilidad genética.**

- **La proporción de las diferencias interindividuales del fenotipo que se explican por diferencias en factores genéticos.**

- **Tipos de muestra (Estudios con gemelos, grupos familiares extensos, hermanos adoptados)**

Heredabilidad de diferentes fenotipos relacionados con arteriosclerosis

INFARTO AGUDO DE MIOCARDIO: **h^2 = 0.56**.
(Nora JJ, et al. Circulation 1980;61:503-8.)

MORTALIDAD POR CARDIOPATÍA ISQUÉMICA: h2 =0.53-0.57
(Zdravkovic S, et al. J Intern Med 2002;252:247-54. Wienke A, et al. Twin Res 2001;4:266-74.)

ARTERIOSCLEROSIS CAROTIDEA: **h^2 = 0.09-0.67**
(Xiang AH, et al. Arterioscler Thromb Vasc Biol 2002;22:843-8; Fox CS, et al. Stroke. 2003;34:397-401; Juo SH, et al. Stroke 2004;35:2243-7; Swan L, et al. Atherosclerosis 2003;166:137-41; North KE, et al. Arterioscler Thromb Vasc Biol 2002;22:1698-703; Hunt KJ, et al. Stroke 2002;33:2775-80.)

CALCIO INTRACORONARIO: h2 = 0.42
(Peyser PA, et al. Circulation 2002;106:304-8.)

Genome wide linkage studies

Wang X et al.
Am J Hum Genet 2005;77:1-16.

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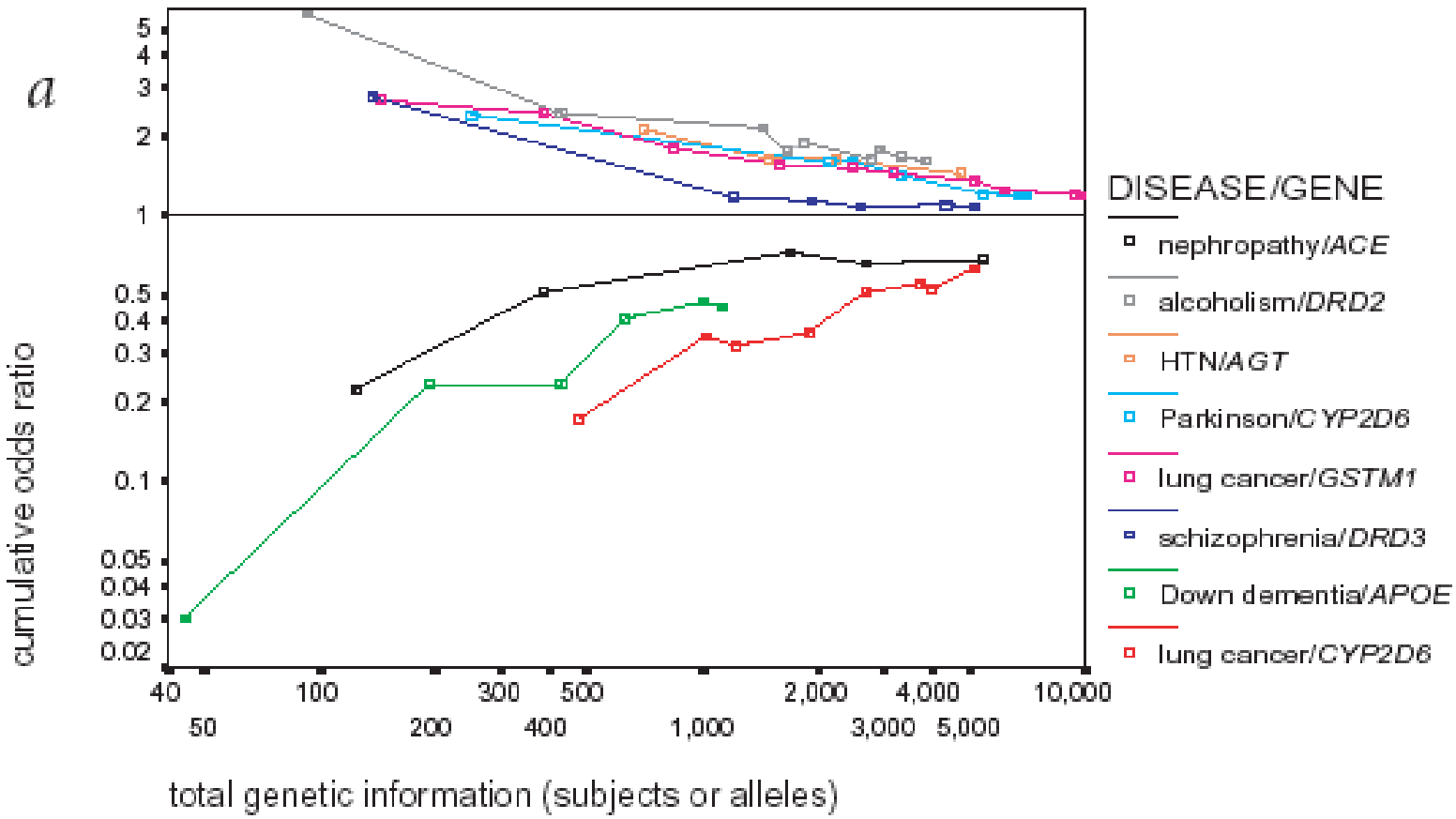
Association studies: a critical vision.



Ionnadis. Nat Gen 2001

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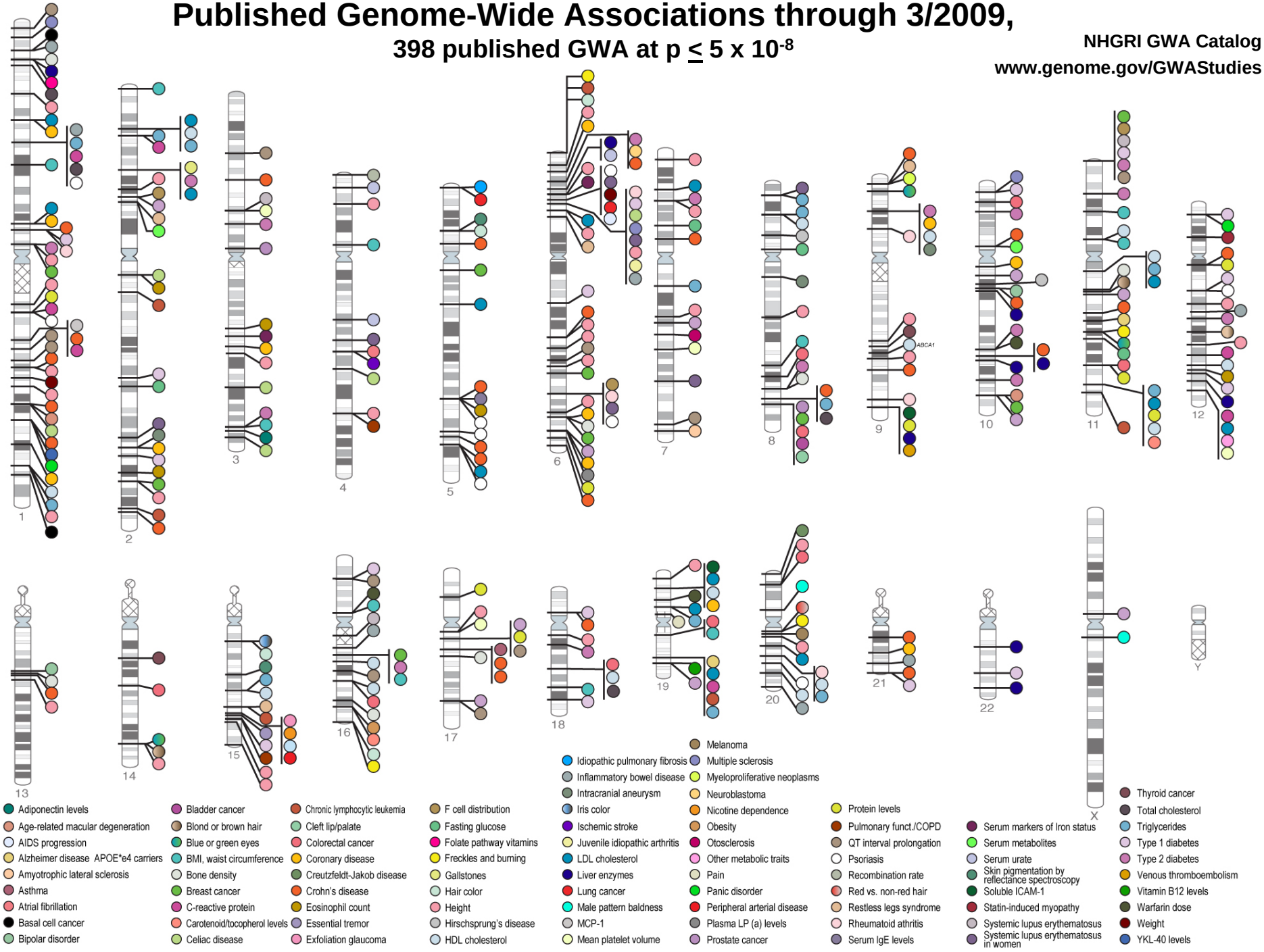
Published Genome-Wide Associations through 3/2009,

398 published GWA at $p \leq 5 \times 10^{-8}$

NHGRI GWA Catalog
www.genome.gov/GWAStudies



New variants for MI or CAD via GWAS

Sciencexpress Report

A Common Variant on Chromosome 9p21 Affects the Risk of Myocardial Infarction

Anna Helgadottir,[1]* Gudmar Thorleifsson,[1]* Andrei Manolescu,[1]* Solveig Gretarsdottir,[1] Thorarinn Blondal,[1] Aslaug Jonasdottir,[1] Adalbjorg Jonasdottir,[1] Asgeir Sigurdsson,[1] Adam Baker,[1] Arnar Palsson,[1] Gisli Masson,[1] Daniel Gudbjartsson,[1] Kristinn P. Magnusson,[1] Karl Andersen,[2] Allan I. Levey,[3] Valgerdur M. Backman,[1] Sigurborg Matthiasdottir,[1] Thorbjorg Jonsdottir,[1] Stefan Palsson,[1] Helga Einarsdottir,[1] Steinunn Gunnarsdottir,[1] Arnaldur Gylfason,[1] Viola Vaccarino,[3] W. Craig Hooper,[3] Muredach P. Reilly,[4] Christopher B. Granger,[5] Harland Austin,[3] Daniel J Rader,[4] Svati H. Shah,[5] Arshed A. Quyyumi,[3] Jeffrey R Gulcher,[1] Gudmundur Thorgeirsson,[3] Unnur Thorsteinsdottir,[1] Augustine Kong,[1]† Kari Stefansson[1]†

[1]deCODE genetics Inc, Reykjavik, Iceland. [2]National University Hospital, Reykjavik, Iceland. [3]Emory University School of Medicine, Atlanta, GA 30322, USA. [4]University of Pennsylvania School of Medicine, Philadelphia, PA 19104, USA. [5]Duke University School of Medicine, Durham, NC 27710, USA.

*These authors contributed equally to this work.

A Common Allele on Chromosome 9 Associated with Coronary Heart Disease

Ruth McPherson,[1*†] Alexander Pertsemlidis,[2*] Nihan Kavaslar,[1] Alexandre Stewart,[1] Robert Roberts,[1] David R. Cox,[3] David A. Hinds,[3] Len A. Pennacchio,[4] Anne Tybjaerg-Hansen,[5] Aaron R. Folsom,[6] Eric Boerwinkle,[7] Helen H. Hobbs,[2,8] Jonathan C. Cohen[2,8†]

[1]Division of Cardiology, University of Ottawa Heart Institute, Ottawa K1Y4W7, Canada. [2]Donald W. Reynolds Cardiovascular Clinical Research Center and the Eugene McDermott Center for Human Growth and Development, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA. [3]Perlegen Sciences, Mountain View, CA 94043; USA. [4]Genomics Division, Lawrence Berkeley National Laboratory, Berkeley, CA 94720, USA & U.S. Department of Energy Joint Genome Institute, Walnut Creek, CA 94598, USA. [5]Department of Clinical Biochemistry, Rigshospitalet, Copenhagen University Hospital, Copenhagen DK-2100, Denmark. [6]Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN 55454, USA. [7]Human Genetics Center and Institute for Molecular Medicine, University of Texas Health Science Center, Houston, TX 77030, USA. [8]Center for Human Nutrition and the [9]Howard Hughes Medical Institute at the University of Texas Southwestern Medical Center, Dallas, TX 75390, USA.

*These authors contributed equally to this work.

†To whom correspondence should be addressed. E-mail: jonathan.cohen@utsouthwestern.edu or rmcpherson@ottawaheart.ca

The NEW ENGLAND JOURNAL of MEDICINE

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 Braenne, 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*

nature genetics

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nature genetics

Genome-wide association of early-onset myocardial infarction with single nucleotide polymorphisms and copy number variants

Myocardial Infarction Genetics Consortium*

New susceptibility locus for coronary artery disease on chromosome 3q22.3

Jeanette Erdmann[1], Anika Großhennig[1,2], Peter S Braund[3], Inke R König[2], Christian Hengstenberg[4], Alistair S Hall[5], Patrick Linsel-Nitschke[1], Sekar Kathiresan[6], Ben Wright[7], David-Alexandre Trégouët[8], Francois Cambien[8], Petra Bruse[1], Zouhair Aherrahrou[1], Arnika K Wagner[1], Klaus Stark[4], Stephen M Schwartz[9], Veikko Salomaa[10], Roberto Elosua[11], Olle Melander[12], Benjamin F Voight[13], Christopher J O'Donnell[14], Leena Peltonen[15], David S Siscovick[9], David Altshuler[16], Piera Angelica Merlini[17], Flora Peyvandi[18], Luisa Bernardinelli[19,20], Diego Ardissino[21], Arne Schillert[2], Stefan Blankenberg[22], Tanja Zeller[22], Philipp Wild[22], Daniel F Schwarz[2], Laurence Tiret[8], Claire Perret[8], Stefan Schreiber[23], Nour Eddine El Mokhtari[23], Arne Schäfer[23], Winfried März[24–26], Wilfried Renner[25], Peter Bugert[27], Harald Klüter[27], Jürgen Schrezenmeir[28], Diana Rubin[28], Stephen G Ball[5], Anthony J Balmforth[5], H-Erich Wichmann[29,30], Thomas Meitinger[31,32], Marcus Fischer[4], Christa Meisinger[29], Jens Baumert[29], Annette Peters[29], Willem H Ouwehand[33], Italian Atherosclerosis, Thrombosis, and Vascular Biology Working Group[34], Myocardial Infarction Genetics Consortium[34], Wellcome Trust Case Control Consortium[34], Cardiogenics Consortium[34], Panos Deloukas[15], John R Thompson[7], Andreas Ziegler[2], Nilesh J Samani[3] & Heribert Schunkert[1]

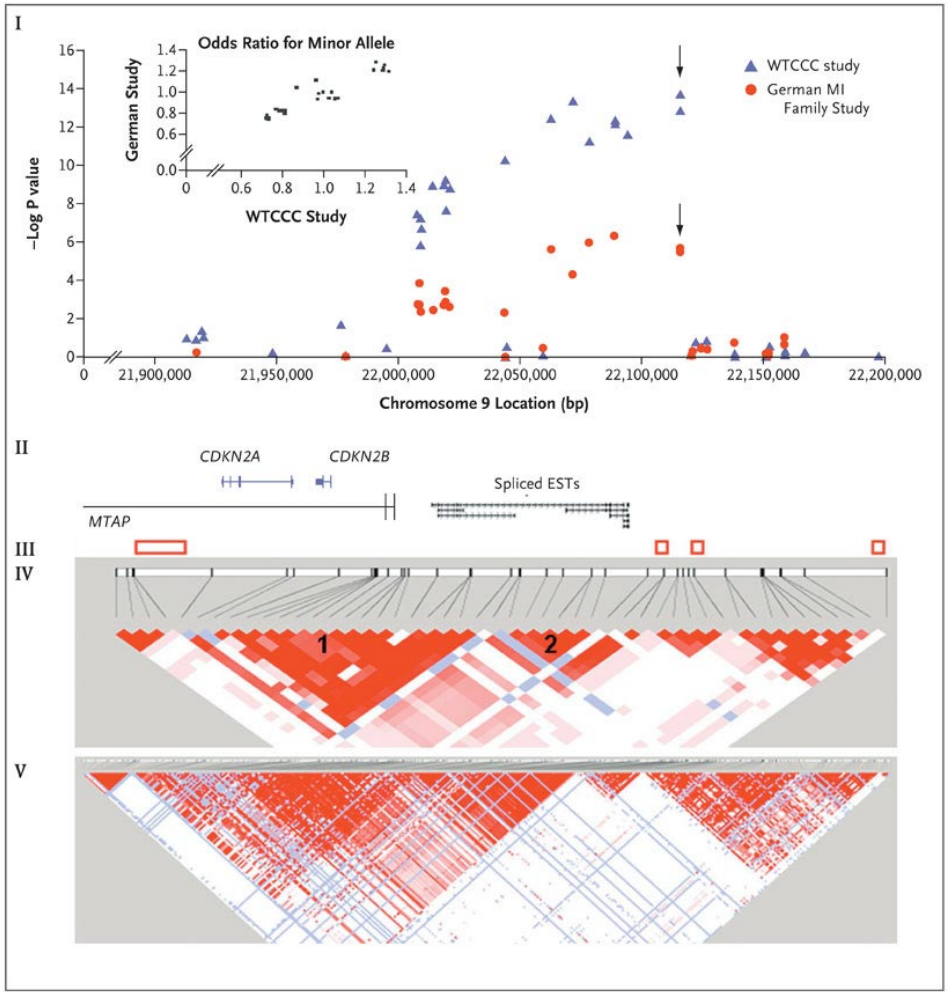
We present a three-stage analysis of genome-wide SNP data in 1,222 German individuals with myocardial infarction and 1,298 controls, *in silico* replication in three additional genome-wide datasets of coronary artery disease (CAD) and subsequent replication in ~25,000 subjects. We identified one new CAD risk locus on 3q22.3 in *MRAS* ($P = 7.44 \times 10^{-13}$; OR = 1.15, 95% CI = 1.11–1.19), and suggestive association with a locus on 12q24.31 near *HNF1A-C12orf43* ($P = 4.81 \times 10^{-7}$; OR = 1.08, 95% CI = 1.05–1.11).

Recent genome-wide association studies (GWAS) of coronary artery disease (CAD) have focused on a few chromosomal regions with strong signals[1–4]. We hypothesized that the application of stringent statistical thresholds may have dismissed SNPs with modest effects or low allele frequencies (**Supplementary Fig. 1** and **Supplementary Table 1** online). For this study, we started by identifying SNPs meeting a less-stringent cutoff for association ($P \leq 1 \times 10^{-3}$) in a new GWAS for myocardial infarction.

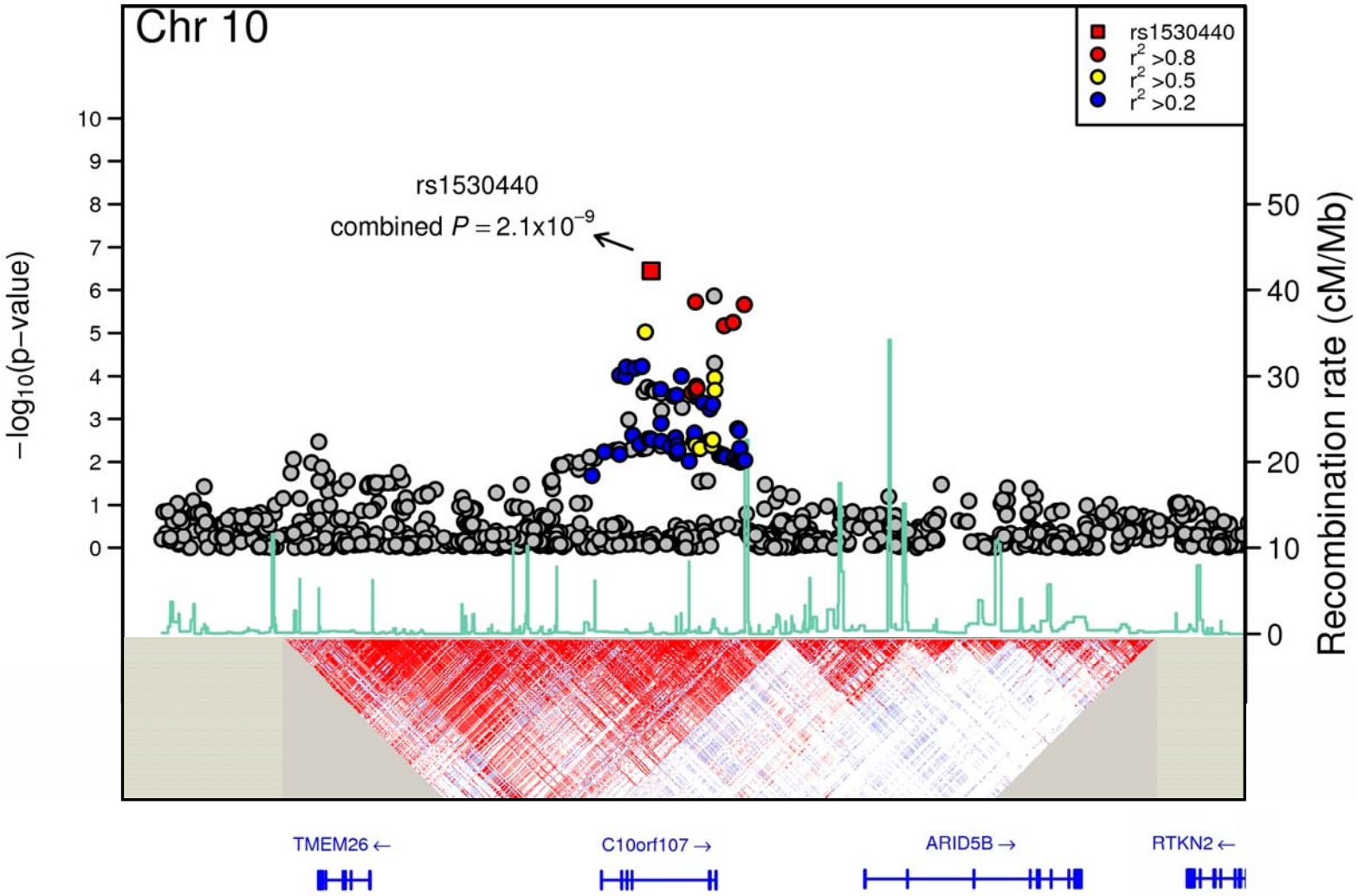
In stage 1, we genotyped 869,224 autosomal SNPs from the Affymetrix Genome-Wide Human SNP Array 6.0 in 1,222 myocardial infarction cases (German MI Family Study II (GerMIFS II); **Supplementary Methods** online) with premature disease onset and positive family history and 1,298 population-based Germans of European descent. After quality control (**Supplementary Fig. 2** online), 567,119 SNPs remained. The inflation factor estimated for all SNPs that passed quality control is 1.04 (s.e.m. = 9.2×10^{-5}). Of these, 694 SNPs showed association with myocardial infarction at $P \leq 1 \times 10^{-3}$ in a two-sided trend test. These SNPs were evaluated by *in silico* analysis in three additional GWAS datasets (stage 2), comprising a

+ otros 3 artículos publicados en el mismo número

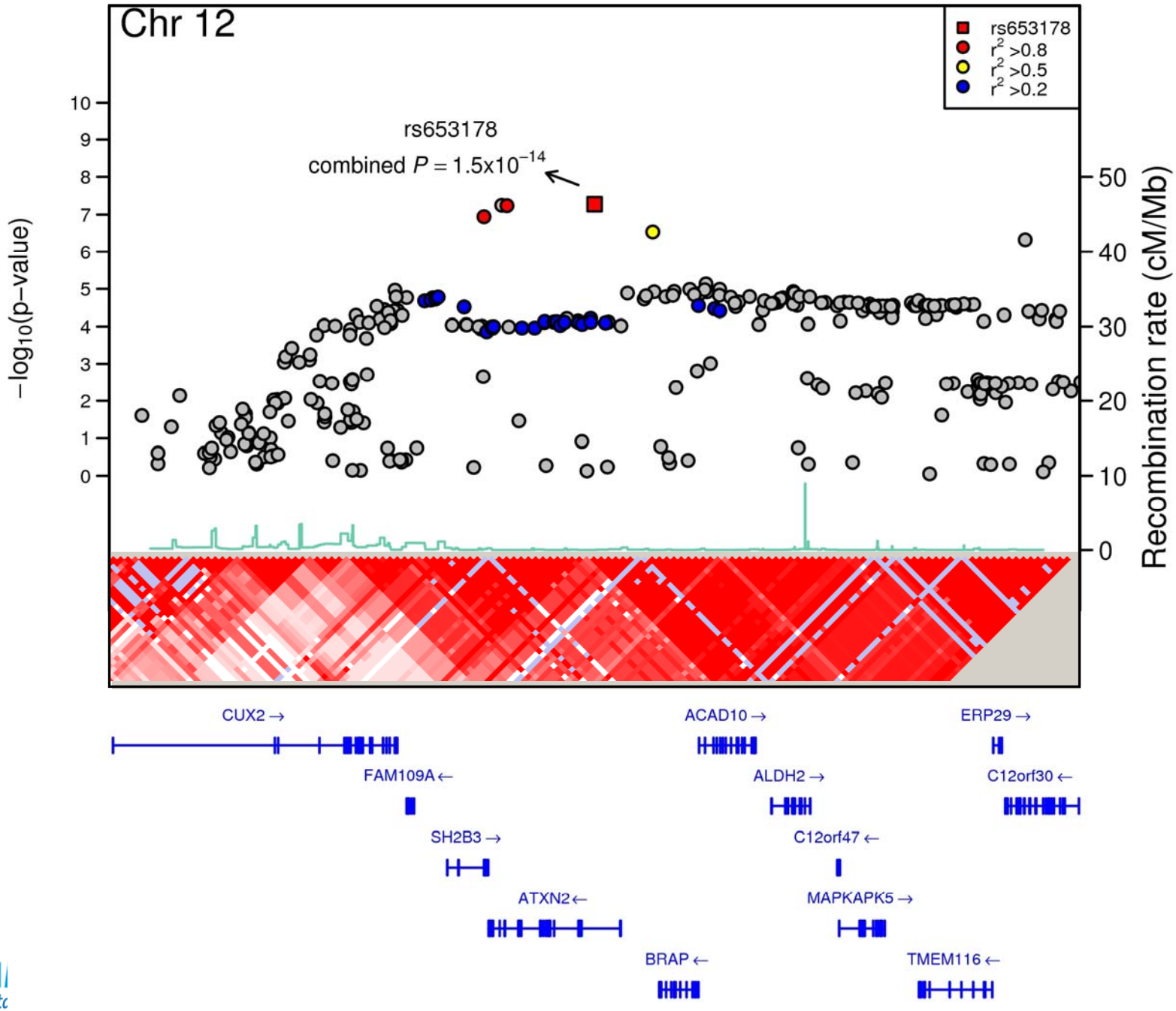
Genome Wide Association Studies-CHD: WTCCC



Samani NJ. N Engl J Med. 2007;357:443-53.



Newton-Cheh C et al. Nat Genet. 2009 May 10.



Newton-Cheh C et al. Nat Genet. 2009 May 10.

Missing heritability

- **Genetic heterogeneity of complex traits.**

Box 3 | **How many genetic variants do we expect to find for complex traits?**

The 18 genetic variants that have been associated with type 2 diabetes (FIG. 2) have minor allele frequencies (MAFs) ranging from 0.073 to 0.50 and odds ratios (ORs) ranging from 1.05 to 1.15, except for the *TCF7L2* gene, which has an OR of 1.37. These MAFs and ORs are typical of what is observed for the genetic variants discovered in genome-wide association (GWA) studies for other diseases and complex phenotypic traits. Altogether, these 18 variants explain less than 4% of the total liability of the trait, which is only a small fraction of the estimated heritability. This implies that there are many more genes to be identified that contribute to the genetic components of the disease. Assuming that the undiscovered genetic variants have similar MAFs and ORs as those that have been identified, and estimating 40% heritability, more than 800 genetic variants are required (Y. Pawitan, personal communication). If we assume that the undiscovered genetic variants are largely rare (BOX 4) with MAFs that are ~10 times smaller than those identified to date (0.0073 to 0.05) and ORs that are ~10 times larger (1.63 to 4.05), then ~85 variants are required (Y. Pawitan, personal communication).

Frazer KA et al Human genetic variation and complex traits Nat Gen Review 2009

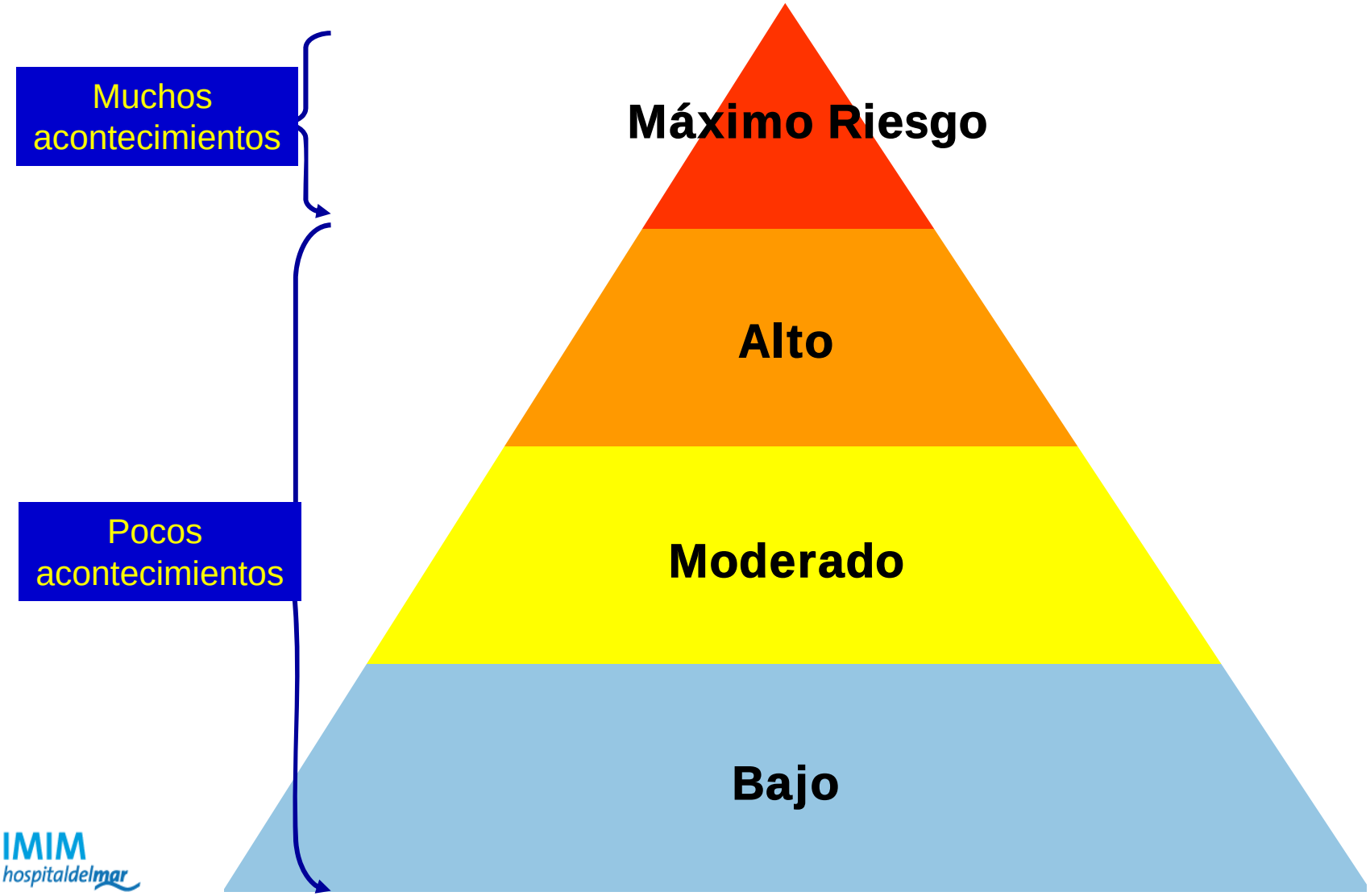
Enfermedades cardiovasculares:

- de las poblaciones a los genes

- de los genes a las poblaciones

Las tablas de riesgo que nos gustarían…

Adaptado de Braunwald, JACC 2006



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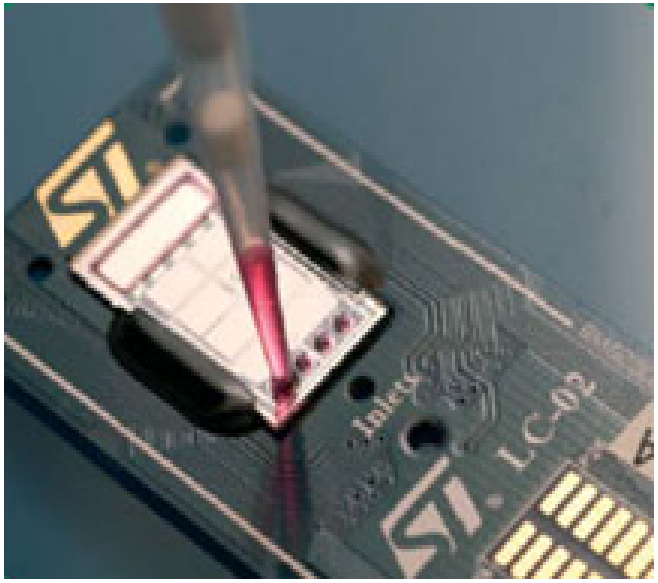
Distribución del riesgo y de acontecimientos cardiovasculares en el estudio VERIFICA

	Riesgo medio	% Población	% Acontecimientos CV
Riesgo >15%	20	4,9	14,4%
Riesgo 5-15%	8,2	34,4	53,6%
Riesgo < 5%	2,6	60,7	31,9%

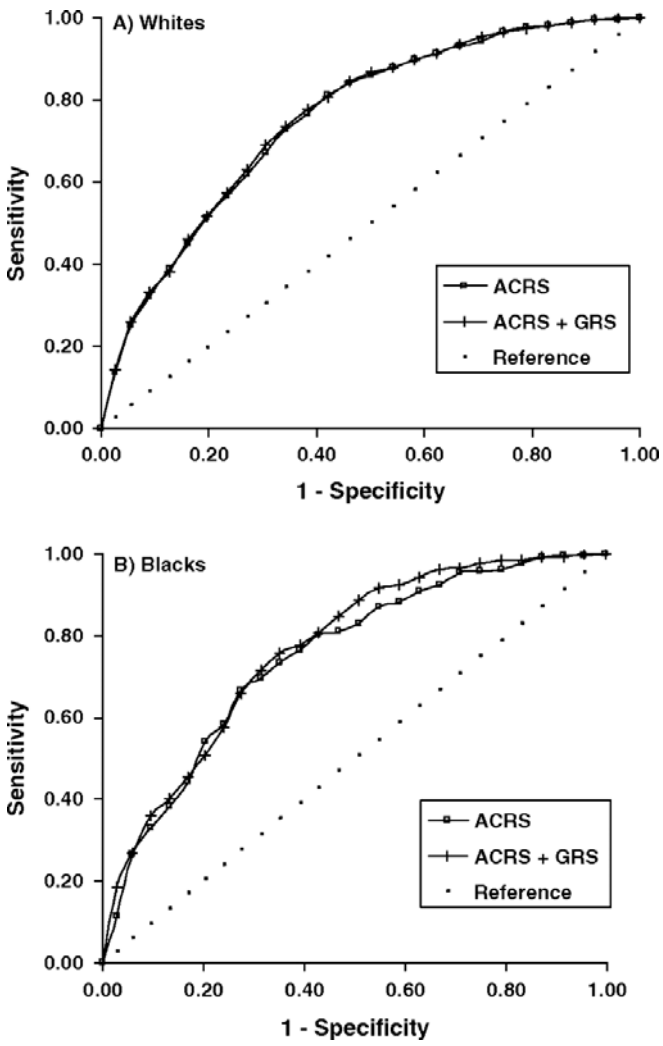
Marrugat J. The VERIFICA Study. J Epidemiol Community Health 2007;61:40-47

Pruebas genéticas

- **Chips diagnósticos / pronósticos**

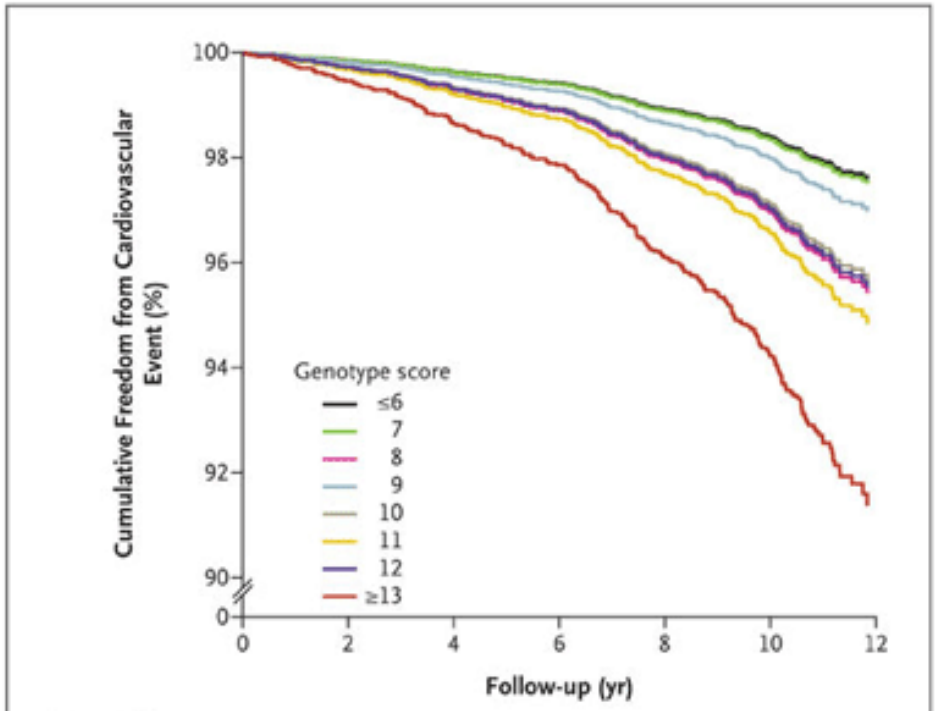


Receiver operating characteristic curves using the Atherosclerosis Risk in Communities study cardiovascular risk score (ACRS) alone and incorporating the genetic risk score (GRS) for Whites (A) and Blacks (B), United States, 1986-2001



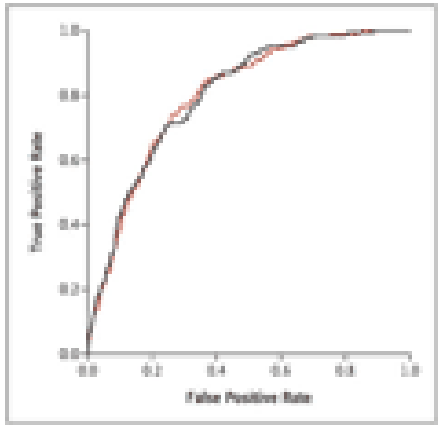
Morrison, A. C. et al. Am. J. Epidemiol. 2007 166:28-35.

Asociación / Capacidad predictiva de marcadores genéticos



No. at Risk

Genotype score						
≤6	122	122	120	116	112	105
7	309	304	302	298	293	267
8	574	573	566	556	538	481
9	894	894	886	872	844	757
10	913	900	887	876	849	757
11	726	719	711	696	679	604
12	465	462	456	447	434	398
≥13	229	228	218	215	207	184



Kathiresan S et al. N Engl J Med 2008

Circulation: Cardiovascular Genetics. 2009
Published online before print April 21, 2009, doi: 10.1161/CIRCGENETICS.108.817338

Original Article

Impact of adding a single allele in the 9p21 locus to traditional risk factors on reclassification of coronary heart disease risk and implications for lipid-modifying therapy in the Atherosclerosis Risk in Communities (ARIC) study

Ariel Brautbar[1]; Christie M. Ballantyne[1,7]; Kim Lawson[2]; Vijay Nambi[3]; Lloyd Chambless[4]; Aaron R. Folsom[5]; James T. Willerson[6] and Eric Boerwinkle[2]

[1] Baylor College of Medicine, Houston, TX;
[2] University of Texas–Houston Health Science Center, Houston, TX;
[3] Methodist DeBakey Heart Vascular Center & Baylor College of Medicine, Houston, TX;
[4] University of North Carolina, Chapel Hill, NC;
[5] University of Minnesota School of Public Health, Minneapolis, MN;
[6] Texas Heart Institute & the University of Texas–Houston Health Science Center, Houston, TX

[7] E-mail: cmb@bcm.tmc.edu

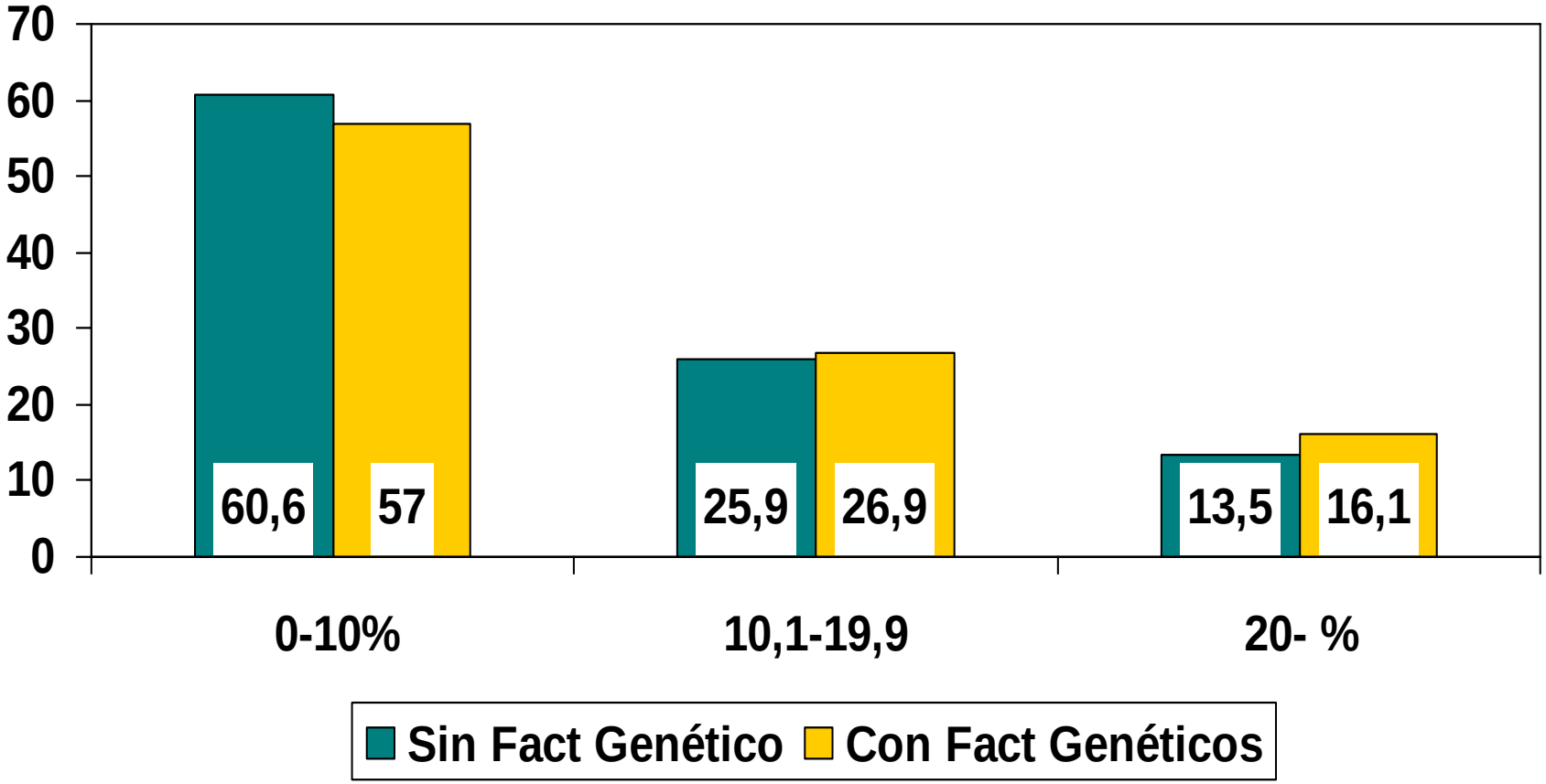
Background—A single nucleotide polymorphism on chromosome 9p21, rs10757274 (9p21 allele), has been shown to predict coronary heart disease (CHD) in whites. We evaluated whether adding the 9p21 allele to traditional risk factors (RF) improved CHD risk prediction in whites from the Atherosclerosis Risk in Communities (ARIC) study, and whether changes in risk prediction would modify lipid therapy recommendations.

Methods and Results—Whites (n=9,998) in the ARIC study for whom the 9p21 genotype and traditional RF information was available were included. Using Cox proportional hazards models, the ARIC Cardiovascular Risk Score (ACRS) which is based on traditional RF, was determined. A total of 1,349 individuals (13.5%) developed incident CHD events during a period of 14.6 years. Adding the 9p21 allele to traditional RF was associated with hazard ratio (HR) of incident CHD of 1.2 per allele ($p<0.000003$) and a significant increase in the area under the curve of the receiver operating characteristic from 0.782 to 0.786 (95% CI= [0.001, 0.007]). The 9p21 allele's greatest influence to the ACRS was observed in the intermediate-low (>5% to ≤10% 10-year CHD risk) and intermediate-high (>10% to ≤20% 10-year CHD risk) categories with 12.1% and 12.6% reclassified, respectively. This may impact therapy since 90% of these reclassified individuals had LDL-C>100 mg/dL.

Conclusion—Adding the 9p21 allele to traditional RF in whites in the ARIC study modestly improved CHD risk prediction in the intermediate categories.

Key Words: genetics • heart diseases • lipids • risk factors

Capacidad predictiva de marcadores genéticos: participantes que desarrollan acontecimiento cardiovascular



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Kathiresan S et al. N Engl J Med 2008

Estudio de la relación causal entre un biomarcador y una enfermedad

Antioxidants Vitamins and coronary heart disease: observational studies

Antioxidant vitamins and coronary heart disease risk: a pooled analysis of 9 cohorts[1–3]

Paul Knekt, John Ritz, Mark A Pereira, Eilis J O'Reilly, Katarina Augustsson, Gary E Fraser, Uri Goldbourt, Berit L Heitmann, Göran Hallmans, Simin Liu, Pirjo Pietinen, Donna Spiegelman, June Stevens, Jarmo Virtamo, Walter C Willett, Eric B Rimm, and Alberto Ascherio

ABSTRACT

Background: Epidemiologic studies have suggested a lower risk of coronary heart disease (CHD) at higher intakes of fruit, vegetables, and whole grain. Whether this association is due to antioxidant vitamins or some other factors remains unclear.

Objective: We studied the relation between the intake of antioxidant vitamins and CHD risk.

Design: A cohort study pooling 9 prospective studies that included information on intakes of vitamin E, carotenoids, and vitamin C and that met specific criteria was carried out. During a 10-y follow-up, 4647 major incident CHD events occurred in 293 172 subjects who were free of CHD at baseline.

Results: Dietary intake of antioxidant vitamins was only weakly related to a reduced CHD risk after adjustment for potential nondietary and dietary confounding factors. Compared with subjects in the lowest dietary intake quintiles for vitamins E and C, those in the highest intake quintiles had relative risks of CHD incidence of 0.84 (95% CI: 0.71, 1.00; $P = 0.17$) and 1.23 (1.04, 1.45; $P = 0.07$), respectively, and the relative risks for subjects in the highest intake quintiles for the various carotenoids varied from 0.90 to 0.99. Sub-

inconsistent (1, 4). Most previous cohort studies have investigated α-tocopherol or vitamin E, vitamin C, and total carotene or β-carotene, and only scarce information exists on other carotenoids. Few studies have reported on vitamin supplement intake. The inconsistency of the results from these studies may, in part, be due to a lack of power to detect associations, misclassification of antioxidant intake, unsatisfactory control for potential confounding factors, or an inability to investigate subpopulations. Randomized intervention trials in primary prevention of cardiovascular disease have not shown substantial benefits from α-tocopherol (5, 6) or β-carotene (5–9) supplementation.

In the present Pooling Project of Cohort Studies on Diet and Coronary Disease, we studied the relations of the intakes of vitamin E, 5 carotenoids, and vitamin C to the incidence of all major CHD events (nonfatal myocardial infarction or fatal CHD) and CHD mortality by pooling primary data from 9 major cohort studies with the use of a standardized approach. This large database enabled us to examine several issues that would be difficult to address in any single cohort study, such as whether *1*)

Conclusions: The results suggest a reduced incidence of major CHD events at high supplemental vitamin C intakes. The risk reductions at high vitamin E or carotenoid intakes appear small. *Am J Clin Nutr* 2004;80:1508–20.

Vitamin C and coronary heart disease: randomized clinical trial

Type of major vascular event	Vitamin-allocated (10 269)	Placebo-allocated (10 267)	Event rate ratio (95% CI)
Coronary events			
Non-fatal MI	464 (4·5%)	467 (4·5%)	
Coronary death	664 (6·5%)	630 (6·1%)	
Subtotal: major coronary event	**1063 (10·4%)**	**1047 (10·2%)**	**1·02 (0·94–1·11) p=0·7**
Strokes			
Non-fatal stroke	430 (4·2%)	435 (4·2%)	
Fatal stroke	108 (1·1%)	107 (1·0%)	
Subtotal: any stroke	**511 (5·0%)**	**518 (5·0%)**	**0·99 (0·87–1·12) p=0·8**
Revascularisations			
Coronary	623 (6·1%)	615 (6·0%)	
Non-coronary	472 (4·6%)	510 (5·0%)	
Subtotal: any revascularisation	**1058 (10·3%)**	**1086 (10·6%)**	**0·98 (0·90–1·06) p=0·6**
ANY MAJOR VASCULAR EVENT	**2306 (22·5%)**	**2312 (22·5%)**	**1·00 (0·94–1·06) p>0·9**

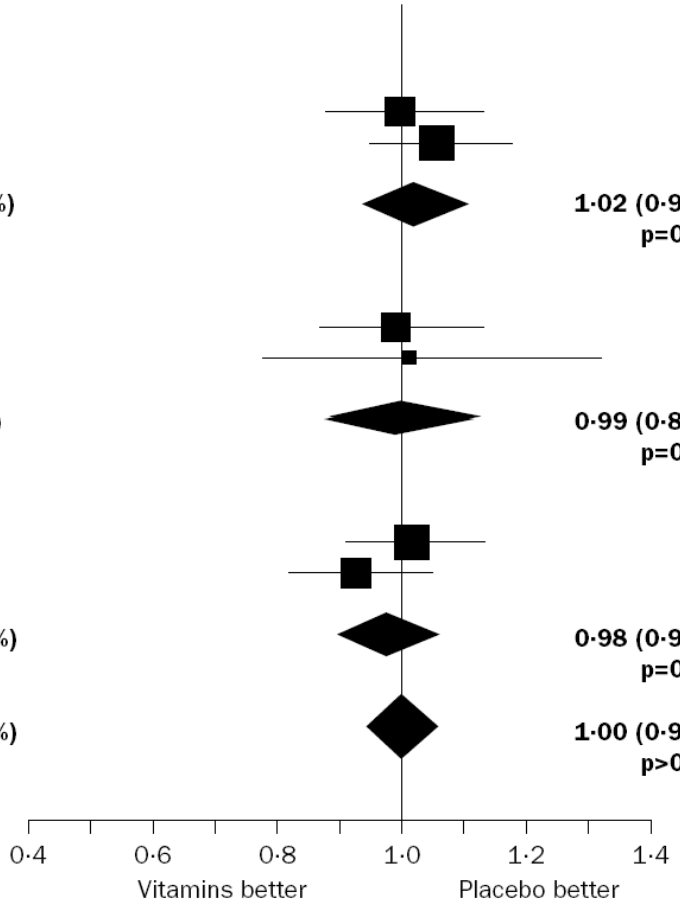

Figure 3: **Effects of vitamin allocation on first major coronary event, stroke, and revascularisation (defined prospectively as "major vascular events")**

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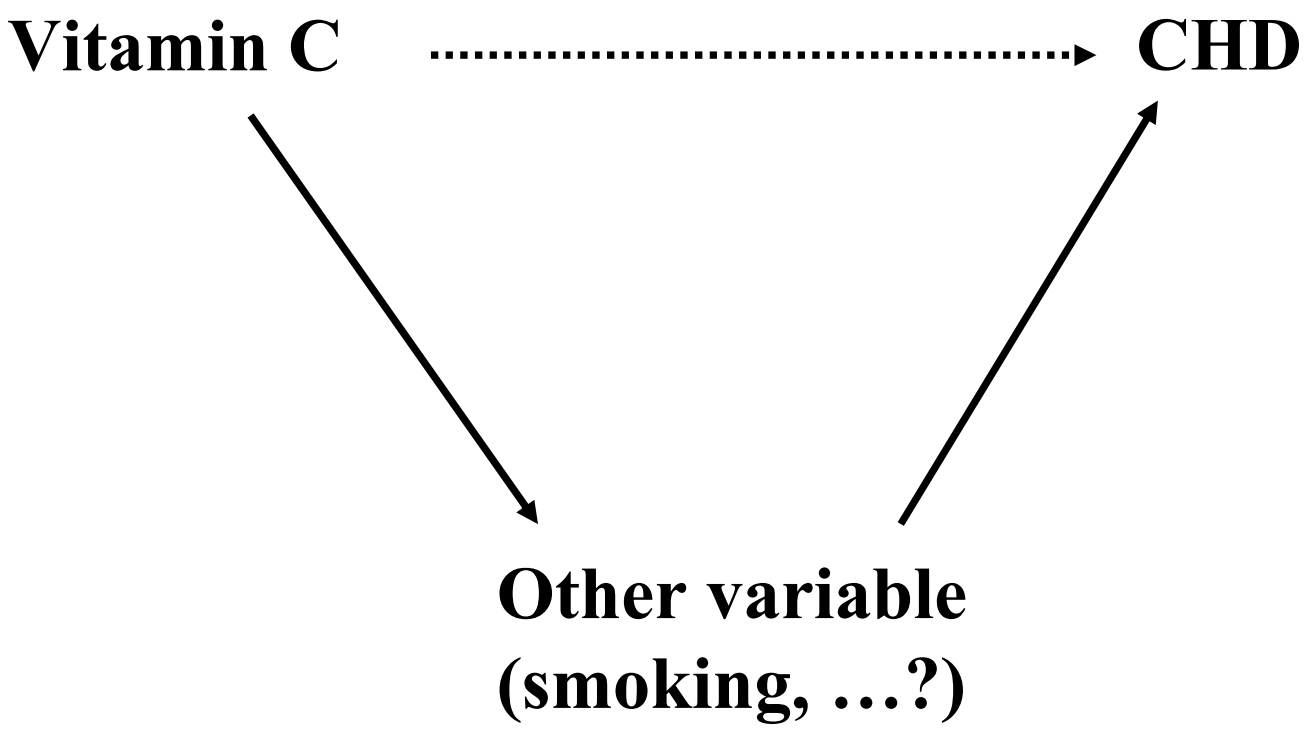
Heart protection study. Lancet 2002

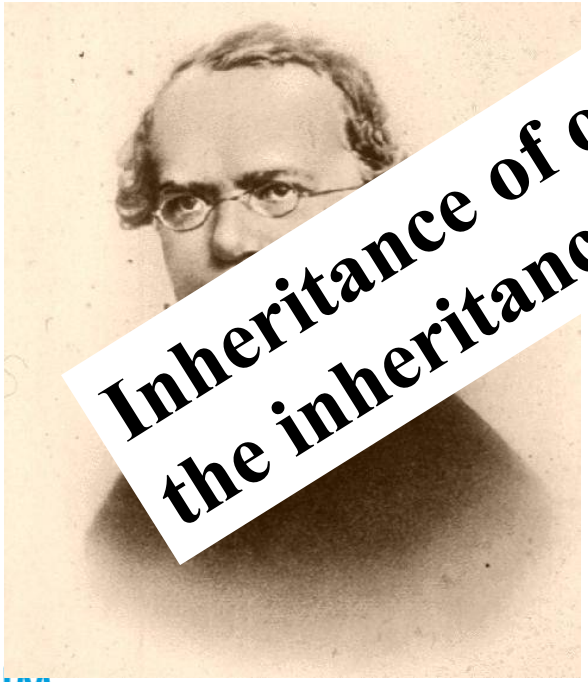
Confounding

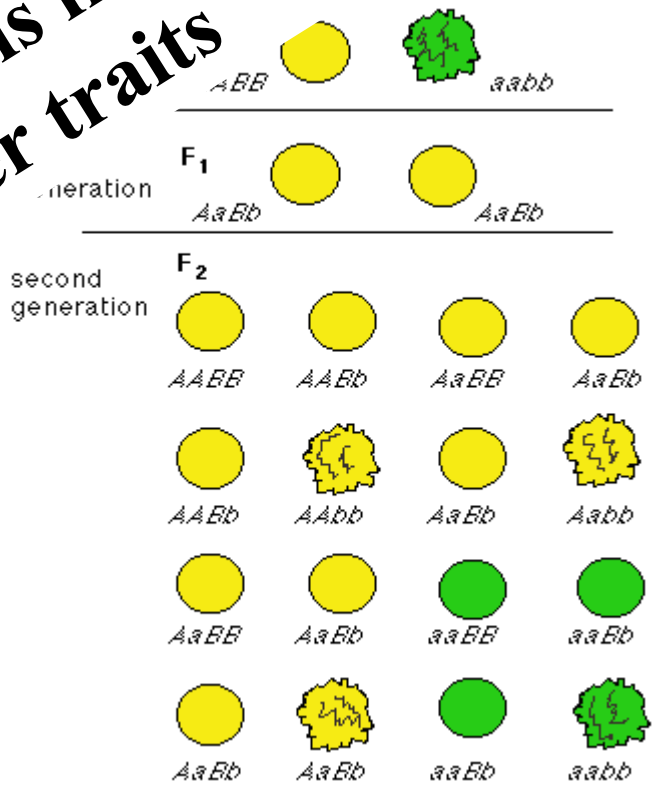


Mendelian randomization

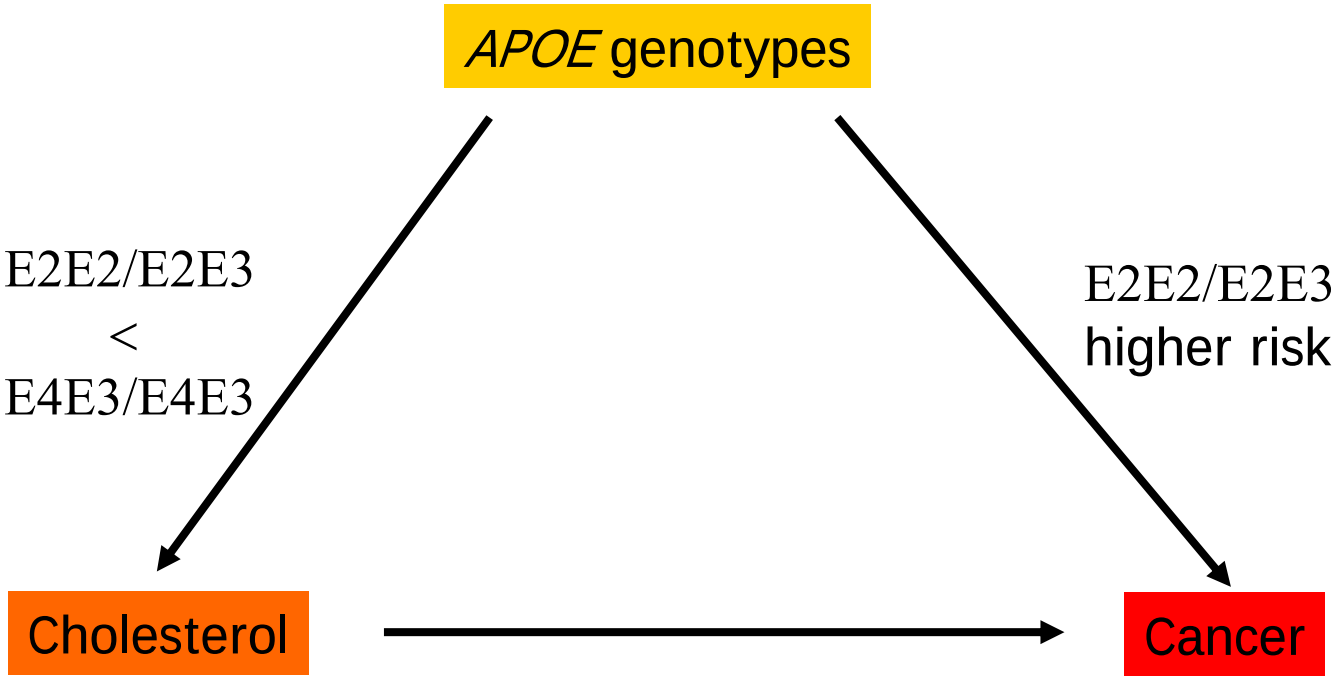
- Based on Mendel's laws: "random assortment o he time of gamete formation. Therefore, the behavi differentiating characteristics in hybrid ent of other differences between the two o

Inheritance of one trait is independent of the inheritance of other traits



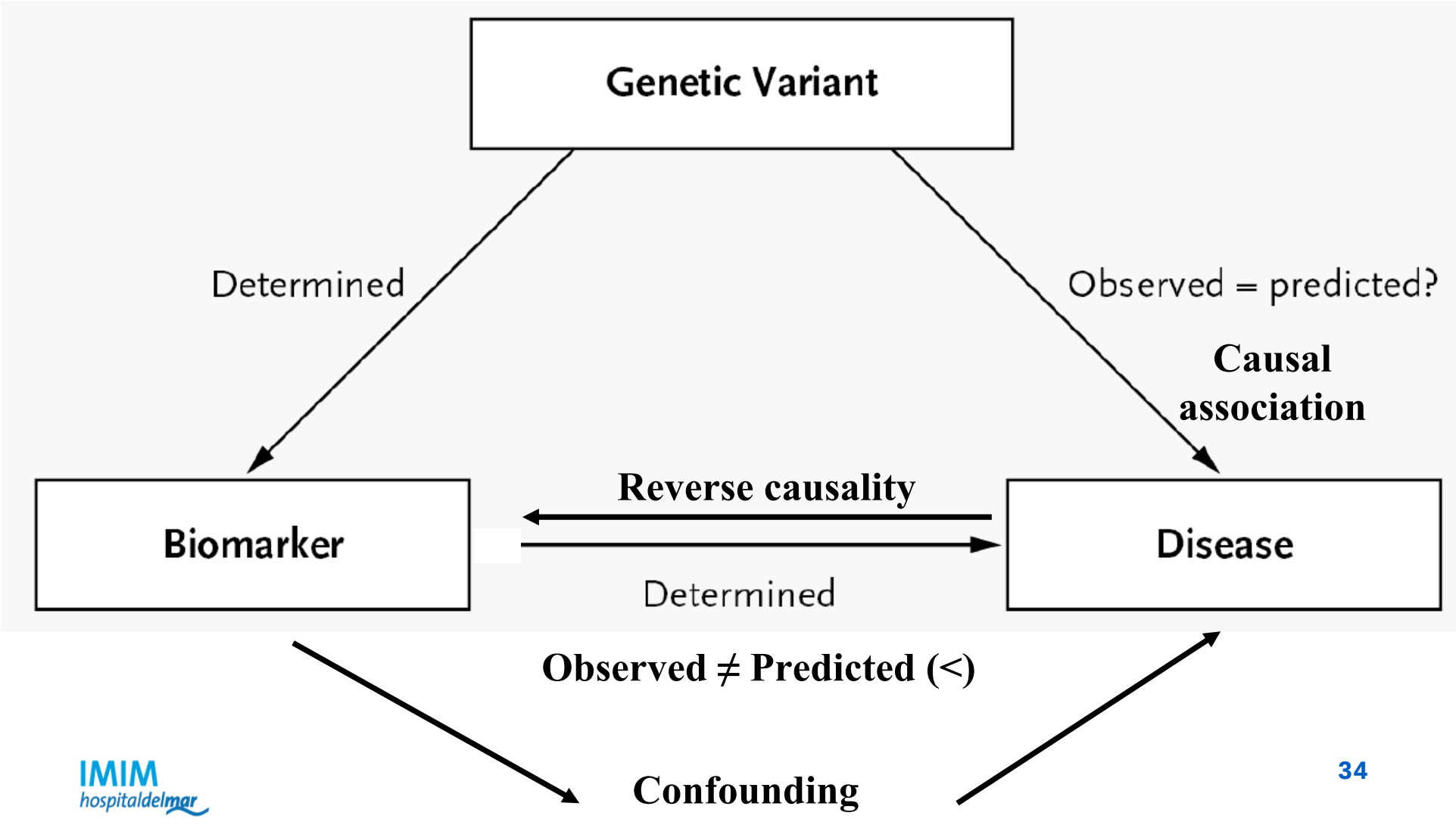


Mendelian randomization



Katan B. Lancet 1986;i:507-8.

Mendelian randomization: scheme



IMIM
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