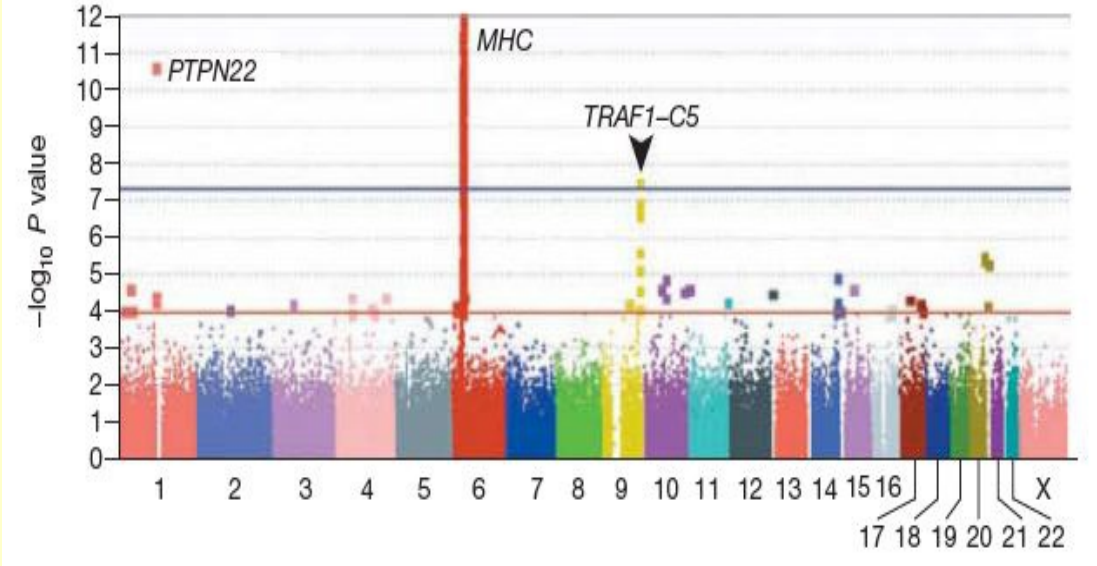
Your Genes and Your Health

http://bio84.stanford.edu/

Linking Genes to Diseases: 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

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 (smoking, drinking drugs & other addictions)
  - Many complex diseases can also be monitored by increased vigilance (another behavioral modification)

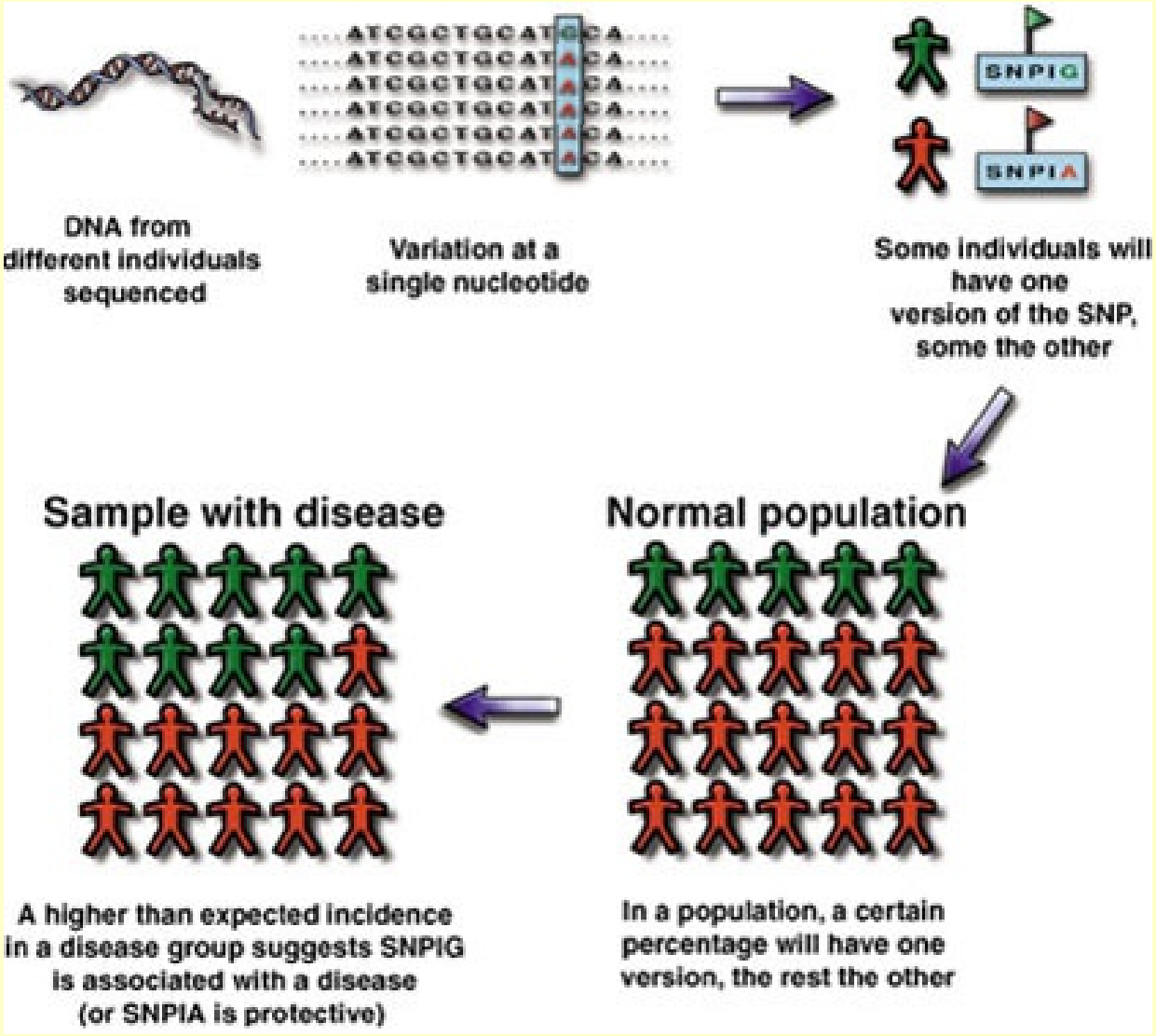
Gene Variations Associated with Common Diseases

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

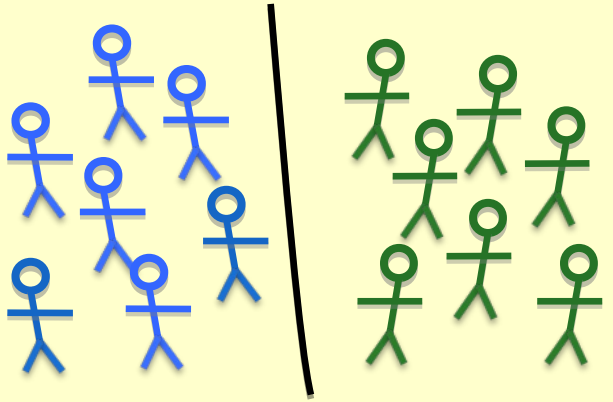
Using SNPs to Track Predisposition to Disease and other Genetic Traits



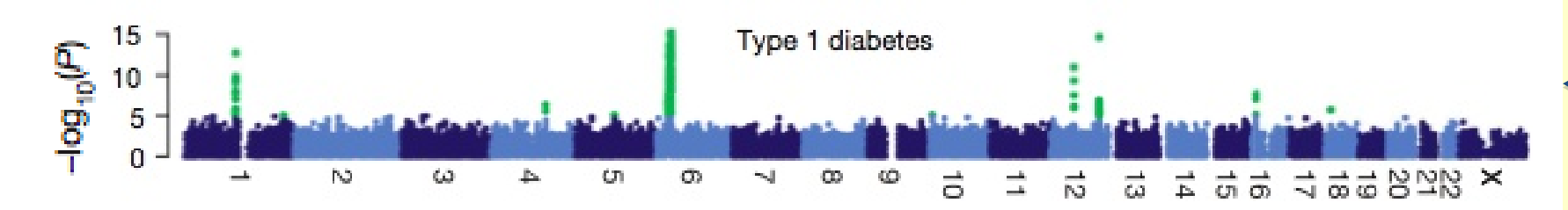
Genome-Wide Association Study: A Brief Primer

Control Population

Disease Population



SNP chip



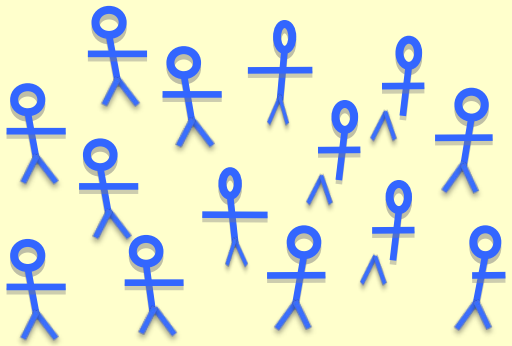
WTCCC, Nature 2007

Courtesy of Daniel Newburger

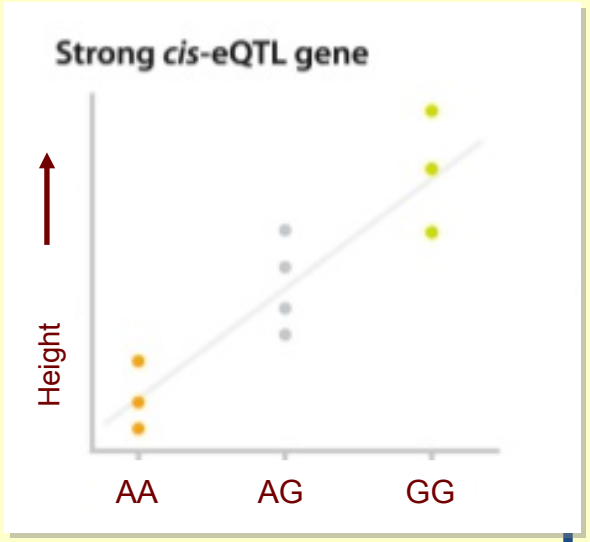
Manhattan at Night

A Quantitative Gene-Expression Association

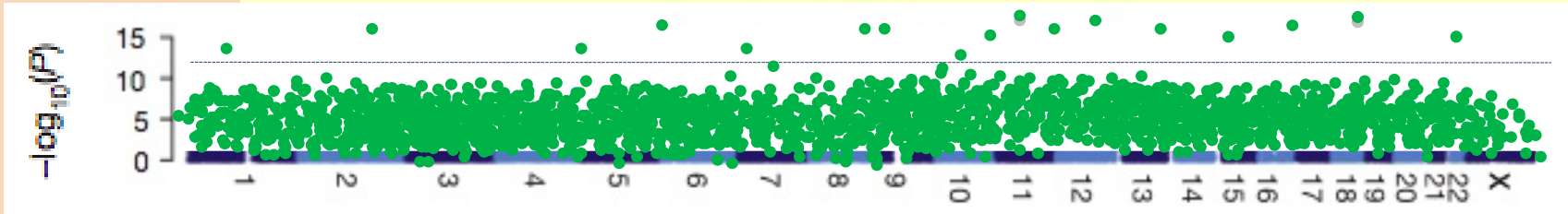
Sample Population



Measure Height



Quantitative Trait Loci (QTLs)



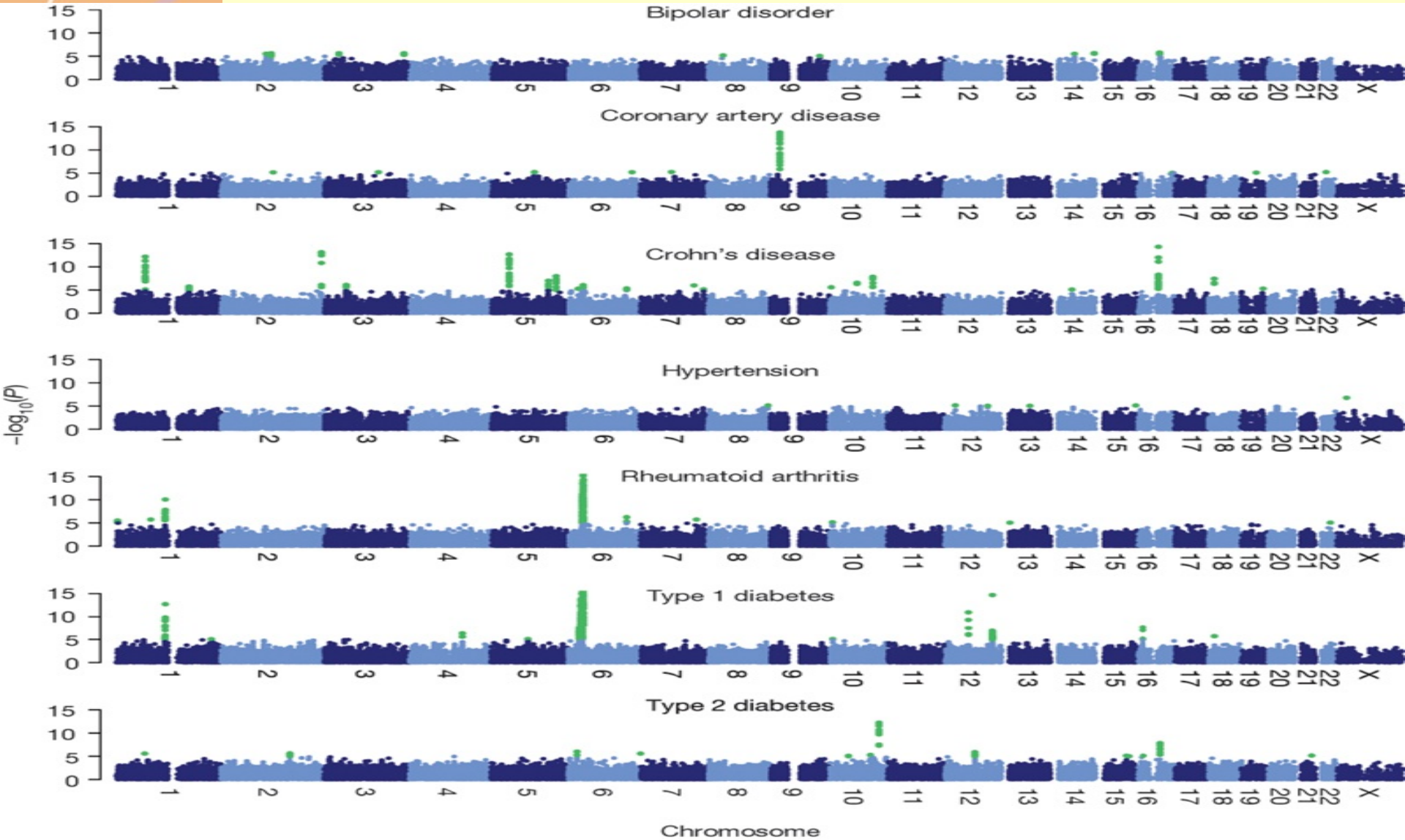
Modified from WTCCC, Nature 2007

Courtesy of Daniel Newburger

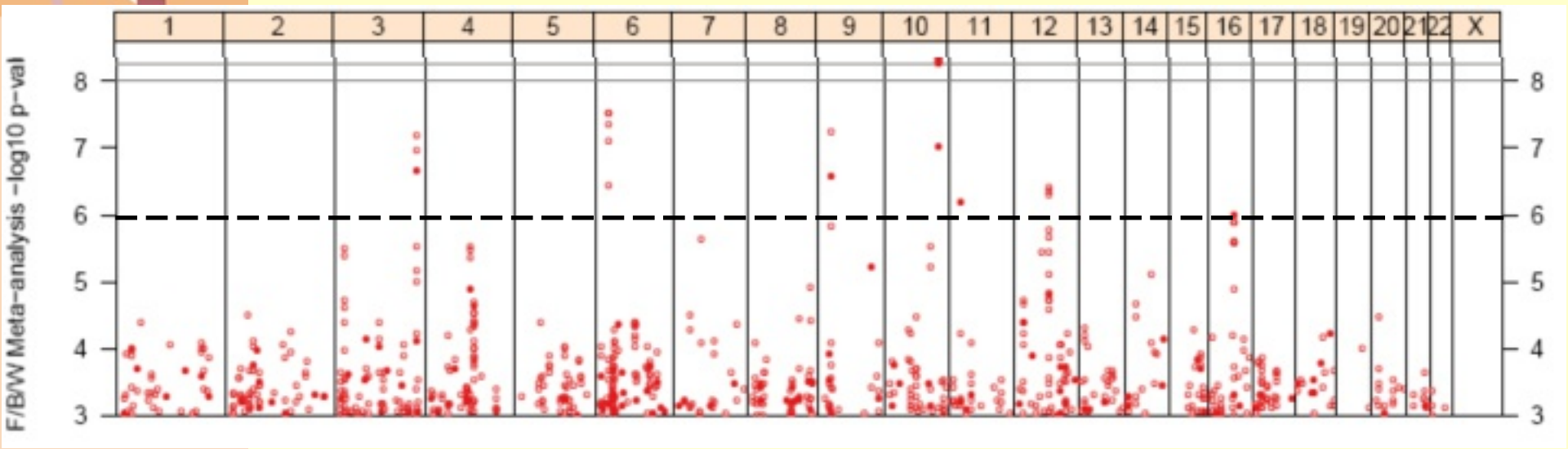
The Wellcome Trust Case Control Consortium

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

Nature 447, 661-678 (7 June 2007)

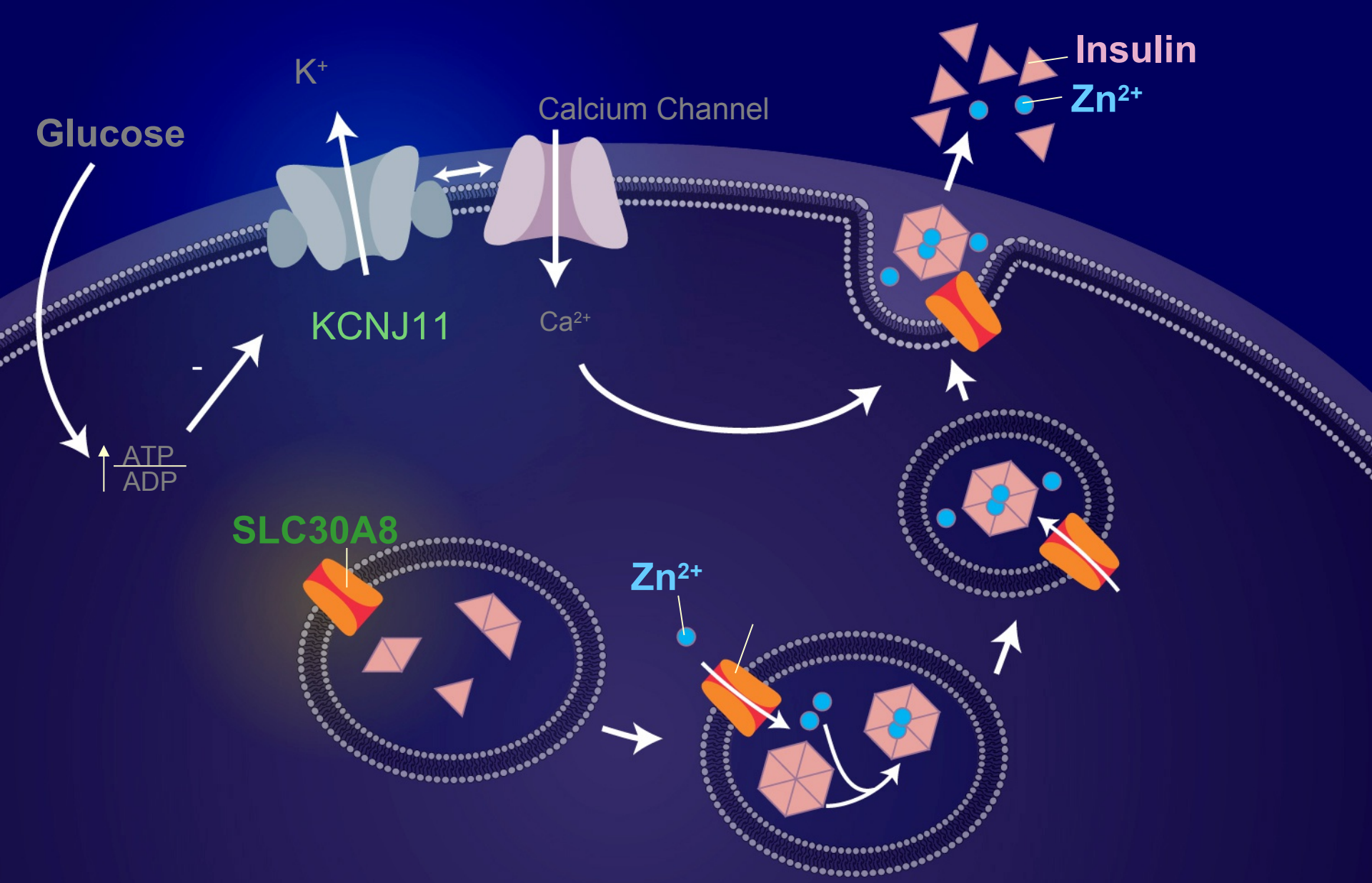


Genome Wide Association of type 2 Diabetes 4549 cases, 5579 controls & 317,503 SNPs



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}



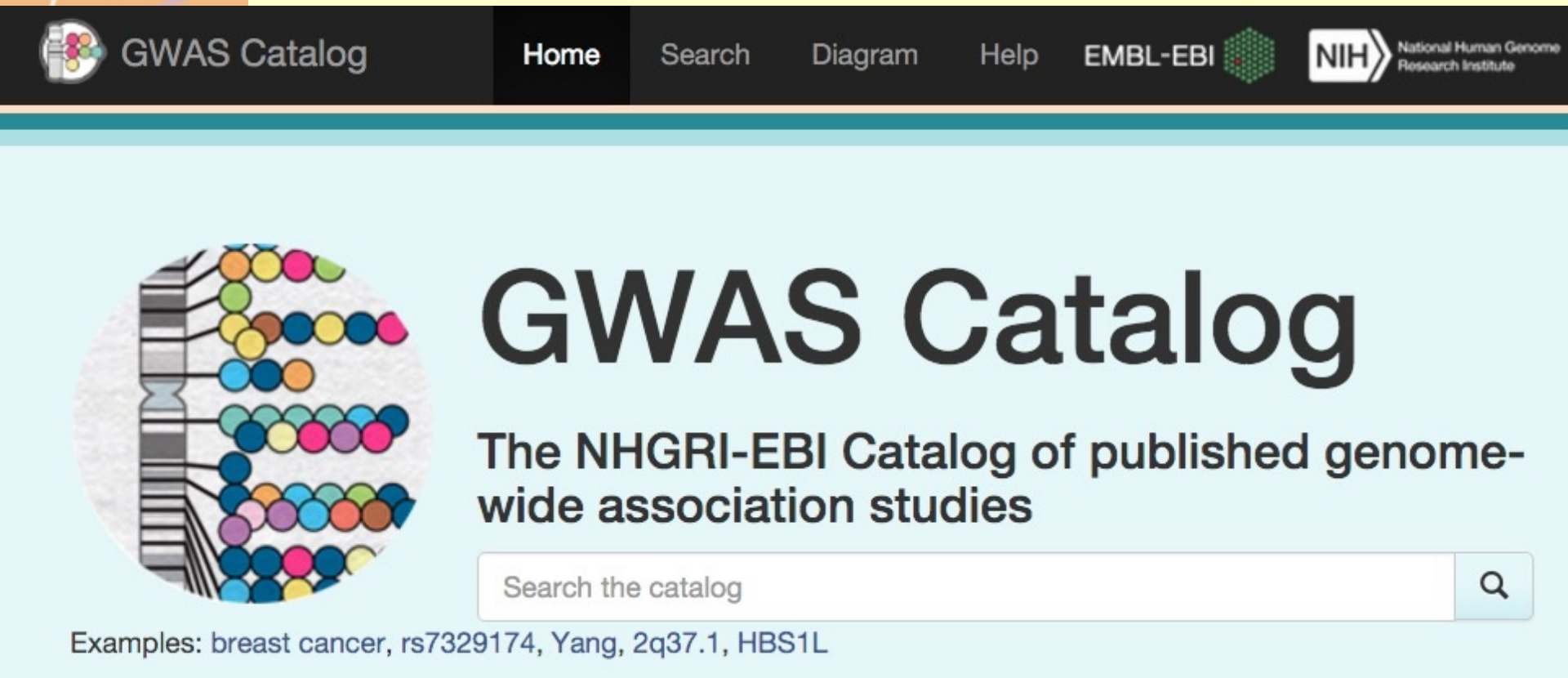
SLC30A8 – A Beta Cell Zinc Transporter

The Great Wave of GWAS Studies

http://gwas.nih.gov/

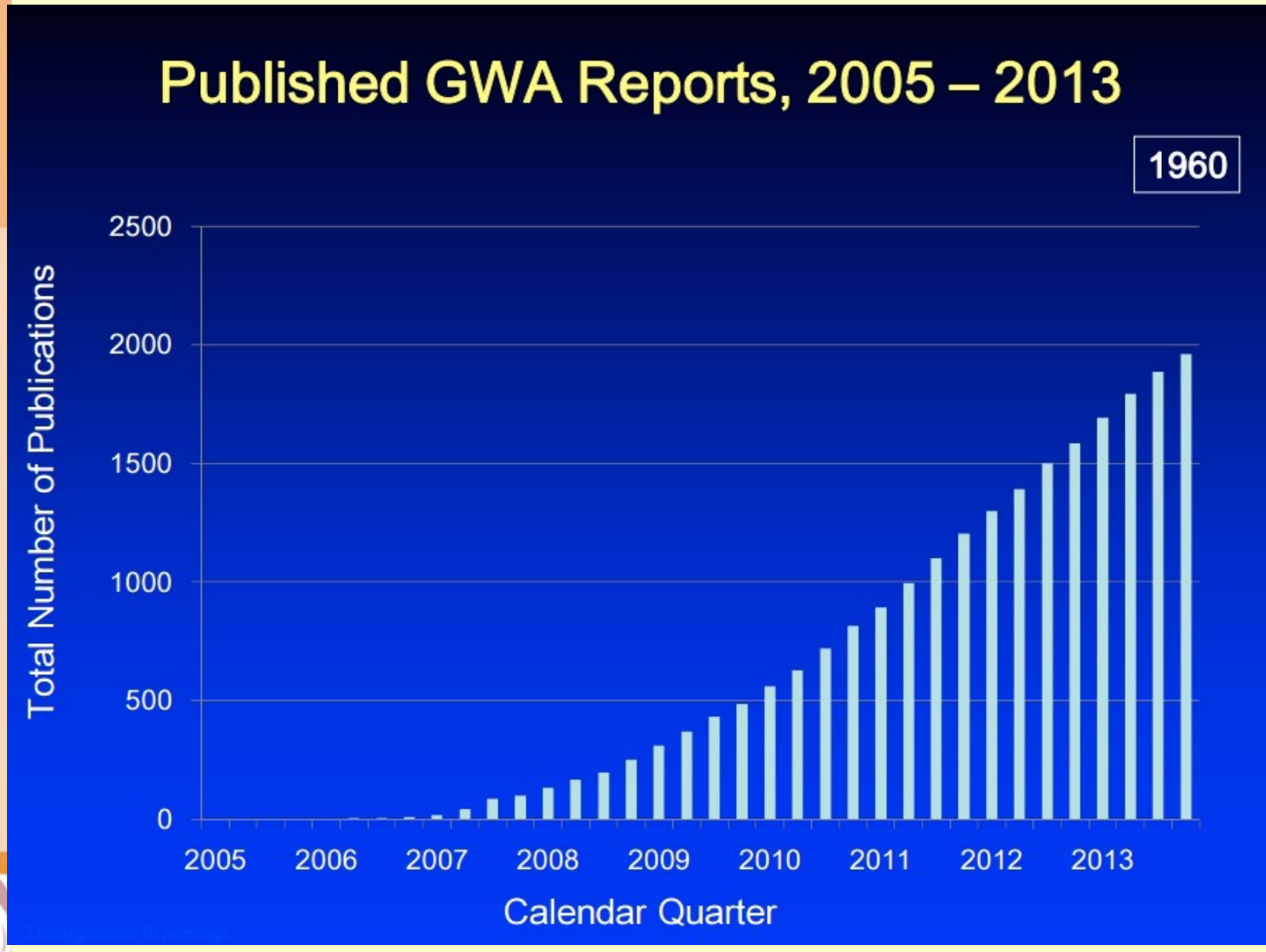
Hokusai, K. *The Great Wave*

Catalog of GWAS Studies
https://www.ebi.ac.uk/gwas/



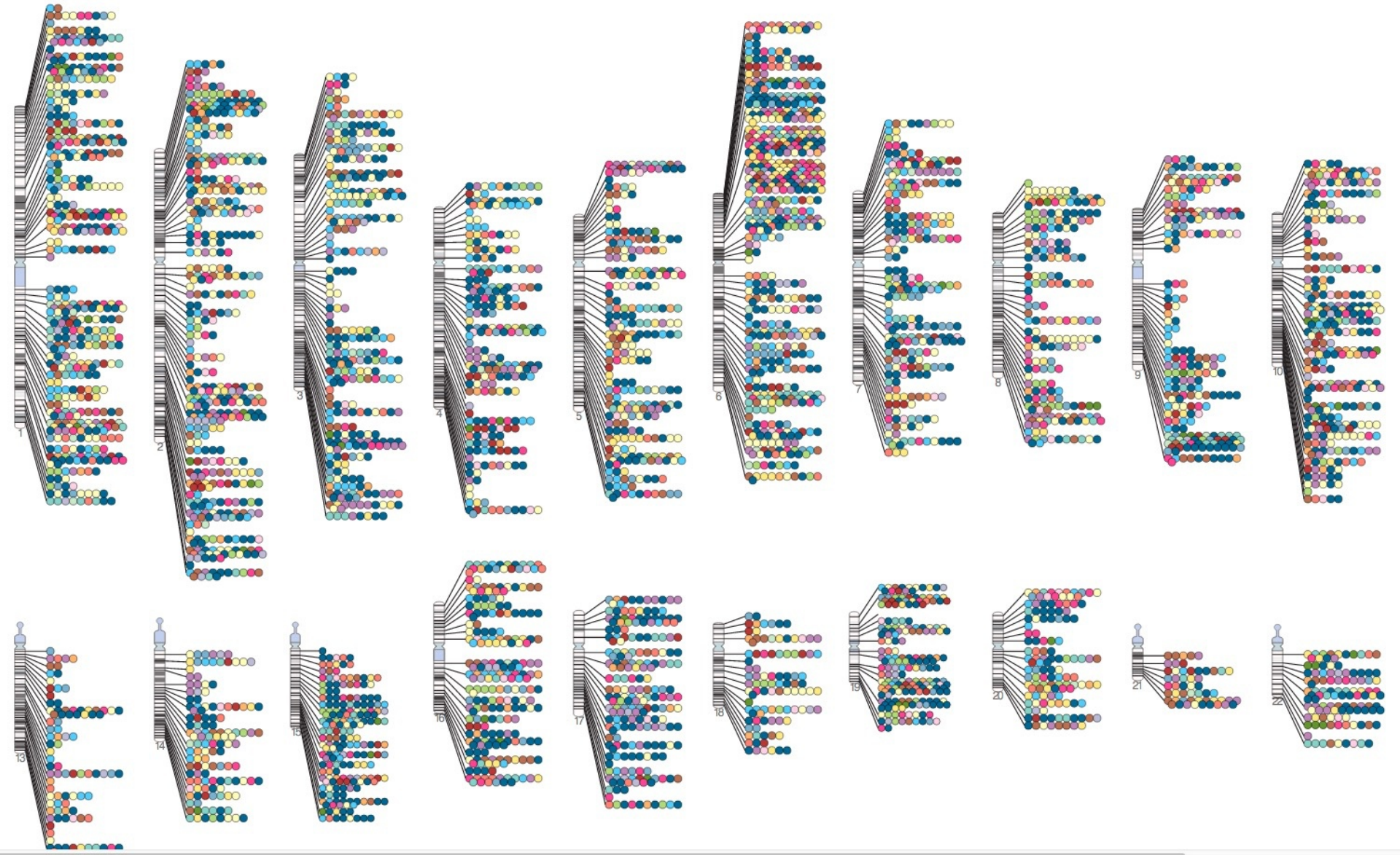
Published Genome-Wide Associations through 6/2010

http://www.genome.gov/GWAStudies

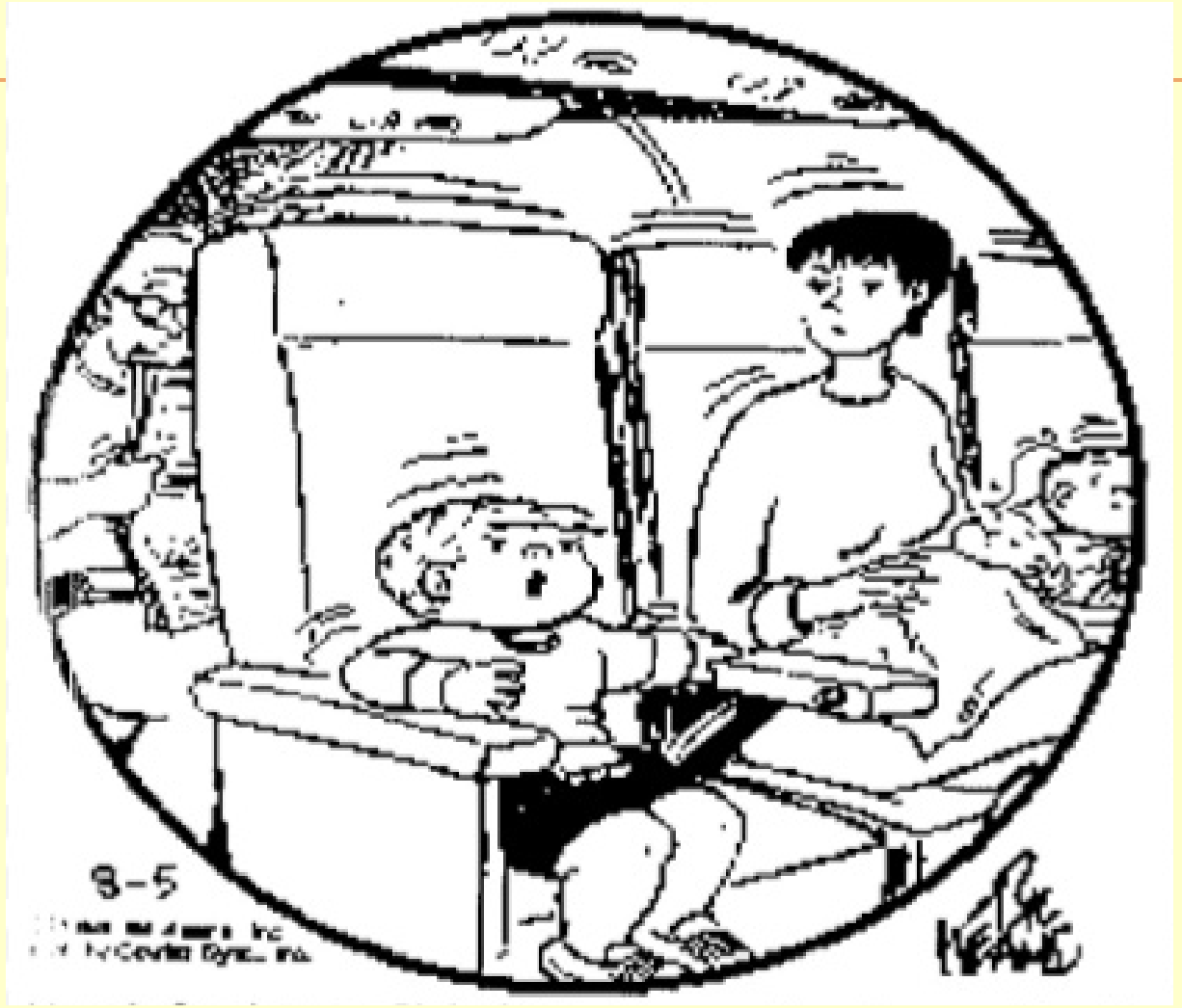


Published Genome-Wide Associations as of February 10, 2016

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



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

The McDermott Center for Human Growth and Development

Center for Human Genetics

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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.

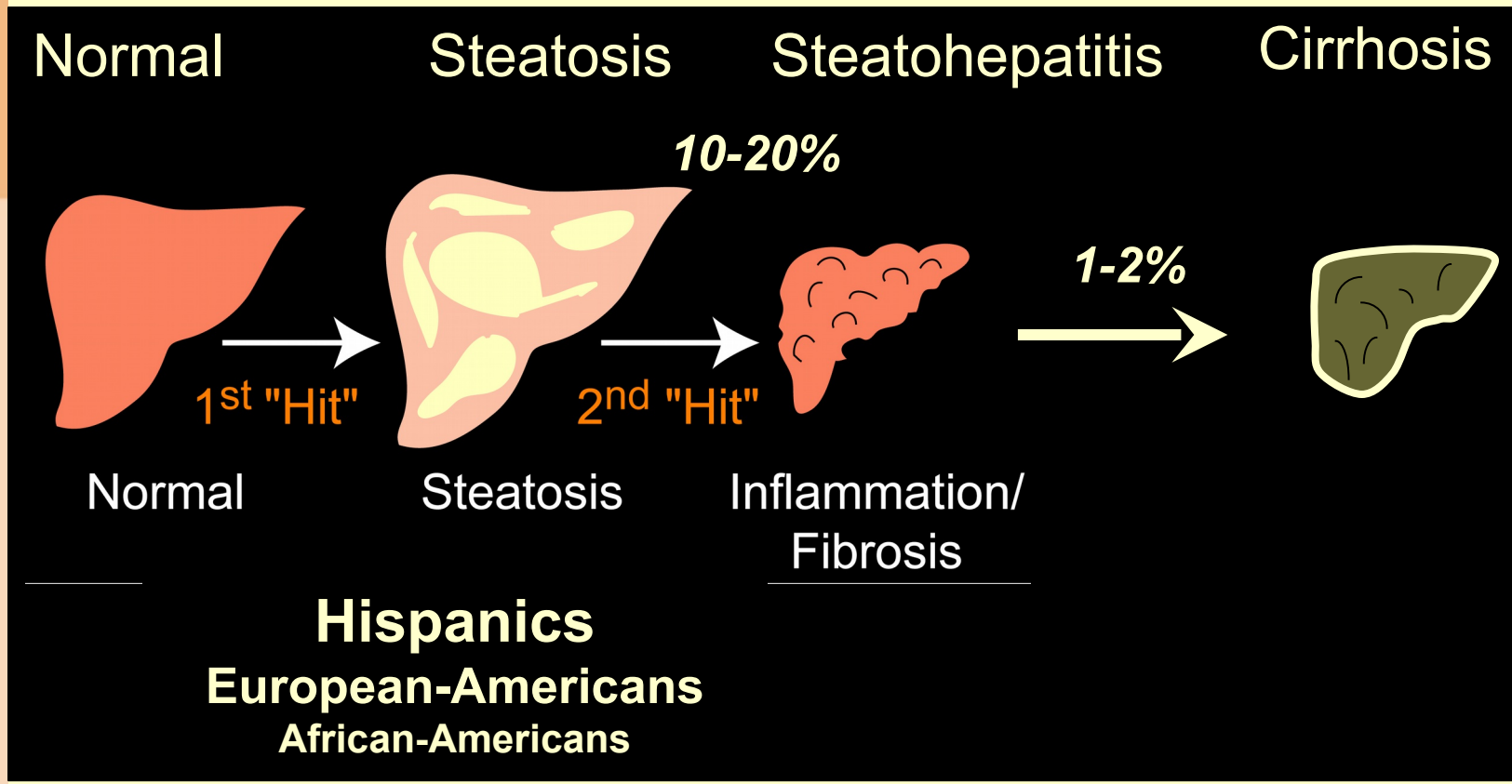
4. Cohen J.C., Kiss R.S., Pertsemlidis A., Marcel Y.L., McPherson R., Hobbs H.H. (2004) Multiple rare alleles contribute to low plasma levels of HDL cholesterol. Science 305:869-872.

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?

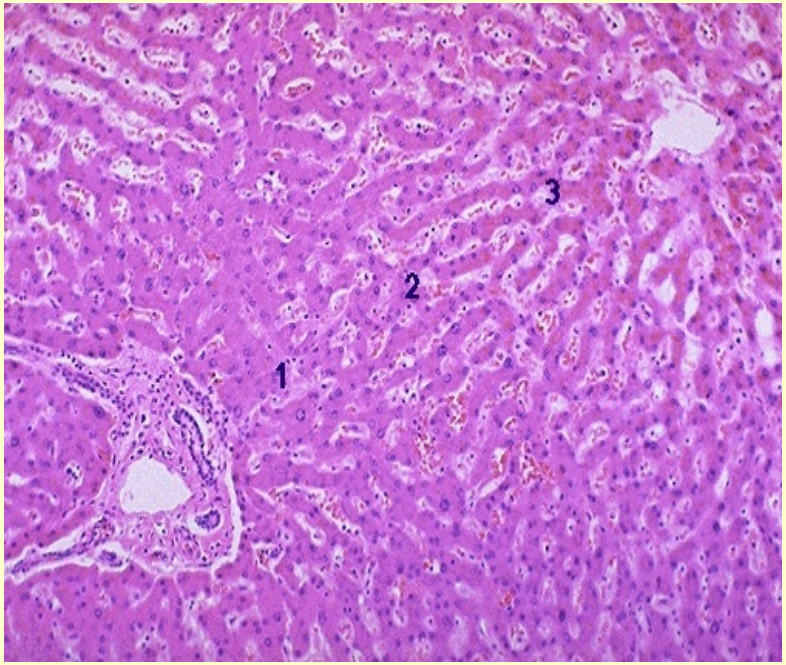


First Hit
- Obesity
- Type 2 diabetes
- Ethanol
- Hepatitis C

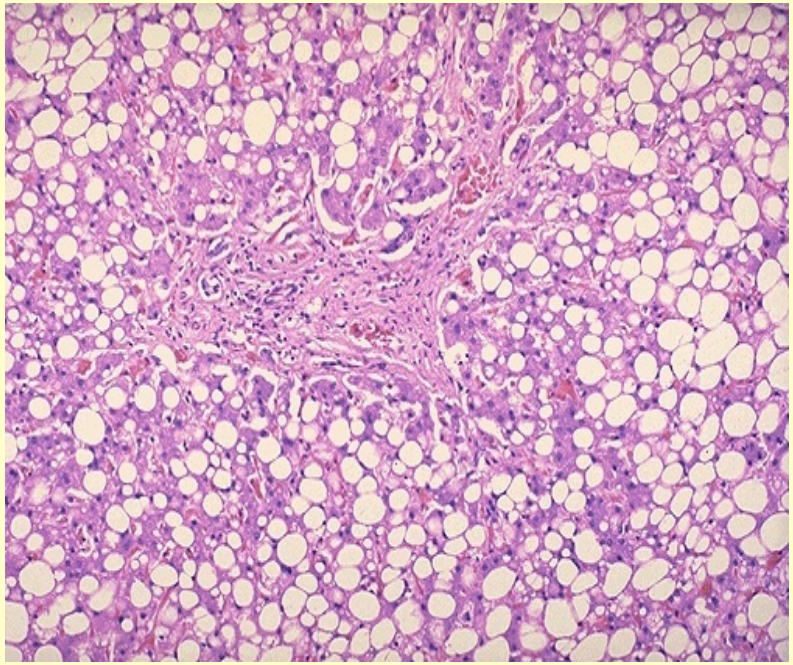
Second Hit
- Oxidative Stress
- Lipid Peroxidation
- Anti-virals
- Cytokines

Hepatic Steatosis

Normal



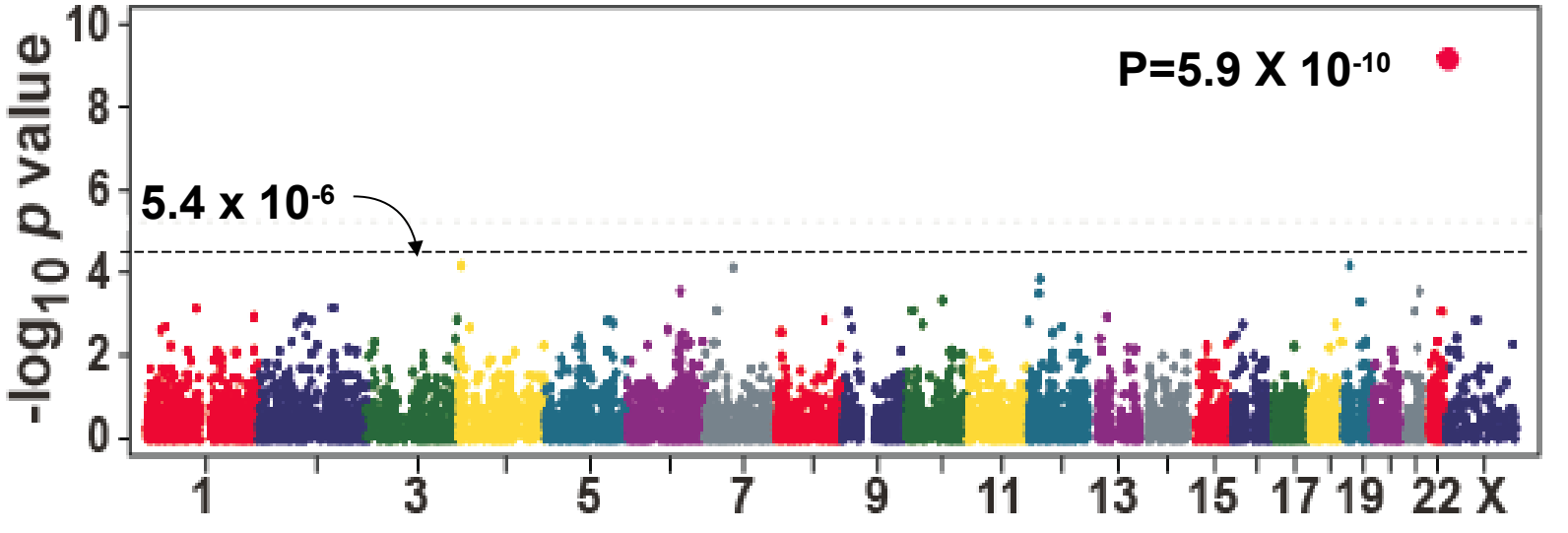
Hepatic Steatosis



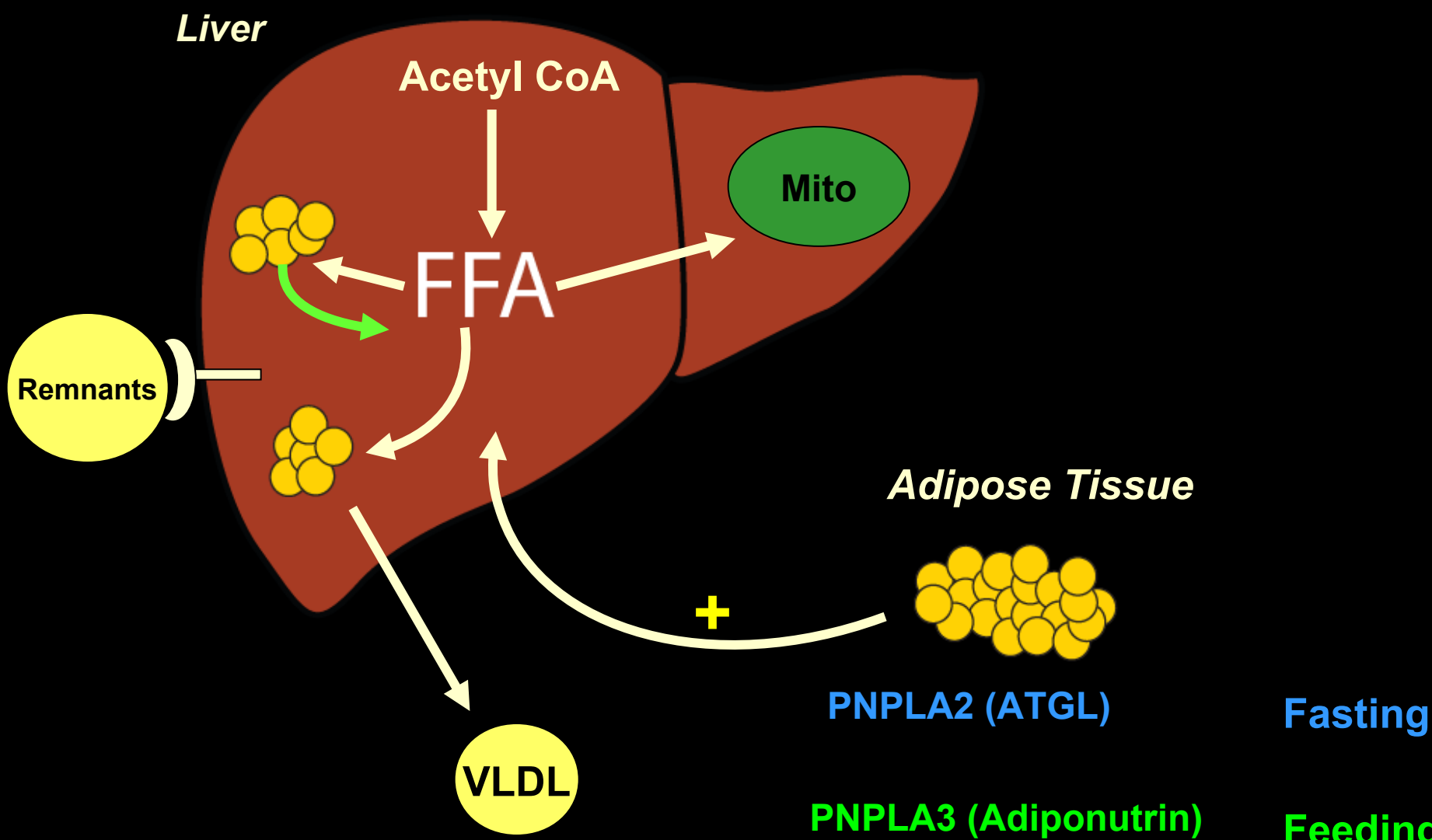
- Obesity
- Type 2 diabetes
- Ethanol
- Hepatitis C

Genome-wide Association Study of Fatty Liver in Dallas Heart Study Cohort

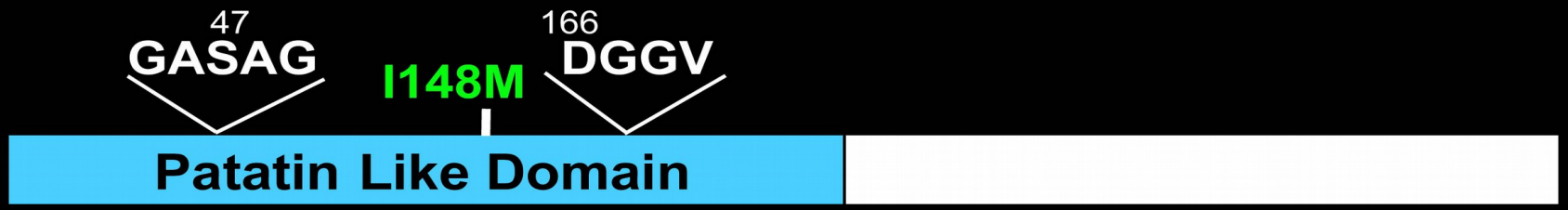
(2,111 patients and 2,299 controls)

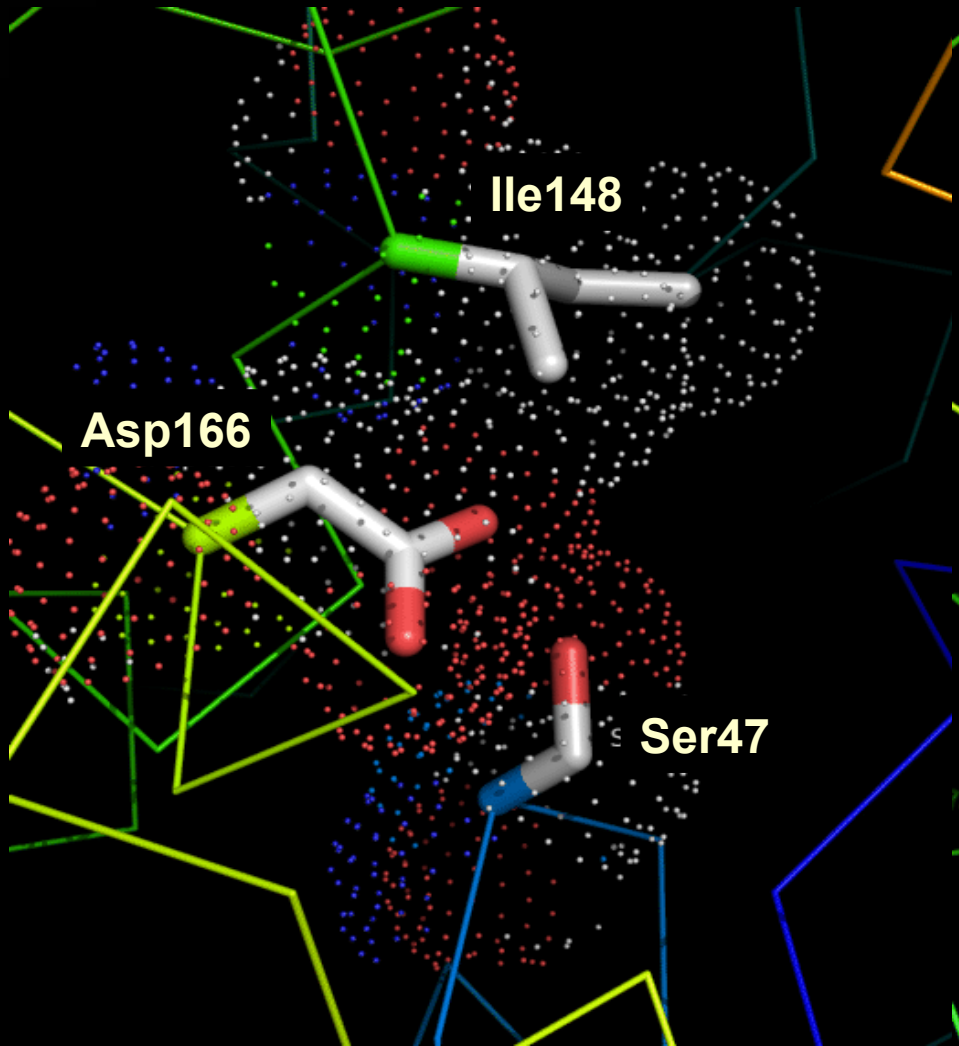


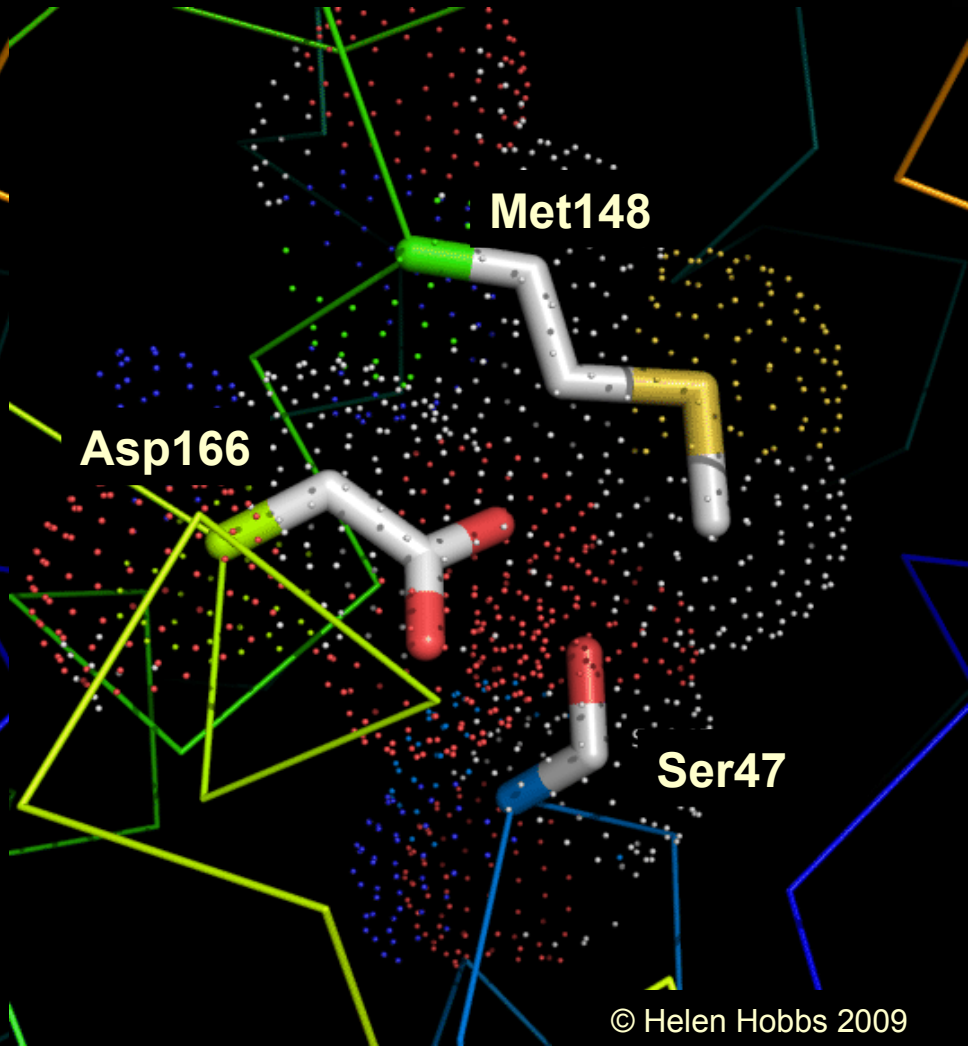
PNPLA3 & Hepatic Triglyceride Metabolism



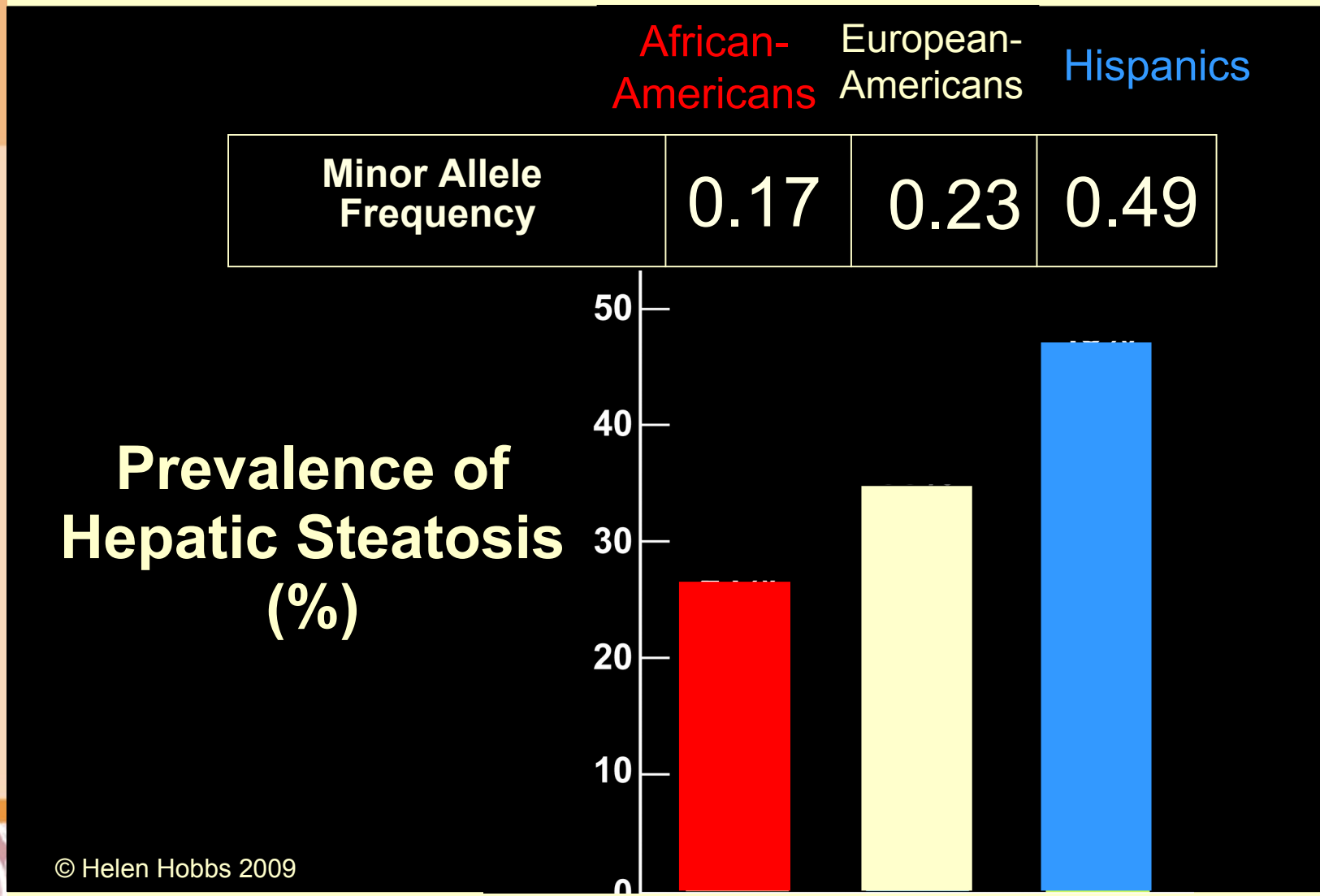
I148M & Catalytic Site of PNPLA3







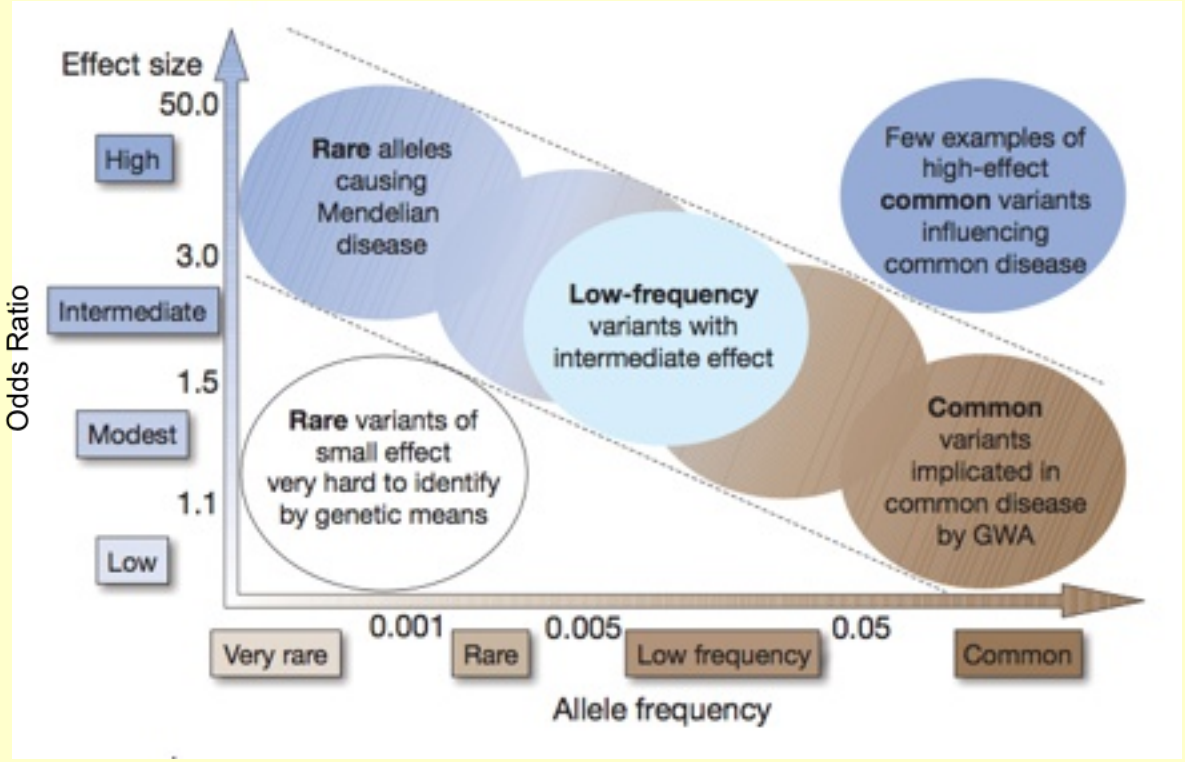
Genetic Contribution to Ethnic Differences in Hepatic Steatosis



Summary

- Genome-wide association studies make no assumptions about disease mechanism or cause
- Genome-wide association studies usually discover only gene regions correlated with disease, NOT genes that cause the disease.
- Genome-wide associations indicate
  - Genes and regions to reanalyze by complete sequencing for causal genes or variations
  - Subpopulations that may be enriched for causal variations
  - 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 that could not have been predicted
  - Unexpected 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

Low Heritability of Common SNPs



- Rare High Penetrance Variants Carry High Risk
- Common SNPs Carry Low 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 or Subpopulations

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

Genome Wide Association Study
Third Homework Suggestion

- Step 1: Read:
- **How to Use an Article About Genetic Association: A: Background Concepts**
  John Attia et al. (2009) ***JAMA 301, 74-81***

- Please search the GWAS Catalog for a disease of interest to you.

- After you find a GWA Study on a disease of interest to you, please read the paper describing the genome-wide association study and report to me 1) the reference for the paper and 2) genes or SNPs that are most highly correlated with the disease. 3) the odds ratio and heritability of each gene and 4) Also please tell me if knowledge of those SNPs or genes sheds any light on the basis for the disease.
- A more advanced treatment of reading GWAS papers is:
- **How to Interpret a Genome-wide Association Study**
  Thomas A. Pearson; Teri A. Manolio (2008) ***JAMA 299, 1335-1344***

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

The HapMap and Genome-Wide Associations Studies in Diagnosis and Therapy
. Teri Manolio and Francis Collins. 2009 Annual Review of MedicineVol. 60, 443-456.

Romeo, et al.(2008) **Genetic Variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease.**
Nature Genetics 40, 1461-1465,

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)

The Case of the Missing Heritability. Brendan Maher (2008) Nature 456, 18-21.

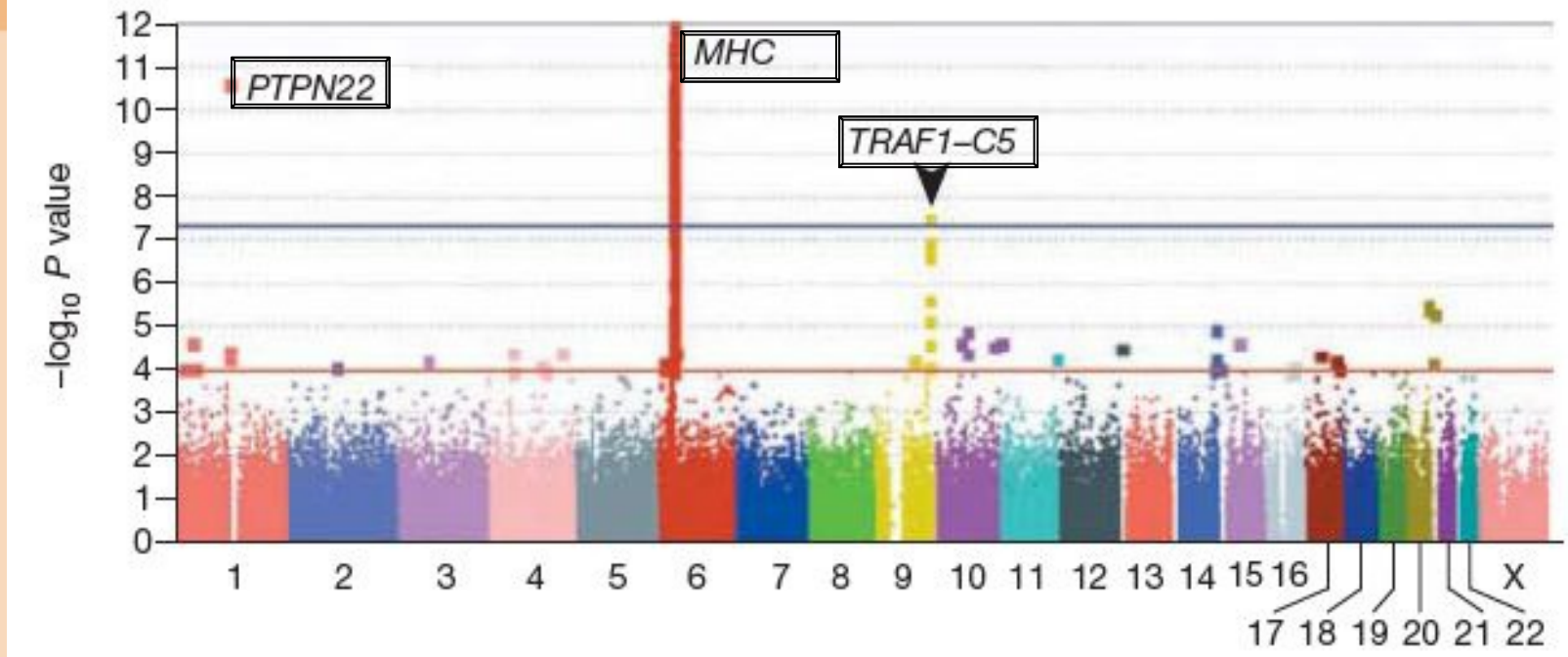
Manolio, T.A. et. al.,(2009**) Finding the missing heritability of complex diseases. Nature 461, 747-753.**

Missing heritability and strategies for finding the underlying causes of complex disease.
Eichler et al. (2010) Nature Reviews 10, 446-450.

Johansen et al. (2010)
Excess of rare variants in genes identified by genome-wide association study of hypertriglyceridema.
Nature Genetics 42, 684-7.

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