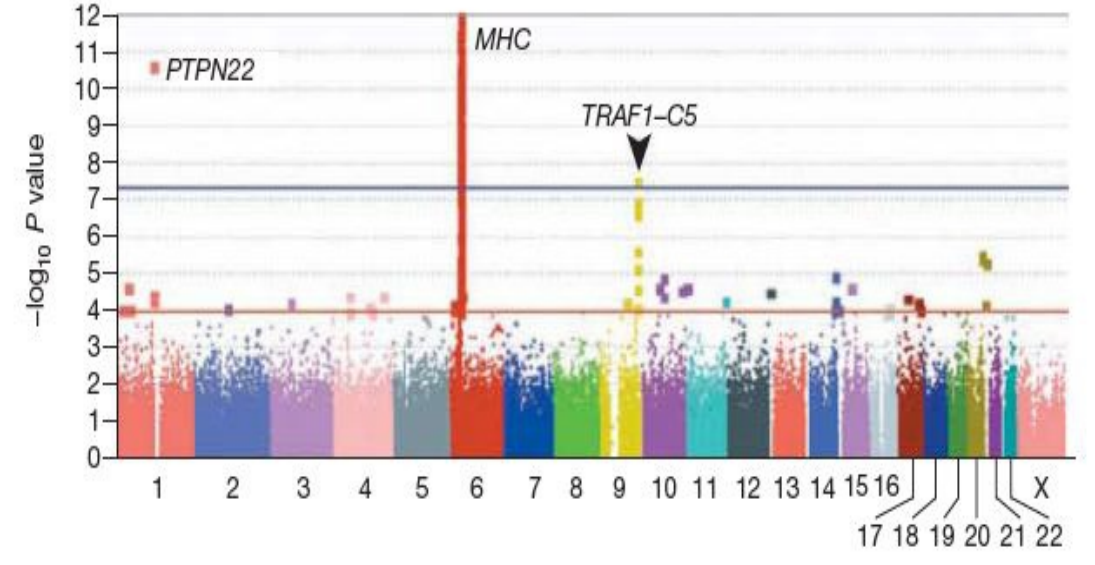
Genomics & Medicine

http://biochem118.stanford.edu/

Linking Genes to Disease: Leveraging the Human Genome

Figure 3. Genome-wide Association Findings in Rheumatoid Arthritis

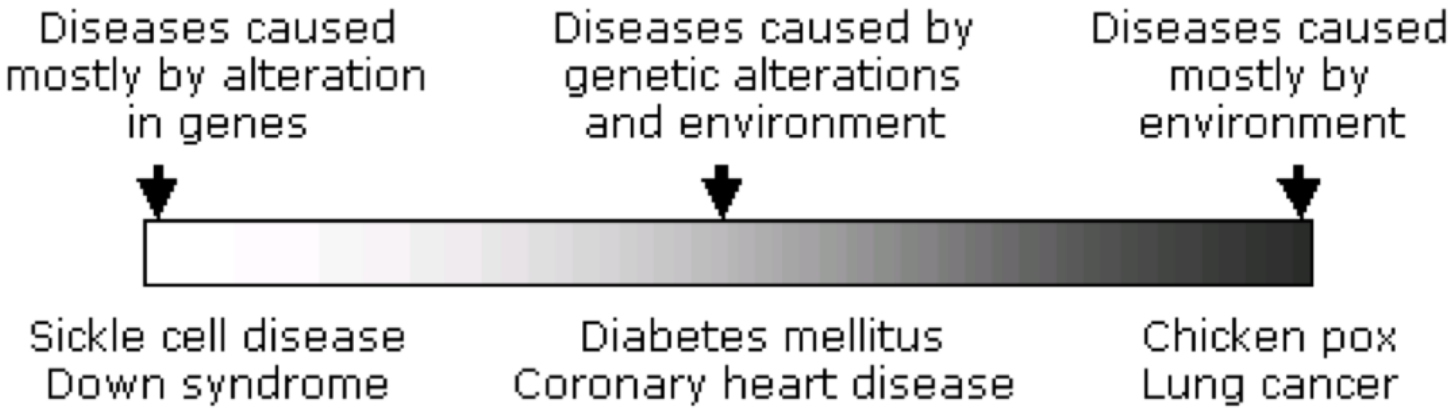


Doug Brutlag, Professor Emeritus of Biochemistry & Medicine (by courtesy)
Stanford University School of Medicine

Homeworks

- Most difficult in course
- Frequent patterns are modifications not functions. Should be verified in PTM table.
- Biological function usually validated by GO terms, but sometimes shared families and sometimes shared motifs.
- Everything statistically significant is biologically significant but not vice versa.
- Research report should contain your results (screen dumps, cut and paste from output)
- Research reports are not short answers, conclusions should be written out in full sentences and paragraphs.

Genetic Penetrance



Genetic diseases, at the left of the spectrum, are categorized as **single gene** or **chromosomal** disorders, depending on the specific genetic cause.

Diseases in the middle of the spectrum — including most common diseases — are **multifactorial**, and result from the interaction or additive effect of genetic and non-genetic factors.

Genetic Penetrance of Inherited Diseases

- Many inherited diseases are Mendelian and highly penetrant
  - Sickle cell disease
  - Thalassemias
  - Huntington's disease
  - Color blindness
  - Cystic fibrosis
- Most common diseases are complex (multifactorial - caused by multiple genes or multiple pathways as well as multiple environmental factors) and of low penetrance
  - Familial
  - Predisposition to disease
  - Very large environmental and/or behavioral component
    - Type I diabetes and other autoimmune diseases (lupus, rheumatoid arthritis, hyperthyroidism, Crohn's disease, Celiac Sprue, irritable bowel disease etc.)
    - Type 2 diabetes
    - Coronary heart disease (atherosclerosis)
    - Asthma, COPD, pulmonary fibrosis
  - Many complex diseases can be avoided with diet, nutrition, exercise or behavioral modification
  - Many complex diseases can also be monitored by increased vigilance (another behavioral modification)

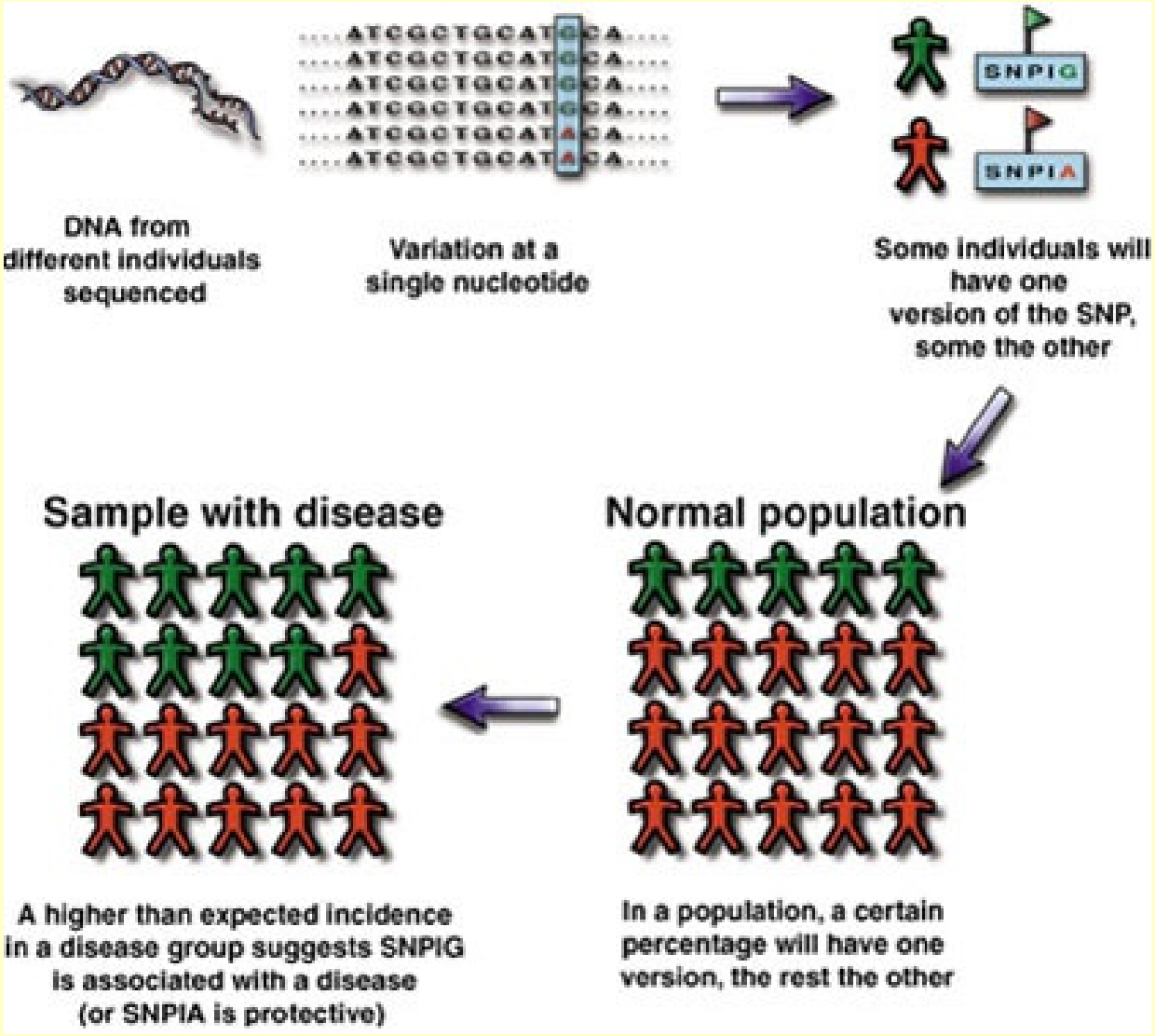
Gene Variations Associated with Common Diseases

By comparing the frequencies of gene variations in patients with a disease (cases) and people without the disease (controls) one can often identify susceptibility and protective genes. The are called case-control studies.

Case-Control studies primarily find correlations of genes with disease. Only rarely do case-control studies discover genes that cause the disease.

Phenotype	Gene	Variant
Peptic ulcer	ABO	O
IDDM*	HLA	DR3,4
Alzheimer dementia	APOE	E4
Deep venous thrombosis*	F5 (R506Q)	Leiden
*Falciparum malaria**	HBB	β^S
AIDS*	CCR5	$\Delta 32$
Colorectal cancer*	APC	3920A
NIDDM*	PPARγ	12A

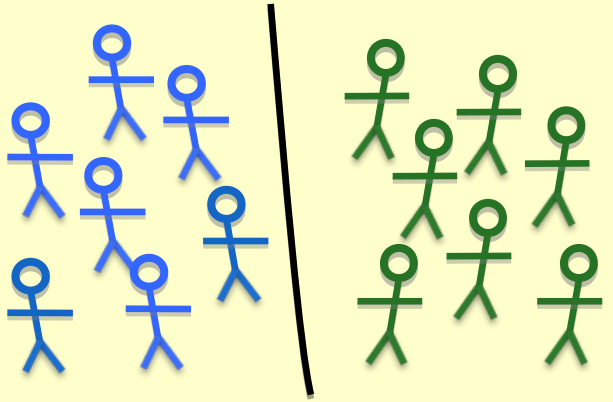
Using SNPs to Track Predisposition to Disease and other Genetic Traits



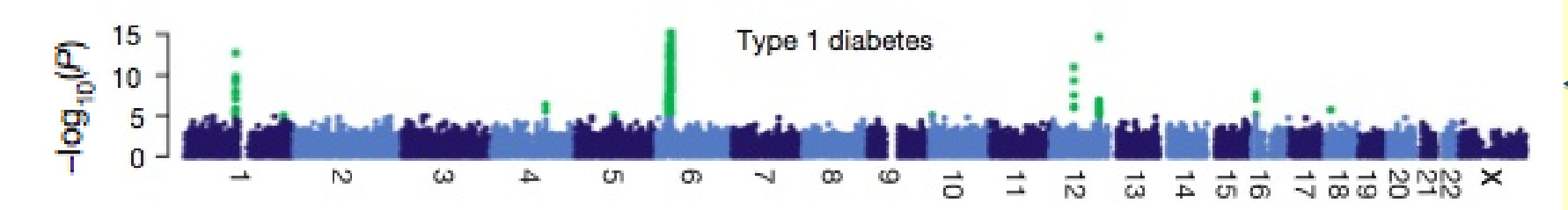
Genome-Wide Association Study: A Brief Primer

Control Population

Disease Population



SNP chip

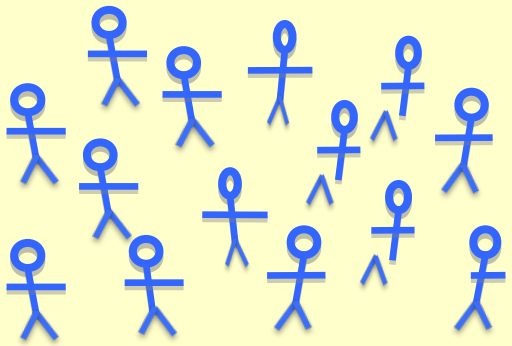


WTCCC, Nature 2007

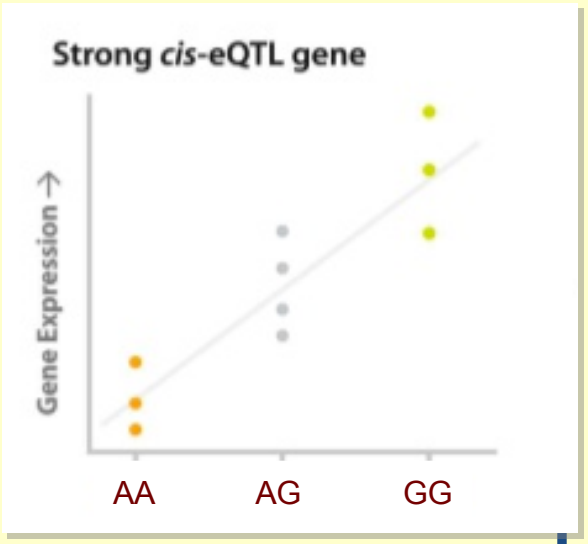
Courtesy of Daniel Newburger

A Quantitative Gene-Expression Association

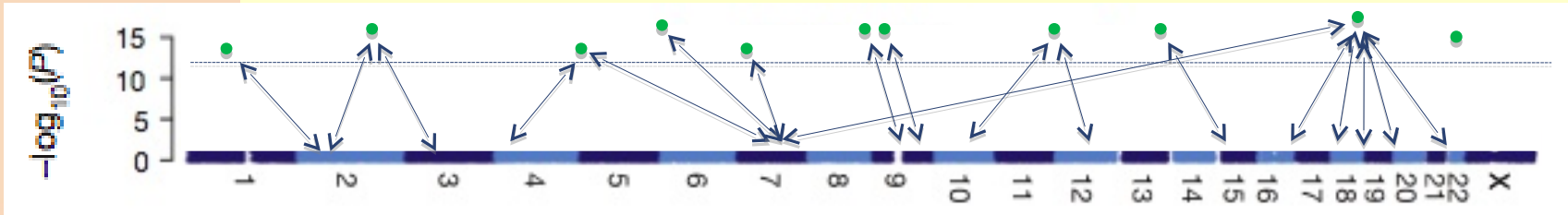
Sample Population



cDNA Levels



Expression Quantitative Trait Loci (eQTLs)

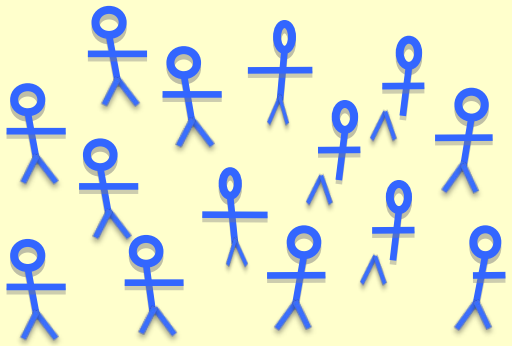


Modified from WTCCC, Nature 2007

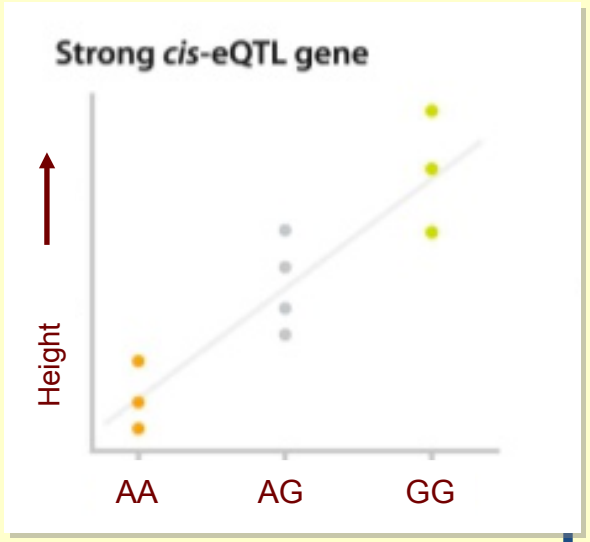
Courtesy of Daniel Newburger

A Quantitative Gene-Expression Association

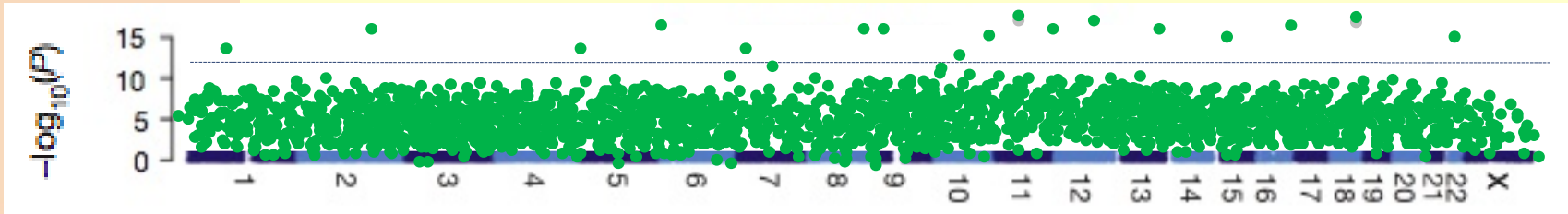
Sample Population



Measure Height



Quantitative Trait Loci (QTLs)



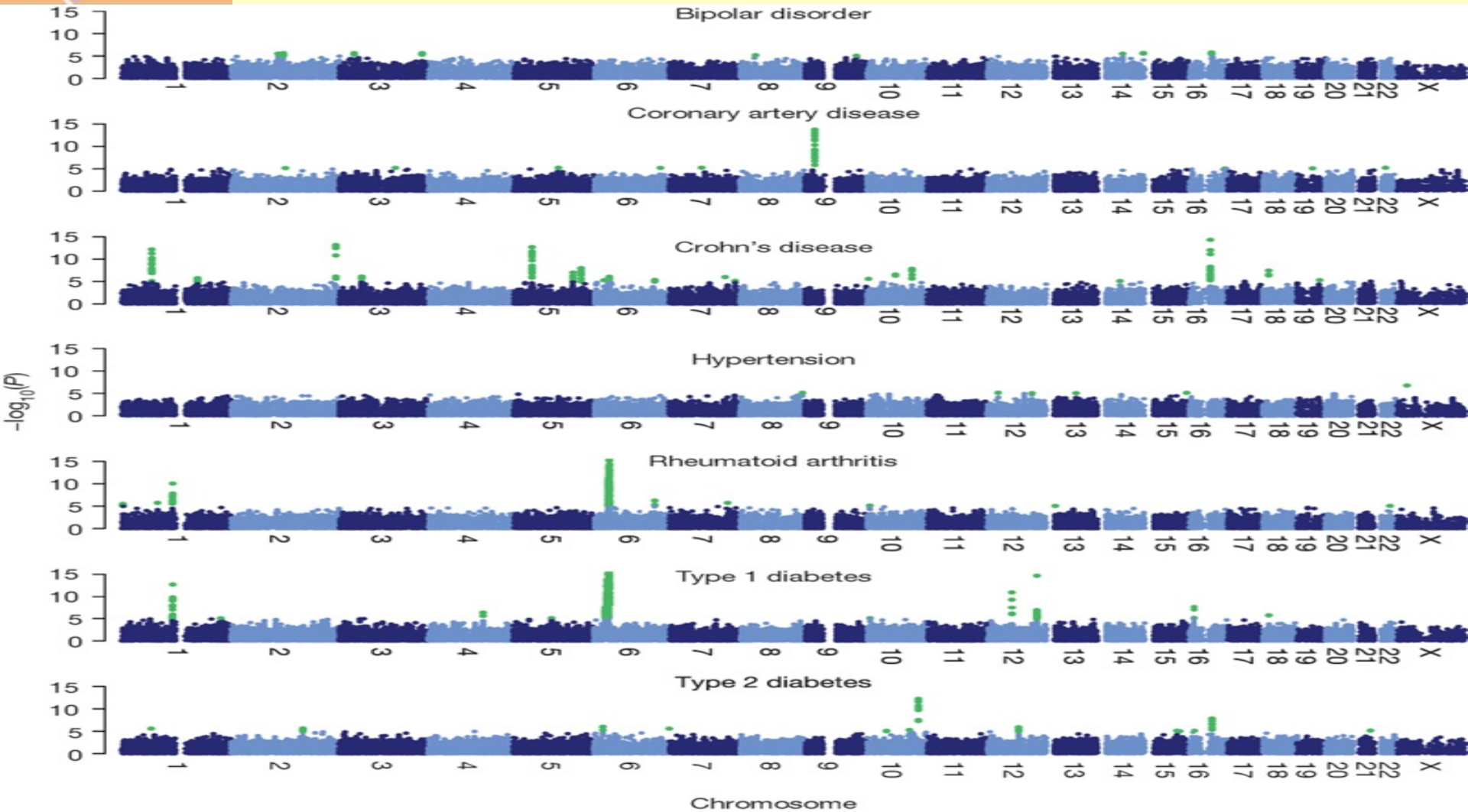
Modified from WTCCC, Nature 2007

Courtesy of Daniel Newburger

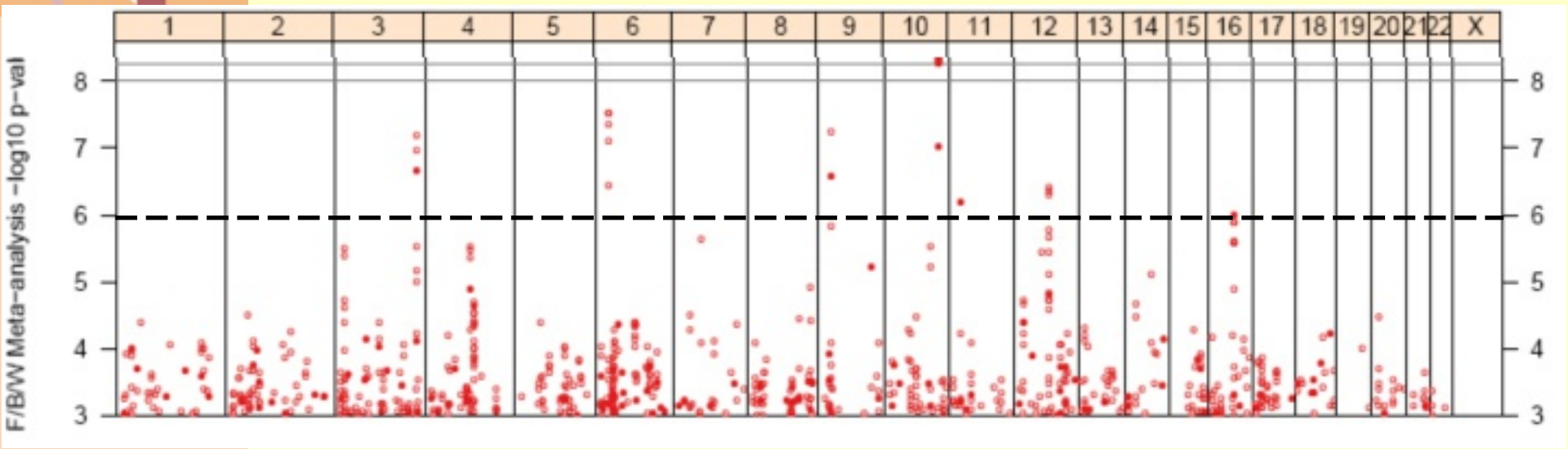
The Wellcome Trust Case Control Consortium

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

Nature 447, 661-678 (7 June 2007)



Genome Wide Association of type 2 Diabetes 4549 cases, 5579 controls & 317,503 SNPs

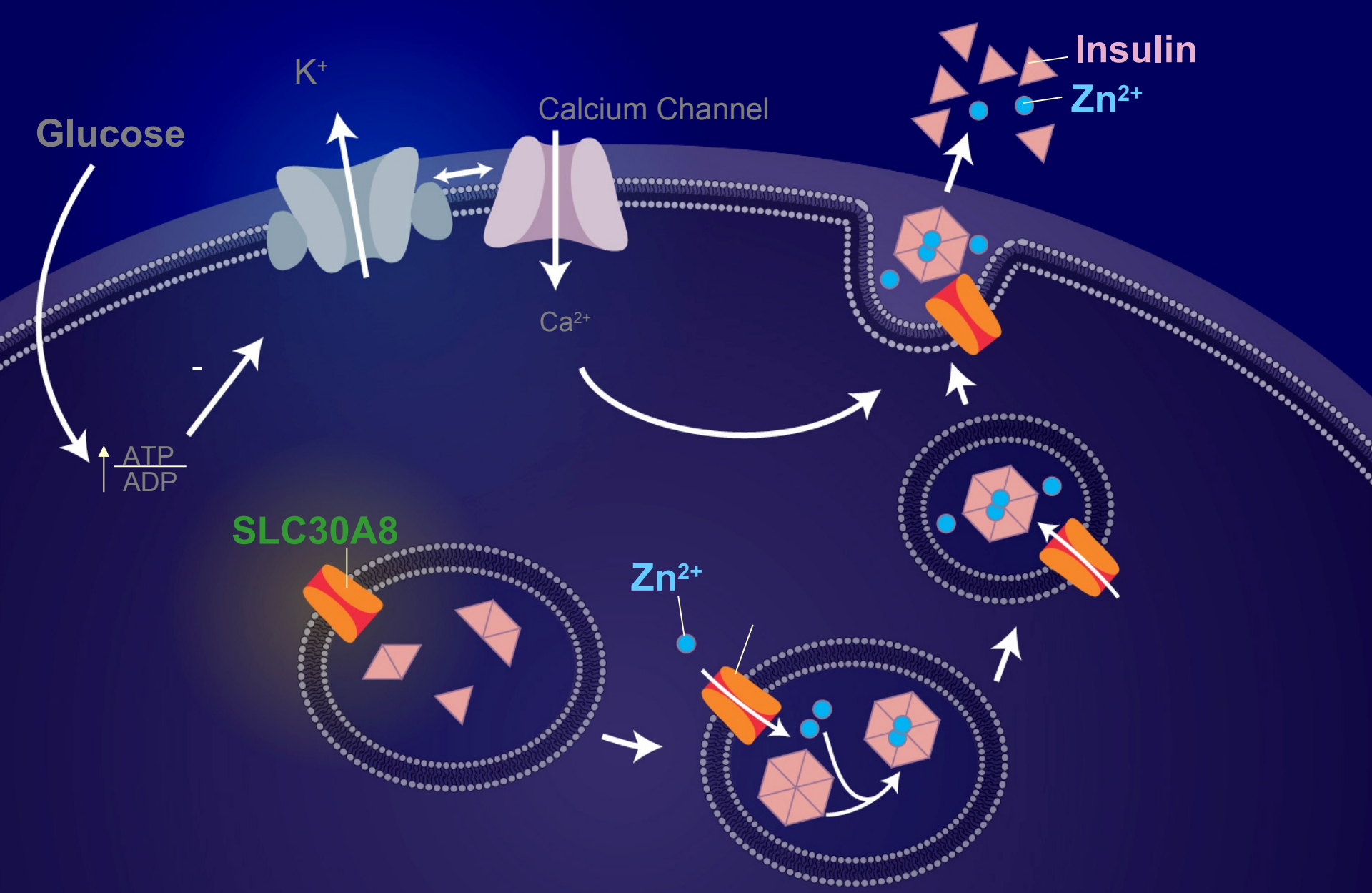


Combined data from FUSION, WTCCC and DGI

FUSION: Finland-United States Investigation of NIDDM
WTCCC: Welcome Trust Case-Control Consortium
DGI: Diabetic Genetics Initiative at the Broad Institute MIT

Top 10 Diabetes Genes from Genome-Wide Association Study

Gene	Statistics: Odds Ratio	Statistics: p-value
TCF7L2	1.37	1.0×10^{-48}
IGF2BP2	1.14	8.9×10^{-16}
CDKN2A/B	1.20	7.8×10^{-15}
FTO	1.17	1.3×10^{-12}
CDKAL1	1.12	4.1×10^{-11}
KCNJ11	1.14	6.7×10^{-11}
HHEX	1.13	5.7×10^{-10}
SLC30A8	1.12	5.3×10^{-8}
Chr 11	1.23	4.3×10^{-7}
PPARG	1.14	1.7×10^{-6}



SLC30A8 – A Beta Cell Zinc Transporter

The Great Wave of GWAS Studies

Hokusai, K. *The Great Wave*

Catalog of GWAS Studies

http://www.ebi.ac.uk/gwas/

GWAS Catalog

The NHGRI-EBI Catalog of published genome-wide association studies

Search the catalog

Examples: breast cancer, rs7329174, Yang, 2q37.1, HBS1L

About

A description of the GWAS Catalog, including background and citation information.

Diagram

An interactive visualisation of all SNP-trait associations with genome-wide significance ($p \leq 5 \times 10^{-8}$).

Download

Including a full copy of the GWAS Catalog in spreadsheet format.

Search

You can search the Catalog in a number of ways, including by trait, SNP identifier, study and gene.

Methods

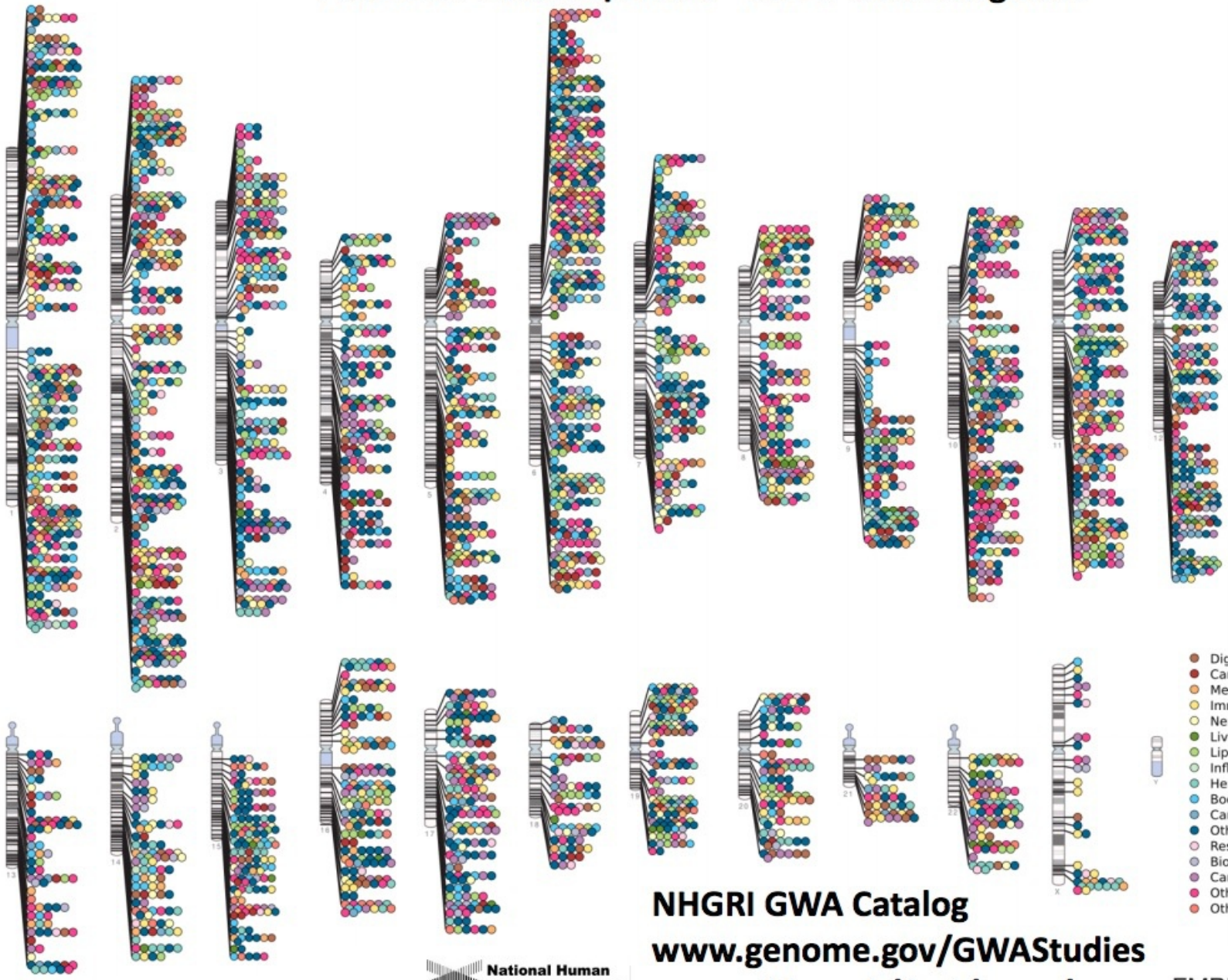
A full description of the Catalog eligibility criteria and methods.

Ontology

Details of the ontology representation of GWAS Catalog traits.

Published Genome-Wide Associations through 12/2013

Published GWA at p≤5X10^{-8} for 17 trait categories



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

National Human Genome Research Institute

EMBL-EBI


Abdominal aortic aneurysm
Acute lymphoblastic leukemia
Adhesion molecules
Adiponectin levels
Age-related macular degeneration
AIDS progression
Alcohol dependence
Alopecia areata
Alzheimer disease
Amyloid A levels
Amyotrophic lateral sclerosis
Angiotensin-converting enzyme activity
Ankylosing spondylitis
Arterial stiffness
Asparagus anosmia
Asthma
Atherosclerosis in HIV
Atrial fibrillation
Attention deficit hyperactivity disorder
Autism
Basal cell cancer
Behcet's disease
Bipolar disorder
Biliary atresia
Bilirubin
Bitter taste response
Birth weight
Bladder cancer
Bleomycin sensitivity
Blond or brown hair
Blood pressure
Blue or green eyes
BMI, waist circumference
Bone density
Breast cancer
C-reactive protein
Calcium levels
Cardiac structure/function
Cardiovascular risk factors
Carnitine levels
Carotenoid/tocopherol levels
Celiac disease
Celiac disease and rheumatoid arthritis
Cerebral atrophy measures
Chronic lymphocytic leukemia
Chronic myeloid leukemia
Cleft lip/palate
Coffee consumption
Cognitive function
Conduct disorder
Colorectal cancer
Corneal thickness
Coronary disease
Creutzfeldt-Jakob disease
Crohn's disease
Crohn's disease and celiac disease
Cutaneous nevi
Cystic fibrosis severity
Dermatitis
DHEA-s levels
Diabetic retinopathy
Dilated cardiomyopathy
Drug-induced liver injury
Drug-induced liver injury (amoxicillin-clavulanate)
Endometrial cancer
Endometriosis
Eosinophil count
Eosinophilic esophagitis
Erectile dysfunction and prostate cancer treatment
Erythrocyte parameters
Esophageal cancer
Essential tremor
Exfoliation glaucoma
Eye color traits
F cell distribution
Fibrinogen levels
Folate pathway vitamins
Follicular lymphoma
Fuch's corneal dystrophy
Freckles and burning
Gallstones
Gastric cancer
Glioma
Glycemic traits
Hair color
Hair morphology
Handedness in dyslexia
HDL cholesterol
Heart failure
Heart rate
Height
Hemostasis parameters
Hepatic steatosis
Hepatitis
Hepatocellular carcinoma
Hirschsprung's disease
HIV-1 control
Hodgkin's lymphoma
Homocysteine levels
Hypospadias
Idiopathic pulmonary fibrosis
IFN-related cytopeni
IgA levels
IgE levels
Inflammatory bowel disease
Insulin-like growth factors
Intracranial aneurysm
Iris color
Iron status markers
Ischemic stroke
Juvenile idiopathic arthritis
Keloid
Kidney stones
LDL cholesterol
Leprosy
Leptin receptor levels
Liver enzymes
Longevity
LP (a) levels
LpPLA(2) activity and mass
Lung cancer
Magnesium levels
Major mood disorders
Malaria
Male pattern baldness
Mammographic density
Matrix metalloproteinase levels
MCP-1
Melanoma
Menarche & menopause
Meningococcal disease
Metabolic syndrome
Migraine
Moyamoya disease
Multiple sclerosis
Myeloproliferative neoplasms
Myopia (pathological)
N-glycan levels
Narcolepsy
Nasopharyngeal cancer
Natriuretic peptide levels
Neuroblastoma
Nicotine dependence
Obesity
Open angle glaucoma
Open personality
Optic disc parameters
Osteoarthritis
Osteoporosis
Otosclerosis
Other metabolic traits
Ovarian cancer
Pancreatic cancer
Pain
Paget's disease
Panic disorder
Parkinson's disease
Periodontitis
Peripheral arterial disease
Personality dimensions
Phosphatidylcholine levels
Phosphorus levels
Photic sneeze
Phytosterol levels
Platelet count
Polycystic ovary syndrome
Primary biliary cirrhosis
Primary sclerosing cholangitis
PR interval
Progranulin levels
Progressive supranuclear palsy
Prostate cancer
Protein levels
PSA levels
Psoriasis
Psoriatic arthritis
Pulmonary funct. COPD
QRS interval
QT interval
Quantitative traits
Recombination rate
Red vs.non-red hair
Refractive error
Renal cell carcinoma
Renal function
Response to antidepressants
Response to antipsychotic therapy
Response to carbamazepine
Response to clopidogrel therapy
Response to hepatitis C treat
Response to interferon beta therapy
Response to metaformin
Response to statin therapy
Restless legs syndrome
Retinal vascular caliber
Rheumatoid arthritis
Ribavirin-induced anemia
Schizophrenia
Serum metabolites
Skin pigmentation
Smoking behavior
Speech perception
Sphingolipid levels
Statin-induced myopathy
Stroke
Sudden cardiac arrest
Suicide attempts
Systemic lupus erythematosus
Systemic sclerosis
T-tau levels
Tau AB1-42 levels
Telomere length
Testicular germ cell tumor
Thyroid cancer
Thyroid volume
Tooth development
Total cholesterol
Triglycerides
Tuberculosis
Type 1 diabetes
Type 2 diabetes
Ulcerative colitis
Urate
Urinary albumin excretion
Urinary metabolites
Uterine fibroids
Venous thromboembolism
Ventricular conduction
Vertical cup-disc ratio
Vitamin B12 levels
Vitamin D insuffiency
Vitiligo
Warfarin dose
Weight
White cell count
White matter hyperintensity
YKL-40 levels

The McDermott Center for Human Growth and Development

Center for Human Genetics

Helen H. Hobbs, M.D.
Howard Hughes Investigator
Director, McDermott Center
Chief, Division of Clinical Genetics, Internal Medicine
Professor of Internal Medicine and Molecular Genetics

Graduate Program:
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Research Interests:

- Genetic determinants of plasma lipid levels
- LDL metabolism
- Role of ABC transporters in lipid transport

Lab Personnel

Recent Publications:

1. Romeo S., Pennacchio L.A., Fu Y., Boerwinkle E., Tybjaerg-Hansen A., Hobbs H.H., Cohen, JC (2007) Population-based resequencing of ANGPTL4 uncovers variations that reduce triglycerides and increase HDL in Caucasians. Nat. Genet. 39:513-516.

2. McPherson R., Pertsemlidis A., Kavaslar N., Stewart A., Robert R., Cox D.R., Hinds D.A., Pennacchio L.A., Tybjaerg-Hansen A., Folsom A.R., Boerwinkle E., Hobbs H.H., Cohen J.C. (2007) A common allele on chromosome 9 associated with coronary heart disease. Science 316:1488-1491.

3. Cohen J.C., Boerwinkle E., Mosley T.H., Hobbs H.H. (2006) Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N. Engl. J. Med. 354:1264-1272.

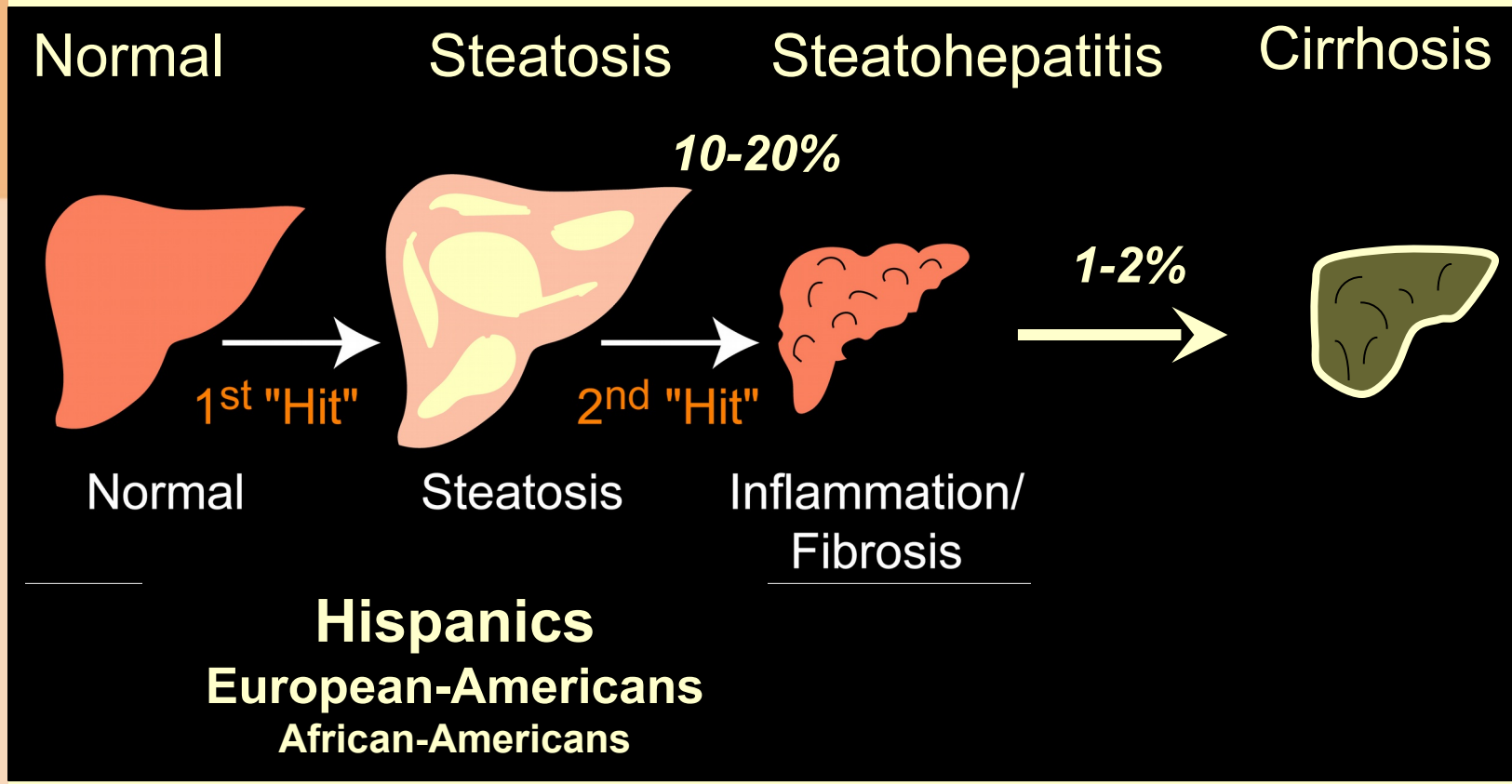
4. Cohen J.C., Kiss R.S., Pertsemlidis A., Marcel Y.L., McPherson R., Hobbs H.H. (2004) Multiple rare alleles contribute to low plasma levels of HDL cholesterol. Science 305:869-872.

For additional publications: Search PubMed

Education:

- Stanford University, Palo Alto, CA, B.A., Human Biology, 1974
- Case Western Reserve University School of Medicine, Cleveland , OH , M.D., Medicine, 1979
- UT Southwestern Medical Center , Dallas, TX, Postdoctoral Fellow, Endocrinology and Molecular Genetics, 1987

Do genetic differences between ethnic groups contribute to differences in fatty liver disease?

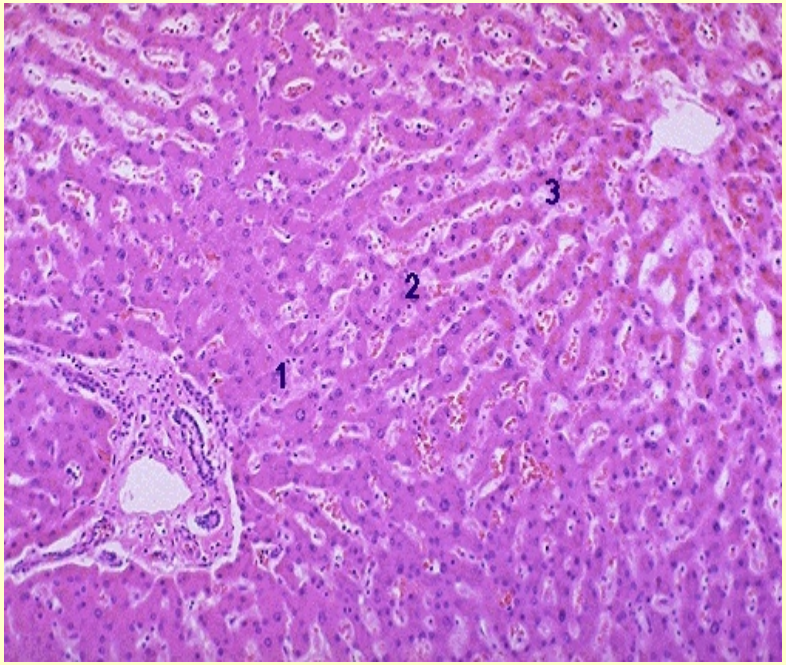


First Hit
- Obesity
- Type 2 diabetes
- Ethanol
- Hepatitis C

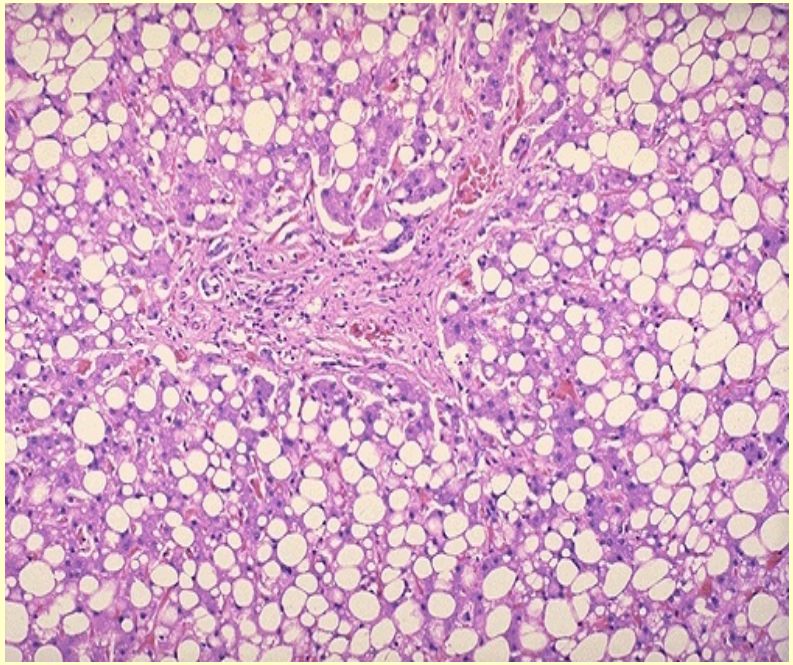
Second Hit
- Oxidative Stress
- Lipid Peroxidation
- Anti-virals
- Cytokines

Hepatic Steatosis

Normal



Hepatic Steatosis



- Obesity
- Type 2 diabetes
- Ethanol
- Hepatitis C

Genome-wide Association Study for Hepatic Triglyceride Content in the Dallas Heart Study

- Restricted to non-synonymous SNPs
- Chip-based oligonucleotide hybridization
- Quality filter: N = 12,138 è 9,229

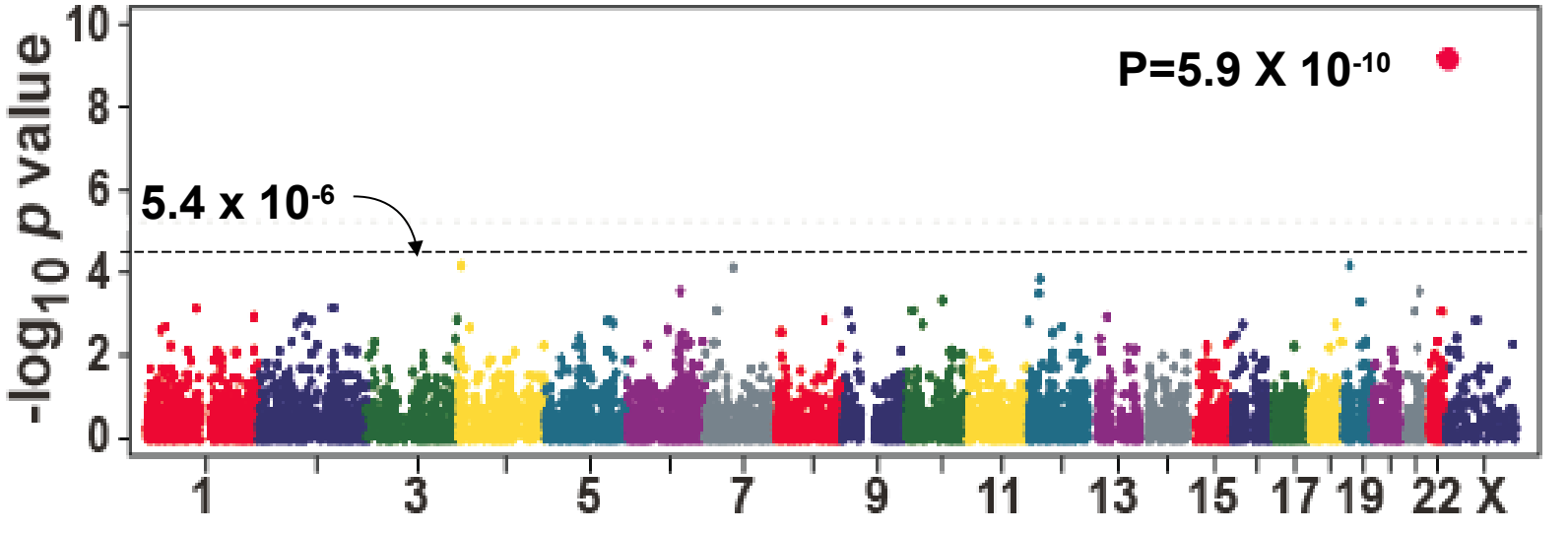
1,032 African-Americans
696 European-Americans
383 Hispanics

N = 2,111

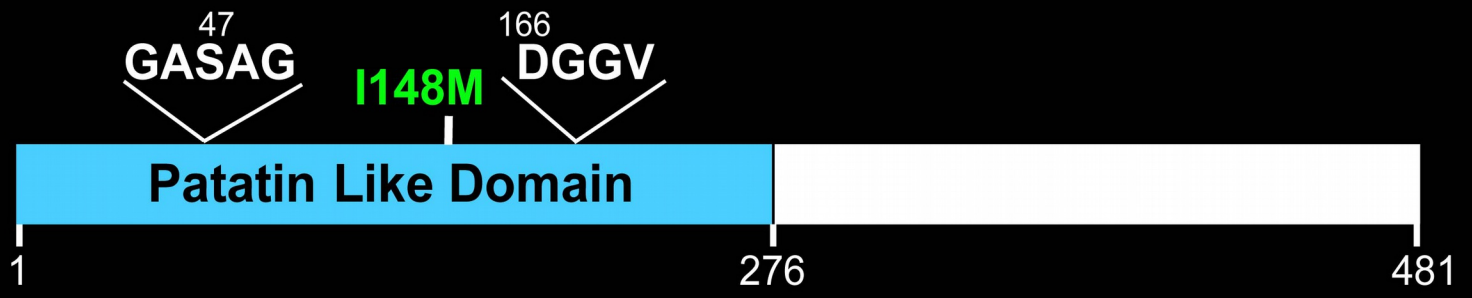
Romeo, et al.(2008) Genetic Variation in PNPLA3 confers susceptibility
Nature Genetics 40, 1461-1465

Genome-wide Association Study of Liver Triglyceride Levels in Dallas Heart Study Cohort

(2,111 patients and 9,299 Non-synonymous SNPs)

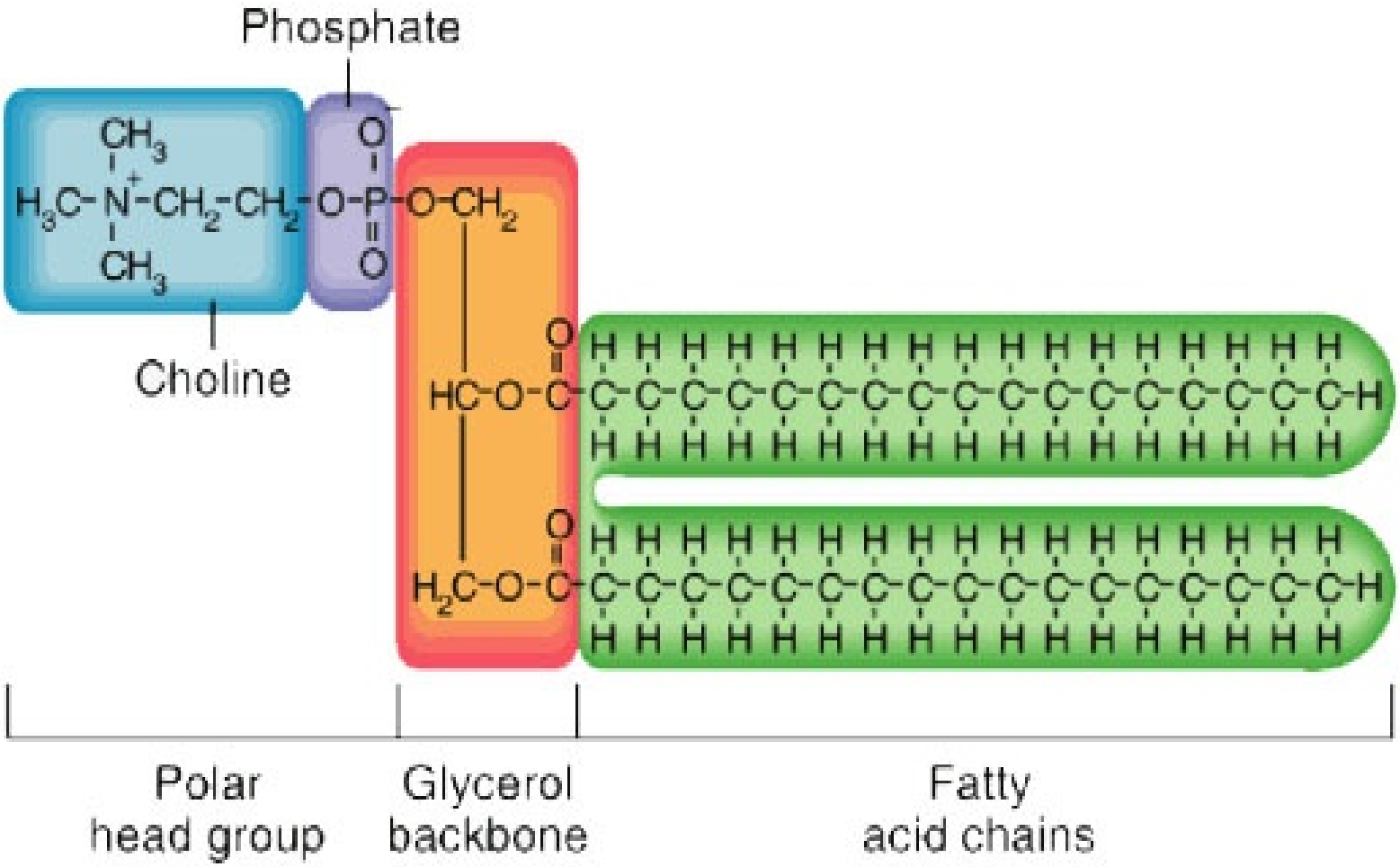


PNPLA3: A Member of the Patatin-like Phospholipase Family



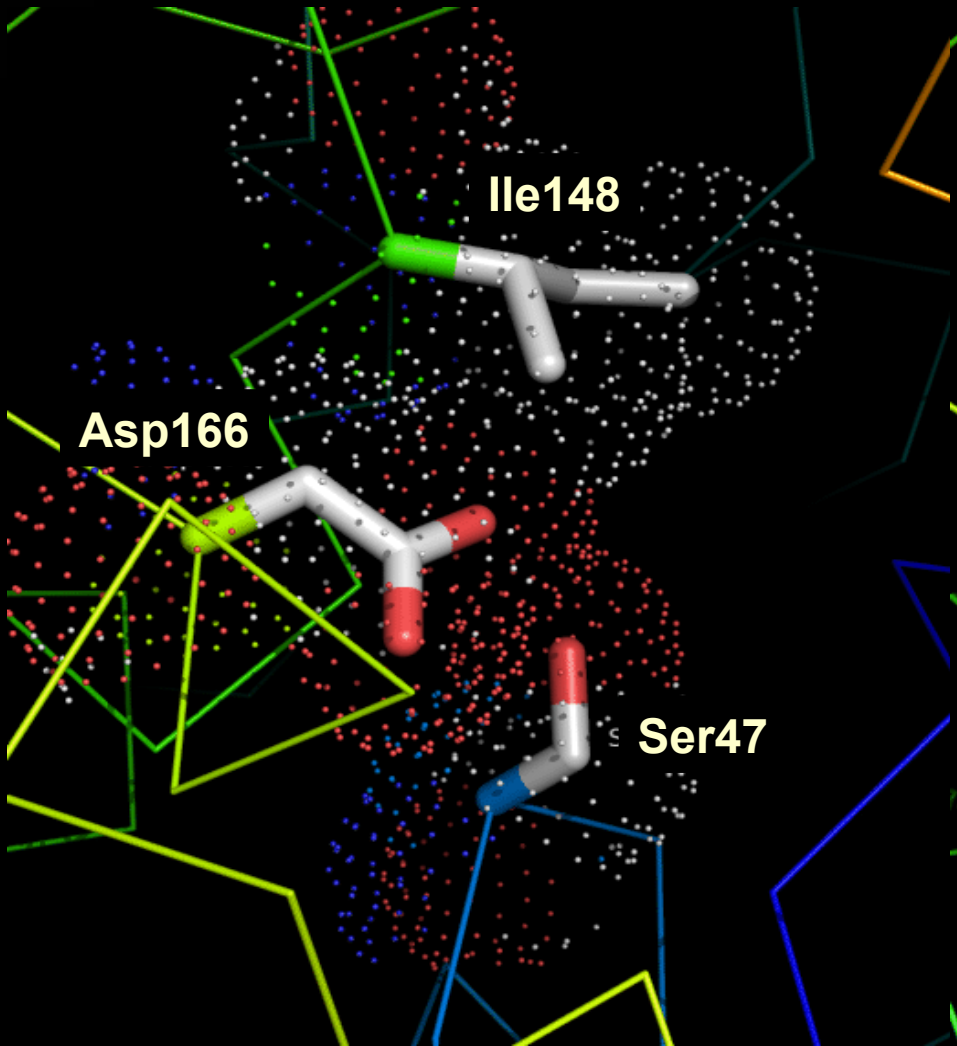
- Resembles patatin: major potato protein
- Nonspecific lipid acyl hydrolase activity
- Expressed high level in fat & liver
- Increased with feeding (especially carbohydrates)

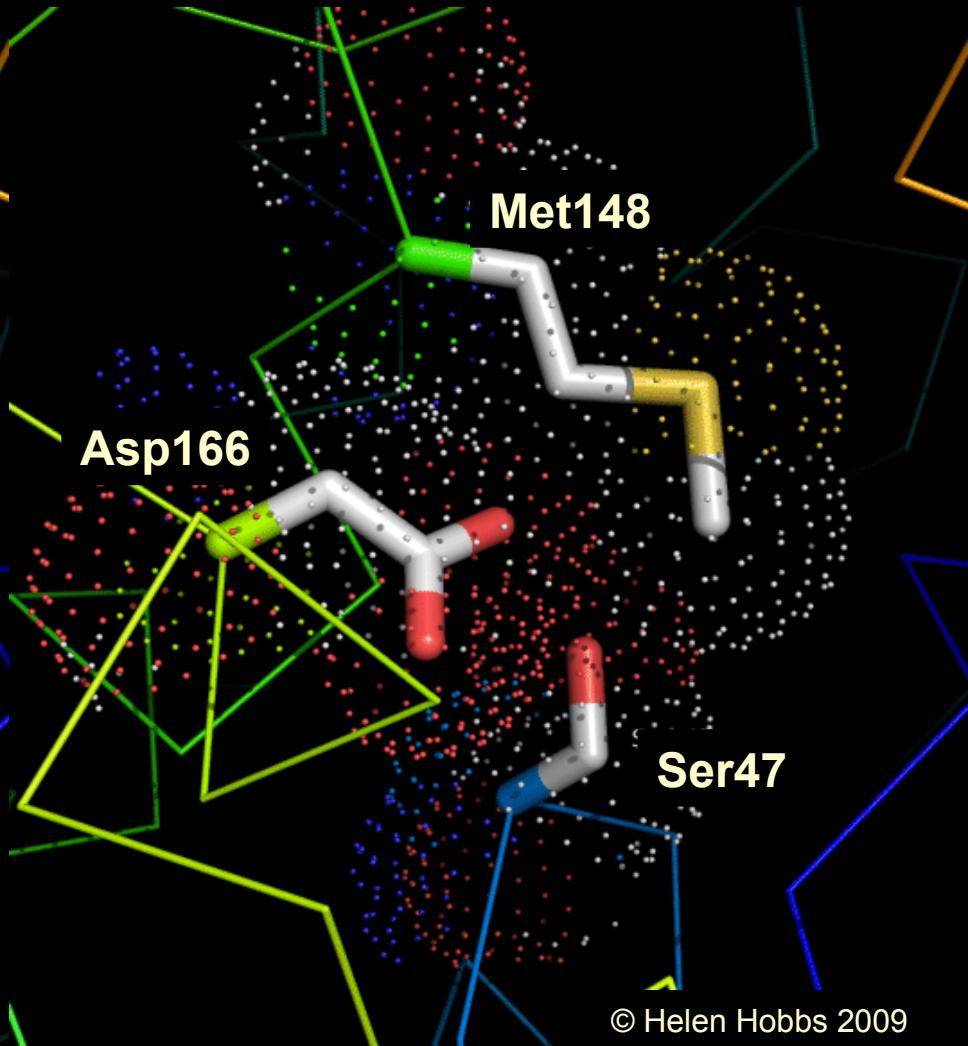
A Typical Phospholipid Phophotidyl Choline



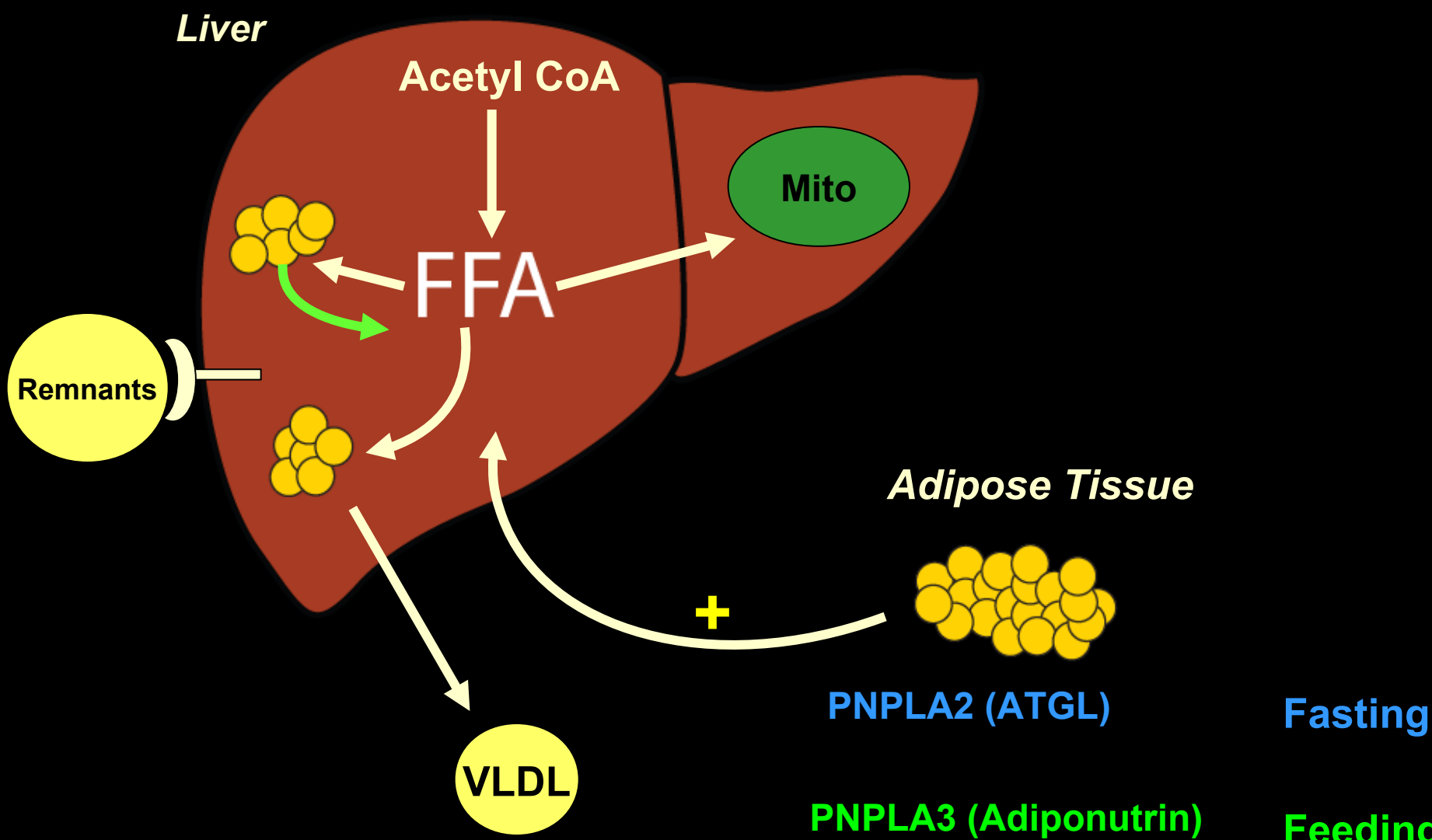
http://www.uic.edu/classes/bios/bios100/lectf03am/phospholipid.jpg

I148M & Catalytic Site of PNPLA3



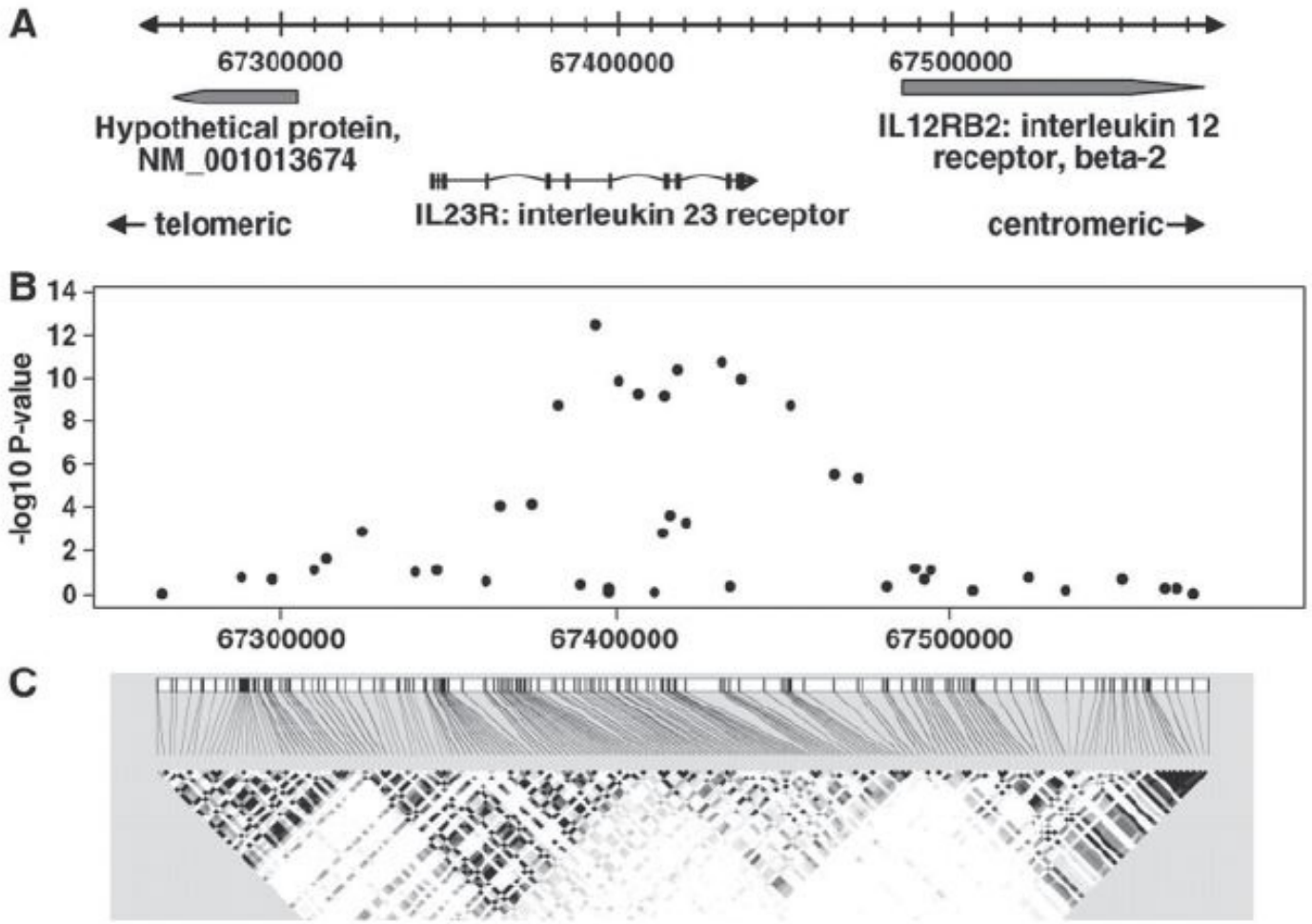


PNPLA3 & Hepatic Triglyceride Metabolism



Interleukin 23R & Inflammatory Bowel Disease

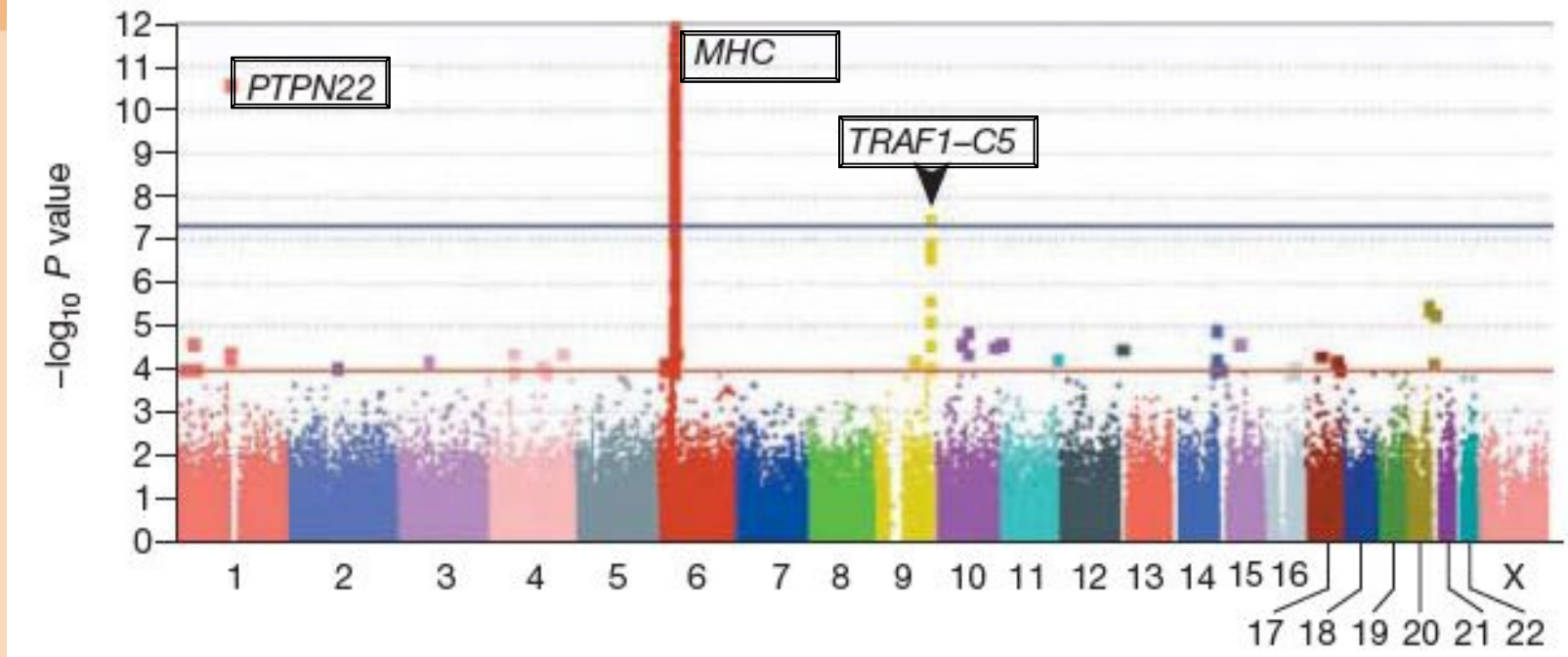
Figure 2. Associations in the *IL23R* Gene Region Identified by a Genome-wide Association Study of Inflammatory Bowel Disease



Pearson, T. A. et al. JAMA 2008;299:1335-1344

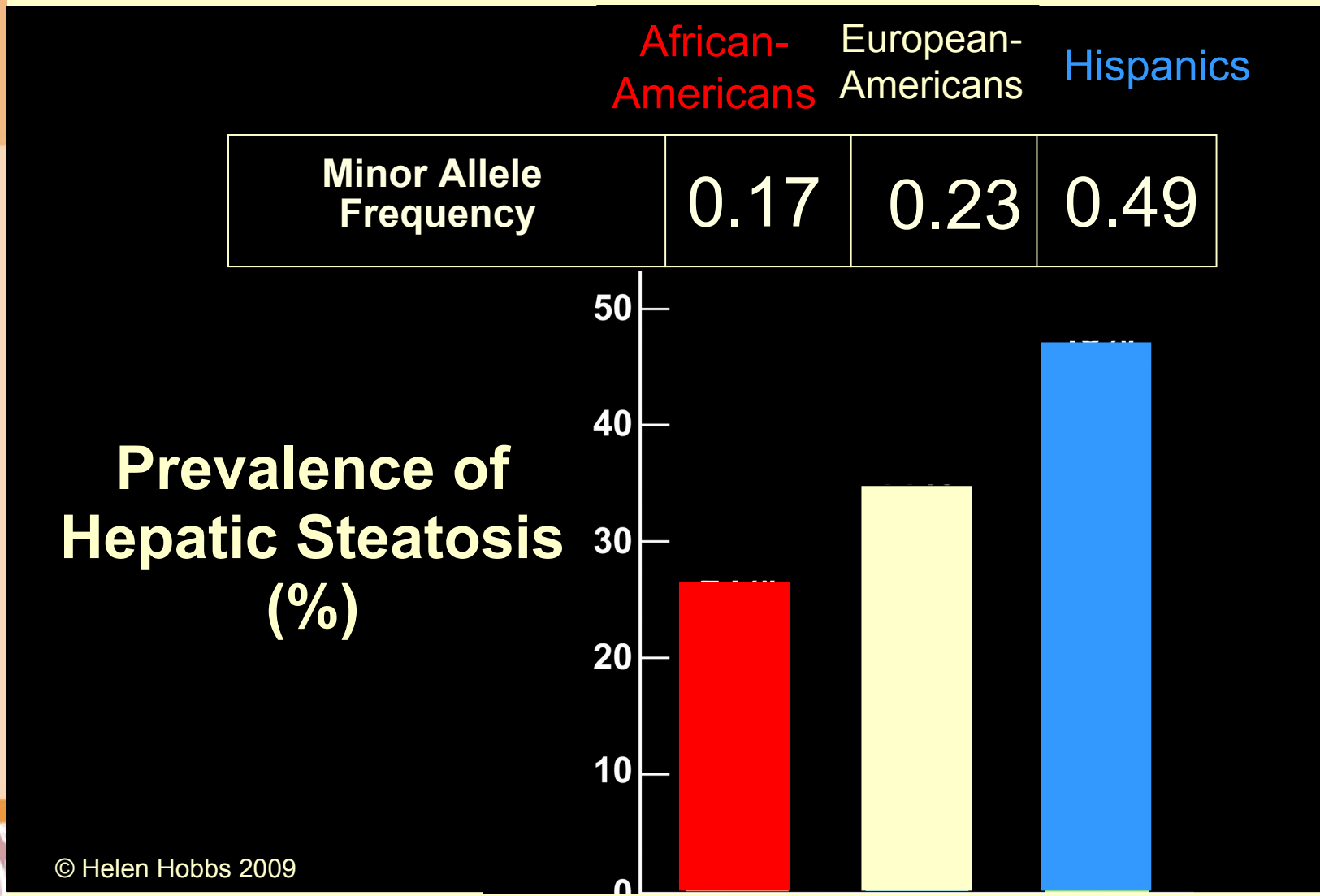
Genome Wide Associations in Rheumatoid Arthritis

Figure 3. Genome-wide Association Findings in Rheumatoid Arthritis

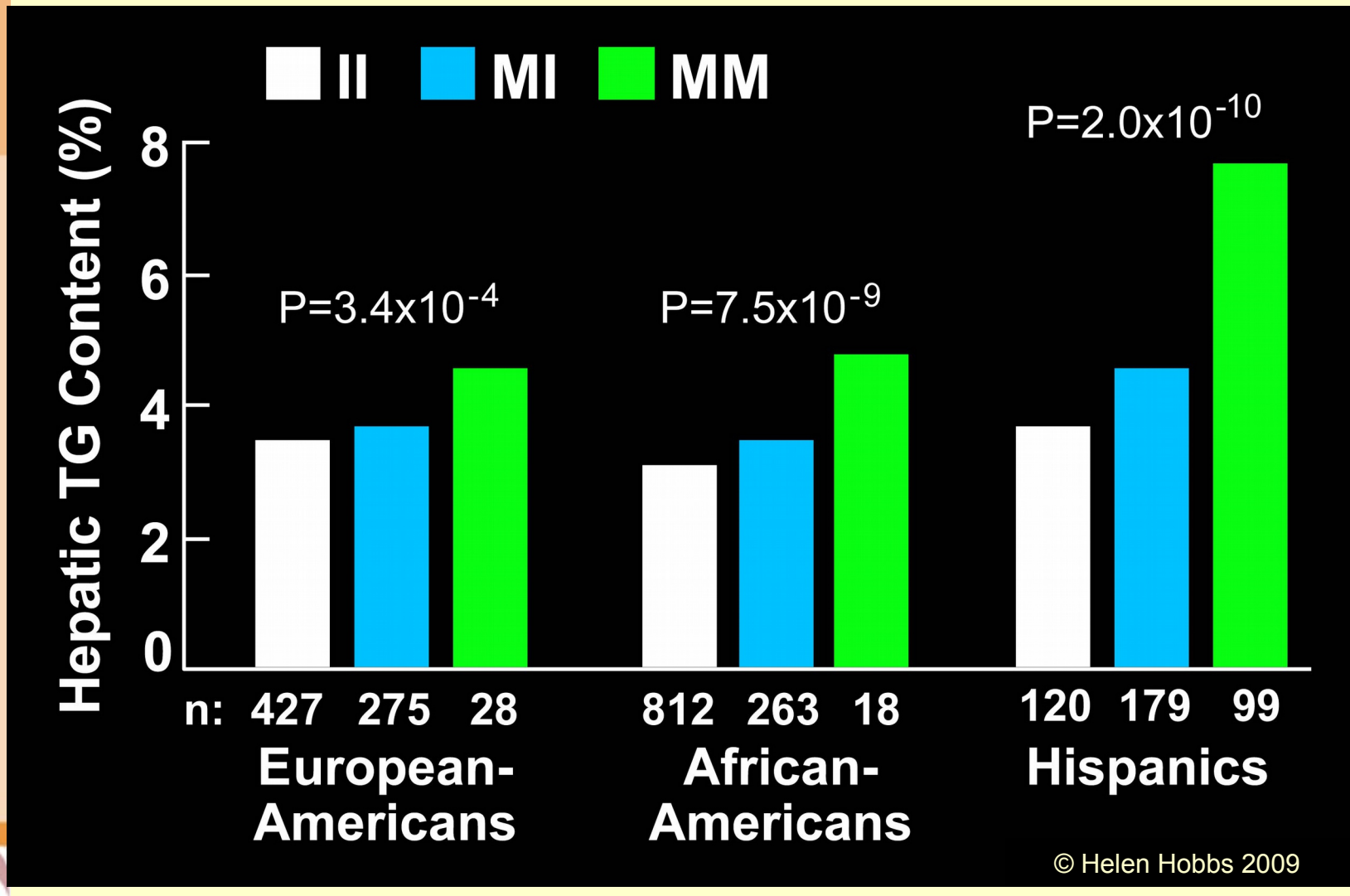


Pearson, T. A. et al. JAMA 2008;299:1335-1344

Genetic Contribution to Ethnic Differences in Hepatic Steatosis



PNPLA3: I148M Genotype and Hepatic Triglyceride Content



Genome-Wide Association Project

http://biochem118.stanford.edu/Homeworks/04%20gwas-project.html

Read Thomas A. Pearson; Teri A. Manolio (2008) How to Interpret a Genome-wide Association Study. JAMA, March 19, 2008; 299: 1335 - 1344.

Please search either PubMed, Google Scholar or (preferably) the GWAS Catalog for a multifactorial disease of interest to you. To help you with the PubMed search, "Genome-Wide Association Study" is a defined MeSH term so your search can look like this: '"Genome-Wide Association Study"[MaJR] AND Disease-name-or-Disease-MeSH-term

For Google Scholar you will have to do two searches, one with the phrase "Genome-Wide Association Study" AND disease-name and another search for "GWAS AND disease-name".

Read the papers that have performed genome-wide association studies on your disease of interest. Please write a 4 page summary of the genome-wide association studies on your disease of interest. Please include the following information in your summary and the implication of each observation:

1) The URL or UID of the papers you read.

2) A description of the study including the population or ethnic group involved, whether it is a case/control study or a cohort study or a study of trios, the number of patients and controls examined, any stratification that was performed, the number of SNPs examined and any other information about the study that is critical for its interpretation.

3) A paragraph describing the genes and/or the SNPs that are most highly correlated with the disease. You should examine the function of each gene in the NCBI Gene database or the UniProt Protein Database and report any functions (gene ontology terms) that may be relevant to the disease.

4) The odds ratio and heritability of each SNP correlation if given. If not, state that the data was not present.

5) Report if the association studies been repeated in different laboratories, or different populations or subpopulation or ethnic groups?

6) Report of any causal mutations been detected or suggested from any of the data?

7) Also please report if knowledge of those SNPs or genes sheds any light on the molecular basis for the disease.

Please remember that this is a research report, not a list of short answers. You should write full paragraphs on each of the topics above.

Association of Alleles & Genotypes

Table 3. Association of Alleles and Genotypes of rs6983267 on Chromosome 8q24 With Colorectal Cancer[a]

	Number and Frequency of rs6983267 Alleles in Colorectal Cancer					Number and Frequency of rs6983267 Genotypes in Colorectal Cancer						
	C	T	χ^2 (1*df*)	*P* Value	OR	CC	CT	TT	χ^2 (2*df*)	*P* Value	OR	OR
Cases	875 (56.5)	675 (43.5)	24.8	6.3×10^{-7}	1.35[b]	250 (32.3)	375 (48.4)	150 (19.4)	24.5	4.7×10^{-6}	1.33[c]	1.81[d]
Controls	1860 (48.9)	1940 (51.1)				460 (24.2)	940 (49.4)	500 (26.3)				

Abbreviation: OR, odds ratio.
[a] Data are hypothetical; adapted from Tomlinson et al.[56]
[b] Denotes allelic odds ratio.
[c] Denotes heterozygote odds ratio.
[d] Denotes homozygote odds ratio.

Pearson, T. A. et al. JAMA 2008;299:1335-1344

Experimental Designs Used in Genome-wide Association Studies

Table 1. Study Designs Used in Genome-wide Association Studies

	Case-Control	Cohort	Trio
Assumptions	Case and control participants are drawn from the same population Case participants are representative of all cases of the disease, or limitations on diagnostic specificity and representativeness are clearly specified Genomic and epidemiologic data are collected similarly in cases and controls Differences in allele frequencies relate to the outcome of interest rather than differences in background population between cases and controls	Participants under study are more representative of the population from which they are drawn Diseases and traits are ascertained similarly in individuals with and without the gene variant	Disease-related alleles are transmitted in excess of 50% to affected offspring from heterozygous parents
Advantages	Short time frame Large numbers of case and control participants can be assembled Optimal epidemiologic design for studying rare diseases	Cases are incident (developing during observation) and free of survival bias Direct measure of risk Fewer biases than case-control studies Continuum of health-related measures available in population samples not selected for presence of disease	Controls for population structure; immune to population stratification Allows checks for Mendelian inheritance patterns in genotyping quality control Logistically simpler for studies of children's conditions Does not require phenotyping of parents
Disadvantages	Prone to a number of biases including population stratification Cases are usually prevalent cases, may exclude fatal or short episodes, or mild or silent cases Overestimate relative risk for common diseases	Large sample size needed for genotyping if incidence is low Expensive and lengthy follow-up Existing consent may be insufficient for GWA genotyping or data sharing Requires variation in trait being studied Poorly suited for studying rare diseases	May be difficult to assemble both parents and offspring, especially in disorders with older ages of onset Highly sensitive to genotyping error

Pearson, T. A. et al. JAMA 2008;299:1335-1344

Examples of Multistage Designs in Genome-wide Association Studies

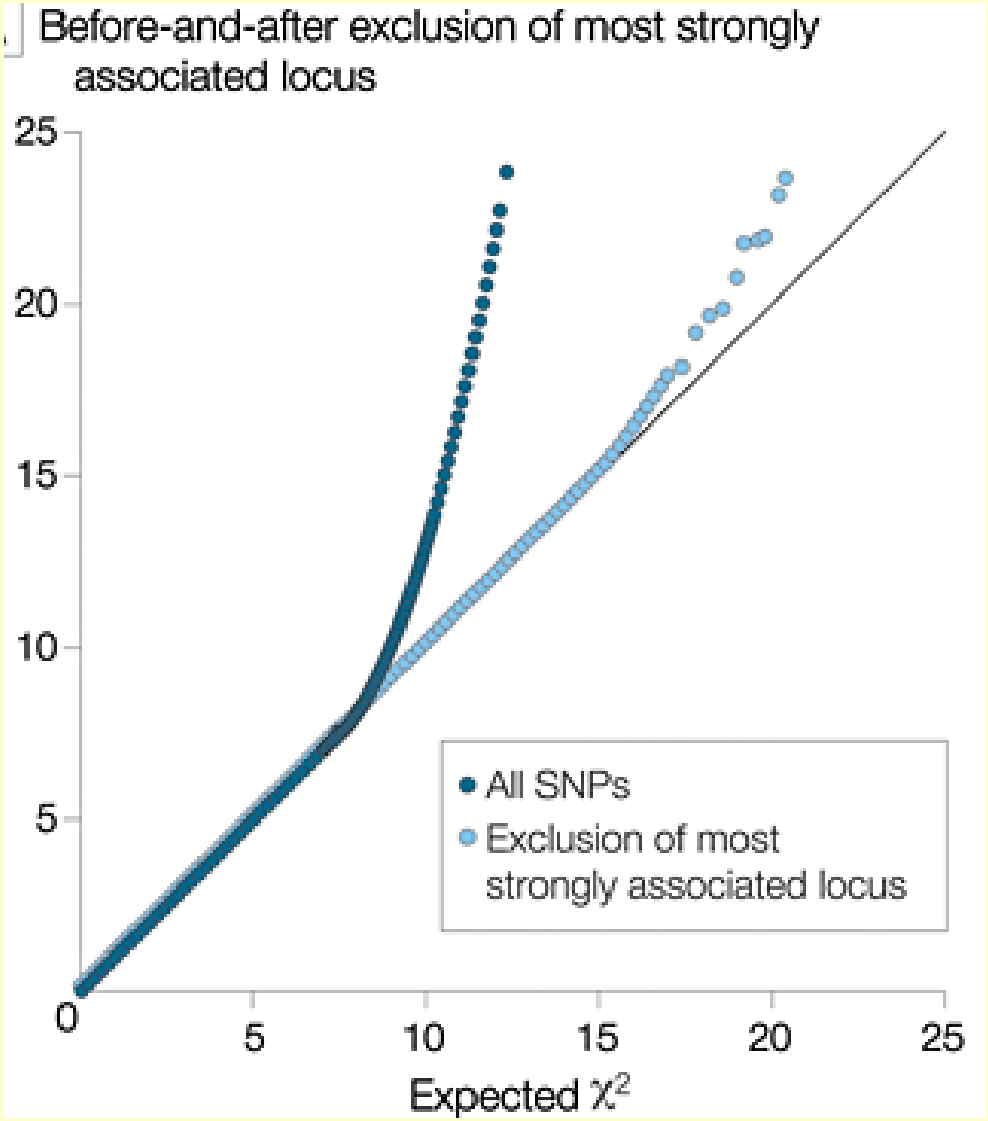
Table 2. Examples of Multistage Designs in Genome-wide Association Studies[a]

	3-Stage Study[b]		4-Stage Study[c]	
Stage	Case Participants/ Control Participants	SNPs Analyzed	Case Participants/ Control Participants	SNPs Analyzed
1	400/400	500 000	2000/2000	100 000
2	4000/4000	25 000	2000/2000	1000
3	20 000/20 000	25	2000/2000	20
4			2000/2000	5

Abbreviation: SNP, single-nucleotide polymorphism.
[a] Based on hypothetical data.
[b] Five SNPs associated with disease.
[c] Two SNPs associated with disease.

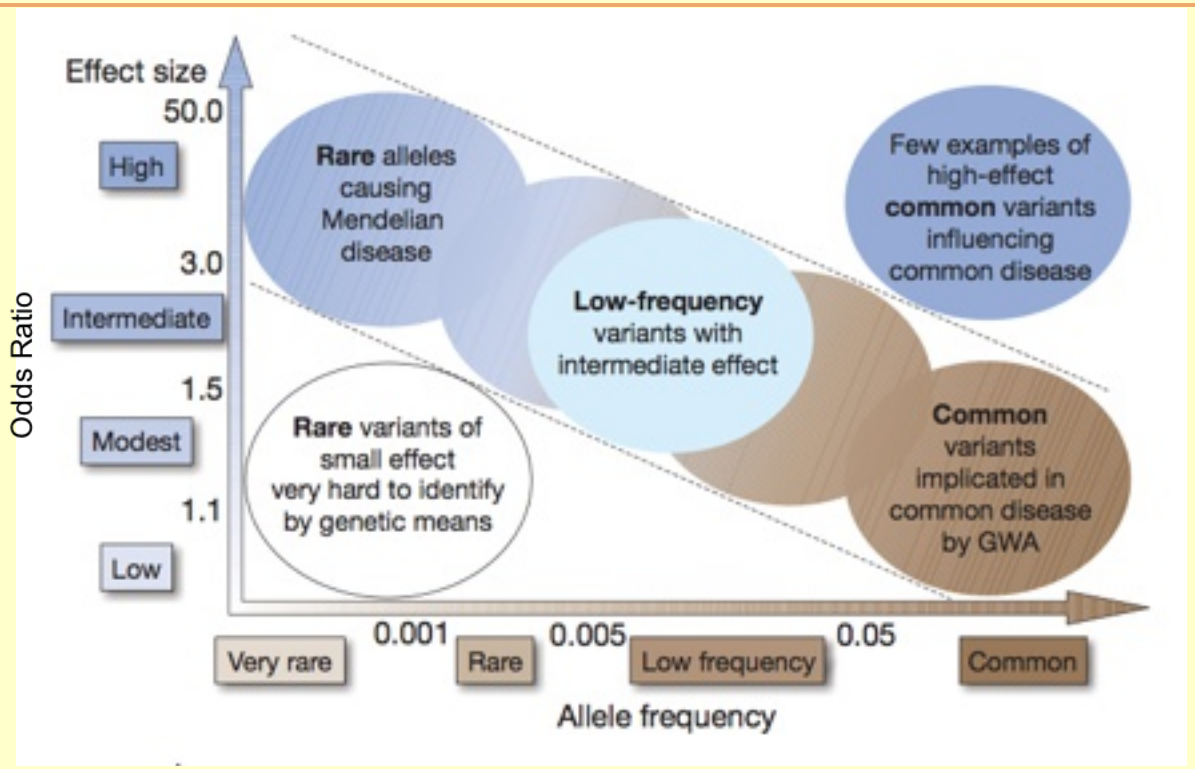
Pearson, T. A. et al. JAMA 2008;299:1335-1344

Quantile-Quantile Plots in Genome-wide Association Studies



Pearson, T. A. et al. JAMA 2008;299:1335-1344

Low Heritability of Common SNPs



- Common SNPs carry low risk while rarer high penetrance variants carry high risk
- Multiple variants may increase risk synergistically
- Common SNPs associated with genes containing high risk alleles
- Common SNPs associations can suggest regions to sequence in cohorts or trios

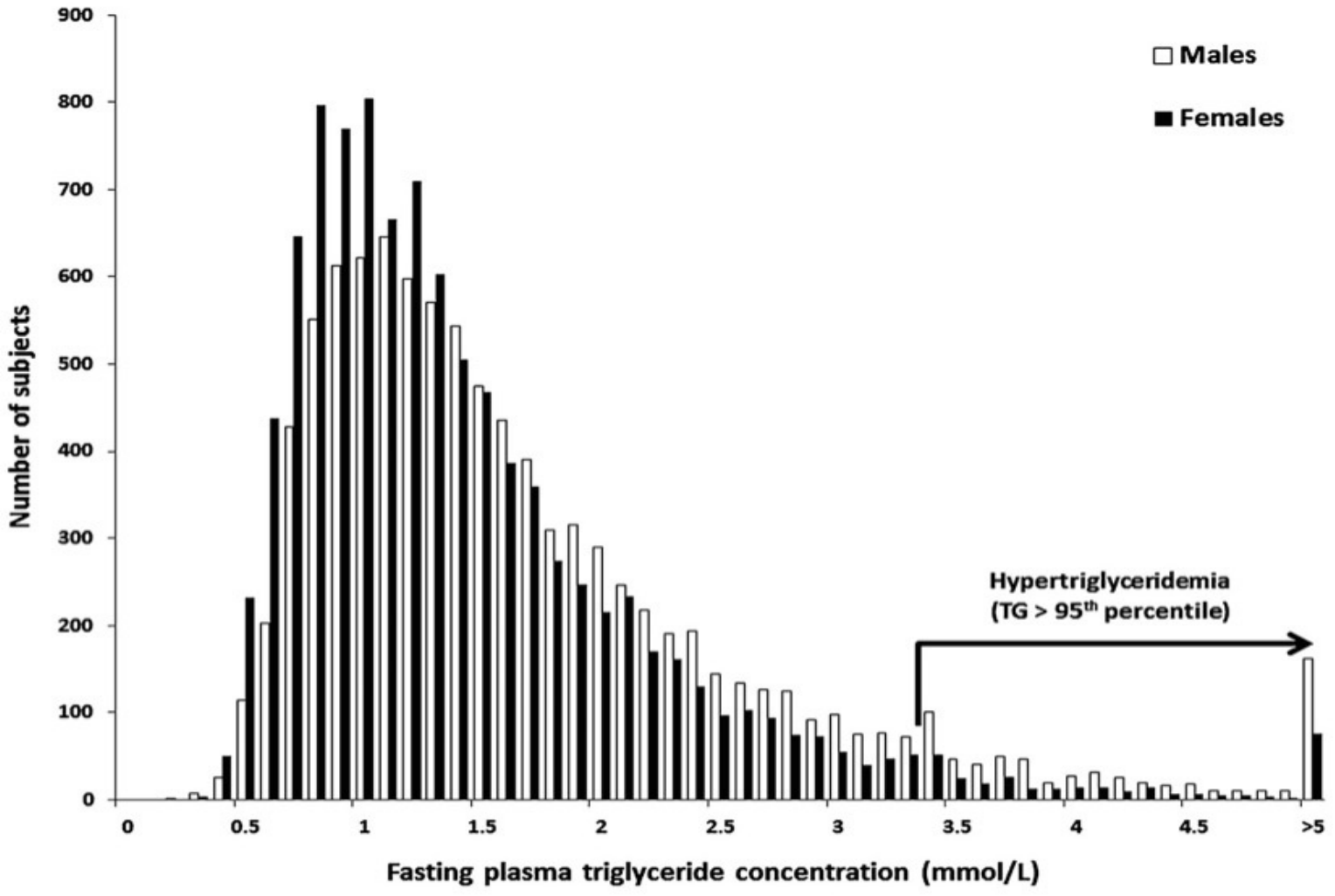
Manolio et al. Nature 461, 747-753 (2009)

Disease Genes are Often Enriched in Subpopulations

- Subpopulations are often enriched for disease alleles
- Subpopulations can cause synthetic SNP associations
- Focusing on a subpopulations will eliminate synthetic SNP associations
- Egypt is a haplotype heaven!
  - Highest frequency of genetic (SNP) variations
  - High numbers of genetic subpopulations due to multiple migrations and invasions
  - Greeks, Romans, Turks, Persians etc.

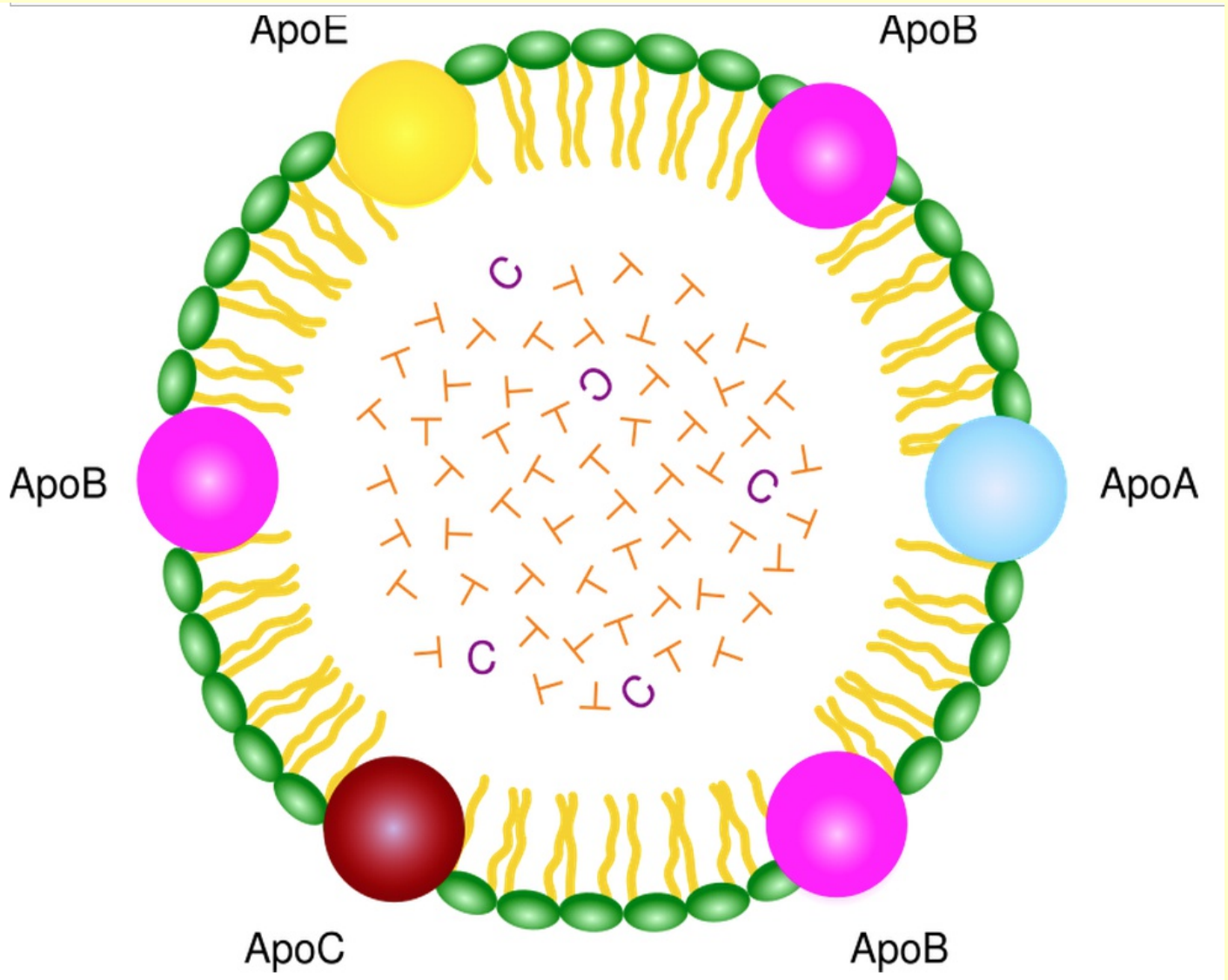
Triglyceride Frequency Distribution

http://www.ncbi.nlm.nih.gov/pubmed/21041806

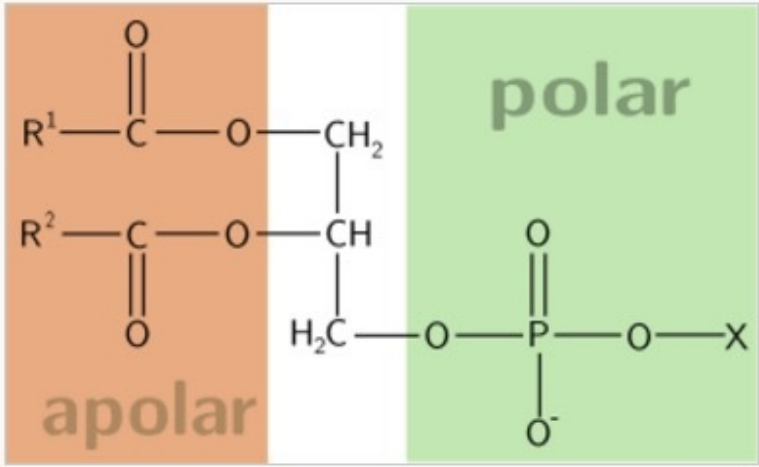


Johansen et al. J Lipid Res 52:182-206, 2011

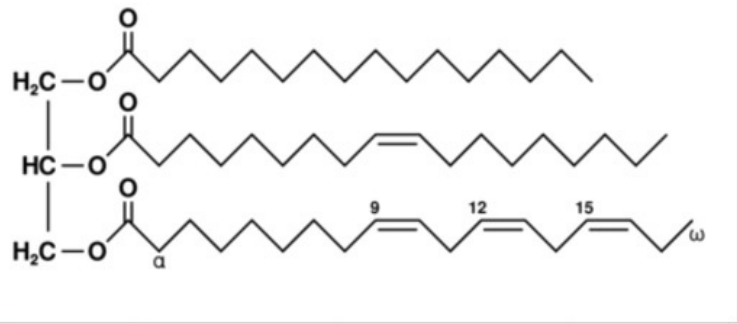
Chylomicron Vesicle Structure http://en.wikipedia.org/wiki/Chylomicron



Phosphoglycerides and Triglycerides



Phosphoglycerides



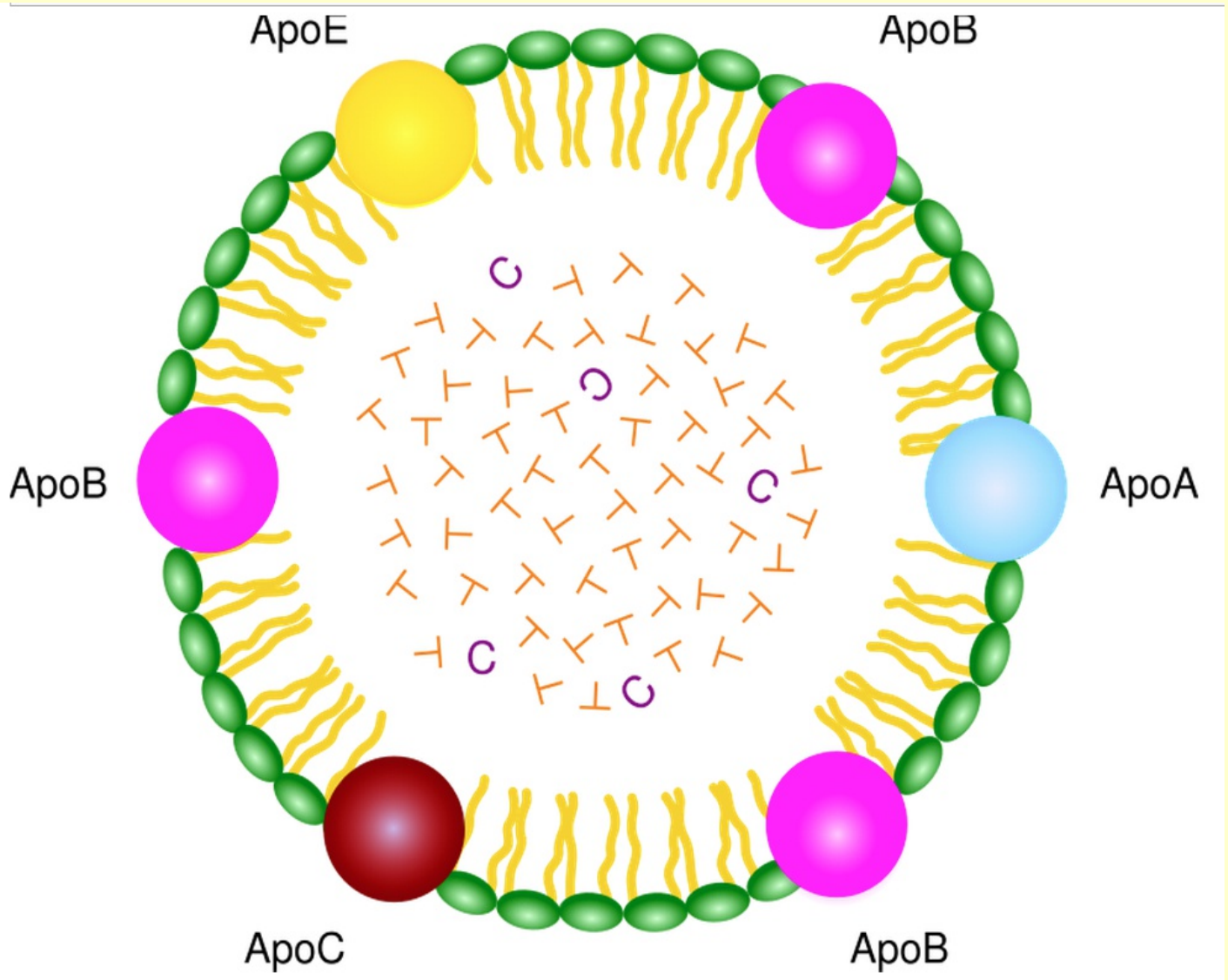
Example of an unsaturated fat triglyceride. Left part: glycerol, right part from top to bottom: palmitic acid, oleic acid, alpha-linolenic acid. Chemical formula: $C_{55}H_{98}O_6$

Triglycerides

From: https://en.wikipedia.org/

Chylomicron Structure

http://en.wikipedia.org/wiki/Chylomicron



Genetic Loci Associated with Hypertriglyceridemia

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3017369/

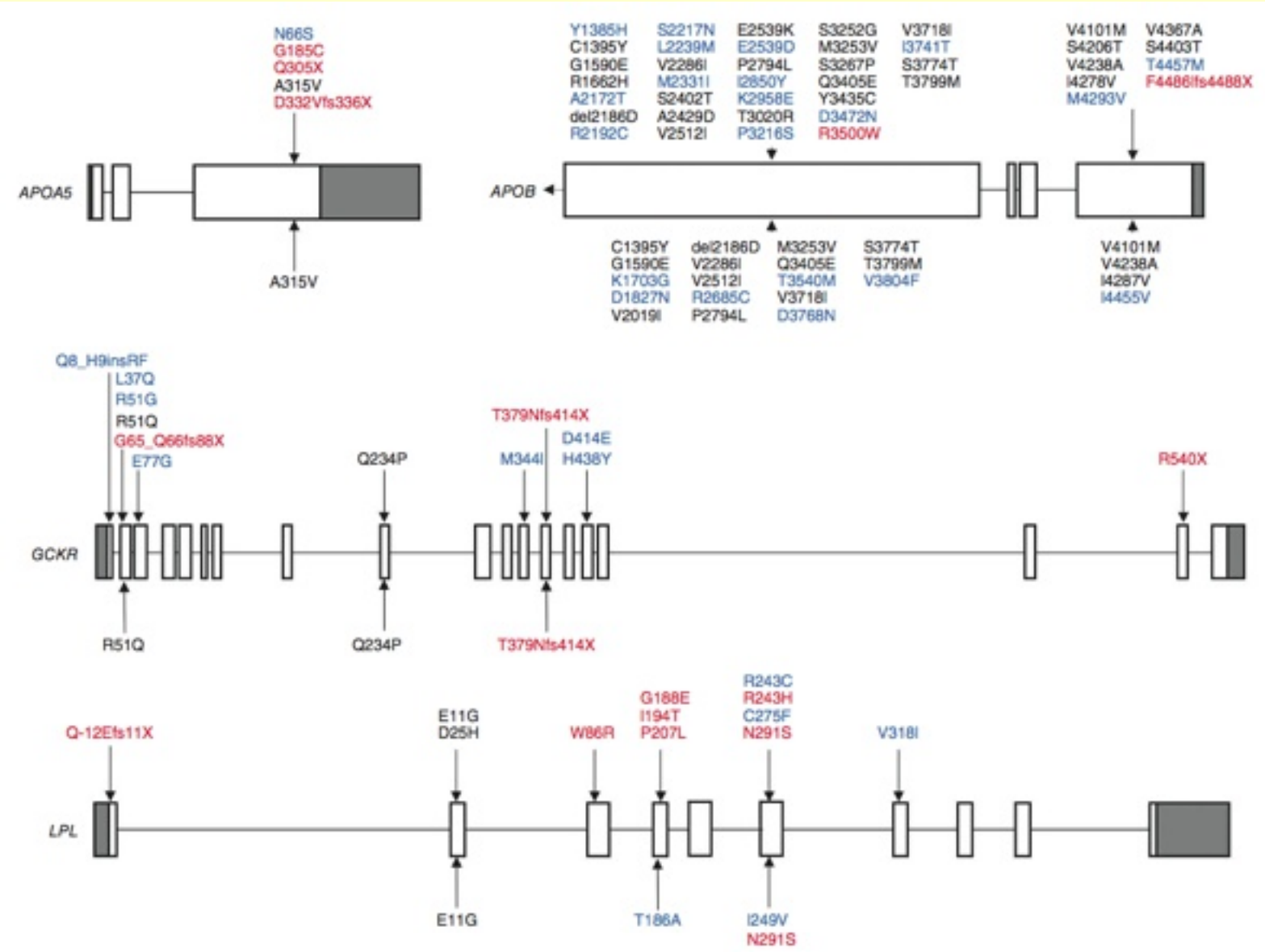
Table 2 Genetic loci associated with HTG

Locus	SNP	Chr.	Position	Minor allele	HTG MAF	Control MAF	OR (95% CI)	*P*
APOA5	rs964184	11	116.2	G	0.33	0.14	3.28 (2.61–4.14)	5.4×10^{-24}
GCKR	rs1260326	2	2.8	T	0.52	0.41	1.75 (1.45–2.12)	6.5×10^{-9}
LPL	rs7016880	8	19.9	C	0.03	0.10	0.32 (0.21–0.49)	2.0×10^{-7}
APOB	rs4635554	2	21.2	G	0.39	0.31	1.67 (1.38–2.02)	2.0×10^{-7}
MLXIPL	rs714052	7	72.5	G	0.07	0.13	0.44 (0.31–0.62)	0.000003
TRIB1	rs2954029	8	126.6	T	0.37	0.46	0.71 (0.59–0.86)	0.0004
ANGPTL3	rs10889353	1	62.9	C	0.27	0.32	0.73 (0.59–0.89)	0.002
NCAN	rs17216525	19	19.5	T	0.07	0.09	0.71 (0.50–1.00)	0.05
FADS	rs174547	11	61.3	C	0.40	0.33	1.20 (0.99–1.44)	0.07
XKR6	rs7819412	8	11.1	G	0.46	0.50	0.87 (0.72–1.05)	0.14
PLTP	rs7679	20	44.0	C	0.20	0.19	1.17 (0.94–1.47)	0.16

Nat Genet. 2010 Aug;42(8):684-7. Epub 2010 Jul 25.

Excess of rare variants in genes identified by genome-wide association study of hypertriglyceridemia.

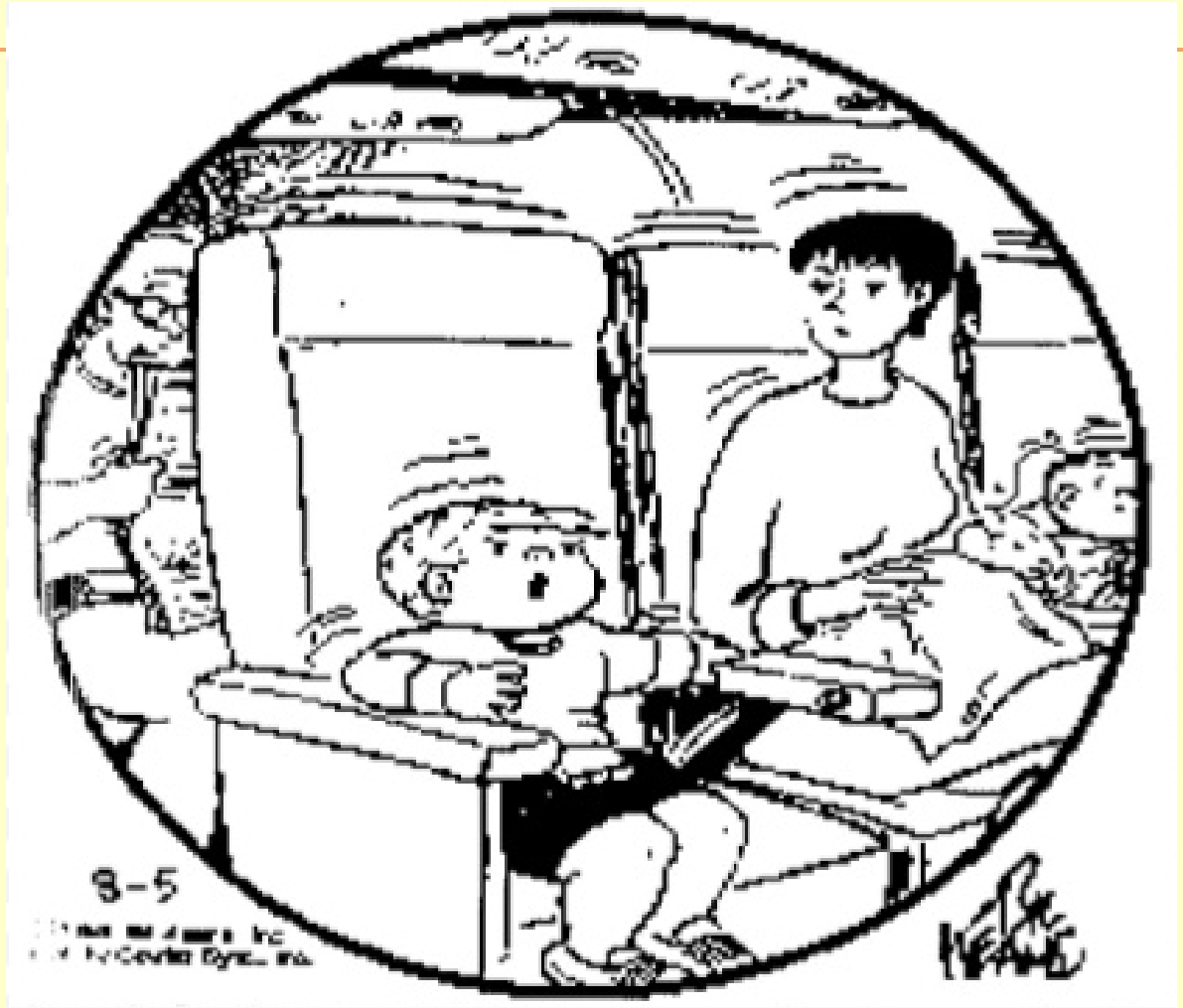
Novel Rare Variants in GWAS Genes for Hypertriglyceridemia
http://www.ncbi.nlm.nih.gov/pubmed/20657596



Summary of GWA Studies

- Genome-wide association studies make no assumptions about disease mechanism or cause
- Genome-wide association studies usually discover only genetic correlations, not cause

Association versus Causality



I wish they didn't turn on that seatbelt sign so much!
Every time they do, it gets bumpy.

Courtesy David Feldman

Summary of GWA Studies

- Genome-wide association studies make no assumptions about disease mechanism or cause
- Genome-wide association studies usually discover only genetic correlations, not cause
- Genome-wide associations indicate
  - Genes and regions to analyze by resequencing for causal alleles
  - Subpopulations that may be enriched for causal or preventive alleles
  - Genes and gene products for functional and structural studies
  - Genes to examine for regulatory studies

Summary

- Genome-wide association studies make no assumptions about disease mechanism or cause
- Genome-wide association studies usually discover only genetic correlations, not cause
- Genome-wide associations indicate
  - Genes and regions to analyze by resequencing for causal alleles
  - Subpopulations that may be enriched for causal or preventive alleles
  - Genes and gene products for functional and structural studies
  - Genes to examine for regulatory studies
- Genome-wide association studies coupled with proper biological and structural studies can lead to:
  - Unexpected causes for disease
  - Novel mechanisms for disease (missense mutations, regulatory changes, alternative splicing, copy number variation etc.)
  - Multiple pathways and multiple genes involved in disease
  - Novel diagnostics and prognosis
  - Novel treatments

Genome-Wide Association Project

http://biochem118.stanford.edu/Homeworks/04%20gwas-project.html

Genome-Wide Association Study Research Project

Read Thomas A. Pearson; Teri A. Manolio (2008) How to Interpret a Genome-wide Association Study. JAMA, March 19, 2008; 299: 1335 - 1344.

Please search either PubMed, Google Scholar or (preferably) the GWAS Catalog for a multifactorial disease of interest to you. To help you with the PubMed search, "Genome-Wide Association Study" is a defined MeSH term so your search can look like this: '"Genome-Wide Association Study"[MaJR] AND Disease-name-or-Disease-MeSH-term

For Google Scholar you will have to do two searches, one with the phrase "Genome-Wide Association Study" AND disease-name and another search for "GWAS AND disease-name".

Read the papers that have performed genome-wide association studies on your disease of interest. Please write a 4 page summary of the genome-wide association studies on your disease of interest. Please include the following information in your summary and the implication of each observation:

1) The URL or UID of the papers you read.

2) A description of the study including the population or ethnic group involved, whether it is a case/control study or a cohort study or a study of trios, the number of patients and controls examined, any stratification that was performed, the number of SNPs examined and any other information about the study that is critical for its interpretation.

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6) Report of any causal mutations been detected or suggested from any of the data?

7) Also please report if knowledge of those SNPs or genes sheds any light on the molecular basis for the disease.

GWAS References

How to Use an Article About Genetic Association: A: Background Concepts John Attia et al. (2009)
JAMA 301, 74-81

How to Interpret a Genome-wide Association Study Thomas A. Pearson; Teri A. Manolio (2008)
JAMA 299, 1335-1344

The Genome Gets Personal: Almost
W. Gregory Feero; Alan E. Guttmacher; Francis S. Collins *JAMA. 2008;299(11):1351-1352*

Mapping Genes for NIDDM:
Design of the Finland–United States Investigation of NIDDM Genetics(FUSION) Study Valle et al.
DIABETES CARE, VOLUME 21, NUMBER 6, JUNE 1998

Romeo, et al.(2008) Genetic Variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. Nature

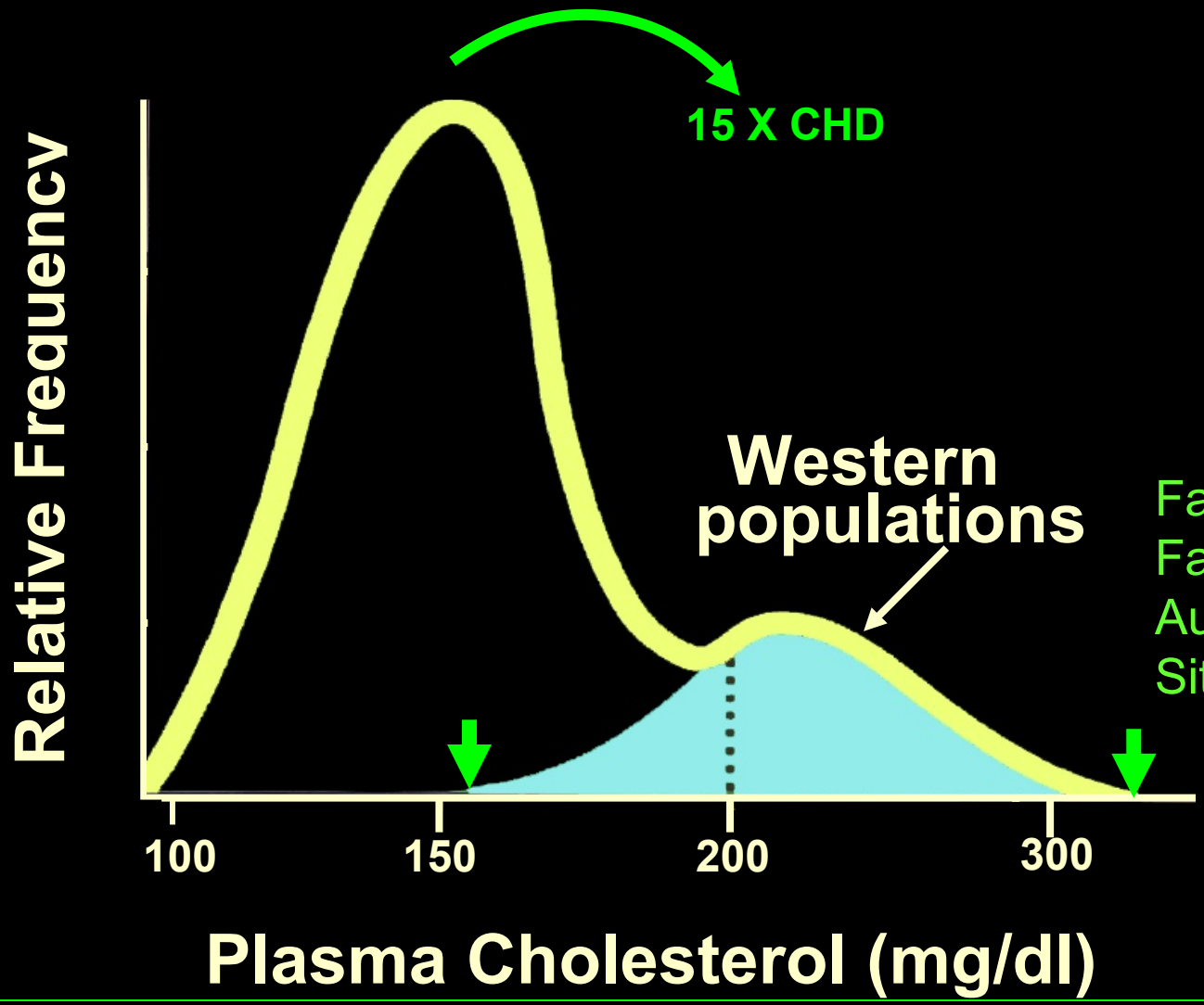
The Wellcome Trust Case Control Consortium.
Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls . Nature 447, 661-678 (7 June 2007)

Manolio, T.A. et. al.,(2009) Finding the missing heritability of complex diseases. Nature 461, 747-753.

Dickson, S. P.. et al. (2010) Rare Variants Create Synthetic Genome-Wide Associations. PLOS Biology 8, 1-12.

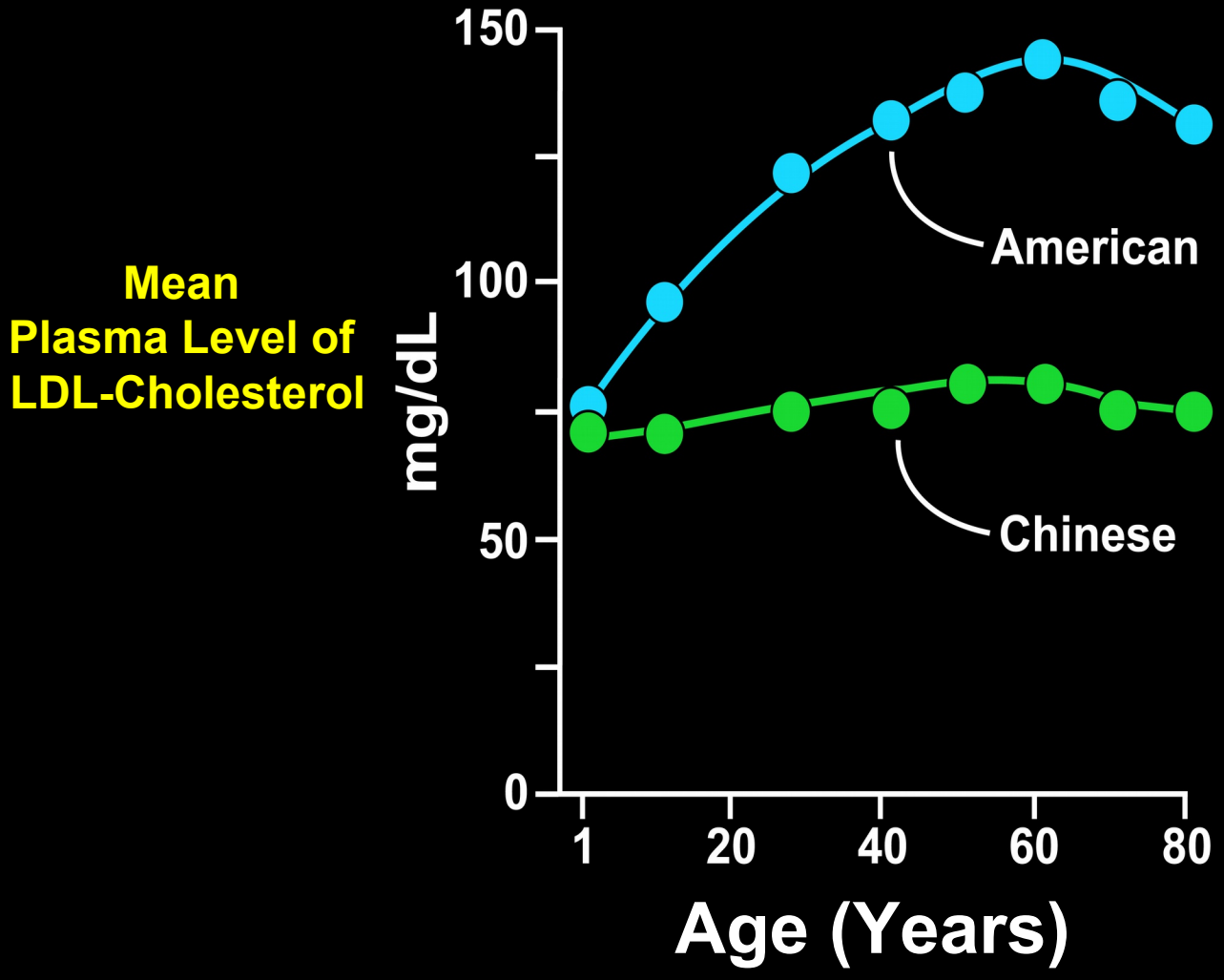
Johansen et al. (2010) Excess of rare variants in genes identified by genome-wide association study of hypertrigly

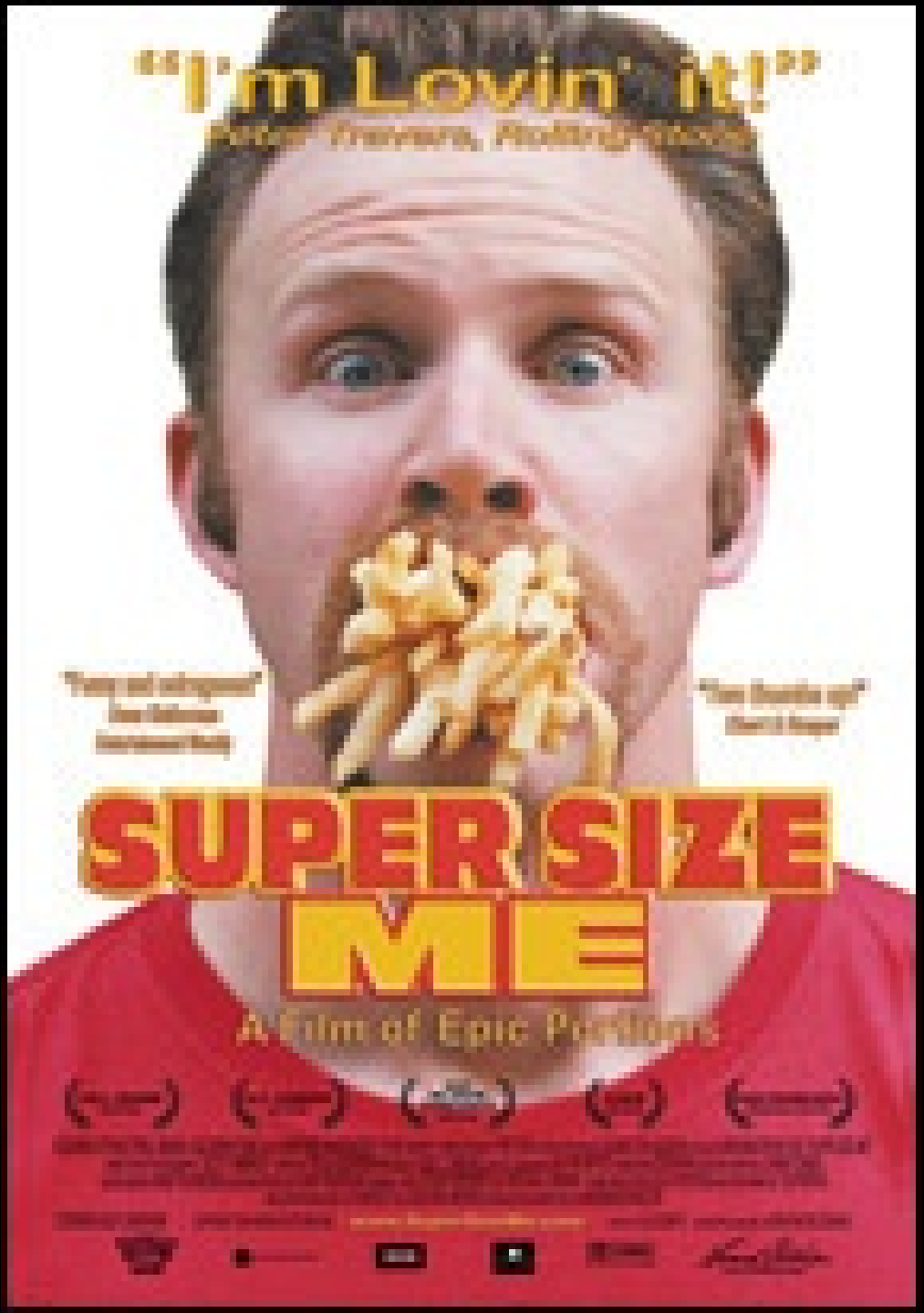
Global Distribution of Cholesterol



What would be the effect of a lifetime of lower plasma levels of LDL on coronary heart disease?

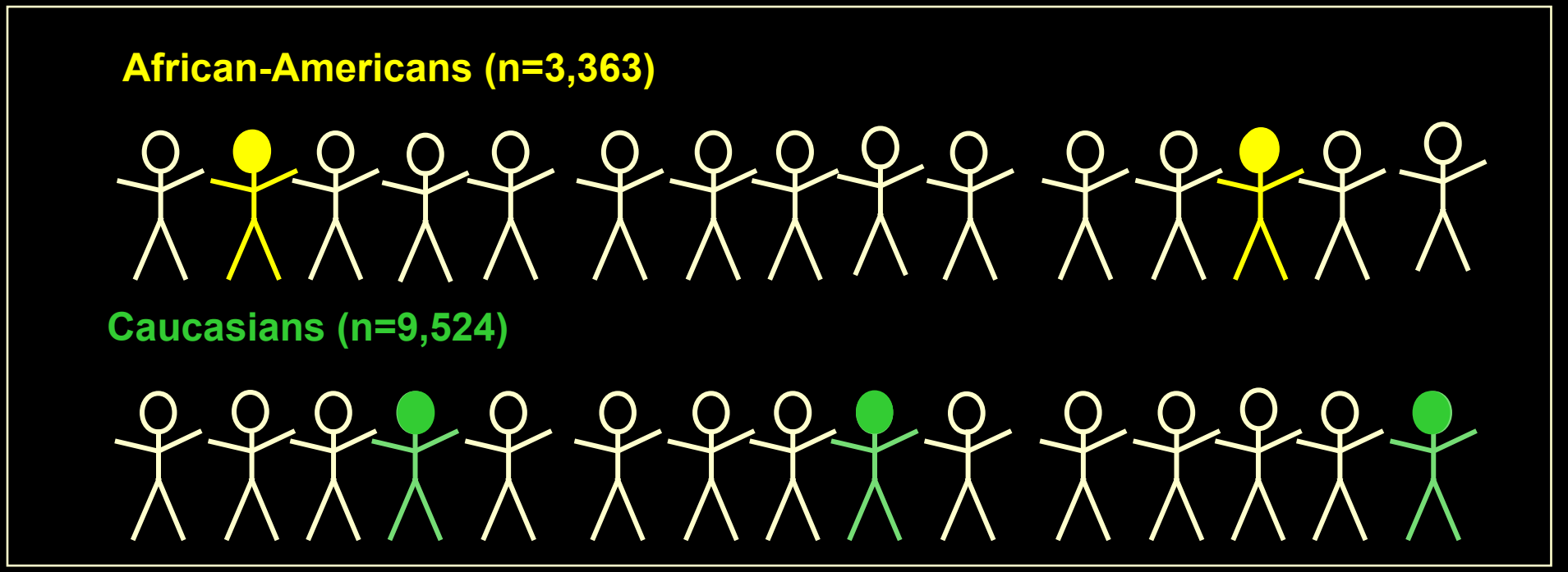
Plasma LDL-Cholesterol Levels: American vs. Chinese Men





What is the Effect of Having a Lower LDL-C on CHD?

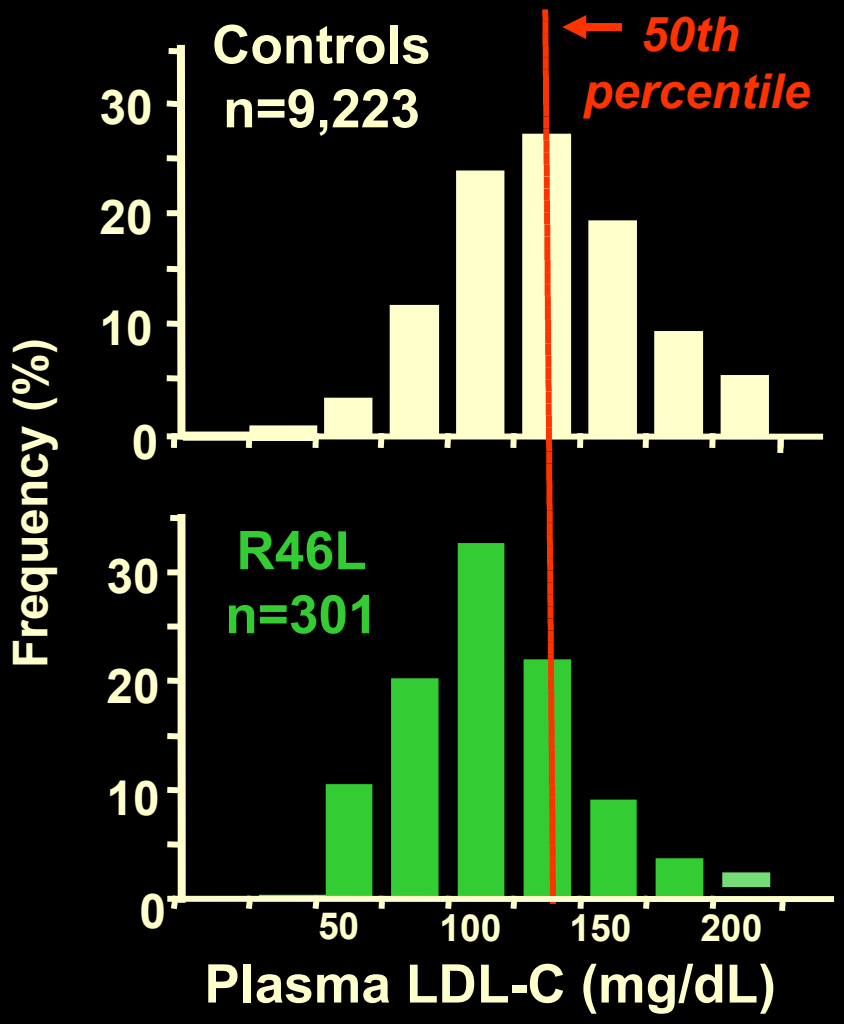
Atherosclerosis Risk in Communities Study (ARIC)- 15 Year Follow-up

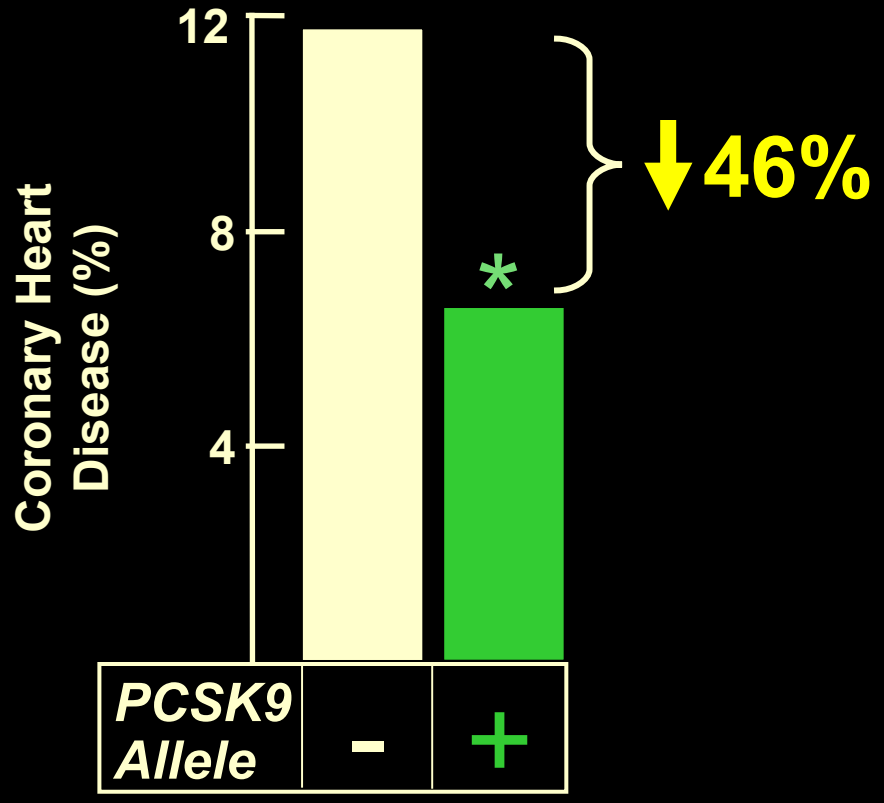


Combined Endpoints: MI, CHD death, bypass/angioplasty

= no variant = Y142X+C679X = R46L

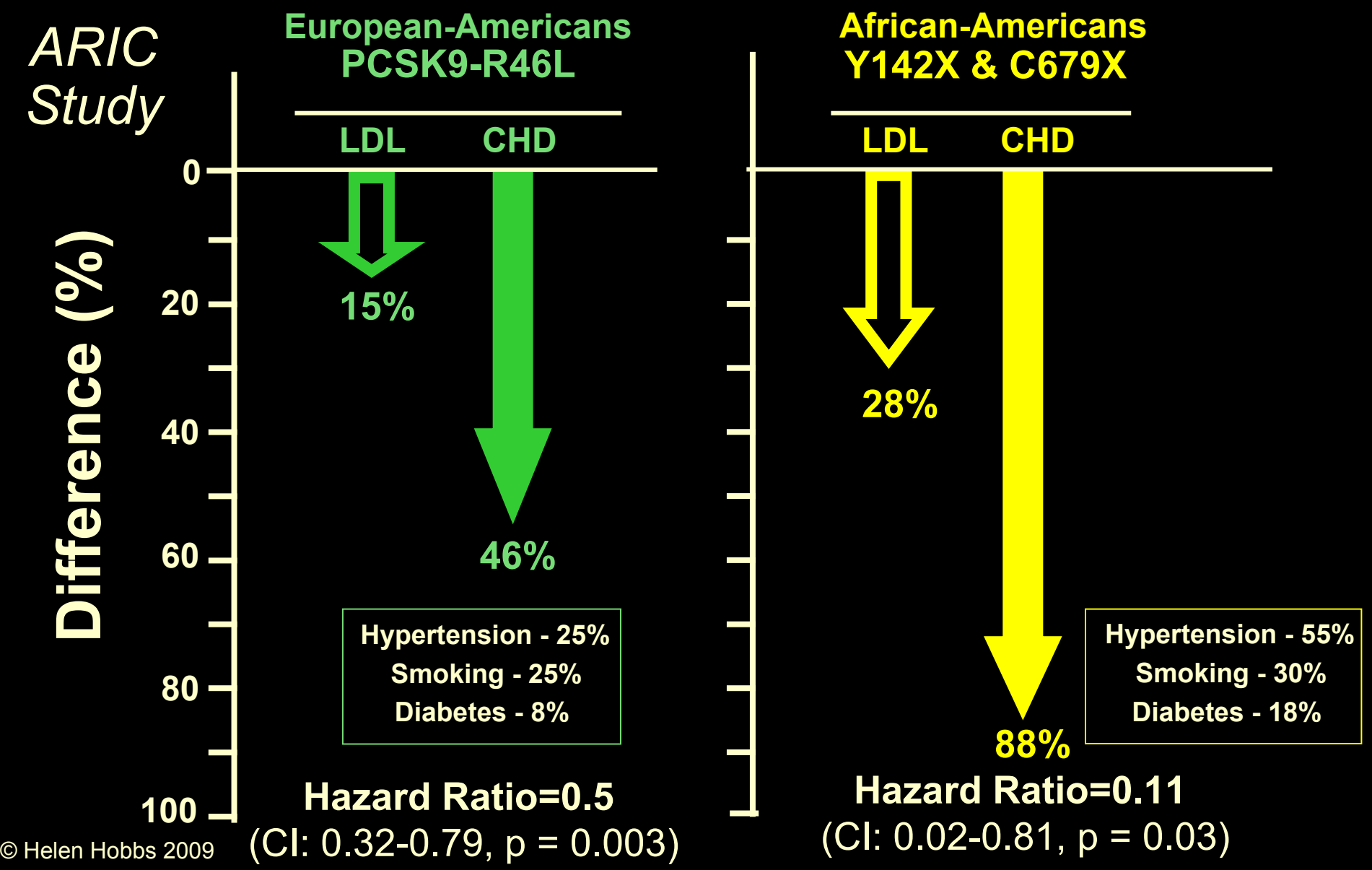
R46L Decreases LDL-C by 15% in Caucasians



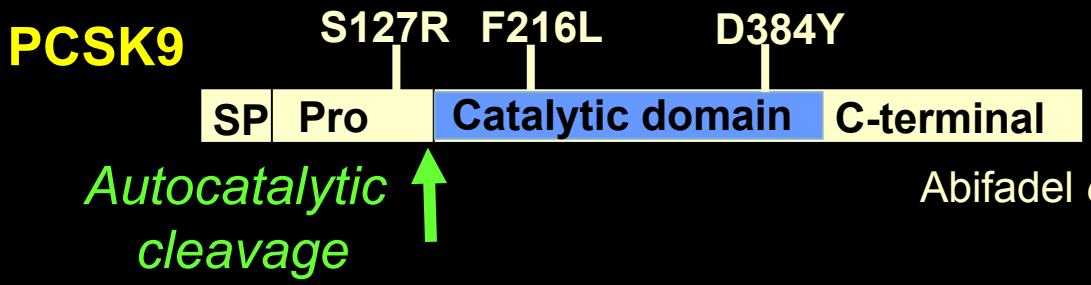


Hazard Ratio=0.5
(CI: 0.32-0.79, p = 0.003)

What is the Effect of a Life-long Reduction in LDL Levels on CHD?

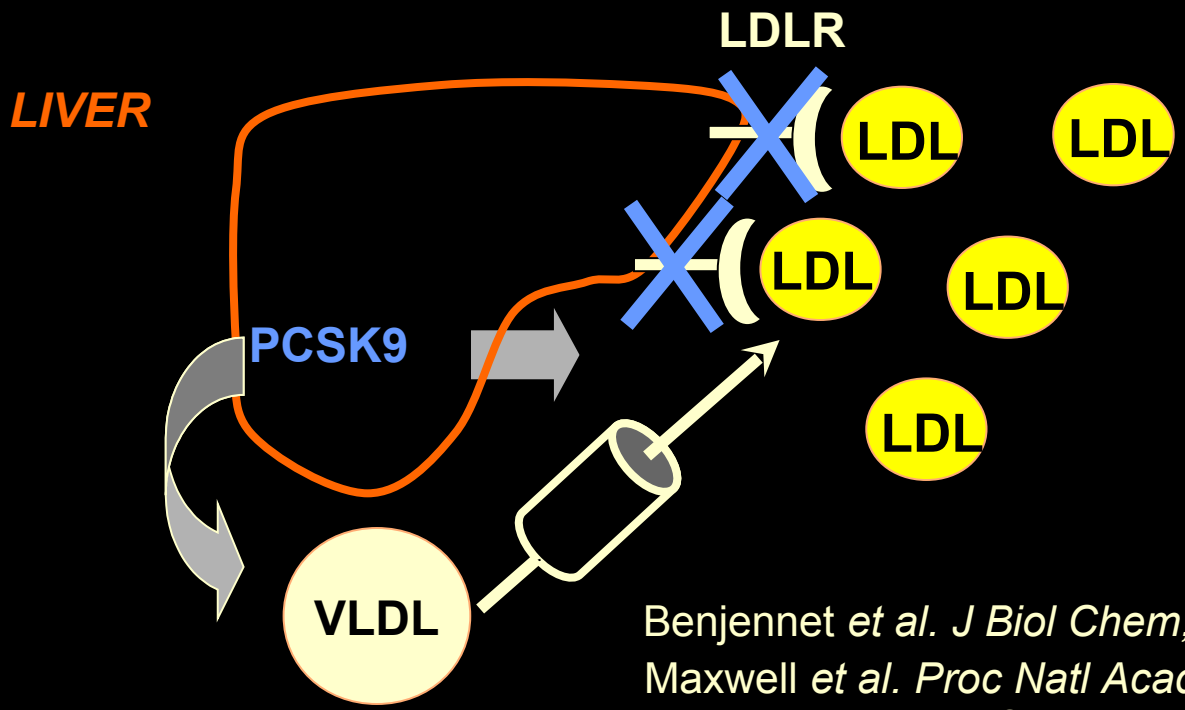


Proprotein Convertase Subtilisin/Kexin-Type 9 (PCSK9): A Secreted Protein



Abifadel *et al. Nat Genet, 2003*

- Expressed in liver, small intestine, kidney, brain
- Regulated by SREBPs



Benjennet *et al. J Biol Chem, 2004*

Maxwell *et al. Proc Natl Acad Sci, 2004*

Parks *et al. J Biol Chem, 2004*

Lucas and Mr. Potato Head

Meta Study of Genes Associated with Hypertriglyceridemia

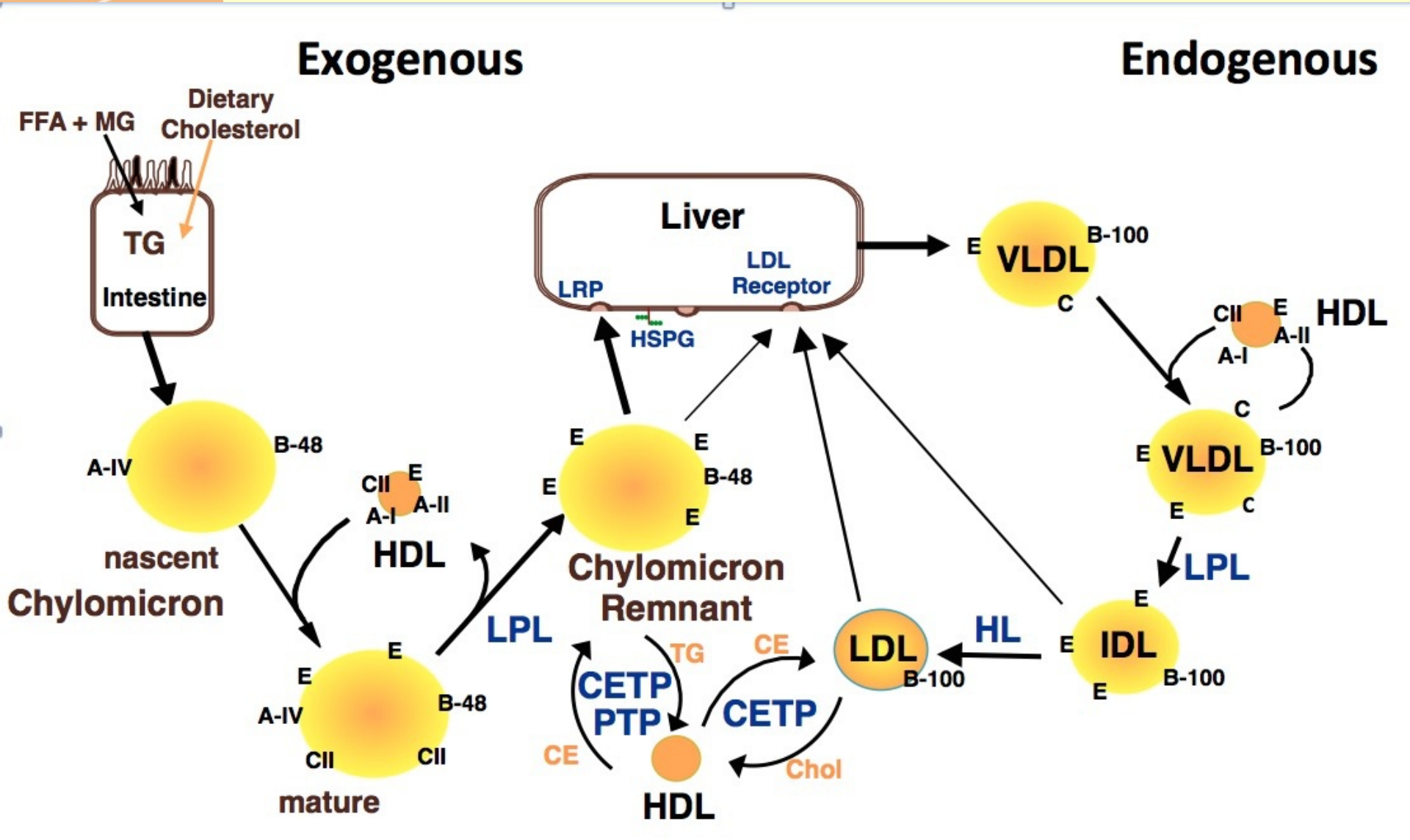
Locus	TG Effect	*P* value
APOA5	16.95	$7x10^{-240}$
GCKR	8.76	$6x10^{-133}$
LPL	13.64	$2x10^{-115}$
MLXIPL	7.91	$9x10^{-59}$
TRIB1	5.64	$3x10^{-55}$
APOB	5.99	$1x10^{-45}$
ANGPTL3	4.94	$2x10^{-43}$
APOE	5.50	$1x10^{-30}$
CILP2	7.83	$2x10^{-29}$
FADS1-2-3	3.82	$5x10^{-24}$
PLTP	3.32	$5x10^{-18}$
HLA	2.99	$2x10^{-15}$
NAT2	2.97	$4x10^{-14}$
GALNT2	2.76	$2x10^{-14}$
LIPC	2.99	$2x10^{-13}$
CETP	2.88	$1x10^{-12}$

Locus	TG Effect	*P* value
JMJD1C	2.38	$3x10^{-12}$
TIMD4	2.63	$4x10^{-12}$
KLHL8	2.25	$9x10^{-12}$
FRMD5	5.13	$2x10^{-11}$
MAP3K1	2.57	$1x10^{-10}$
COBLL1	2.01	$2x10^{-10}$
LRP1	2.70	$4x10^{-10}$
TYW1B	7.91	$1x10^{-9}$
PINX1	2.01	$1x10^{-8}$
ZNF664	2.42	$1x10^{-8}$
CAPN3	7.00	$2x10^{-8}$
CYP26A1	2.28	$2x10^{-8}$
IRS1	1.89	$2x10^{-8}$
CTF1	2.13	$3x10^{-8}$
MSL2L1	2.22	$3x10^{-8}$
PLA2G6	1.54	$4x10^{-8}$

Global Lipids Genetics Consortium
~100,000 subjects

Teslovich et al. Nature 466:707-713, 2010

Triglyceride-rich Lipoprotein Metabolism



Courtesy of Frederic Kraemer

Catalog of GWAS Studies

http://www.genome.gov/GWAStudies/

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Division of Genomic Medicine

A Catalog of Published Genome-Wide Association Studies

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Current uses of and future directions for the Genome-Wide Association Studies Catalog new

On Thursday, July 18th, 2013, the Division of Genomic Medicine held a webinar to highlight current uses and explore priorities and future directions for the GWAS catalog. See archived video and presentations.

Additional information has been added to the HTML catalog columns below. For a description of column headings for the HTML catalog, go to: Catalog Heading Descriptions PDF new

Potential etiologic and functional implications of genome-wide association loci for human diseases and traits PDF

Click here to read our recent *Proceedings of the Academy of Sciences (PNAS)* article on catalog methods and analysis.

View the Interactive Diagram new | View the Full Catalog | Download the Catalog | Search the Catalog

The genome-wide association study (GWAS) publications listed here include only those attempting to assay at least 100,000 single nucleotide polymorphisms (SNPs) in the initial stage. Publications are organized from most to least recent date of publication, indexing from online publication if available. Studies focusing only on candidate genes are excluded from this catalog. Studies are identified through weekly PubMed literature searches, daily NIH-distributed compilations of news and media reports, and occasional comparisons with an existing database of GWAS literature (HuGE Navigator).

SNP-trait associations listed here are limited to those with p-values < 1.0 x 10-5 (see full methods for additional details). Multipliers of powers of 10 in p-values are rounded to the nearest single digit; odds ratios and allele frequencies are rounded to two decimals. Standard errors are converted to 95 percent confidence intervals where applicable. Allele frequencies, p-values, and odds ratios derived from the largest sample size, typically a combined analysis (initial plus replication studies), are recorded below if reported; otherwise statistics from the

Genome-Wide Association Studies

http://gwas.nih.gov/

U.S.Department of Health & Human Services

www.hhs.gov

www.nih.gov

NIH Genomic Data Sharing (GDS)

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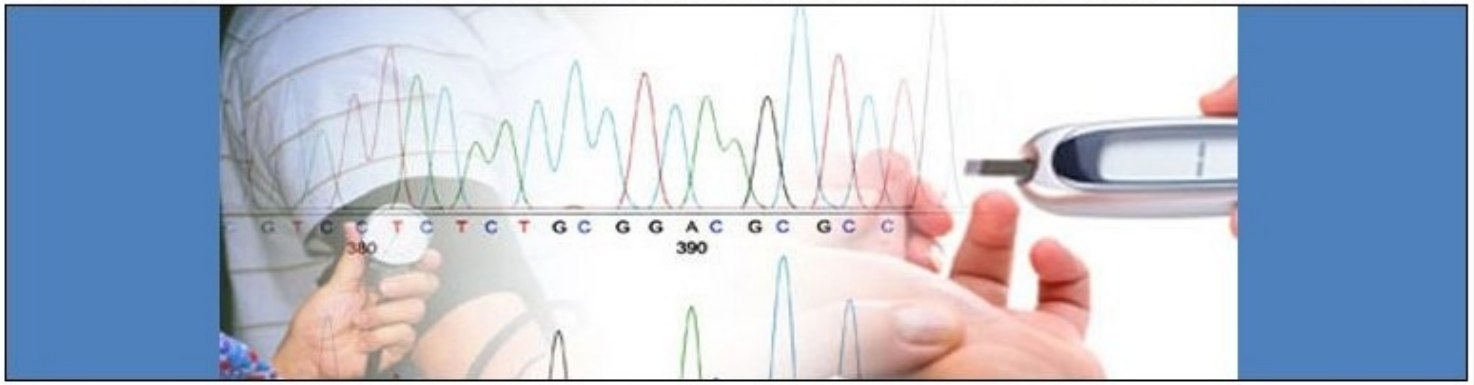

Introduction

Genomic research advances our understanding of factors that influence health and disease. In January 2008, NIH established expectations for sharing data obtained through NIH-funded genome-wide association studies (GWAS) with the implementation of the GWAS Policy. GWAS research compares DNA markers across the genome (an individual's complete genetic material) in people with a disease or particular trait to people without the disease or trait.

Information and resources related to the GWAS Policy can be found on this website. Any questions about the Policy can be e-mailed to GWAS@mail.nih.gov.