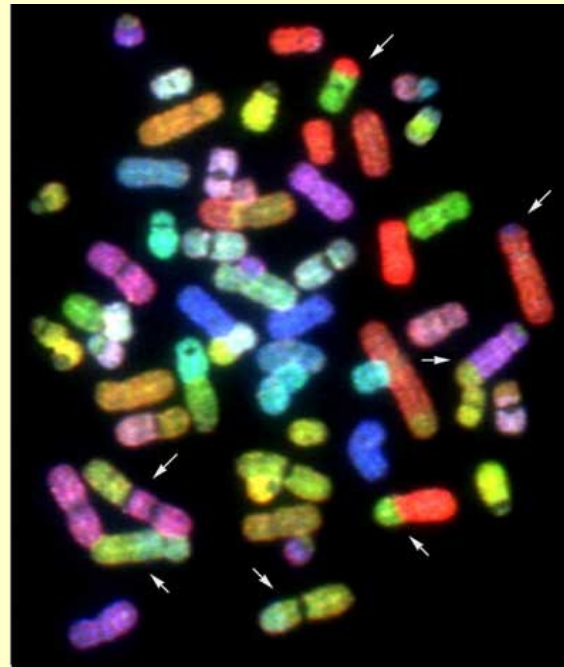


Genome-Wide Association Studies:  
Linking Genes to Disease




Doug Brutlag  
Professor Emeritus  
Biochemistry & Medicine (by courtesy)

# A Primer of Genome Science Gibson and Muse

## A Primer of Genome Science

THIRD  
EDITION



TAGCACCTAGAATCATGGAGAGATAATTGGTGAGAATTAATGGAGAGATTGCATAGAGAACTGCGAACTG

GREG GIBSON • SPENCER V. MUSE



# Preventive Medicine

上医医未病之病  
中医医将病之病  
下医医已病之病

~ 黄帝内经 ~

“Superior Doctors Prevent the Disease.  
Mediocre Doctors Treat the Disease Before Evident.  
Inferior Doctors Treat the Full Blown Disease.”

*-Huang Dee: Nai - Ching (2600 B.C. 1st Chinese Medical Text*

# Preventive Medicine

---

- Prevent disease from occurring
- Identify the cause of the disease
- Treat the cause of the disease rather than the symptoms
  - Example peptic ulcers
  - Pyrogens
- Genomics identifies the cause of disease
- “All medicine may become pediatrics”  
Paul Wise, Professor of Pediatrics, Stanford Medical School, 2008
- Effects of environment, accidents, aging, penetrance ...
- Health care costs can be greatly reduced if
  - invests in preventive medicine
  - one targets the cause of disease rather than symptoms

# Penetrance and Environmental Factors

---

- Highly penetrant Mendelian single gene diseases
  - Huntington's Disease caused by excess CAG repeats in huntingtin's protein gene
  - Autosomal dominant, 100% penetrant, invariably lethal
- Reduced penetrance, some genes lead to a predisposition to a disease
  - BRCA1 & BRCA2 genes can lead to a familial breast or ovarian cancer
  - Disease alleles lead to 80% overall lifetime chance of a cancer, but 20% of patients with the rare defective genes show no cancers
- Complex diseases requiring alleles in multiple genes
  - Many cancers (solid tumors) require somatic mutations that induce cell proliferation, mutations that inhibit apoptosis, mutations that induce angiogenesis, and mutations that cause metastasis
  - Cancers are also influenced by environment (smoking, carcinogens, exposure to UV)
  - Atherosclerosis (obesity, genetic and nutritional cholesterol)
- Some complex diseases have multiple causes
  - Genetic vs. spontaneous vs. environment vs. behavior
- Some complex diseases can be caused by multiple pathways
  - Type 2 Diabetes can be caused by reduced beta-cells in pancreas, reduced production of insulin, reduced sensitivity to insulin (insulin resistance) as well as environmental conditions (obesity, sedentary lifestyle, smoking etc.).

# Genes & Disease

<http://www.ncbi.nlm.nih.gov/books/bookres.fcgi/gnd/tocstatic.html>



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[Click on a Chromosome](#)
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[Ear, Nose, and Throat](#)



[Diseases of the Eye](#)



[Female-Specific Diseases](#)



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[The Heart and Blood Vessels](#)



[Diseases of the Immune System](#)



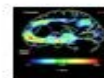
[Male-Specific Diseases](#)



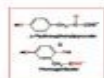
[Muscle and Bone](#)



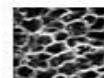
[Neonatal Diseases](#)



[The Nervous System](#)



[Nutritional and Metabolic Diseases](#)



[Respiratory Diseases](#)



[Skin and Connective Tissue](#)

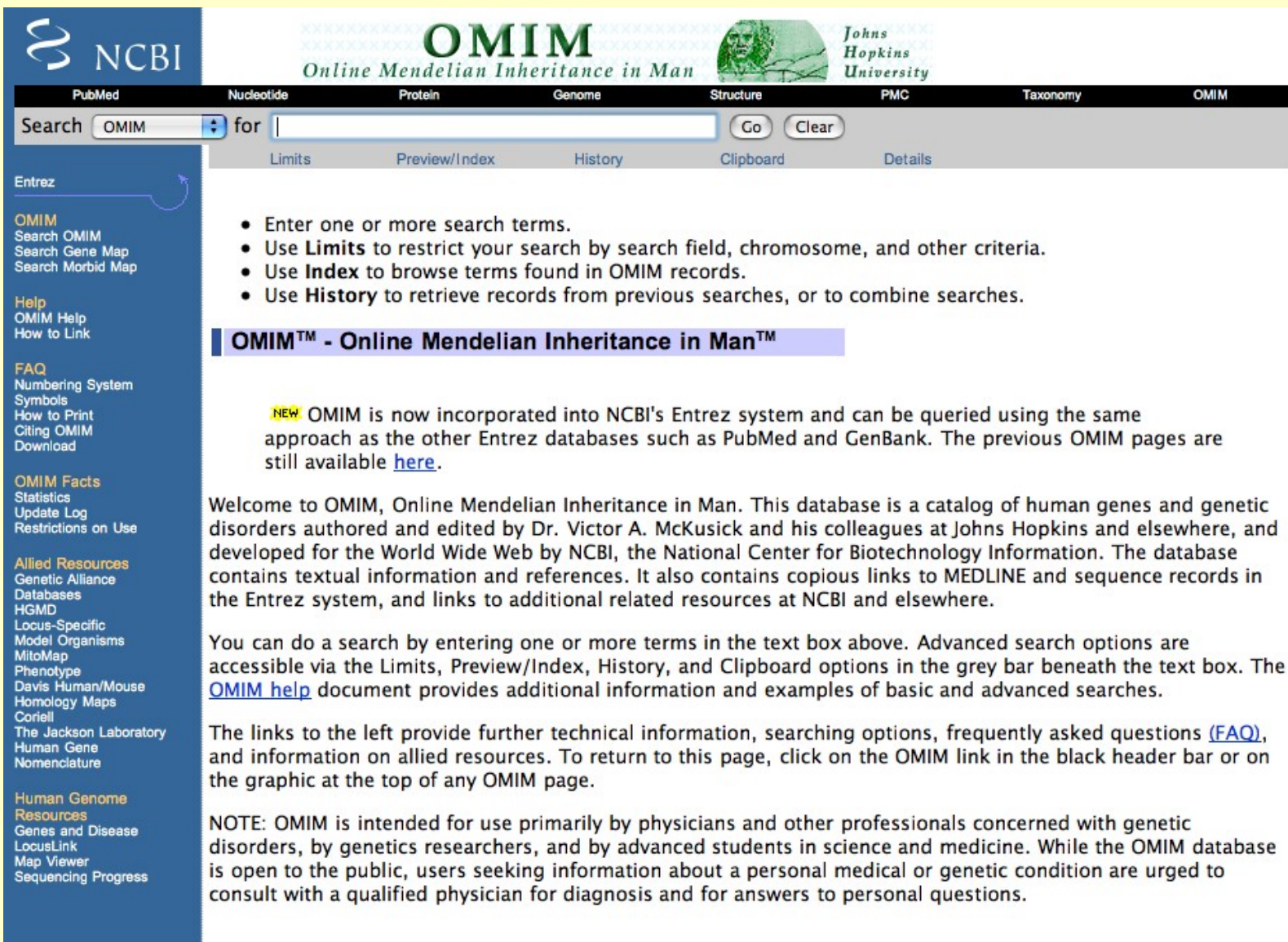


[Chromosome Map](#)

[Copyright and Disclaimer](#)

# OMIM Home Page

<http://www.ncbi.nlm.nih.gov/omim/>



The screenshot shows the OMIM Home Page interface. At the top, there is a navigation bar with links for PubMed, Nucleotide, Protein, Genome, Structure, PMC, Taxonomy, and OMIM. Below this is a search bar with a dropdown menu set to 'OMIM' and a search box containing the text 'for'. To the right of the search box are 'Go' and 'Clear' buttons. Below the search bar is a grey bar with navigation options: Limits, Preview/Index, History, Clipboard, and Details. On the left side, there is a sidebar with various links under the heading 'Entrez', including OMIM, Search OMIM, Search Gene Map, Search Morbid Map, Help, OMIM Help, How to Link, FAQ, Numbering System, Symbols, How to Print, Citing OMIM, Download, OMIM Facts, Statistics, Update Log, Restrictions on Use, Allied Resources, Genetic Alliance, Databases, HGMD, Locus-Specific, Model Organisms, MitoMap, Phenotype, Davis Human/Mouse, Homology Maps, Coriell, The Jackson Laboratory, Human Gene, Nomenclature, Human Genome Resources, Genes and Disease, LocusLink, Map Viewer, and Sequencing Progress. The main content area features a list of search tips and a section titled 'OMIM™ - Online Mendelian Inheritance in Man™' with a 'NEW' tag, stating that OMIM is now incorporated into NCBI's Entrez system. Below this is a welcome message and a paragraph about the database's history and content. Further down, there is a paragraph about search options and a link to the 'OMIM help' document. The next paragraph discusses the availability of technical information and frequently asked questions. Finally, a 'NOTE' section explains the intended use of the database by professionals and students, and advises consulting a physician for personal medical or genetic conditions.

[PubMed](#)   [Nucleotide](#)   [Protein](#)   [Genome](#)   [Structure](#)   [PMC](#)   [Taxonomy](#)   [OMIM](#)

Search  for

[Limits](#)   [Preview/Index](#)   [History](#)   [Clipboard](#)   [Details](#)

Entrez

**OMIM**  
[Search OMIM](#)  
[Search Gene Map](#)  
[Search Morbid Map](#)

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**Allied Resources**  
[Genetic Alliance](#)  
[Databases](#)  
[HGMD](#)  
[Locus-Specific](#)  
[Model Organisms](#)  
[MitoMap](#)  
[Phenotype](#)  
[Davis Human/Mouse](#)  
[Homology Maps](#)  
[Coriell](#)  
[The Jackson Laboratory](#)  
[Human Gene](#)  
[Nomenclature](#)

**Human Genome Resources**  
[Genes and Disease](#)  
[LocusLink](#)  
[Map Viewer](#)  
[Sequencing Progress](#)

- Enter one or more search terms.
- Use **Limits** to restrict your search by search field, chromosome, and other criteria.
- Use **Index** to browse terms found in OMIM records.
- Use **History** to retrieve records from previous searches, or to combine searches.

**OMIM™ - Online Mendelian Inheritance in Man™**

**NEW** OMIM is now incorporated into NCBI's Entrez system and can be queried using the same approach as the other Entrez databases such as PubMed and GenBank. The previous OMIM pages are still available [here](#).

Welcome to OMIM, Online Mendelian Inheritance in Man. This database is a catalog of human genes and genetic disorders authored and edited by Dr. Victor A. McKusick and his colleagues at Johns Hopkins and elsewhere, and developed for the World Wide Web by NCBI, the National Center for Biotechnology Information. The database contains textual information and references. It also contains copious links to MEDLINE and sequence records in the Entrez system, and links to additional related resources at NCBI and elsewhere.

You can do a search by entering one or more terms in the text box above. Advanced search options are accessible via the Limits, Preview/Index, History, and Clipboard options in the grey bar beneath the text box. The [OMIM help](#) document provides additional information and examples of basic and advanced searches.

The links to the left provide further technical information, searching options, frequently asked questions ([FAQ](#)), and information on allied resources. To return to this page, click on the OMIM link in the black header bar or on the graphic at the top of any OMIM page.

**NOTE:** OMIM is intended for use primarily by physicians and other professionals concerned with genetic disorders, by genetics researchers, and by advanced students in science and medicine. While the OMIM database is open to the public, users seeking information about a personal medical or genetic condition are urged to consult with a qualified physician for diagnosis and for answers to personal questions.

# Genetics Home Reference

<http://ghr.nlm.nih.gov/>



## Genetics Home Reference

Your Guide to Understanding Genetic Conditions

[About](#) [Site Map](#) [Contact Us](#)

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### What's New

- juvenile Paget disease
- Paget disease of bone
- 3-beta-hydroxysteroid dehydrogenase deficiency
- More...

### Newborn Screening

Detecting genetic disorders for early treatment

### In the Spotlight

- Learning Activities
- The Genetic Information Nondiscrimination Act (GINA)
- Information Rx

### Genetic Disorders A to Z and related genes and chromosomes

#### Genetic Conditions

The genetics of more than 450 health conditions, diseases, and syndromes.



#### Genes

More than 700 genes, health effects of genetic differences, and gene families.



#### Chromosomes

Chromosomes, mitochondrial DNA, and associated health conditions.



### Concepts & Tools for understanding human genetics

#### Handbook

Learn about mutations, inheritance, genetic counseling, genetic testing, genomic research, and more.



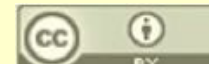
#### Glossary

Medical and genetics definitions.



#### Resources

Links to other genetics information and organizations.





# Medline Plus

<http://medlineplus.gov/>

[Skip navigation](#)



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Start here with 800 topics on conditions, diseases and wellness

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About your prescription and over-the-counter medicines, herbs and supplements

## ▶ Medical Encyclopedia

Includes pictures and diagrams

## ▶ Dictionary

Spellings and definitions of medical words

## ▶ News

Current health news and press announcements

## ▶ Directories

Find doctors, dentists and hospitals

## ▶ Go Local

A service for finding local resources for health-related issues

## ▶ Other Resources

Local health services, libraries, organizations, international sites and more

## ▶ Multiple Languages

Health information in over 40 languages

## Current Health News

- ▶ [Sinus Surgery Brings Relief to Many](#)
- ▶ [Laser Deemed Best Treatment for Diabetic Retinopathy](#)
- ▶ [Effects of Diet on Diabetes Risk Vary by Ethnicity](#)
- ▶ [More news](#)

## Featured Site



**Fight those holiday pounds!**  
Learn about [controlling your weight](#)

## In the Spotlight

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Studies for new drugs and treatments



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Health information for older adults



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Doug Brutlag 2010

# Common Gene Variation in Complex Disease

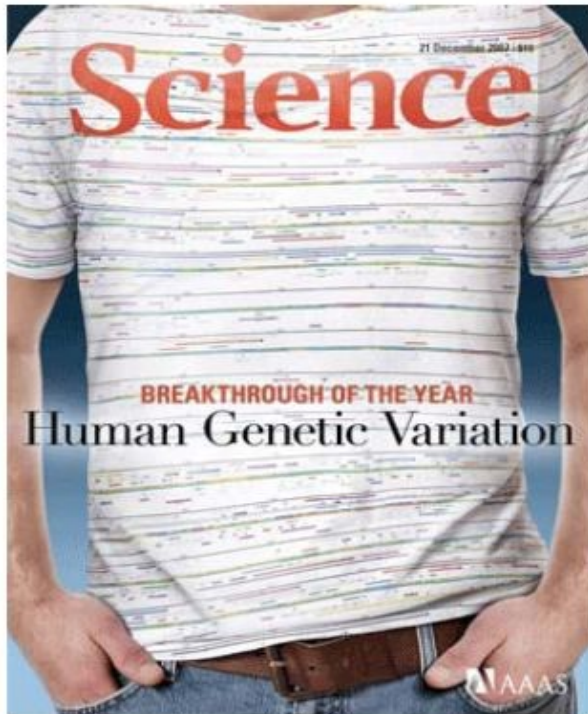
Case-control studies, comparing the frequencies of common gene variants can identify susceptibility and protective alleles. Many have multiple identified genes (\*)

Phenotype	Gene	Variant
Peptic ulcer	ABO	B
IDDM*	HLA	DR3,4
Alzheimer dementia	APOE	E4
Deep venous thrombosis*	F5	Leiden
<i>Falciparum malaria</i> *	HBB	$\beta^s$
AIDS*	CCR5	$\Delta 32$
Colorectal cancer*	APC	3920A
NIDDM*	PPAR $\gamma$	12A



# 2007 SCIENTIFIC BREAKTHROUGH OF THE YEAR

Science Magazine, December 21, 2007



**“It’s all about me!”**

## Single Nucleotide Polymorphisms (SNPs)

	SNP		SNP	
Chromosome 1	↓	A A C A <b>C</b> G C C A . . . .	↓	T T C G <b>G</b> G G T C . . . .
Chromosome 2		A A C A <b>C</b> G C C A . . . .		T T C G <b>A</b> G G T C . . . .
Chromosome 3		A A C A <b>T</b> G C C A . . . .		T T C G <b>G</b> G G T C . . . .
Chromosome 4		A A C A <b>C</b> G C C A . . . .		T T C G <b>G</b> G G T C . . . .

<http://www.sciencemag.org/cgi/content/full/318/5858/1842>



# International HapMap Project

<http://www.hapmap.org/>



## International HapMap Project

[Home](#) | [About the Project](#) | [Data](#) | [Publications](#) | [Tutorial](#)

[中文](#) | [English](#) | [Français](#) | [日本語](#) | [Yoruba](#)

The International HapMap Project is a partnership of scientists and funding agencies from Canada, China, Japan, Nigeria, the United Kingdom and the United States to develop a public resource that will help researchers find genes associated with human disease and response to pharmaceuticals. See "[About the International HapMap Project](#)" for more information.

### Project Information

[About the Project](#)  
[HapMap Publications](#)  
[HapMap Tutorial](#)  
[HapMap Mailing List](#)  
[HapMap Project Participants](#)  
[HapMap Mirror Site in Japan](#)

### Project Data

[HapMap Genome Browser \(Phase 1, 2 & 3 - merged genotypes & frequencies\)](#)  
[HapMap Genome Browser \(Phase 3 - genotypes, frequencies & LD\)](#)  
[HapMap Genome Browser \(Phase 1 & 2 - full dataset\)](#)  
[GWAs Karyogram](#)  
[HapMart](#)  
[HapMap FTP](#)  
[Bulk Data Download](#)  
[Data Freezes for Publication](#)  
[ENCODE Project](#)  
[Guidelines For Data Use](#)

### News

- 2009-12-14: **Notice to Haploview users**

Recently, there are several questions about Haploview data format errors, and these errors were observed when users tried to analyze HapMap release 27 data dumped from HapMap. The current Haploview version (4.1) does not work with release 27 data. Haploview will generate a software error similar to "Hapmap data format error: NA06984" when trying to open the data.

The r27 data format will be supported by next Haploview version. There is a beta test version that is supposed to work and it can be obtained from <http://www.broadinstitute.org/haploview/haploview-downloads>. But since it is NOT an official release version, please use it base on your own judgment.

- 2009-12-10: **Corrected HapMap3 phased haplotypes available for chromosome X**

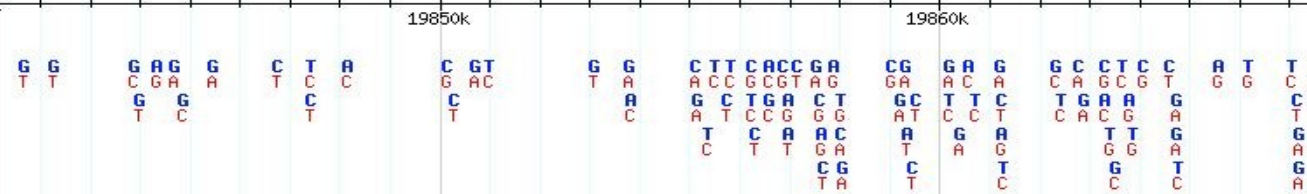
Phased haplotypes for consensus HapMap3 release 2 data for chromosome X has been corrected and the new data are now **available for bulk download**. Sorry for any inconvenience this might have caused.

- 2009-12-02: **HapMap3 phased haplotypes available for chromosome X**

Phased haplotypes for consensus HapMap3 release 2 data has been phased for chromosome X and are now available for bulk download. [Update: The downloading was disabled because several users have found that there are repeating data in some of the chrX phasing data files. The data source is being contacted and the downloading will be enabled as soon as the problem is cleared.]



Genotyped SNPs



Entrez genes

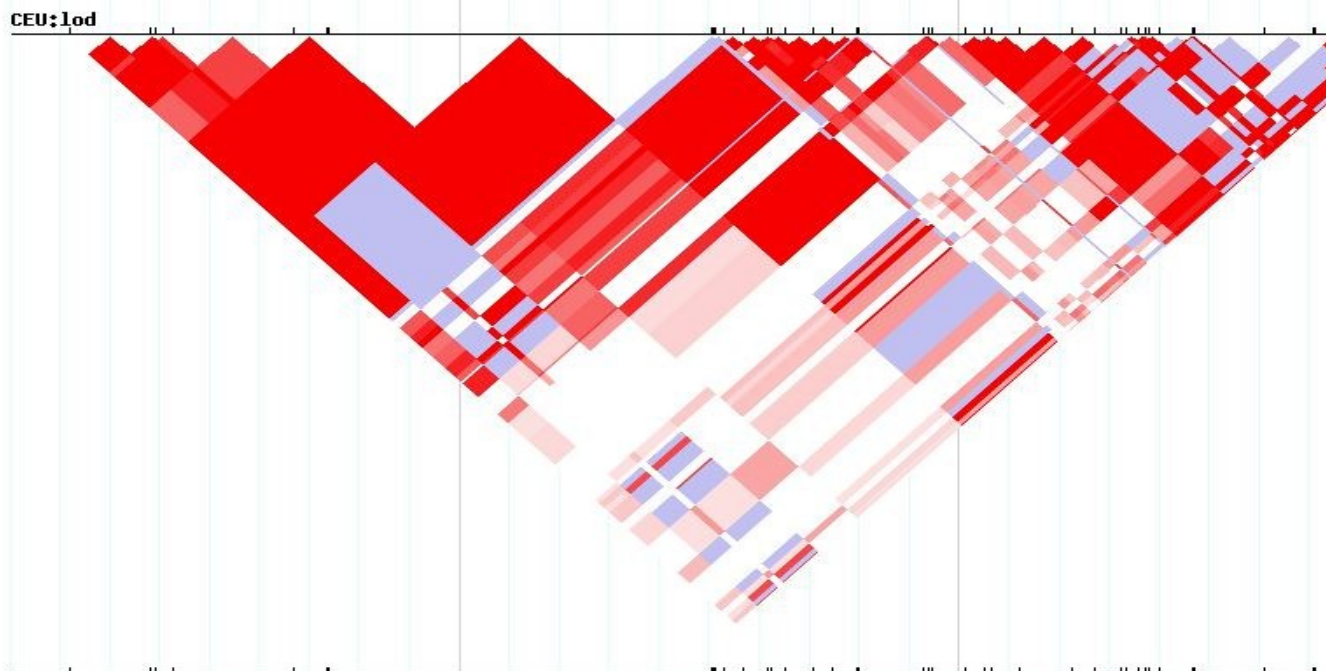


Reactome pathways

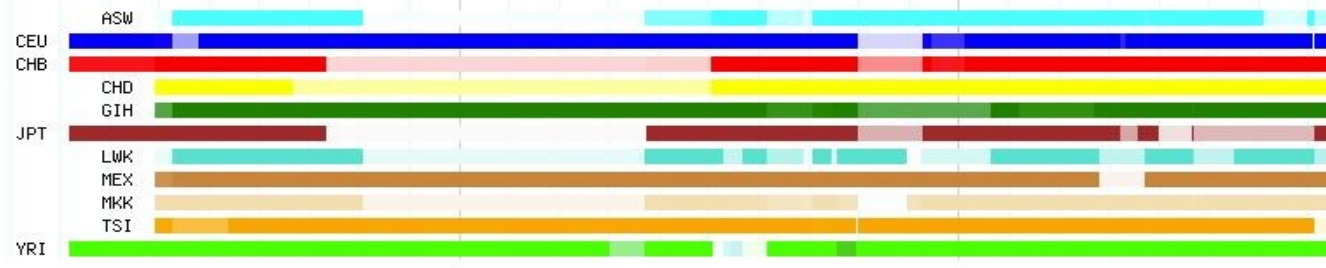


Genome-Wide Association studies (NHGRI Catalog)

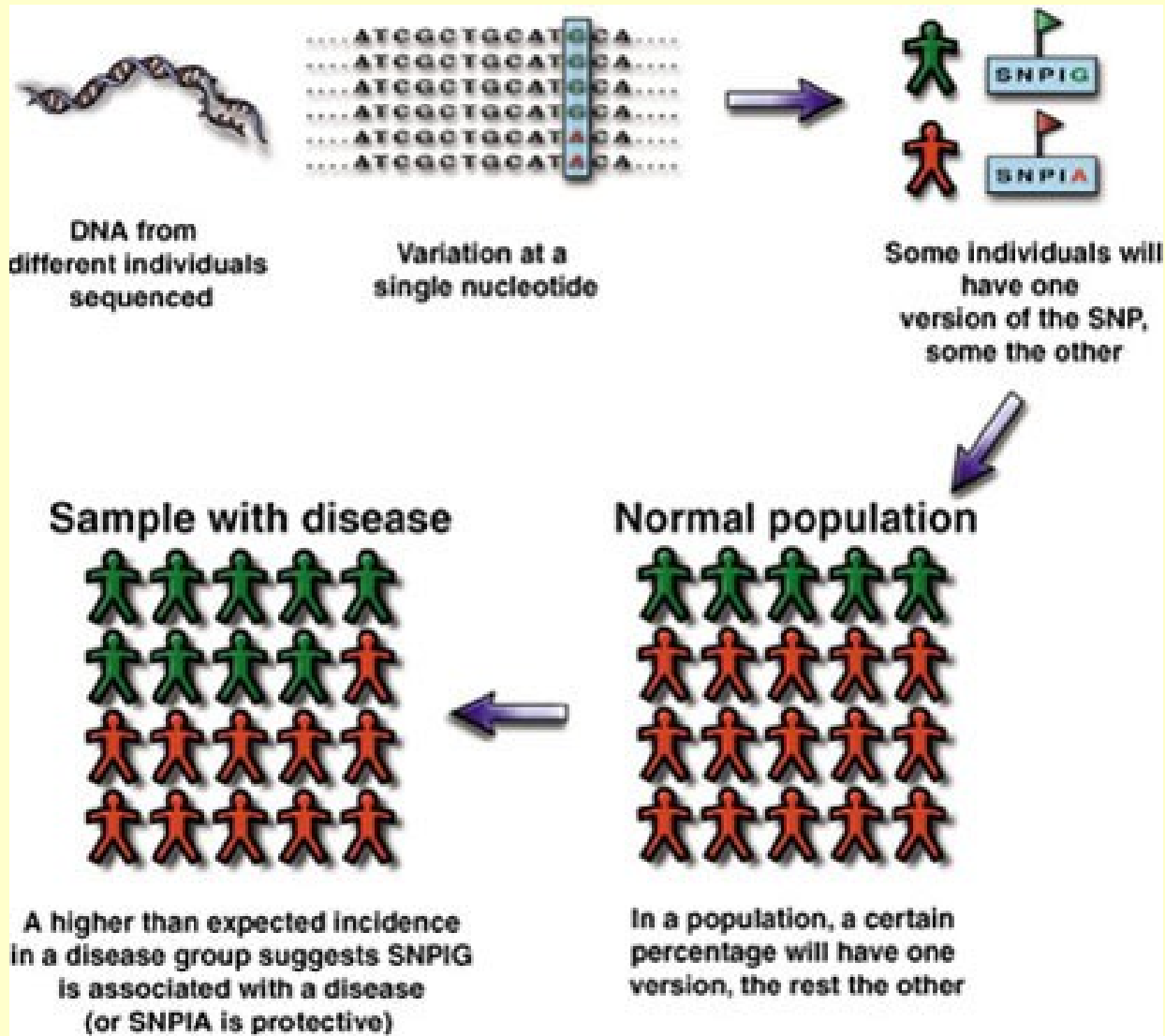
LD Plot



LD Heat Plot

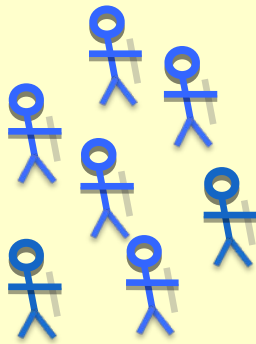


# Using SNPs to Track Predisposition to Disease and other Genetic Traits

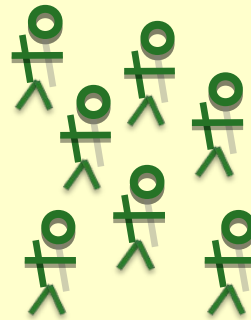


# GWAS: Genome-Wide Association Study A Brief Primer

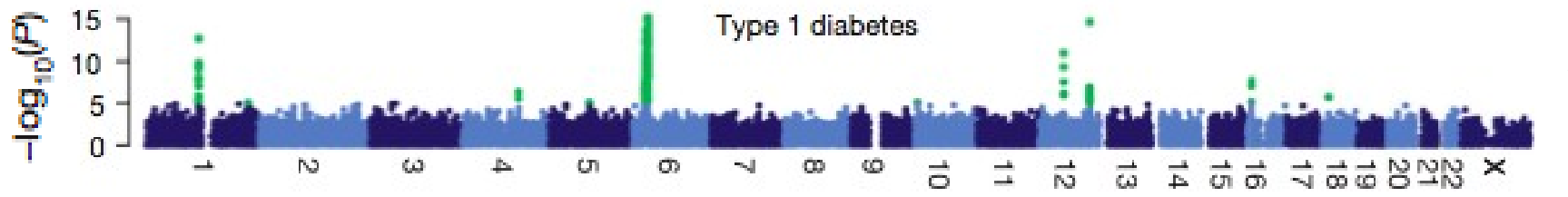
Control  
Population



Disease  
Population



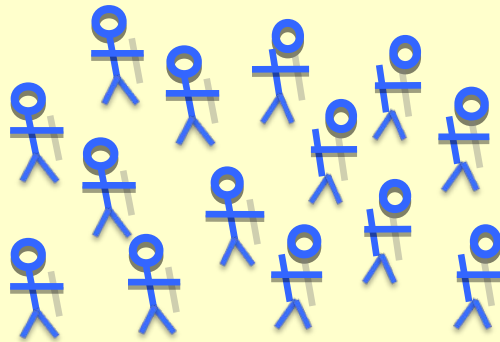
SNP chip



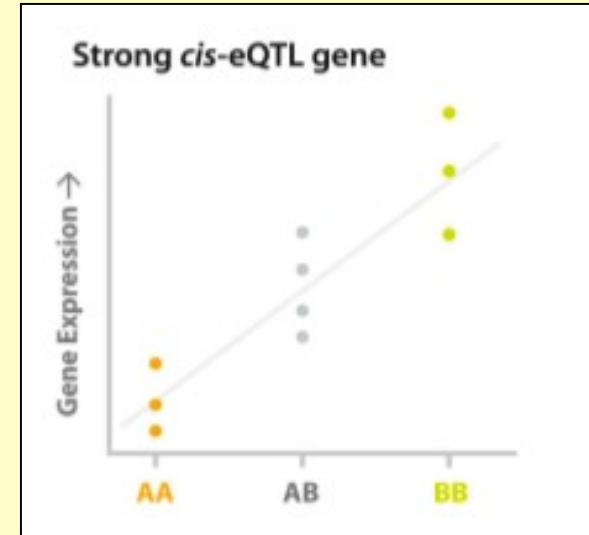


# A Quantitative Gene-Expression Association

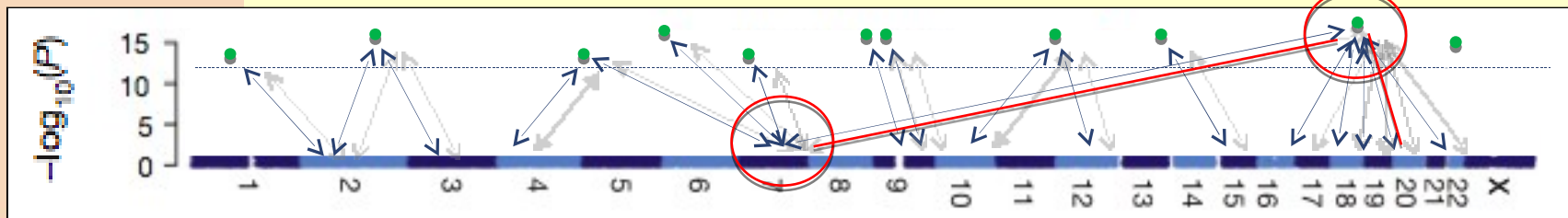
## Sample Population



cDNA Levels



## Expression Quantitative Trait Loci (eQTLs)



Modified from WTCCC, Nature 2007

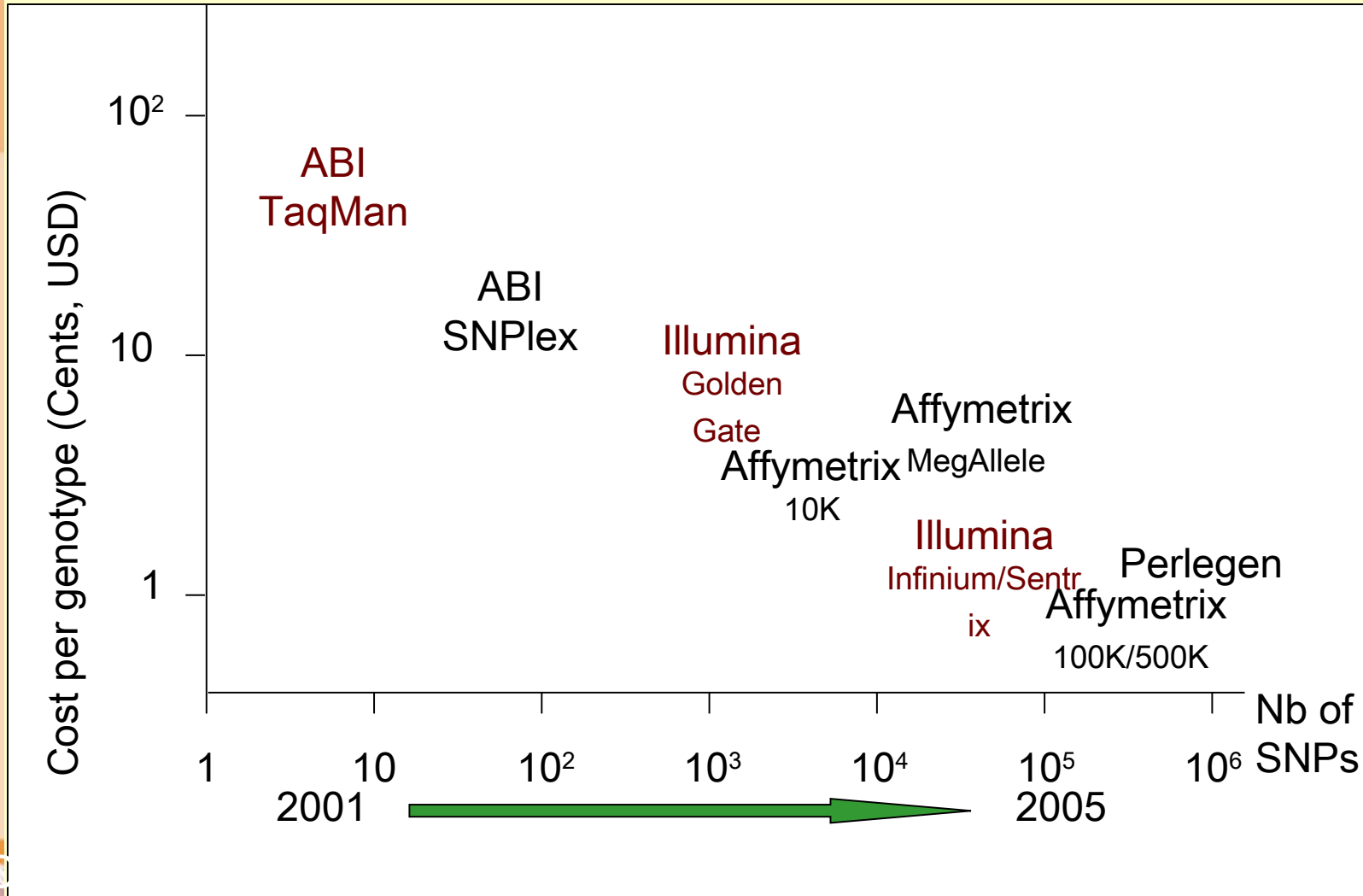
Thanks to Daniel Newburger

# Genome-Wide Association Approach to Common and Complex Diseases

---

- Identify all 10 million common SNPs
- Collect 1,000 cases and 1,000 controls
- Genotype all DNAs for all SNPs
- That adds up to 20 billion genotypes
  
- In 2002, this approach cost 50 cents a genotype.
- That's \$10 billion for each disease – completely out of the question

# Progress in Genotype Technology



# Genome-Wide Association Approach to Common and Complex Diseases

---

- Identify an optimum set of 300,000 tag SNPs
- Collect 1,000 cases and 1,000 controls
- Genotype all DNAs for all SNPs
- That adds up to 600 million genotypes
  
- In 2008, genotyping dropped to \$0.0010, amounting to \$600,000 for each disease



# The FUSION Study

## Finland-United States Investigation of NIDDM

---

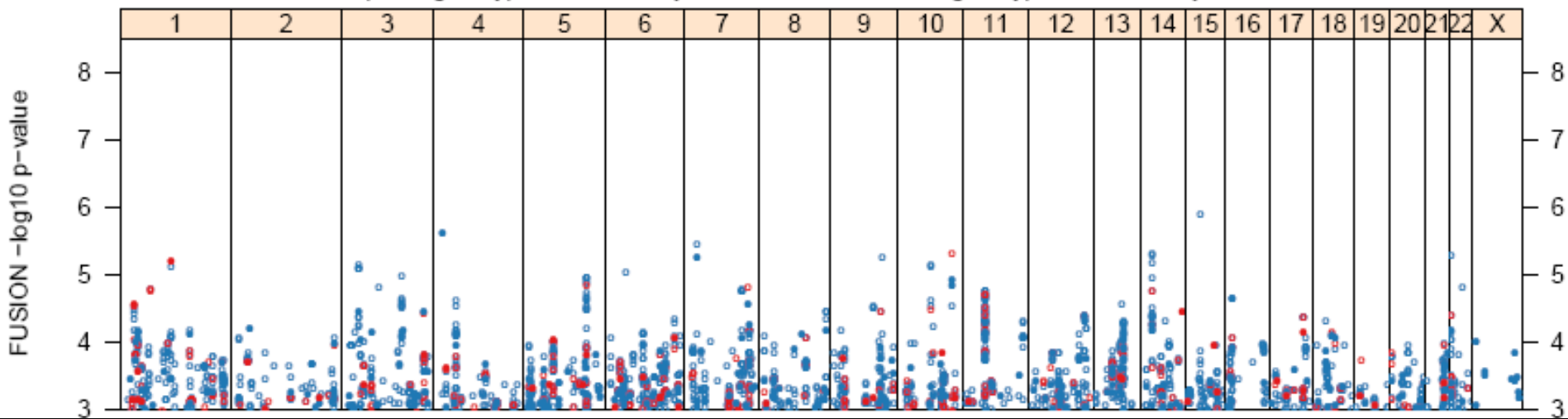
**n = 10,068**



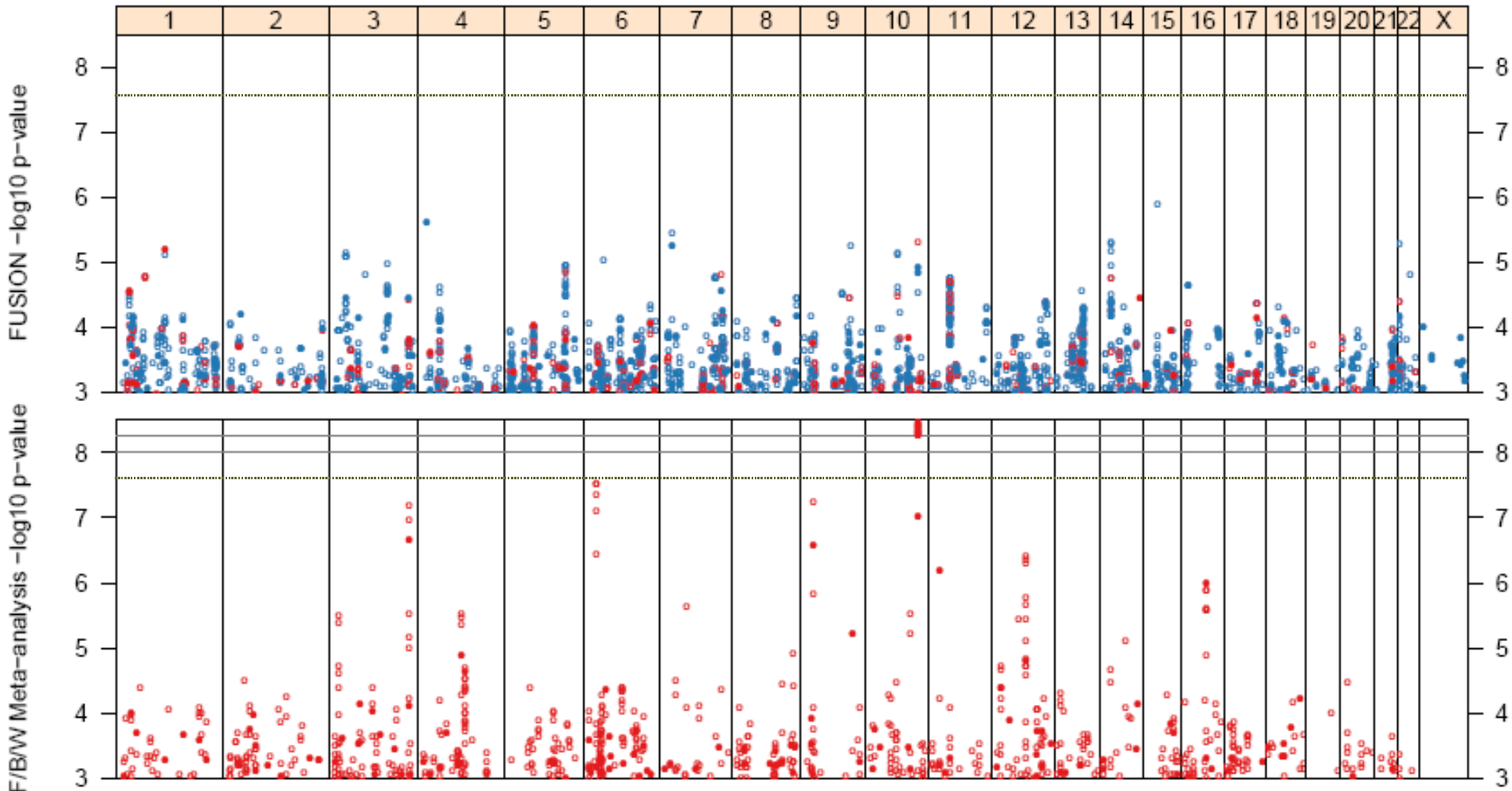
- Subject Recruitment and Clinical Testing
  - National Public Health Institute
  - Helsinki, Finland
- Molecular Genetics
  - National Human Genome Research Institute, Bethesda, MD
  - University of North Carolina, Chapel Hill, NC
- Biochemical Measurements
  - USC Keck School of Medicine, Los Angeles, CA
- Statistical Analysis
  - University of Michigan School of Public Health, Ann Arbor, MI

# Results of Genome-Wide Association of Type 2 Diabetes with 317,503 SNPs

Stage 1: FUSION only (1161 cases + 1174 controls)



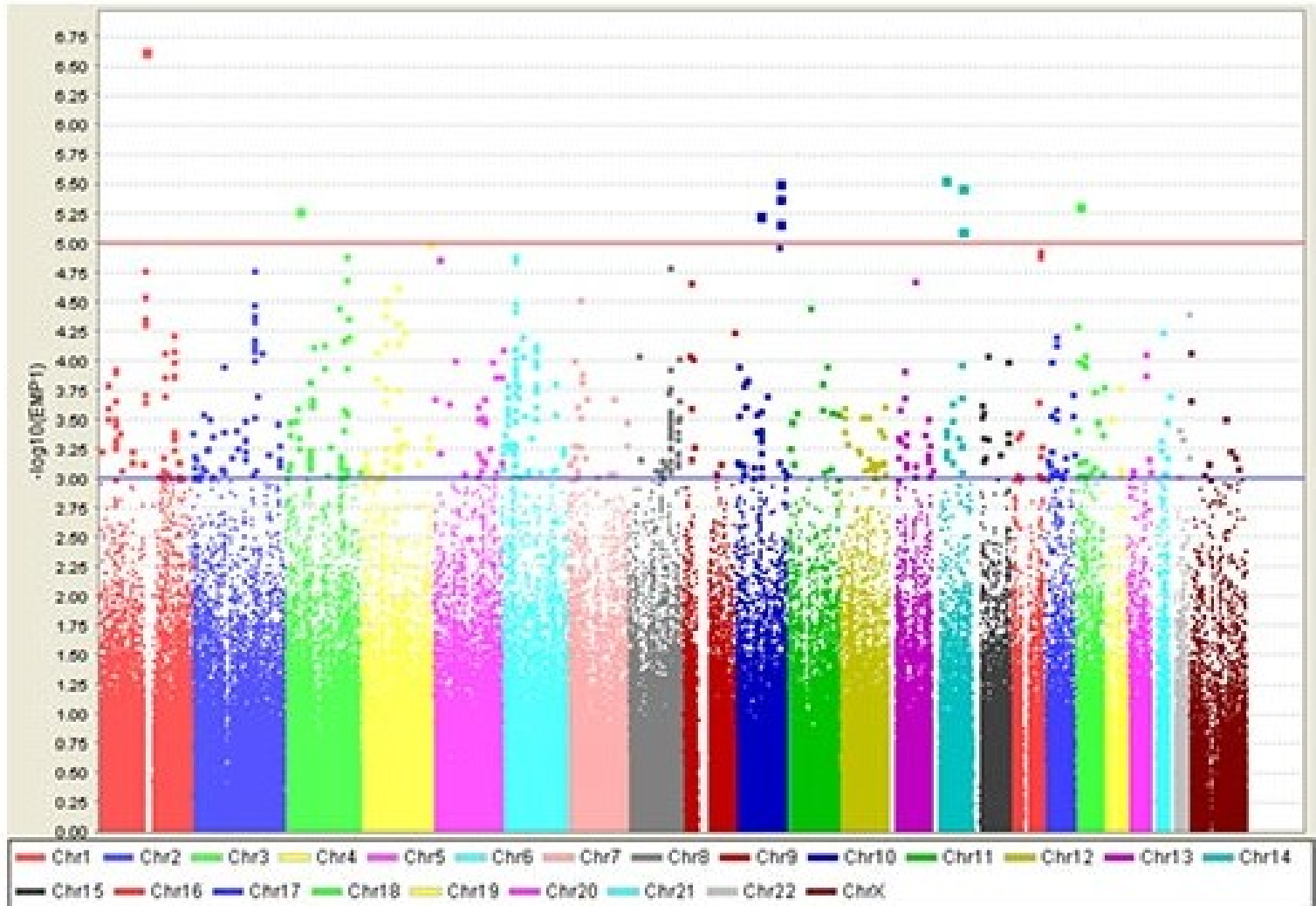
# Results of Genome-Wide Association of Type 2 Diabetes with 317,503 SNPs



Stage 2 – FUSION + DGI + WTCCC  
(4549 cases + 5579 controls)



# Genome-Wide Scan for Type 2 Diabetes in a Scandinavian Cohort

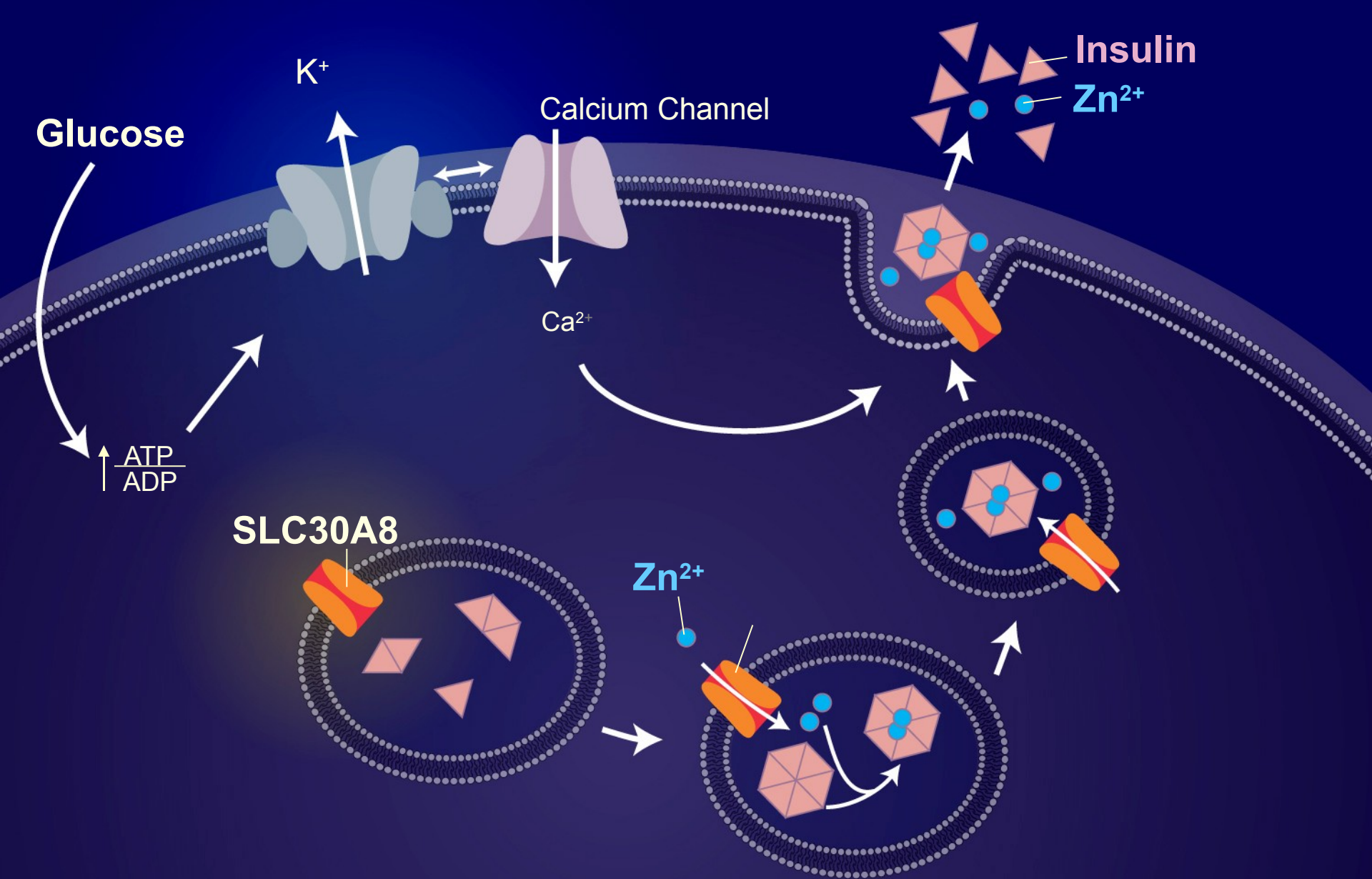


# Top 10 Results From Combined Analysis

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

# Top 10 Results From Combined Analysis

Gene	FUSION		DGI		WTCCC/UKT2D		All Samples	
	OR	p-value	OR	p-value	OR	p-value	OR	p-value
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CDKN2A/B	1.20	.0022	1.20	5.4 x 10 <sup>-8</sup>	1.19	4.9 x 10 <sup>-7</sup>	1.20	7.8 x 10 <sup>-15</sup>
FTO	1.11	0.016	1.03	0.25	1.23	7.3 x 10 <sup>-14</sup>	1.17	1.3 x 10 <sup>-12</sup>
CDKAL1	1.12	0.0095	1.08	0.0024	1.16	1.3 x 10 <sup>-8</sup>	1.12	4.1 x 10 <sup>-11</sup>
<b>KCNJ11</b>	<b>1.11</b>	<b>0.013</b>	<b>1.15</b>	<b>1.0 x 10<sup>-7</sup></b>	<b>1.15</b>	<b>0.0013</b>	<b>1.14</b>	<b>6.7 x 10<sup>-11</sup></b>
HHEX	1.10	0.026	1.14	1.7 x 10 <sup>-4</sup>	1.13	4.6 x 10 <sup>-6</sup>	1.13	5.7 x 10 <sup>-10</sup>
<b>SLC30A8</b>	<b>1.18</b>	<b>7.0 x 10<sup>-5</sup></b>	<b>1.07</b>	<b>0.047</b>	<b>1.12</b>	<b>7.0 x 10<sup>-5</sup></b>	<b>1.12</b>	<b>5.3 x 10<sup>-8</sup></b>
Chr 11	1.48	5.7 x 10 <sup>-8</sup>	1.16	0.12	1.13	0.068	1.23	4.3 x 10 <sup>-7</sup>
<b>PPARG</b>	<b>1.20</b>	<b>0.0014</b>	<b>1.09</b>	<b>0.019</b>	<b>1.23</b>	<b>0.0013</b>	<b>1.14</b>	<b>1.7 x 10<sup>-6</sup></b>

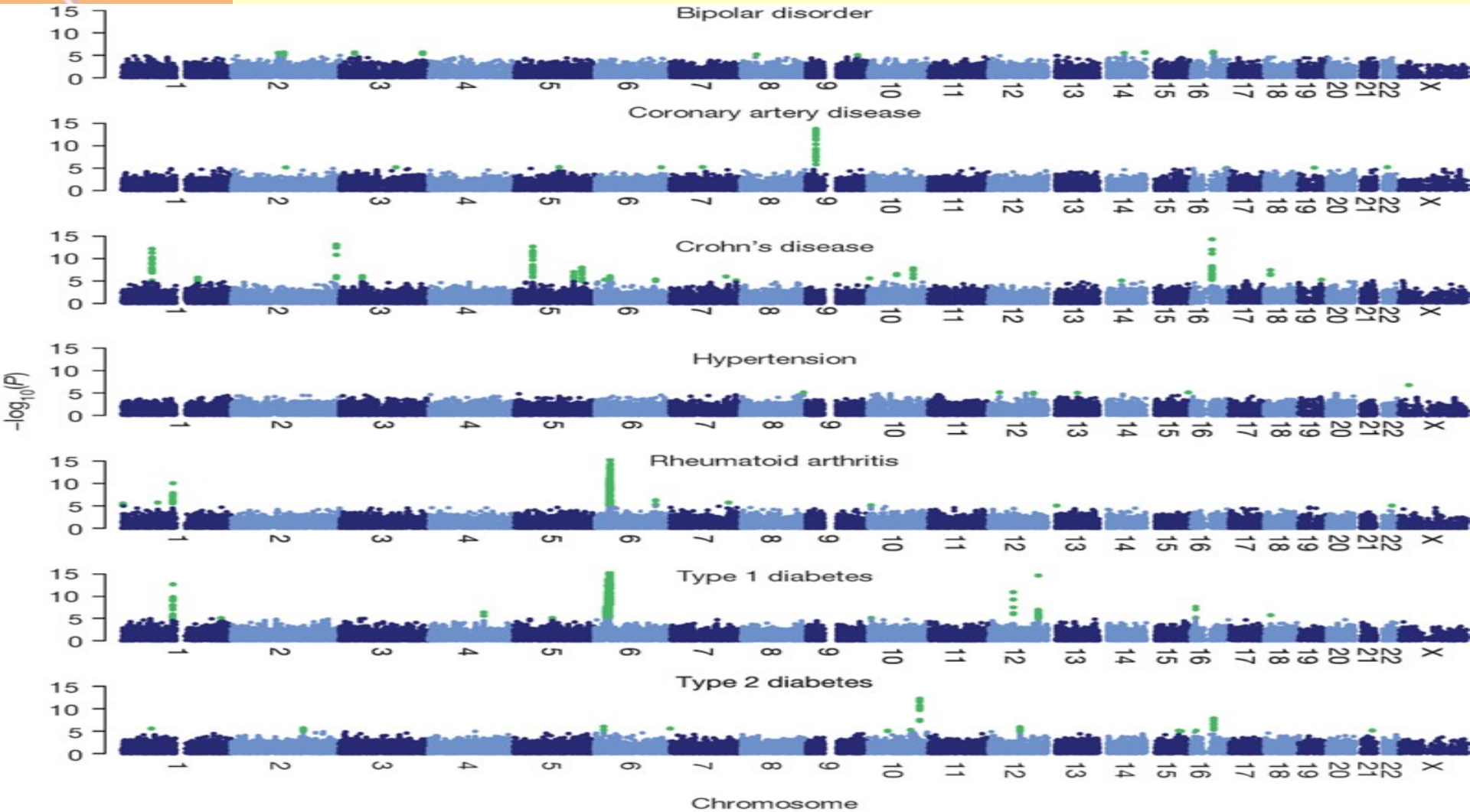


# SLC30A8 – A Beta Cell Zinc Transporter

# 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)




# 2007: The Year of GWA Studies?



Hokusai



# The Genomics Gold Rush



<b>Disease</b>	<b>Gene or Loci</b>	<b>Date Reported</b>
<b>Prostate Cancer</b>	<b>8q24</b>	<b>April 1, 2007</b>
<b>Acute Lymphoblastic Leukemia</b>	<b>PAX 5 and others</b>	<b>April 12, 2007</b>
<b>Obesity</b>	<b>FTO</b>	<b>April 12, 2007</b>
<b>Multiple Solid Tumors</b>	<b>CASP8</b>	<b>April 22, 2007</b>
<b>Diabetes, Type II</b>	<b>CDKAL1 and 6 others</b>	<b>April 26, 2007</b>
<b>Myocardial Infarction, Coronary Artery Disease</b>	<b>9p21</b>	<b>May 3, 2007</b>
<b>Breast Cancer</b>	<b>FGFR2, TNCR9, MAP3K1, LSP and others</b>	<b>May 27, 2007</b>
<b>Crohn's Disease</b>	<b>IRGM</b>	<b>June 7, 2007</b>
<b>Diabetes, Type I</b>	<b>12q24 and others</b>	<b>June 7, 2007</b>
<b>Bipolar Disorder</b>	<b>16p12</b>	<b>June 7, 2007</b>
<b>Rheumatoid Arthritis</b>	<b>6p21, 1p13</b>	<b>June 7, 2007</b>
<b>Celiac Disease</b>	<b>IL-2, IL-21</b>	<b>June 10, 2007</b>
<b>Atrial Fibrillation</b>	<b>4q25</b>	<b>July 1, 2007</b>

# The Genomics Gold Rush

<b>Disease</b>	<b>Gene or Loci</b>	<b>Date Reported</b>
Diabetes, Type II	WFS1	July 1, 2007
Prostate Cancer	TCF2; 17p	July 1, 2007
Asthma (childhood)	ORMDL3	July 4, 2007
Colon, Prostate Cancer	8q24	July 8, 2007
Diabetes, Type I	KIAA0350	July 15, 2007
Gallstone Disease	ABCG8	July 15, 2007
Restless Leg Syndrome	MEIS1, BTBD9, MAP2K5	July 18, 2007
Coronary Artery Disease	6q25, 2q36	July 18, 2007
Age-Related Macular Degeneration	CF3	July 18, 2007
HIV Host Control	HLA-B*5701	July 19, 2007
Multiple Sclerosis	IL7R $\alpha$ ; IL2R $\alpha$	July 28, 2007
Amyotrophic Lateral Sclerosis	FLJ10986	August 1, 2007
Diabetes, Type I	IL2R $\alpha$	August 5, 2007
Glaucoma	LOXL1	August 9, 2007
Rheumatoid Arthritis	TRAF1-C5	August 31, 2007



# The Genomics Gold Rush

<b>Disease</b>	<b>Gene or Loci</b>	<b>Date Reported</b>
<b>Colorectal Cancer</b>	<b>SMAD7</b>	<b>October 14, 2007</b>
<b>Ankylosing Spondylitis</b>	<b>ARTS1, IL23R</b>	<b>October 21, 2007</b>
<b>Autoimmune Thyroid Disease</b>	<b>TSHR, FCRL3</b>	<b>October 21, 2007</b>
<b>Rheumatoid Arthritis</b>	<b>6q23</b>	<b>November 4, 2007</b>
<b>Psoriasis</b>	<b><math>\beta</math>-Defensin CNV</b>	<b>December 2, 2007</b>
<b>Systemic Lupus Erythematosus</b>	<b>TNFSF4</b>	<b>December 2, 2007</b>
<b>Amyotrophic Lateral Sclerosis</b>	<b>DPP6</b>	<b>December 16, 2007</b>
<b>Colorectal Cancer</b>	<b>CRAC1 (HMPS)</b>	<b>December 16, 2007</b>
<b>Systemic Lupus Erythematosus</b>	<b>PXK, KIAA1542, BANK1, C8orf-BLK, ITGAM</b>	<b>January 20, 2008</b>
<b>Lipoprotein Disorders</b>	<b>MLX1PL and Multiple Others</b>	<b>January 13, 2008</b>
<b>Hypercholesterolemia</b>	<b>CELSR2</b>	<b>February 9, 2008</b>
<b>Prostate Cancer</b>	<b>2p15, Xp11.22 and Others</b>	<b>February 10, 2008</b>
<b>Gout</b>	<b>SLC2A9</b>	<b>March 9, 2008</b>
<b>Schizophrenia</b>	<b>ERBB4, SLC1A3 and Others</b>	<b>March 27, 2008</b>

# The Genomics Gold Rush

<b>Disease</b>	<b>Gene or Loci</b>	<b>Date</b>
Colorectal Cancer	10p14,8q23.3,18q21,11q23	March 30, 2008
Diabetes, Type 2	JA2F1 and others	March 30, 2008
Nicotine Add, Lung Ca, PAD	15q25	April 3, 2008
Hypertension	SLC12A3, SLC12A1,KCNJ1	April 6, 2008
Crohn's Disease and Ulcerative Colitis	ECM1and others PTPN2, HERC2, STAT3	April 27, 2008
Breast Cancer (ER +)	5p12	April 27, 2008
Osteoporosis	RANKL1,OPG, ESR	April 29, 2008
Obesity	MC4R	May 4, 2008
Neuroblastoma	6p22	May 7, 2008
Melanoma and Basal Cell Ca	20q11.22, ASIP, TYR	May 18, 2008
Gastric Cancer	PSCA	May 18, 2008
Macular Degeneration	ARMS2	May 30, 2008
Alzheimer's Disease	CALHM1	June 27, 2008
Crohn's Disease	JAK2, CDKAL1, ITLN1, more	June 29, 2008
Obesity	PCSK1	July 7, 2008
Knee Osteoarthritis	DVWA	July 14, 2008
Statin Myopathy	SLCO1B1	July 24, 2008

# The Genomics Gold Rush

<b>Disease</b>	<b>Gene or Loci</b>	<b>Date</b>
Restless Leg Syndrome	PTPRD	July 27, 2008
Schizophrenia	1q21, 15q13	July 31, 2008
Systemic Lupus Erythematosus	TNAIP3	August 1, 2008
Sarcoidosis	ANXA11	August 10, 2008
Bipolar Disorder	ANK3, CACNA1C	August 17, 2008
Diabetes, Type II	KCNQ1	August 17, 2008
Crohn's Disease	IRGM	August 24, 2008
Prostate Cancer	HNF1B	August 31, 2008
CLL	2q13, 2q37, and others	August 31, 2008
Pediatric Inflammatory Bowel Dz	20q13, 21q22	August 31, 2008
Rheumatoid Arthritis	CD40, CD244, 10p15, 12q13, 22q13	September 14, 2008
Bladder Cancer	8q24	September 14, 2008
ESRD, Focal Glomerulosclerosis	MYH9	September 14, 2008
Narcolepsy	CPT1B, CHKB	September 28, 2008
Fatty Liver Disease (non-EtOH)	PNPLA3	September 28, 2008
Gout	SLC2A9, SLC17A3	October 1, 2008

# The Genomics Gold Rush

<b>Disease</b>	<b>Gene or Loci</b>	<b>Date</b>
<b>Male Pattern Baldness</b>	<b>20p11</b>	<b>October 12, 2008</b>
<b>Basal Cell Carcinoma</b>	<b>1p36, 1q42</b>	<b>October 12, 2008</b>
<b>Asthma</b>	<b>17q21</b>	<b>October 15, 2008</b>
<b>Lung Cancer</b>	<b>5p15, 6p21</b>	<b>November 2, 2008</b>
<b>Diabetes, Type 1</b>	<b>4q27, BACH2, PRKCQ</b>	<b>November 2, 2008</b>
<b>Multiple Sclerosis</b>	<b>KIF1B</b>	<b>November 9, 2008</b>
<b>Intracranial Aneurysm</b>	<b>SOX17, 2p33</b>	<b>November 9, 2008</b>
<b>Colon Cancer</b>	<b>BMP4, CDH1, RHPN2, 20p12</b>	<b>November 16, 2008</b>

# Catalog of GWAS Studies

<http://www.genome.gov/26525384>



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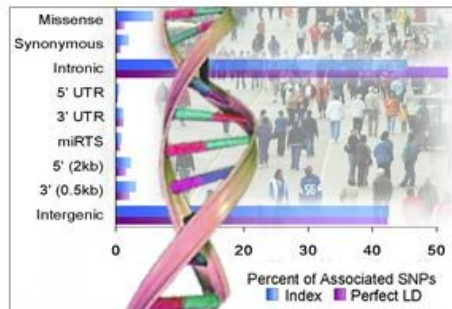
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## Online GWAS Catalog Helps Guide Disease Research



**Researchers who want to sift through the biomedical literature** to find genome-wide association results relevant to their research pursuits face an enormous challenge. But, thanks to the efforts of a dedicated team of National Human Genome Research Institute (NHGRI) scientists, they now have an online resource that can make the task a bit less daunting.

Genome-wide association studies, commonly called GWAS, efficiently scan markers across the DNA, or genomes, of large groups of people looking for variations between individuals with and without a health condition. Over the past few years, this

approach has successfully plucked from our DNA code hundreds of the pesky one-letter genetic variations that contribute to the risk of common health conditions, such as obesity and Type 2 diabetes.

The recent deluge of GWAS results coming from these studies is exactly why NHGRI created a resource called [A Catalog of Published Genome-Wide Association Studies](#). The catalog, which has been frequently cited in scientific publications, contains descriptive and association data on hundreds of published common genetic variations and their relationship with nearly 100 complex diseases and traits.

On a weekly basis, epidemiologists from NHGRI's Office of Population Genomics manually curate information from published GWAS and add them to the catalog. Researchers can search the catalog by journal name, first author, disease/trait, statistical significance of association and other categories. Data from the entire catalog can also be directly downloaded as an Excel spreadsheet.

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PNAS, May 18, 2009

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# Catalog of GWAS Studies

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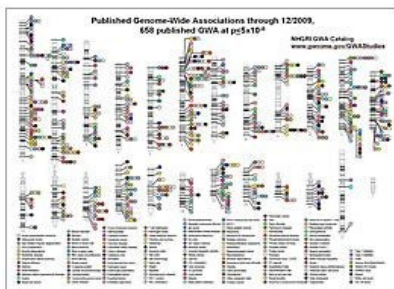
## A Catalog of Published Genome-Wide Association Studies

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



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

[Go to the Catalog](#)



*Published Genome-Wide Associations*  
Credit: Darryl Leja and Teri Manolio

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**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  $< 1.0 \times 10^{-5}$  (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 initial study sample are recorded. For quantitative traits, information on % variance explained, SD increment, or unit difference is reported where available. Odds ratios  $< 1$  in the original paper are converted to  $OR > 1$  for the alternate allele. Where results from multiple genetic models are available, we prioritized effect sizes (OR's or beta-coefficients) as follows: 1) genotypic model, per-allele estimate; 2) genotypic model, heterozygote estimate, 3) allelic model, allelic estimate.

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# Catalog of GWAS Studies

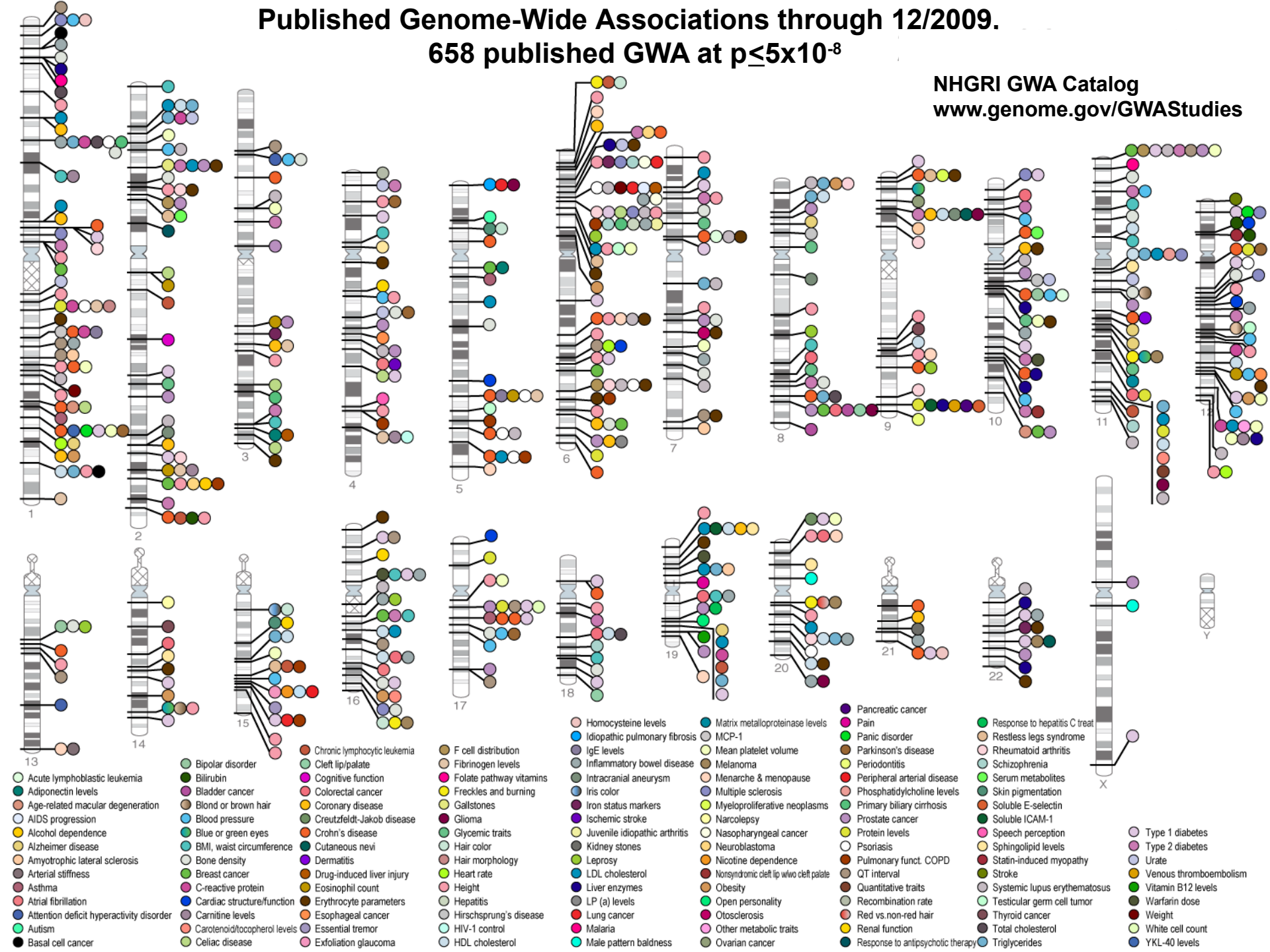
As of 03/02/10, this table includes 496 publications and 2341 SNPs.

Date Added to Catalog (since 11/25/08)	First Author/Date/ Journal/Study	Disease/Trait	Initial Sample Size	Replication Sample Size	Region	Reported Gene(s)	Strongest SNP-Risk Allele	Risk Allele Frequency in Controls	P-value
03/02/10	Shi February 02, 2010 <i>Mol Psychiatry</i> <a href="#">Genome-wide association study of recurrent early-onset major depressive disorder</a>	Major depressive disorder	1,020 European cases, 1,636 European controls	NR	18q22.1	<i>DSEL</i>	<a href="#">rs17077540-G</a>	0.11	$2 \times 10^{-7}$
					21q21.2	<i>Intergenic</i>		0.31	$4 \times 10^{-7}$
					1p13.3	<i>GNAT2, GNAI3, AMPD2</i>	<a href="#">rs2828520-G</a>	0.17	$1 \times 10^{-6}$
					5p13.2	<i>GDNF</i>	<a href="#">rs6537837-T</a>	0.69	$1 \times 10^{-6}$
					2p23.2	<i>FAM179A, C2orf71</i>	<a href="#">rs270545-G</a>	0.29	$2 \times 10^{-6}$
					3p14.2	<i>FHIT, PTPRG</i>	<a href="#">rs882632-T</a>	0.94	$4 \times 10^{-6}$
					1p13.3	<i>ATXN7L2, SYPL2, CYB561D1</i>	<a href="#">rs10514718-C</a>	0.14	$6 \times 10^{-6}$
					7p15.3	<i>SP4</i>		0.04	$6 \times 10^{-6}$
					13q21.33	<i>Intergenic</i>	<a href="#">rs12049330-G</a> <a href="#">rs17144465-G</a> <a href="#">rs9572423-G</a>	0.88	$9 \times 10^{-6}$
02/28/10	Petersen January 24, 2010 <i>Nat Genet</i> <a href="#">A genome-wide association study identifies pancreatic cancer susceptibility loci on chromosomes 13q22.1, 1q32.1 and</a>	Pancreatic cancer	3,851 cases, 3,934 controls	NR	13q22.1	<i>KLF5, KLF12</i>	<a href="#">rs9543325-C</a>	0.37	$3 \times 10^{-11}$
					1q32.1	<i>NR5A2</i>	<a href="#">rs3790844-T</a>	0.76	$2 \times 10^{-10}$
					5p15.33	<i>CLPTM1L</i>	<a href="#">rs401681-T</a>	0.45	$7 \times 10^{-7}$

# Published Genome-Wide Associations through 12/2009.

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

NHGRI GWA Catalog  
[www.genome.gov/GWASudies](http://www.genome.gov/GWASudies)



- Acute lymphoblastic leukemia
- Adiponectin levels
- Age-related macular degeneration
- AIDS progression
- Alcohol dependence
- Alzheimer disease
- Amyotrophic lateral sclerosis
- Arterial stiffness
- Asthma
- Atrial fibrillation
- Attention deficit hyperactivity disorder
- Autism
- Basal cell cancer

- Bipolar disorder
- Bilirubin
- Bladder cancer
- Blood pressure
- Blue or green eyes
- BMI, waist circumference
- Myotrophic lateral sclerosis
- Bone density
- Breast cancer
- C-reactive protein
- Cardiac structure/function
- Carnitine levels
- Carotenoid/tocopherol levels
- Celiac disease
- Chronic lymphocytic leukemia
- Cleft lip/palate
- Cognitive function
- Colorectal cancer
- Coronary disease
- Creutzfeldt-Jakob disease
- Crohn's disease
- Cutaneous nevi
- Dermatitis
- Drug-induced liver injury
- Eosinophil count
- Erythrocyte parameters
- Esophageal cancer
- Essential tremor
- Exfoliation glaucoma

- F cell distribution
- Fibrinogen levels
- Folate pathway vitamins
- Freckles and burning
- Gallstones
- Glycemic traits
- Hair color
- Hair morphology
- Height
- Heart rate
- Hepatitis
- Hirschsprung's disease
- HIV-1 control
- HDL cholesterol

- Homocysteine levels
- Idiopathic pulmonary fibrosis
- IgE levels
- Inflammatory bowel disease
- Intracranial aneurysm
- Iris color
- Iron status markers
- Ischemic stroke
- Juvenile idiopathic arthritis
- Kidney stones
- Leprosy
- LDL cholesterol
- Liver enzymes
- LP (a) levels
- Lung cancer
- Malaria
- Male pattern baldness

- Matrix metalloproteinase levels
- MCP-1
- Mean platelet volume
- Melanoma
- Menarche & menopause
- Multiple sclerosis
- Myeloproliferative neoplasms
- Nasopharyngeal cancer
- Neuroblastoma
- Nicotine dependence
- Narcolepsy
- Nonsyndromic cleft lip w/w cleft palate
- Obesity
- Open personality
- Otosclerosis
- Other metabolic traits
- Ovarian cancer

- Pancreatic cancer
- Pain
- Panic disorder
- Parkinson's disease
- Periodontitis
- Peripheral arterial disease
- Phosphatidylcholine levels
- Primary biliary cirrhosis
- Prostate cancer
- Protein levels
- Psoriasis
- Pulmonary funct. COPD
- QT interval
- Quantitative traits
- Systemic lupus erythematosus
- Statin-induced myopathy
- Stroke
- Systemic lupus erythematosus
- Stetacular germ cell tumor
- Thyroid cancer
- Total cholesterol
- Triglycerides

- Response to hepatitis C treat
- Restless legs syndrome
- Rheumatoid arthritis
- Schizophrenia
- Serum metabolites
- Skin pigmentation
- Soluble E-selectin
- Soluble ICAM-1
- Speech perception
- Sphingolipid levels
- Statin-induced myopathy
- Stroke
- Systemic lupus erythematosus
- Stetacular germ cell tumor
- Thyroid cancer
- Total cholesterol
- Triglycerides

- Type 1 diabetes
- Type 2 diabetes
- Urate
- Venous thromboembolism
- Vitamin B12 levels
- Warfarin dose
- Weight
- White cell count
- YKL-40 levels

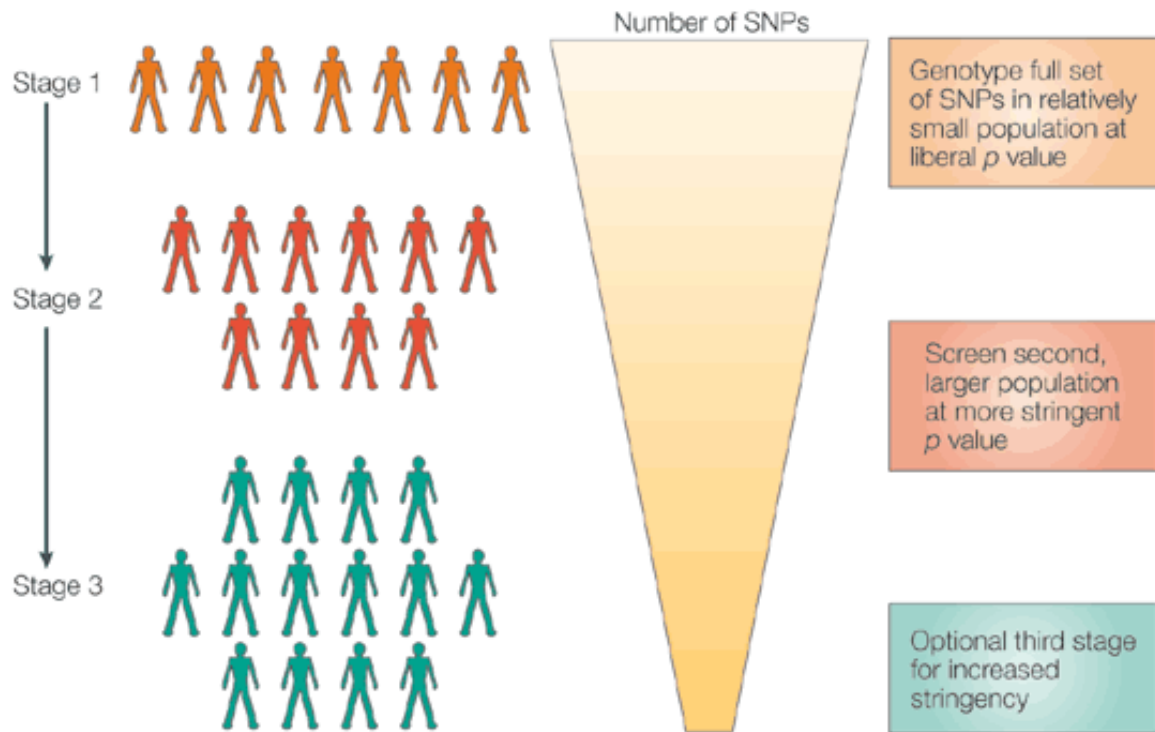


# Study Designs Used in Genome-wide Association Studies

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

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

# Replication A Must



Replication

Replication

Replication

Nature Reviews | **Genetics**

Hirschhorn & Daly Nat. Genet. Rev. 6: 95, 2005

NCI-NHGRI Working Group on Replication Nature 447: 655, 2007



# Examples of Multistage Designs in Genome-wide Association Studies

**Table 2.** Examples of Multistage Designs in Genome-wide Association Studies<sup>a</sup>

Stage	3-Stage Study <sup>b</sup>		4-Stage Study <sup>c</sup>	
	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

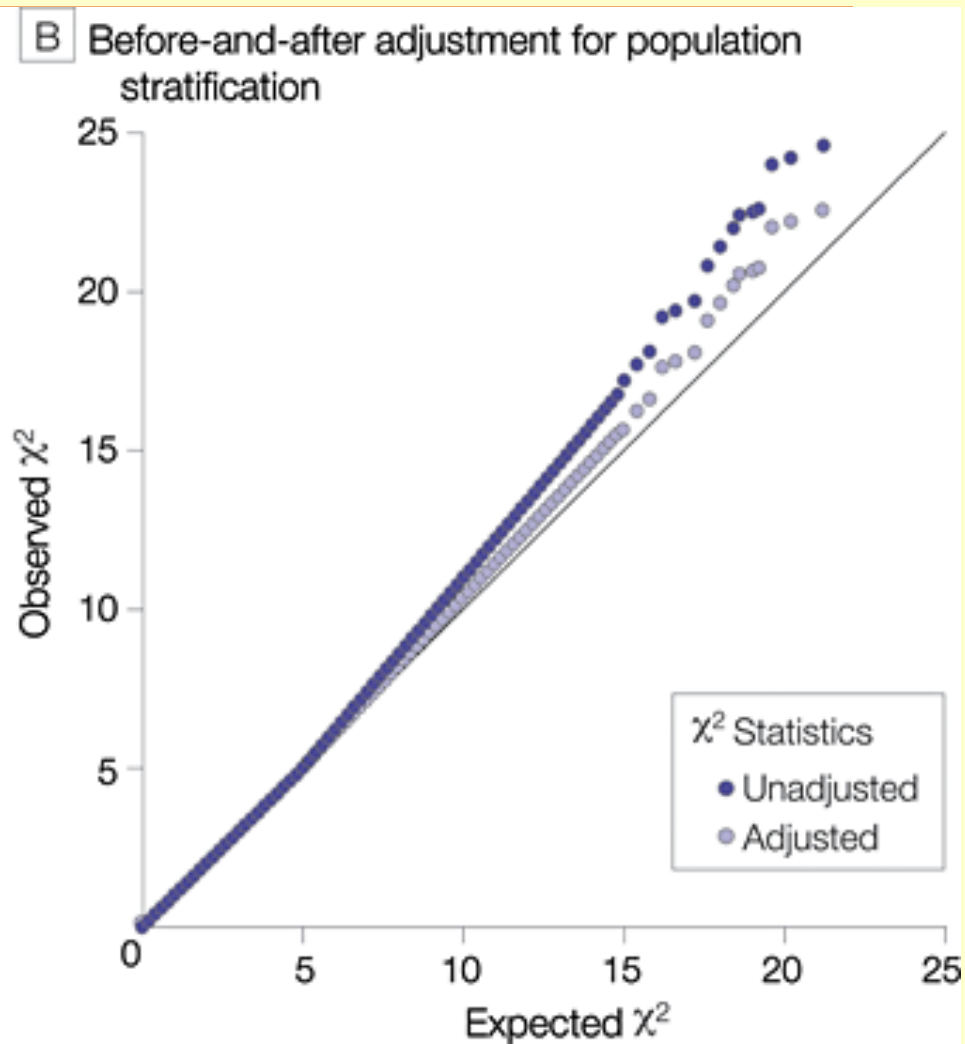
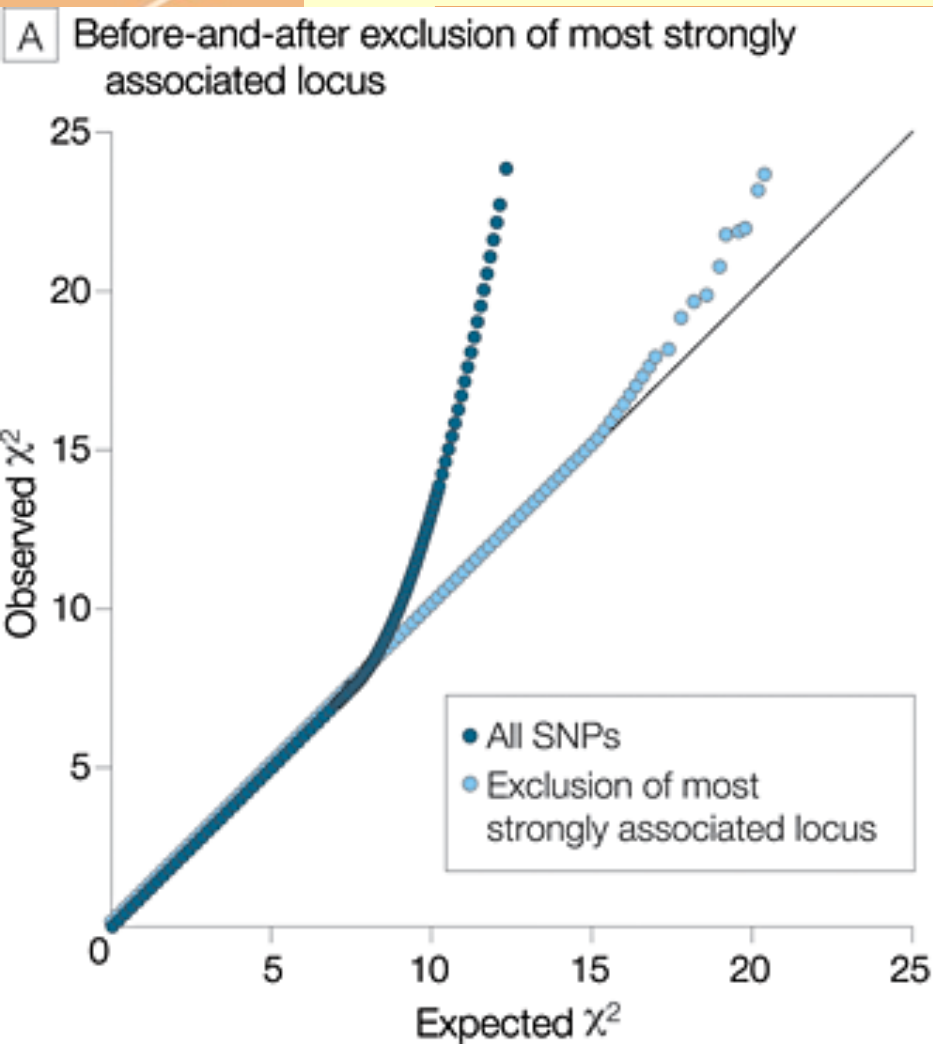
Abbreviation: SNP, single-nucleotide polymorphism.

<sup>a</sup>Based on hypothetical data.

<sup>b</sup>Five SNPs associated with disease.

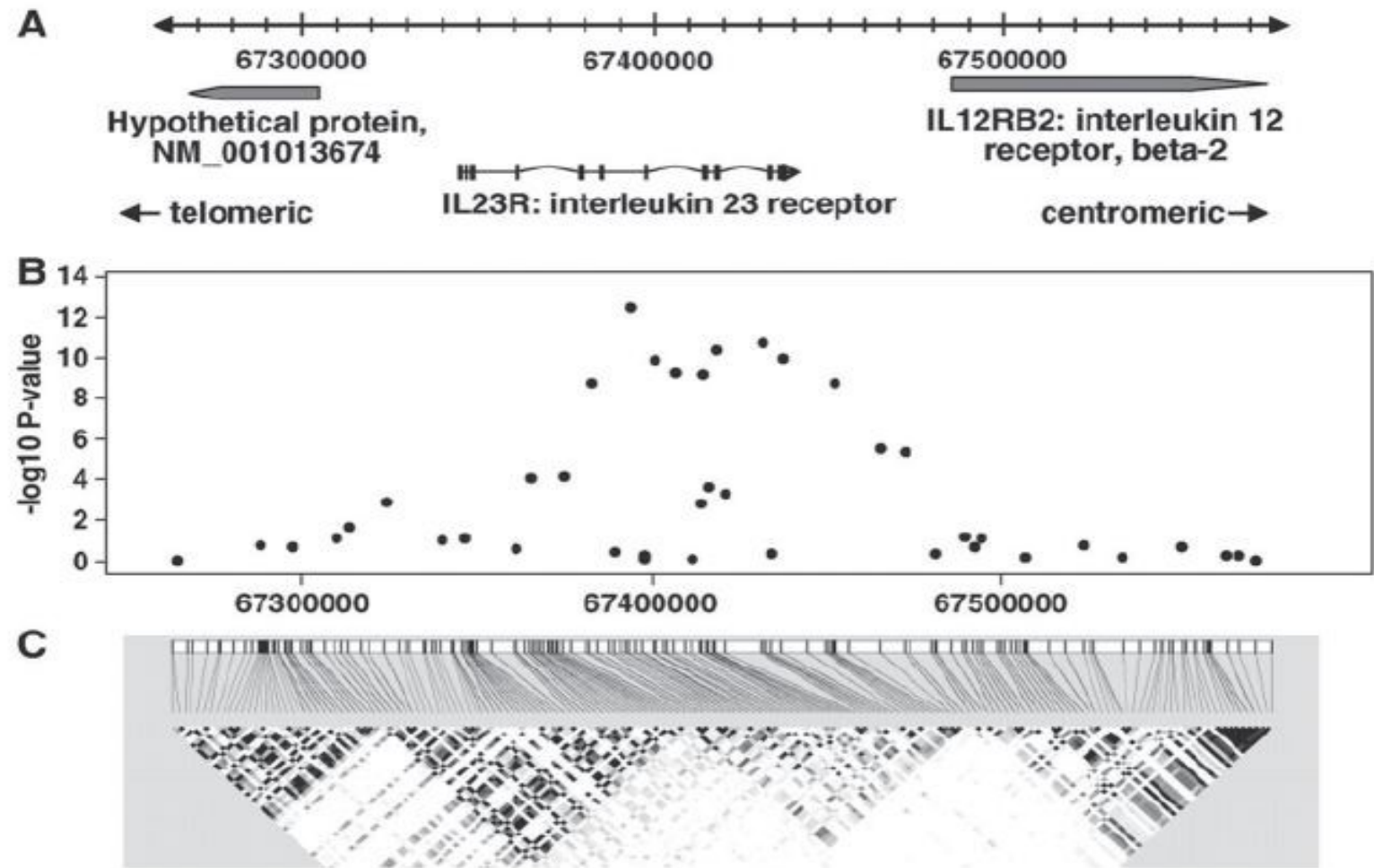
<sup>c</sup>Two SNPs associated with disease.

# Hypothetical Quantile-Quantile Plots in Genome-wide Association Studies



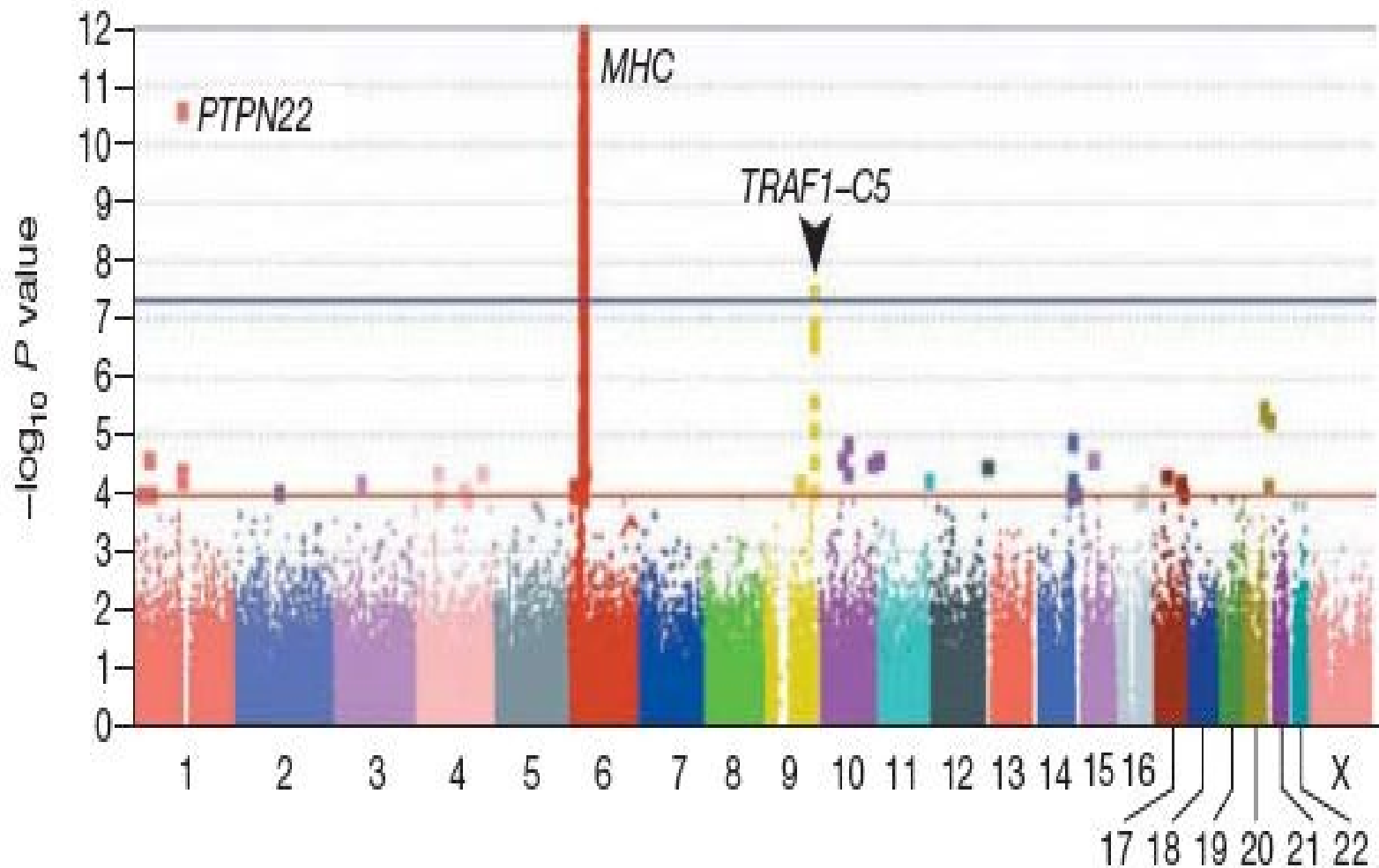
# Interleukin 23R & Inflammatory Bowel Disease

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



# Genome-Wide Associations in Rheumatoid

**Figure 3.** Genome-wide Association Findings in Rheumatoid Arthritis



### Number and Frequency of rs6983267 Alleles in Colorectal Cancer

### Number and Frequency of rs6983267 Genotypes in Colorectal Cancer

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

Abbreviation: OR, odds ratio.

<sup>a</sup>Data are hypothetical; adapted from Tomlinson et al.<sup>56</sup>

<sup>b</sup>Denotes allelic odds ratio.

<sup>c</sup>Denotes heterozygote odds ratio.

<sup>d</sup>Denotes homozygote odds ratio.



# Ten Basic Questions to Ask About a Genome-wide Association Study Report

---

- 1. Are the cases defined clearly and reliably so that they can be compared with patients typically seen in clinical practice?
- 2. Are case and control participants demonstrated to be comparable to each other on important characteristics that might also be related to genetic variation and to the disease?
- 3. Was the study of sufficient size to detect modest odds ratios or relative risks (1.3-1.5)?
- 4. Was the genotyping platform of sufficient density to capture a large proportion of the variation in the population studied?
- 5. Were appropriate quality control measures applied to genotyping assays, including visual inspection of cluster plots and replication on an independent genotyping platform?
- 6. Did the study reliably detect associations with previously reported and replicated variants (known positives)?
- 7. Were stringent corrections applied for the many thousands of statistical tests performed in defining the *P value for significant associations*?
- 8. *Were the results replicated in independent population samples?*
- 9. *Were the replication samples comparable in geographic origin and phenotype definition, and if not, did the differences extend the applicability of the findings?*
- 10. *Was evidence provided for a functional role for the gene polymorphism identified?*





**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:**  
Genetics and Development

**Phone:** 214-648-6724

**Mailing Address:**

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**Fax:** 214-648-7539

**Research Interests:**

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

**Lab Personnel**

**Recent Publications:**

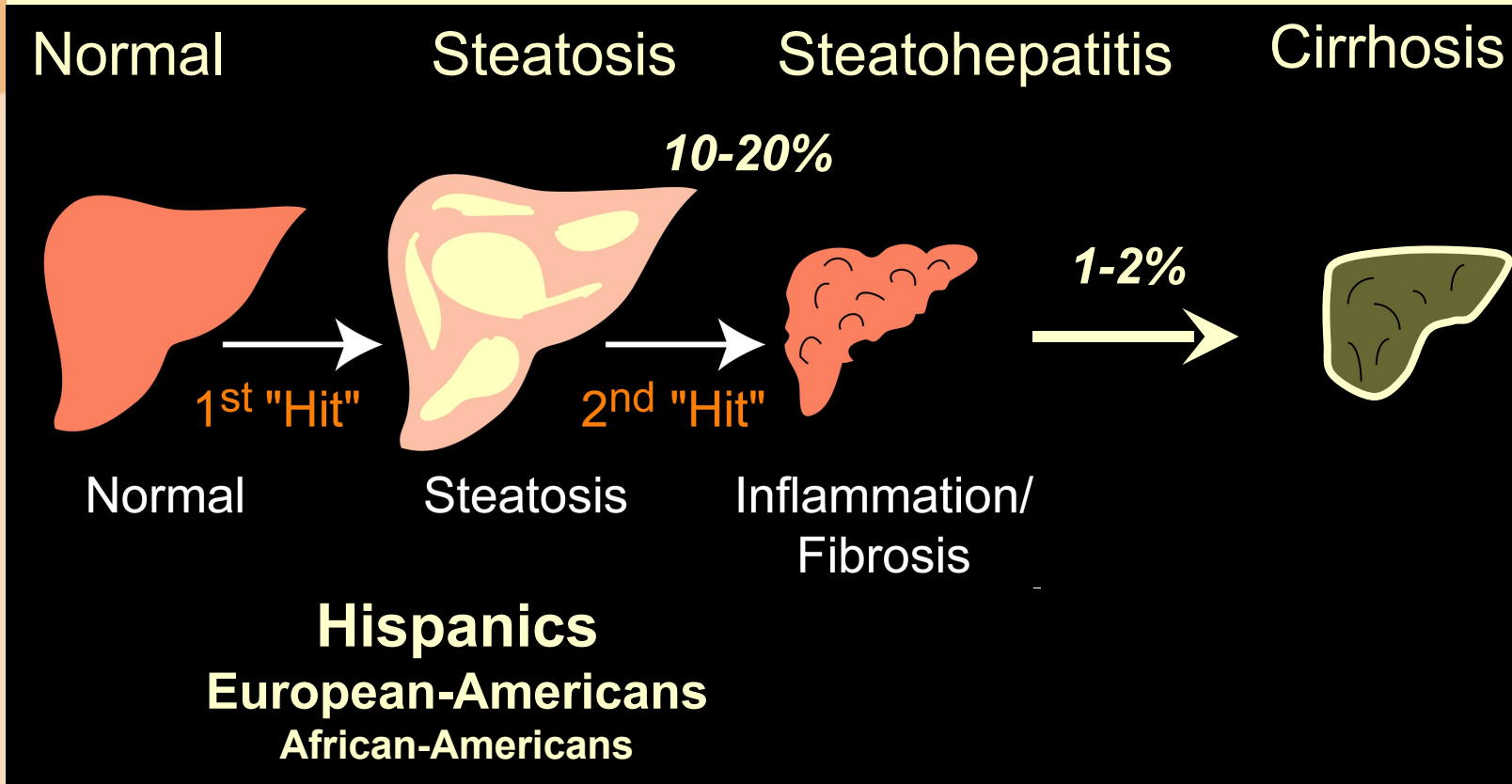
1. Romeo S., Pennacchio L.A., Fu Y., Boerwinkle E., Tybjaerg-Hansen A., Hobbs H.H., Cohen, JC (2007) Population-based resequencing of ANGPTL4 uncovers variations that reduce triglycerides and increase HDL in Caucasians. *Nat. Genet.* 39:513-516.
2. McPherson R., Pertsemlidis A., Kavaslar N., Stewart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

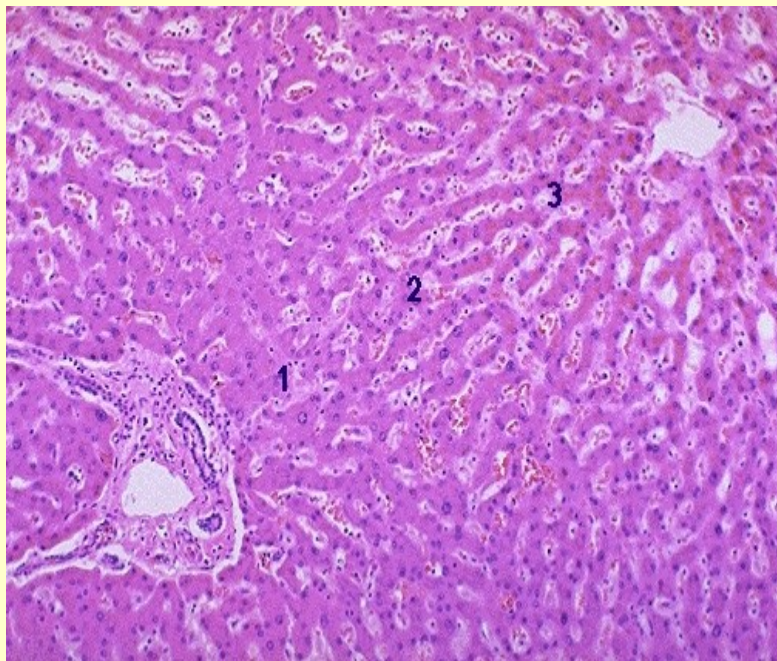
# Do genetic differences between ethnic groups contribute to differences in fatty liver disease?



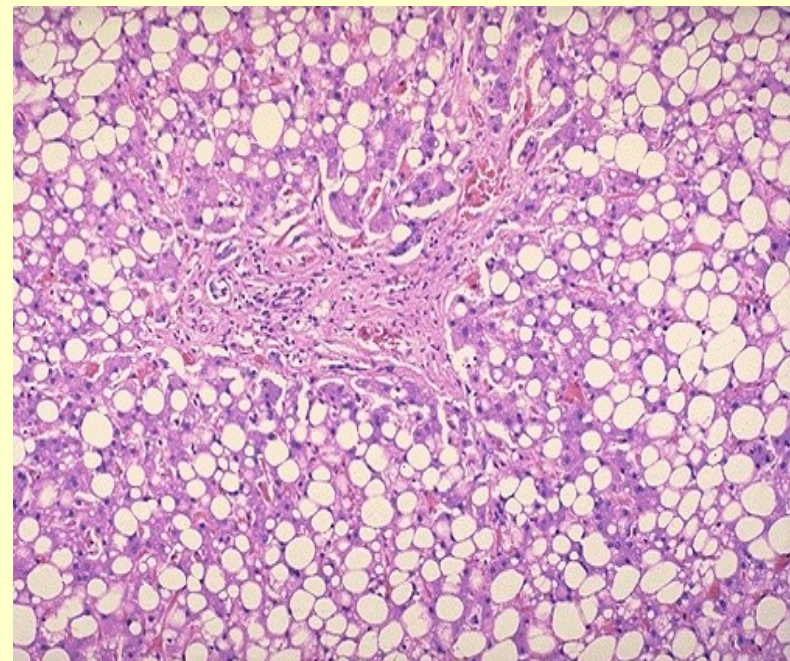
# Hepatic Steatosis

---

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 nonsynonymous SNPs

Chip-based oligonucleotide hybridization (Perlegen)

Quality filter:  $n = 12,138 \rightarrow 9,229$

Association with hepatic fat, adjusted for ancestry  
(2,270 ancestry informative SNPs)

1,032 African-Americans

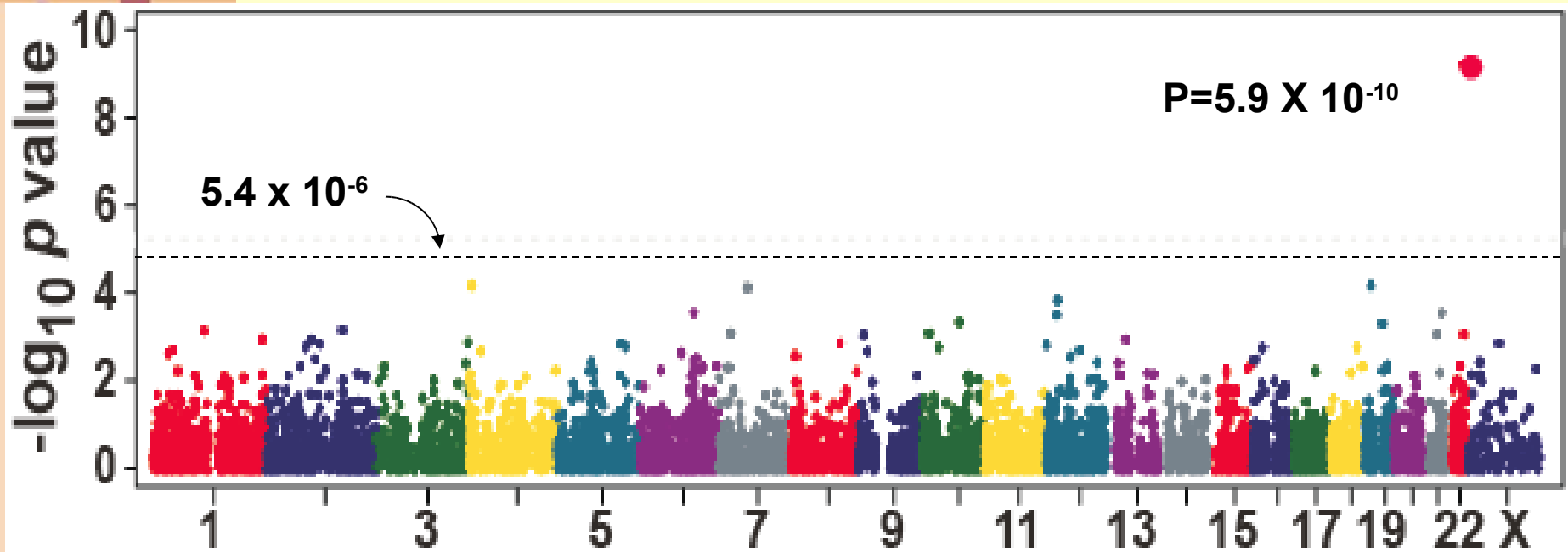
696 European-Americans

383 Hispanics

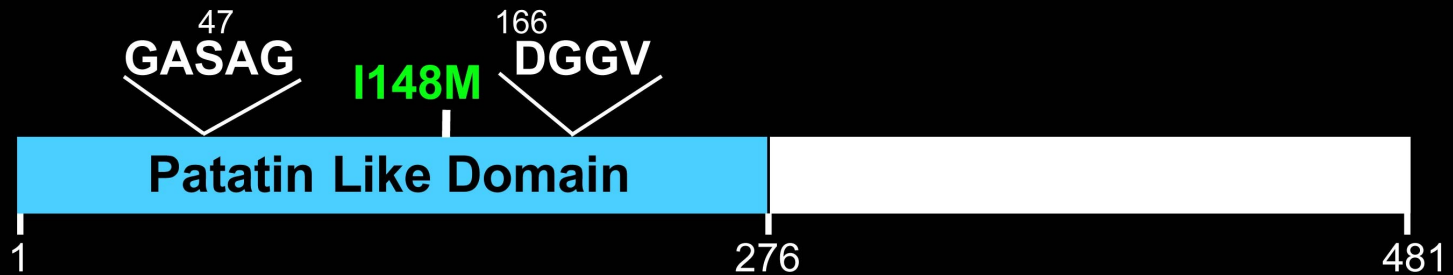
$n = 2,111$

Romeo, et al.(2008) Genetic Variation in PNPLA3 confers susceptib

# Genome-wide Association Study in DHS Non-synonymous SNPs (n = 9,229)



# PNPLA3: A Member of the Patatin-like Phospholipase Family

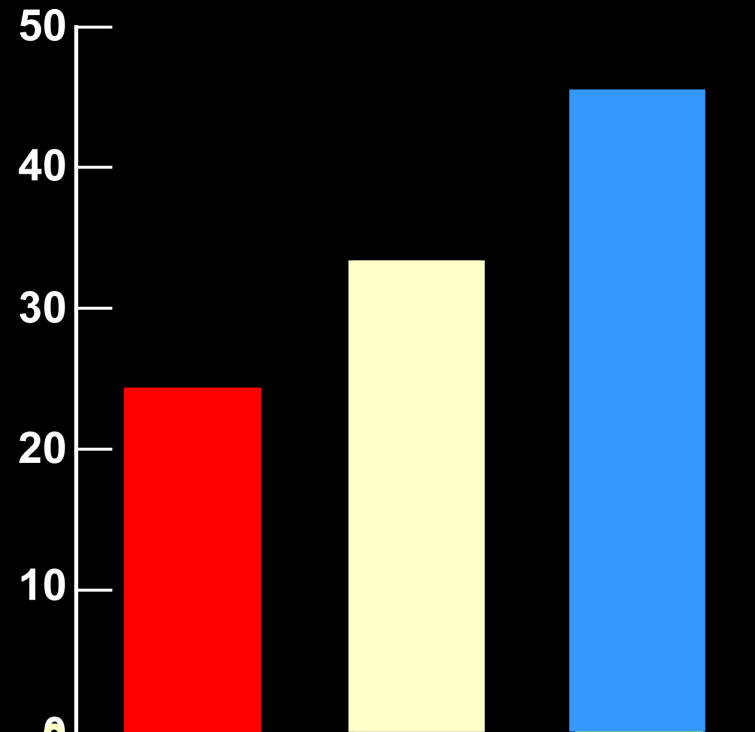


- Resembles patatin: major potato protein
- Nonspecific lipid acyl hydrolase activity (TG>PL)
- Expressed high level in fat & liver
- Increased with feeding (especially carbohydrates)

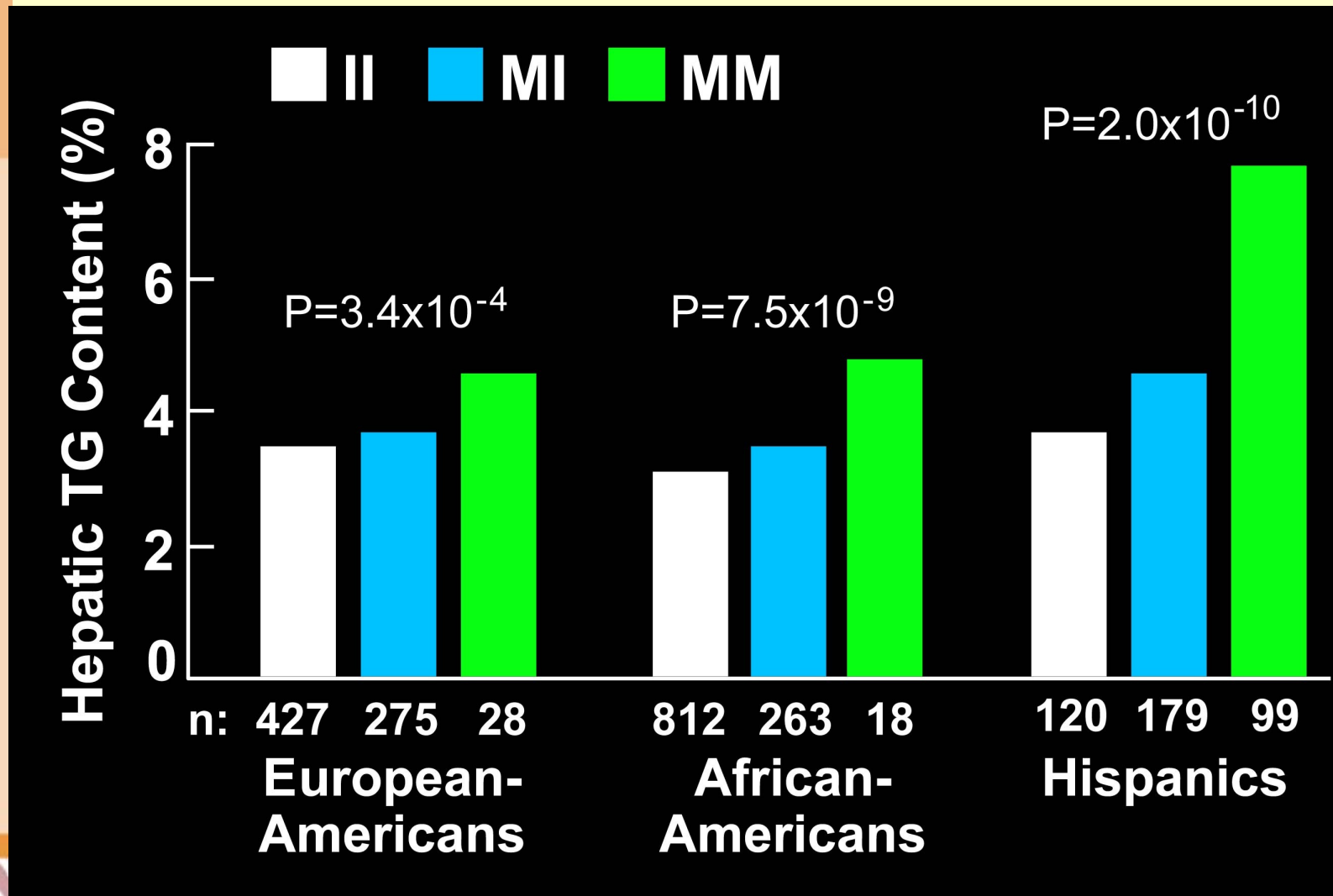
# Ethnic Differences in the Frequency of PNPLA3-I148M

	African-Americans	European-Americans	Hispanics
<b>Minor Allele Frequency</b>	<b>0.17</b>	<b>0.23</b>	<b>0.49</b>

**Prevalence of  
Hepatic Steatosis  
(%)**



# PNPLA3: I148M and Hepatic TG Content

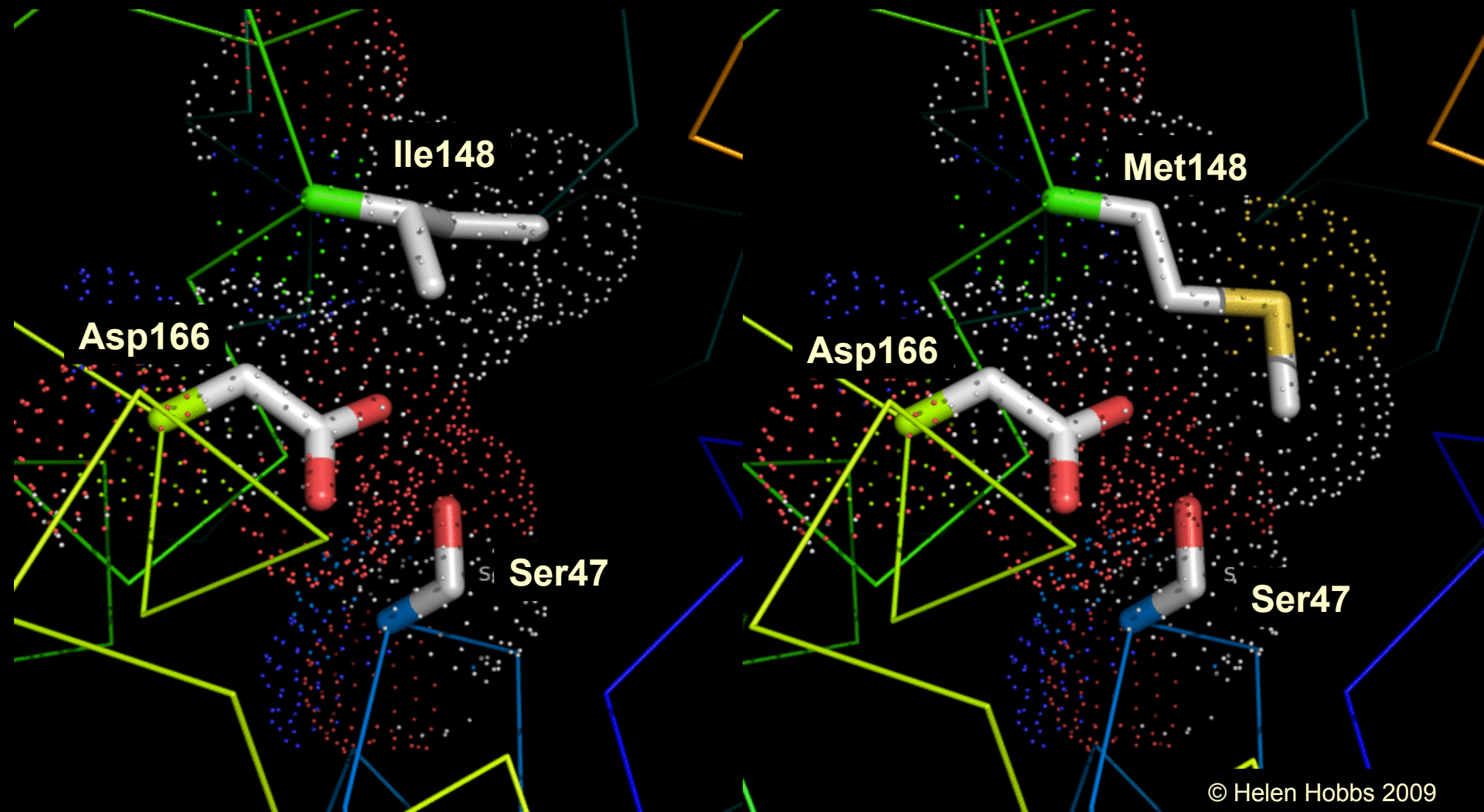




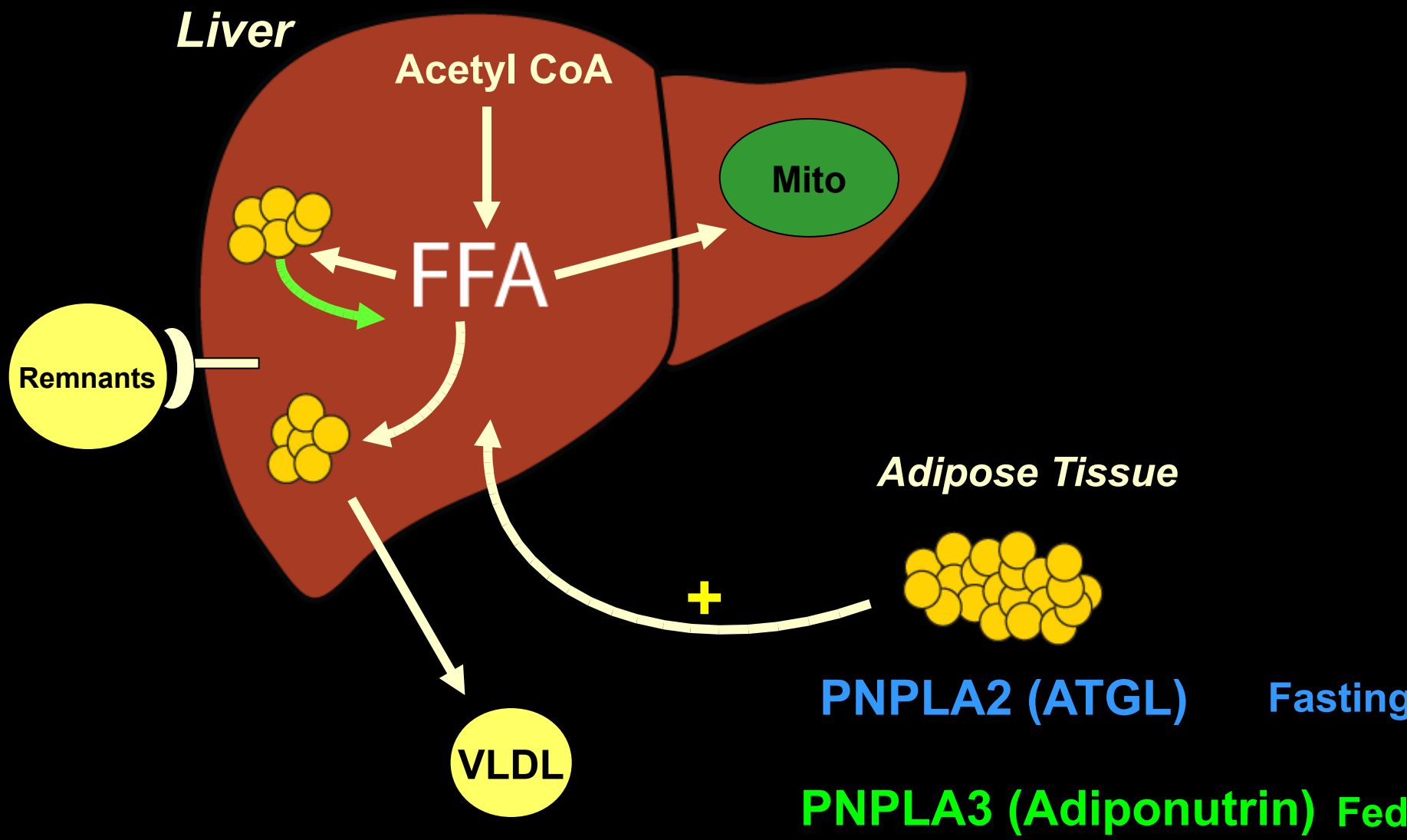
# I148M & Catalytic Dyad of PNPLA3



Patatin Like Domain



# PNPLA3 & Hepatic Triglyceride Metabolism



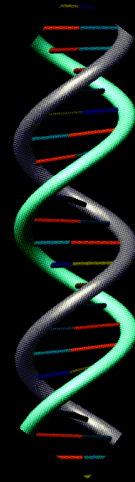
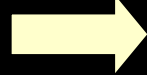
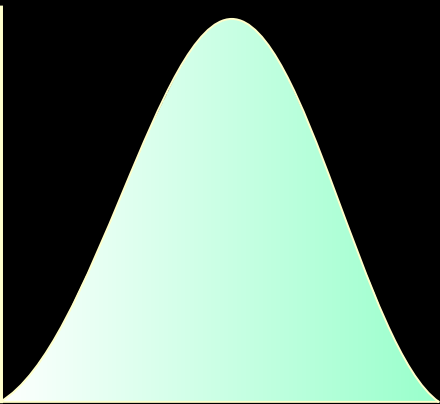
**TRAIT**



**GENE**



**PUBLIC  
HEALTH**



- ***PNPLA3***:  
TG metabolism

- Therapeutic target
- Prevention strategy
- Risk stratification

# DNADirect: Clinical Genetic Testing C



PROFESSIONALS Register Login

## DNADirect Clinical Genetic Testing Online

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### New! 3 Gene Panel for Drug Response

When it comes to medications, one size doesn't fit all. Our 3 Gene Drug Response Panel can predict how you respond to many of the most commonly prescribed drugs. [Learn More >>](#)

### Family History

If it runs in your family it doesn't have to be your destiny. Find out if genes are really involved - and what you can do about them. [Learn More >>](#)

### DNAarchive

As seen in Science December 2007  
*preserving genetic history for the future*  
Home DNA Storage based on revolutionary new technology >>

### Fertility & Pregnancy

Looking for carrier screening? Having difficulty getting pregnant? [Learn More >>](#)

### Signs & Symptoms

Do you have a chronic, undiagnosed condition? It could be genetic. [Learn More >>](#)

### Ethnic Risks

Are you more or less likely to carry certain disease-related genes? [Learn More >>](#)

### Lifestyle Issues

If you carry certain genes, you can take steps to live longer and healthier. [Learn More >>](#)

### 5 Questions You Should Ask

The National Society of Genetic Counselors recommends you ask 5 important questions before genetic testing. DNA Direct can help you answer them. [Learn More >>](#)

### Senate Passes GINA

The Genetic Information Non-Discrimination Act was passed on April 24, 2008. When signed into law, consumers will be reassured that their genetic information is protected against misuse by employers and insurance companies. [Learn More >>](#)

### MEDICAL GENETIC TESTING

- Alpha-1 Antitrypsin Deficiency
- Ashkenazi Jewish Carrier Screening
- Blood Clotting Disorders
- Breast & Ovarian Cancer
- Colon Cancer Screening
- Cystic Fibrosis
- Diabetes Risk - deCODE T2™
- Hemochromatosis (Iron Overload)
- Infertility
- Recurrent Pregnancy Loss

### DRUG RESPONSE TESTING

- 2D6, 2C9 & 2C19 Gene Tests
- Warfarin Response
- Tamoxifen 2D6

### ANCESTRY, ETHNICITY & PATERNITY

- Ancestry & Ethnicity Testing
- Paternity Testing

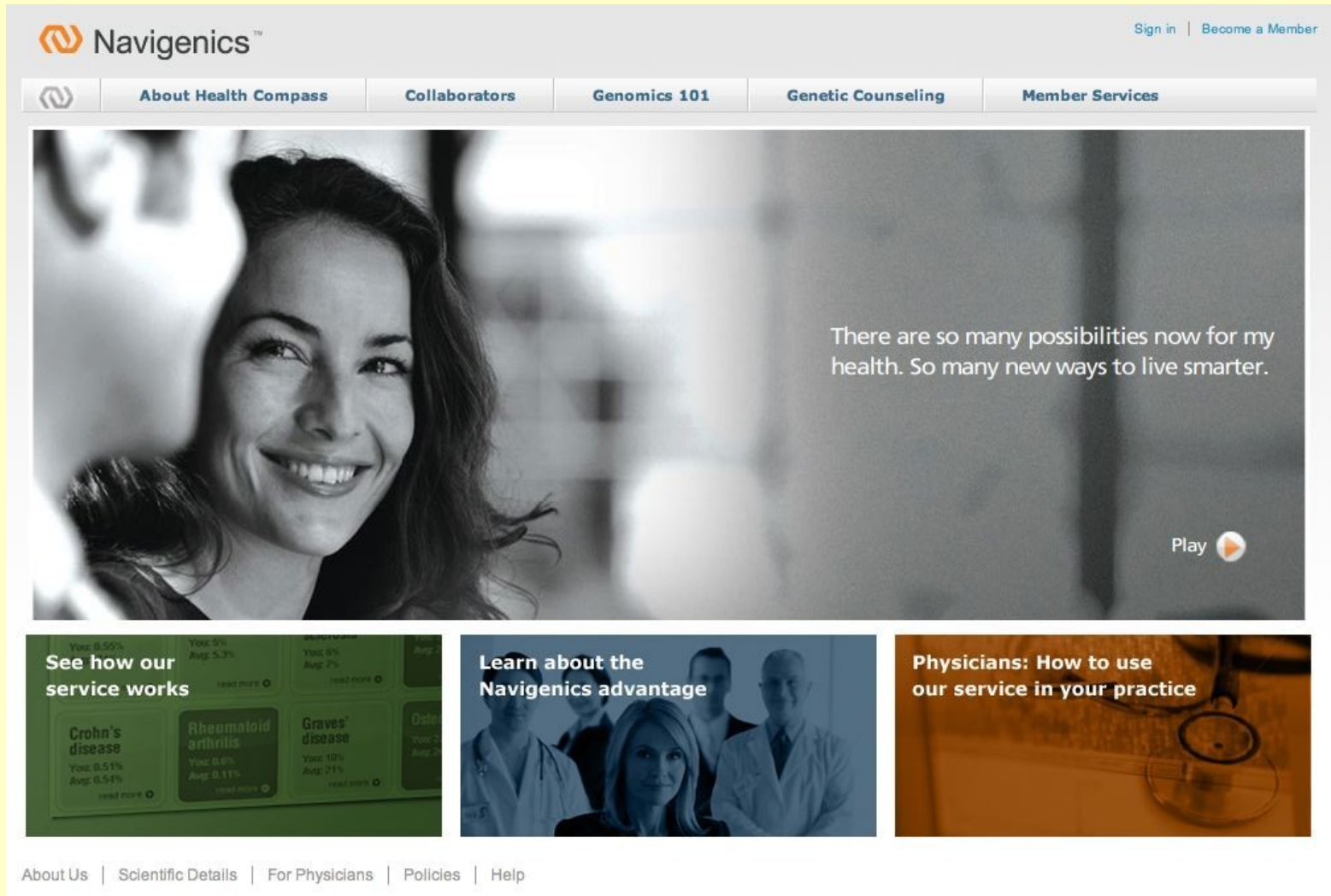

### HOME DNA STORAGE

- DNA Archive™

### PERSONAL GENOME COUNSELING

- Genome Scans
- Whole-Genome Sequencing

# Navigenics



The screenshot shows the Navigenics website homepage. At the top left is the Navigenics logo. On the top right, there are links for "Sign in" and "Become a Member". Below the logo is a navigation menu with five items: "About Health Compass", "Collaborators", "Genomics 101", "Genetic Counseling", and "Member Services". The main content area features a large video player with a black and white image of a smiling woman. The video title is "There are so many possibilities now for my health. So many new ways to live smarter." and it includes a "Play" button. Below the video are three promotional tiles: "See how our service works" (with sub-tiles for Crohn's disease, Rheumatoid arthritis, and Graves' disease), "Learn about the Navigenics advantage" (with an image of a group of people), and "Physicians: How to use our service in your practice" (with an image of a stethoscope). At the bottom of the page is a footer with links for "About Us", "Scientific Details", "For Physicians", "Policies", and "Help".



# 23andMe



genetics just got personal.

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[our service](#)

[genetics 101](#)

[for the experts](#)

[store](#)

[about us](#)

[order now](#) [try a demo](#)

1866: Gregor Mendel discovers the laws of inheritance.

200,000 years ago: *Homo sapiens* walks the Earth.

2003: The Human Genome Project maps a single person's genome.

## 2007: 23andMe introduces the first Personal Genome Service.

Unlock the secrets of your own DNA. Today.

175,000 years ago: The mother of all present-day humans is born in Africa.

1953: Watson and Crick uncover the double-helix structure of DNA.

Welcome to 23andMe, a web-based service that helps you read and understand your DNA. After providing a saliva sample using an at-home kit, you can use our interactive tools to shed new light on your distant ancestors, your close family and most of all, yourself.

[Sign up for our Email Newsletter](#)

### news What's new at 23andMe

**Apr 23, 2008:** 23andMe redesigns its Personal Genome Service and adds two new Gene Journal topics. [Try a demo](#) or [order our service](#) today!

### Gene Journal



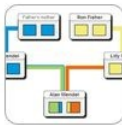
What do your genes say about you?

### Ancestry



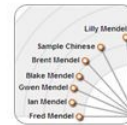
Who were your ancient ancestors?

### Family Inheritance



Do you have your mother's sense of taste?

### Genome Labs



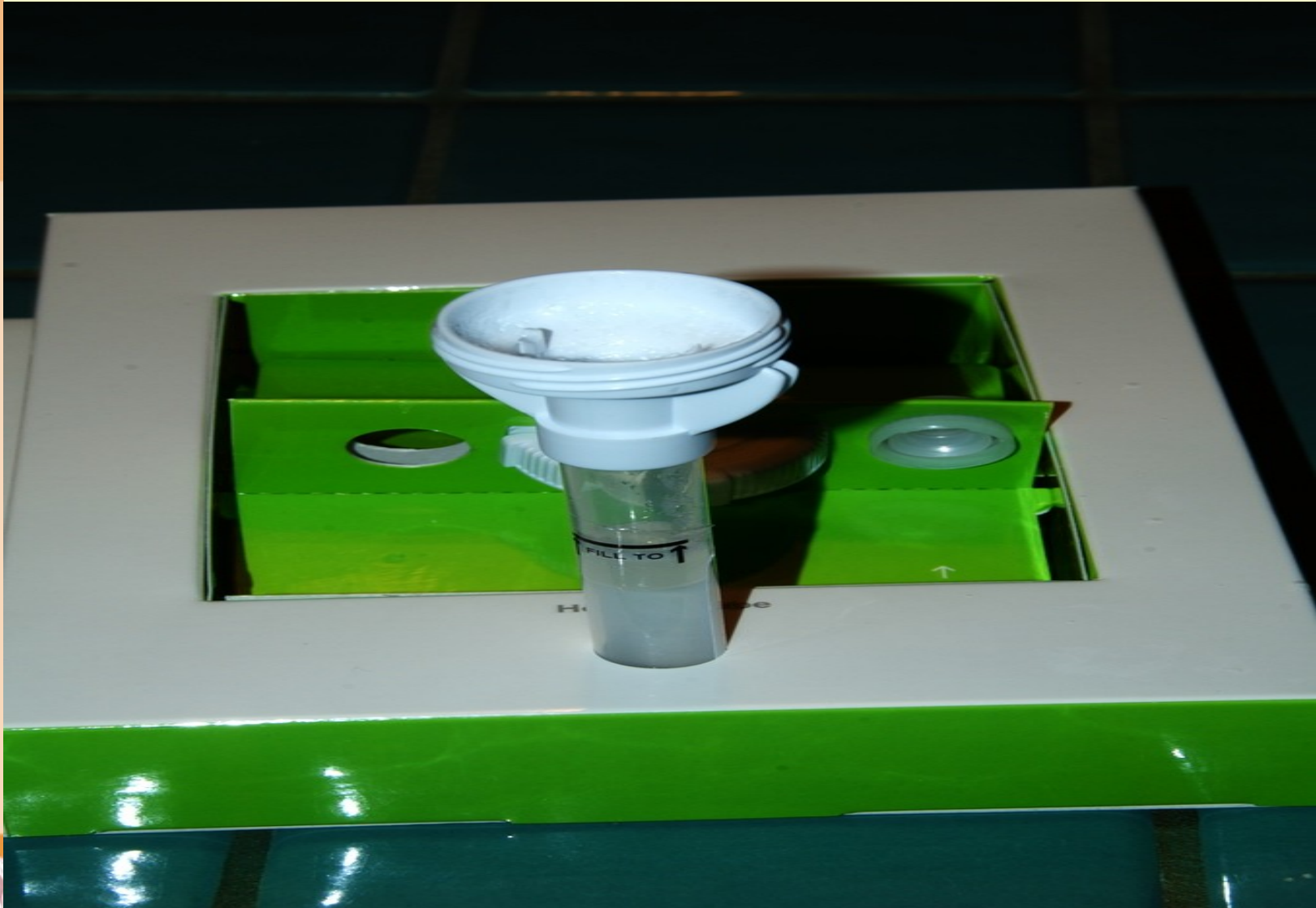
Would you like to search your genome?



# 23andMe Kit



# 23andMe Spittoon





# 23andMe Sample Tube

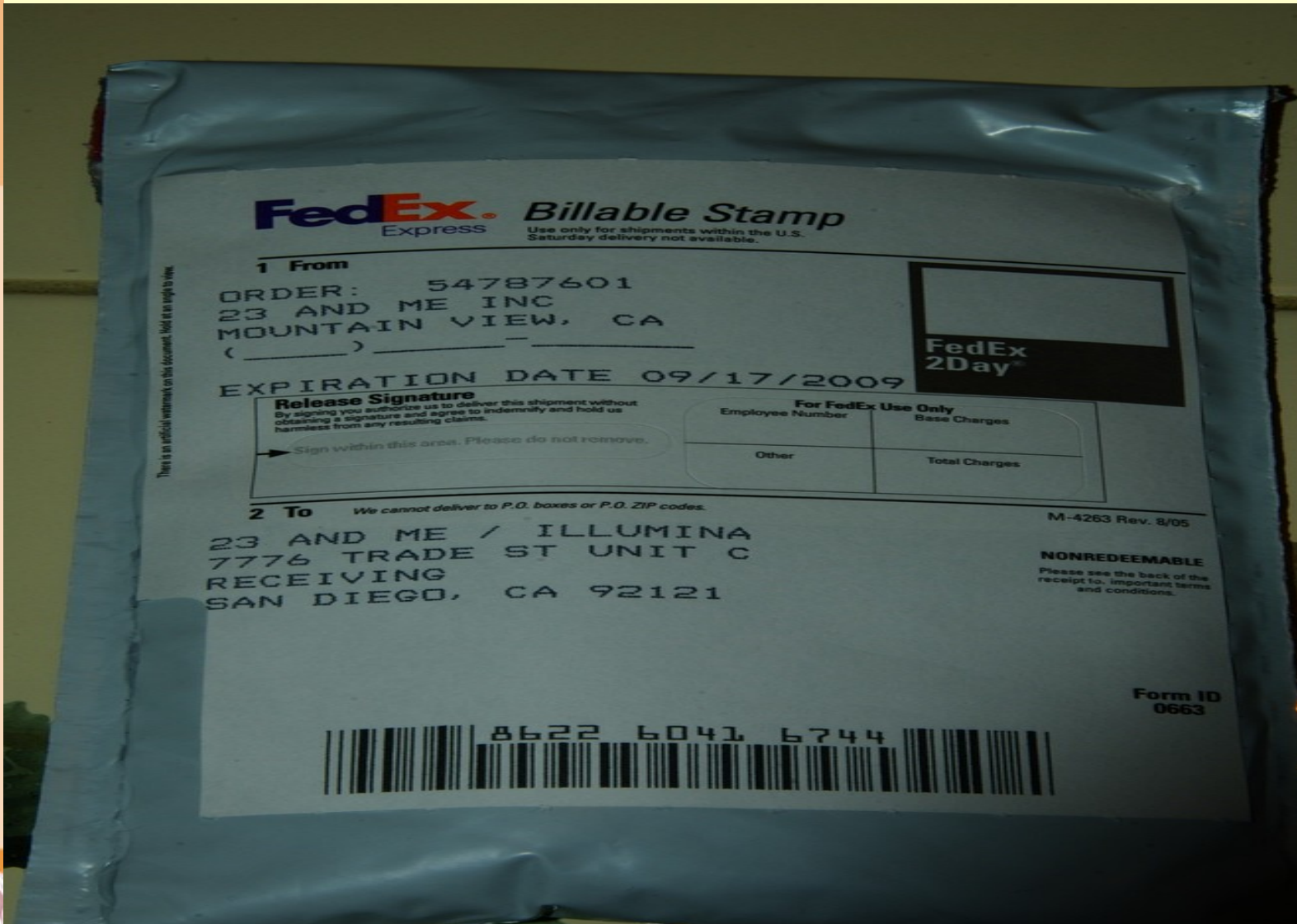


# 23andMe Tube in Envelope





# 23andMe FedEx Mailer



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# welcome to you.

## New at 23andMe



## You've got relatives.

Introducing **Relative Finder**, 23andMe's premier tool to help you explore your ancestry.

Connect with living relatives and discover whole new branches of your family tree!

[Visit Relative Finder](#)



New articles added to **My Health and Traits**.

- Oral Contraceptives, Hormone Replacement Therapy and Risk of Venous Thromboembolism
- Drinking, Smoking, and Esophageal Cancer
- Response to Hepatitis C Treatment

[» view all reports](#)



Three new surveys added to **23andWe**.

- H1N1 Flu (Swine Flu)
- Longevity
- Sports Injuries

[» view all surveys](#)



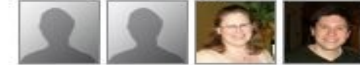
Support disease research through **Research Revolution**.

Join our most ambitious effort yet to let our customers direct and advance human knowledge of how genes and environment affect health. Any 23andMe customer can vote to support research.

[» vote!](#)

## Currently Shared Genome

Extended Level (5)



[» Edit sharing preferences](#)

## Help/Contact Us

- See our [Frequently Asked Questions](#). For other questions or feedback, please email [help@23andme.com](mailto:help@23andme.com).



Need more kits? [Visit the store](#)

## Before you view your data...

Knowing your genetic information can have serious and unexpected consequences. Consider the following before you view your genetic data regarding Breast/Ovarian Cancer:

- **The influence of environmental factors:** The risk for breast and ovarian cancer is only partially determined by genetics. Environmental factors, including but not limited to diet and lifestyle, also play significant roles.
- **This is not the entire genetic picture:** The mutations reported by 23andMe account for only a portion of the entire genetic contribution to breast and ovarian cancer. There are other known mutations, including many in BRCA1 and BRCA2, for which 23andMe does not provide data. If you are concerned about these, you should consult a medical professional about taking specific tests that offer a more complete assessment of these two genes. There are also unidentified genetic factors that affect breast cancer risk.
- **Your ancestry affects your chances of having these mutations:** Though extremely rare in the general population, these mutations are much more common in families with Ashkenazi Jewish ancestry.
- **The mutations described here cannot predict definitively whether you will develop breast or ovarian cancer:** Though having these mutations greatly increases the risk for both diseases, many people who have them will never get the disease. Conversely, lacking these mutations does not substantially reduce your breast or ovarian cancer risk.
- **These mutations are also relevant to men:** Although men are not at risk for ovarian cancer and are at very low risk for breast cancer, BRCA1 and BRCA2 mutations can increase a man's risk for prostate cancer and male breast cancer. Men who carry one of these mutations have a 50% chance of passing it on to their daughters, who would then be at increased risk for breast and ovarian cancer. The mothers and sisters of men who carry one of these mutations also have a 50% chance of being carriers.
- **The wishes of members in your account:** You are about to unlock results for everyone in your account, including the following individuals:

### Douglas Brutlag

If any of these people do not want to know their genetic status with regard to Breast/Ovarian Cancer, it is your responsibility to ensure this information is not revealed to them or others. You may also request to transfer a profile to a separate account by emailing [help@23andme.com](mailto:help@23andme.com).

**If, after considering these points, you still wish to view your data, click [here](#).**

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**Disease Risks (12)** ?

📊	Type 1 Diabetes
📊	Type 2 Diabetes
📊	Rheumatoid Arthritis
📊	Crohn's Disease
📊	Age-related Macular Degeneration

[See all 12 risk reports...](#)

**Traits (10)** ?

Alcohol Flush Reaction	✖	Does Not Flush
Bitter Taste Perception	✖	Can Taste
Earwax Type	✖	Wet
Eye Color	✖	Likely Brown
Lactose Intolerance	✖	Likely Tolerant

[See all 10 traits...](#)

**Carrier Status (21)** ?

Alpha-1 Antitrypsin Deficiency	Va
BRCA Cancer Mutations (Selected)	Va
Bloom's Syndrome	Va
Canavan Disease	Va
Connexin 26-Related Sensorineural Hearing Loss	Va

[See all 21 carrier st](#)

**Drug Response (8)** ?

Clopidogrel (Plavix®) Efficacy	Gr
Alcohol Consumption, Smoking and Risk of Esophageal Cancer <span style="background-color: #f4a460; padding: 2px;">new</span>	Ty
Response to Hepatitis C Treatment <span style="background-color: #f4a460; padding: 2px;">new</span>	Ty
Abacavir Hypersensitivity	Ty
Fluorouracil Toxicity	Ty

[See all 8 drug respo](#)

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The genotyping services of 23andMe are performed in LabCorp's CLIA-certified laboratory. The tests have not been cleared or approved by the FDA but have been analytically validated according to CLIA standards.

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### Elevated Risk ?

Name	Absolute Risk ?	Relative Risk ?	Last Update
No diseases in this category.			

### Decreased Risk ?

Name	Absolute Risk ?	Relative Risk ?	Last Update
<a href="#">Celiac Disease</a>	0.03% 	0.26	Jul 7, 2013
<a href="#">Age-related Macular Degeneration</a>	2.3% 	0.33	May 21, 2013
<a href="#">Crohn's Disease</a>	0.3% 	0.50	Jul 16, 2013
<a href="#">Rheumatoid Arthritis</a>	1.4% 	0.59	Aug 6, 2013
<a href="#">Type 2 Diabetes</a>	17% 	0.70	Feb 2, 2013
<a href="#">Type 1 Diabetes</a>	0.8% 	0.78	Jul 30, 2013

### Typical Risk ?

Name	Absolute Risk ?	Relative Risk ?	Last Update
<a href="#">Prostate Cancer</a> 	18% 	1.03	Oct 22, 2013
<a href="#">Parkinson's Disease</a>	1.6% 	0.98	Sep 29, 2013
<a href="#">Venous Thromboembolism</a>	12% 	0.96	Jul 30, 2013
<a href="#">Psoriasis</a>	9.9% 	0.87	Jul 7, 2013
<a href="#">Atrial Fibrillation</a>	23% 	0.85	Oct 29, 2013
<a href="#">Breast Cancer</a>  <a href="#">update</a> 	Not Applicable		Feb 18, 2013

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## research reports

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Research Reports give you information from research that has not yet gained enough scientific consensus to be included in our Clinical Reports. It also includes established research that does not have a dramatic influence on a person's risk for a disease.

Sort groups by: [Name](#) | [Research Confidence](#) | [Last Updated Date](#)

### Elevated Risk ?

Name	Research Confidence	Last Updated
● Colorectal Cancer	★★★★★	Jul 16, 2012
● Exfoliation Glaucoma	★★★★★	Jun 25, 2012
● Restless Legs Syndrome	★★★★★	Jul 16, 2012
● Abdominal Aortic Aneurysm	★★★★	Nov 21, 2011
● Ankylosing Spondylitis	★★★★	Feb 21, 2012
● Asthma	★★★★	May 12, 2012
● Brain Aneurysm	★★★★	Nov 21, 2011
● Cellac Disease: Preliminary Research	★★★★	Apr 9, 2012
● Chronic Lymphocytic Leukemia	★★★★	Nov 21, 2011
● Neuroblastoma	★★★★	May 9, 2012
● Tuberculosis	★★★★	Apr 23, 2012
● Cleft Lip and Cleft Palate	★★★	Jun 18, 2012
● Developmental Dyslexia	★★★	Feb 21, 2012
● Gout	★★★	Apr 21, 2012



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Name	Status ▾	Last Up
<a href="#">Alpha-1 Antitrypsin Deficiency</a>	Variant Absent	Apr 9
<a href="#">BRCA Cancer Mutations (Selected)</a>	Variant Absent	Feb 12
<a href="#">Bloom's Syndrome</a>	Variant Absent	Jan 7
<a href="#">Canavan Disease</a>	Variant Absent	Nov 19
<a href="#">Connexin 26-Related Sensorineural Hearing Loss</a>	Variant Absent	Nov 19
<a href="#">Cystic Fibrosis</a>	Variant Absent	Nov 19
<a href="#">Factor XI Deficiency</a>	Variant Absent	Nov 19
<a href="#">Familial Dysautonomia</a>	Variant Absent	Nov 19
<a href="#">Fanconi Anemia (FANCC-related)</a>	Variant Absent	Nov 19
<a href="#">G6PD Deficiency</a>	Variant Absent	Aug 27
<a href="#">Gaucher Disease</a>	Variant Absent	Nov 19
<a href="#">Glycogen Storage Disease Type 1a</a>	Variant Absent	Jan 7
<a href="#">Hemochromatosis</a>	Variant Absent	Dec 18
<a href="#">Limb-girdle Muscular Dystrophy</a>	Variant Absent	Nov 19
<a href="#">Maple Syrup Urine Disease Type 1B</a>	Variant Absent	Nov 19
<a href="#">Mucopolidosis IV</a>	Variant Absent	Nov 19
<a href="#">Niemann-Pick Disease Type A</a>	Variant Absent	Nov 19
<a href="#">Rhizomelic Chondrodysplasia Punctata Type 1 (RCDP1)</a>	Variant Absent	Nov 19
<a href="#">Sickle Cell Anemia &amp; Malaria Resistance</a>	Variant Absent	Sep 3
<a href="#">Tay-Sachs Disease</a>	Variant Absent	Nov 19
<a href="#">Torsion Dystonia</a>	Variant Absent	Nov 19

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Name ▲	Outcome	Last Updated
<a href="#">Alcohol Flush Reaction</a> ✕	Does Not Flush	Dec 19, 2007
<a href="#">Bitter Taste Perception</a> ✕	Can Taste	Nov 19, 2007
<a href="#">Earwax Type</a> ✕	Wet	Nov 19, 2007
<a href="#">Eye Color</a> ✕	Likely Brown	Mar 25, 2008
<a href="#">Lactose Intolerance</a> ✕	Likely Tolerant	Nov 19, 2007
<a href="#">Malaria Resistance (Duffy Antigen)</a> ✕	Not Resistant	Feb 28, 2008
<a href="#">Muscle Performance</a> ✕	Likely Sprinter	Nov 19, 2007
<a href="#">Non-ABO Blood Groups</a>	See Report	Mar 25, 2008
<a href="#">Norovirus Resistance</a>	Not Resistant	Jul 23, 2008
<a href="#">Resistance to HIV/AIDS</a>	Not Resistant	Jan 27, 2008

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# 23andMe Maternal Inheritance

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[My Gene Journal \(60\)](#)  
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## maternal line

Your mitochondrial DNA determines your maternal haplogroup. [What is a haplogroup?](#)

**Map**

History

Haplogroup Tree

### Maternal Haplogroup: U5

Locations of haplogroup U5 circa 500 years ago, before the era of intercontinental travel.



Haplogroup U5 arose among early colonizers of Europe around 40,000 years ago; maternal descendants of those early colonizers persist in the region to this day. After the last Ice Age two subgroups of U5 expanded across Europe and into northern Africa and the Near East. Today, one subgroup, U5b1b, is shared by groups as diverse as the northern African desert-dwelling Berbers and the Scandinavian Arctic-dwelling Saami, also known as the Lapps.

**Haplogroup:** U5, a subgroup of [U](#)

**Age:** 40,000 years

**Region:** Europe, Near East, North Africa

**Populations:** Basques, Saami (Lapps) of northern Scandinavia

**Highlight:** Though primarily a European haplogroup, U5 was recently found in mitochondrial DNA extracted from the remains of a 6th-century AD Chinese chieftain.

### Your Family and Friends

[K1a1b1a](#) Simone Brutlag

[U5b2](#) Douglas Brutlag

[L3e](#) Nigerian Man

[D5a2](#) Chinese Man

[D4e2](#) Japanese Man



# 23andMe Paternal Inheritance

## me

- My Gene Journal (60)
- Browse Raw Data

## family & friends

- Compare Genes
- Family Inheritance

## my ancestors

- Maternal Line
- ▶ Paternal Line
- Ancestry Painting
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## paternal line

Your Y chromosome DNA determines your paternal haplogroup. [What is a haplogroup?](#)

- Map**
- History
- Haplogroup Tree

### Paternal Haplogroup: E3b1a

Locations of haplogroup E3b1a circa 500 years ago, before the era of intercontinental travel.



E3b is most common in northern Africa and southern Europe. It arose about 17,000 years ago in eastern Africa and spread into the Mediterranean region after the Ice Age. E3b1a, a subgroup of E3b, expanded out of the Near East 8,000 years ago into northern Africa and southern Europe. Today it is one of the most common haplogroups in those regions.

**Haplogroup:** E3b1a, a subgroup of [E3b](#)

**Age:** 14,000 years

**Region:** Northern Africa, Southern Europe

**Populations:** Berbers, Iberians, Balkans

**Highlight:** Two different migrations brought E3b1a into Europe.

### Your Family and Friends

- [N](#) Chinese Man
- [E3a8a](#) Nigerian Man
- [E3b1a](#) Douglas Brutlag**
- [D2](#) Japanese Man
- [N/A](#) Simone Brutlag



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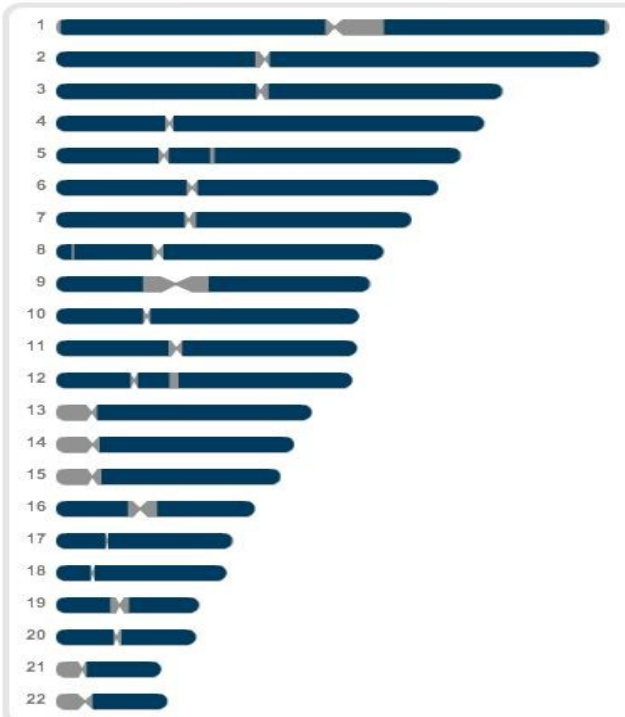
## ancestry painting

Trace the ancestry of your chromosomes, one segment at a time. Last updated [April 23th, 2008](#).





### Chromosome View

-  Solid segments indicate that both chromosomes come from the same geographic region. [See a Cambodian Woman's painting.](#)
-  Dual-colored segments indicate chromosomes from different geographic regions. [See an African American Man's painting.](#)

Select a person:



### Douglas Brutlag

-  Europe 100%
-  Asia 0%
-  Africa 0%
-  Not Genotyped

### Worldwide Examples

Click on the icons in the map below to see sample paintings of individuals from across the globe.



### Tell Me About...

- [...using Ancestry Painting.](#)
- [...the three reference populations.](#)
- [...why only three populations are used.](#)
- [...why it says I'm European/African/Asian when I'm really an American/Australian/South African.](#)
- [...how the percentages are calculated.](#)
- [...where the X and Y chromosomes are.](#)

# Genome-Wide Association Study References

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