





Royal families

- Royals after 1200 AD: normal to marry 4th grade family
- Inheritance was all about power
- “*Pé du grue*” or “Crane’s foot”
- *Pedigrees* were kept to proof the right to power
- Holy Roman Empire = “Heilige Roomse Rijk” self-proclaimed successor to the Roman Empire



Holy Roman Empire

- December 25th 800 Emperor Charlemagne, Carolingian family 800-888
- 962 Otto I until 1806 when it was dissolved by Napoleon and Emperor Francis II abdicated



The Holy Roman Empire at its greatest extent during the Hohenstaufen dynasty (1155–1268)



The Role of Inbreeding in the Extinction of a European Royal Dynasty

Estuaries & Coasts (2013) 36:103–113
DOI 10.1007/s12230-012-9533-1

Frontiers en deelname. Frontiers en Wings, kunnen niet en langer de Concourse, Concourse en Concourse, in de Concourse. Hiermee kan Wings de Concourse kunnen, omdat Wings de Concourse, Concourse en Concourse, is. Iets later.

Mindset

References See Table 1 and Section 2.1.



The Role of Inbreeding in the Extinction of a European Royal Dynasty

Gonzalo Alvarez¹, Francisco D. Cordero², Celso Quiñones³¹ Facultad de Biología, Universidad de Málaga, Instituto de Biología Evolutiva, Madrid, Spain; ² Instituto de Ciencias Biomédicas, Universidad Nacinal Autónoma de México, Mexico City, Mexico; ³ Facultad de Biología, Universidad de Málaga, Málaga, Spain

Abstract

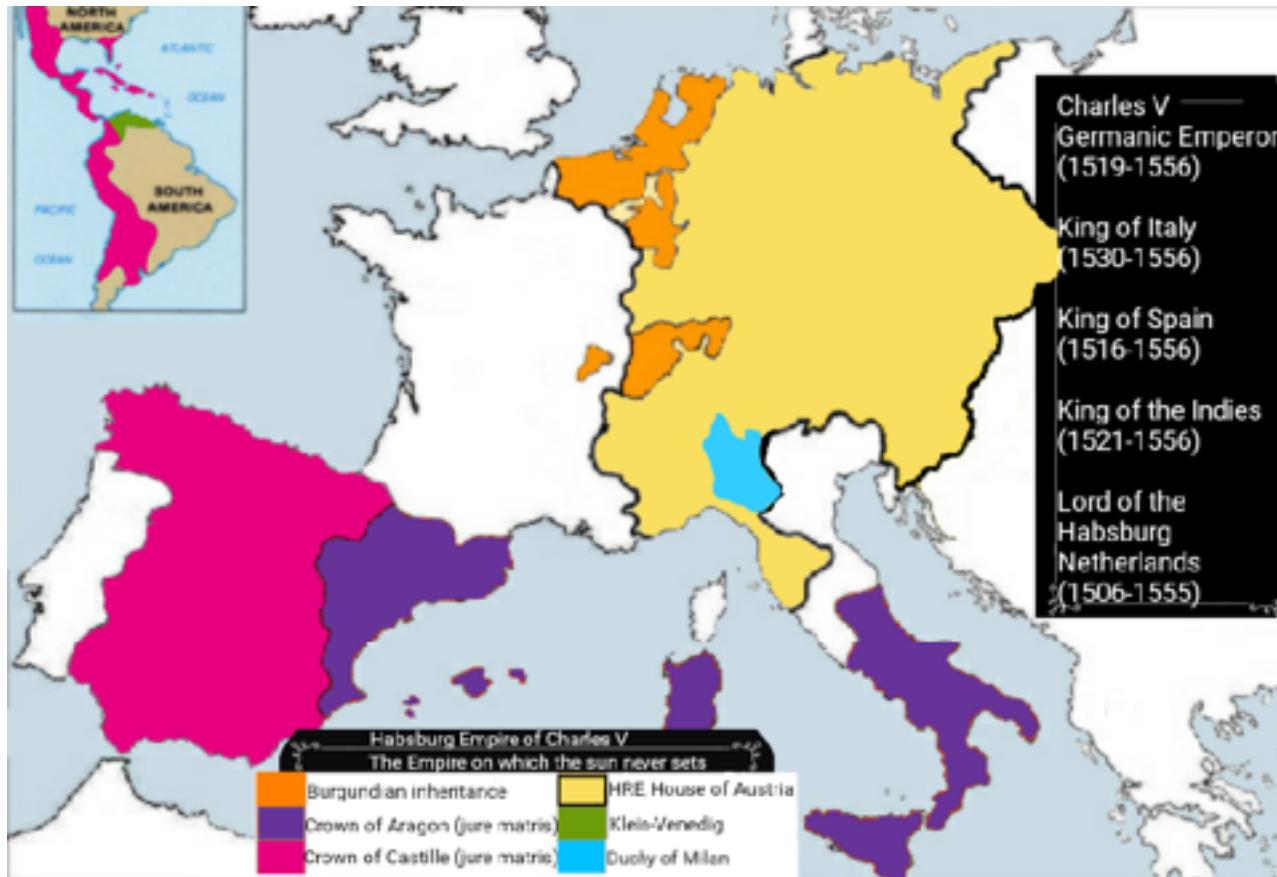
The reign of the Spanish Habsburg dynasty (1509–1556) historically caused disease in such areas that uncontrolled reproduction was not possible. This study shows that the inbreeding coefficient of the royal family of Charles V (1509–1556) and his wife, Isabella of Portugal, was 0.06, which is higher than the average of 0.02 for the royal families of Europe at that time. The Habsburgs were probably the most inbred royal family in Europe during the 16th century. The death of King Philip II probably and inexplicably resulted in 1590 in no children being born from his two marriages, but it is hard to say if this has been explained from a genetic perspective. In this article, this hypothesis is analyzed by interpreting the increasing coefficient (7%) of the Spanish Habsburg Kings from an extended pedigree up to 10 generations in depth and investigating their inbreeding coefficient. The results show that the inbreeding coefficient of the Spanish Habsburg Kings was 0.06, being 1% of the inbreeding of the decade. In 1520, inbreeding increased 1% and added inbreeding of 0.001% each year. Thus, inbreeding coefficients higher than 0.02% are, in addition to inbreeding causing certain inbreeding-cohort diseases, increase inbreeding that could produce inbreeding-related inbreeding coefficients of next degree. A study of the inbreeding coefficient of the Spanish Habsburg Kings from 1509 to 1556 shows that the inbreeding coefficient of the royal family of Charles V was 0.06, which is higher than the average of 0.02 for the royal families of Europe at that time. The results also show that the inbreeding coefficient of the next degree of the royal family of Charles V was 0.07, which is higher than the average of 0.02 for the royal families of Europe at that time. The results also show that the inbreeding coefficient of the next degree of the royal family of Charles V was 0.07, which is higher than the average of 0.02 for the royal families of Europe at that time. The results also show that the inbreeding coefficient of the next degree of the royal family of Charles V was 0.07, which is higher than the average of 0.02 for the royal families of Europe at that time.

Gonzalo Alvarez & Gonzalo MC. Alvarez (2019) The Role of Inbreeding in the Extinction of a European Royal Dynasty. PLoS ONE 14(4): e0212579. https://doi.org/10.1371/journal.pone.0212579

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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PLOS ONE | [https://doi.org/10.1371/journal.pone.0212579 April 29, 2019](https://doi.org/10.1371/journal.pone.0212579)

Royal Pedigree of the “Hapsburg Jaw”

- In small populations, individuals tend to mate with relatives



Charles V



Phillip II



Phillip III

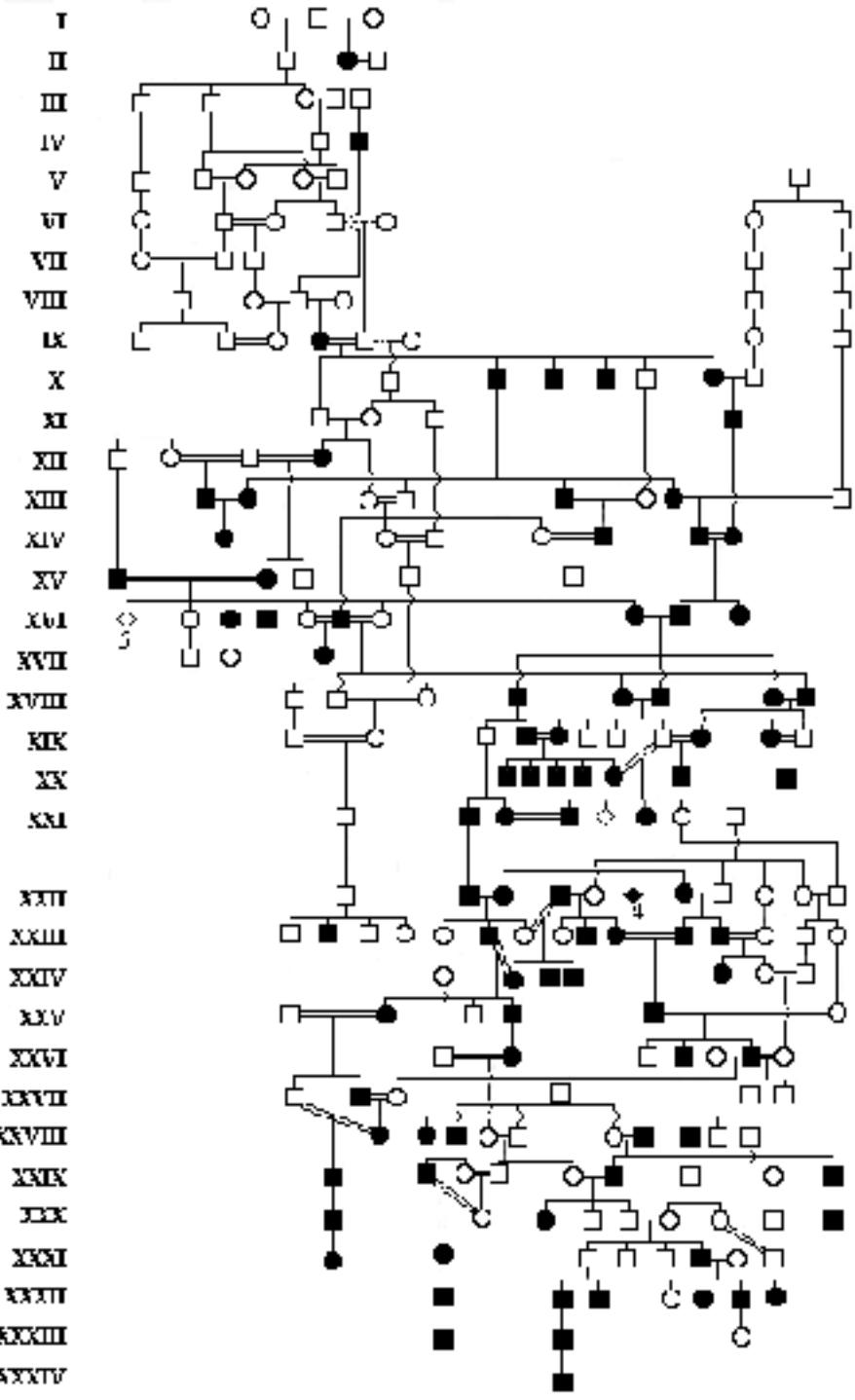


Phillip IV



Charles II

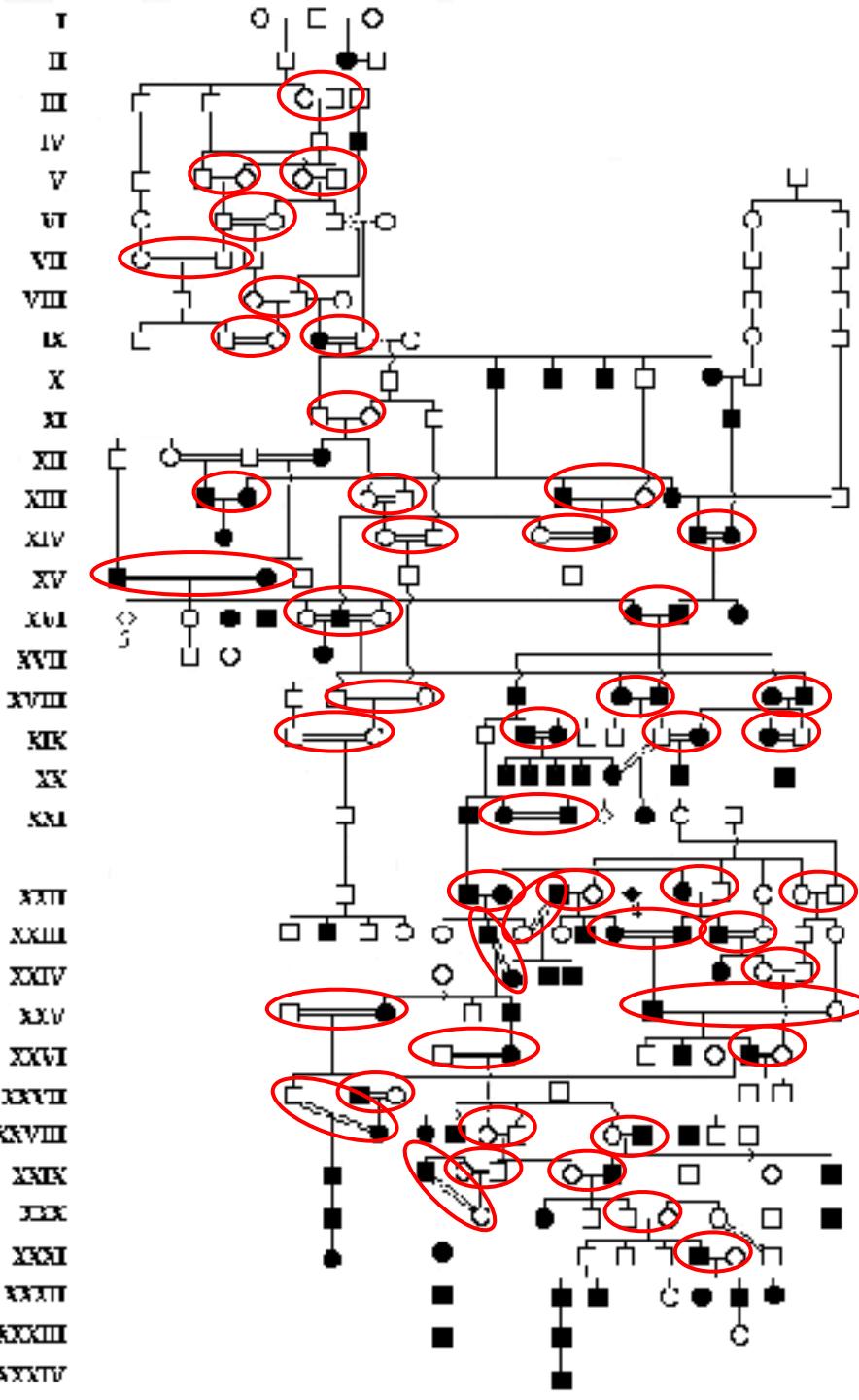
■ ● = Expression of the disorder



Royal Pedigree of the “Hapsburg Jaw”

- Inbreeding within the Royal Families of Europe was genetically “disastrous”
- Causing *genetic drift*: loss of allelic diversity

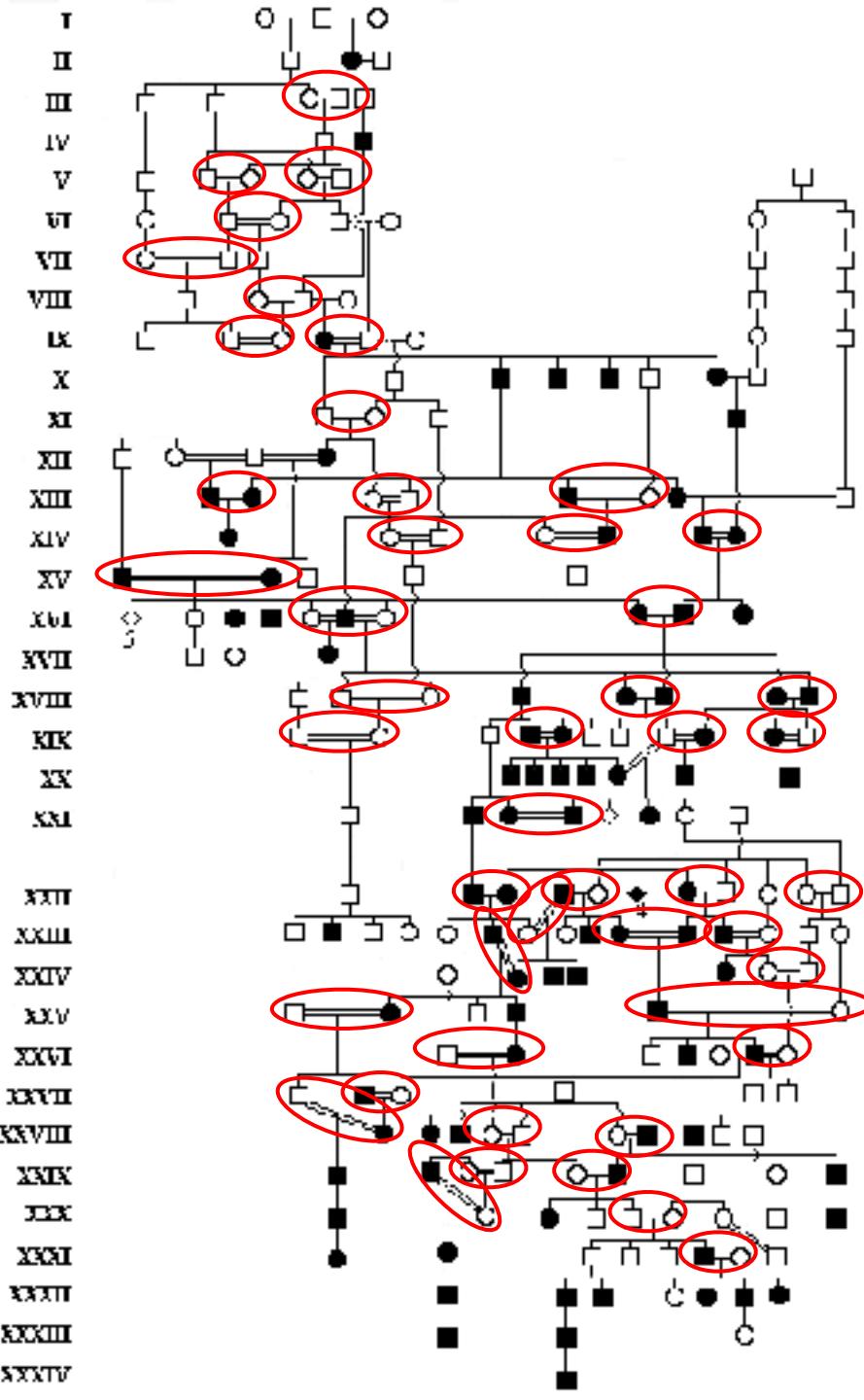
 = Expression of the disorder
 = Marriage with close relative



Royal Pedigree of the “Hapsburg Jaw”



- = Expression of the disorder
- = Marriage with close relative



The Habsburgs: exemplar human inbreeding?



Health 2013, 1(1), 114–121
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ORIGINAL ARTICLE

Royal dynasties as human inbreeding laboratories: the Habsburgs

PC Góbelas and G. Álvarez

The European royal dynasties of the Early Modern Age provide a useful framework for human inbreeding research. In this article, consanguineous marriage, inbreeding depression and the purging of deleterious alleles within a consanguineous population are investigated in the Habsburgs, a royal dynasty with a long history of consanguinity over generations. Genealogical information from a number of historical sources was used to compute kinship and inbreeding coefficients for the Habsburgs. The marriages contracted by the Habsburgs from 1450 to 1710 presented an extremely high mean kinship ($0.0628 \pm 0.05\%$), which was the result of the matrimonial policy conducted by the dynasty to establish political alliances through marriage. A strong inbreeding depression for both infant and child survival was detected in the pedigree of 71 Habsburg marriages in the period 1450–1800. The inbreeding load for child survival experienced a pronounced decrease from 3.98 ± 0.47 in the period 1450–1600 to 0.93 ± 0.62 in the period 1600–1800, but temporal changes in the inbreeding depression for infant survival were not evaluated. Such a reduction in inbreeding depression for child survival in a relatively small number of generations could be caused by elimination of deleterious alleles of a large effect according with predictions from purging models. The differential purge of the infant and child inbreeding loads suggest that the genetic basis of inbreeding depression was probably very different for infant and child survival in the Habsburg lineage. Our findings provide empirical support that human inbreeding depression for some fitness components might be purged by selection within consanguineous populations.

Heredit 2013, 1(1), 114–121; doi:10.1089/her.2013.25; published online 10 April 2013

Keywords: royal inbreeding; Habsburg dynasty; consanguineous marriage; inbreeding depression; purging of inbreeding depression

INTRODUCTION

In humans, the most extreme case of consanguinity can frequently found in royal dynasties. Indeed, brother-sister and parent-child marriages were not unusual in ancient royal dynasties such as the Egyptian pharaohs or the Persian dynasty (Middleton, 1962; Röhl, 1982a,b; Agar, 2003). Unfortunately, the study of inbreeding from ancient royal dynasties suffers from a number of limitations. First of all, it is difficult to construct full pedigrees from these dynasties because the genealogical information from the ancient record present many gaps and uncertainties. In the royal families of Egypt, for example, the pharaohs and many other and very many others, it is such a pity that it was not easy to establish unequivocally a successor who was the mother of his successor (Middleton, 1962; Röhl, 1982a,b). Even in the most ancient Egyptian royal family as the Phoenician dynasty, some fulfilling marriages are controversial because they are not well documented. Secondly, the adverse effect of consanguineous marriage on fitness traits such as survival and fertility seems to really incorporate in these dynasties because information on such characters is hardly available from the ancient record. A very interesting issue of the literature in the study of inbreeding from ancient dynasties is exemplified in an analysis of recessive loci of a number of royal members of the 18th Egyptian dynasty (Hawwa et al., 2010). The analysis of genetic relationships among individuals from those molecular studies allowed the identification of close relatives in such a way that a five-generation pedigree that included Alabaster and Tetikheima

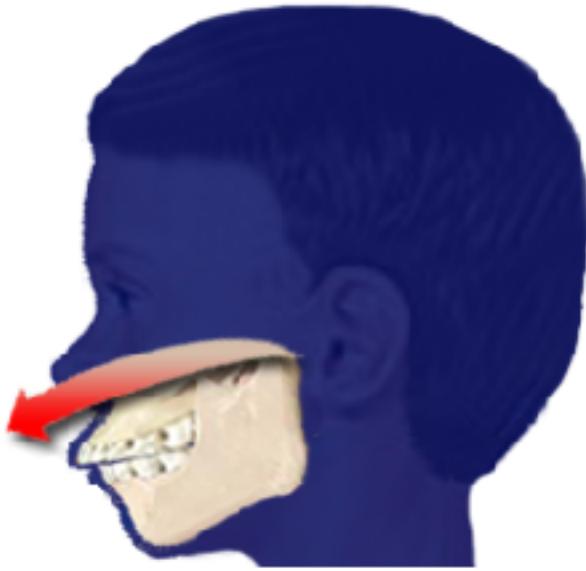
pharaohs was inferred. Further research on the ancient royal dynasties based on molecular genetic studies is needed before those royal dynasties can be used in breeding studies.

The European royal dynasties of the Early Modern Age, unlike the ancient dynasties, provide a useful framework for human inbreeding research. Firstly, it is known that close inbreeding such as uncle-niece, first cousins and other consanguineous unions occurred frequently in such dynasties along prolonged periods of time. Secondly, the genealogical records for the European dynasties available in historical sources are very extensive and accessible in such a way that such dynasties may be considered as pedigree populations where inbreeding coefficients can be computed with extreme precision from estimated pedigrees (Álvarez et al., 2010, 2011). Thirdly, the mortality and fertility data for European royal families are also complete in the historical sources so that such dynasties may be very useful for the study of inbreeding depression, that is, the reduced survival and fertility of offspring of related individuals caused by increased homozygosity for deleterious alleles (Charlesworth and Charlesworth, 1990; Charlesworth and Willis, 2009). In summary, most of the empirical evidence on inbreeding depression comes from the pedigree of first cousins because this is the most common form of consanguineous union in current human populations (Khoury et al., 1987; Bates and Ned, 1996; Bates and Black, 2000; Hanauer et al., 2011). The magnitude of inbreeding depression for inbreeding load higher than that corresponding to first cousins (inbreeding coefficient, $F=0.0625$) is not known so that, at present, the relationship

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Prognathism



Maxillary
prognathism



Jaw without
prognathism

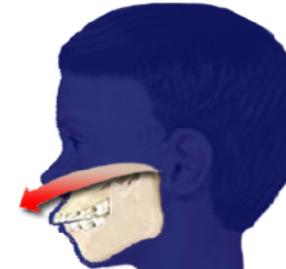


Mandibular
prognathism

Charles II dies November 1st 1700. Autopsy reveals: "did not contain a single drop of blood; his heart was the size of a peppercorn; his lungs corroded; his intestines rotten and gangrenous; he had a single testicle, black as coal, and his head was full of water"

Prognathism

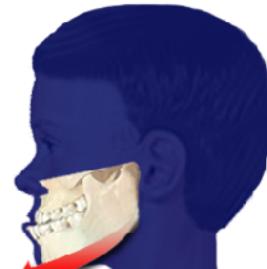
- Effects
 - Mastication = chewing
 - Speech
 - Psychosocial well-being
- Causes:
 - Hyper- or hypoplasia of maxilla or mandibula
 - Or combination
- Treatment:
 - Braces
 - Surgery



Maxillary
prognathism



Jaw without
prognathism



Mandibular
prognathism

Inbreeding

- Inbreeding coefficient (F): how much of your DNA you share with someone else

Relationship	Average % DNA Shared	Range
Identical Twin	100%	N/A
Parent / Child Full Sibling	50%	Varies by specific relationship
Grandparent / Grandchild Aunt / Uncle Niece / Nephew Half Sibling	25%	Varies by specific relationship
1st Cousin	12.5%	7.31% - 13.8%
1st Cousin once removed	6.25%	3.3% - 8.51%
2nd Cousin	3.13%	2.85% - 5.04%
2nd Cousin once removed	1.5%	0.57% - 2.54%
3rd Cousin	0.78%	0.3% - 2.0%
4th Cousin	0.20%	0.07% - 0.5%
5th Cousin	0.05%	Variable
6th Cousin	0.01%	Variable

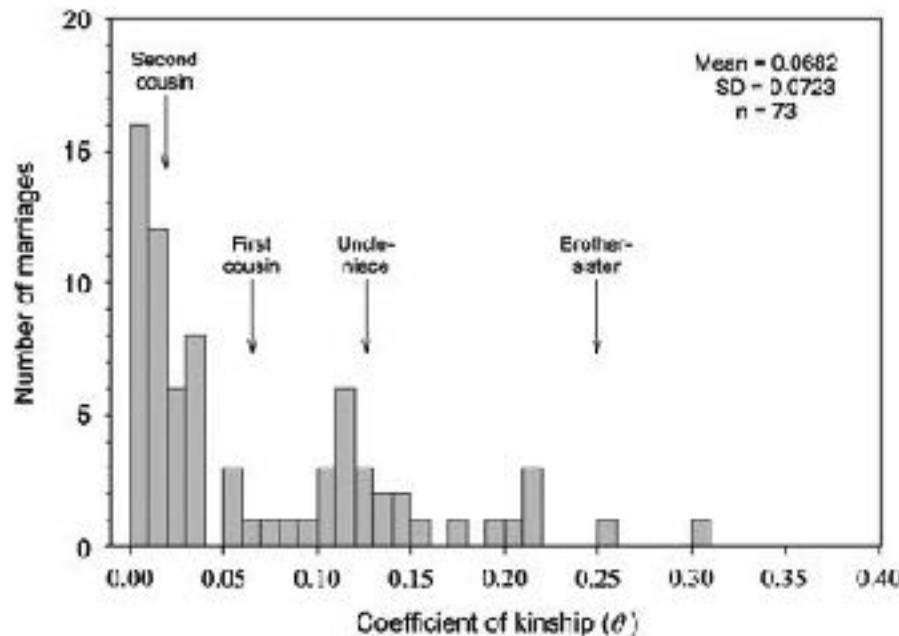
Inbreeding

- Inbreeding coefficient (F): how much of your DNA you share with someone else

Hereditas (2013) 1(5): 104–12
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ORIGINAL ARTICLE
Royal dynasties as human inbreeding laboratories:
the Habsburgs

J.C. Ceballos and G. Álvarez



Álvarez, G., et al. PLoS ONE; 4(4):e5174 2009; <https://doi.org/10.1371/journal.pone.0005174>

<https://customercare.23andme.com/hc/en-us/articles/212170668-Average-percent-DNA-shared-between-relatives>

Inbreeding

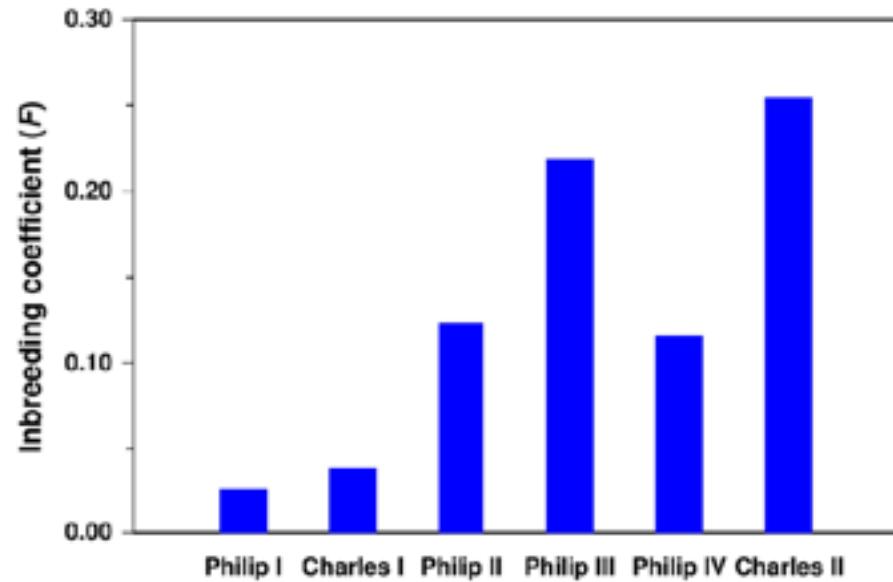
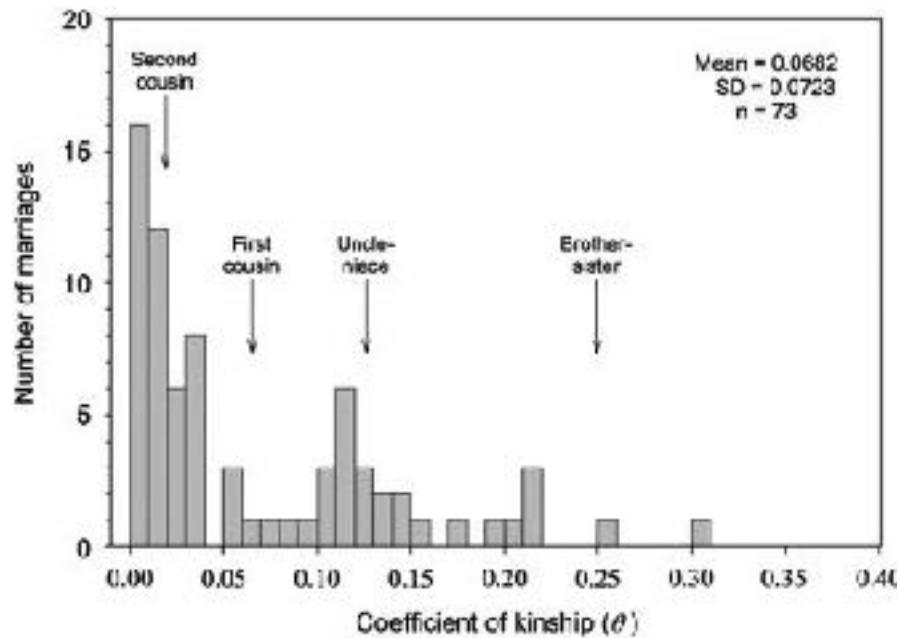
- Inbreeding coefficient (F): how much of your DNA you share with someone else

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ORIGINAL ARTICLE

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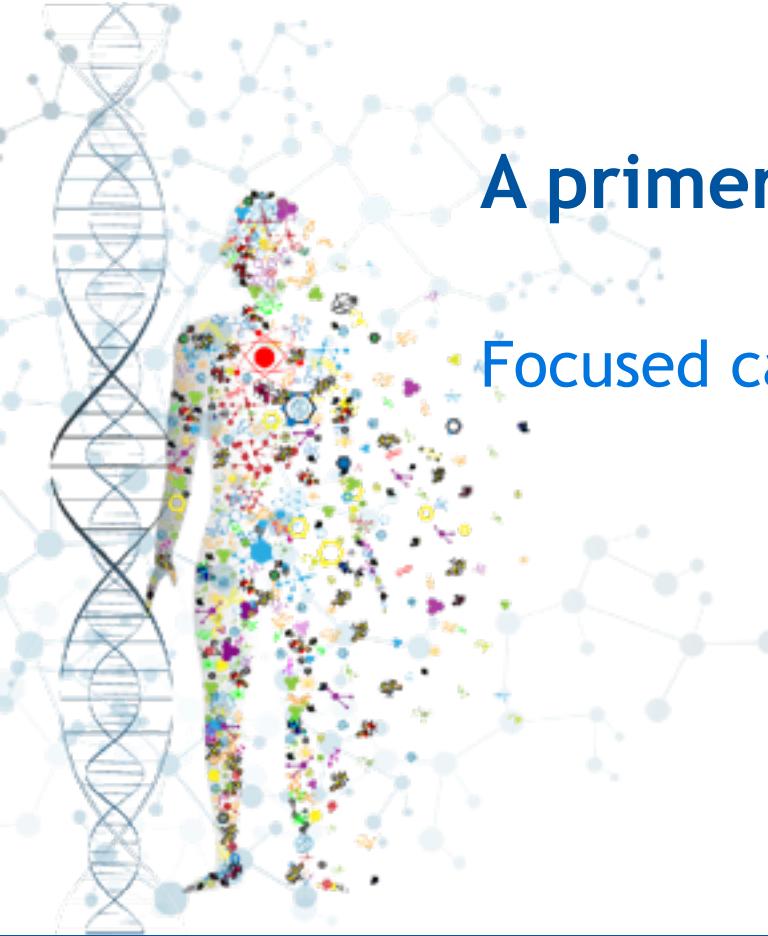
JC Ceballos and G Alvarez











A primer in (complex) human genetics

Focused cardiovascular disease

Sander W. van der Laan, PhD

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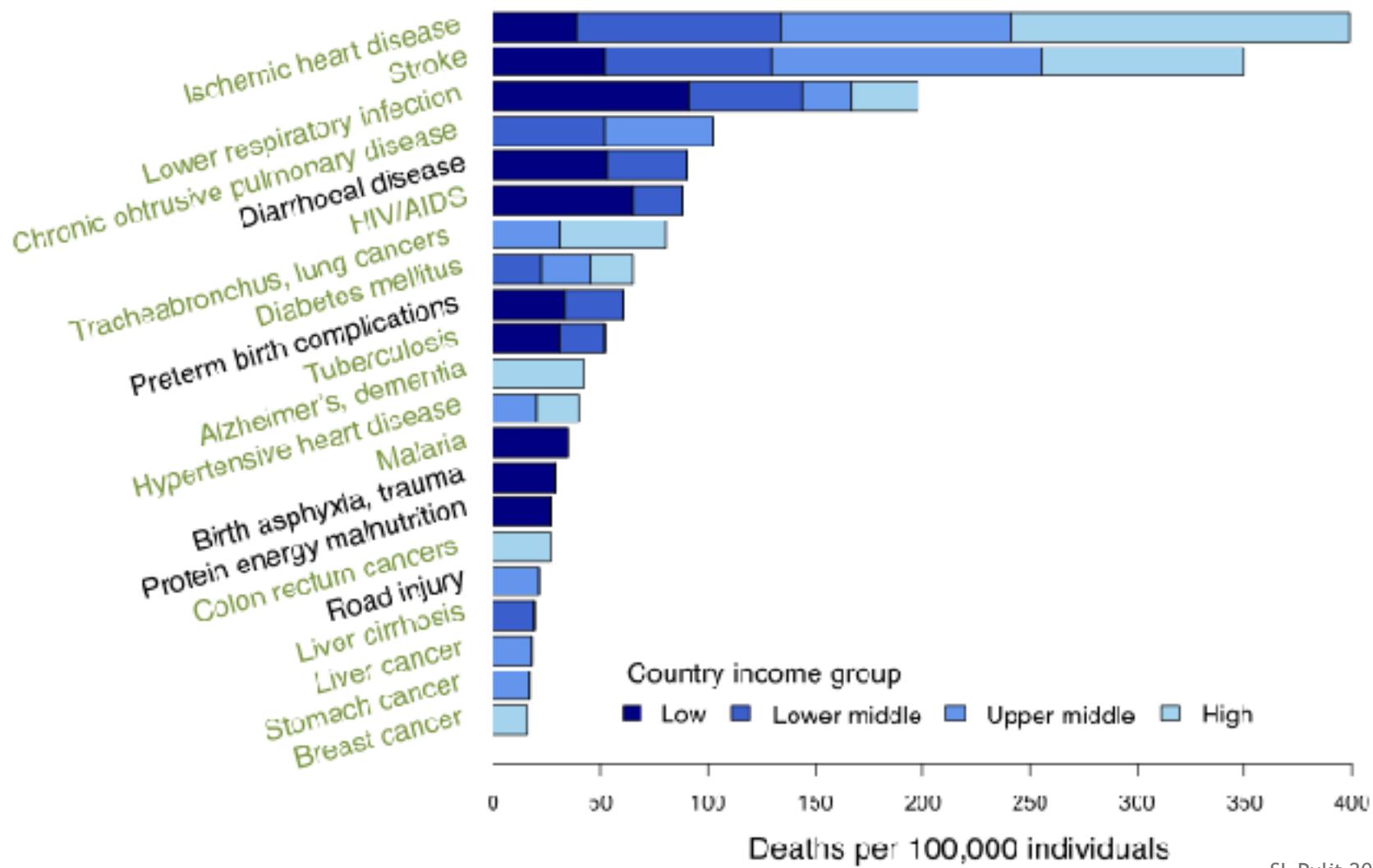


UMC Utrecht
Center for Circulatory Health

UMC Utrecht
Athero-Express Biobank Studies



Human disease around the globe



SL Pulit 2016

The spectrum(s) of disease

Age of onset

Early onset

Late onset

Genetic architecture

One gene

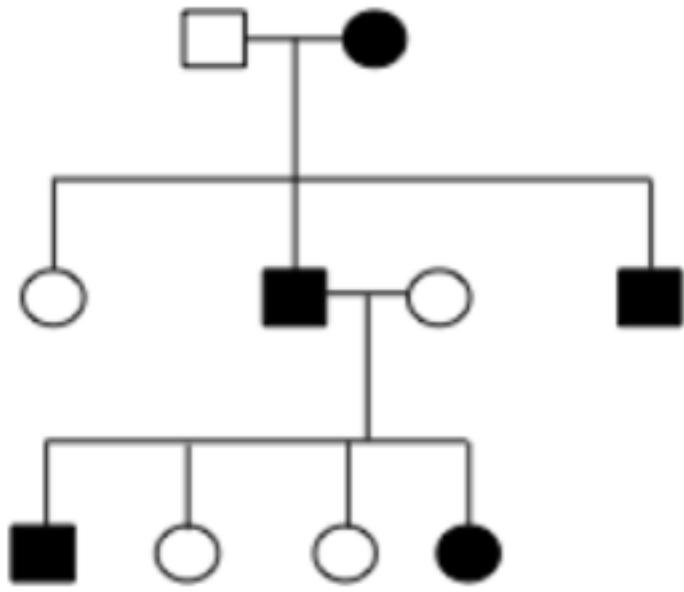
Many genes

Environmental architecture

No role

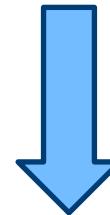
Major role

Rare (Mendelian) diseases



family-based studies

Genotype



Disease



Environment

Rare (Mendelian) diseases

1983

A polymorphic DNA marker genetically linked to Huntington's disease

James F. Gusella^{*}, Nancy S. Wexler^{†‡}, P. Michael Conneally[‡], Susan L. Naylor^{*}, Mary Anne Anderson^{*}, Rudolph E. Tanzi^{*}, Paul C. Watkins^{*}, Kathleen Ottina^{*}, Margaret R. Wallace^{*}, Alan Y. Sakaguchi^{*}, Anne B. Young^{*}, Ira Shoulson^{*}, Ernesto Bonilla[§] & Joseph B. Martin^{*}

* Neurology Department and Genetics Unit, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts

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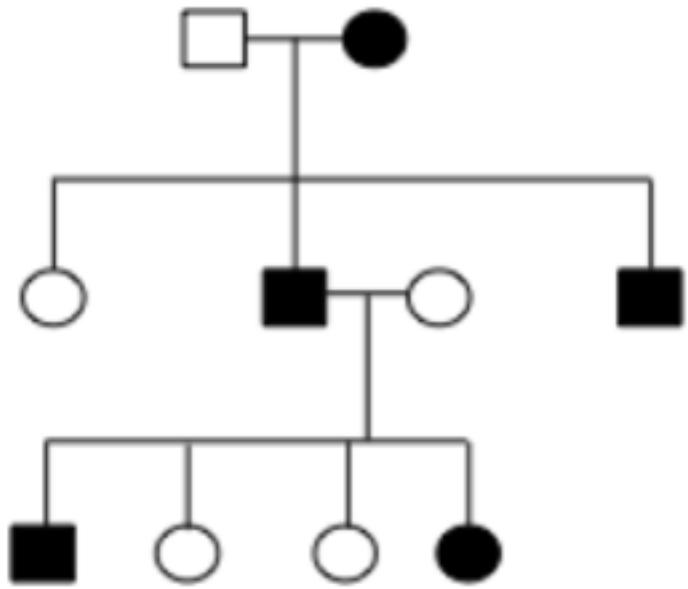
| Venezuela Collaborative Huntington's Disease Project[¶]

Family studies show that the Huntington's disease gene is linked to a polymorphic DNA marker that maps chromosome 4. The chromosomal localization of the Huntington's disease gene is the first step in using recombinant DNA technology to identify the primary genetic defect in this disorder.

1989

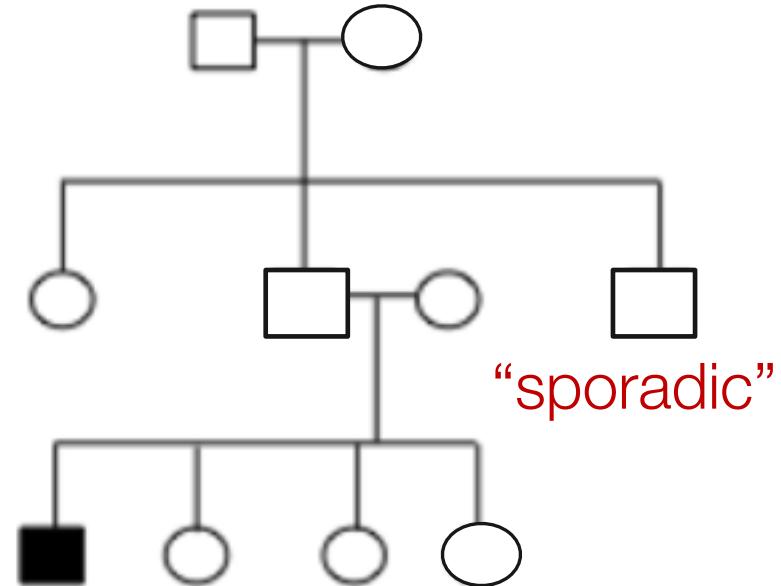
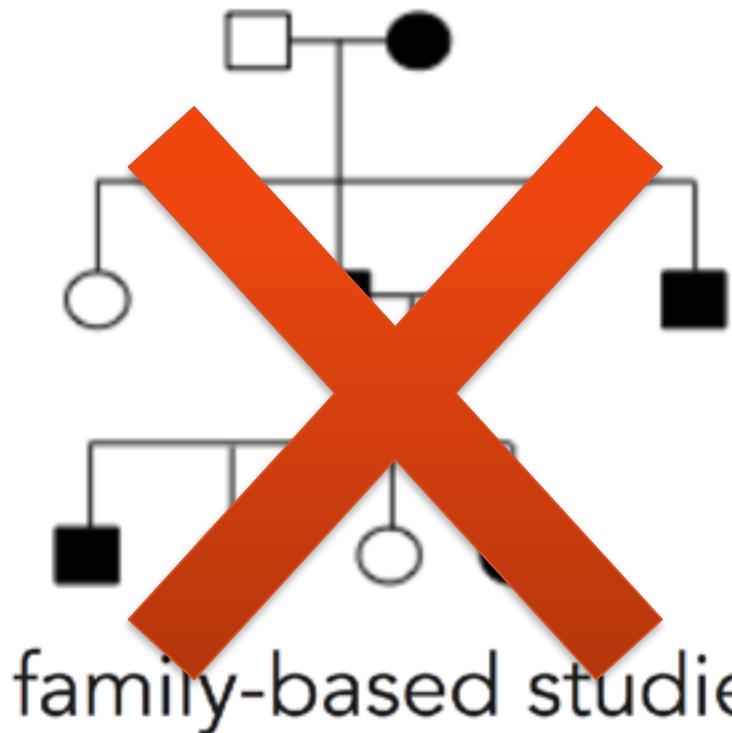


Common (complex) diseases



family-based studies

Common (complex) diseases



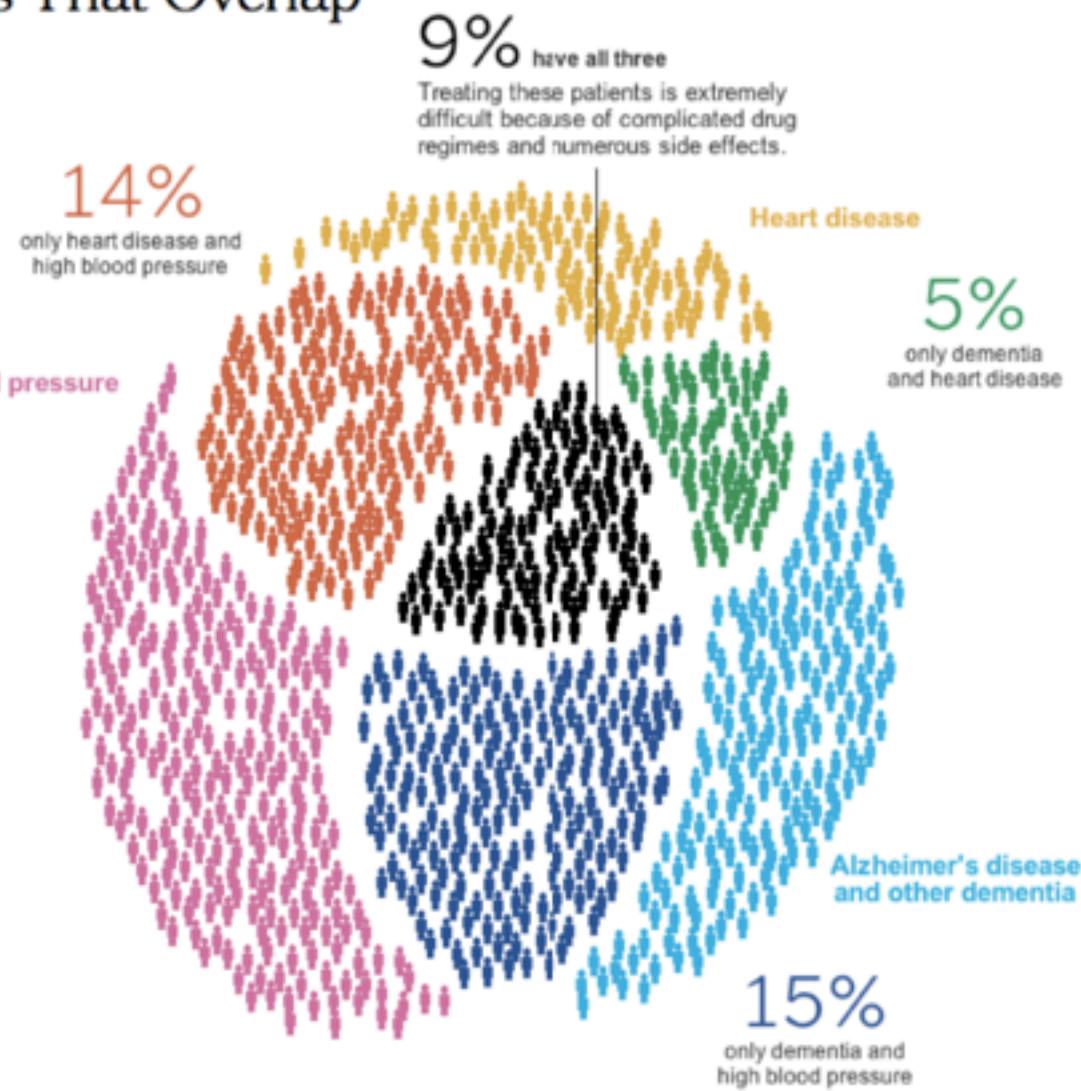
The challenges of common disease

- Heterogeneity
- Late (or broad age range for) onset
- Interaction of genes and environment (multifactorial)
- Overlap with other diseases

For the Elderly, Diseases That Overlap

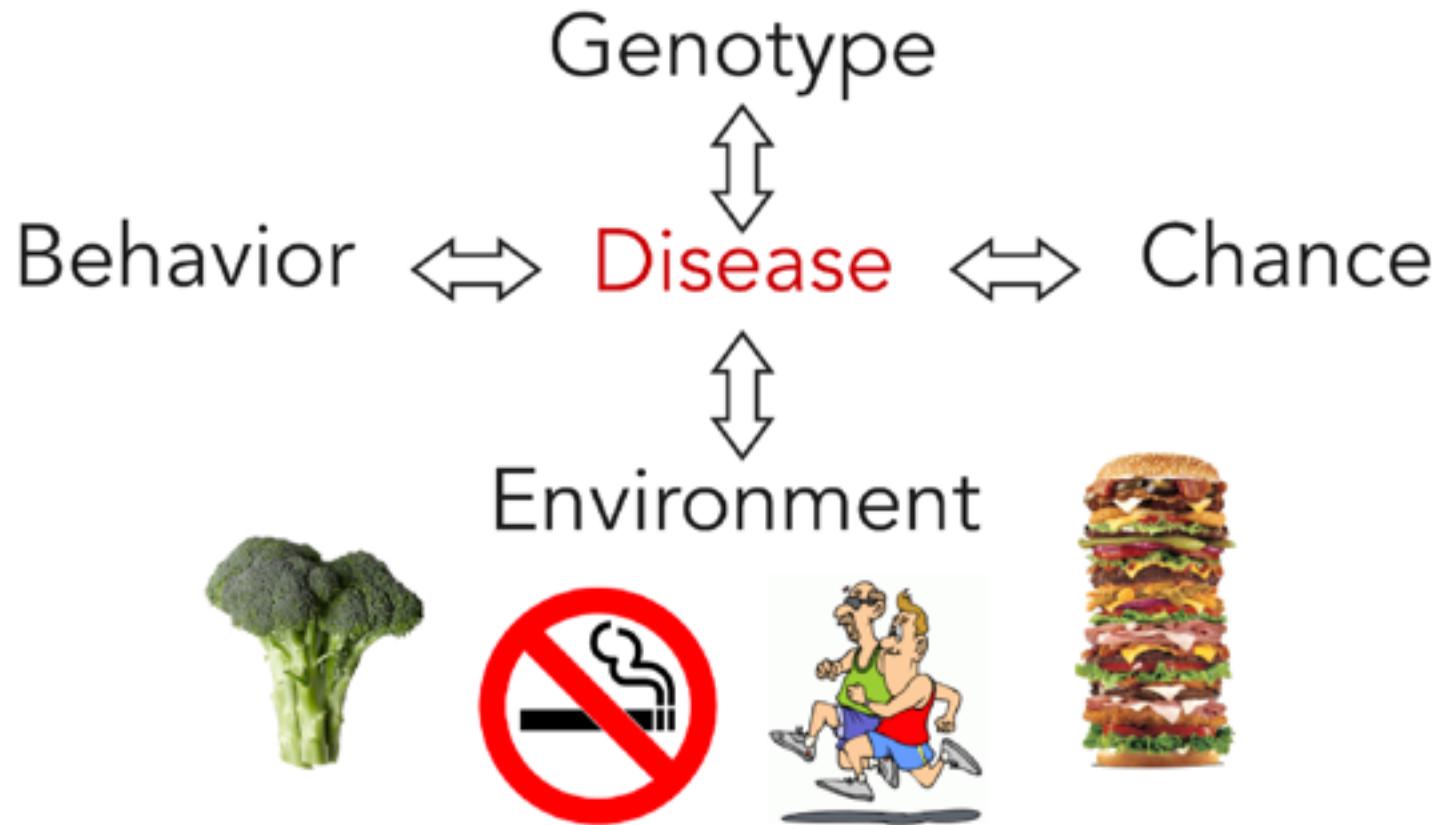
1 2 3 4 5 6 7 NEXT »

Researchers are beginning to focus more intently on the overlaps and possible interconnections, and some scientists argue that it may not be possible to treat dementia without treating vascular problems.

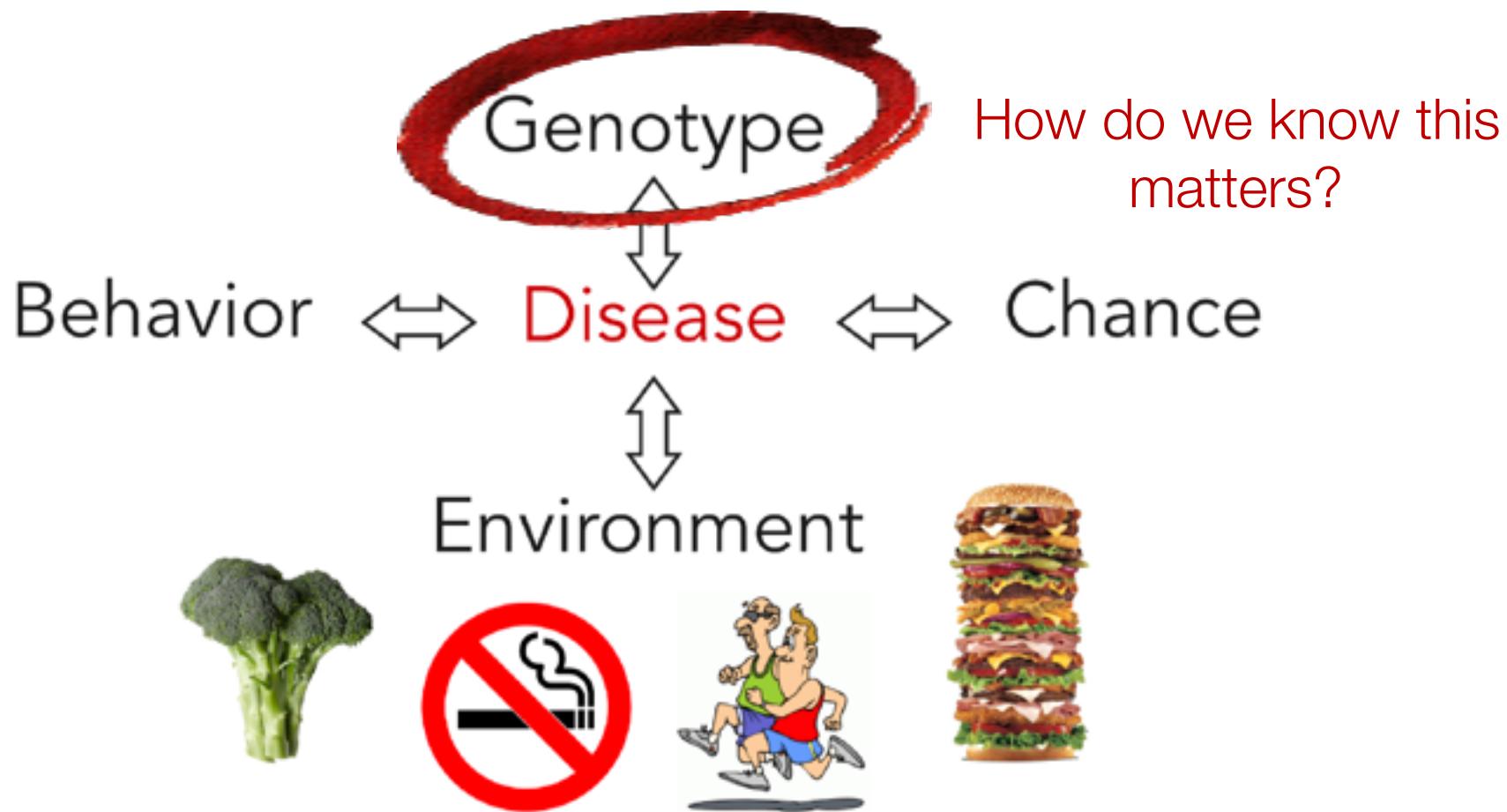


The New York Times, 15 April 2013

Multifactorial disease



Multifactorial disease

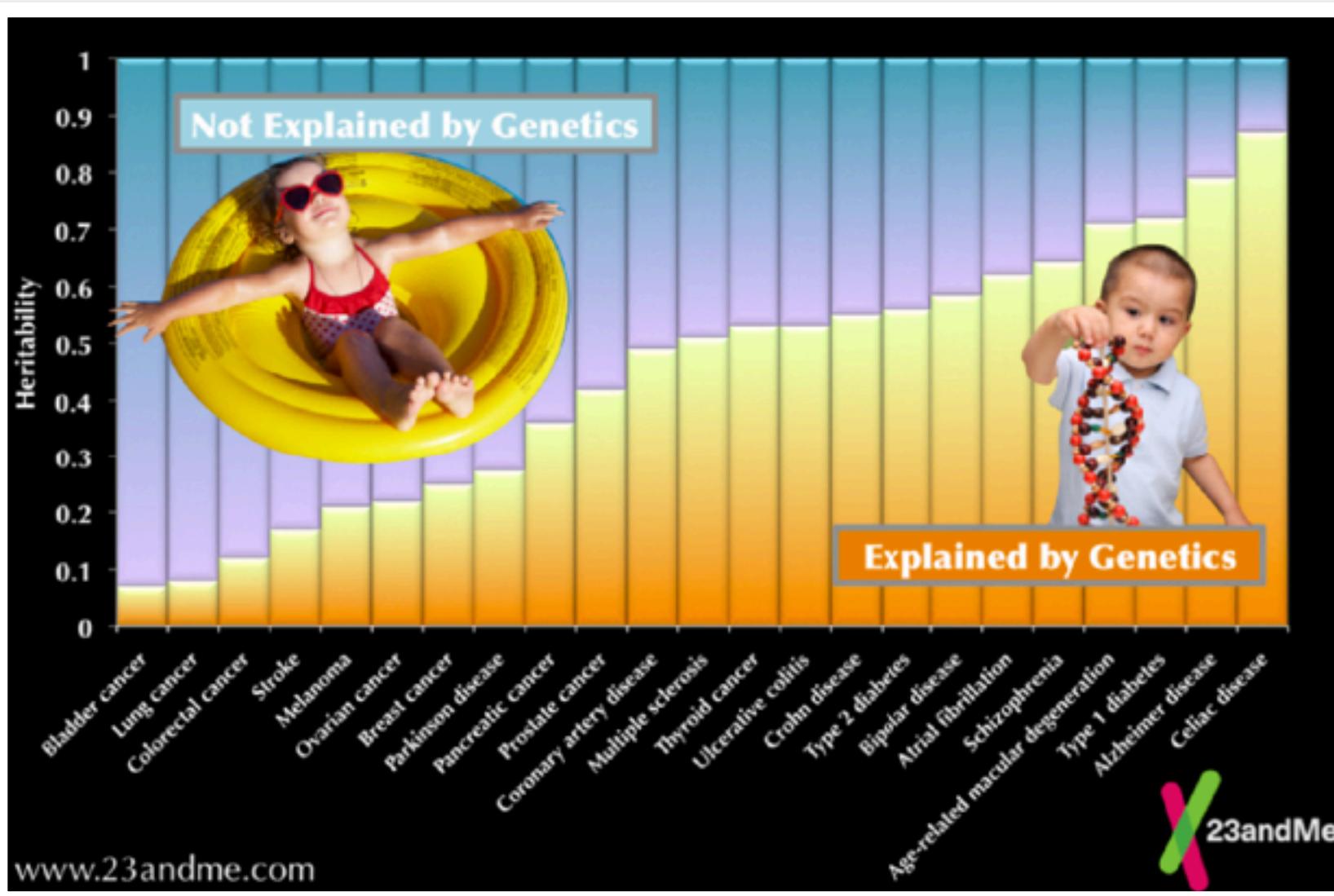


Heritability

Given I am a patient, what is risk of disease for...

	Type 1	Type 2
Your neighbor (unrelated)?	0.4%	5-10%
Your sibling?	6%	30%
Your identical twin?	30-50%	>80%

The range of heritability estimates



Family history

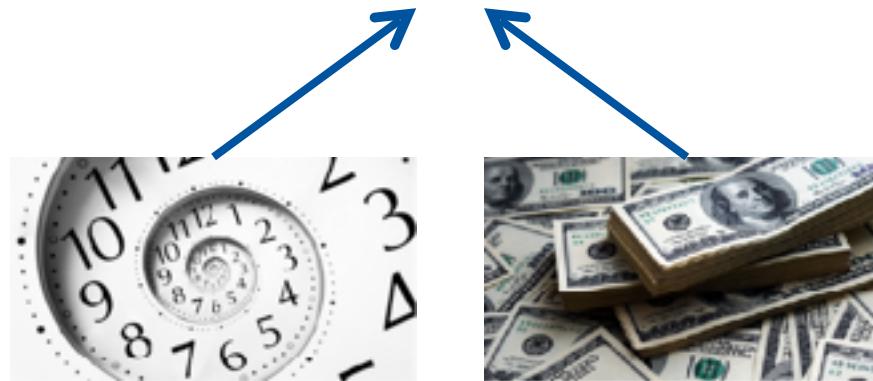
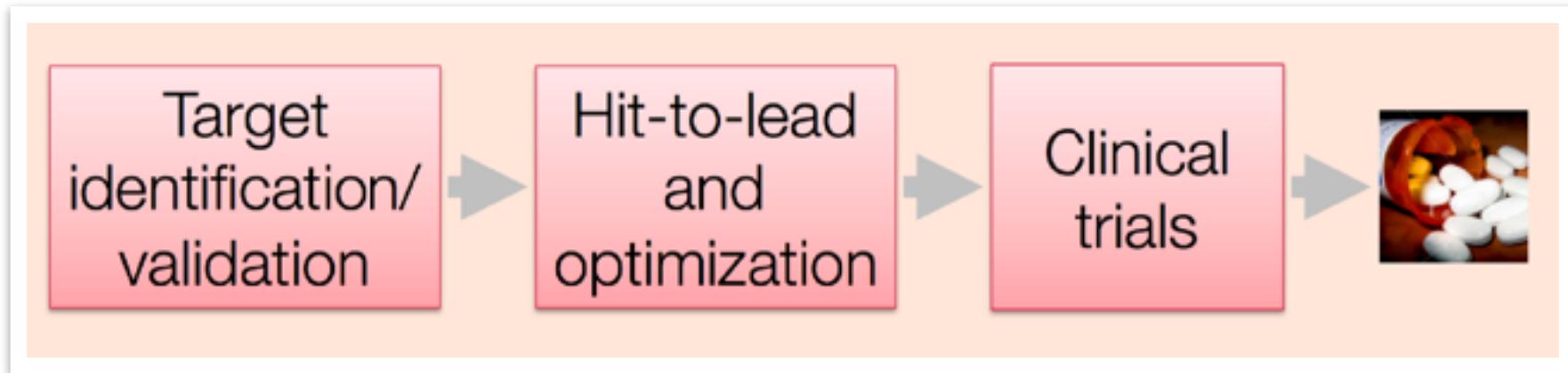
- Framingham Heart Study | www.framinghamheartstudy.org
 - A positive history of cardiovascular disease and associated risk factors tend to aggregate in families
 - Familial aggregation heritability of CVD estimated $\geq 90\%$ (before 46 years)
 - Family history is an independent risk factor (FHS)
 - Positive family history associated with pre-clinical atherosclerosis as measured by carotid IMT, $h^2 \approx 0.35$
- High concordance rate among monozygotic twins, compared to dizygotic twins
- Heritability of atherosclerosis (carotid IMT) $h^2 \approx 0.21-0.64$ and is increased by age and cardiovascular risk factors

There is clearly a heritability factor for atherosclerotic and consequent cardiovascular disease

Why do some individuals have a higher risk for a disease than others?

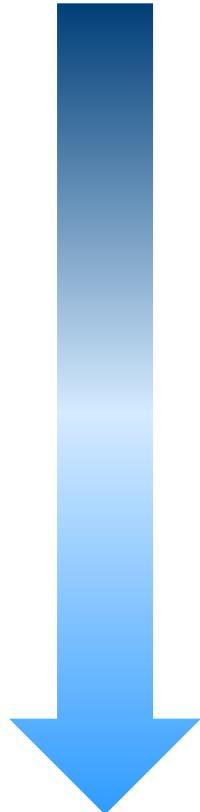
How can we alleviate disease burden in the human population?

Drug development



What's the modern goal of genetics?

- Understanding true causal disease pathways
 - Identify risk factors
 - Inform novel research directions
 - Enable rational and efficient drug development
- Precision medicine
 - Evaluate individual disease risk
 - Early disease identification or prevention
 - Understand patient's therapeutic response



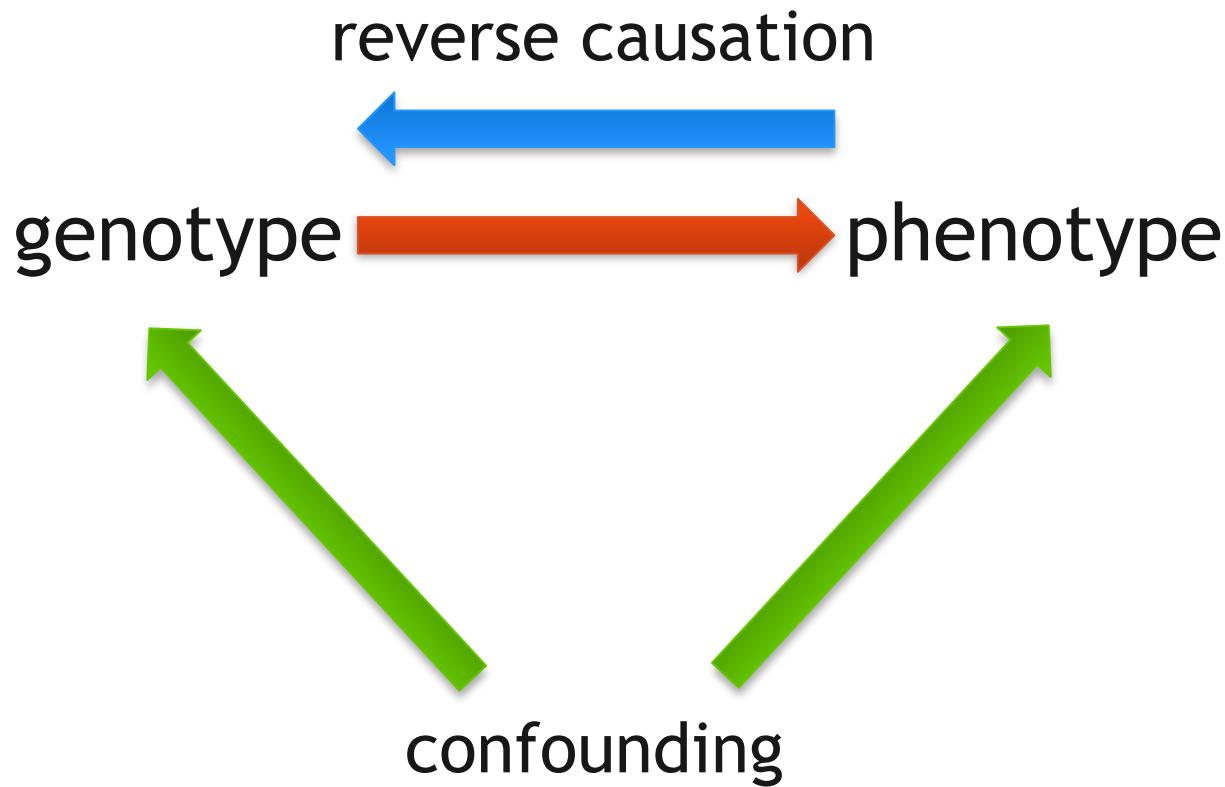
Why genetics at all?

- Genotypes are randomly assigned at meiosis
 - Nature's randomized clinical trial
- Genotypes are fixed and unaltered by the disease
 - Exception: somatic mutations in cancer
- We have become increasingly good at measuring genotypes
 - Lots and lots of data

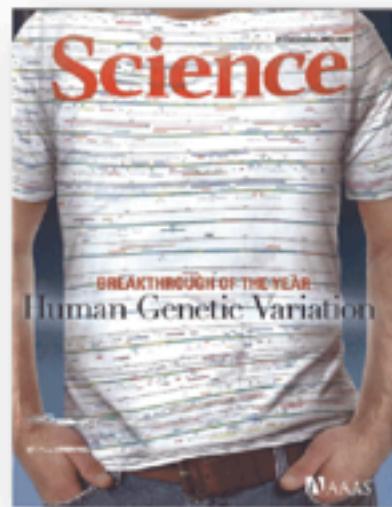
The limitations of genetics

genotype  phenotype

The limitations of genetics



Where we've been and where we are

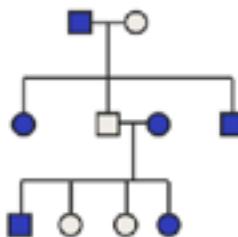


Linkage analysis

Candidate gene studies

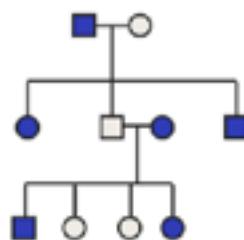
GWAS

Sequencing





Linkage analysis



Linkage-analysis

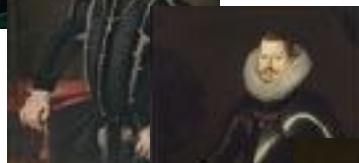
- Trace disease through families



Charles V



Phillip II



Phillip III

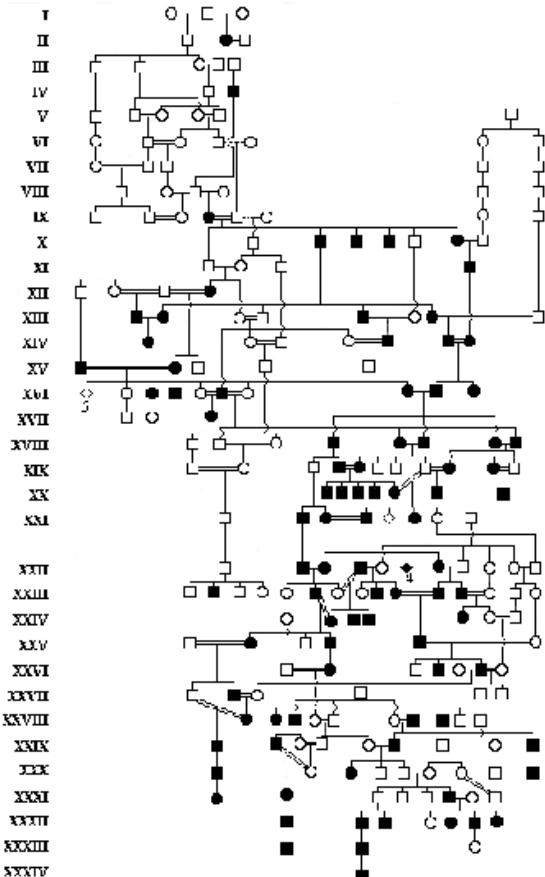


Phillip IV



Charles II

= Expression of the disorder



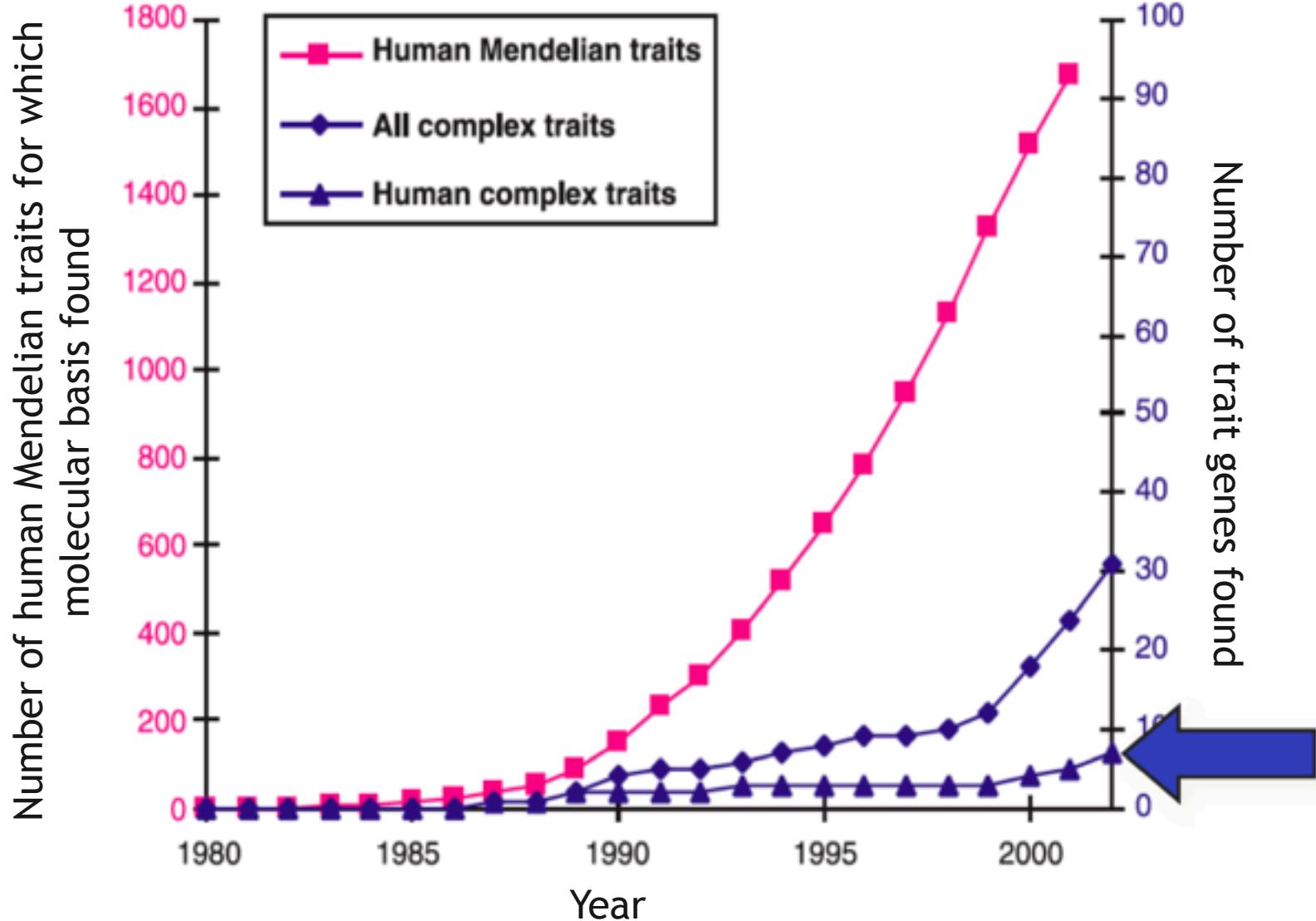
Maxillary
prognathism

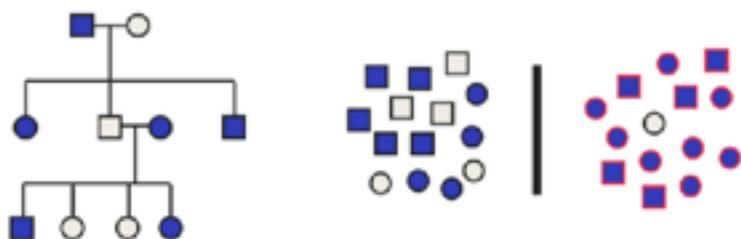


Jaw without
prognathism



Mandibular
prognathism





Candidate gene study

- Pick a gene that might have a role in your disease
arbitrary
- Genotype individuals at a few sites around that gene
 - Typically 1,000 - 2,000 samples
no power
- Test genetic sites for association

A poor history of candidate gene studies

March/April 2002 • Vol. 4 • No. 2

review

A comprehensive review of genetic association studies

Joel N. Hirschhorn, MD, PhD^{1–3}, Kirk Lohmueller¹, Edward Byrne¹, and Kurt Hirschhorn, MD⁴

Most common diseases are complex genetic traits, with multiple genetic and environmental components contributing to susceptibility. It has been proposed that common genetic variants, including single nucleotide polymorphisms (SNPs), influence susceptibility to common disease. This proposal has begun to be tested in numerous studies of association between genetic variation at these common DNA polymorphisms and variation in disease susceptibility. We have performed an extensive review of such association studies. We find that over 600 positive associations between common gene variants and disease have been reported; these associations, if correct, would have tremendous importance for the prevention, prediction, and treatment of most common diseases. However, most reported associations are not robust: of the 166 putative associations which have been studied three or more times, only 6 have been consistently replicated. Interestingly, of the remaining 160 associations, well over half were observed again one or more times. We discuss the possible reasons for this irreproducibility and suggest guidelines for performing and interpreting genetic association studies. In particular, we emphasize the need for caution in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility. *Genet Med* 2002;4(2):45–61.

Key Words: human genetics, association studies, common disease, polymorphisms

Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

PloS Medicine, 2005

The candidate gene problem:

- Lack of statistical rigor (effect size)
- Lack of large samples
- Lack of data quality control
- Lack of replication data
- Lack of community-wide standards
- Population stratification

Need systematic, unbiased approach

Important side note: this still happens

OPEN  ACCESS Freely available online

PLOS GENETICS

AVPR1a and SLC6A4 Gene Polymorphisms Are Associated with Creative Dance Performance

Psychiatr Q (2014) 85:257–265
DOI 10.1007/s11126-013-9287-x

ORIGINAL PAPER

The 2-Repeat Allele of the MAOA Gene Confers an Increased Risk for Shooting and Stabbing Behaviors

SCIENTIFIC REPORTS



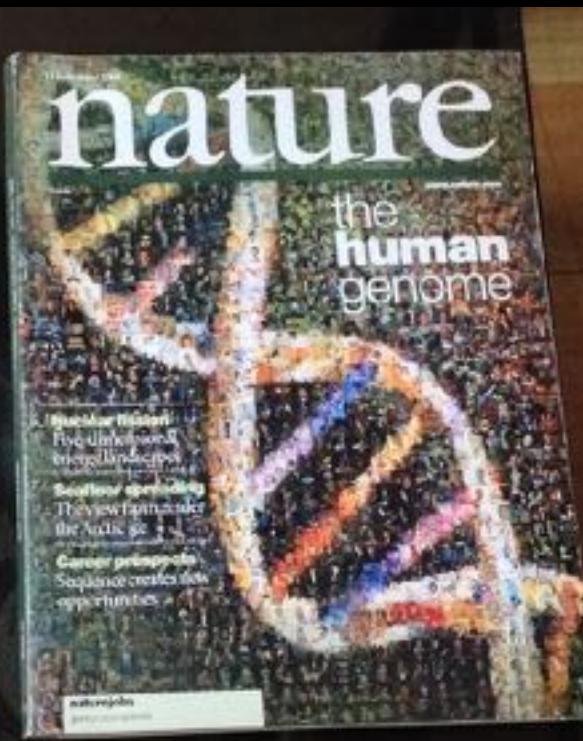
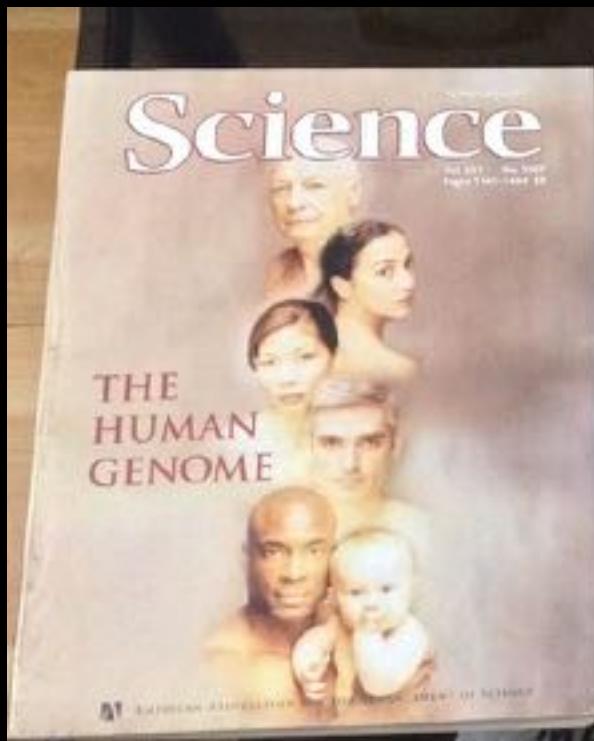
OPEN The association between romantic relationship status and 5-HT1A gene in young adults

SUBJECT AREAS:
HUMAN BEHAVIOR
BEHAVIORAL GENETICS



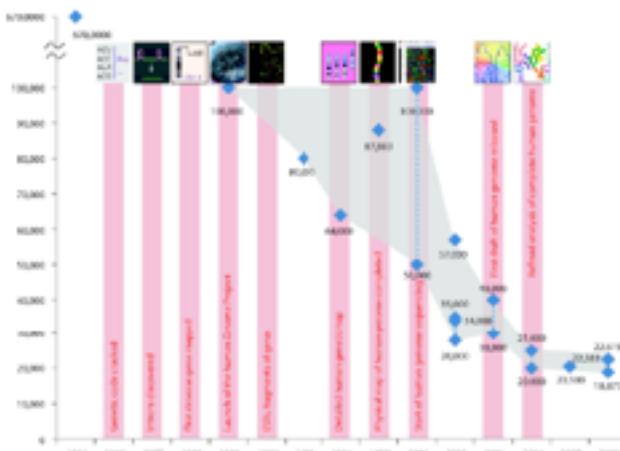
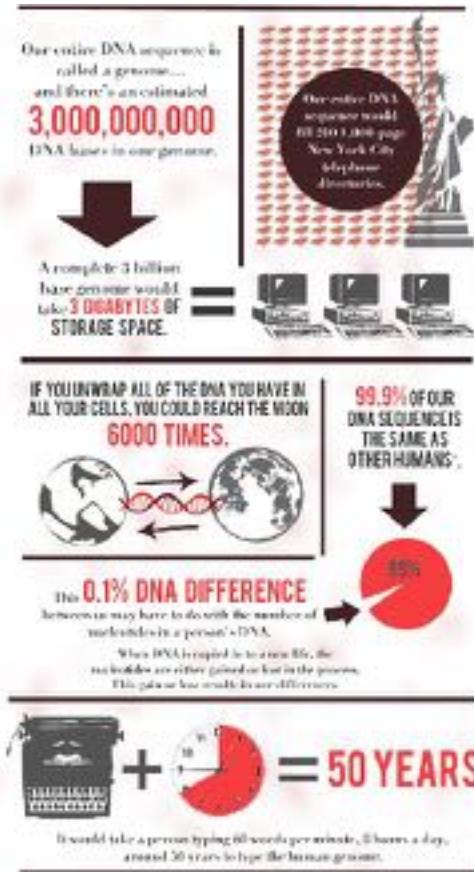


The Human Genome Project “paid forward” and paved the way for modern day genomics



Human Genome: *some statistics*

- 3.2 billion base pairs in the haploid genome
- ≈ 18,000-25,000 genes
 - ≈23,000 coding for proteins
 - Only 1.5% of the total genome
- Rest of the genome:
 - Non-coding RNA (rRNA, tRNA)
 - Regulatory sequences, e.g. promoter, enhancer regions
 - Repetitive elements and other variations
 - Transposable elements
- (So there's no such thing as “junk DNA”...)



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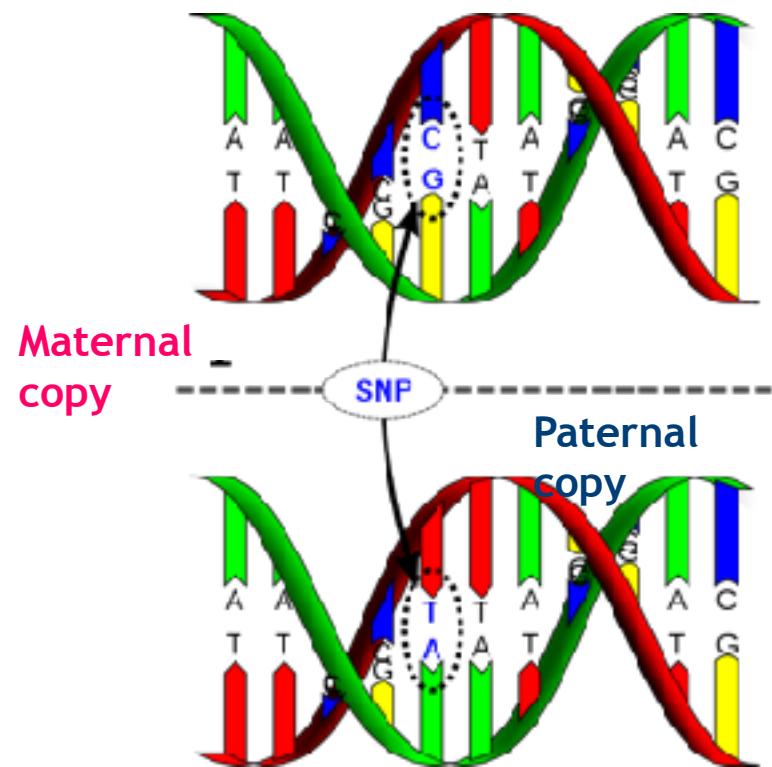
Most of genetic variation is due to *single nucleotide polymorphisms (SNPs)* --single base changes that are common in the general population

Single-Nucleotide Polymorphism

- “one base pair variation”
 - > 1% general population
(common)
 - ≈80 million SNPs (≈0.25% genome)
 - Makes you and me unique
 - Most common type of genetic variation



www.hapmap.org



Human genome: *individual variations*

- Human genome is ~99 % similar between individuals
- 0.5-1% different
- ~100 million variants

articles

A map of human genome sequence variation containing 1.42 million single nucleotide polymorphisms

The International SNP Map Working Group*

* A full list of authors appears at the end of this paper.

We describe a map of 1.42 million single nucleotide polymorphisms (SNPs) distributed throughout the human genome, providing an average density on available sequence of one SNP every 1.9 kilobases. These SNPs were primarily discovered by two projects: The SNP Consortium and the analysis of clone overlaps by the International Human Genome Sequencing Consortium. The map integrates all publicly available SNPs with described genes and other genomic features. We estimate that 60,000 SNPs fall within exon (coding and untranslated regions), and 85% of exons are within 5 kb of the nearest SNP. Nucleotide diversity varies greatly across the genome, in a manner broadly consistent with a standard population genetic model of human history. This high-density SNP map provides a public resource for defining haplotype variation across the genome, and should help to identify biomedically important genes for diagnosis and therapy.

The International HapMap Project

Phase I

1.1 million SNPs

270 individuals from 4 populations



Phase II

3.1 million SNPs

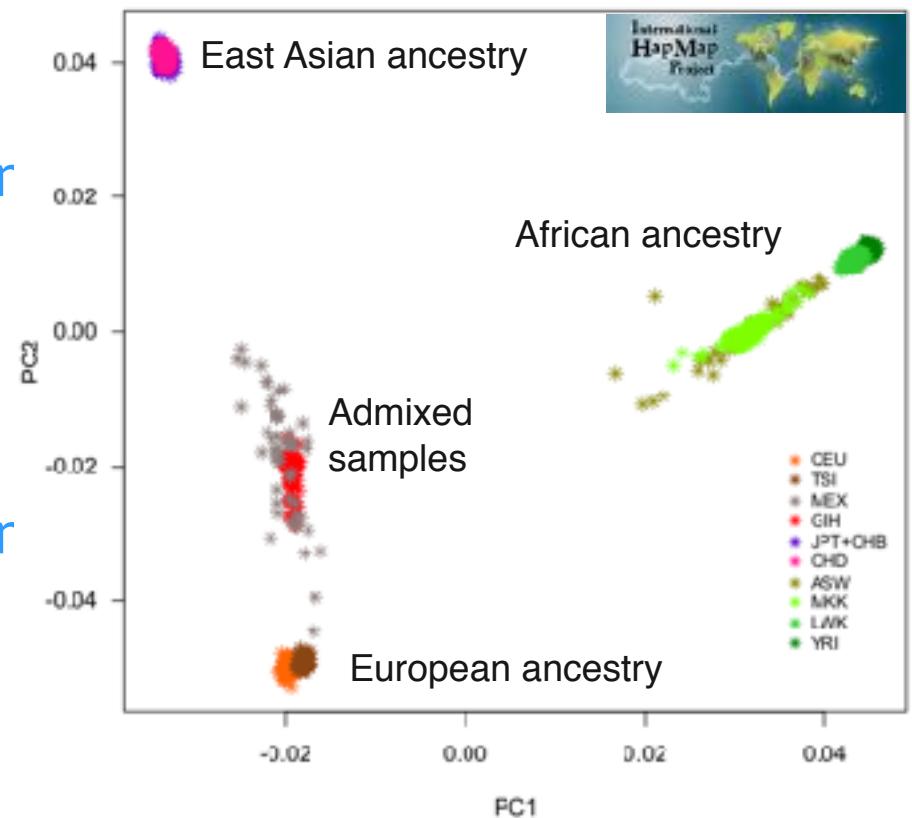
270 individuals from 4 populations



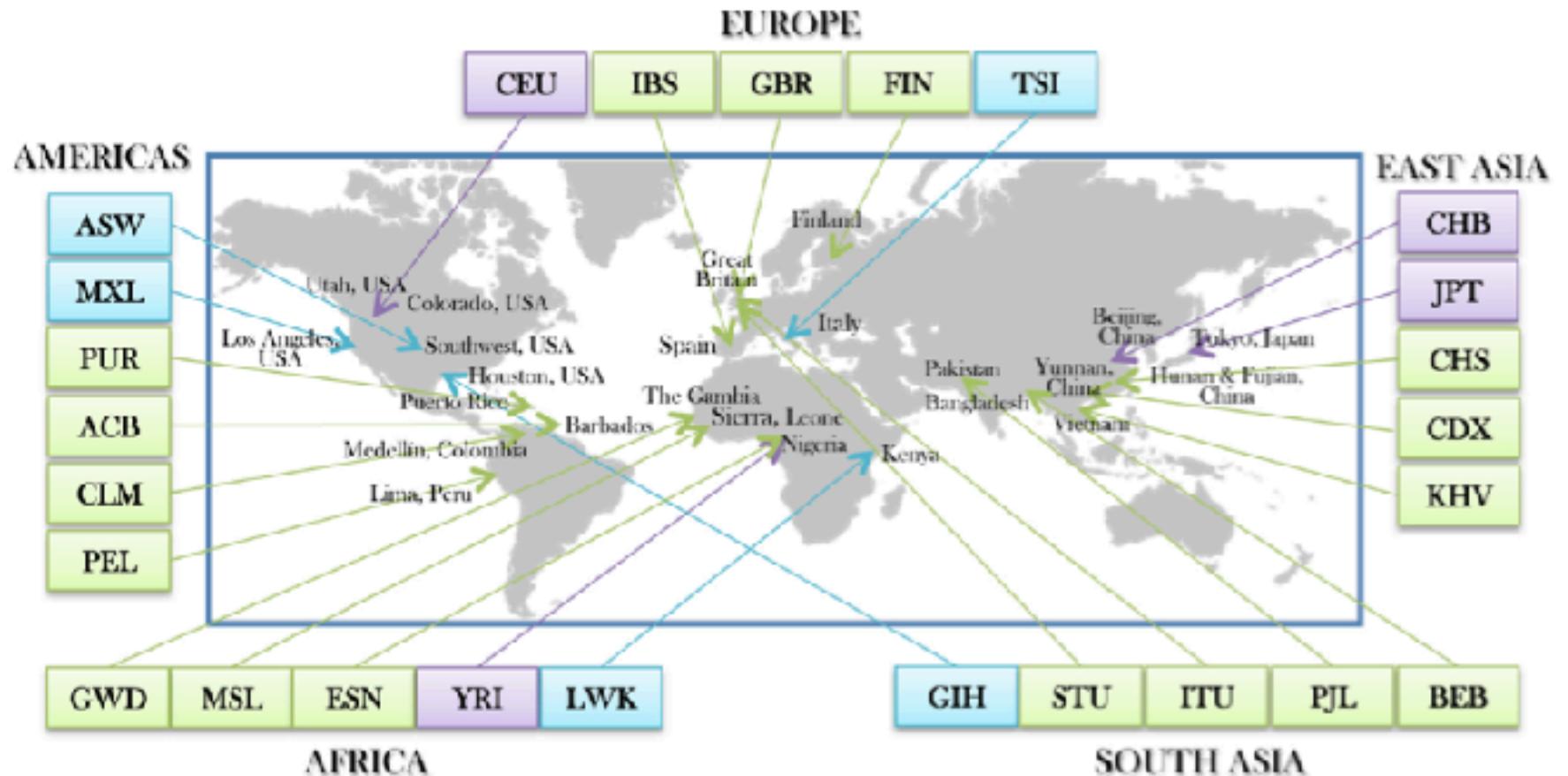
Phase III

1.6 million SNPs

1,184 individuals from 11 populations



The 1000 Genomes Project

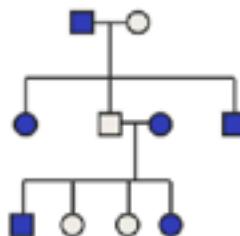
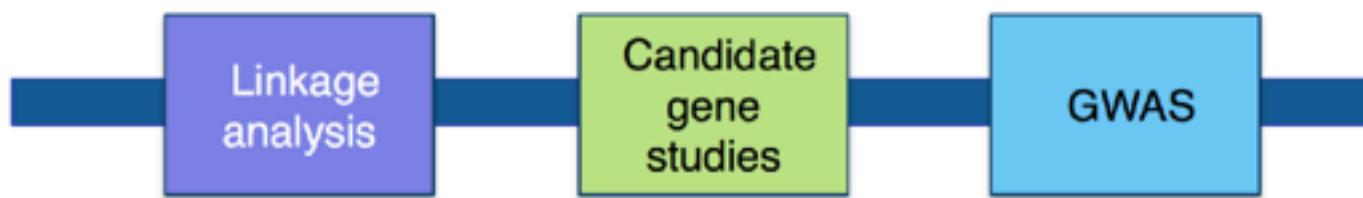
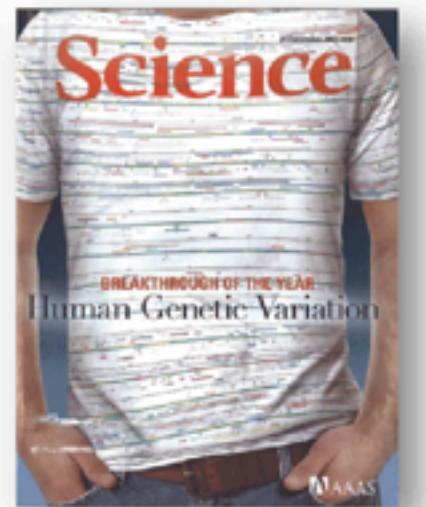


International HapMap Population

HapMap 3 Population

New 1000 Genomics Population





Common variant, common disease hypothesis

- Most common diseases happen later in life
- If common variants are not selected against, they may associate to late-onset (after reproduction) disease
- Common variants are easier to find and characterize

The beginnings of GWAS

HapMap Phase I

HapMap Phase II

SNP arrays

WTCCC GWAS

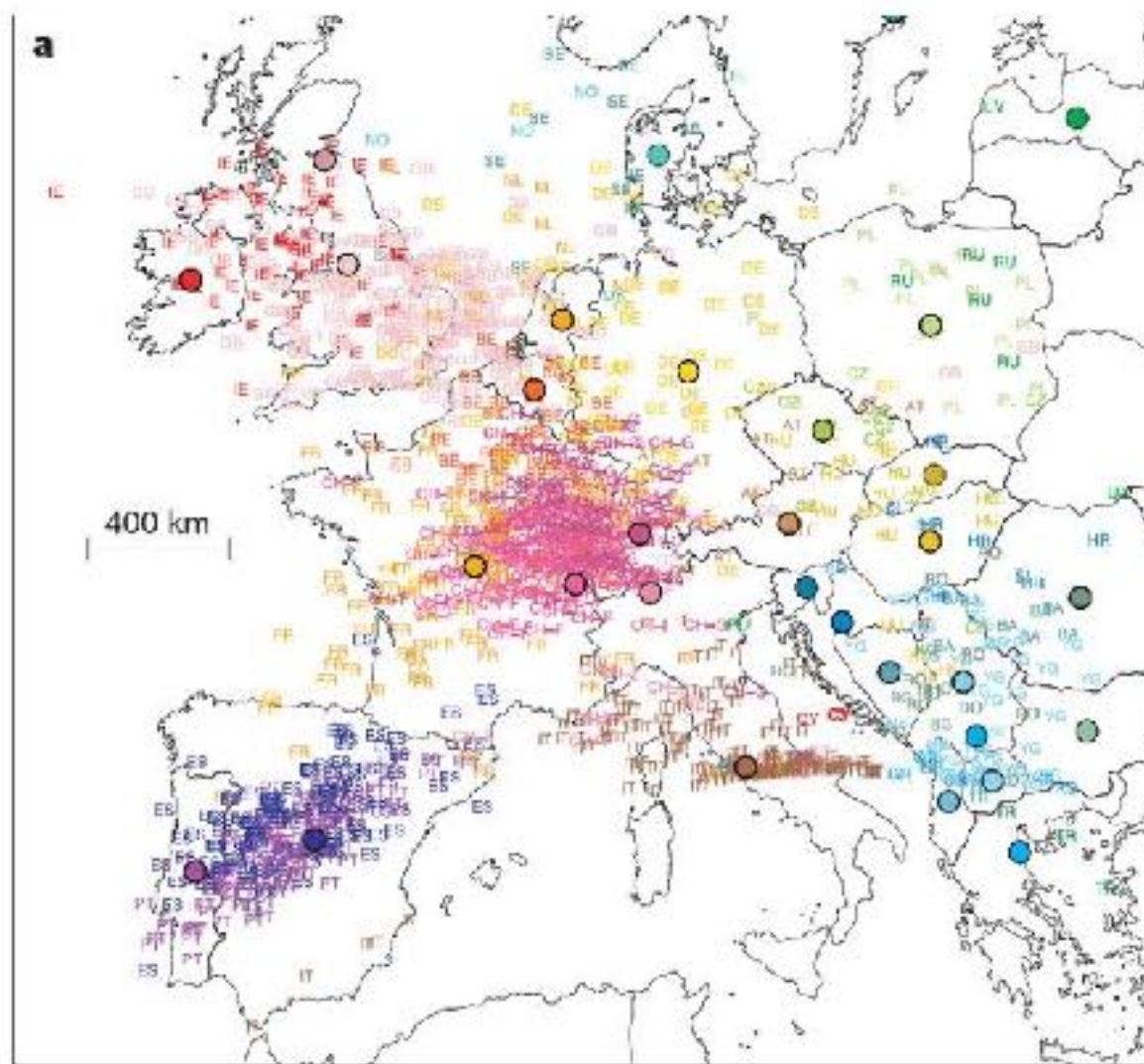
HapMap Phase III



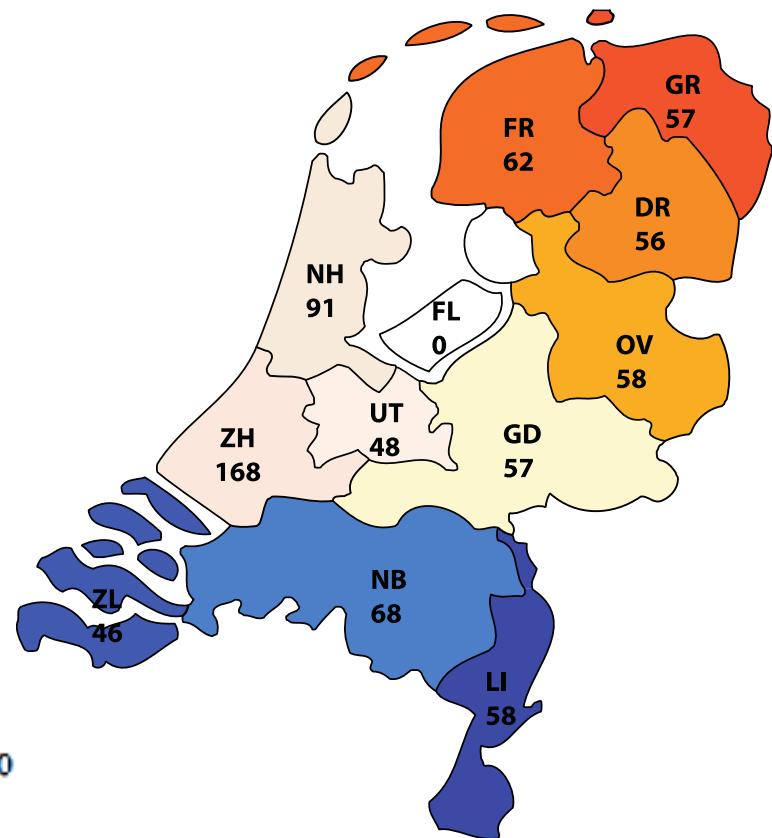
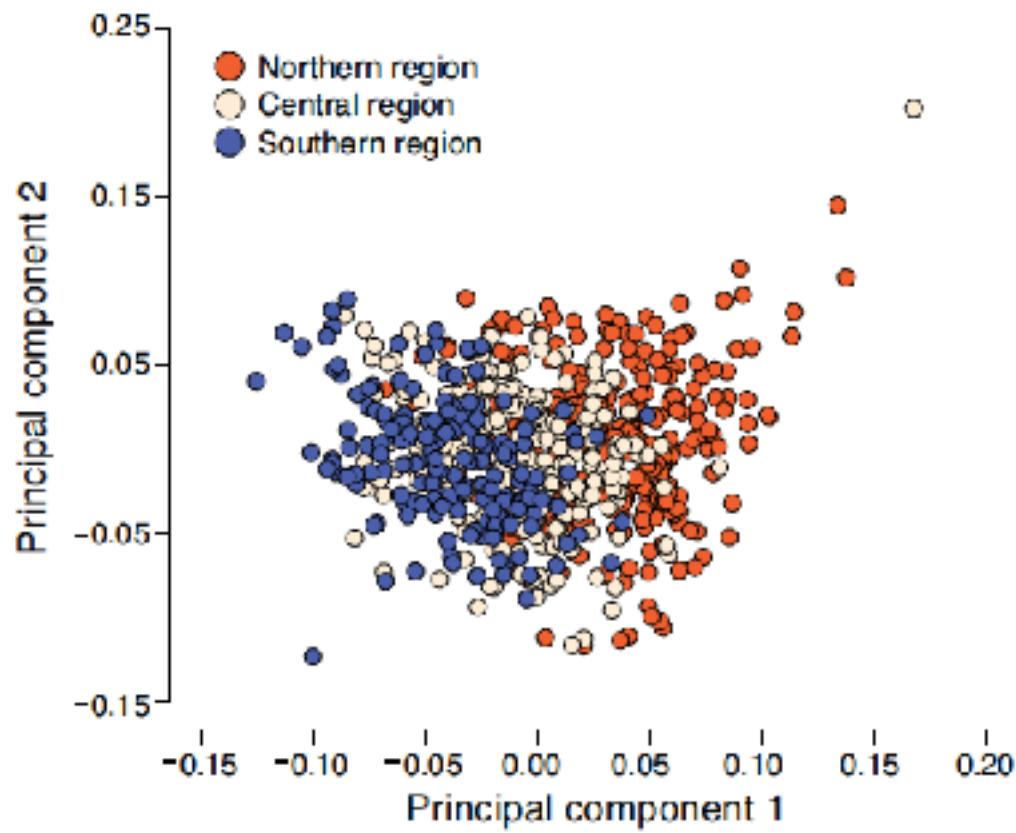
2003

2010

Differentiation of populations



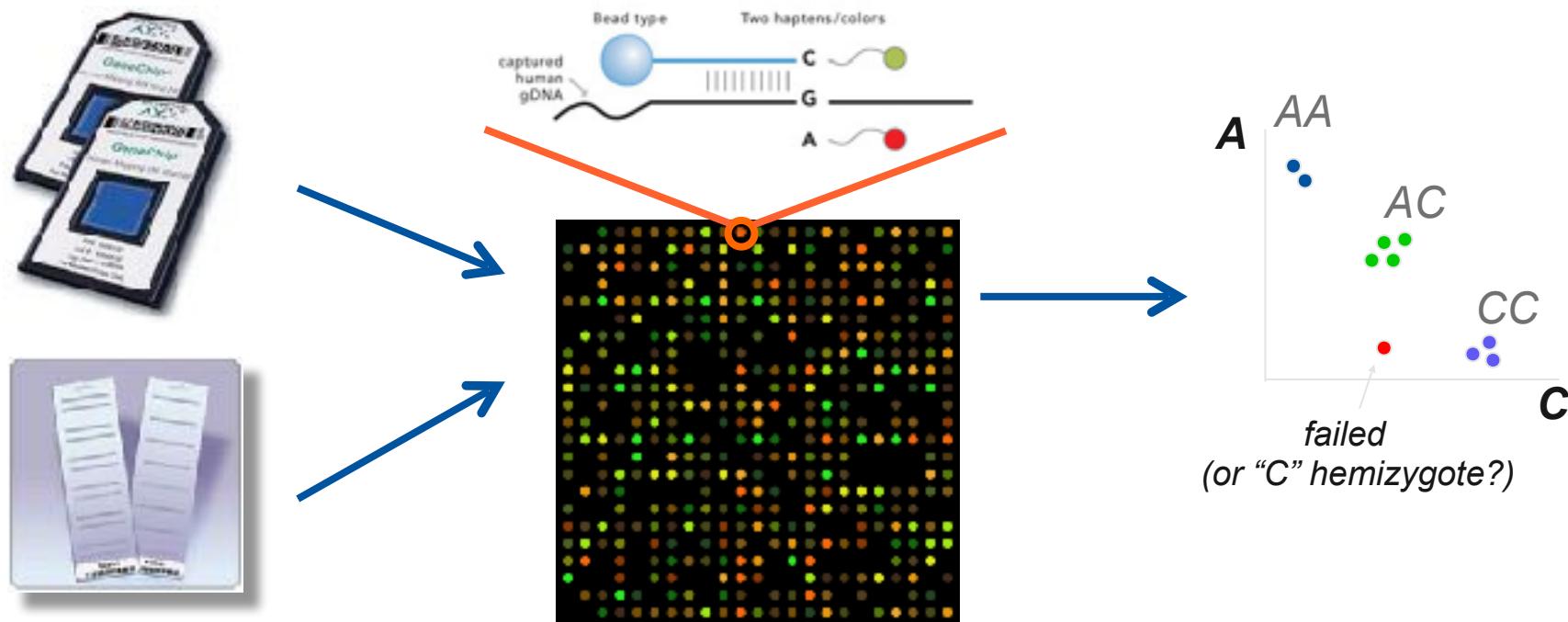
Within the Netherlands, North-South substructure



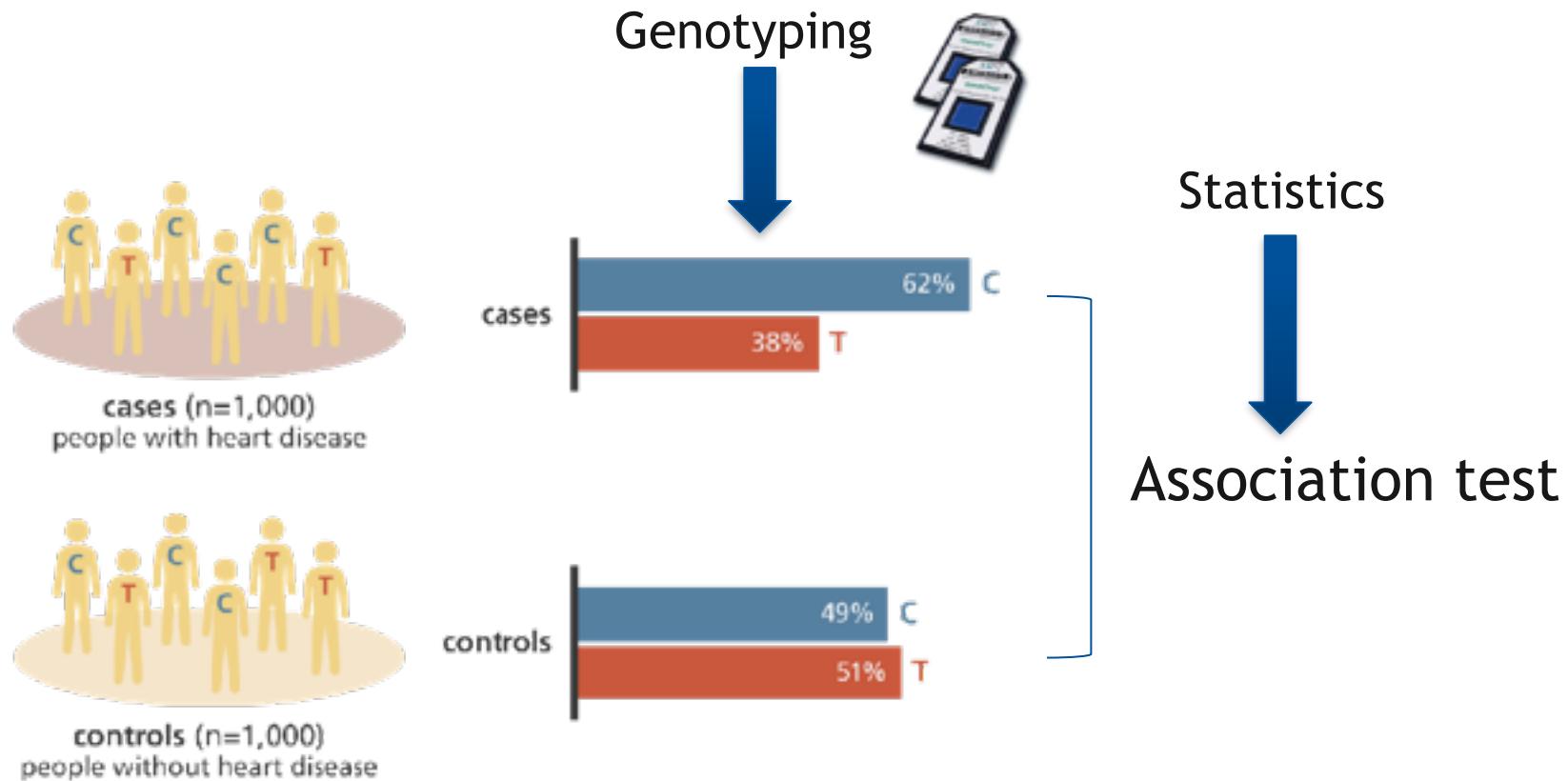
Genome of the Netherlands (250 families whole-genome sequenced)

Genotyping platforms

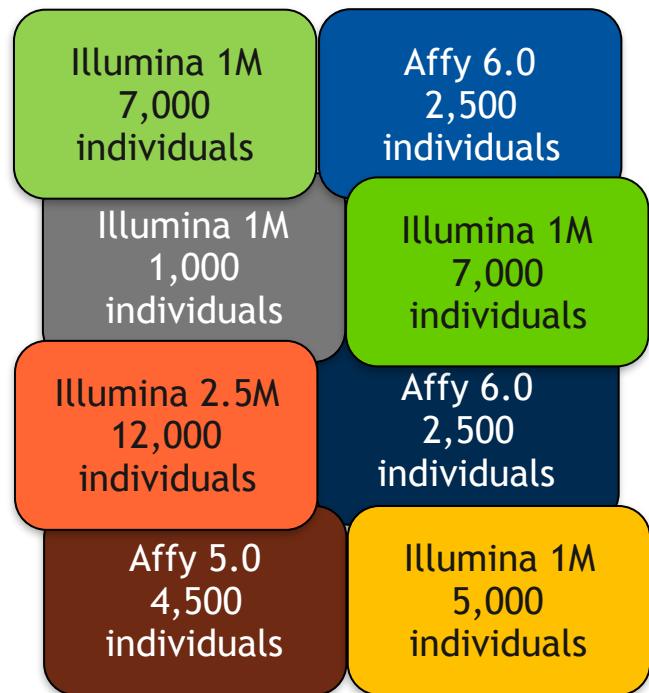
- Genome-wide SNP microarrays allow measurement of genotypes of 100,000's of SNPs in a single experiment
- Variety of microarrays (different SNP density, cost, etc.) by Illumina and Affymetrix



GWAS (the big picture)

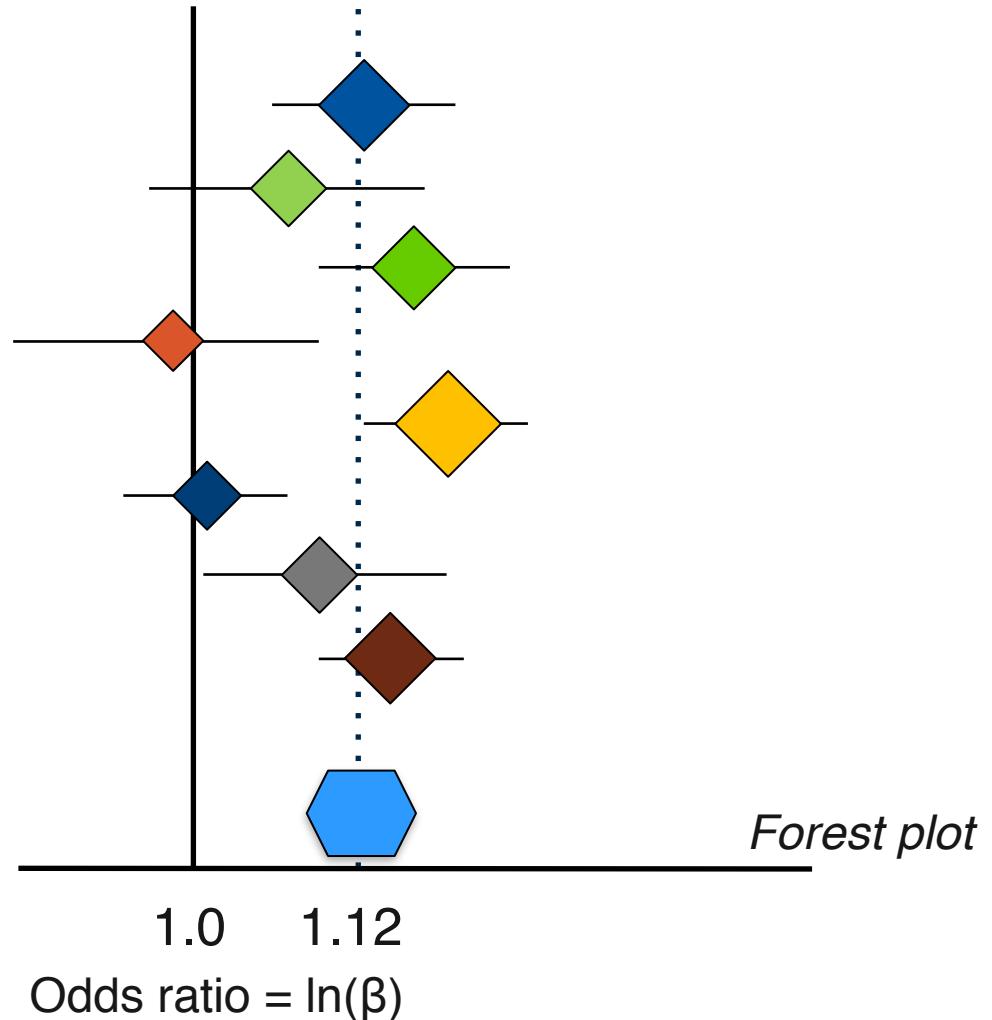


Combining GWAS datasets



↓
Imputation
↓
Meta-analysis of GWAS

Results for one SNP



deCODE Genetics, Inc.

- >50% adult population of Iceland (>140,000) in biobank (blood)
- Pedigree information going back to the first settlements (\approx 1000 years ago)
- Extensive medical records & genotypic data
- Over 250 high-impact publications (Nature, Science, ...)
- 50 common diseases
 - Stroke (=CVA) association with *ALOX5AP*
 - MI association with *ALOX5AP*
 - Association of a variant on 9p21.1 with Abdominal aortic aneurysm (AAA), intracranial aneurysm, stroke and MI



The gene encoding 5-lipoxygenase activating protein confers risk of myocardial infarction and stroke

Anna Helgadottir¹, Andri Mardjani¹, Gudrun Thorleifsson¹, Sveinbjörn Gudmundsson¹, Helga Jónsdóttir¹, Þuríður Þorvaldsdóttir¹, Þóra Jónsdóttir¹, Gudrún Þóra Þorvaldsdóttir¹, Straus J. A. Gruber², Christopher H. Palmer³, Ryan Thompson⁴, David E. Gersh⁵, Steven P. Massell⁶, Michael Mann⁷, Ödafi Guðmundsson¹, Mark E. Goran⁸, Nancy J. Hopkins⁹, Kristinn Thorleifsson¹, Magni Andreasson¹⁰, Michael L. Pugh¹¹, Vicki Thompson¹², George R. King¹³, Vilhjálmur Ólafsson¹⁴, Þórunn Ólafsdóttir¹⁵, Jeffrey S. Gelernter¹⁶, Karen M. Johnson¹⁷

We mapped a gene predisposing to myocardial infarction to a locus on chromosome 1q21.1. This locus encodes a single nucleotide polymorphism (SNP) haplotype in the 3' untranslated region (3'UTR) of encoding 5-lipoxygenase activating protein (5-LAP). 5-LAP is associated with a low blood pressure and myocardial infarction in patients. The haplotype has a similar effect on stroke and myocardial infarction. Another ALOX5AP haplotype is associated with myocardial infarction in individuals from the UK. Household members from individuals with myocardial infarction produce more leukotriene B₄, a key product in the 5-lipoxygenase pathway, than do unaffected controls, and this difference is largely abolished by statins. Patients who carry the 5-LAP haplotype, are carriers of variants of SNPs that are involved in the pathophysiology of myocardial infarction and stroke by increasing leukotriene production and infiltration in the arterial wall.

Helgadottir, A., et al. *Nature Genetics*; volume 36, 233; 2004

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

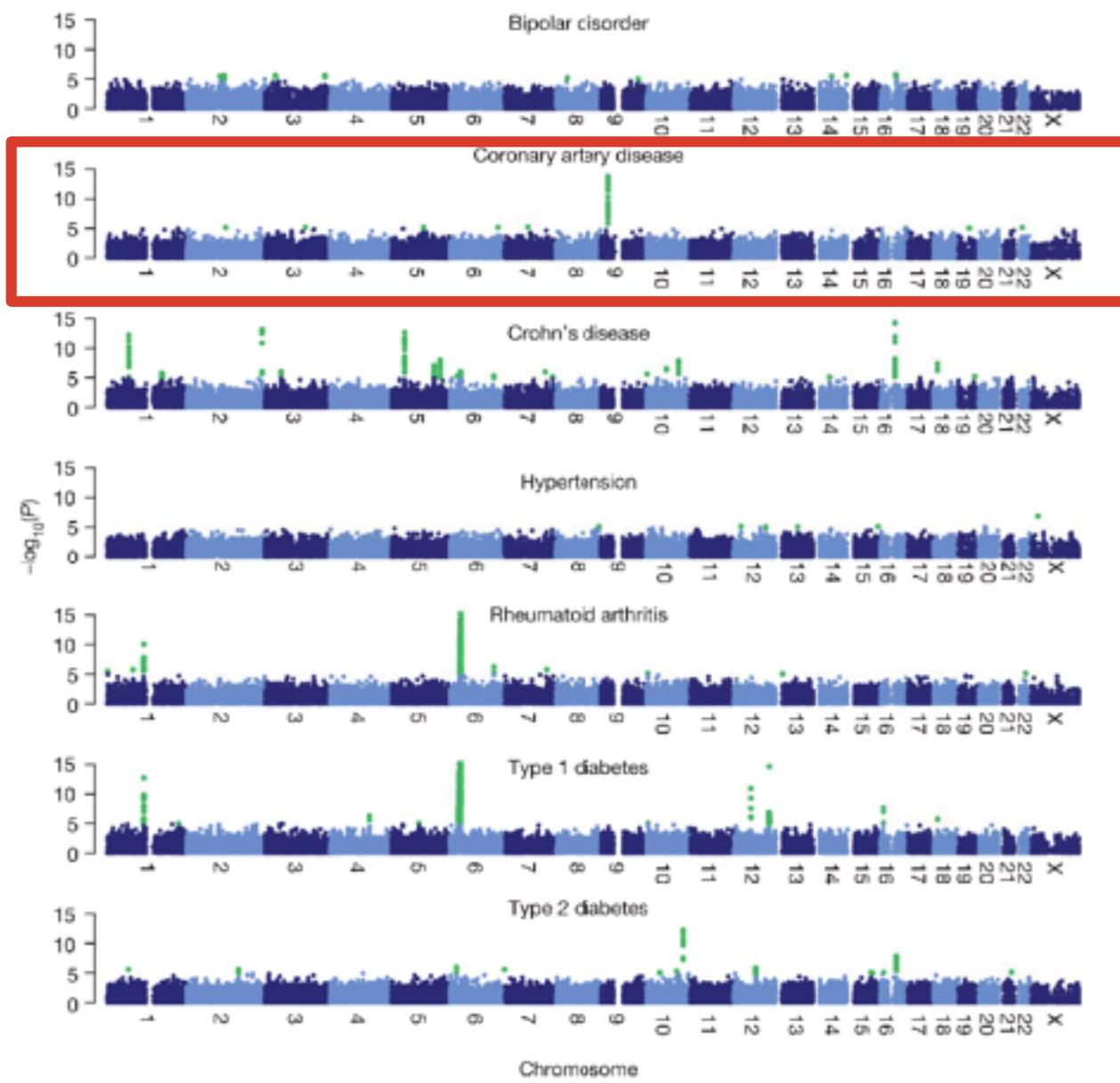
Anna Helgadottir,^{1,2} Gudrun Thorleifsson,^{1,4} Andri Mardjani,^{1,5} Sveinbjörn Gudmundsson,¹ Þórunn Ólafsdóttir,¹ Áslaug Ólafsdóttir,¹ Adalbjörg Jónsdóttir,¹ Angel Þórhólmur,¹ Þórdís Þorvaldsdóttir,¹ Anna Þóra Jónsdóttir,¹ Þóra Þóra Þorvaldsdóttir,¹ Þórunn Gunnarsdóttir,¹ Kárlí Andersen,⁶ Alan I. Levy,⁷ Valgerður M. Þórnkvist,⁸ Sigrún Ólafsdóttir,⁹ Thorberg Þorsteinsdóttir,¹⁰ Þórunn Ólafsdóttir,¹¹ Þórunn Gunnarsdóttir,¹² Ásgerður Gylfason,¹³ Þóra Ólafsdóttir,¹⁴ Kristinn Thorleifsson,¹⁵ Andri Ólafsson,¹⁶ Ólafur Ólafsson,¹⁷ Christopher B. Gauger,¹⁸ Farhad Austin,¹⁹ David J. Reber,¹ David H. Shah,²⁰ Ashraf A. Qayyum,²¹ Jeffrey K. Galster,²² Guðrún Ólafsdóttir,²³ Úlfur Þorsteinsdóttir,²⁴ Agustine Kong,²⁵ Kárlí Stólmansdóttir¹

Helgadottir, A., et al. *Science* volume 316, 1491; 2007

Wellcome Trust Case-Control Consortium

- 1,500 1958 Birth Cohort Controls (58BC)
- 1,500 UK Blood Services Controls (UKBS)
- 14,000 cases of seven common diseases
 - Bipolar disorder
 - Coronary artery disease
 - Crohn's disease
 - Hypertension
 - Rheumatoid arthritis
 - Type 1 diabetes
 - Type 2 diabetes

The image shows a journal cover from the magazine 'nature'. At the top left, it says 'Vol 447 | 7 June 2007 doi:10.1038/nature05911'. To the right is the 'nature' logo. Below the title, the word 'ARTICLES' is written in large, light-colored capital letters. A horizontal line separates the header from the main title. The main title of the article is 'Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls'. At the bottom, it credits 'The Wellcome Trust Case Control Consortium*'. The background of the cover is white.



One famous example

- deCODE Genetics was the first to discover a SNP associated with myocardial infarction (MI) in 2007
 - WTCCC, McPherson, and Samani were able to replicate the same finding in the same year, and many have reconfirmed it in different populations



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

A Common Allele on Chromosome 9 Associated with Coronary Heart Disease

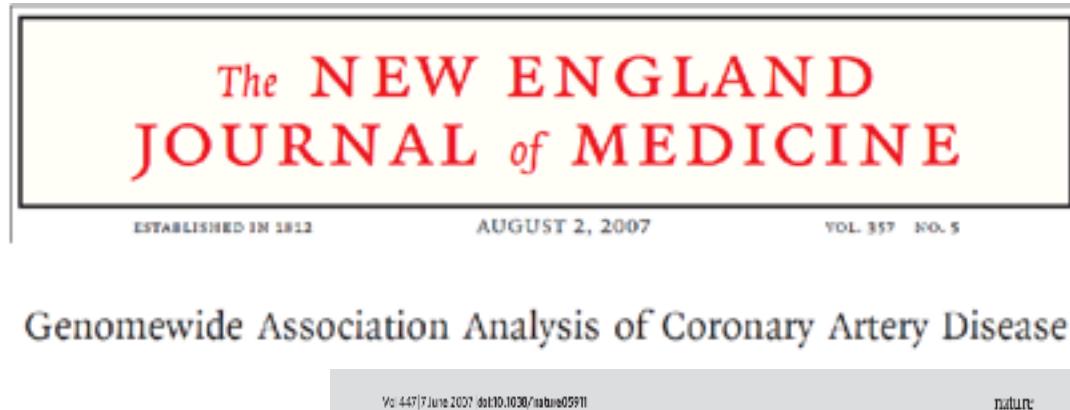
Ruth McPherson,^{1,2}† Alexander Perbemlidis,² Nihan Kavaslar,¹ Alexandre Stewart,¹ Robert Roberts,³ David R. Cox,³ David A. Hinds,¹ Len A. Pennacchio,^{4,5} Anne Tybjaerg-Hansen,⁶ Aaron R. Folsom,⁷ Eric Boerwinkle,⁸ Helen H. Hobbs,^{2,9} Jonathan C. Cohen^{2,10}†

Helgadottir, A., et al. Science; 316(5830):1491-1493, 2007

McPherson, R., et al. *Science*; 316(5830):1488-1491, 2007

Wellcome Trust Case Control Consortium. *Nature*; 447(7145):661-678, 2007

Samani, N.J., et al. N Engl J Med; 357(5):443-453, 2007



Genomewide Association Analysis of Coronary Artery Disease

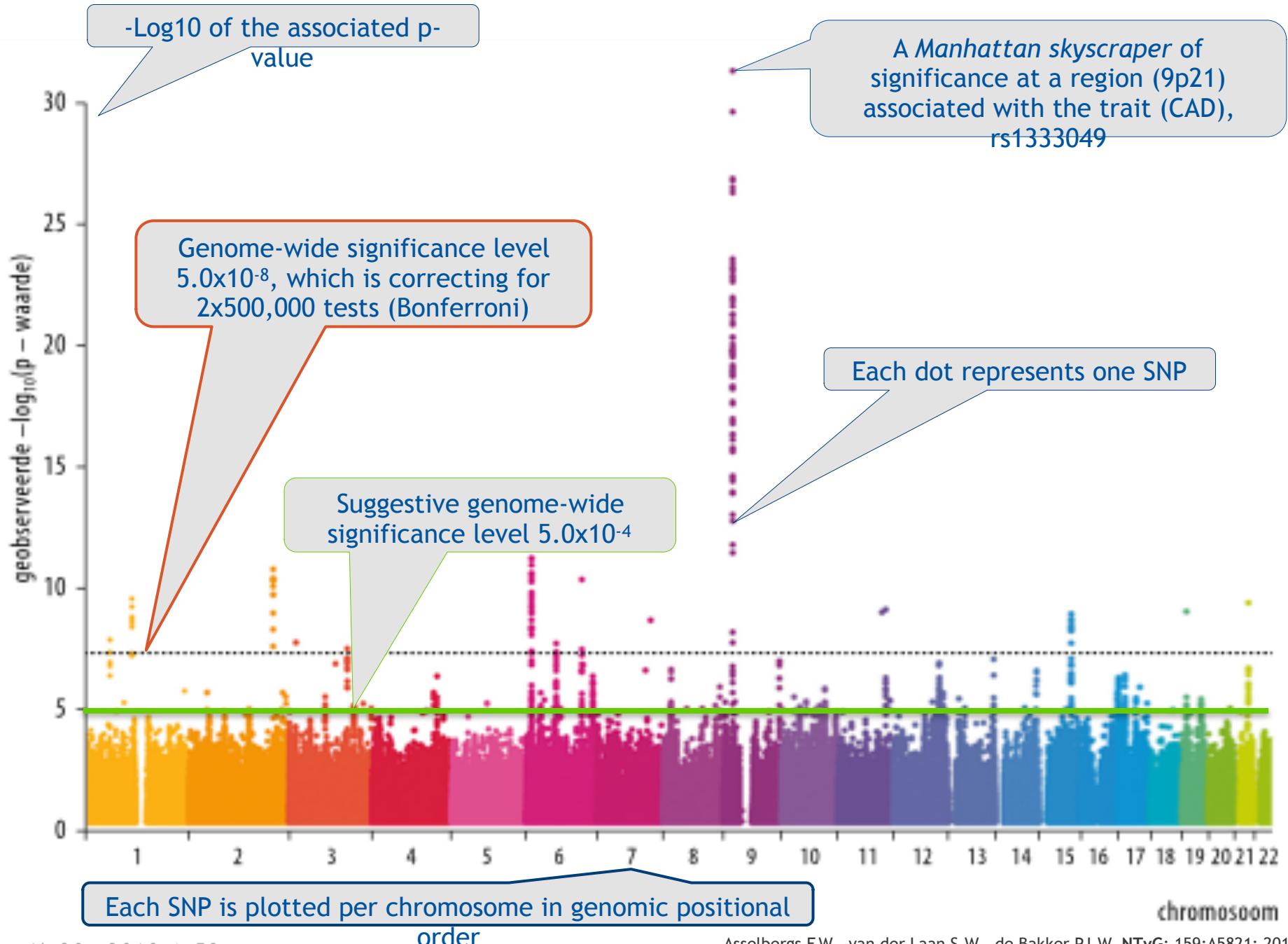
Yg 447 | 7 June 2022 doi:10.1038/nature05321

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ARTICLES

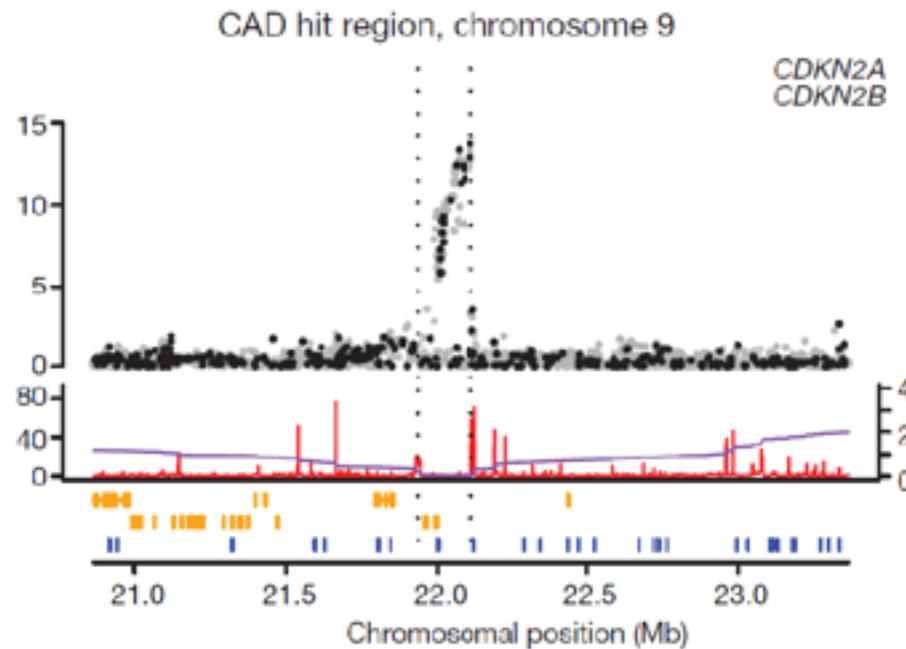
Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls

The Wellcome Trust Case Control Consortium



9p21 and cardiovascular disease

- The SNPs associated with CAD on 9p21.1 are rs1333049, rs10757274, rs2383207, rs2891168, and rs10757278
- They are found in an *intergenic region*
- Genes nearby: *CDKN2A*, *CDKN2B*
 - also associated with *type 2 diabetes mellitus*
 - regulating cell proliferation, cell aging and the associated degeneration, and programmed cell death of many cell types



Wellcome Trust Case Control Consortium. Nature; 447(7145):661-678, 2007

A closer look at the results...

Table 3 | Regions of the genome showing the strongest association signals

Collection	Chromosome	Region (Mb)	SNP	Trend P value	Genotypic P value		$\log_{10}(OR)$, additive	$\log_{10}(OR)$, general	Risk allele	Minor allele	Heterozygote odds ratio	Homozygote odds ratio	Control MAF	Case MAF	
CAD	9p21	21.93-22.12	rs1333049	1.79×10^{-14}	Standard analysis		1.16×10^{-13}	11.66	11.19	C	C	1.47 (1.27-1.70)	19 (161-2.24)	0.474	0.554

- CAD: coronary artery disease
- 9p21: chromosome 9, short arm (p)
- Region: 21.93-22.12 megabase pairs
- rs1333049: official dbSNP ID

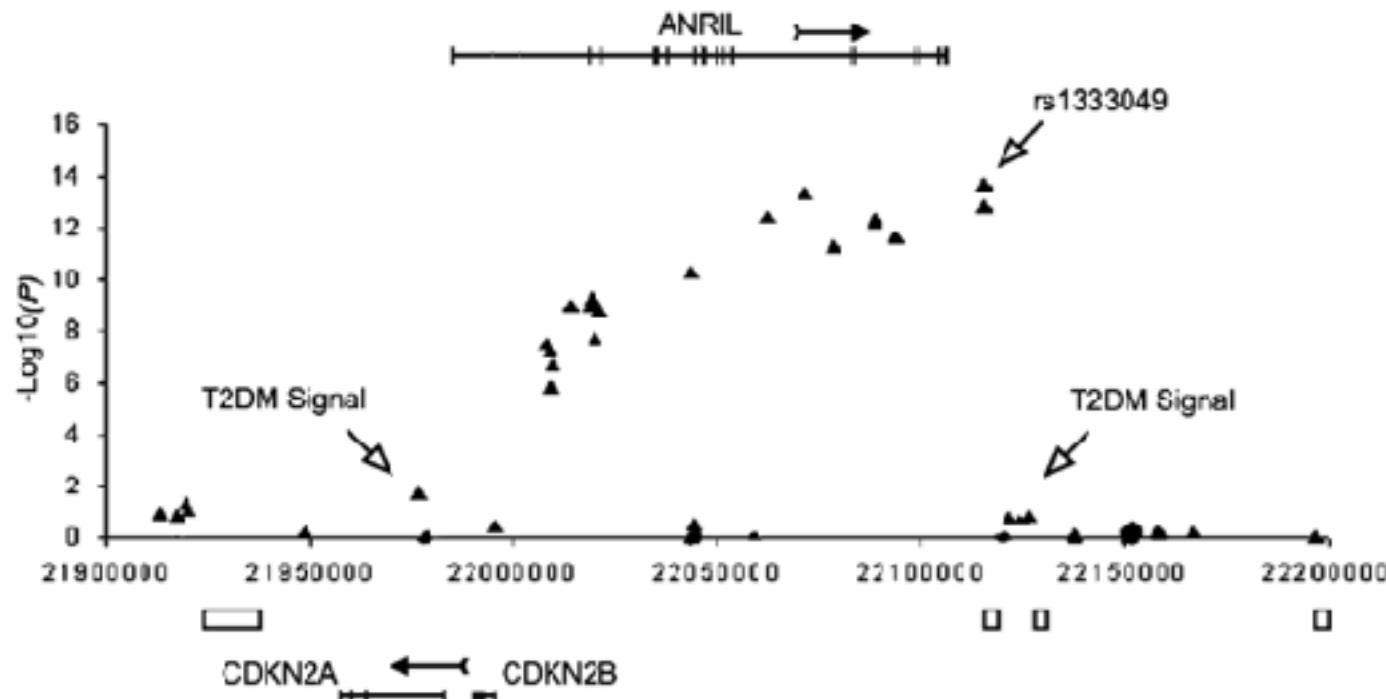
Risk allele: minor allele
 Odds ratio: the odds of exposure between cases and controls

P-value of association test: AA vs. AB vs. BB

Minor allele frequency: the frequency of the risk (minor) allele in the population

9p21 points to a RNA gene

- Resequencing unveiled a RNA gene, *ANRIL*
- Current efforts are aimed to elucidate the role of *ANRIL* in (A)MI
- Might be involved in *early-onset MI* (before age of 50 years)



Samani, NJ., et al. Circ Cardiovasc Genet; 1:81-84,
2008

CARDIoGRAMplusC4D Study

- Coronary Artery Disease Genome-Wide Replication And Meta-Analysis Study: CARDIoGRAM
- > 63,000 cases and > 130,000 controls
 - Myocardial infarction (MI), coronary artery disease (CAD) or both
 - CAD: MI, CABG, PTCA, AP
 - Age limit: 45-66
- Sample size greatly influences power and effect size to discover new variants
- CARDIoGRAMplusC4D sought to solves this issue
- 55 susceptibility loci for CAD were discovered



ARTICLES

Large-scale association analysis identifies new risk loci for coronary artery disease

The CARDIoGRAMplusC4D Consortium¹

Coronary artery disease (CAD) is the commonest cause of death. Here, we report an association analysis in 63,746 CAD cases and 130,461 controls identifying 15 loci reaching genome-wide significance, taking the number of susceptibility loci for CAD to 46, and a further 104 independent variants ($P < 0.25$) strongly associated with CAD at a 5% false discovery rate (FDR). Together, these variants explain approximately 10.6% of CAD heritability. Of the 46 genome-wide significant lead SNPs, 12 show a significant association with a lipid trait, and 5 show a significant association with blood pressure, but none is significantly associated with diabetes. Between analysis with 233 candidate genes (at 1% FDR), 1,086 generated 5 interaction networks comprising 85% of these putative genes involved in CAD. The four most significant pathways mapping to these networks are linked to lipid metabolism and inflammation, underscoring the causal role of these activities in the genetic etiology of CAD. Our study provides insights into the genetic basis of CAD and identifies key biological pathways.

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Coronary artery disease (CAD) is a leading cause of death worldwide. Although, epidemiological studies have identified a range risk factors for CAD, including plasma lipid concentrations, blood pressure, smoking, diabetes and measures of inflammation, a causal role has been proven only for some (for example, low-density lipoprotein (LDL)-cholesterol and blood pressure primarily through randomized-control trials of drug therapy directed at the risk factor². Twin and family studies have demonstrated that a significant proportion (10–10%) of susceptibility to CAD is heritable (for a review see ref. 3). Because gene effects are often modulated by environmental exposures, genetic studies have the potential to define which of factors are relevant to causal to identify pathways and therapeutic targets^{4,5}. To date, genome-wide association studies (GWAS) have only entirely reported a total of 36 loci associated with CAD risk at genome-wide significance ($P < 5 \times 10^{-8}$). However, variants at these loci explain less than 10% of the heritability of CAD. One likely reason for this is that, given the polygenic nature of complex traits and the relatively small observed effect sizes of the loci identified, many genes may have variants that do not reach the stringent P -value threshold for genome-wide significance. Indeed, there is increasing evidence that the genome-wide distribution of variants creates a large number of causative alleles with very small effect^{6,7}. Addressing this will require the discovery of additional risk while leveraging large-scale genomic data to identify the molecular pathways underlying the pathophysiology. A key discovery is facilitated by building molecular networks, on the basis of DNA, RNA and protein interactions, which have nodes of known biological function that also show evidence of association with risk variants (for CAD and related metabolic traits).

In the largest GWAS meta-analysis of CAD to date to be done by the Coronary Artery Disease Genome-wide Replication and

Molecular analysis (CARDIoGRAM) Consortium⁸, which draws on 12,239 cases and 16,762 controls, in addition to loci reaching genome-wide significance, a linkage disequilibrium (LD)-based set of 6,212 variants achieved a nominal association P -value of less than 1.61. Here, we test these 6,222 SNPs in a meta-analysis of over 193,000 individuals, with the primary aim of identifying any additional susceptibility loci for CAD. In this study, we used the Metaregression approach⁹, which is a custom DIRECT+ map (Bioconductor) containing 104,873 SNPs, designed to fit follow-up position associations in several cardiovascular traits, including CAD, and 101 free-map conditioned loci for these traits. All SNPs on the latter were taken from the CARDIoGRAM study sample considered for analysis (20,014 SNPs), of which 1,217 were the significant SNPs and 20,376 were fine-mapping SNPs in the 22 CAD susceptibility loci identified at the time at which the array was designed, the remaining 849Ps were inherited by the other consortia contributing to the Metaregression⁹. In addition, we assess whether the genome-wide significant CAD risk alleles are through their heritability by considering the available longitudinal data for these traits^{10–12}. Finally, we identify a large set of CAD predisposing variants as the BYER thresholds for association with CAD and use this set to undertake a new analysis to find key biological pathways underlying the pathogenesis of CAD.

RESULTS

Study design

We expanded the CARDIoGRAM (coronary artery disease 63,746 cases and 130,461 controls), stage 1, with 24 additional CAD samples (for a total of 149,721) to represent mostly Asian descent, comprising 40,273 cases and 40,309 controls. Study design, power and sample characteristics are given in Supplementary Tables 1 and 2a, review 1(a) and underlie both a 2-stage meta-analysis to test SNPs on the Metaregression array.

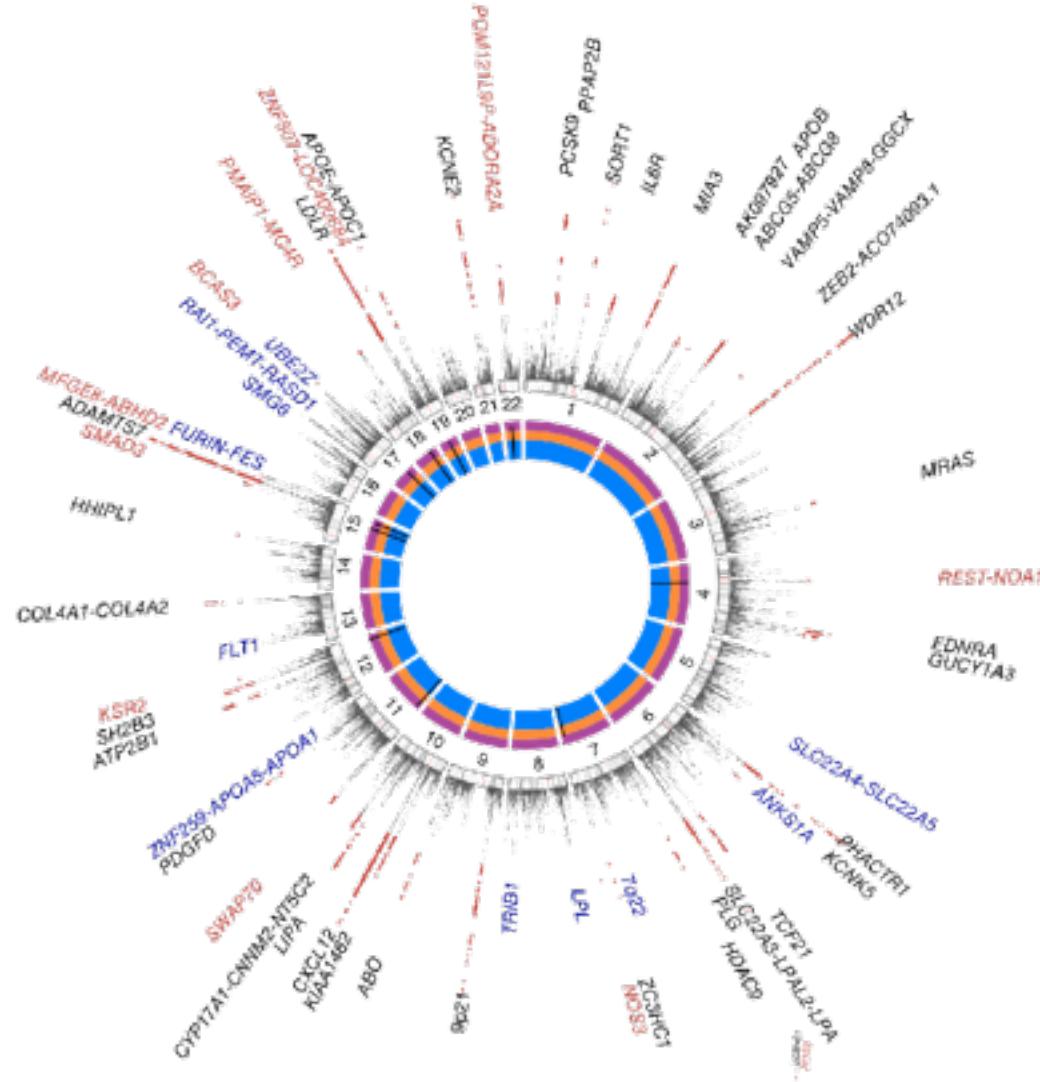
DOI: 10.1038/ng.2947; published online 11 April 2013; doi:10.1038/ng.2947

Received 24 April 2012; revised 27 November 2012; published online 1 December 2012; corrected 18 March 2013; accepted 18 March 2013.

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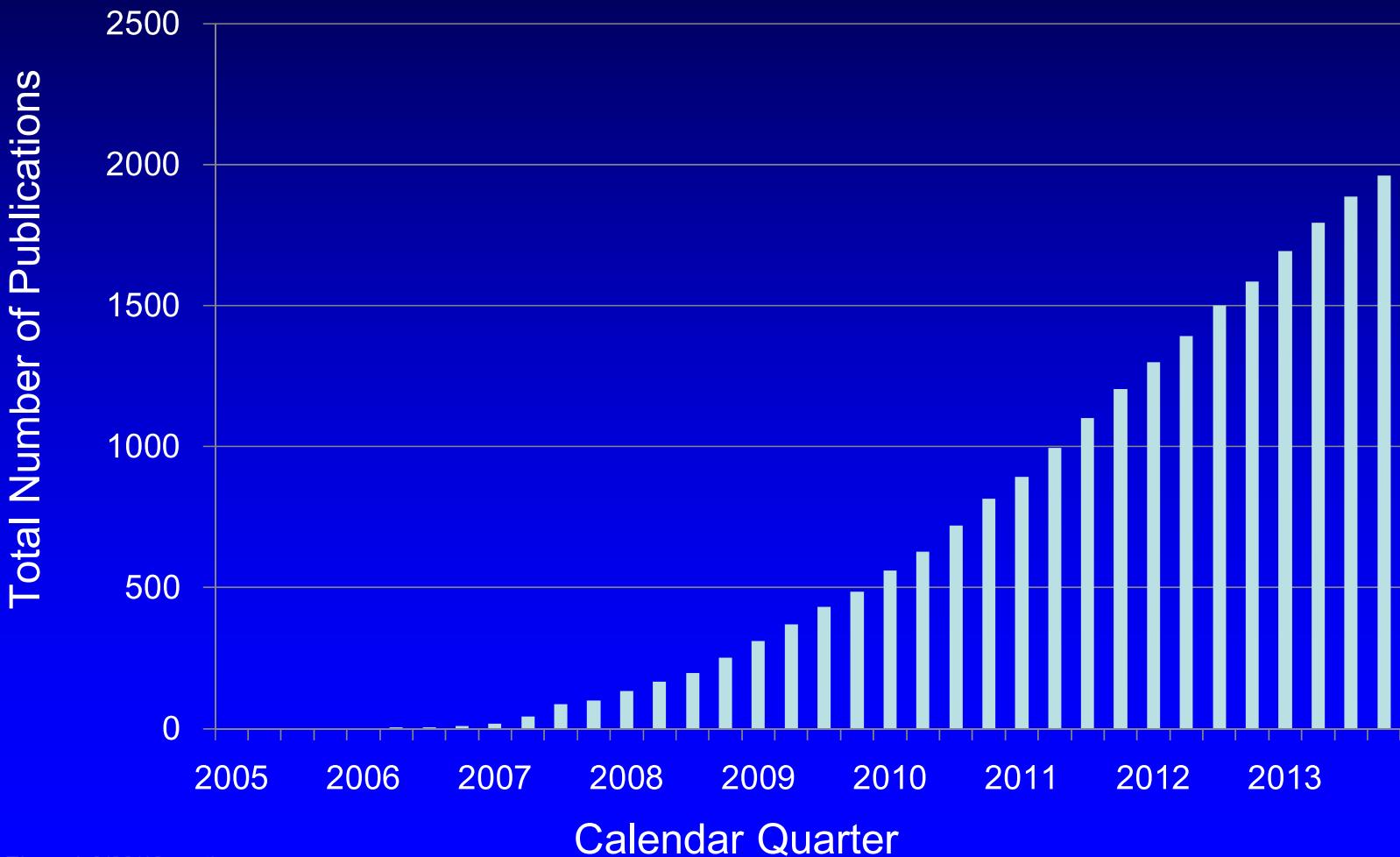
And 8 years later (>15 times more samples)



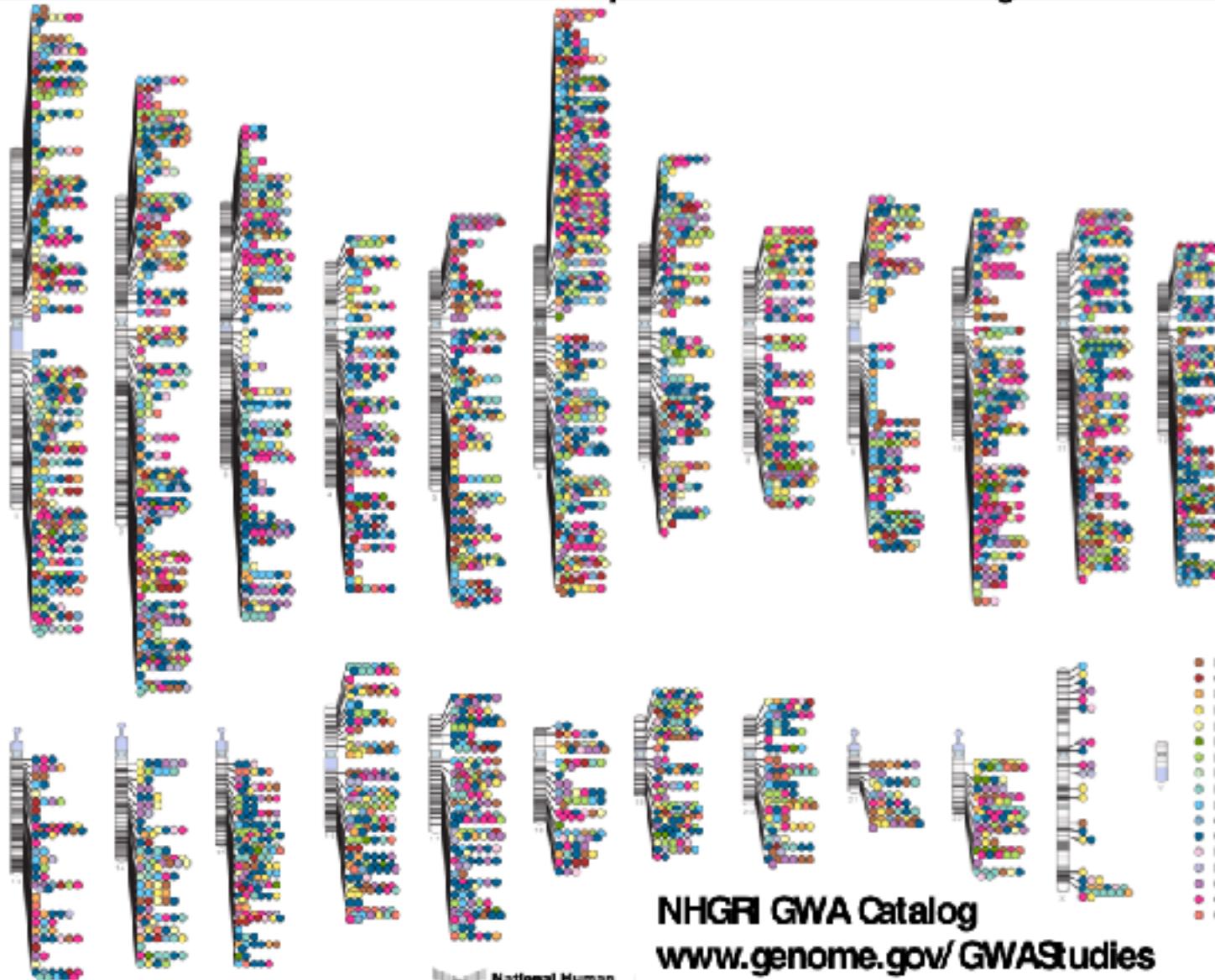
9p21 plus an additional 47 loci (!)

Published GWA Reports, 2005 – 2013

1960



Published Genome-Wide Associationst through 12/2013
Published GWA at $p \leq 5 \times 10^{-8}$ for 17 trait categories



NHGRI GWA Catalog
www.genome.gov/GWASStudies
www.ebi.ac.uk/fgpt/gwas/



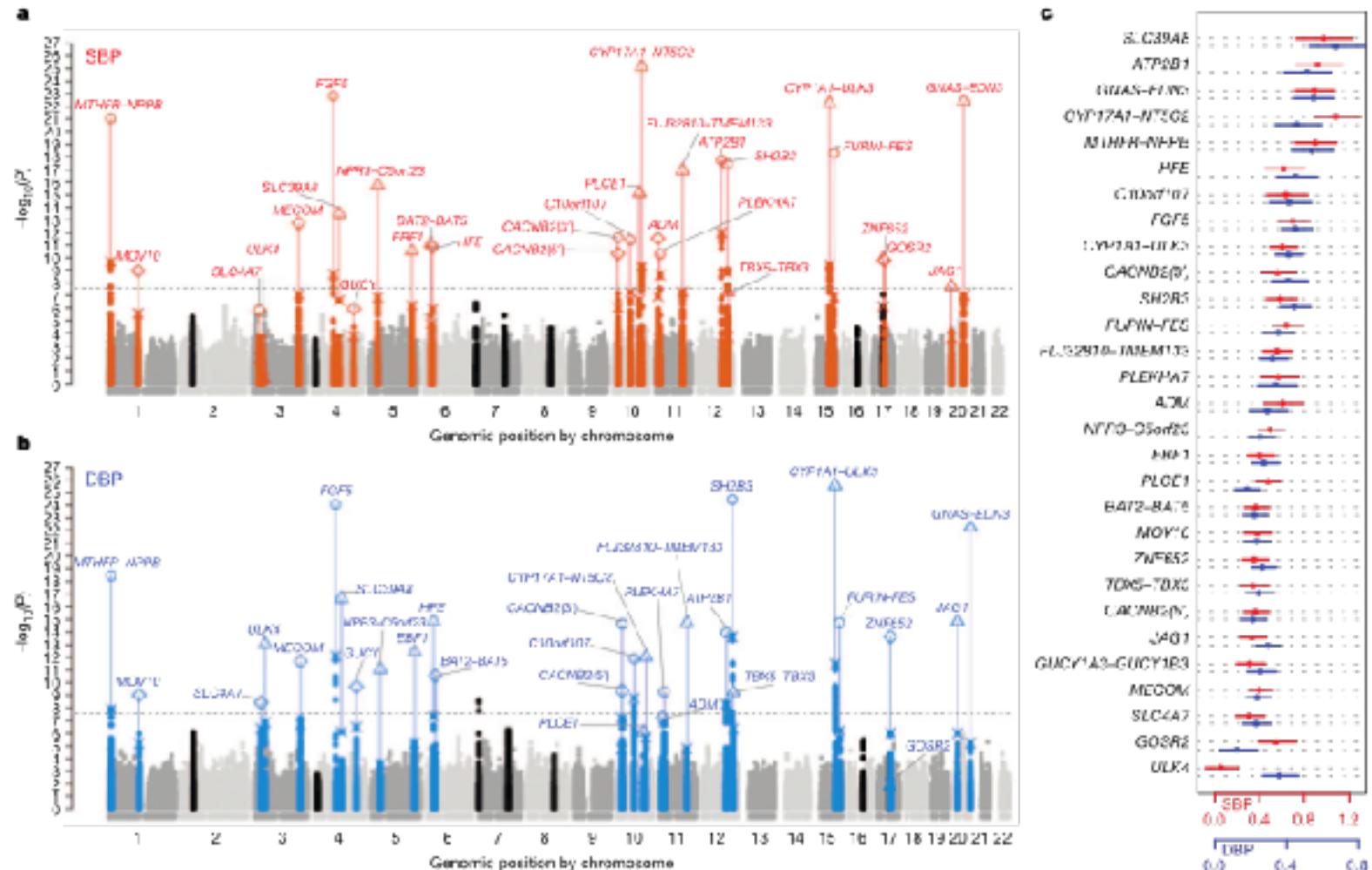


Figure 1 Genome-wide $-\log_{10} P$ -value plots and effects for significant loci. **a, b**, Genome-wide $-\log_{10} P$ -value plots are shown for SBP (a) and DBP (b). SNPs within loci reaching genome-wide significance are labelled in red for SBP and blue for DBP (± 2.5 Mb of lowest P value) and lowest P values in the initial genome-wide analysis as well as the results of analysis including validation data are labelled separately. The lowest P value in the initial GWAS are denoted with a X. The range of different sample sizes in the final meta-

analysis including the validation data are indicated as: circle (96,000–140,000), triangle ($> 140,000$ –180,000) and diamond ($> 180,000$ –220,000). SNPs near unconfirmed loci are in black. The horizontal dotted line is $P = 2.5 \times 10^{-8}$. GUCY denotes GUCY1A3, GUCY1B3. **c**, Effect size estimates and 95% confidence bars per blood-pressure-increasing allele of the 29 significant variants for SBP (red) and DBP (blue). Effect sizes are expressed in mm Hg per allele.

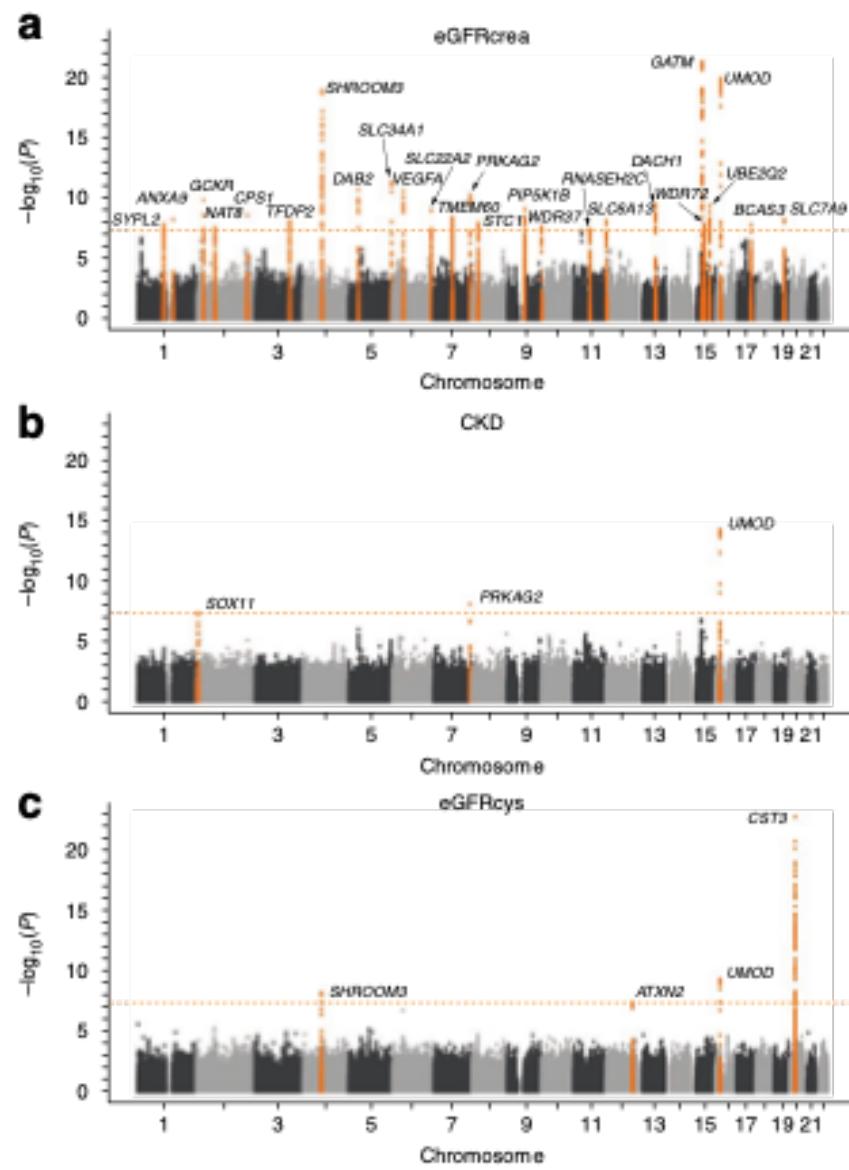


Figure 1 Genome-wide $-\log_{10} P$ value plot from stage 1. (a–c) Plots show discovery analysis of eGFRcrea (a), CKD (b) and eGFRcys (c). The dotted line indicates the genome-wide significance threshold at $P = 5 \times 10^{-8}$.

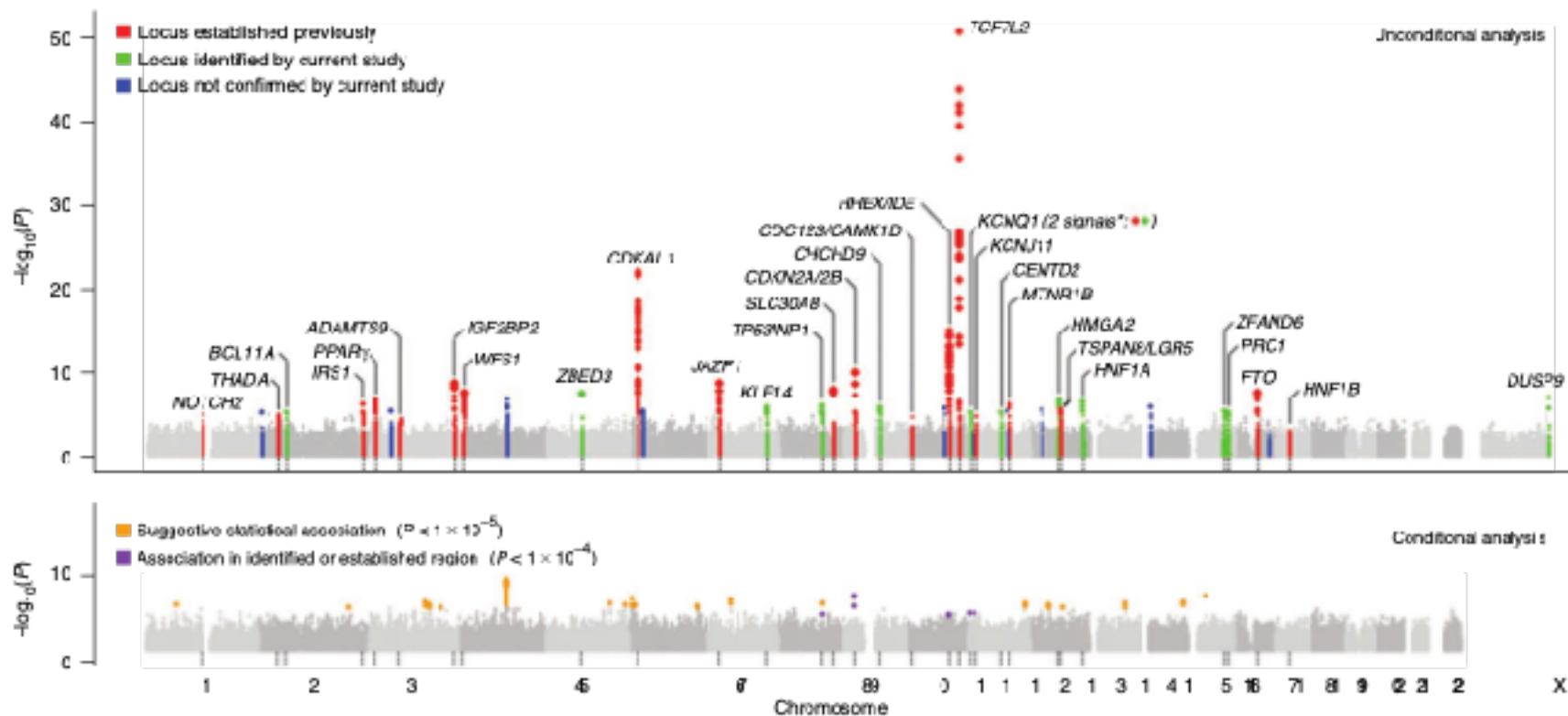
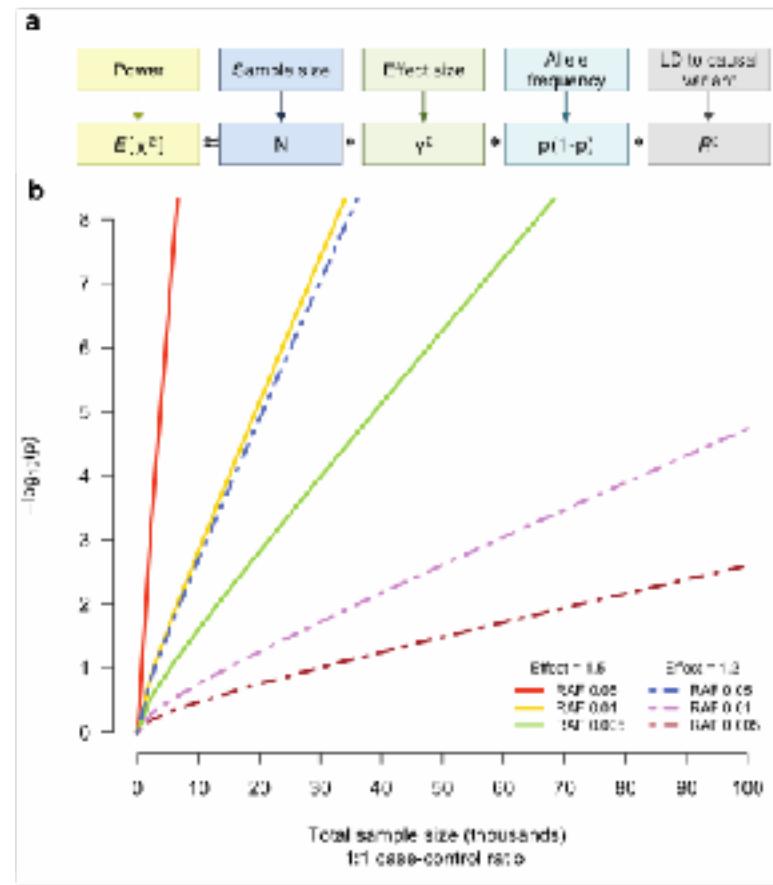
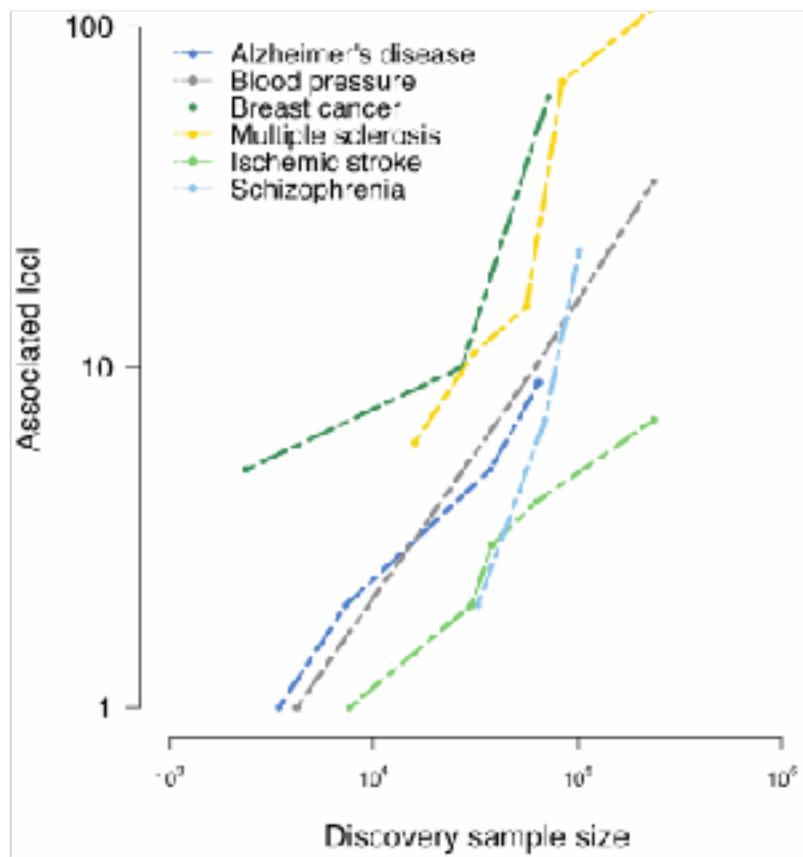
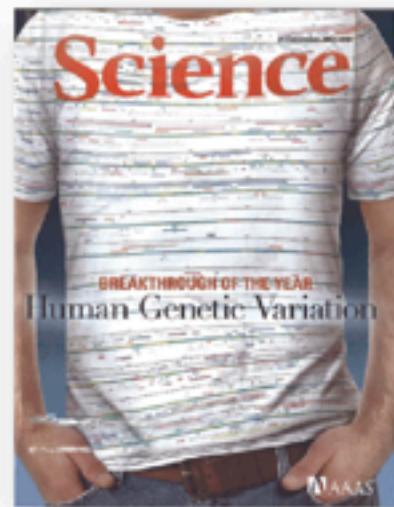


Figure 1 Genome-wide Manhattan plots for the DIAGRAM+ stage 1 meta-analysis. Top panel summarizes the results of the unconditional meta-analysis. Previously established loci are denoted in red and loci identified by the current study are denoted in green. The ten signals in blue are those taken forward but not confirmed in stage 2 analyses. The genes used to name signals have been chosen on the basis of proximity to the index SNP and should not be presumed to indicate causality. The lower panel summarizes the results of equivalent meta-analysis after conditioning on 30 previously established and newly identified autosomal T2D-associated SNPs (denoted by the dotted lines below these loci in the upper panel). Newly discovered conditional signals (outside established loci) are denoted with an orange dot if they show suggestive levels of significance ($P < 10^{-5}$), whereas secondary signals close to already confirmed T2D loci are shown in purple ($P < 10^{-4}$).

Power, Effect size, Sample size...



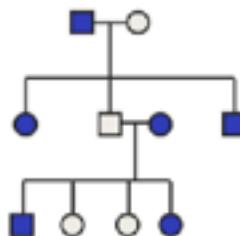


Linkage analysis

Candidate gene studies

GWAS

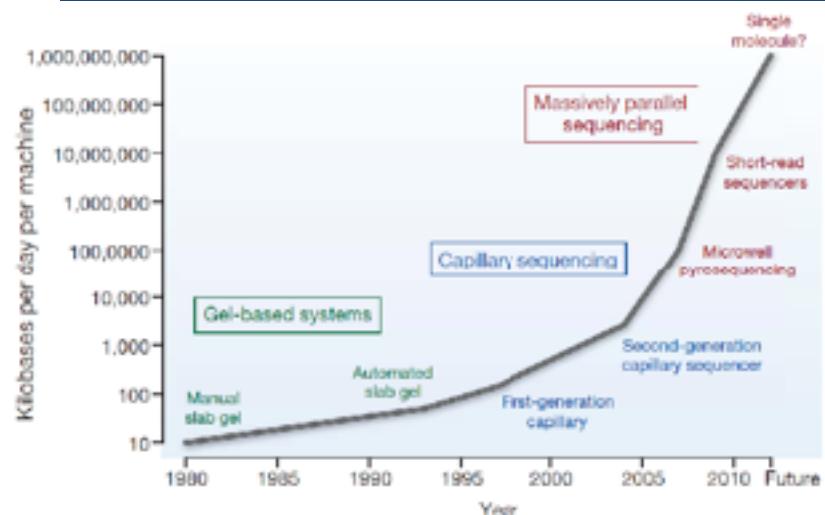
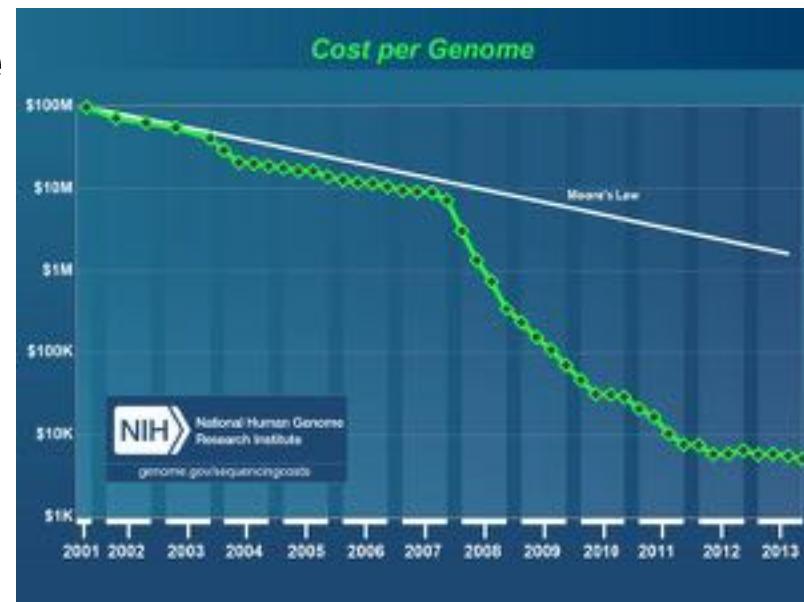
Sequencing



Next-generation sequencing

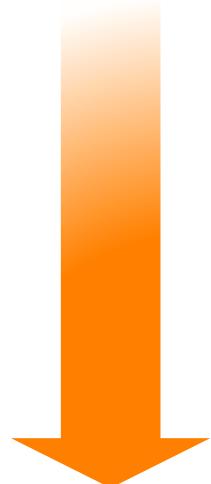
Milestone: \$1000 dollar genome
(2014, Illumina HiSeq X Ten Sequencer)

But how much money needs to be spent on annotation and (even more important) interpretation of the results?

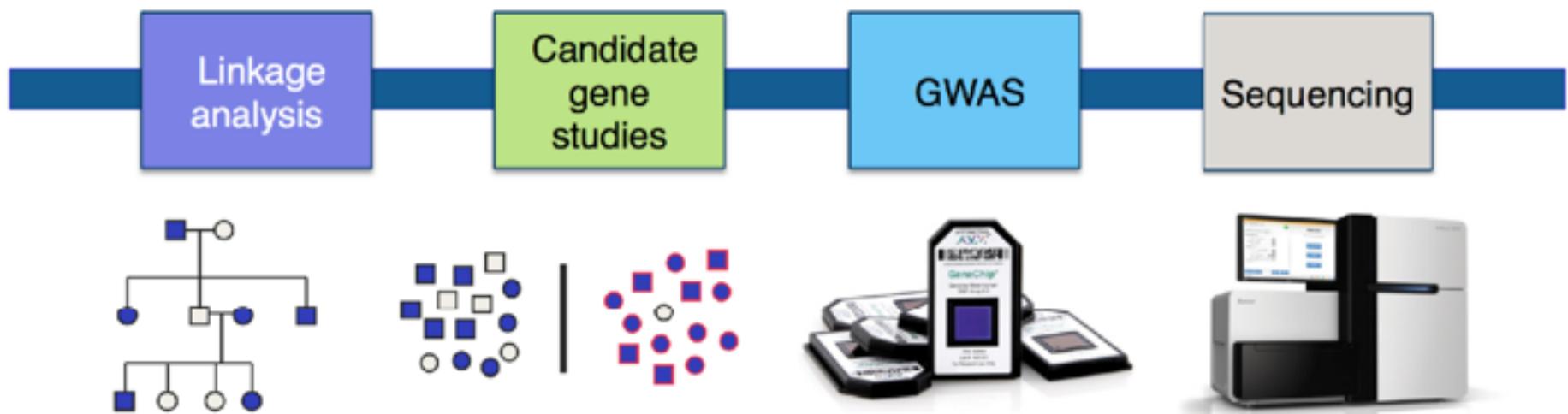


Summary: what's been (being) done?

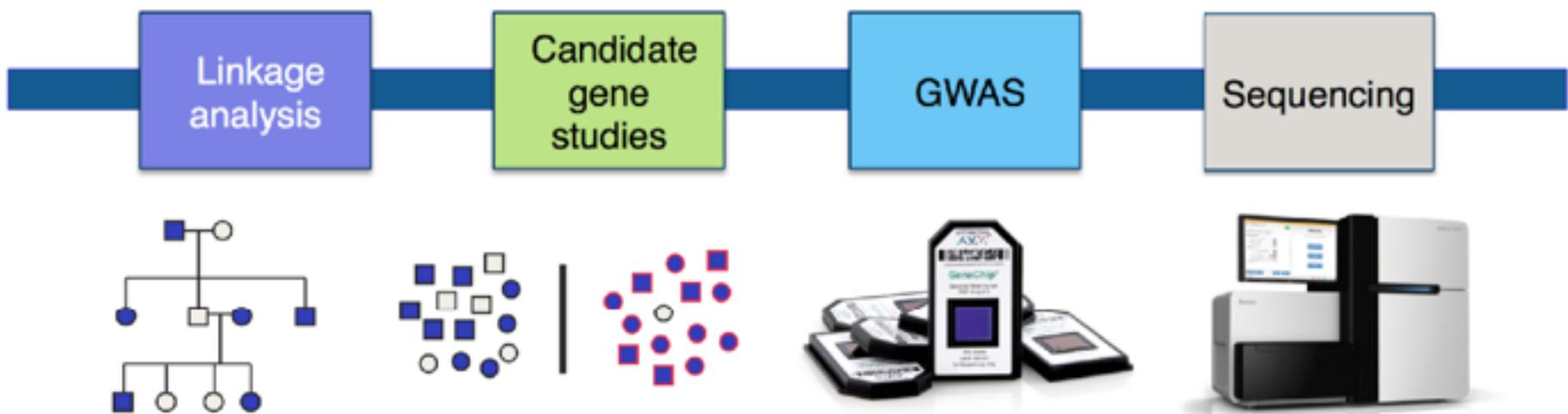
- Family-based linkage studies
 - Rare, Mendelian traits
- Candidate gene association studies
 - Many claims, few robust findings
 - Terrible track record in terms of reproducibility
- Genome-wide association studies (GWAS)
 - Complex traits and common diseases
- Whole-exome sequencing studies
 - Rare, Mendelian diseases (unsolved cases)
 - Complex traits and common diseases
- Whole-genome sequencing studies



What have we learned in the field of cardiovascular genetics?



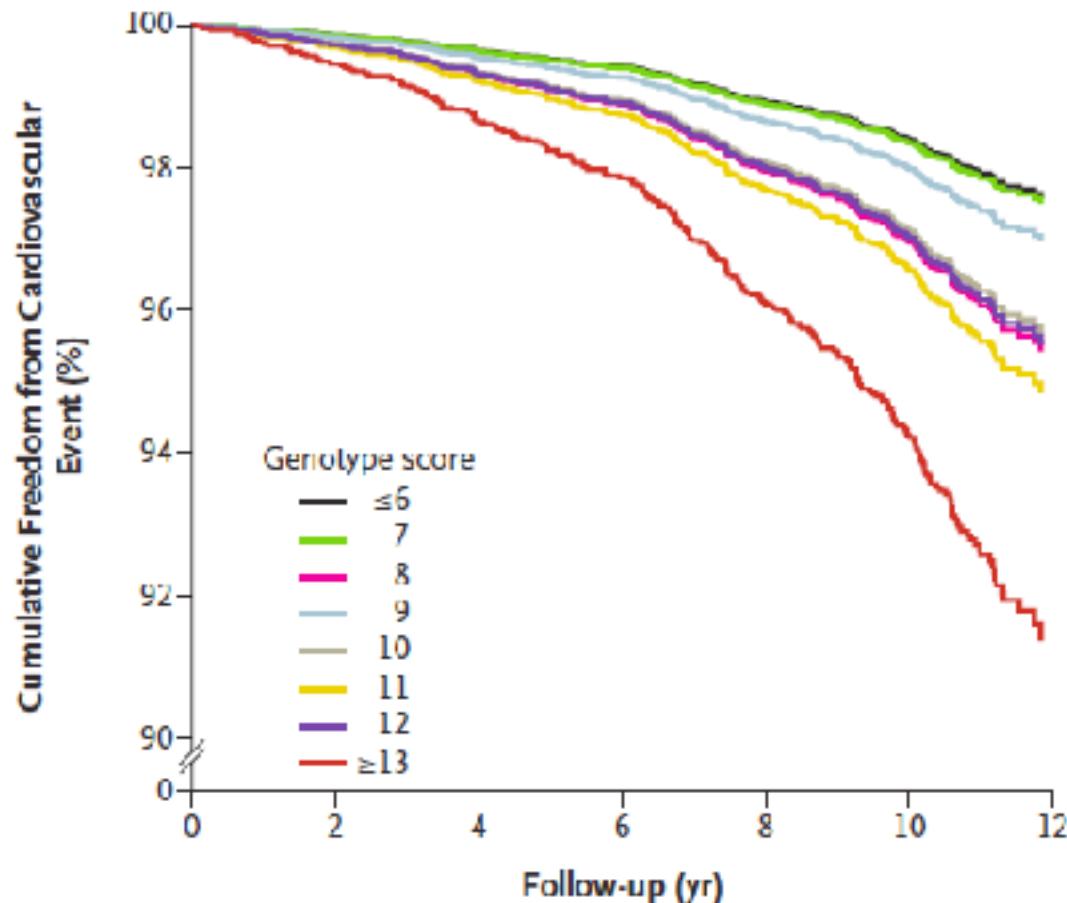
Prediction?



9 SNPs associations with CVD

Table 4. Multivariable Analysis of the Association between Genotype Score and the Time to First Cardiovascular Event^a

	Multivariable-Adjusted Hazard Ratio (95% CI)	P Value
Age, per SD	1.37 (1.37–2.07)	<0.001
Male sex	1.61 (1.29–2.17)	0.007
Parent or sibling with history of myocardial infarction	1.52 (1.17–1.97)	0.002
Cholesterol, per SD		
LDL	1.13 (0.99–1.29)	0.08
HDL	0.75 (0.61–0.91)	0.003
Log triglycerides, per SD	0.87 (0.73–1.04)	0.12
Blood pressure, per SD		
Systolic	1.29 (1.08–1.54)	0.005
Diastolic	1.16 (0.97–1.38)	0.11
Hypertension index, per SD	1.04 (0.94–1.25)	0.26
Diabetes mellitus	1.47 (1.02–2.13)	0.04
Status of cigarette smoking,		<0.0001†
Former versus never	1.17 (0.85–1.59)	
Current versus never	2.00 (1.41–2.83)	
Log C-reactive protein, per SD	1.14 (0.99–1.38)	0.06
Drug therapy		
Lipid lowering	1.29 (0.63–2.64)	0.48
Antihypertensive	1.46 (1.08–1.97)	0.01
Genotype score, per single unfavorable allele	1.15 (1.07–1.24)	<0.001



But does not aid risk prediction

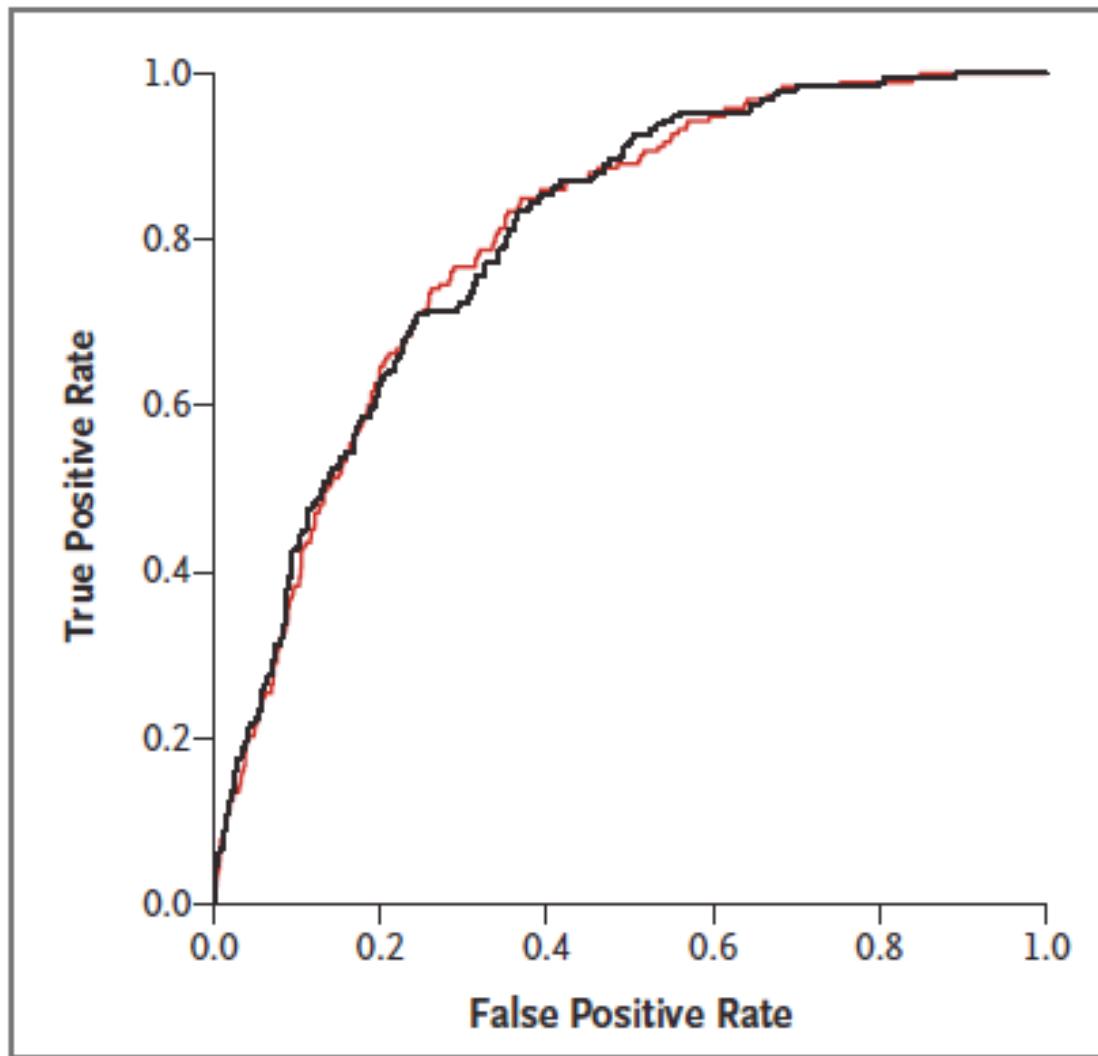


Figure 2. Receiver-Operating-Characteristic (ROC) Curves for Incident Myocardial Infarction, Ischemic Stroke, or Death from Coronary Heart Disease during 10-Year Follow-up.

The curves are based on risk-prediction models incorporating 14 clinical covariates that either included the genotype score (black line) or did not include the genotype score (red line). The C statistic (area under the ROC curve) for total cardiovascular events was the same (0.80) for both risk models.

MENU ▾

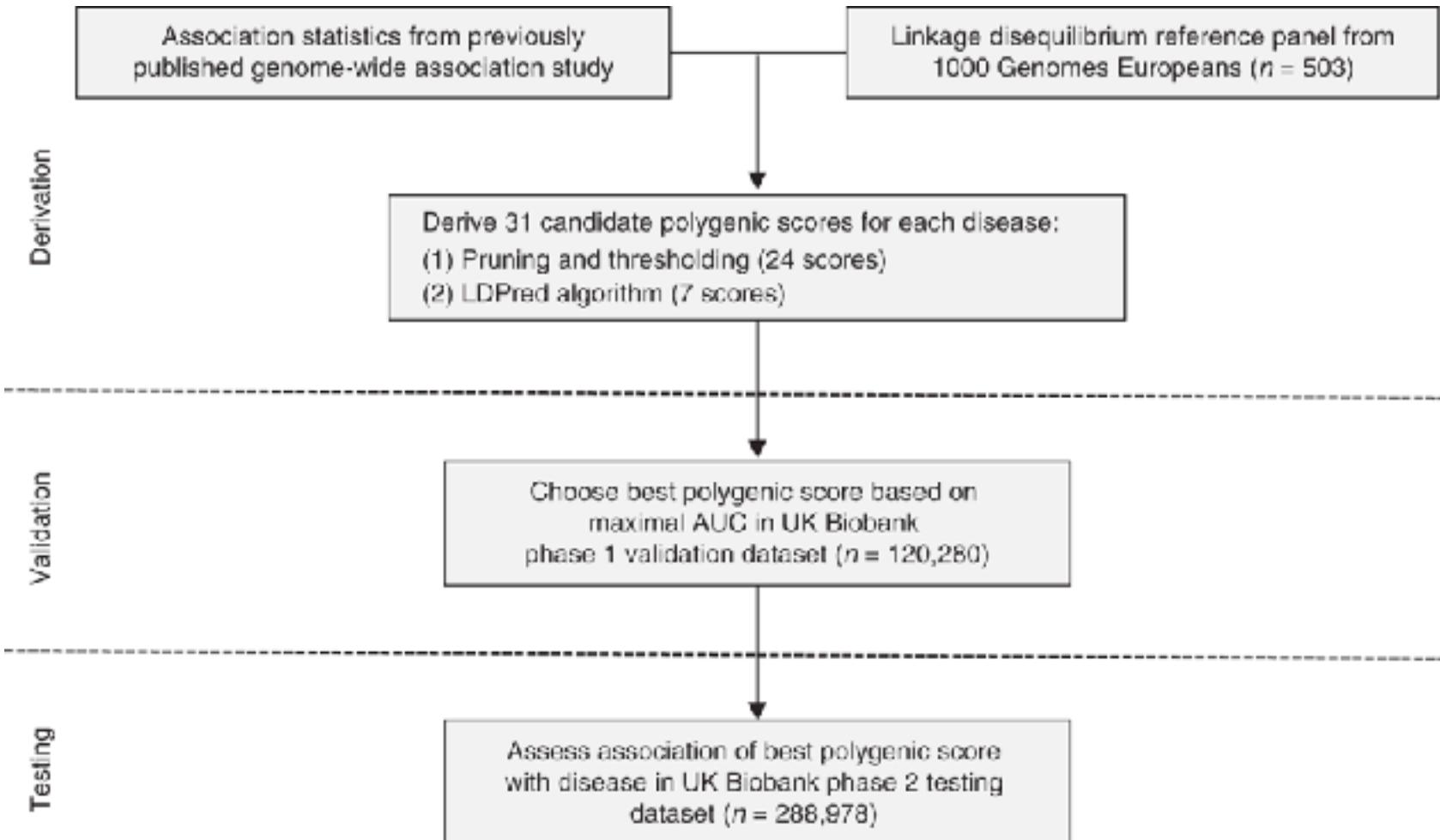
Letter | Published: 13 August 2018

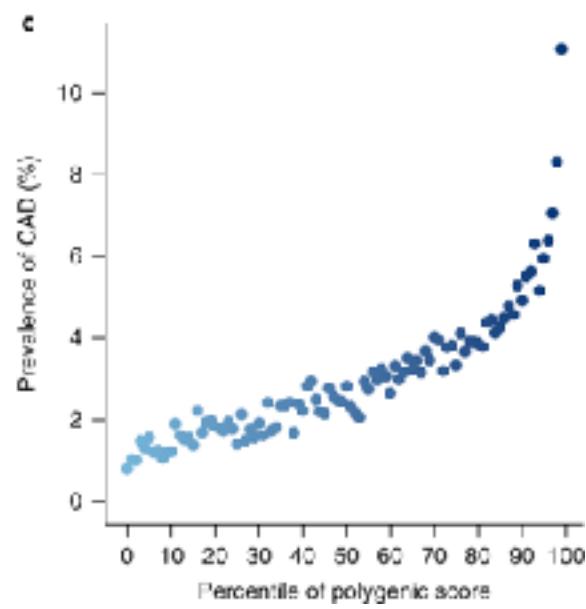
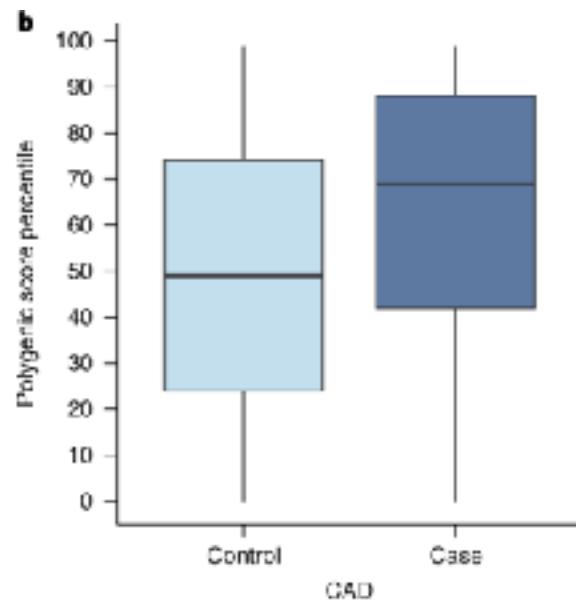
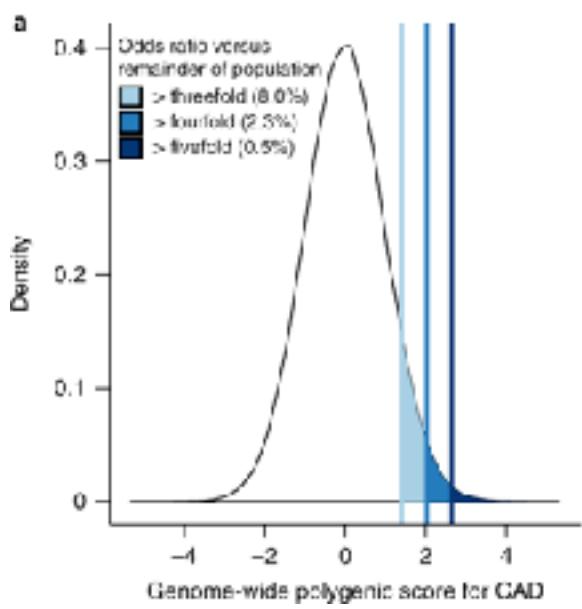
Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations

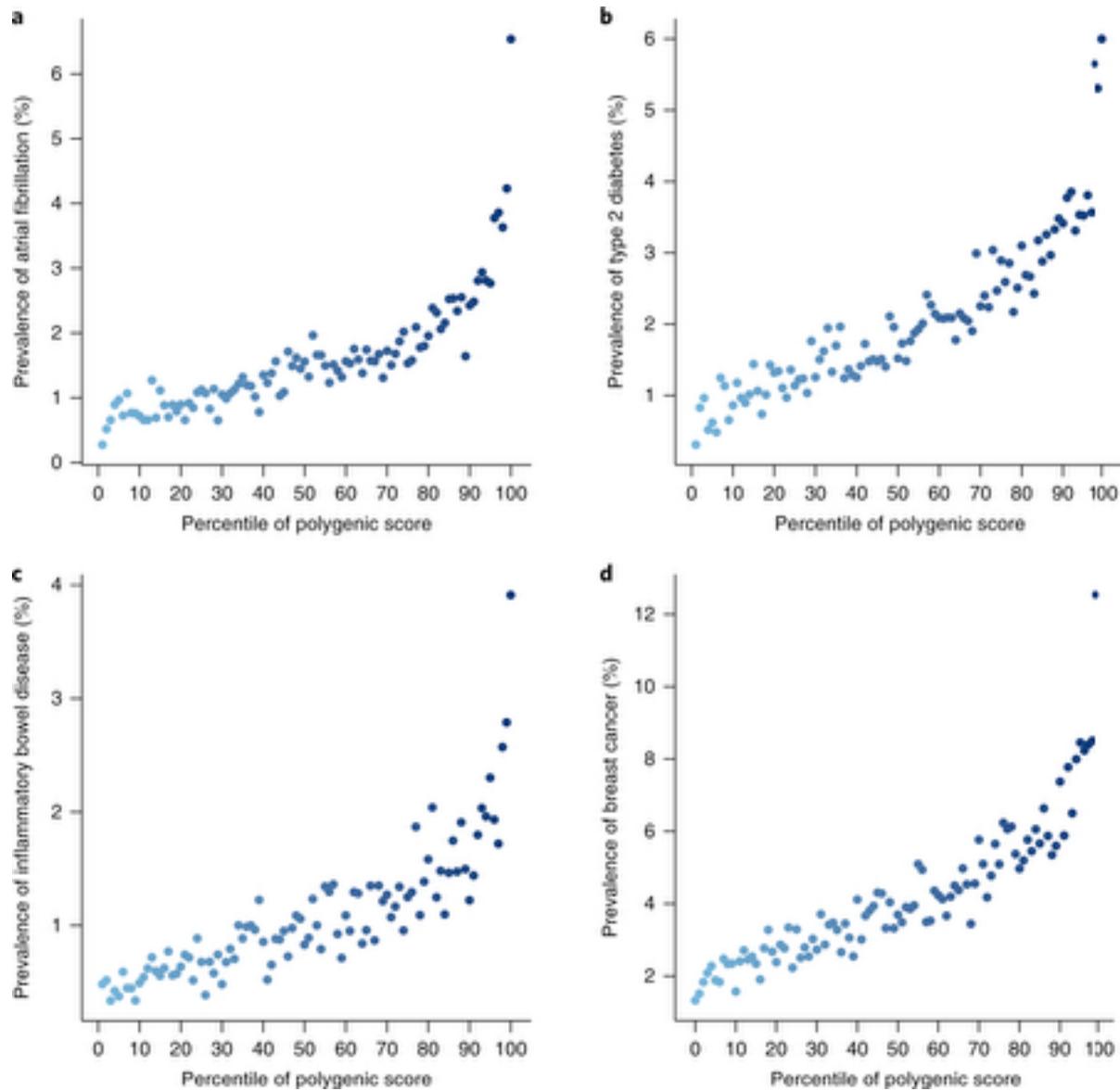
Amit V. Khera, Mark Chaffin, Krishna G. Aragam, Mary E. Haas, Carolina Roselli, Seung Hoan Choi, Pradeep Natarajan, Eric S. Lander, Steven A. Lubitz, Patrick T. Ellinor & Sekar Kathiresan✉

Nature Genetics **50**, 1219–1224 (2018) | Download Citation ↴

Include millions of variants of small effects







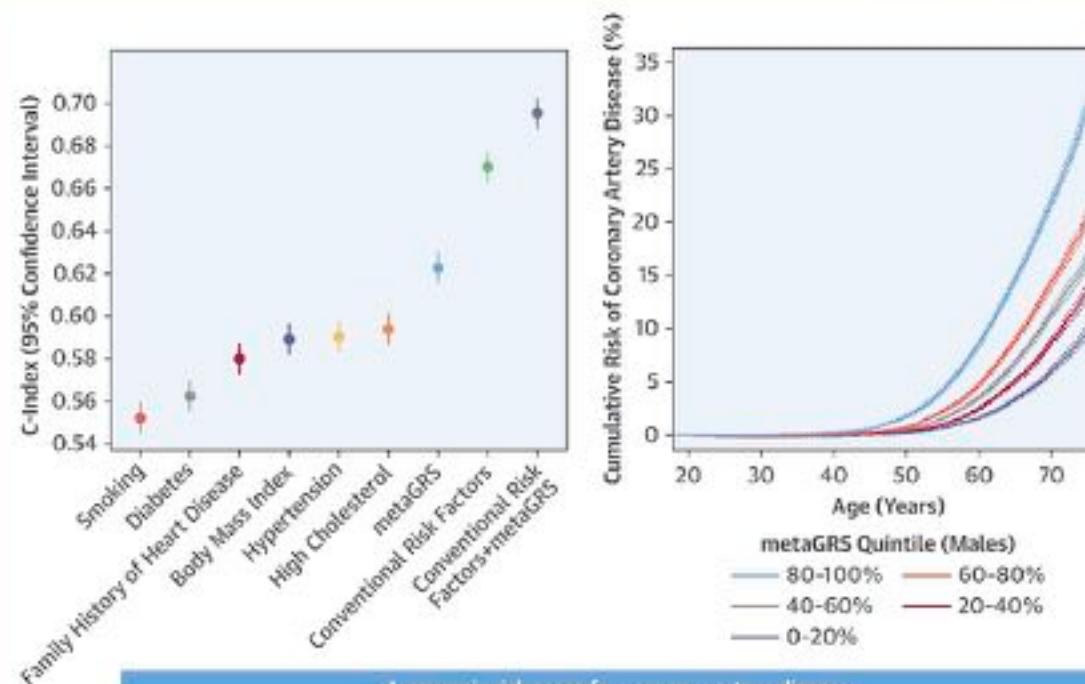
High GPS definition	Individuals in testing dataset (n)	% of individuals
Odds ratio ≥3.0		
CAD	23,119/288,978	8.0
Atrial fibrillation	17,627/288,978	6.1
Type 2 diabetes	10,099/288,978	3.5
Inflammatory bowel disease	9,209/288,978	3.2
Breast cancer	2,369/157,895	1.5
Any of the five diseases	57,115/288,978	19.8
Odds ratio ≥4.0		
CAD	6,631/288,978	2.3
Atrial fibrillation	4,335/288,978	1.5
Type 2 diabetes	578/288,978	0.2
Inflammatory bowel disease	2,297/288,978	0.8
Breast cancer	474/157,895	0.3
Any of the five diseases	14,029/288,978	4.9
Odds ratio ≥5.0		
CAD	1,443/288,978	0.5
Atrial fibrillation	2,020/288,978	0.7
Type 2 diabetes	144/288,978	0.05
Inflammatory bowel disease	571/288,978	0.2
Breast cancer	158/157,895	0.1
Any of the five diseases	4,305/288,978	1.5

Genomic Risk Prediction of Coronary Artery Disease in 480,000 Adults

Implications for Primary Prevention

Michael Inouye, Gad Abraham, Christopher P. Nelson, Angela M. Wood, Michael J. Sweeting, Frank D'Onofrio, Florence Y. Le, Shailaja Kapileshwar, Maite Brosgeska, Tingting Wang, Siu Ye, Thomas R. Webb, Martin C. Rutter, Joanna Tavarek, Mayur K. Patel, Mark J.B. Lewis, Jennifer Braund, Harry Hoenigswald, John Thompson, Hugh Williams, Dawn Johnson, Emanuele Di Angelantonio, Adam S. Butterworth, John Danesh, Nilesh J. Samani and for the UK Biobank CardioMetabolic Consortium/CHD Working Group

CENTRAL ILLUSTRATION: Genomic Risk Score for Coronary Artery Disease



A genomic risk score for coronary artery disease

Greater association with future coronary artery disease than any single conventional risk factor

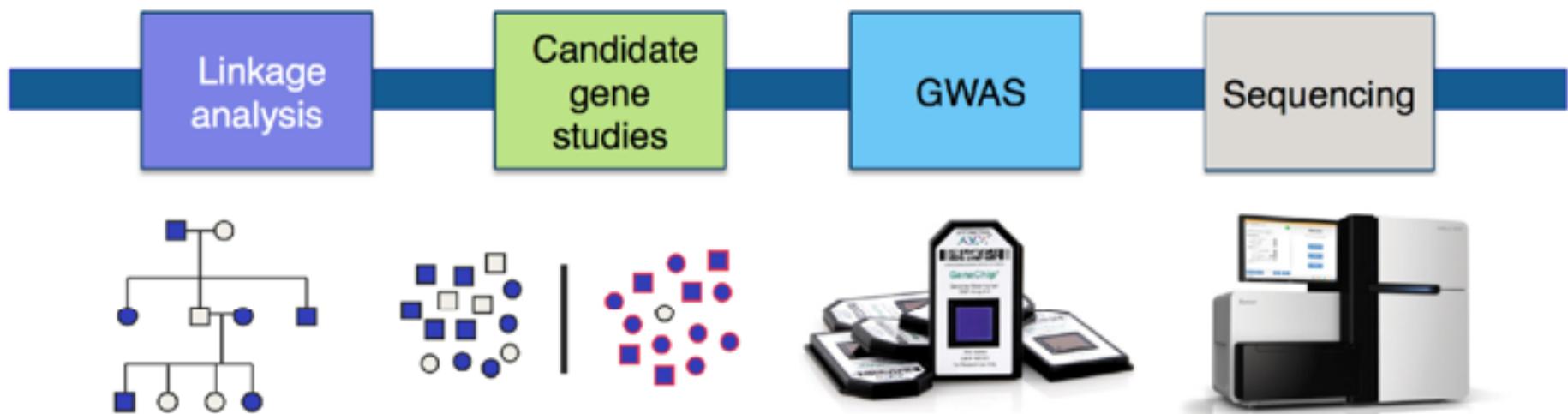
Independent of yet complements conventional risk factors

Provides meaningful lifetime risk estimates of coronary artery disease

Quantifiable at or before birth and shows potential for risk screening in early life

Inouye, M. et al. J Am Coll Cardiol. 2018;72(16):1883-93.

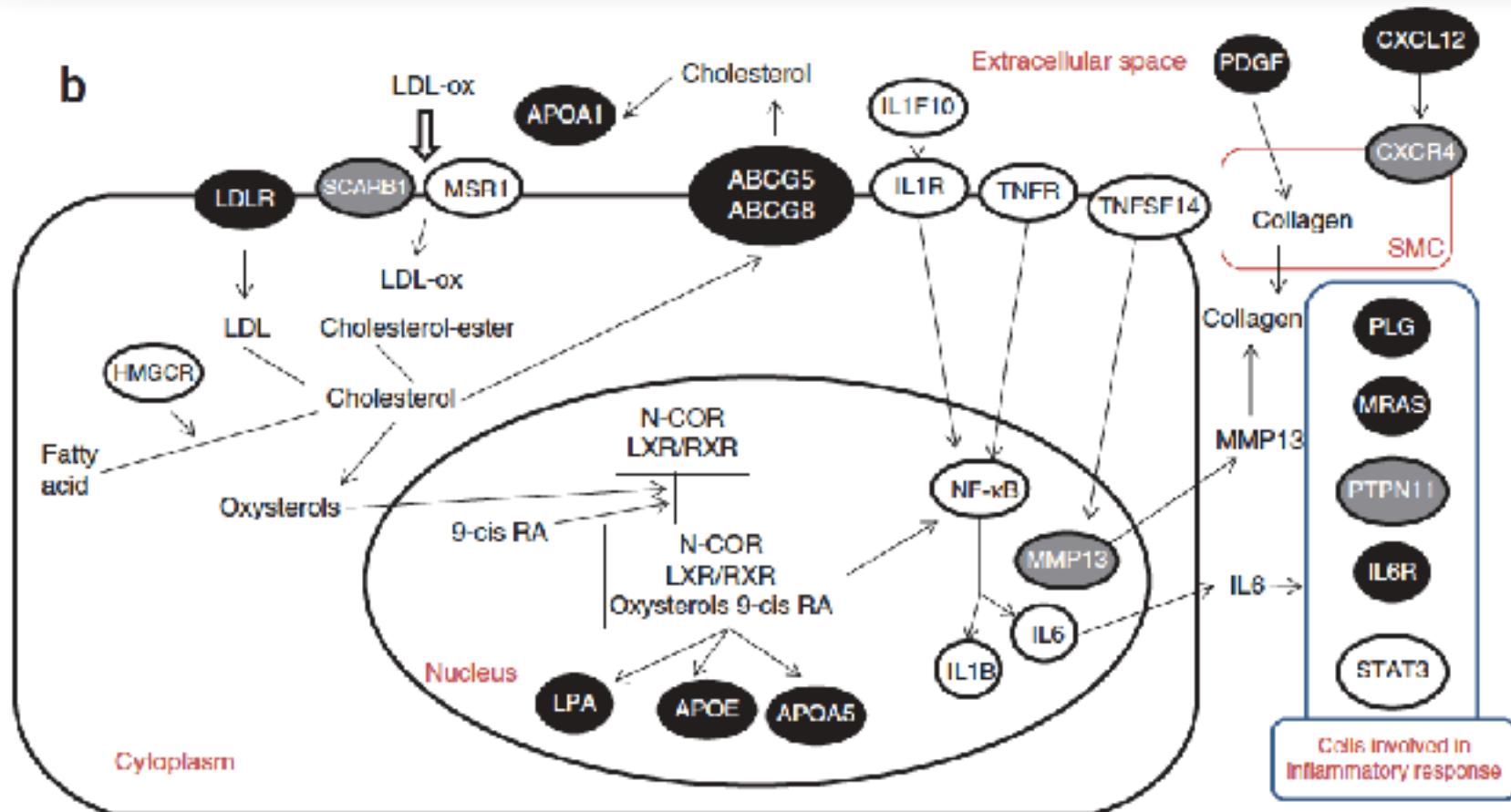
Biological mechanisms?



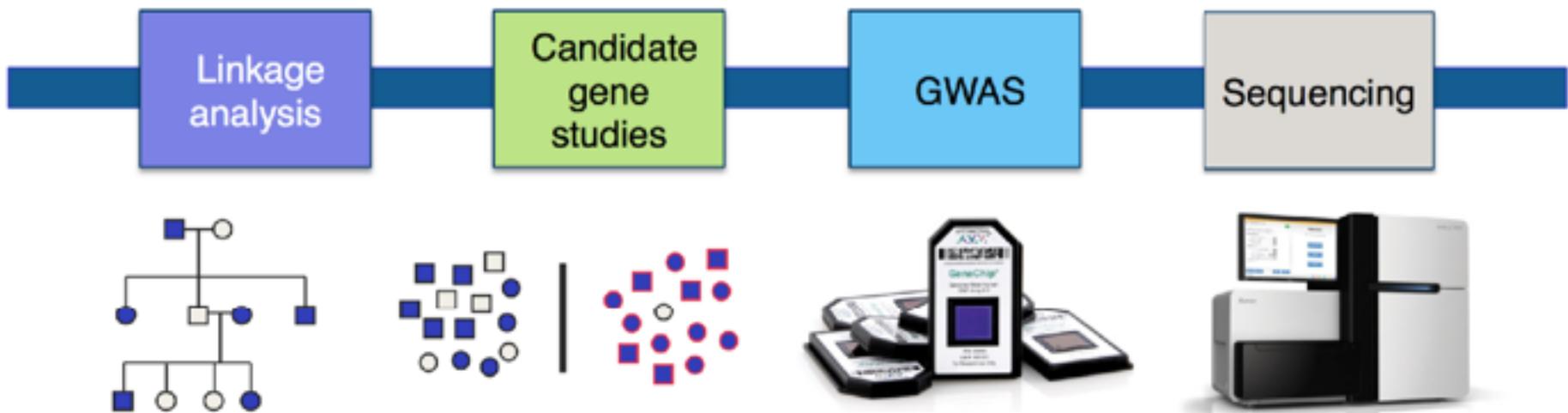
Large-scale association analysis identifies new risk loci for coronary artery disease

63,746 cases and 130,681 controls: 46 CAD loci

The CARDIoGRAMplusC4D Consortium¹



Causality: Mendelian Randomization?



APOLIPROTEIN E ISOFORMS, SERUM CHOLESTEROL, AND CANCER

SR.—It is unclear whether the relation between low serum cholesterol levels and cancer¹ is causal. In many studies occult tumour may have depressed cholesterol levels though in others the relation was found when serum cholesterol had been measured many years before the cancer was diagnosed. The relation is probably not explained by diet, because in the Seven Countries Study cohorts with widely different diets and corresponding differences in mean cholesterol levels experienced similar mean cancer rates.^{2,3} On the other hand, within each region cancer incidence was higher in men with a serum cholesterol in the lowest part of the cholesterol distribution for that country.³ Thus, naturally low cholesterol levels are sometimes associated with increased cancer risk.^{1,3}

Differences in the aminoacid sequence of apolipoprotein E (apo E) are major determinants of differences in plasma cholesterol levels within a population. Apo E has a key role in the clearance of cholesterol from plasma.⁴ The synthesis of apo E is under the control of three independent alleles, located at a single gene locus, coding for the major isoforms E-2, E-3, and E-4 with respective population frequencies of about 8, 77, and 15%.⁵ The homozygous E-3/E-3 is the most common phenotype encountered and E-2/E-2 is the least common. From apo E-2 to apo E-3, one cysteine residue is replaced by arginine, and from apo E-3 to apo E-4 another cysteine residue is replaced. As a result the avidity of apo E containing lipoproteins for lipoprotein receptors increases from apo E-2 to apo E-3 to apo E-4. In several populations,^{6,8} including the Finns and the Japanese (Dr G. Utermann, personal communication), the gradient in serum cholesterol levels in the population is associated with a gradient in apo E phenotype, E-2 being associated with lower serum low-density lipoprotein and total cholesterol levels than E-3 and E-4. Thus, if a naturally low cholesterol favours tumour

growth, then subjects with the E-2/E-2 or E-2/E-3 phenotype should have an increased risk of cancer.

Unlike most other indices of lipid metabolism, apolipoprotein aminoacid sequences are not disturbed by disease, and the apo E phenotype found in a patient will have been present since birth. A comparison of apo E phenotypes in cancer patients with those in matched controls might thus shed light on the relation between low cholesterol and cancer. If it is causal then the E-2 allele should be more common among patients and E-3 and E-4 more common among controls. On the other hand, equal distribution of apo E phenotypes among cases and controls would suggest that the association between low cholesterol and cancer is spurious. Measurement of apo E phenotype by isoelectric focusing of plasma is a routine determination in lipid laboratories; epidemiologists interested in cholesterol and cancer should include it in their studies.

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6706 BC Wageningen, Netherlands

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1. McMichael AJ, Jensen OM, Parkin DM, Zardini DG. Dietary and endogenous cholesterol and human cancer. *Epidemiol Rev* 1984; 6: 192-216.
2. Keys A, Aravanis C, Blackburn H, et al. Serum cholesterol and cancer mortality in the seven countries study. *Am J Epidemiol* 1985; 121: 870-83.
3. Katan MB. Effects of cholesterol-lowering diets on the risk for cancer and other non-cardiovascular diseases. In: Nestel PJ, et al., eds. Atherosclerosis VII: Proceedings of the Seventh International Atherosclerosis Symposium. Amsterdam: Elsevier, 1986.
4. Brown MS, Kovacs PT, Goldstein JL. Regulation of plasma cholesterol by lipoprotein receptors. *Science* 1981; 212: 628-35.
5. Utermann G, Steinmann B, Weber W. Genetic control of human apolipoprotein B polymorphism: comparison of one- and two-dimensional techniques of isoelectric analysis. *Hum Genet* 1982; 60: 944-51.
6. Utermann G, Kindermann I, Kaffarnik H, Siemers A. Apolipoprotein E phenotypes and hyperlipidemia. *Hum Genet* 1984; 65: 332-36.
7. Robertson FW, Cumming AM. Effects of Apolipoprotein E Polymorphisms on Serum Lipoprotein Concentration. *Atherosclerosis* 1985; 5: 283-92.
8. Utermann G. Genetic polymorphisms of apolipoprotein E: impact on plasma lipoprotein metabolism. In: Crepaldi G, et al., eds. Diabetes, obesity and hyperlipidemias III. Amsterdam: Elsevier, 1985: 1-28.

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IC focusing of plasma lipoproteins; epidemiologists interested in carcinogenesis and cancer should include it in their studies.

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MARTIJN B. KATAN

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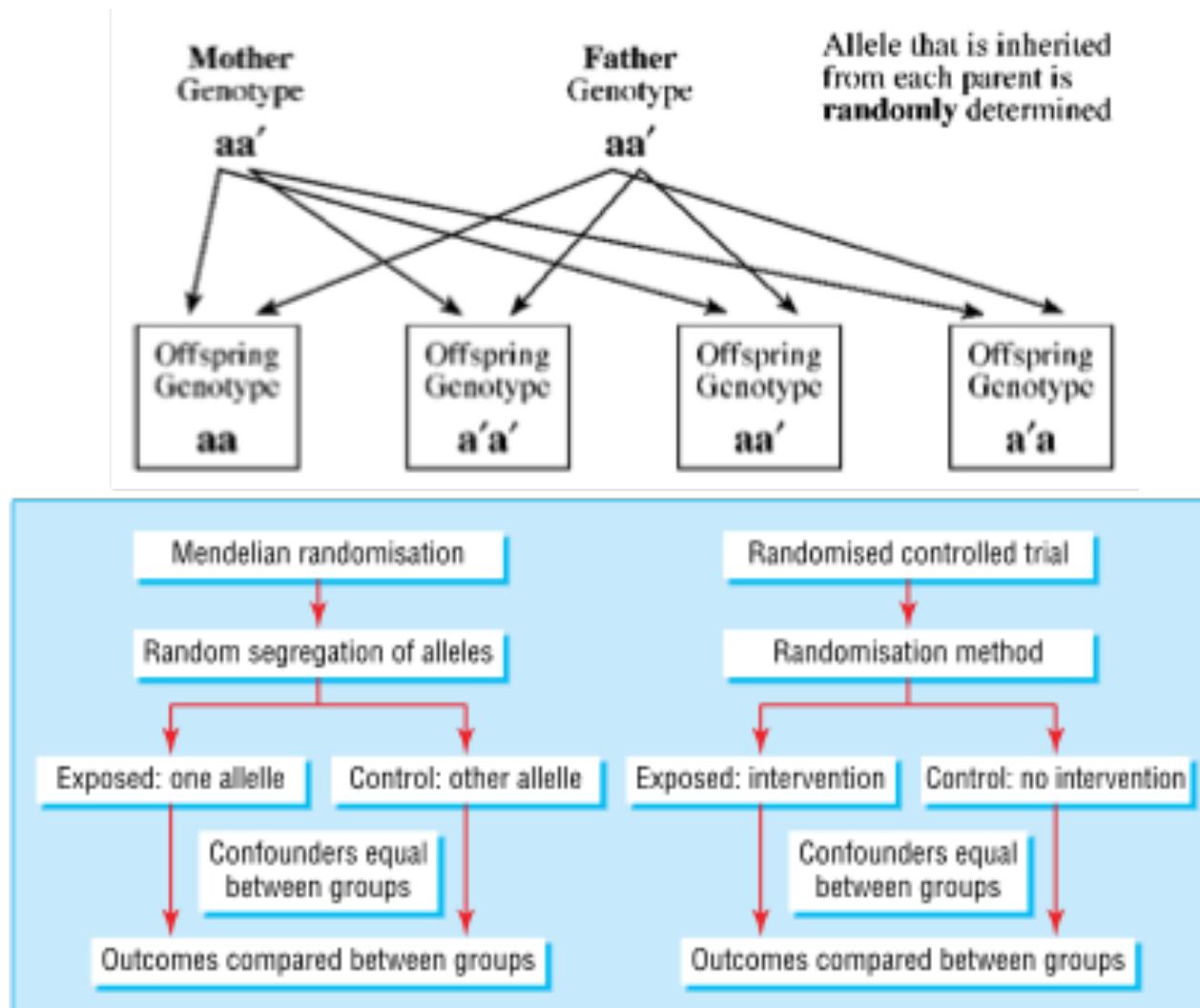
cardiovascular diseases. In: Nestel PJ, et al., eds. *Atherosclerosis VII: Proceedings of the Seventh International Atherosclerosis Symposium*. Amsterdam: Elsevier, 1986.

4. Brown MS, Kotwani PT, Goldstein JL. Regulation of plasma cholesterol by lipoprotein receptors. *Science* 1981; **212**: 628-35.
5. Utermann G, Steinmann B, Weber W. Genetic control of human apolipoprotein B polymorphism: comparison of one- and two-dimensional techniques of isoelectric analysis. *Hum Genet* 1982; **60**: 944-51.
6. Utermann G, Kindermann J, Kaffarnik H, Scimone A. Apolipoprotein E phenotypes and hyperlipidemia. *Hum Genet* 1984; **65**: 338-34.
7. Robertson FW, Cumming AM. Effects of Apolipoprotein E Polymorphisms on Serum Lipoprotein Concentration. *Arteriosclerosis* 1985; **5**: 283-92.
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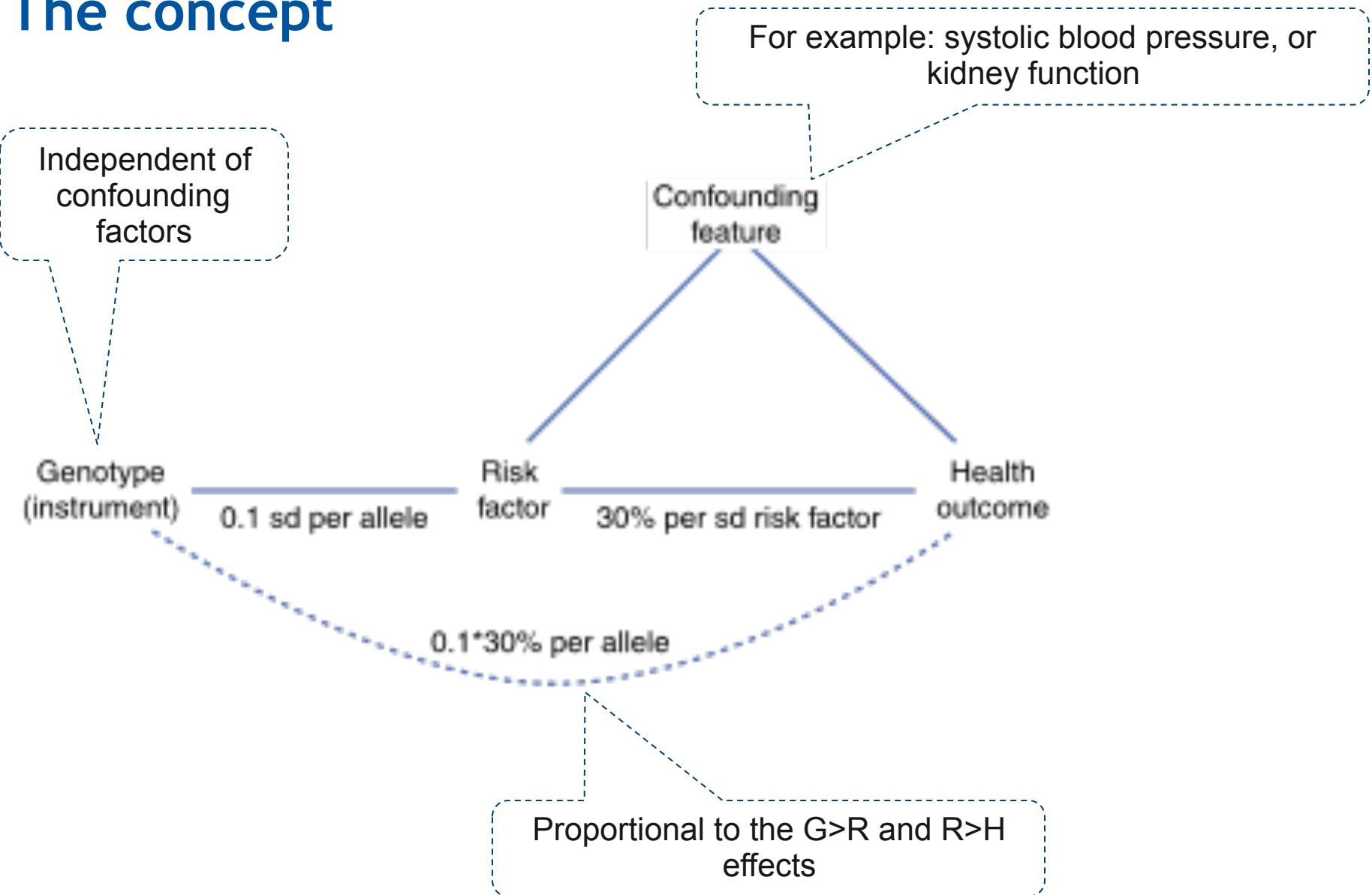


Gregor Johann Mendel - 20 July 1822 – 6 January 1884

Alleles are randomly assigned: a “natural” treatment in a “natural” randomized trial



The concept



Hypothesis: Inhibition of CETP might lead to raised HDL

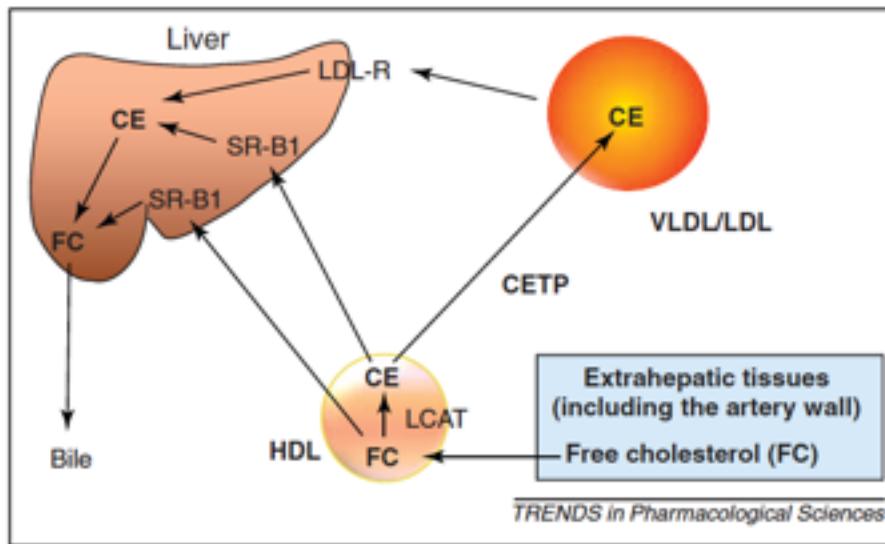


Figure 1. The role of CETP in plasma cholesterol transport. Cells in extra-hepatic tissues eliminate any cholesterol that is surplus to their needs by transferring it as free (unesterified) cholesterol (FC) to HDLs in the extracellular space. The FC in HDLs is then either delivered to the liver in a process dependent on hepatic scavenger receptor (SR)-B1 or converted into cholesteryl esters (CE) by lecithin cholesterol acyltransferase (LCAT). The CE formed in HDLs is subsequently transported to the liver by either of two pathways: a direct pathway mediated by SR-B1 and an indirect pathway in which HDL CE is first transferred to the VLDL/LDL fraction by CETP and then taken up by the liver following binding of LDL to hepatic LDL receptors (LDL-R).

CETP inhibitors

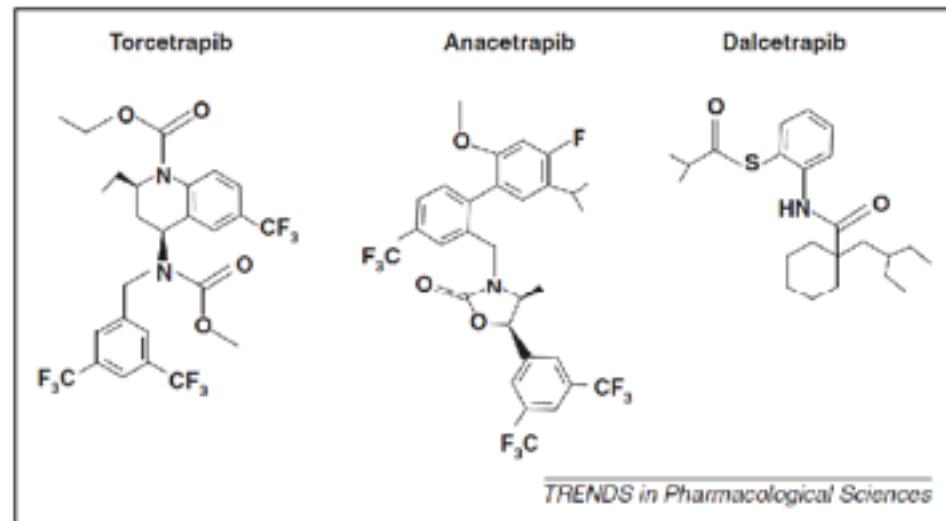


Figure 2. Structures of torcetrapib, anacetrapib and dalcetrapib.

- Torcetrapib - ILLUMINATE halted due to safety issues
- Dalcetrapib (raises HDL, does not lower LDL) stopped by Roche (no clinical benefit)
- Anacetrapib (raises HDL, lowers LDL) - DEFINE
- Evacetrapib (raises HDL, lowers LDL)

The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

NOVEMBER 22, 2007

VOL. 357 NO. 21

Effects of Torcetrapib in Patients at High Risk for Coronary Events

Philip J. Barter, M.D., Ph.D., Mark Caulfield, M.D., M.B., B.S., Mats Eriksson, M.D., Ph.D.,
Scott M. Grundy, M.D., Ph.D., John J.P. Kastelein, M.D., Ph.D., Michel Komajda, M.D., Jose Lopez-Sendon, M.D., Ph.D.,
Lori Mosca, M.D., M.P.H., Ph.D., Jean-Claude Tardif, M.D., David D. Waters, M.D., Charles L. Shear, Dr.P.H.,
James H. Revkin, M.D., Kevin A. Buhr, Ph.D., Marian R. Fisher, Ph.D., Alan R. Tall, M.B., B.S.,
and Bryan Brewer, M.D., Ph.D., for the ILLUMINATE Investigators*

After 12 months, significant HDL increase (72%)
and LDL decrease (25%), but increased risk for
CVD (HR=1.3) and death (HR=1.6)

Health

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© Health © NYT
GAMES**Pfizer Ends Studies on Drug for Heart Disease**By ALEXANDRA
Published: December 3, 2008

Pfizer announced last night that it had discontinued research on its most important experimental drug, a treatment for heart disease. The decision is a stunning development that is likely to seriously damage the company's prospects through the next decade.

Preliminary research found that the drug, torcetrapib, appeared to be linked with deaths and heart problems in the patients who were taking it. For people with heart disease, Pfizer's decision to stop the trial represents the failure of a heart attack and stroke.

Torcetrapib is designed to raise levels of so-called good cholesterol. It was to be used in combination with older drugs called statins, like Lipitor and Zocor, which reduce so-called bad cholesterol.

As recently as Thursday, Pfizer executives had hailed the drug as a major advance in efforts to reduce cardiovascular risk. "This will be one of the most important companies of our generation," said Jeffrey R. Kindler, Pfizer's chief executive.

Pfizer is the world's biggest drug company, with 106,000 employees and \$53 billion in sales in 2008.

In a news release issued yesterday, the company said that it would immediately halt clinical trials of the drug and its development. The decision was based on interim results from a 15,000-patient clinical trial. The trial, called ILLUMINATE, was scheduled to be completed in 2009. Pfizer had hoped it would prove that the combination of the two drugs was significantly more likely to reduce heart attacks and strokes than Lipitor alone does.

Even before yesterday's announcement, some cardiologists had raised concerns about torcetrapib, noting that the drug raised blood pressure in many patients, a serious side



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MOST POPULAR - HEALTH

F WILLEN R GOODMAN V PERRY

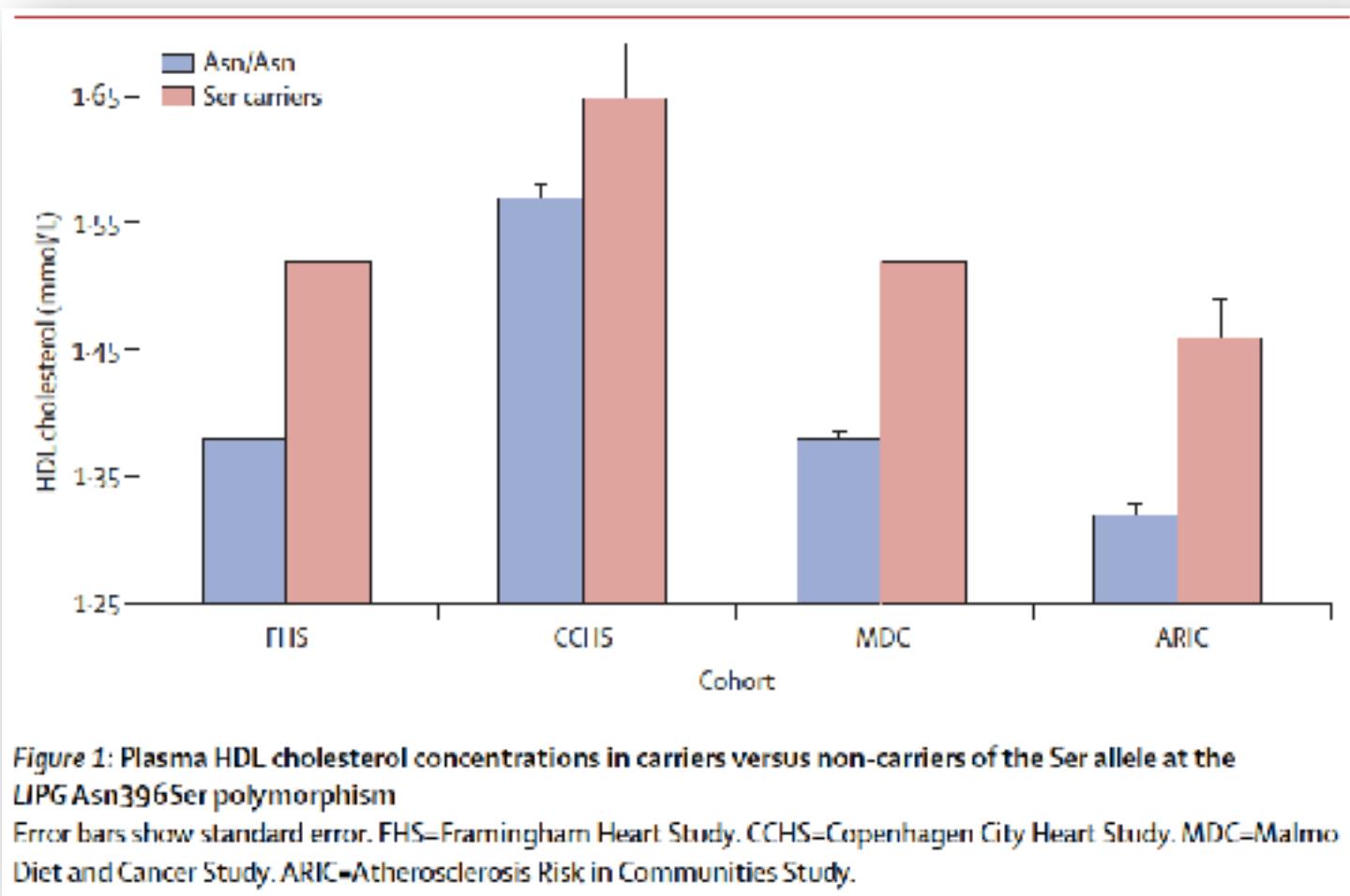
1. Well: A Richer Life by Living the Older Half Well
2. Drugs Help Tailor Treatment of Prostate Cancer
3. Well: New Data on Harms of Prostate Screening
4. Well: Really? Never Touch Your Teeth Immediately After a Meal
5. Well: Sleep Apnea tied to Increased Cancer Risk
6. Basics for Healthy Cultural Groups, Plus a Sure Sign
7. A Long View on Health Care: Think Like a...
Lionist
8. More Care Up Front for 40s & 50s
9. Well: How Far Will Harmless Brain Numbness Go in Common Drugs?
10. Well: The Doctor's Remedy: Blame Feedback for Stress

Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study

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Asn396Ser in *LIPG* increases HDL-C, and does not
affect other relevant factors
(BP, T2D, BMI, CRP, LDL)

HDL increased in Ser carriers



But no protection against MI

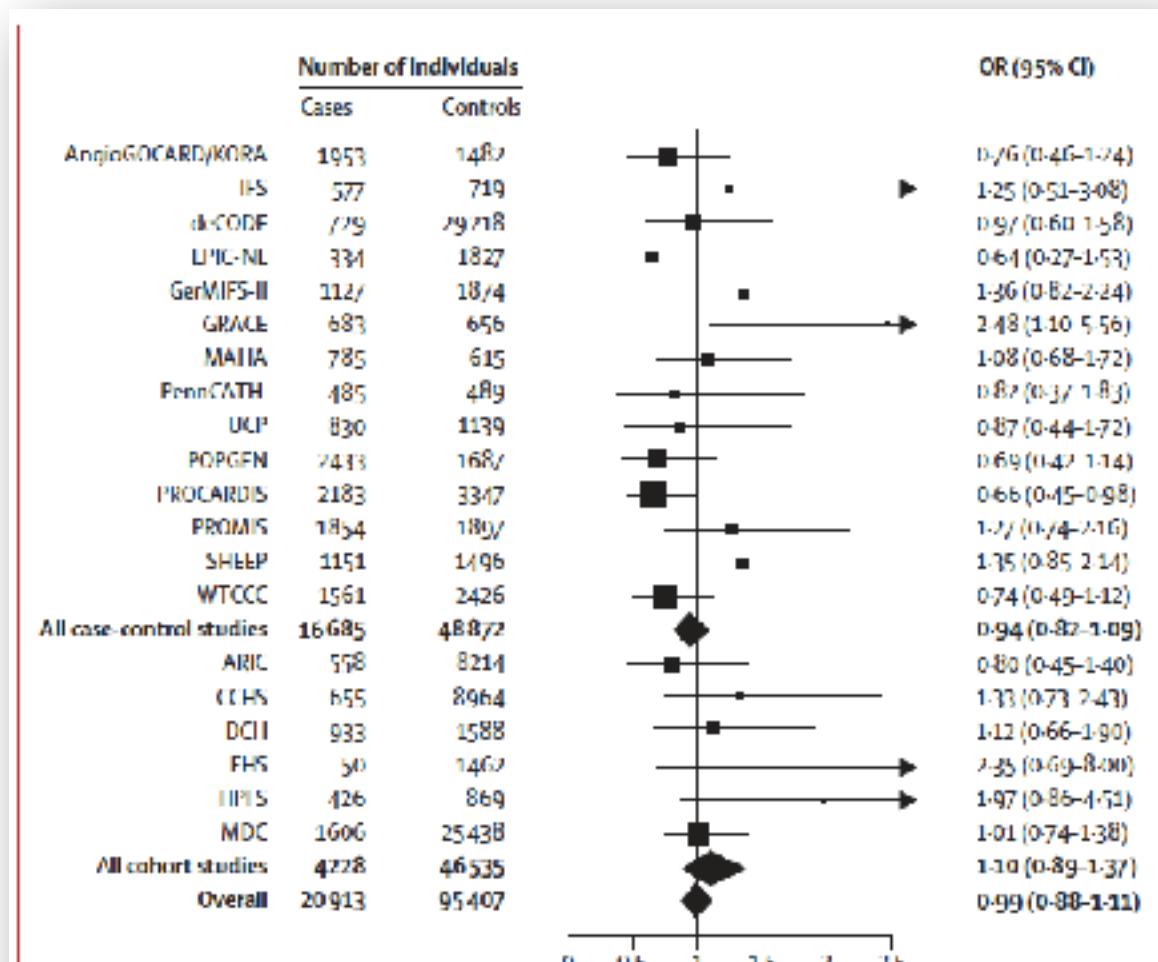


Figure 2: Association of LIPG Asn396Ser with myocardial infarction in 116 320 participants from 20 studies. In each study, the LDL-cholesterol-raising serine allele was modelled.

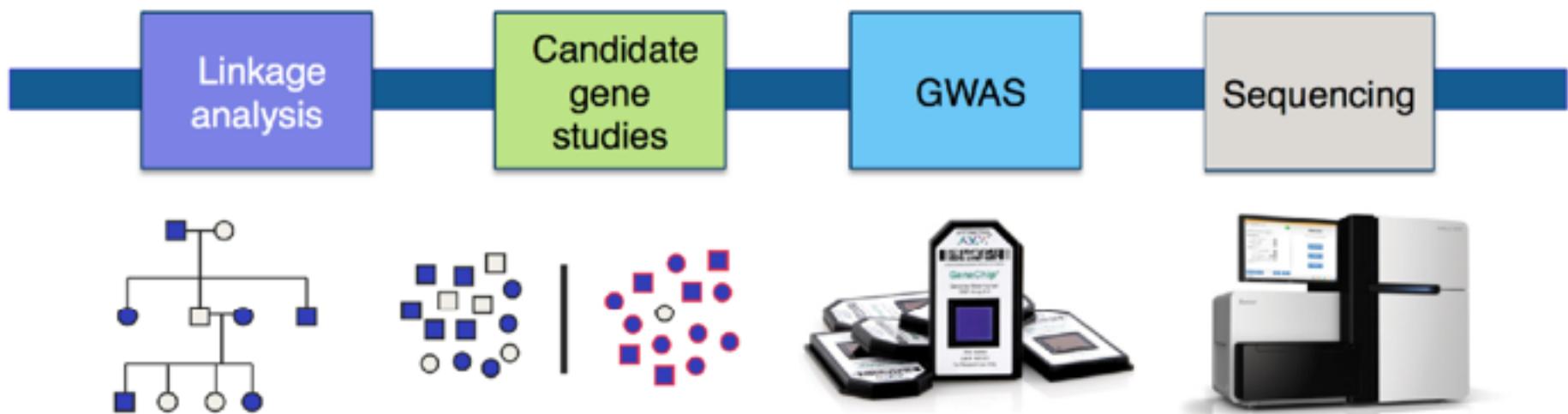
HDL has no impact on myocardial infarction risk

	Odds ratio (95% CI) per SD increase in plasma lipid based on observational epidemiology*	Odds ratio (95% CI) per SD increase in plasma lipid conferred by genetic score†
LDL cholesterol	1·54 (1·45-1·63)	2·13 (1·69-2·69), $p=2\times10^{-19}$
HDL cholesterol	0·62 (0·58-0·66)	0·93 (0·68-1·26), $p=0·63$ 

*Observational epidemiology estimates derived from more than 25 000 individuals from prospective cohort studies as shown in the appendix p 22. †LDL genetic score consisting of 13 single nucleotide polymorphisms (SNPs) as shown in the appendix p 27; HDL genetic score consisting of 14 SNPs as shown in the appendix p 28.

Table 4: Estimate of the association of genetically raised LDL cholesterol or HDL cholesterol and risk of myocardial infarction using multiple genetic variants as instruments

Drug discovery & validation



Drug discovery

- Each locus likely harbors a disease-driving gene (or regulatory element)
- The magnitude of the odds ratio does not indicate
 - Potential biological value
 - Potential for therapy (“druggability”)
- Examples
 - *PPARG* in type 2 diabetes (thiazolidinediones)
 - *KCNJ11* and type 2 diabetes (sulfonylureas)
 - *PCSK9* and myocardial infarction (*PCSK9* inhibitors)

ORIGINAL ARTICLE

Sequence Variations in PCSK9, Low LDL, and Protection against Coronary Heart Disease

Jonathan C. Cohen, Ph.D., Eric Boerwinkle, Ph.D., Thomas H. Mosley, Jr., Ph.D., and Helen H. Hobbs, M.D.

- **PCSK9 first discovered in familial hypercholesterolemia**
- Then discovered in a GWAS of EOMI



LDL and PCSK9 in two populations

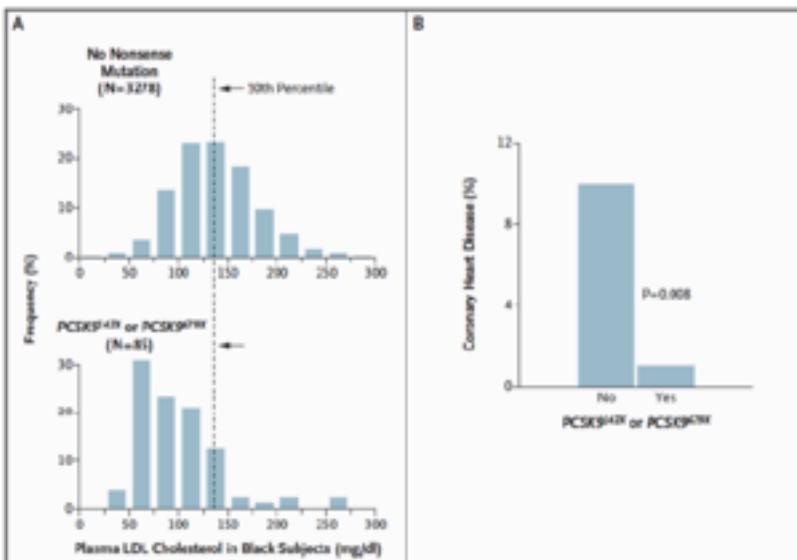


Figure 1. Distribution of Plasma LDL Cholesterol Levels (Panel A) and Incidence of Coronary Heart Disease (Panel B) among Black Subjects, According to the Presence or Absence of a *PCSK9^{H/H}* or *PCSK9^{H/H}* Allele.

In Panel A, the distribution of plasma LDL cholesterol levels at baseline among 3278 black subjects who did not have a *PCSK9^{H/H}* or *PCSK9^{H/H}* allele (top) is compared with the distribution of levels among the 85 black subjects who had one of these two alleles (bottom). Panel B shows the percentage of participants from these two groups who had no evidence of coronary heart disease at baseline and in whom coronary heart disease developed during the 15-year follow-up period. To convert values for LDL cholesterol to millimoles per liter, multiply by 0.02586.

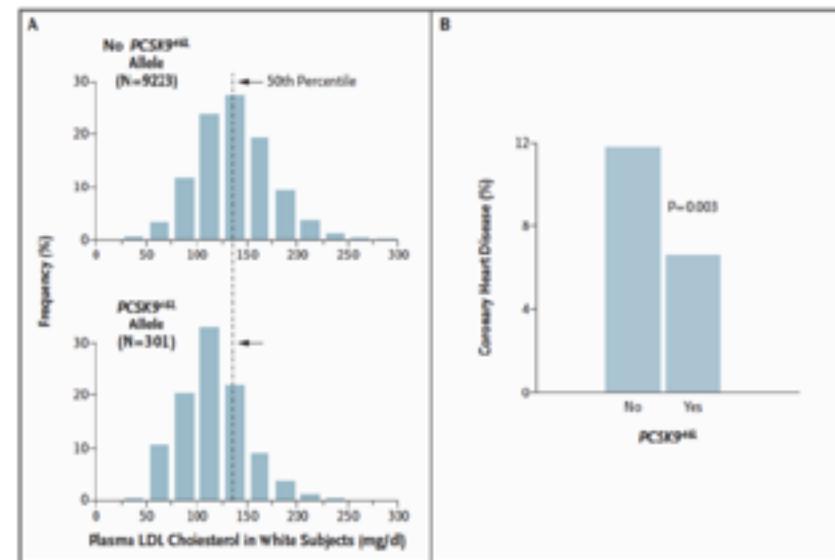
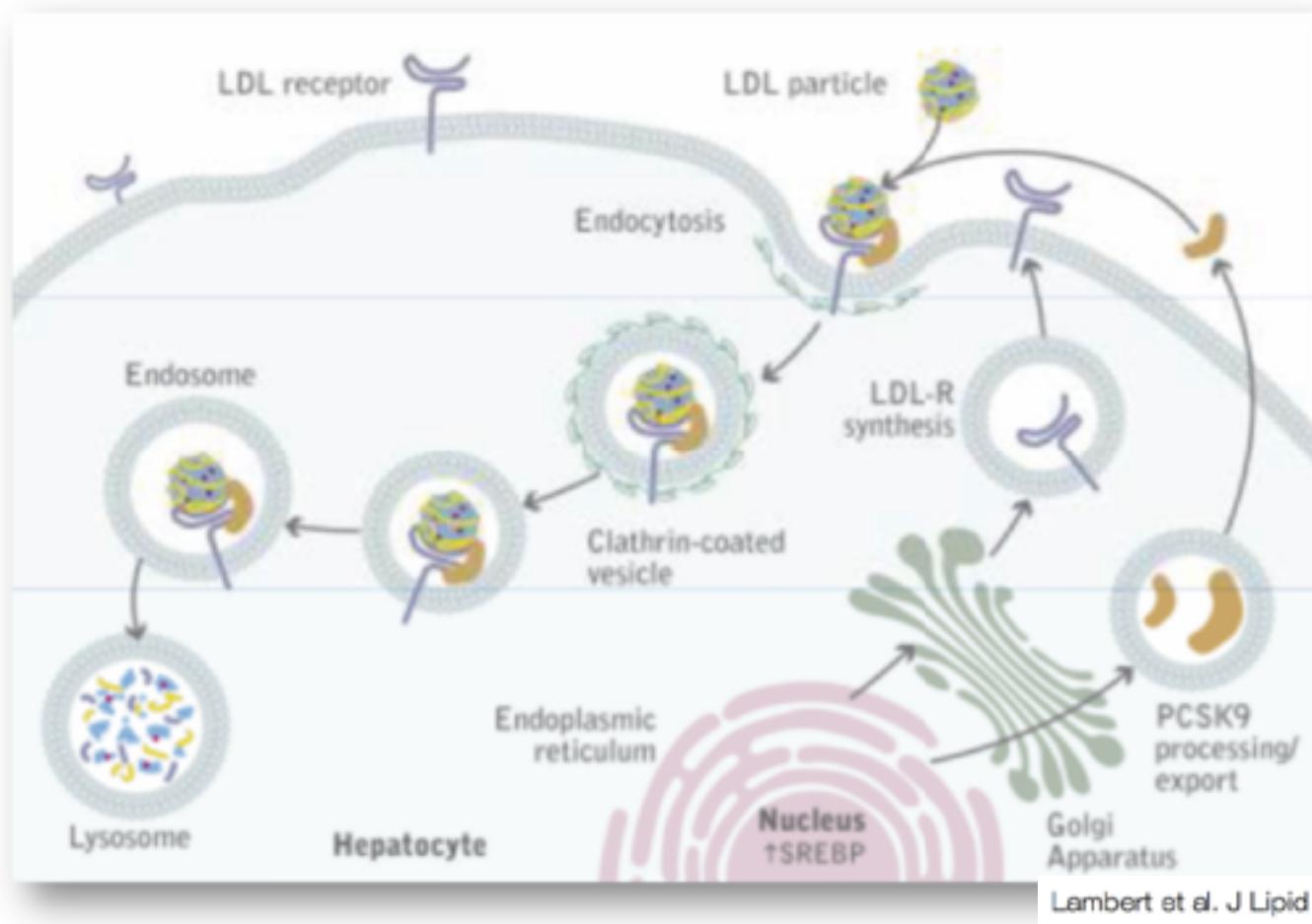


Figure 2. Distribution of Plasma LDL Cholesterol Levels (Panel A) and Incidence of Coronary Events (Panel B) among White Subjects, According to the Presence or Absence of a *PCSK9^{H/H}* Allele.

In Panel A, the distribution of plasma LDL cholesterol levels at baseline among 9223 white subjects who did not have a *PCSK9^{H/H}* allele (top) is compared with the distribution of levels among the 301 white subjects who were either heterozygous or homozygous for this allele (bottom). Panel B shows the percentage of participants from these two groups who had no evidence of coronary heart disease at baseline and in whom coronary heart disease developed during the 15-year follow-up period. To convert values for LDL cholesterol to millimoles per liter, multiply by 0.02586.

PCSK9 promotes *LDLR* degradation



Conclusions

- The genomic sequence is set at conception, no need to worry about confounding factors
- GWAS have been and will continue to be very successful
- Still need large sample sizes for sufficient power
- Complex genetics studies useful to gain information causality and drug discovery
- The jury is still out with respect to risk prediction
- Interpretation and translation will be the major challenge in the next decade

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Research topics

Biomarker Discovery & Validation

Athero-Express | AAA-Express | CTMM | many more

Ischemic stroke

GWAS | 4C | MR | CRISPR-Cas9

Cardiovascular Genomics

Next-Gen Sequencing | eQTL | pQTL | Transcriptomics | Epigenomics | MR

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