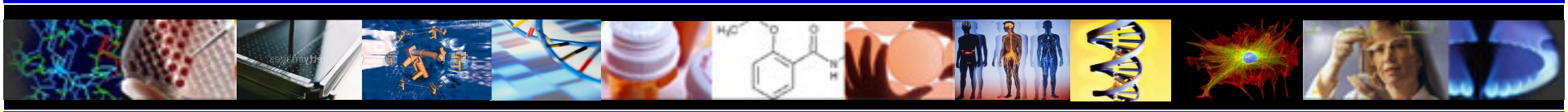
Cardiovascular Genomics in 2007: Careers in Genomics and Proteomics



Christopher J. O'Donnell MD MPH

No Disclosures

ACC How to Become a Cardiovascular Investigator

November 9, 2007

My Story: the Sculpting of a Cardiovascular Investigator

1987 Medical School

Residency
1st Clin Research

Contagious passion for epi & outcomes research

CV Fellowship
Epi Fellow+MPH

"What am I good at→ move on→enjoy and succeed"

Faculty Job I
"50/50"

Focus on research, play focussed clinical role

1997

Faculty Job IIa
"80/20" NIH+Hospital
"Major" in Genetic Epidemiology

Be rigorous, publish, focus on genetics and imaging

Faculty Job IIb
"90/10" NIH+Hospital
Immerse in Gen Epi, Genomics & Programs

Join a collaborative genomic community

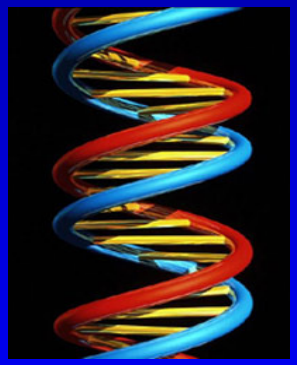
2007

Lead novel genomic programs at Framingham & NHLBI

Progression from Risk Factors to Clinical Cardiovascular Disease

Major Traditional Risk Factors: SBP, DBP, Cholesterol, LDL, HDL, Diabetes Mellitus BioMarkers: Inflammation, Met. Syndrome, Thrombosis

Genetic



Determinants

Environmental

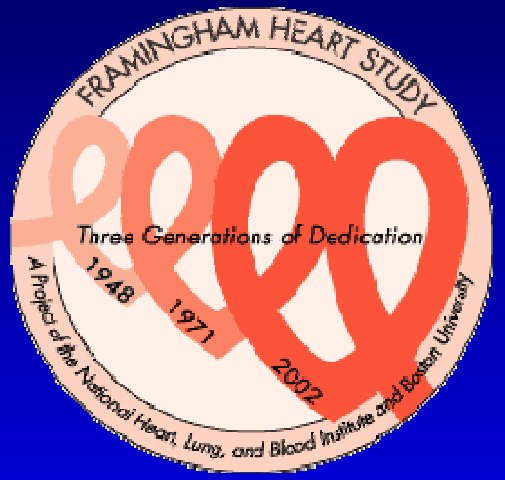
Modification

Subclinical Disease of Ventricle, Conduction System and Arteries

Clinical Cardiovascular Disease: Heart Failure, Arrhythmia, Myocardial Infarction, and Stroke

Framingham Heart Study

Downtown Framingham, MA (circa 1960)



1948 → 1958 → 1968 → 1978 → 1988 → 1998 → 2008

1948 → → → → → → → 2008

Original cohort: N = 5209 men and women (ages 28-62)
1644 spouse pairs, 596 extended families

1972 → → → → 2008

Offspring study: N = 5124 men and women (ages 5-70)
1576 spouse pairs, 3514 biological offspring

Third Generation study: 2002 →
N=~4000 men and women

Premature CVD in Parents* Leads to Increased Relative Risk of CVD

Model Adjustment	Positive Parental History of Premature CVD		
	None	Both	≥1 Parent
Men			
Age-adjusted	1.0	**3.1**	**2.6**
Multivariable-adjusted*	1.0	**2.4**	**2.0**
Women			
Age-adjusted	1.0	**4.1**	**2.3**
Multivariable-adjusted*	1.0	**2.8**	**1.7**

*Lloyd-Jones et al. JAMA 2004;291:2204. Adj. for age, total/HDL, SBP, anti-HTN Rx, AODM, BMI, current smoking.

Heritability of CVD Risk Factors & Subclinical Disease: Framingham Study

Variable	Heritability
Risk Factors*	
Fasting Glucose	32%
Systolic Blood Pressure	42%
Maximum BMI	40%
Biomarkers	
CRP	26%
PAI-1 Antigen	26%
Platelet Aggregation (Epi)	48%
Subclinical LV & Conduction Disease**	
LV Hypertrophy	26%
QT Duration	35%
Subclinical Vascular Disease	
Wall Thickness,Carotid Artery†	38%
Calcium, Aorta or Coronaries‡	38%

*L. A. Cupples, ASHG 1996. *E. Benjamin, AHA 2000. †C Fox, Stroke 2002,
‡P Peyser, Circulation 2002, ††C O'Donnell, Circulation 2002, Newton-Cheh, Heart Rhythm 2005.

2000-05: Genome-Wide Linkage for CHD/MI

Source	Phenotype	N of families	Locus
Pajukanta, AJHG 2000	Premature CHD	156 Finnish	2q21, X
Francke, Hu M Gen 2001	CHD or AODM	99 Indian	16p13
Broeckel, Nat Gen 2002	Premature MI	513 German	14q32
Harrap, ATVB 2002	ACS	63 Austral. (sibpairs)	2q36
Wang, AJHG 2004	Premature CHD	428 Caucasian US	1p34-36
Helgadottir, Nat Gen 2004	MI	296 ext. Icelandic	13q12-13
Hauser, AJHG 2004	Premature CHD	438 US	3q13
Samani, AJHG 2005	Premature CHD, MI	1,933 (sibpairs)	Chr 2
Farrall, Plos Gen 2006	Premature MI or ACS	2026 (sibpairs)	Chr 3, 11, 17
Bowden, Diabetes 2006	CVD in AODM	358 Caucasian	Chr 3, 4, 14

Meta-analysis (Chiodini and Lewis. ATVB 2003) of first four studies above showed overlap for 3q26-27. CHD=coronary heart disease, MI=myocardial infarction, AODM=Adult onset diabetes, ACS=Acute coronary syndrome.

1990's: Single Candidate Gene Variants Studied for Coronary Heart Disease

Gene	Variant	Relative Risk	N of Studies	N of Cases / Controls
Apo E	ε4/ε4	1.42	48	15,492 / 32,965
MTHFR	C677T	1.21	72	12,193 / 11,945
ACE	D/I	1.21	19	2,848 / 10,256
Apolipo B	Ins/Del	1.19	22	6,007 / 5,609
PAI-1	4G/5G	1.20	10	1,515 / 1,866
Fibrinogen B	G-455A	0.68	4	745 / 816
ENOS	Intron-4	1.34	16	6,212 / 6,737

Adapted from Ginsburg G et al. JACC 200546:1615.

The Human Genome and Hapmap Projects

Nature October 21 2004;431:931.

articles

Finishing the euchromatic sequence of the human genome

International Human Genome Sequencing Consortium*

* *A list of authors and their affiliations appears in the* Supplementary Information

The sequence of the human genome encodes the genetic instructions for human physiology, as well as rich information about human evolution. In 2001, the International Human Genome Sequencing Consortium reported a draft sequence of the euchromatic portion of the human genome. Since then, the international collaboration has worked to convert this draft into a genome sequence with high accuracy and nearly complete coverage. Here, we report the result of this finishing process. The current genome sequence (Build 35) contains 2.85 billion nucleotides interrupted by only 341 gaps. It covers ~99% of the euchromatic genome and is accurate to an error rate of ~1 event per 100,000 bases. Many of the remaining euchromatic gaps are associated with segmental duplications and will require focused work with new methods. The near-complete sequence, the first for a vertebrate, greatly improves the precision of biological analyses of the human genome including studies of gene number, birth and death. Notably, the human genome seems to encode only 20,000–25,000 protein-coding genes. The genome sequence reported here should serve as a firm foundation for biomedical research in the decades ahead.

"2.85 billion nucleotides …encode only 20,000-25,000 protein-coding genes" & all genomic data freely available on the web

The genome consists of ~ 1 SNP per 1000 bp and "a block-like structure of linkage disequilibrium…leading to substantial correlations of SNPs with…their neighbours"

Science October 27 2005;431:931

nature

ARTICLES

A haplotype map of the human genome

The International HapMap Consortium*

Inherited genetic variation has a critical but as yet largely uncharacterized role in human disease. Here we report a public database of common variation in the human genome: more than one million single nucleotide polymorphisms (SNPs) for which accurate and complete genotypes have been obtained in 269 DNA samples from four populations, including ten 500-kilobase regions in which essentially all information about common DNA variation has been extracted. These data document the generality of recombination hotspots, a block-like structure of linkage disequilibrium and low haplotype diversity, leading to substantial correlations of SNPs with many of their neighbours. We show how the HapMap resource can guide the design and analysis of genetic association studies, shed light on structural variation and recombination, and identify loci that may have been subject to natural selection during human evolution.

2006: Genome-Wide Association Studies (GWAS) of 100K-1,000K SNPs

With completion of the human genome sequence & "HapMap":

- High throughput genotyping at acceptable cost
- Several companies now selling genome-wide screening CHIPs of 250,000-1,000,000 SNPs
- Technology has outpaced the conduct of research
- Critical issues now are control for multiple testing, large sample sizes (1000's of subjects), replication using multiple independent studies, nailing the functional significance of novel gene discoveries

GWAS (Case-Control) Studies to Date

Cancer

- Prostate Cancer
- ALL
- Breast Cancer
- Colon Cancer

Lung

- Asthma

Eye

- Macular Degeneration
- Glaucoma (XFG)

Cardiovascular and Risk Factors

- Obesity
- Hypertension
- Diabetes, Type 1
- Diabetes, Type 2
- ECG QT interval
- MI, CAD
- Atrial Fibrillation

Rheumatic Diseases

- SLE (Lupus)
- Celiac Disease
- Rheumatoid Arthritis
- Crohn's Disease

Infectious Disease

- HIV Host Control

Bone

- Osteoarthritis

Neurology and Psychiatry

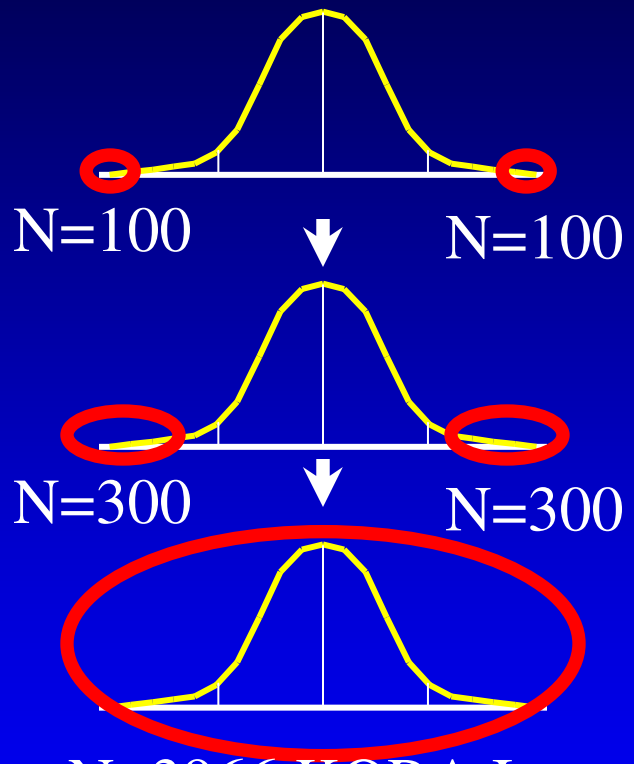
- Bipolar Disorder
- Restless Leg Syndrome
- Multiple Sclerosis
- ALS

GWA Study (100K): *NOS1* Regulator Gene *CAPON* Variant and Cardiac Repolarization

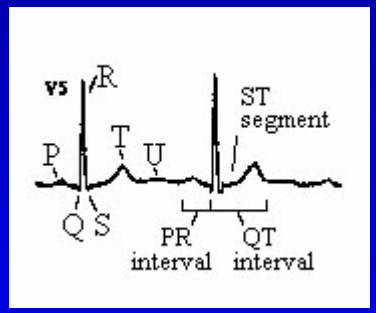
Stage I: ~100K GWAS, Women Only KORA I

Stage II: Top 10 SNPs, Women Only KORA I

Stage III: Top 7 SNPs, Men & Women KORA I

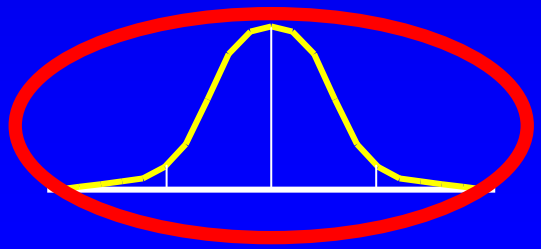


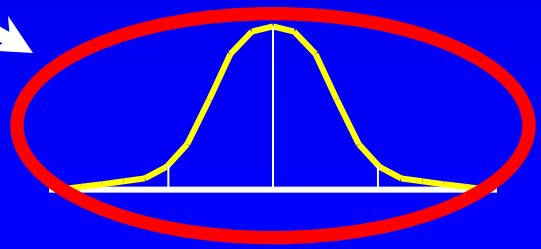
Phenotype:
Age-, sex- and RR-adjusted QT interval



Reference: Arking DE et al. Nature Genetics 2006; epub.

NOS1AP (CAPON)
QTc_5.3
FGFR2
QTc_14.1
KCNK1
ITPR1
CACNA2D1


N=2646 KORA II


N=1805 Fram. Heart Study

Diabetes Mellitus GWAS 2007

Sciencexpress Report

Replication of Genome-Wide Association Signals in U.K. Samples Reveals Risk Loci for Type 2 Diabetes

Eleftheria Zeggini,[1,2*] Michael N. Weedon,[3,4*] Cecilia M. Lindgren,[1,2*] Timothy M. Frayling,[3,4*]
Katherine S. Elliott,[2] Hana Lango,[3,4] Nicholas J. Timpson,[2,5] John R. B. Perry,[3,4] Nigel W. Rayner,[1,2]
Rachel [illegible]
Christop[illegible]
Lon R. [illegible]
The We[illegible]

A Genome-Wide Association Study of Type 2 Diabetes in Finns Detects Multiple Susceptibility Variants

Laura J. Scott,[1] Karen L. Mohlke,[2] Lori L. Bonnycastle,[3] Cristen J. Willer,[1] Yun Li,[1] William L. Duren,[1] Michael R. Erdos,[3] Heather M. Stringham,[1] Peter S. Chines,[3] Anne U. Jackson,[1] Ludmila Prokunina-Olsson,[3] Chia-Jen Ding,[1] Amy J. Swift,[3] Narisu Narisu,[3] Tianle Hu,[1] Randall Pruim,[4] Rui Xiao,[1] Xiao-Yi Li,[1] Karen N. Conneely,[1] Nancy L. Riebow,[3] Andrew G. Sprau,[3] Maurine Tong,[3] Peggy P. White,[1] Kurt N. Hetrick,[5] Michael W. Barnhart,[5] Craig W. Bark,[5] Janet L. Goldstein,[5] Lee Watkins,[5] Fang Xiang,[1] Jouko Saram[illegible]
R. Abe[illegible]
Franci[illegible]

Genome-Wide Association Analysis Identifies Loci for Type 2 Diabetes and Triglyceride Levels

Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes for BioMedical Research*†

Top 10 Results Combined Analysis Of Stages 1 + 2, Three Studies (14602 cases + 17968 controls)

	FUSION		DGI		WTCCC/UKT2D		All Samples	
Gene	OR	p-value	OR	p-value	OR	p-value	OR	p-value
TCF7L2	1.34	1.3×10^{-8}	1.38	2.3×10^{-31}	1.37	6.7×10^{-13}	1.37	1.0×10^{-48}
IGF2BP2	1.18	2.1×10^{-4}	1.17	1.7×10^{-9}	1.11	1.6×10^{-4}	1.14	8.9×10^{-16}
CDKN2A/B	1.20	.0022	1.20	5.4×10^{-8}	1.19	4.9×10^{-7}	1.20	7.8×10^{-15}
FTO	1.11	0.016	1.03	0.25	1.23	7.3×10^{-14}	1.17	1.3×10^{-12}
CDKAL1	1.12	0.0095	1.08	0.0024	1.16	1.3×10^{-8}	1.12	4.1×10^{-11}
KCNJ11	1.11	0.013	1.15	1.0×10^{-7}	1.15	0.0013	1.14	6.7×10^{-11}
HHEX	1.10	0.026	1.14	1.7×10^{-4}	1.13	4.6×10^{-6}	1.13	5.7×10^{-10}
SLC30A8	1.18	7.0×10^{-5}	1.07	0.047	1.12	7.0×10^{-5}	1.12	5.3×10^{-8}
Chr 11	1.48	5.7×10^{-8}	1.16	0.12	1.13	0.068	1.23	4.3×10^{-7}
PPARG	1.20	0.0014	1.09	0.019	1.23	0.0013	1.14	1.7×10^{-6}

Common Allele on Chr 9p21 Associated with Coronary Heart Disease 2007

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] Ha[illegible] Austin,[3] Daniel J Rader,[4] Sanjay H. Shah,[5] Arshed A. Quyyumi,[3] Jeffrey R. Gulcher,[1] Gudmundur Thorg[illegible]

[1]deCODE genetics Inc, Reykjavik, Iceland. [2]Emory University School of Medicine, Atlanta, GA 30322, US[illegible] [3]Emory University School of Medicine, [illegible]

*These authors contributed equal[illegible]

†To whom correspondence shoul[illegible]

The global endemic of cardiova[illegible] improved risk assessment and t[illegible] describe an association betwee[illegible] (MI) and a common sequence v[illegible] 9p21. This study included a tota[illegible] controls. The identified variant [illegible] suppressor genes *CDKN2A* and [illegible] to the disease with high signific[illegible] Approximately 21% of individu[illegible] homozygous for this variant an[illegible] 1.64-fold greater risk of sufferi[illegible] than non-carriers. The corresp[illegible] early onset cases. The populatio[illegible] is 21% for MI in general and 3[illegible]

A Common Allele on Chromosome 9 Associated with Coronary Heart[illegible]

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

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

Coronary heart disease (CHD) is a major cause of death in Western countries. Here we used genome-wide association scanning to identify a 58 kilobase interval on chromosome 9p21 that was consistently associated with CHD in six independent samples (n > 23,000 participants) from four Caucasian populations. This interval, which is located near the *CDKN2A* and *CDKN2B* genes, contains no annotated genes and is not associated with established CHD risk factors such as plasma lipoproteins, hypertension or diabetes. Homozygotes for the risk allele comprise 20-25% of Caucasians and have a ~30-40% increased risk of CHD.

Weinberg equilibrium (P<0.001) or d[illegible] control criteria (*3*) and 17,500 were s[illegible] allele frequency <1%) in the sample. [illegible] SNPs were entered into the analysis a[illegible] associated with CHD at a nominal sig[illegible] 0.025 (table S2). These 2,586 SNPs w[illegible] independent sample of 311 cases and [illegible] Ottawa (OHS-2) using the same crite[illegible] Of these, 50 were associated with CH[illegible] significance threshold of 0.025, with [illegible] effect (Table S2).

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*

ABSTRACT

BACKGROUND

Modern genotyping platforms permit a systematic search for inherited components of complex diseases. We performed a joint analysis of two genomewide association studies of coronary artery disease.

METHODS

We first identified chromosomal loci that were strongly associated with coronary artery disease in the Wellcome Trust Case Control Consortium (WTCCC) study (which involved 1926 case subjects with coronary artery disease and 2938 controls) and looked for replication in the German MI (Myocardial Infarction) Family Study (which involved 875 case subjects with myocardial infarction and 1644 controls). Data on other single-nucleotide polymorphisms (SNPs) that were significantly associated with coronary artery disease in either study (P<0.001) were then combined to identify additional loci with a high probability of true association. Genotyping in both studies was performed with the use of the GeneChip Human Mapping 500K Array Set (Affymetrix).

RESULTS

Of thousands of chromosomal loci studied, the same locus had the strongest association with coronary artery disease in both the WTCCC and the German studies: chromosome 9p21.3 (SNP, rs1333049) ($P=1.80\times10^{-14}$ and $P=3.40\times10^{-6}$, respectively). Overall, the WTCCC study revealed nine loci that were strongly associated with coronary artery disease ($P<1.2\times10^{-5}$ and less than a 50% chance of being falsely positive). In addition to chromosome 9p21.3, two of these loci were successfully replicated (adjusted P<0.05) in the German study: chromosome 6q25.1 (rs6922269) and chromosome 2q36.3 (rs2943634). The combined analysis of the two studies identified four additional loci significantly associated with coronary artery disease ($P<1.3\times10^{-6}$) and a high probability (>80%) of a true association: chromosomes 1p13.3 (rs599839), 1q41 (rs17465637), 10q11.21 (rs501120), and 15q22.33 (rs17228212).

CONCLUSIONS

We identified several genetic loci that, individually and in aggregate, substantially affect the risk of development of coronary artery disease.

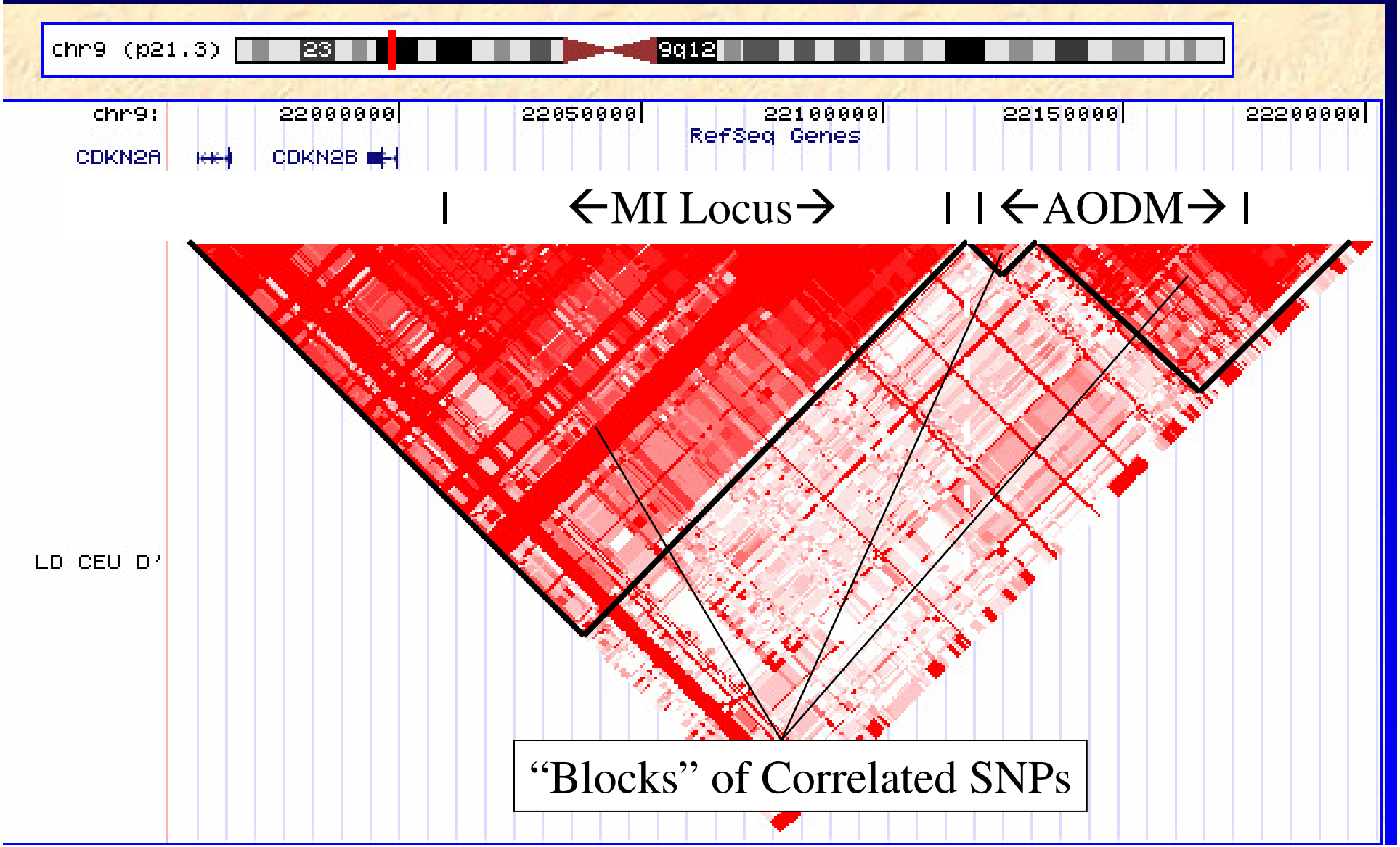
From the University of Leicester, Leicester (N.J.S., M.M., R.J.D., P.B., S.E.S., H.P., M.D.T., J.R.T.); University of Leeds, Leeds (A.S.H., J.H.B., M.M.I., A.J.B., S.G.B.); University of Cambridge and National Health Service Blood and Transplant, Cambridge (W.O.); and the Wellcome Trust Sanger Institute, Hinxton (P.D.) — all in the United Kingdom; Universität zu Lübeck, Lübeck (J.E., B.M., I.R.K., S.S., F.P., W.L., I.B., A.Z., H.S.); Universität Regensburg, Regensburg (C.H., M.F., A.B.); GSF–Nationales Forschungszentrum für Umwelt und Gesundheit, Neuherberg (T.M., H.-E.W., T.M.S., C.G.); Technische Universität München, Munich (T.M.); Ludwig Maximilians University, Munich (H.-E.W., C.G.); and Johannes Gutenberg University Mainz, Mainz (S.B.) — all in Germany; and INSERM, UMRS525, Université Pierre et Marie Curie, Paris (D.-A.T., F.C.). Address reprint requests to Dr. Samani at the Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Leicester LE3 9QP, United Kingdom, or at njs@le.ac.uk or to Dr. Schunkert at Medizinische Klinik II, Universität zu Lübeck, 23538 Lübeck, Germany, or at heribert.schunkert@innere2.uni-luebeck.de.

*Members of the Wellcome Trust Case Control Consortium (WTCCC) and the Cardiogenics Consortium are listed in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

This article [10.1056/NEJMoa072366] was published at www.nejm.org on July 18, 2007.

N Engl J Med 2007;357.

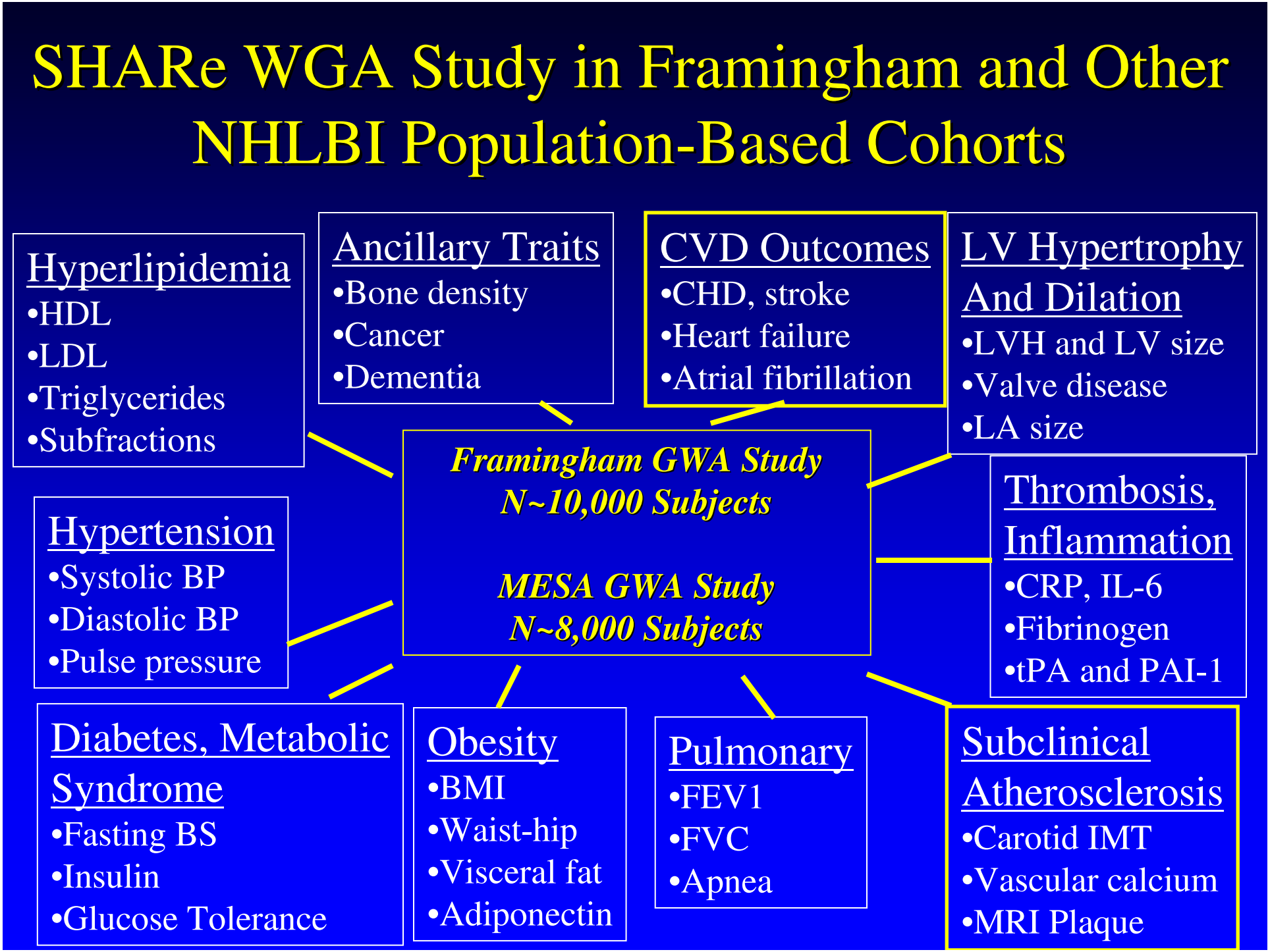
Chomosome 9p21Locus for MI & AODM



GWAS Example: Framingham Heart Study SNP Health Association Resource (SHARe)

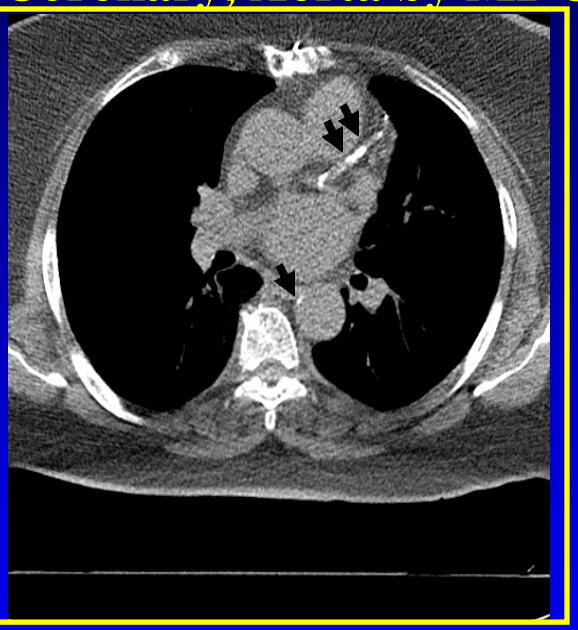
- All consenting subjects from 3 generations—up to N~10,000 Caucasians
- 550,000 SNPs (Affymetrix) in each subject
- Include >>1,000 available risk factor, subclinical and clinical cardiovascular disease 'phenotypes'
  - Original Cohort, Offspring, Third Generation
  - All available examinations going back >50 years
- Comprehensive, web-based database by NCBI, to be shared widely with investigators
- Informatics: 5.5 billion genotypes, >5.5 trillion association tests

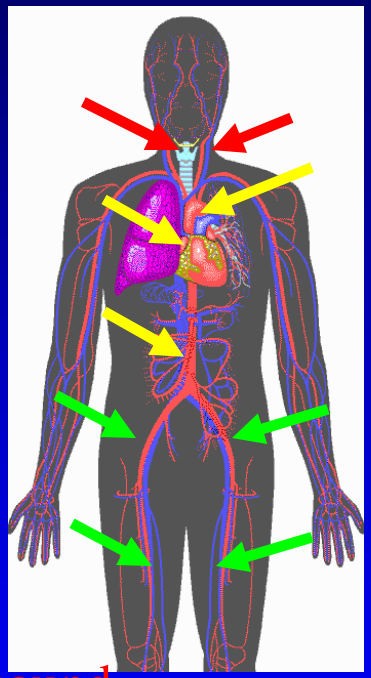
SHARe WGA Study in Framingham and Other NHLBI Population-Based Cohorts



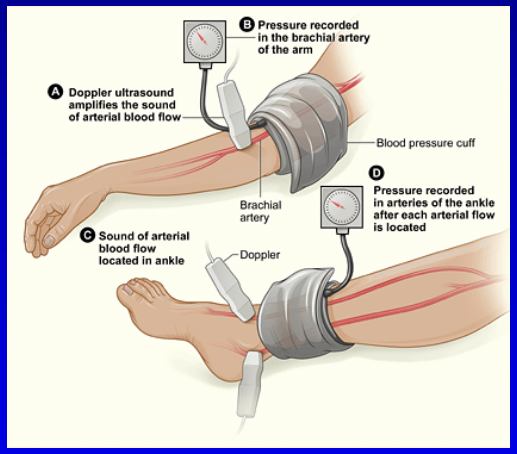
CT and US Imaging for Coronary, Aortic, Carotid and Peripheral Atherosclerosis

Coronary, Aorta by MDCT

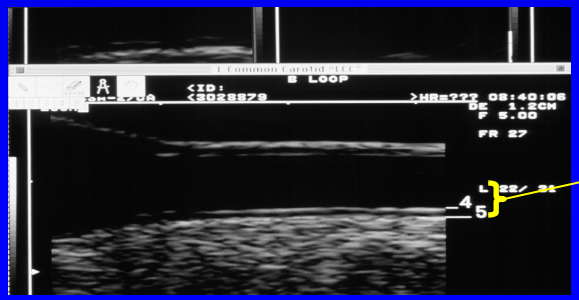




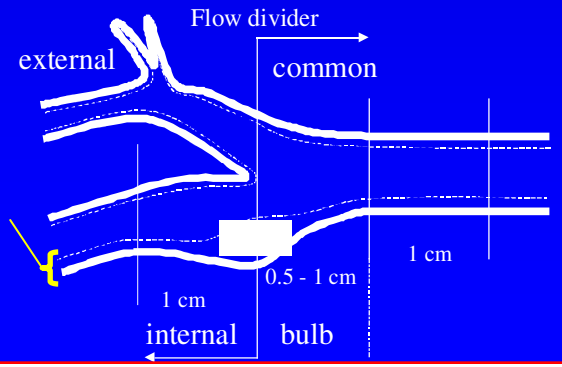
Peripheral Arteries by ABI



Carotid Arteries by Ultrasound



Intimal Medial thickness



NIH GWAS Policy August 2007

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS)

AGENCY: National Institutes of Health, HHS.

ACTION: Notice.

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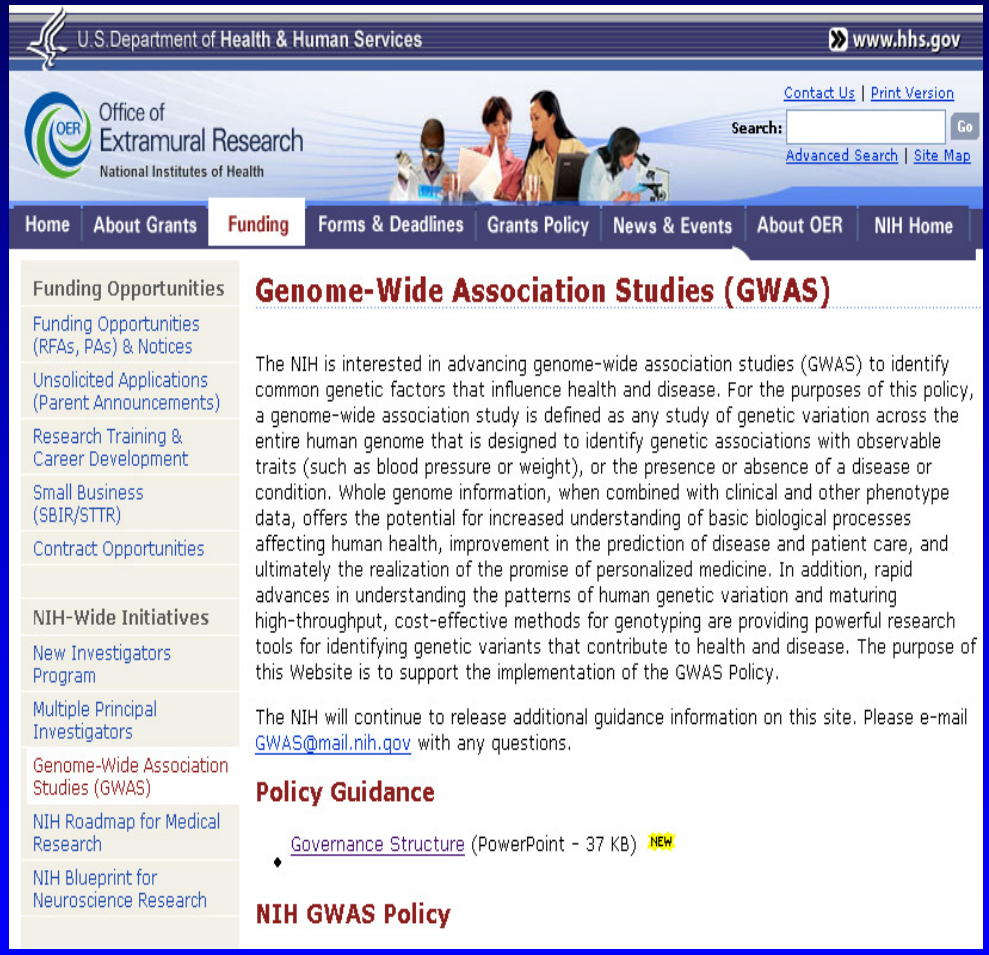


Federal Register: Vol. 72, No. 166
Tuesday, August 28, 2007

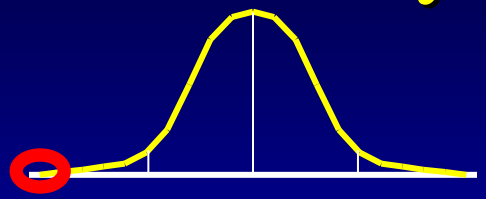
NIH OER Website:
http://grants.nih.gov/grants/gwas/index.htm

NHLBI Genome Wide Association Studies (GWAS): Driving Principle

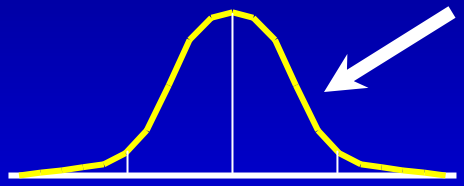
The greatest public benefit will be realized if data from GWAS are made available, under terms and conditions consistent with the informed consent provided by individual participants, in a timely manner to the largest possible number of investigators.

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

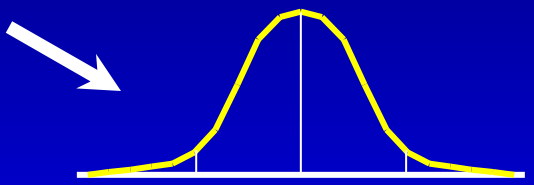
Sequence PCSK9 exons
in patients with low LDL
in Dallas Heart Study



N=128, Nonsense
Mutations Y142X & C679X



N=3363 AA NHLBI ARIC
Mutations



N= 9524 White NHLBI ARIC
Mutations

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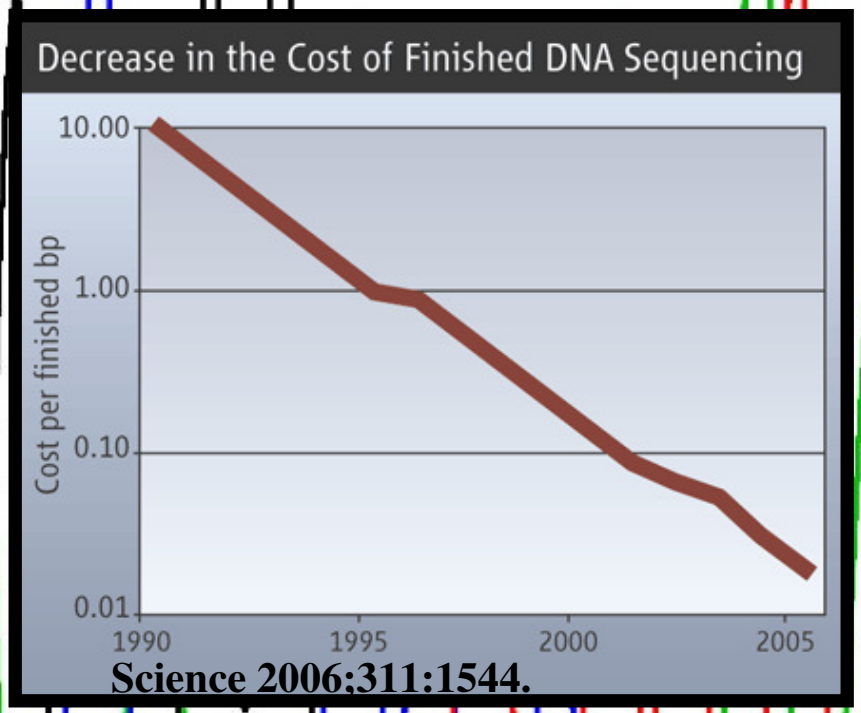
CIMT (mm):	0.73	~0.70
CHD (%):*	10%	~1%

	Yes (2.6%)	No
LDL (mg/dL):**	137	116
CIMT (mm):*	0.73	0.71
CHD (%):*	12	6

*p<0.001; **p<0.01

Reference: Cohen JC et al. NEJM 2006;354:1264.

Decline in DNA Sequencing Costs Towards the "$1000 Genome"



Science 2006;311:1544.

Searching for Cheaper Genome Sequencers

Company	Format	Read Length (bases)	Expected Throughput Mb (million bases)/day
454 Life Sciences	Parallel bead array	100	96
Agencourt Bioscience	Sequencing by ligation	50	200
Applied Biosystems	Capillary electrophoresis	1000	3-4
LI-COR Biosciences	Electronic microchip	20,000	14,000
Microchip Biotechnologies	Parallel bead array	850-1000	7
Network Biosystems	Biochip	800+	5
NimbleGen Systems	Map and survey microarray	30	100
Solexa	Parallel microchip	35	500
VisiGen Biotechnologies	Single-molecule array	NA	1000

NHLBI-Supported Portfolio of Largescale Genetic Association Studies

- SNP Health Association Resource (SHARe)
  - Framingham Heart Study
  - Other SHARe Cohorts (Pending)
- Genome-Wide Association: SNP Genotyping and Analysis (STAMPEED)
- Enhancing Development of Genome-Wide Association Methods (ENDGAMe)
- Candidate Gene Association Resource (CARe)
- Women's Health Genome Study (WHGS)
- Women's Health Initiative (WHI) GWA Study

Finding Genomic Resources on the NHLBI Web Page

Translation From Genomics to Personalized Cardiovascular Genomic Medicine

Where We are Now

Your Next 10-20 Years

Targeted and Genome-Wide Resequencing

↓

Genotype Phenotype Association

↓

Independent Replication

↓

Fine Mapping, Resequencing

↓

Functional Studies

↓

Genomic Clinical Trials

↓

Applications for Genomic Medicine

↓ ↓ ↓

Predict **Prevent** **Personalize**

"Traditional Bench Laboratory" Research versus Genomics and Proteomics

	Traditional Lab	"Omics"
PI/Mentor	Single PI	May be multiple key PIs Collaboration Required
Approach	Highly developed, specific to lab/PI	Rapidly evolving technology/platform(s)
Methods	Single method(s)	Multidisciplinary
Research Questions	Hypothesis based approach	Unbiased approaches for discovery
Analysis	Simple statistics	Bioinformatics or advanced statistics

A Few Genomics Mentoring Examples



S. K.
CAD/Lipid Genomics

↓

Fram Heart Study,
MGH&Broad Institute

↓

K23, Glaxo SK Grants
Plus NIH LRP

↓

MGH Preventive Cards
MGH CVRC/Genetics
+Broad Institute & FHS



S. S.
Chemical Genomics

↓

Harvard Dept. of
Chem&Chem Biology

↓

K08, Other Grants

↓

MGH General Cards
MGH CVRC
+Broad Inst



C. N-C.
Arrhythmia Genomics

↓

Broad Institute and
Fram Heart Study

↓

K23, Other Grants
Plus NIH LRP

↓

MGH Heart Failure
MGH CVRC/Genetics
+Broad Institute & FHS

Genomics and Proteomics Training: Some Considerations

- Major versus Minor
- Basic Science vs Clinical Research
  - If basic science focus: animal models versus cell/tissue
  - Mendelian versus common complex disease
  - Family studies versus populations (GWAS requires LARGE populations)
- Focus on an Area of Specialization
  - Specific area: genomics, proteomics/metabolomics
  - Bioinformatics/statistical genetics
  - Genetic epidemiology
- Focus on Area of Translational Medicine:
  - Discovery of Disease Mechanisms
  - Clinical Trials
  - Prediction/Prognosis
  - Pharmacogenetics
  - Clinical Genetics
  - Outcomes/Clinical Effectiveness/Cost-Effectiveness Research

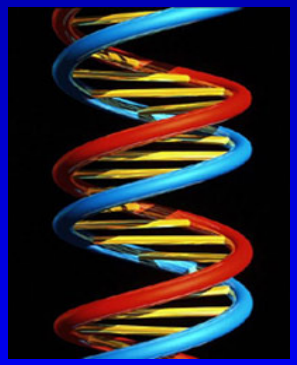
Genomics and Proteomics Training: Additional Random Considerations

- Supplemental Coursework:
  - Genetic, genomics, statistical genetics
  - Epidemiology, statistics and clinical research
  - Bio-informatics
  - NHLBI programs, Gordon Conferences, CSH Symposium
- Joint position/Co-mentor
  - Local genome institute
  - Local basic science institute
  - School of Public Health
- Consider fellowship and career opportunities at NIH
- Essential that your specific project lead to specific, high quality first author manuscript(s)

Progression from Risk Factors to Clinical Cardiovascular Disease

Major Traditional Risk Factors: SBP, DBP, Cholesterol, LDL, HDL, Diabetes Mellitus BioMarkers: Inflammation, Met. Syndrome, Thrombosis

Genetic



Determinants

Environmental

Modification

Subclinical Disease of Ventricle, Conduction System and Arteries

Clinical Cardiovascular Disease: Heart Failure, Arrhythmia, Myocardial Infarction, and Stroke

Premature CVD in Parents* or Siblings** Leads to Increased Relative Risk of CVD

Model Adjustment	Positive Parental History of Premature CVD		
	None	Both	≥1 Parent
Men			
Age-adjusted	1.0	**3.1**	**2.6**
Multivariable-adjusted*	1.0	**2.4**	**2.0**
Women			
Age-adjusted	1.0	**4.1**	**2.3**
Multivariable-adjusted*	1.0	**2.8**	**1.7**

*Lloyd-Jones et al. JAMA 2004;291:2204. Adj. for age, total/HDL, SBP, anti-HTN Rx, AODM, BMI, current smoking.

→ In further multivariable-adjusted** model adjusting for BOTH *Sibling* CVD and *Parental* CVD:
Rel. Risk = 2.0 for Sibling CVD versus
Rel. Risk = 1.5 for Parental CVD

**Murabito et al. JAMA 2006;294:3117-3123. Adj. for age, total/HDL, SBP, anti-HTN Rx, AODM, BMI, current smoking.

Heritability of CVD Risk Factors & Subclinical Disease: Framingham Study

Variable	Heritability
Risk Factors*	
Fasting Glucose	32%
Systolic Blood Pressure	42%
Maximum BMI	40%
Biomarkers	
CRP	26%
PAI-1 Antigen	26%
Platelet Aggregation (Epi)	48%
Subclinical LV & Conduction Disease**	
LV Hypertrophy	26%
QT Duration	35%
Subclinical Vascular Disease	
Wall Thickness,Carotid Artery†	38%
Calcium, Aorta or Coronaries‡	38%

*L. A. Cupples, ASHG 1996. *E. Benjamin, AHA 2000. †C Fox, Stroke 2002,
‡P Peyser, Circulation 2002, ††C O'Donnell, Circulation 2002, Newton-Cheh, Heart Rhythm 2005.

Translation From GWA Studies to Personalized Genomic Medicine

GWAS (Case-Control) Studies to Date

Cancer

- Prostate Cancer
- ALL
- Breast Cancer
- Colon Cancer

Lung

- Asthma

Eye

- Macular Degeneration
- Glaucoma (XFG)

Cardiovascular and Risk Factors

- Obesity
- Hypertension
- Diabetes, Type 1
- Diabetes, Type 2
- ECG QT interval
- MI, CAD
- Atrial Fibrillation

Rheumatic Diseases

- SLE (Lupus)
- Celiac Disease
- Rheumatoid Arthritis
- Crohn's Disease

Infectious Disease

- HIV Host Control

Bone

- Osteoarthritis

Neurology and Psychiatry

- Bipolar Disorder
- Restless Leg Syndrome
- Multiple Sclerosis
- ALS

NIH GWAS Policy August 2007

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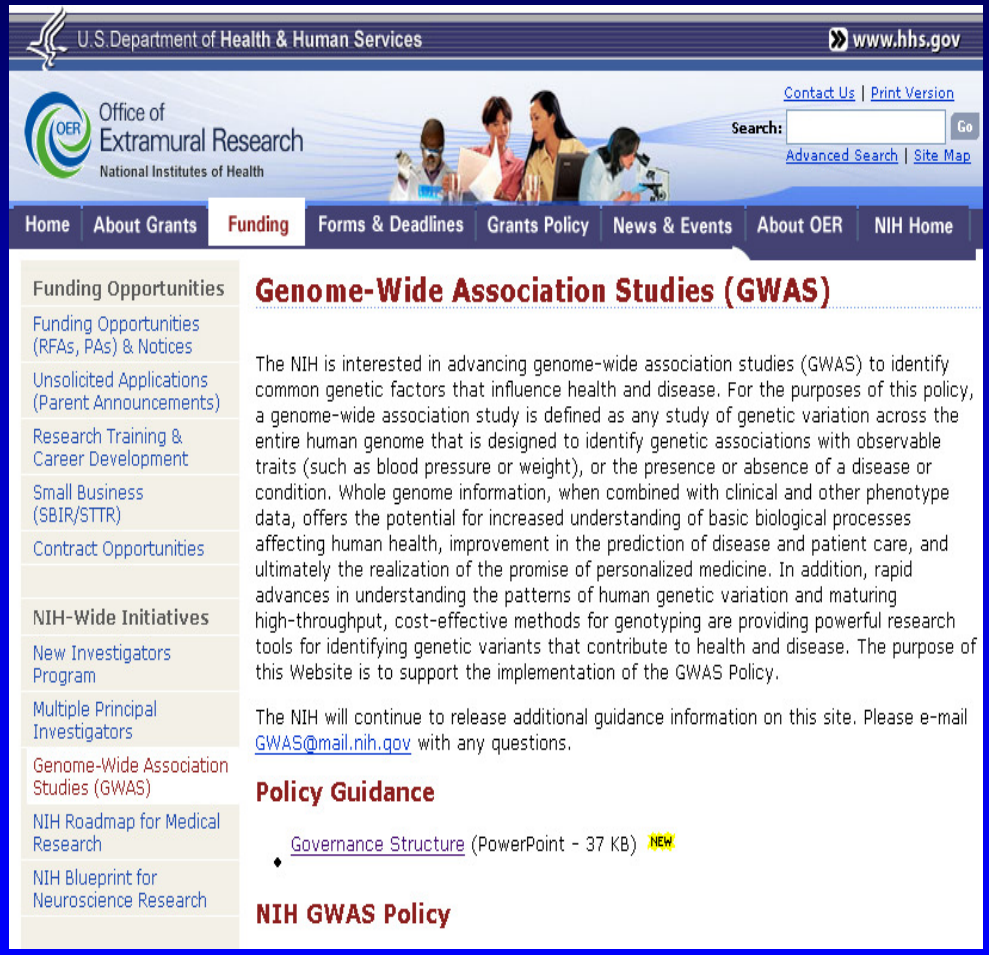

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NIH OER Website:
http://grants.nih.gov/grants/gwas/index.htm


db GaP
GENOTYPE and PHENOTYPE
NCBI
db GaP
GENOTYPE and PHENOTYPE
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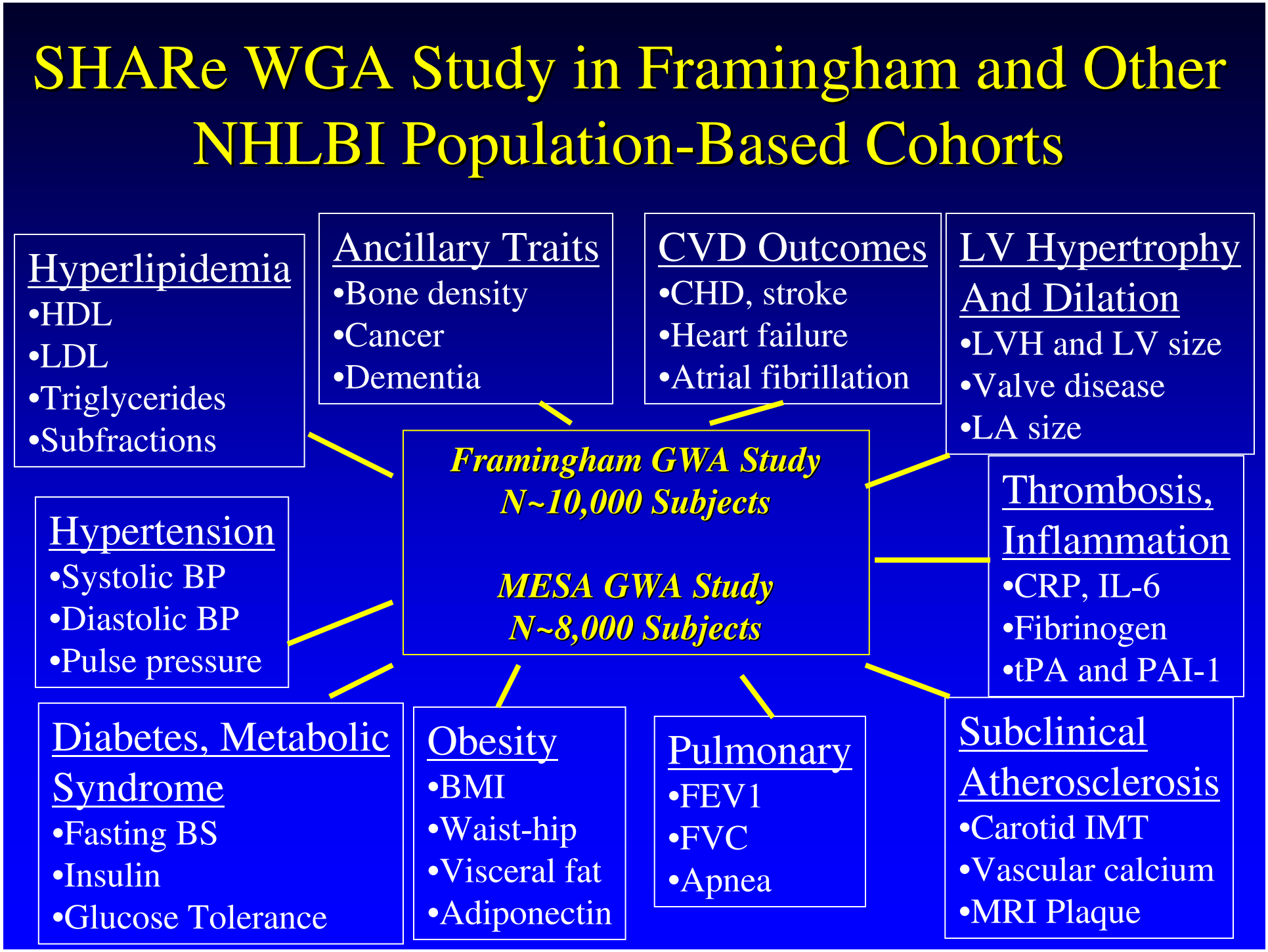
Limits Preview/Index History Clipboard Details
NCBI
dbGaP
About dbGaP
Browse dbGaP
Authorized Access
Email Alerts
dbGaP Tutorial
Security Procedures
FTP Download
GWAS Publications
Contact dbGaP
Other Services
MeSH Browser
Clinical Queries
Browse dbGaP
TUTORIAL
ABOUT dbGAP
By Studies
By Diseases
Advanced Search
Study
Sub-Studies
Variables
Documents
Participants
Type of Study
Collaborative Association Study of Psoriasis - - - 2000 Case-control
Genotyping the 270 HapMap samples for GAIN by Broad - - - 270 Parent-offspring trios
Genotyping the 270 HapMap samples for GAIN by Perlegen - - - 270 Parent-offspring trios
International Multi-Center ADHD Genetics Project - 438 12 2835 Parent-offspring trios
LEAPS - - - 886 Case-control
Linking Genome-Wide Association Study of Schizophrenia - - - 2400 Case-control
Major Depression: Stage 1 Genomewide Association in Population-Based Samples - - - 3786 Case-control
NEI Age-Related Eye Disease Study (AREDS) - 174 37 600 Case-control
NINDS Control Study - 65 2 1813 Control set
NINDS Parkinsonism Study - 40 4 1498 Case-control
Search for Susceptibility Genes for Diabetic Nephropathy in Type 1 Diabetes - - - 3046 Case-control
Whole Genome Association Study of Bipolar Disorder - - - - Case-control

SHARe WGA Study in Framingham and Other NHLBI Population-Based Cohorts



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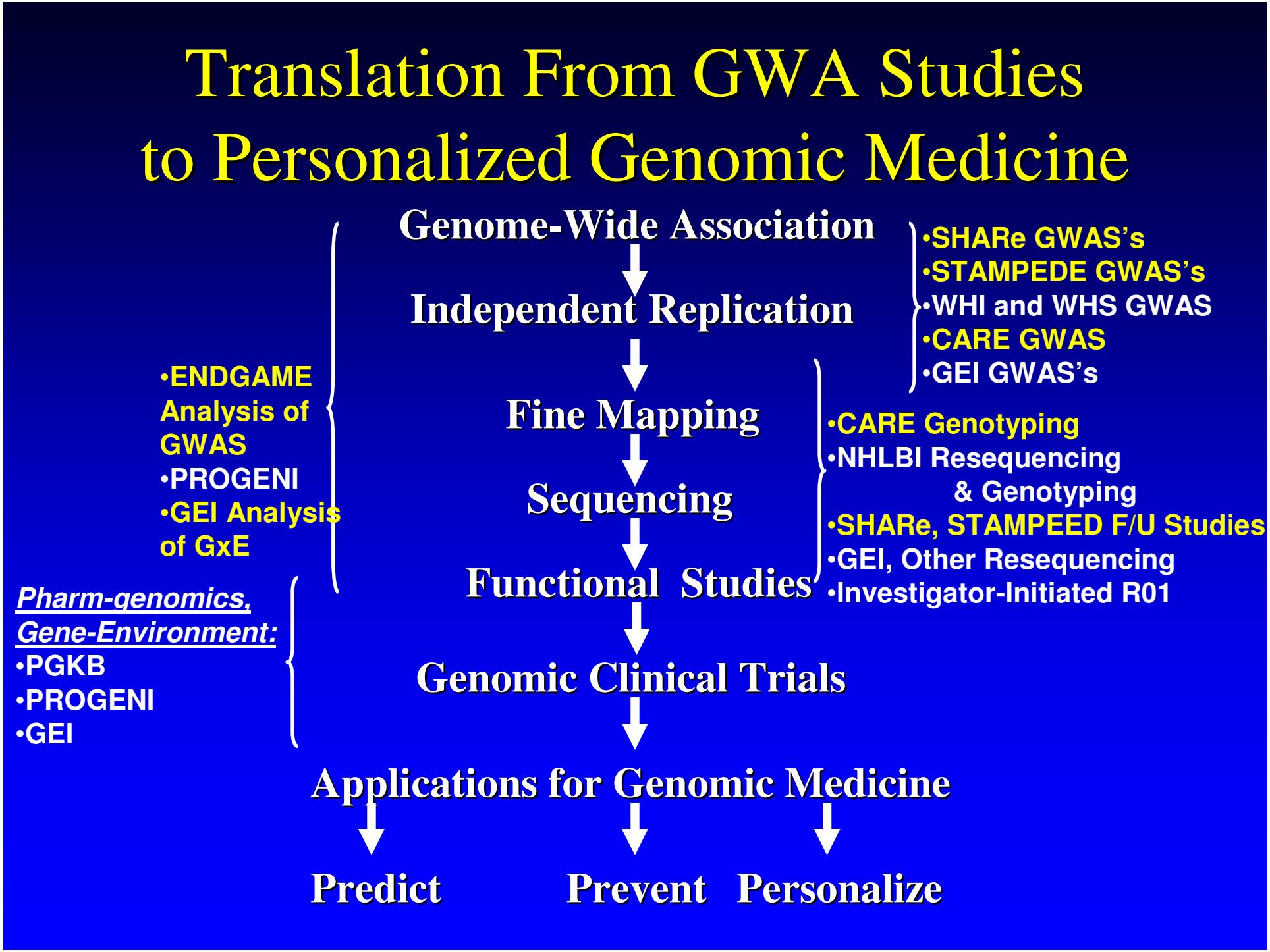

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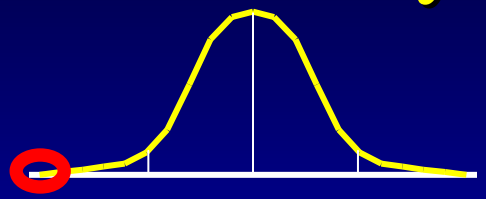

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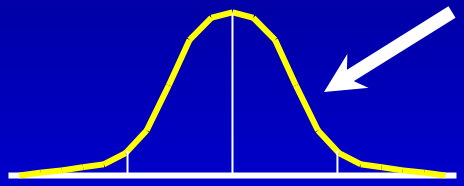

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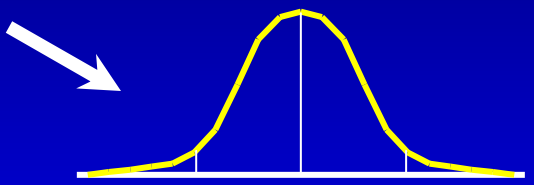

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Genome Wide Sequencing (GWS) Studies towards Personalized Genomic Medicine