# Genomics in Disease Risk Assessment:

## Why is Genomics not Sufficient to Predict Disease Risk on Its Own?


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**Environmental & Occupational Health**

**College of Public Health**

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***International Congress on Bioinformatics and Biomics***

**Kusadasi, May 18-22, 2011**

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# OUTLINE

**Genomics and GWAS**

**GWAS Success Stories**

**A Critique of GWAS**

**Future of Risk Profiling**

# MISSION

**To emphasize the role of the "integromics" as well as the importance of the environment and design**

# Genomics

**Whole genome sequencing**

**Whole exome sequencing**

**CGH array analysis**
**(molecular karyotyping)**

**Genome-wide association study (GWAS)**

**Transcriptomics / Epigenomics**

**(incl miRNAomics)**

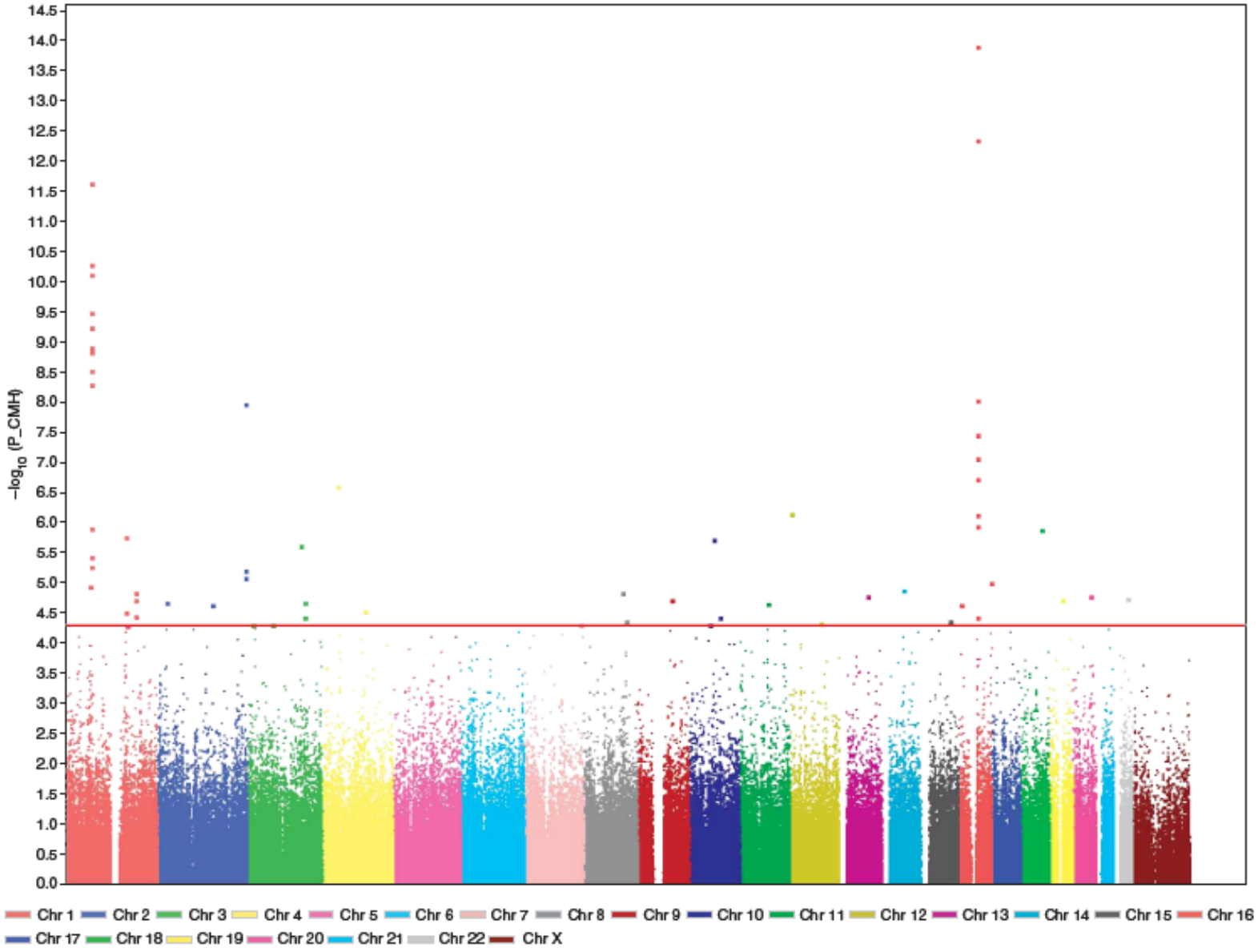


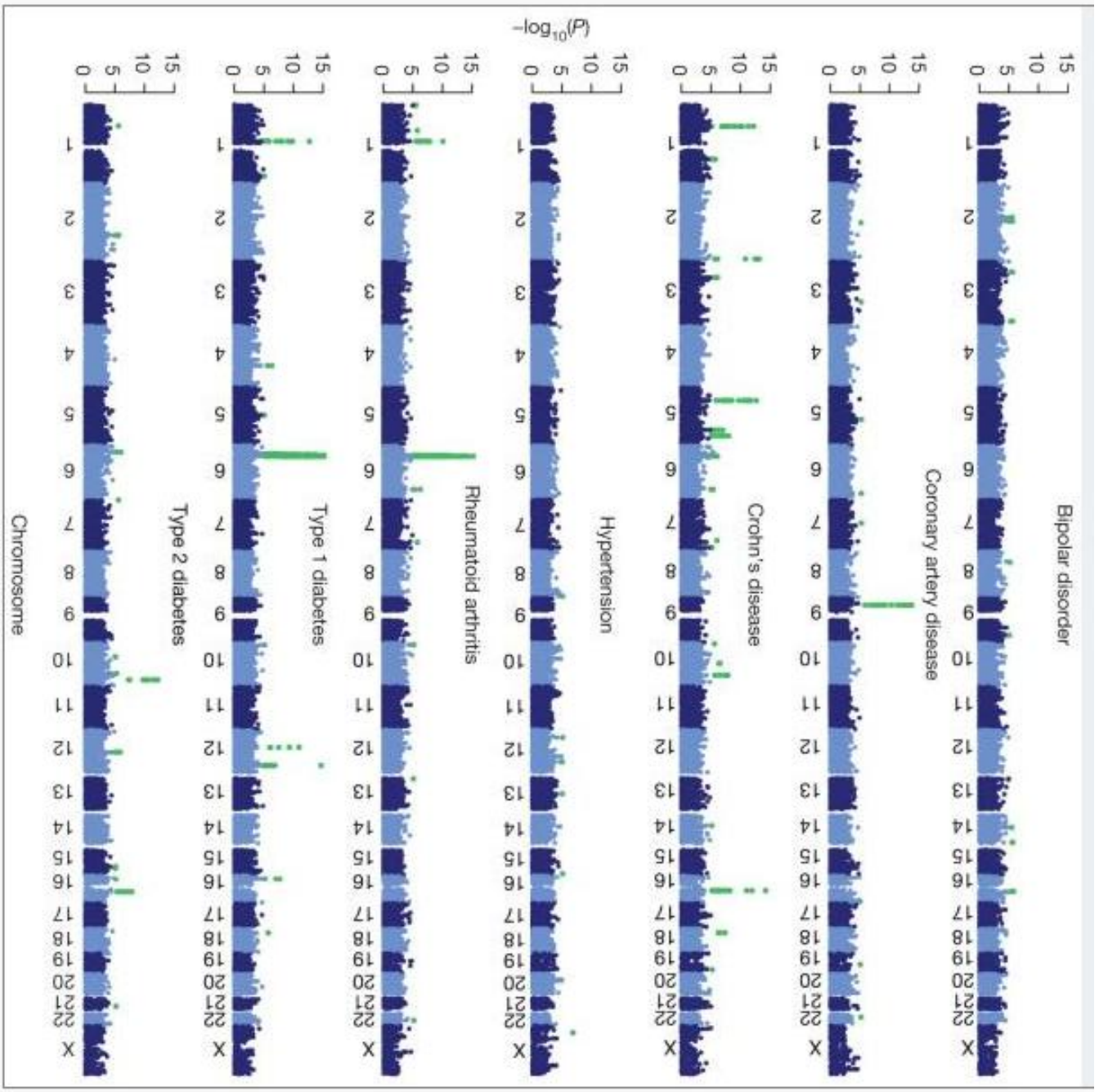

**Figure 1** Genome-wide association results for 946 ileal Crohn disease cases and 977 control samples. Single-marker association results for the combined non-Jewish and Jewish samples using the Cochran-Mantel-Haenszel (CMH) test. Each chromosome is depicted as a different color. The red line indicates the threshold ($P < 5 \times 10^{-5}$) selected to define regions for evaluation in the replication studies. The *P* value thresholds for suggestive and significant associations are $3.28 \times 10^{-6}$ and $1.64 \times 10^{-7}$, respectively, based on a Bonferroni correction for multiple testing. A modest correction factor ($\lambda = 1.056$) is necessary to correct for stratification between cases and controls, but it does not modify the current results.

Vol 447|7 June 2007|doi:10.1038/nature05911 nature

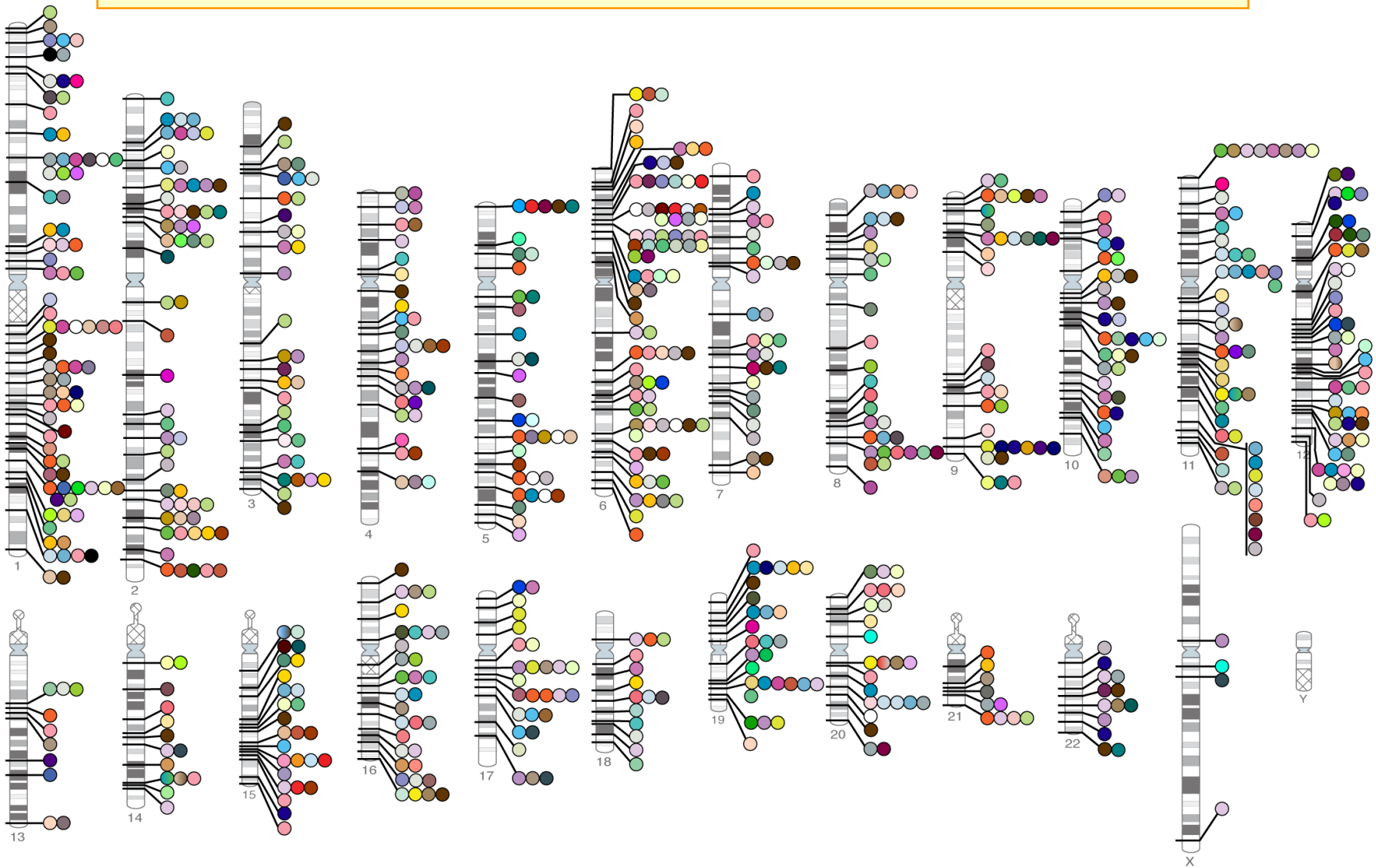
ARTICLES

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

The Wellcome Trust Case Control Consortium*



# Published Genome-Wide Associations through 3/2010: 779 published GWAS at $P < 5 \times 10^{-8}$ for 148 traits

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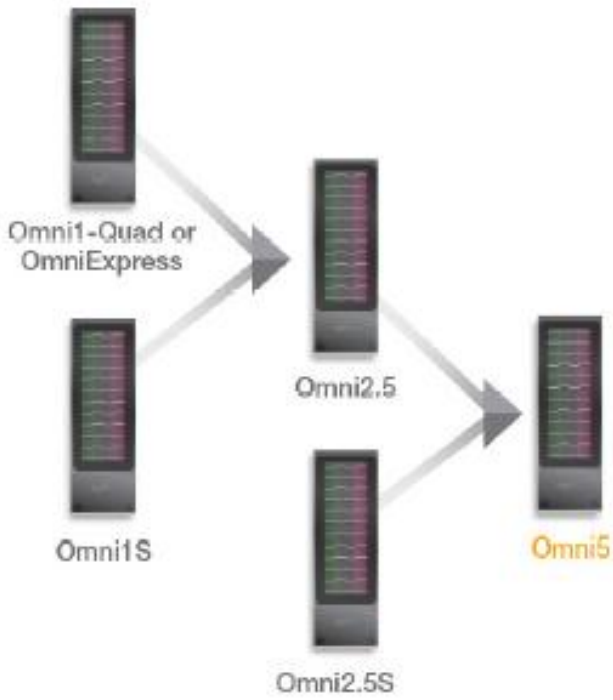
NHGRI GWA Catalog
www.genome.gov/GWAStudies


Acute lymphoblastic leukemia
Adhesion molecules
Adiponectin levels
Age-related macular degeneration
AIDS progression
Alcohol dependence
Alzheimer disease
Amyotrophic lateral sclerosis
Angiotensin-converting enzyme activity
Ankylosing spondylitis
Arterial stiffness
Asthma
Atherosclerosis in HIV
Atrial fibrillation
Attention deficit hyperactivity disorder
Autism
Basal cell cancer
Bipolar disorder
Bilirubin
Bladder cancer
Blond or brown hair
Blood pressure
Blue or green eyes
BMI, waist circumference
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
Eosinophilic esophagitis
Erythrocyte parameters
Esophageal cancer
Essential tremor
Exfoliation glaucoma
F cell distribution
Fibrinogen levels
Folate pathway vitamins
Freckles and burning
Gallstones
Glioma
Glycemic traits
Hair color
Hair morphology
HDL cholesterol
Heart rate
Height
Hemostasis parameters
Hepatitis
Hirschsprung's disease
HIV-1 control
Homocysteine levels
Idiopathic pulmonary fibrosis
IgE levels
Inflammatory bowel disease
Intracranial aneurysm
Iris color
Iron status markers
Ischemic stroke
Juvenile idiopathic arthritis
Kidney stones
LDL cholesterol
Leprosy
Leptin receptor levels
Liver enzymes
LP (a) levels
Lung cancer
Major mood disorders
Malaria
Male pattern baldness
Matrix metalloproteinase levels
MCP-1
Melanoma
Menarche & menopause
Multiple sclerosis
Myeloproliferative neoplasms
Narcolepsy
Nasopharyngeal cancer
Neuroblastoma
Nicotine dependence
Obesity
Open personality
Osteoarthritis
Osteoporosis
Otosclerosis
Other metabolic traits
Ovarian cancer
Pain
Pancreatic cancer
Panic disorder
Parkinson's disease
Periodontitis
Peripheral arterial disease
Phosphatidylcholine levels
Platelet count
Primary biliary cirrhosis
PR interval
Prostate cancer
Protein levels
Psoriasis
Pulmonary funct. COPD
QRS interval
QT interval
Quantitative traits
Recombination rate
Red vs.non-red hair
Renal function
Response to antipsychotic therapy
Response to hepatitis C treatment
Response to statin therapy
Restless legs syndrome
Rheumatoid arthritis
Schizophrenia
Serum metabolites
Skin pigmentation
Speech perception
Sphingolipid levels
Statin-induced myopathy
Stroke
Systemic lupus erythematosus
Telomere length
Testicular germ cell tumor
Thyroid cancer
Tooth development
Total cholesterol
Triglycerides
Type 1 diabetes
Type 2 diabetes
Ulcerative colitis
Urate
Venous thromboembolism
Vitamin B12 levels
Warfarin dose
Weight
White cell count
YKL-40 levels

## FIGURE 1: OMNI MICROARRAYS

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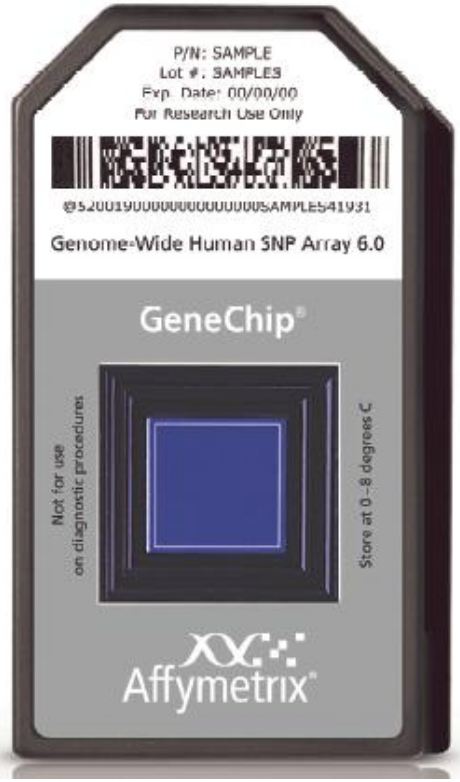


The Genome-Wide Human SNP Array 6.0 features more than 1.8 million markers of genetic variation, including single nucleotide polymorphisms (SNPs) as well as probes for the detection of copy number variation. The SNP Array 6.0 allows researchers to perform association studies with large sample sizes in both initial scan and replication phases, thereby significantly increasing the overall genetic power of their studies.

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# GWAS Success Stories

**Table 1** The genes or loci that were identified by GWA studies or consistently replicated for complex diseases is reviewed in this paper

| *Disease* | *Gene/locus* | *Reference* |
|---|---|---|
| AMD | CFH | 33 |
| | HTRA1 | 34 |
| BMI and obesity | INSIG2 | 35 |
| | FTO | 36 |
| IBD | CARD15/NOD2[a] | 37,38 |
| | 5q31[a] | 37,39 |
| | IL23R[a] | 40,37 |
| | ATG16L1[a] | 41,37 |
| | 10q21[a] | 41,37 |
| | 5p13.1[a] | 37,42 |
| | 5q33 (IRGM) | 37,43 |
| | 3p21 (BSN) | 37,43 |
| | 10q24.2 (NKX2-3) | 37,43 |
| | 18p11 (PTPN22) | 37,43 |
| T2D | PPARG[b] | 44 |
| | KCNJ11[b] | 45 |
| | TCF7L2[b] | 46 |
| | SLC30A8[b] | 47 |
| | LD block contains IDE-KIF11-HHEX[b] | 47 |
| | LD block contains EXT2-ALX4 | 47 |
| | CDKN2A/CDKN2B | 48–50 |
| | CDKAL1 | 48–51 |
| | IGF2BP2 | 48–50 |
| Breast cancer | FGFR2 | 52 |
| | TNRC9 | 52 |
| | MAP3K1 | 52 |
| | LSP1 | 52 |
| | FGFR2 | 53 |
| | 2q35 | 54 |
| | 16q12 | 54 |
| Prostate cancer | 8q24 | 55,56 |

European Journal of Human Genetics (2008) 16, 554–564

www.nature.com/ejhg

REVIEW

**The success of the genome-wide association approach: a brief story of a long struggle**

Ku Chee Seng*[,1] and Chia Kee Seng[1]

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# GWAS Success Stories

***The most robust association in GWAS to date***

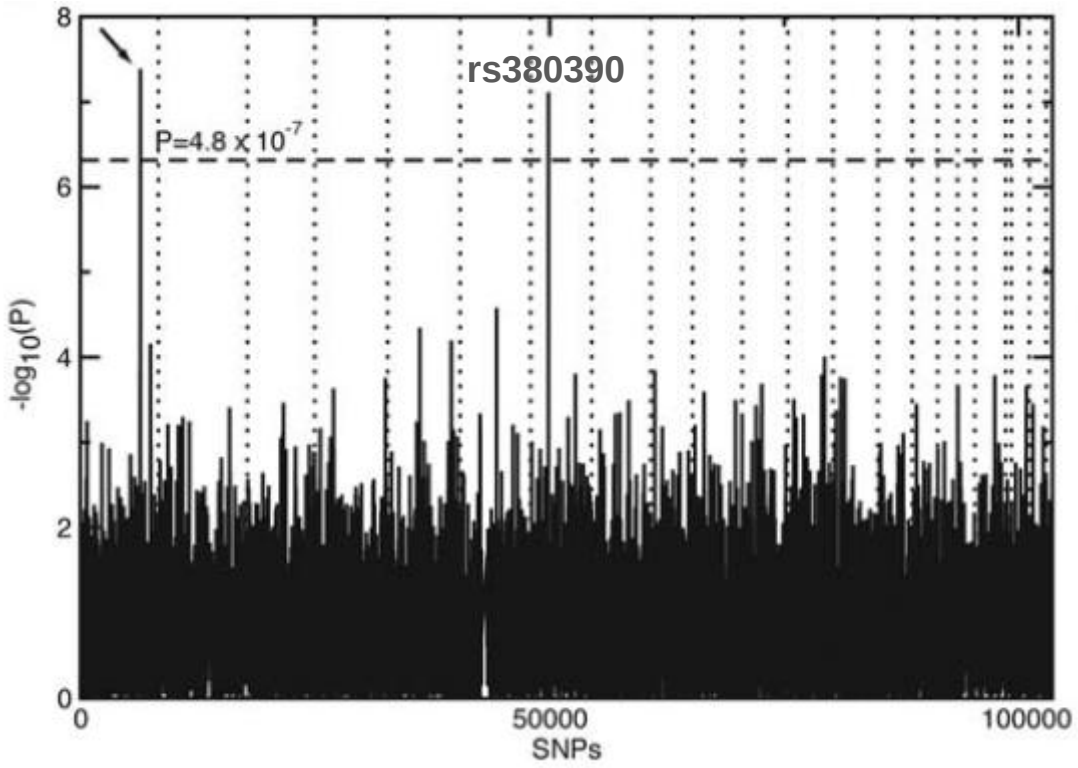


**Fig. 1.** (A) *P* values of genome-wide association scan for genes that affect the risk of developing AMD. $-\log_{10}(p)$ is plotted for each SNP in chromosomal order. The spacing between SNPs on the plot is uniform and does not reflect distances between SNPs on the chromosomes. The dotted horizontal line shows the cutoff for $P = 0.05$ after Bonferroni correction. The vertical dotted lines show chromosomal boundaries. The arrow indicates the peak for SNP rs380390, the most significant association, which was studied further. (B) Variation in genotype frequencies between cases and controls.

**Complement Factor H Polymorphism in Age-Related Macular Degeneration**

Robert J. Klein,[1] Caroline Zeiss,[2*] Emily Y. Chew,[3*] Jen-Yue Tsai,[4*] Richard S. Sackler,[1] Chad Haynes,[1] Alice K. Henning,[5] John Paul SanGiovanni,[3] Shrikant M. Mane,[6] Susan T. Mayne,[7] Michael B. Bracken,[7] Frederick L. Ferris,[3] Jurg Ott,[1] Colin Barnstable,[2] Josephine Hoh[7†]

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# GWAS Success Stories

***The most robust association in GWAS to date***

**rs380390 >>> Y402H**
**OR = 7.4 (r)**
**96 cases & 50 controls**

- **Chromosomal region 1q31 where CFH maps had been identified as a candidate region in six linkage studies**
- **Activated C5b-9 complex has been detected in patients with AMD**
- **Complement factor H levels increase with age and in smokers; two risk factors for AMD**
- **Complement factor H is detectable in the eye**

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Complement Factor H Polymorphism in Age-Related Macular Degeneration

Robert J. Klein,[1] Caroline Zeiss,[2*] Emily Y. Chew,[3*] Jen-Yue Tsai,[4*] Richard S. Sackler,[1] Chad Haynes,[1] Alice K. Henning,[5] John Paul SanGiovanni,[3] Shrikant M. Mane,[6] Susan T. Mayne,[7] Michael B. Bracken,[7] Frederick L. Ferris,[3] Jurg Ott,[1] Colin Barnstable,[2] Josephine Hoh[7†]

# GWAS Success Stories

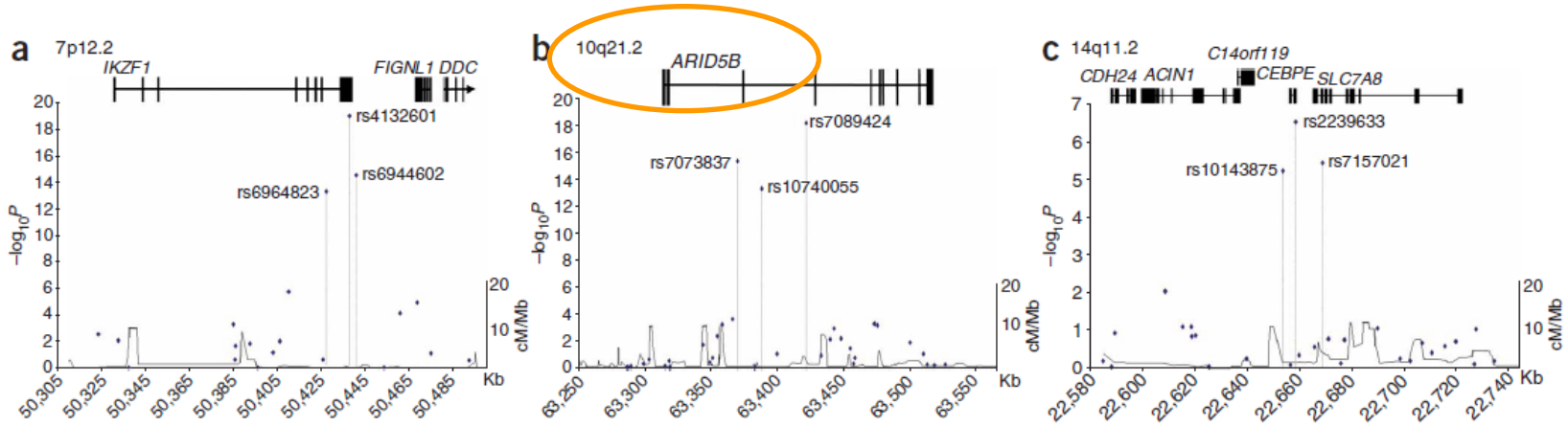


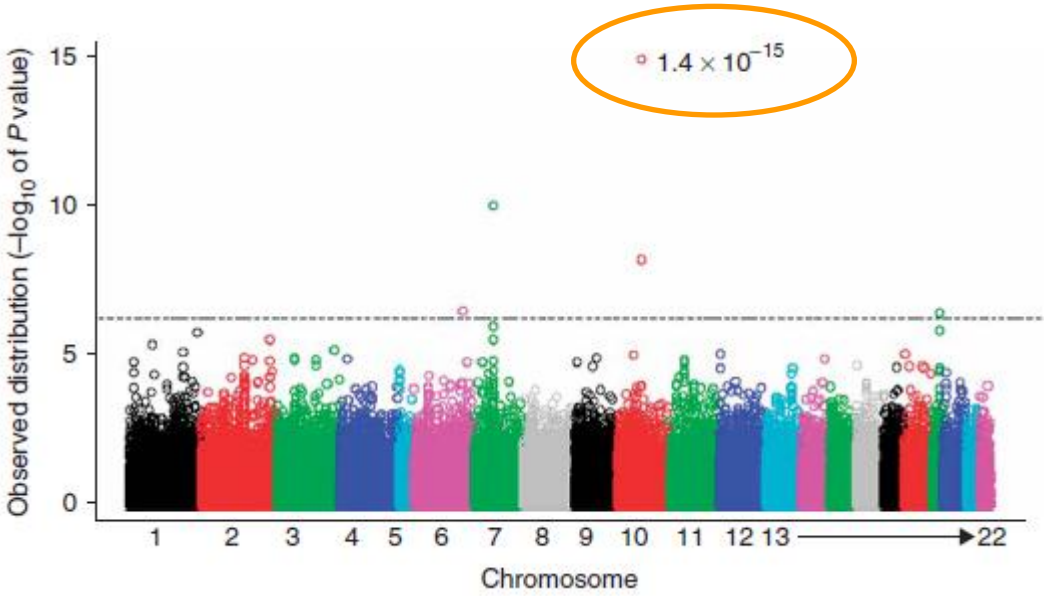

**Figure 1** LD structure and association results for each of the disease-associated regions. (**a**) 7p12.2; (**b**) 10q21.2; (**c**) 14q11.2. Chromosomal positions based on NCBI build 36 coordinates, showing Ensemble (release 48) genes. Armitage trend test *P* values (as $-\log_{10}$ values; left *y* axis) are shown for SNPs analyzed. Recombination rates in HapMap CEU across the region are shown in black (right *y* axis). Also shown are the relative positions of genes mapping to each region of association. Exons of genes have been redrawn to show the relative positions in the gene; therefore, maps are not to physical scale.

Loci on 7p12.2, 10q21.2 and 14q11.2 are associated with risk of childhood acute lymphoblastic leukemia

Elli Papaemmanuil[1], Fay J Hosking[1], Jayaram Vijayakrishnan[1], Amy Price[1], Bianca Olver[1], Eammon Sheridan[2], Sally E Kinsey[3], Tracy Lightfoot[4], Eve Roman[4], Julie A E Irving[5], James M Allan[5], Ian P Tomlinson[6], Malcolm Taylor[7], Mel Greaves[8] & Richard S Houlston[1]

Germline genomic variants associated with childhood acute lymphoblastic leukemia

Lisa R Treviño[1,6], Wenjian Yang[1,6], Deborah French[1], Stephen P Hunger[2], William L Carroll[3], Meenakshi Devidas[4], Cheryl Willman[5], Geoffrey Neale[1], James Downing[1], Susana C Raimondi[1], Ching-Hon Pui[1], William E Evans[1] & Mary V Relling[1]

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# GWAS Success Stories

## Multiple Loci With Different Cancer Specificities Within the 8q24 Gene Desert

Maya Ghoussaini, Honglin Song, Thibaud Koessler, Ali Amin Al Olama, Zsofia Kote-Jarai, Kristy E. Driver, Karen A. Pooley, Susan J. Ramus, Susanne Krüger Kjaer, Estrid Hogdall, Richard A. DiCioccio, Alice S. Whittemore, Simon A. Gayther, Graham G. Giles, Michelle Guy, Stephen M. Edwards, Jonathan Morrison, Jenny L. Donovan, Freddie C. Hamdy, David P. Dearnaley, Audrey T. Ardern-Jones, Amanda L. Hall, Lynne T. O'Brien, Beatrice N. Gehr-Swain, Rosemary A. Wilkinson, Paul M. Brown, John L. Hopper, David E. Neal, Paul D. P. Pharoah, Bruce A. J. Ponder, Rosalind A. Eeles, Douglas F. Easton, Alison M. Dunning; for the UK Genetic Prostate Cancer Study Collaborators/ British Association of Urological Surgeons' Section of Oncology and the UK ProtecT Study Collaborators

**Table 1.** Association of 8q24 single nucleotide polymorphisms with colorectal, ovarian, breast, and prostate cancer*

| Marker SNP (region, relative position) | Reference allele (frequency in controls subjects) | Colorectal cancer† | | Ovarian cancer | | Breast cancer | | Prostate cancer | |
|---|---|---|---|---|---|---|---|---|---|
| | | OR (95% CI) | *P* value‡ | OR (95% CI) | *P* value‡ | OR (95% CI) | *P* value‡ | OR (95% CI) | *P* value‡ |
| rs13254738 (A/C) (1.1) (region 1, 128173525) | A (0.70) | 1.06 (0.99 to 1.13) | 0.22 | 1.02 (0.94 to 1.11) | 0.64 | 0.96 (0.88 to 1.05) | 0.35 | **1.12 (1.01 to 1.24)** | **0.029** |
| rs6983561 (A/C) (1.2) (region 1, 128176062) | A (0.97) | 0.95 (0.81 to 1.11) | 0.65 | 0.90 (0.72 to 1.13) | 0.36 | 0.96 (0.77 to 1.21) | 0.76 | **2.11 (1.65 to 2.71)** | **$1.4 \times 10^{-9}$** |
| rs16901979 (G/T) (1.3) (region 1, 128194098) | G (0.97) | 0.89 (0.77 to 1.06) | 0.36 | 0.89 (0.71 to 1.11) | 0.30 | 0.98 (0.80 to 1.25) | 0.98 | **2.06 (1.61 to 2.65)** | **$4.9 \times 10^{-9}$** |
| rs13281615 (A/G) (2.1) (region 2, 128424800)§ | A (0.60) | 0.94 (0.89 to 1.00) | 0.17 | 0.99 (0.91 to 1.07) | 0.75 | **1.21 (1.11 to 1.32)** | **$1 \times 10^{-5}$** | 0.95 (0.87 to 1.05) | 0.33 |
| rs10505477 (G/A) (3.1) (region 3, 128476625) | G (0.50) | **1.27 (1.19 to 1.33)** | **$2.9 \times 10^{-8}$** | **1.14 (1.04 to 1.23)** | **$2.0 \times 10^{-3}$** | 0.96 (0.88 to 1.04) | 0.35 | **1.43 (1.30 to 1.56)** | **$7.7 \times 10^{-14}$** |
| rs10808556 (A/G) (3.2) (region 3, 128482329) | A (0.59) | **1.26 (1.16 to 1.37)** | **$5.1 \times 10^{-8}$** | **1.13 (1.04 to 1.22)** | **$1.7 \times 10^{-3}$** | 0.99 (0.91 to 1.08) | 0.80 | **1.31 (1.19 to 1.44)** | **$4.2 \times 10^{-8}$** |
| rs6983267§ (A/G) (3.3) (region 3, 128482487)§ | A (0.49) | **1.27 (1.16 to 1.37)** | **$3.6 \times 10^{-8}$** | **1.11 (1.03 to 1.20)** | **$9.9 \times 10^{-3}$** | 0.97 (0.89 to 1.05) | 0.50 | **1.43 (1.30 to 1.56)** | **$7.7 \times 10^{-14}$** |
| rs7000448 (G/A) (4.1) (region 4, 128510352) | G (0.64) | 1.04 (0.98 to 1.11) | 0.32 | 1.04 (0.96 to 1.13) | 0.33 | 0.96 (0.88 to 1.05) | 0.38 | **1.23 (1.11 to 1.35)** | **$2.8 \times 10^{-5}$** |
| rs1447295 (G/T) (5.1) (region 5, 128554220) | G (0.90) | 0.98 (0.89 to 1.08) | 0.82 | 1.07 ( 0.93 to 1.22) | 0.35 | 0.92 (0.80 to 1.07) | 0.28 | **1.86 (1.60 to 2.15)** | **$6.9 \times 10^{-17}$** |

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# GWAS Success Stories

## The common colorectal cancer predisposition SNP rs6983267 at chromosome 8q24 confers potential to enhanced Wnt signaling

Sari Tuupanen[1], Mikko Turunen[2,3], Rainer Lehtonen[1], Outi Hallikas[2,3], Sakari Vanharanta[1,12], Teemu Kivioja[2–4], Mikael Björklund[2,3], Gonghong Wei[2,3], Jian Yan[2,3], Iina Niittymäki[1], Jukka-Pekka Mecklin[5], Heikki Järvinen[6], Ari Ristimäki[7–9], Mariachiara Di-Bernardo[10], Phil East[11], Luis Carvajal-Carmona[11], Richard S Houlston[10], Ian Tomlinson[11], Kimmo Palin[4,12], Esko Ukkonen[4], Auli Karhu[1], Jussi Taipale[2,3] & Lauri A Aaltonen[1]

## The 8q24 cancer risk variant rs6983267 shows long-range interaction with *MYC* in colorectal cancer

Mark M Pomerantz[1,11], Nasim Ahmadiyeh[1,2,11], Li Jia[3], Paula Herman[1], Michael P Verzi[1], Harshavardhan Doddapaneni[4], Christine A Beckwith[1], Jennifer A Chan[5], Adam Hills[1], Matt Davis[1], Keluo Yao[1], Sarah M Kehoe[1], Heinz-Josef Lenz[6], Christopher A Haiman[6], Chunli Yan[3], Brian E Henderson[6], Baruch Frenkel[7], Jordi Barretina[1], Adam Bass[1], Josep Tabernero[8], José Baselga[8], Meredith M Regan[9], J Robert Manak[4], Ramesh Shivdasani[1], Gerhard A Coetzee[3] & Matthew L Freedman[1,10]

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# GWAS Success Stories

**Table 1 | Estimates of heritability and number of loci for several complex traits**

| Disease | Number of loci | Proportion of heritability explained | Heritability measure |
|---|---|---|---|
| Age-related macular degeneration[72] | 5 | 50% | Sibling recurrence risk |
| Crohn's disease[21] | 32 | 20% | Genetic risk (liability) |
| Systemic lupus erythematosus[73] | 6 | 15% | Sibling recurrence risk |
| Type 2 diabetes[74] | 18 | 6% | Sibling recurrence risk |
| HDL cholesterol[75] | 7 | 5.2% | Residual* phenotypic variance |
| Height[15] | 40 | 5% | Phenotypic variance |
| Early onset myocardial infarction[76] | 9 | 2.8% | Phenotypic variance |
| Fasting glucose[77] | 4 | 1.5% | Phenotypic variance |

*Residual is after adjustment for age, gender, diabetes.

## Finding the missing heritability of complex diseases

Teri A. Manolio[1], Francis S. Collins[2], Nancy J. Cox[3], David B. Goldstein[4], Lucia A. Hindorff[5], David J. Hunter[6], Mark I. McCarthy[7], Erin M. Ramos[5], Lon R. Cardon[8], Aravinda Chakravarti[9], Judy H. Cho[10], Alan E. Guttmacher[1], Augustine Kong[11], Leonid Kruglyak[12], Elaine Mardis[13], Charles N. Rotimi[14], Montgomery Slatkin[15], David Valle[9], Alice S. Whittemore[16], Michael Boehnke[17], Andrew G. Clark[18], Evan E. Eichler[19], Greg Gibson[20], Jonathan L. Haines[21], Trudy F. C. Mackay[22], Steven A. McCarroll[23] & Peter M. Visscher[24]

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Box 1 | **Variants identified through GWA for an example of a common human disease**

Type 2 diabetes has been studied using some of the largest genome-wide association (GWA) sample sizes to date. Three large case–control studies were recently subjected to a meta-analysis with a total sample size of 4,549 cases and 5,579 controls[22]: 1,924 cases and 2,938 controls came from the Wellcome Trust Case Control Consortium[78], 1,464 cases and 1,467 controls came from the Diabetes Genetics Initiative[79], and 1,161 cases and 1,174 controls came from the Finland–United States Investigation of Non-Insulin-Dependent Diabetes Mellitus Genetics[80]. The first two studies were performed using a different chip (Affymetrix 500k) from that used in the last study (Illumina 317k), but the imputation of missing genotypes allowed for a combined analysis of 2.2 million SNPs for all 10,128 participants. Twelve SNPs had already been established as associated with type 2 diabetes in these earlier studies, and the meta-analysis confirmed six additional associated SNPs. In total, these 18 variants only explained 6% of the heritability of type 2 diabetes[21]. Furthermore, the underlying causal variant has not definitively been found for any of these significant associations, although potassium inwardly-rectifying channel, subfamily J, member 11 (*KCNJ11*) and Wolfram syndrome 1 (*WFS1*) were already known to contain rare variants that influence the disease, and there is evidence supporting potentially causal common variants in transcription factor 7-like 2 (*TCF7L2*), solute carrier family 30, member 8 (*SLC30A8*) and *KCNJ11* (REFS 81–83). The table shows type 2 diabetes-associated variants reported by Zeggini *et al.*[22]; the maximum odds ratio reported was 1.37.

| SNP | Odds ratio | SNP location |
|---|---|---|
| rs7903146 | 1.37 | Intron of *TCF7L2* |
| rs13071168 | 1.35 | Between *SYN2* and *PPARG* |
| rs7020996 | 1.26 | Near *CDKN2A* and *CDKN2B* |
| rs6931514 | 1.25 | Intron of *CDKAL1* |
| rs1801282 | 1.18 | Exon of *PPARG* |
| rs4402960 | 1.17 | Intron of *IGF2BP2* |
| rs5015480 | 1.17 | Near *HHEX* |
| rs5215 | 1.16 | Exon of *KCNJ11* |
| rs10282940 | 1.15 | Exon of *SLC30A8* |
| rs8050136 | 1.15 | Intron of *FTO* |
| rs7578597 | 1.15 | Exon of *THADA* |
| rs10923931 | 1.13 | Intron of *NOTCH2* |
| rs4580722 | 1.11 | Near *WFS1* |
| rs12779790 | 1.11 | Between *CDC123* and *CAMK1D* |
| rs17705177 | 1.1 | Near *TCF2* |
| rs864745 | 1.1 | Intron of *JAZF1* |
| rs7961581 | 1.09 | Between *TSPAN8* and *LGR5* |
| rs4607103 | 1.09 | Near *ADAMTS9* |

**T2D**

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APPLICATIONS OF NEXT-GENERATION SEQUENCING

Uncovering the roles of rare variants in common disease through whole-genome sequencing

*Elizabeth T. Cirulli and David B. Goldstein*

OPEN ACCESS Freely available online PLoS MEDICINE

# Combining Information from Common Type 2 Diabetes Risk Polymorphisms Improves Disease Prediction

Michael N. Weedon[1], Mark I. McCarthy[2], Graham Hitman[3], Mark Walker[4], Christopher J. Groves[2], Eleftheria Zeggini[2], N. William Rayner[2], Beverley Shields[1], Katharine R. Owen[1], Andrew T. Hattersley[1], Timothy M. Frayling[1*]

PLoS Medicine | www.plosmedicine.org 1877 October 2006 | Volume 3 | Issue 10 | e374

**T2D**

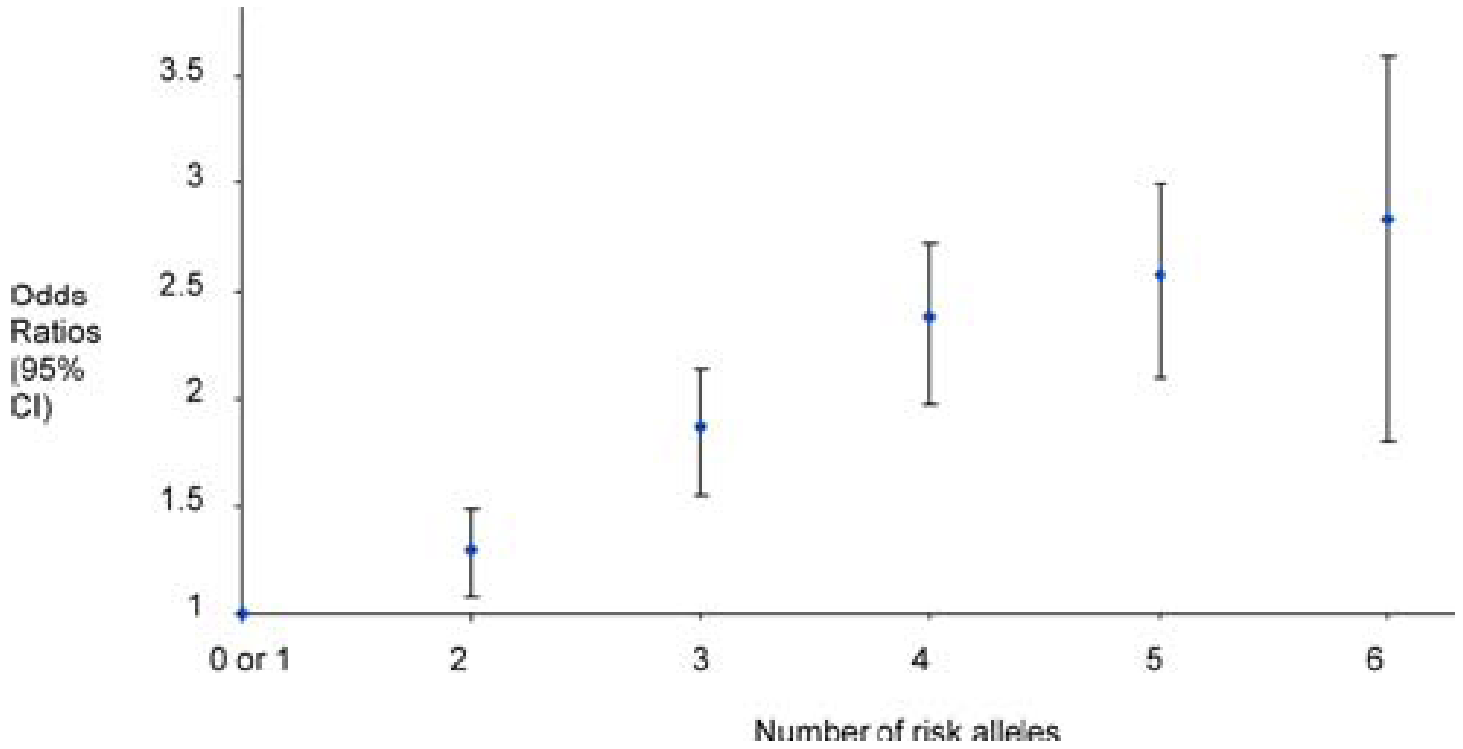
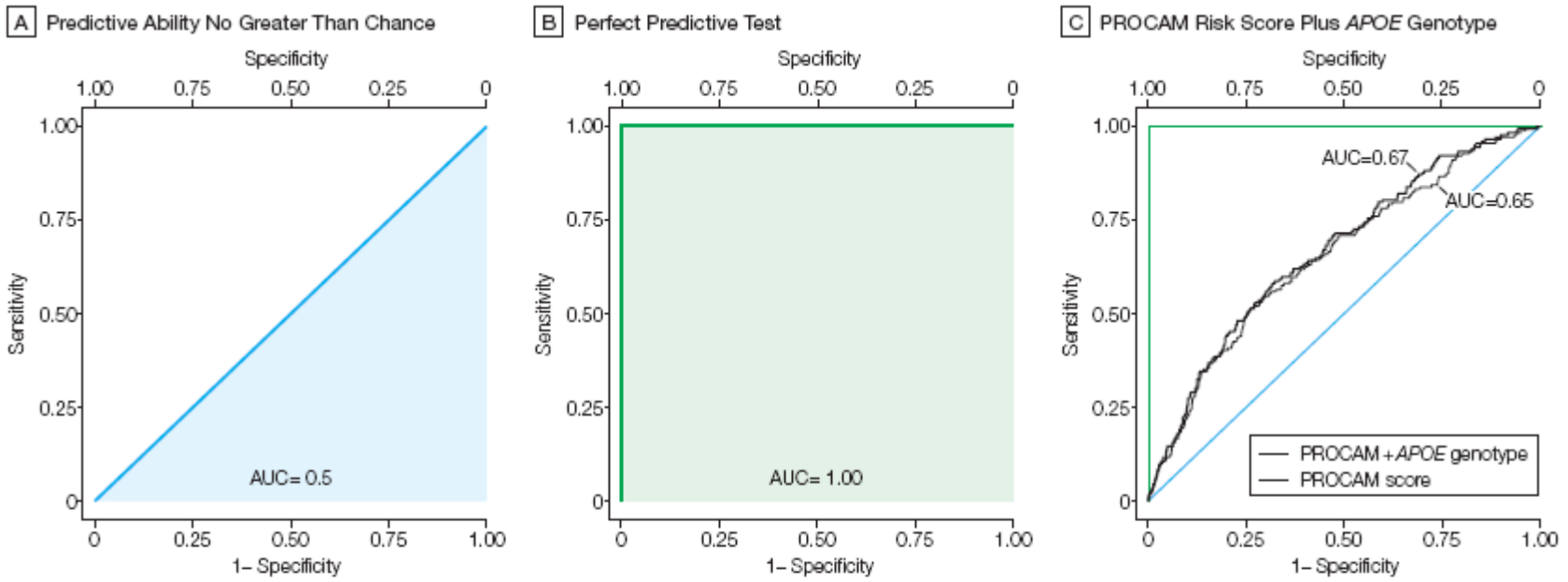



**Figure 3.** ORs and 95% CIs for Participants Carrying Increasing Numbers of Risk Alleles

www

# Development of Predictive Models
## *How to Assess Its Power?*




A, Example of an ROC curve for a test that performs no better than chance. B, Example of an ROC curve for a test with perfect predictive ability (sensitivity = 100%; specificity = 100%). C, ROC curves for cardiovascular disease calculated using PROCAM (Prospective Cardiovascular Munster study) risk score plus *APOE* genotype. Based on 2451 men (of 3012 eligible) who had complete data for PROCAM and *APOE* genotyping. *APOE* genotype was fitted as a class variable with 3 categories 33, 22/23, and 34/44. Factors included age, body mass index, total cholesterol, triglycerides, systolic blood pressure, and family history. Other factors in PROCAM were not measured in all men. For the PROCAM score, the ROC value (95% confidence interval) was 0.65 (0.61-0.70), with a detection rate of 11.7% for a false-positive rate of 5.0%. In univariate analysis, *APOE* genotype was significant at $P = .01$. In multivariate analysis, the area under the curve increased to 0.67 (0.63-0.71) (detection rate,14.0%), but this improvement was not significant ($P = .11$). Panel C data based on Humphries et al.[12]




www

The Journal of Nutrition
**Biomarkers as Indicators of Cancer Risk Reduction Following Dietary Manipulation**

# PSA: A Biomarker for Disease. A Biomarker for Clinical Trials. How Useful Is It?[1,2]

Ian M. Thompson*

Department of Urology, University of Texas Health Science Center at San Antonio, San Antonio, TX 78229

The risk of cancer ranged from 6.6% for values ≤0.5 μg/L to 26.9% for values between 3.1 and 4.0 μg/L. Our subsequent analysis found that the receiver operating characteristic (ROC) curve for PSA had an area under the curve of 0.678 for cancer versus no cancer

OPEN ACCESS Freely available online PLoS MEDICINE

# Combining Information from Common Type 2 Diabetes Risk Polymorphisms Improves Disease Prediction

Michael N. Weedon[1], Mark I. McCarthy[2], Graham Hitman[3], Mark Walker[4], Christopher J. Groves[2], Eleftheria Zeggini[2], N. William Rayner[2], Beverley Shields[1], Katharine R. Owen[1], Andrew T. Hattersley[1], Timothy M. Frayling[1*]

PLoS Medicine | www.plosmedicine.org 1877 October 2006 | Volume 3 | Issue 10 | e374

T2D

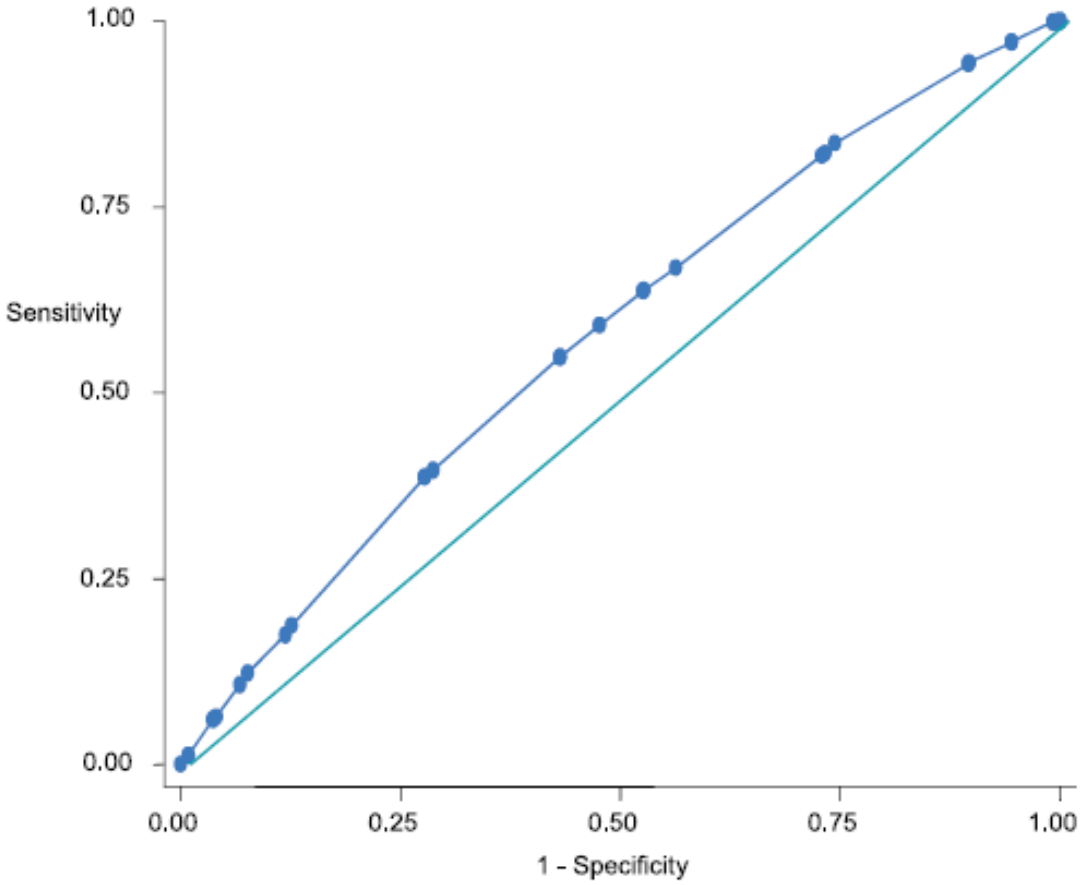



**Figure 4.** ROC for the Information Provided by the Glu23Lys, Pro12Ala, and rs7903146 Variants after Fitting a Logistic Regression Model

AUC = 0.58.

www

T2D

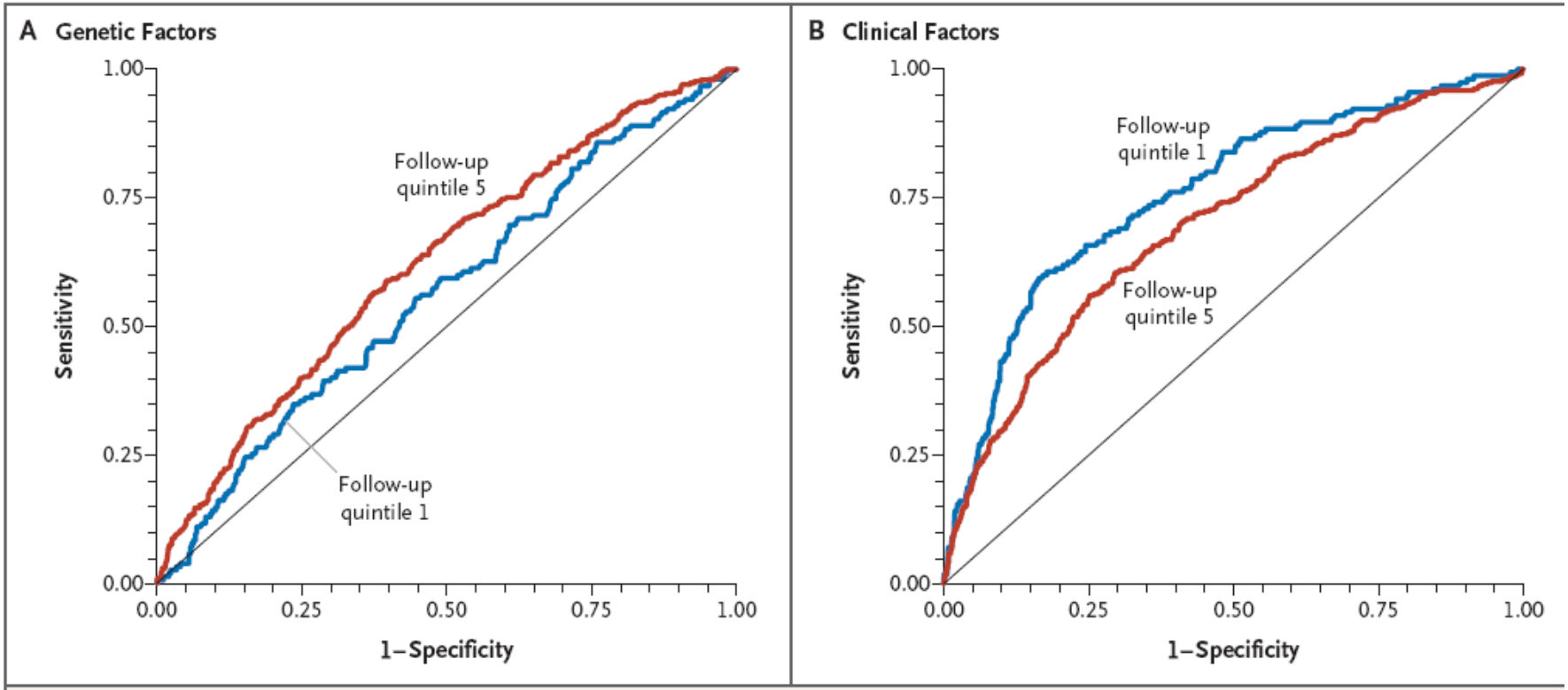


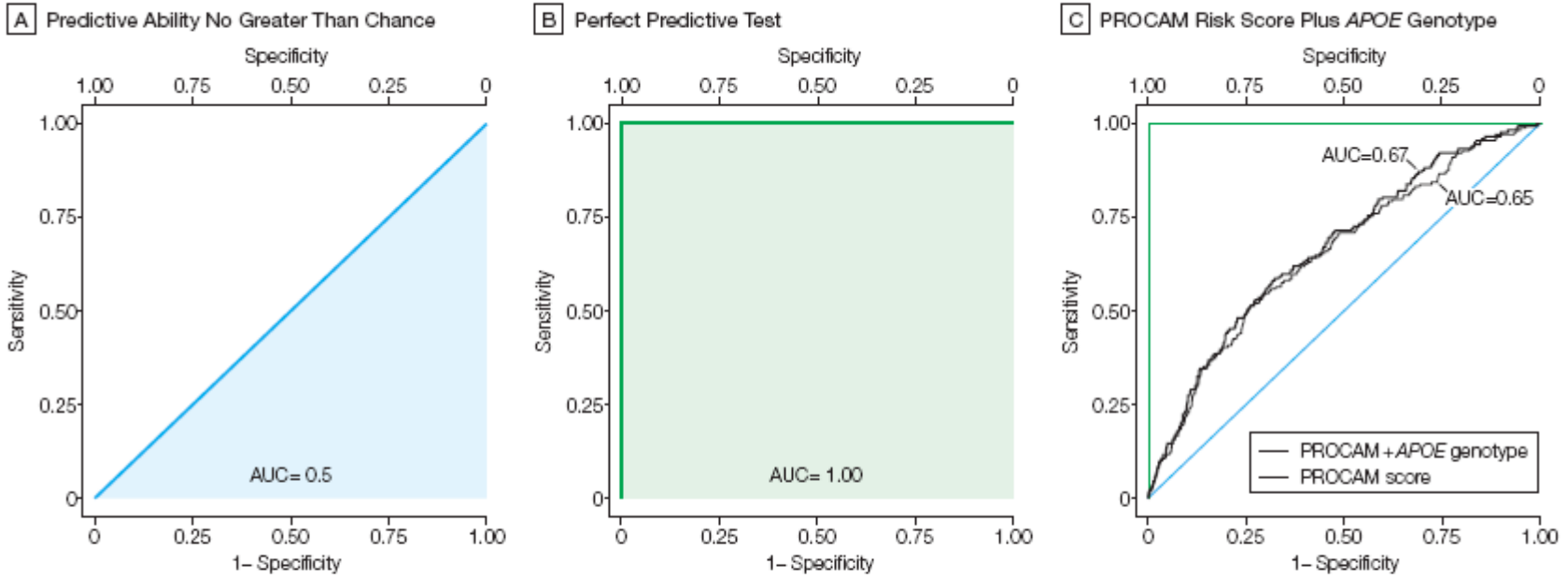

**Figure 4. Area under the ROC Curve (C Statistic) for Clinical and Genetic Models Predicting Type 2 Diabetes, According to the Duration of Follow-up.**

The effect of genetic risk factors increases with the duration of follow-up, with an area under the ROC curve (AUC) of 0.56 in quintile 1 (blue) and 0.62 in quintile 5 (red) (P=0.01) (Panel A), whereas the effect of clinical risk factors decreased with the duration of follow-up, with an AUC of 0.75 in quintile 1 and 0.67 in quintile 5 (P=0.01) (Panel B). The black line indicates reference values.

www

CVD

**Figure.** Example of a Receiver Operating Characteristic (ROC) Curve for Cardiovascular Risk Related to *APOE*




A, Example of an ROC curve for a test that performs no better than chance. B, Example of an ROC curve for a test with perfect predictive ability (sensitivity = 100%; specificity = 100%). C, ROC curves for cardiovascular disease calculated using PROCAM (Prospective Cardiovascular Munster study) risk score plus *APOE* genotype. Based on 2451 men (of 3012 eligible) who had complete data for PROCAM and *APOE* genotyping. *APOE* genotype was fitted as a class variable with 3 categories 33, 22/23, and 34/44. Factors included age, body mass index, total cholesterol, triglycerides, systolic blood pressure, and family history. Other factors in PROCAM were not measured in all men. For the PROCAM score, the ROC value (95% confidence interval) was 0.65 (0.61-0.70), with a detection rate of 11.7% for a false-positive rate of 5.0%. In univariate analysis, *APOE* genotype was significant at $P = .01$. In multivariate analysis, the area under the curve increased to 0.67 (0.63-0.71) (detection rate,14.0%), but this improvement was not significant ($P = .11$). Panel C data based on Humphries et al.[12]

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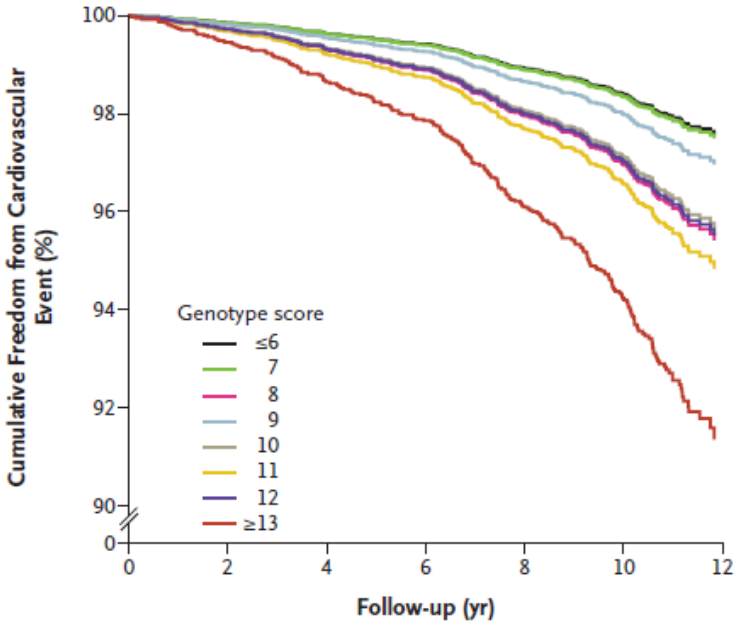


**No. at Risk**

Genotype score

| | | | | | | |
|---|---|---|---|---|---|---|
| ≤6 | 122 | 122 | 120 | 116 | 112 | 105 |
| 7 | 309 | 304 | 302 | 298 | 293 | 267 |
| 8 | 574 | 573 | 566 | 556 | 538 | 481 |
| 9 | 894 | 894 | 886 | 872 | 844 | 757 |
| 10 | 913 | 900 | 887 | 876 | 849 | 757 |
| 11 | 726 | 719 | 711 | 696 | 679 | 604 |
| 12 | 465 | 462 | 456 | 447 | 434 | 398 |
| ≥13 | 229 | 228 | 218 | 215 | 207 | 184 |

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Polymorphisms Associated with Cholesterol and Risk of Cardiovascular Events

Sekar Kathiresan, M.D., Olle Melander, M.D., Ph.D., Dragi Anevski, Ph.D., Candace Guiducci, B.S., Noël P. Burtt, B.S., Charlotta Roos, M.Sc., Joel N. Hirschhorn, M.D., Ph.D., Göran Berglund, M.D., Ph.D., Bo Hedblad, M.D., Ph.D., Leif Groop, M.D., Ph.D., David M. Altshuler, M.D., Ph.D., Christopher Newton-Cheh, M.D., M.P.H., and Marju Orho-Melander, Ph.D.

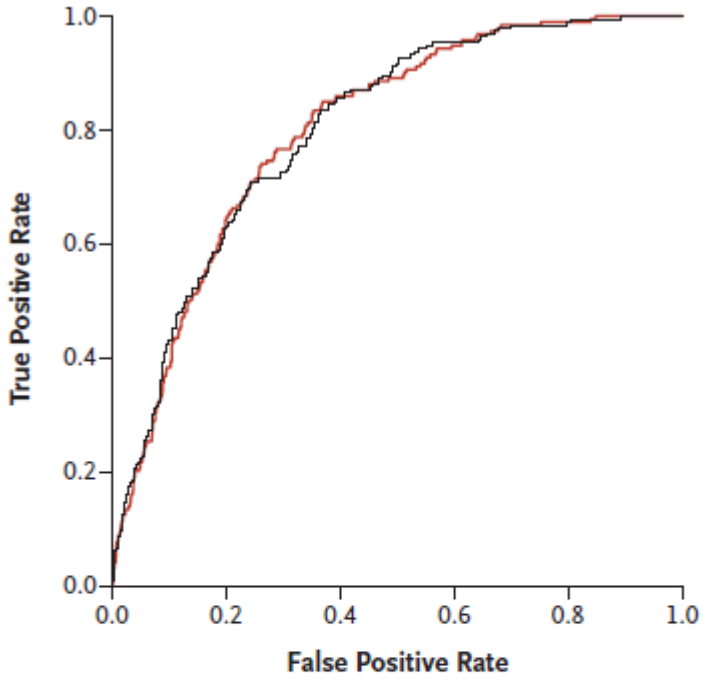


**Figure 2. Receiver-Operating-Characteristic (ROC) Curves for Incident Myocardial Infarction, Ischemic Stroke, or Death from Coronary Heart Disease during 10-Year Follow-up.**

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

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NATURE|Vol 456|6 November 2008

# The case of the missing heritability

When scientists opened up the human genome, they expected to find the genetic components of common traits and diseases. But they were nowhere to be seen. **Brendan Maher** shines a light on six places where the missing loot could be stashed away.

**Table 1. What accounts for the genetic 'dark matter' in cancer studies?[a]**

| Reason | Ability of the different study designs to address these reasons | | |
|---|---|---|---|
| | Population-based case–control studies | Family-based association studies | Genetic linkage studies in pedigrees |
| Biased phenotype definition and ascertainment | Modest and/or poor[b] | Good and/or modest[b] | Good and/or modest[b] |
| Insufficient sample size resulting in low power | Good | Modest | Poor |
| Epistatic (gene–gene) interactions | Modest[c] | Modest[c] | Good and/or modest[c] |
| Gene–environment interactions | Poor | Modest[c] | Good and/or modest[c] |
| Differential effects in different populations | Poor | Poor | Good |
| Incomplete genome coverage for common variants | Good | Good | Good and/or modest[d] |
| Effects of rare alleles | Poor | Poor | Good |
| Parent-of-origin specific effects | Poor | Good and/or poor | Good |

[a]Potential reasons explaining the genetic dark matter and the ability of different study designs to address them.
[b]Dependent on the type of cancer and on clinical/pathological ascertainments that are carried out; some types of cancers (e.g. liver cancer) are particularly prone to misclassification if histology of the tumor samples is not available because the liver is a common site of cancer.
[c]Dependent on the strength of the interaction, here for relatively strong interactions.
[d]In pedigree studies the reduced numbers of genetic recombinations determine a high number of redundant co-segregating genetic markers, and thus high-density coverage by SNP arrays does not allow fine mapping.

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# Beyond genome-wide association studies: genetic heterogeneity and individual predisposition to cancer

Antonella Galvan[1], John P.A. Ioannidis[2,3] and Tommaso A. Dragani[1]


Saturday, March 29, 2008

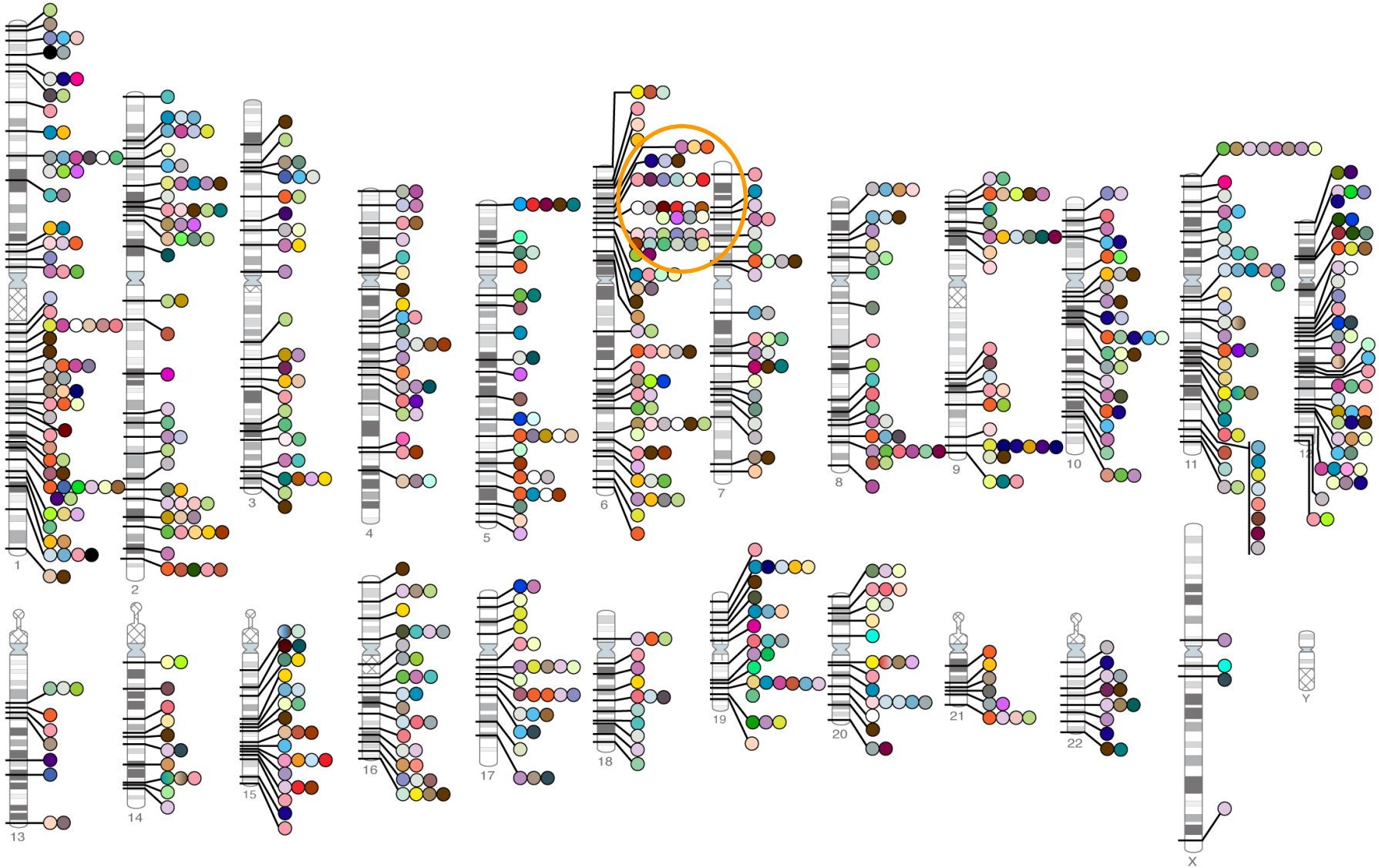
## Why do genome-wide scans fail?

The successes of genome-wide association studies (GWAS) in identifying genetic risk factors for common diseases have been heavily publicised in the mainstream media - barely a week goes by these days that we don't hear about another genome scan that has identified new risk genes for diabetes, lupus, cardiac disease, or any of the other common ailments of Western civilisation.

### Reasons for Failure of GWAS in Identifying a Large Proportion of Heritable Risk

- Insensitivity to rare variants
- Insensitivity to copy number variation
- Insensitivity to epigenetic changes
- Epistatic interactions
- Missing genes and variants in microarray chips
- Contribution to disease etiology by short tandem repeat polymorphisms
- Population differences
- Disease heterogeneity
- Alleles with small effect sizes

# Genome-Wide Associations

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NHGRI GWA Catalog
www.genome.gov/GWAStudies


Saturday, March 29, 2008

**Why do genome-wide scans fail?**

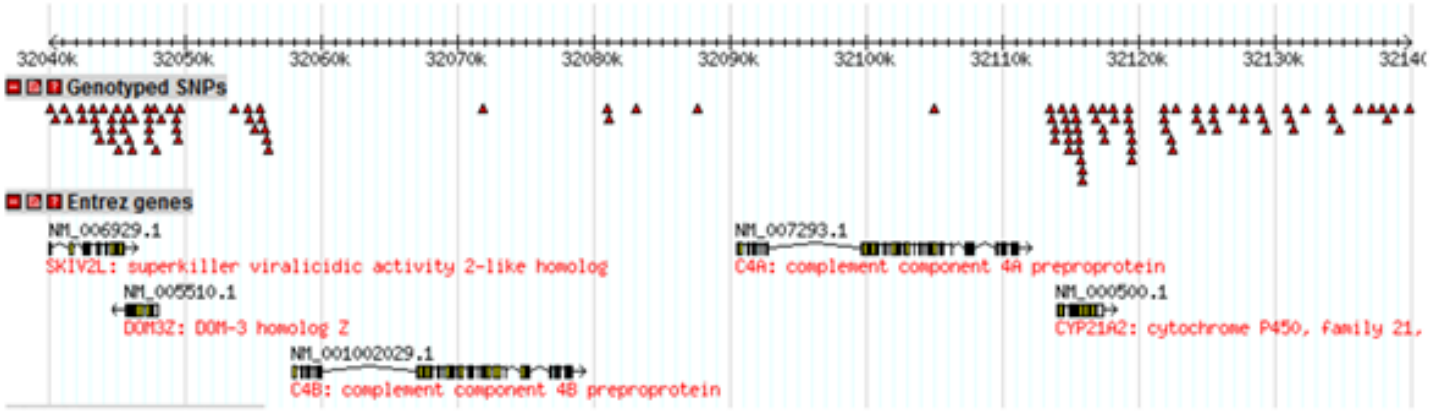


**Figure 2**: HapMap project data (release 27, phase II+III) for the complement subregion of the HLA complex. Note the scarcity of genotyped SNPs for C4A and C4B genes.

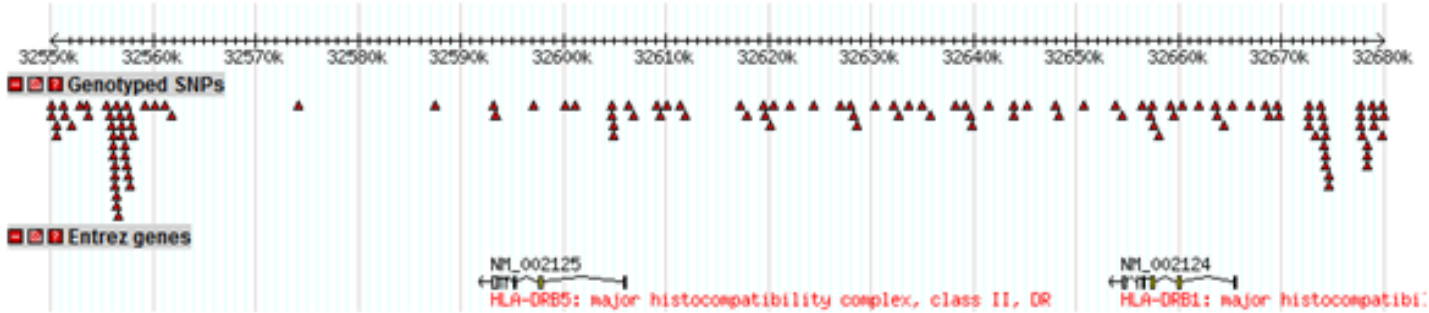


**Figure 3**: HapMap project data (release 27, phase II+III) for the HLA-DRB subregion of the HLA complex.

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# Nature *or* Nature? OR Nature *and* Nature?

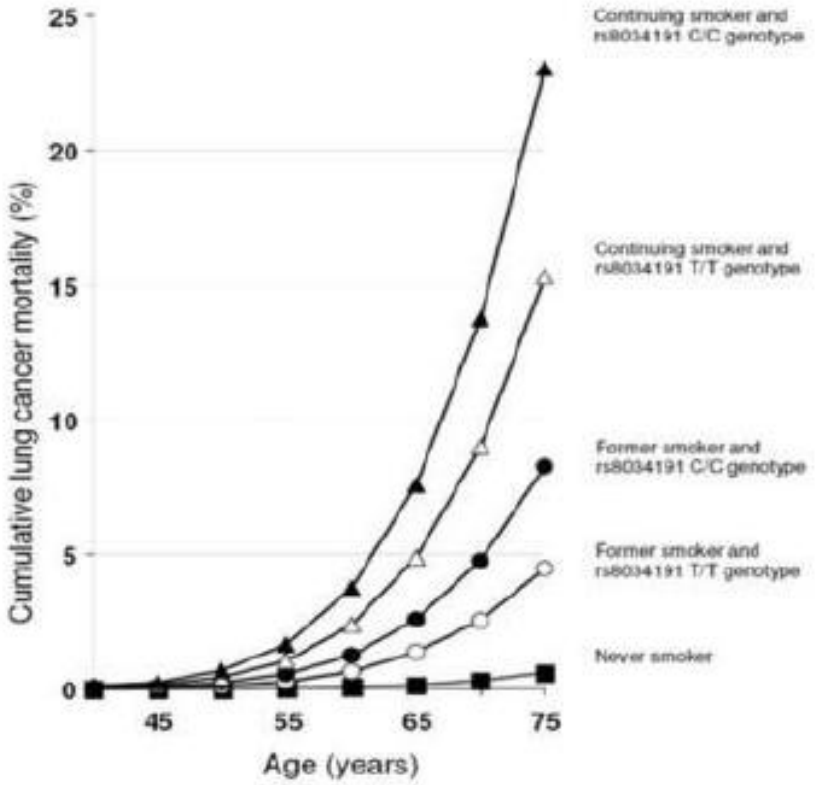


**Figure 1**
**Cumulative risk of lung cancer by rs8034191 genotype.** Relevance of smoking and of rs8034191 genotype to lung cancer mortality in men aged 45-75 years. Cumulative risk (in the absence of other causes of death) based on national lung cancer death rates for men in Poland in the year 2000, assuming that the prevalence of current smoking, former smoking, and never smoking are as in this study and that the relative risks for lung cancer incidence and mortality are similar (Hung *et al* 2008) [1].

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Environmental Health

Commentary

**The impact of new research technologies on our understanding of environmental causes of disease: the concept of clinical vulnerability**

Paolo Vineis*[1], Aneire E Khan[1], Jelle Vlaanderen[2] and Roel Vermeulen[2]

Address: [1]MRC/HPA Centre for Environment and Health, Imperial College, UK and [2]Institute for Risk Assessment Sciences, Utrecht University, Utrecht, the Netherlands

# Effect Modification by an Environmental Factor

## Role of MTHFR genetic polymorphisms in the susceptibility to childhood acute lymphoblastic leukemia

Maja Krajinovic, Stéphanie Lamothe, Damian Labuda, Émilie Lemieux-Blanchard, Yves Théorêt, Albert Moghrabi, and Daniel Sinnett

**The central role of methylenetetrahydrofolate reductase (MTHFR) in the folate metabolism renders *MTHFR* gene polymorphisms (C677T and A1298C) potential modulators of a variety of disorders whose development depends on folate/homocysteine imbalance. Here, we provide additional evidence on the protective role of these polymorphisms in acute lymphoblastic leukemia (ALL), the most common pediatric cancer. A case-control study was conducted in 270 ALL patients and 300 healthy controls of French-Canadian origin. The TT677/AA1298 and CC677/CC1298 individuals were associated with reduced risk of ALL (crude odds ratio [OR] = 0.4; 95% confidence interval [CI], 0.2-0.9; and OR = 0.3; 95% CI, 0.1-0.6; respectively). Further stratification in patients born before and after January 1996 (approximate time of Health Canada recommendation for folic acid supplement in pregnancy) revealed that the protective effect of *MTHFR* variants is accentuated and present only in children born before 1996. Similar results were obtained when a transmission disequilibrium test was performed on a subset of children (n = 95) in a family-based study. This finding suggests gene-environment interaction and its role in the susceptibility to childhood ALL, which is consistent with previous findings associating either folate deficiency or MTHFR polymorphisms with risk of leukemia. (Blood. 2004;103:252-257)**



**Table 4. *MTHFR* genotypes in ALL patients stratified by the year of birth**

| *MTHFR* genotypes | | Born before January 1996, no. (%) | Born after January 1996, no. (%) | Controls, no. (%) | $OR_{before\ 1996}$ (95% CI) | $P_{before\ 1996}$ | $OR_{after\ 1996}$ (95% CI) | $P_{after\ 1996}$ |
|---|---|---|---|---|---|---|---|---|
| C677T | A1298C | | | | | | | |
| CC | AA | 48 (21.6) | 3 (6.3) | 35 (11.7) | 1 (referent) | — | 1 (referent) | — |
| CT | AA | 51 (23.0) | 18 (37.5) | 69 (23.0) | 0.5 (0.3-0.9) | .03 | 3.0 (0.8-11) | .1 |
| TT | AA | 26 (11.7) | 5 (10.4) | 46 (15.3) | 0.4 (0.2-0.8) | .01 | 1.3 (0.3-5.7) | NS |
| CC | AC | 36 (16.2) | 13 (27.1) | 60 (20.0) | 0.4 (0.2-0.8) | < .01 | 2.5 (0.7-9.5) | .3 |
| CT | AC | 49 (22.1) | 9 (18.8) | 59 (19.7) | 0.6 (0.3-1.1) | .1 | 1.8 (0.5-7.0) | .5 |
| CC | CC | 12 (5.4) | 0 (0) | 31 (10.3) | 0.3 (0.1-0.6) | < .01 | ND | .3 |

The frequency of *MTHFR* genotype combinations of each group of ALL patients, born before (n = 222) and after January 1996 (n = 48), was compared with the frequency in controls using CC677/AA1298 individuals as the referent group (OR = 1). When CC677/AA1298 individuals are compared with others, the ALL risk (OR) in the group born before 1996 was 2.2 (95% CI, 1.3-3.5; $P = .001$) and for those born after 1996, OR = 0.5 (95% CI, 0.1-1.8; $P = .4$).

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(www)


Saturday, March 29, 2008

**Why do genome-wide scans fail?**

**Most genetic risk markers are effect modifiers of environmental exposures**

**High technology "omics" still needs data on the environment**

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# Effect Modification by Gender

***Despite that males and females are almost different species, the gender effect is almost always disregarded in the analysis of biomedical research results***

**GENDER EFFECT IN CANCER**

**M. Tevfik Dorak, MD PhD**

Hum Genet (2007) 122:505–514
DOI 10.1007/s00439-007-0430-3

ORIGINAL INVESTIGATION

**Gender specific differences in levels of DNA methylation at selected loci from human total blood: a tendency toward higher methylation levels in males**

Osman El-Maarri · Tim Becker · Judith Junen · Syed Saadi Manzoor · Amalia Diaz-Lacava · Rainer Schwaab · Thomas Wienker · Johannes Oldenburg

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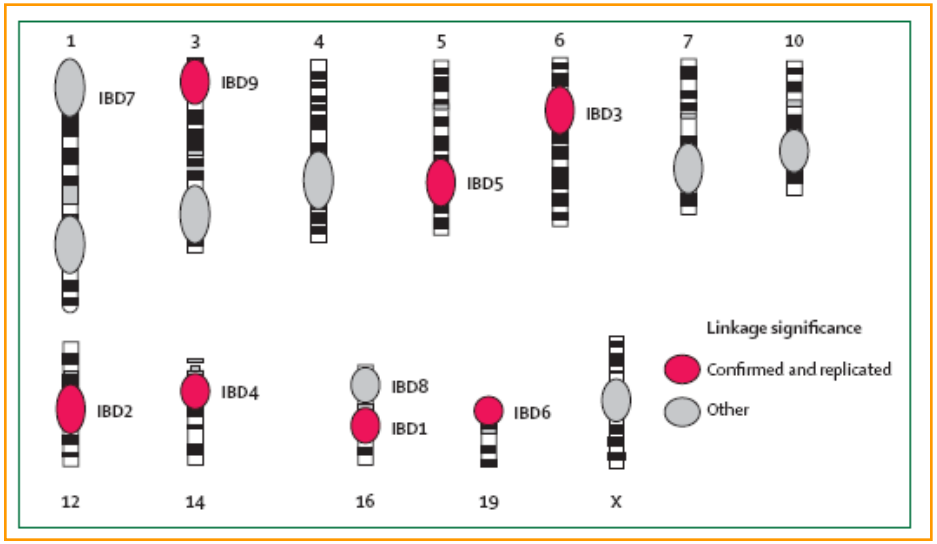
# Inflammatory Bowel Disease

**Table 1 Major regions and genes in IBD**

| Region | Localization | Involved genes |
|---|---|---|
| IBD1 | Chromosome 16 | NOD2/CARD15, IL-4R, CD11B |
| IBD2 | Chromosome 12 | Vitamin D receptor (VDR), STAT6, Interferon γ, β7 integrine. |
| IBD3 | Chromosome 6 | Major hystocompability complex (MHC): Class Ⅰ, Ⅱ, Ⅲ. |
| IBD4 | Chromosome 14 | T- Lymphocyte receptor (TCR) and Leukotriene B4 |
| IBD5 | Chromosome 5 | Organic cations transporter (OCTN), *Drosophila long disc homologue gene 5* (DLG5), *Multidrug resistant gene* (MDR1), IL-6, CD14 |
| IBD6 | Chromosome 19 | Tromboxane A2, Leukotriene B4, ICAM-1 |
| IBD7 | Chromosome 1 | Transforming growth factor Beta (TGFβ), TNFα receptors. |
| IBD8 | Chromosome 16 | Under research |
| IBD9 | Chromosome 9 | CCR-5, CCR9, IL-12 |

NOD2/CARD15: Nucleotide oligomerization domain 2/Caspase-activation recruitment domains 15; STAT6: signal transducer and activator of transcription-6; ICAM-1: intracellular adhesion molecule 1; CCR5: CC-chemokine receptor5.

*World J Gastroenterol* 2007 November 14; 13(42): 5560-5570
*World Journal of Gastroenterology* ISSN 1007-9327




- **IBD3 maps to chromosome 6p in linkage studies and known as the HLA-linked IBD susceptibility locus**

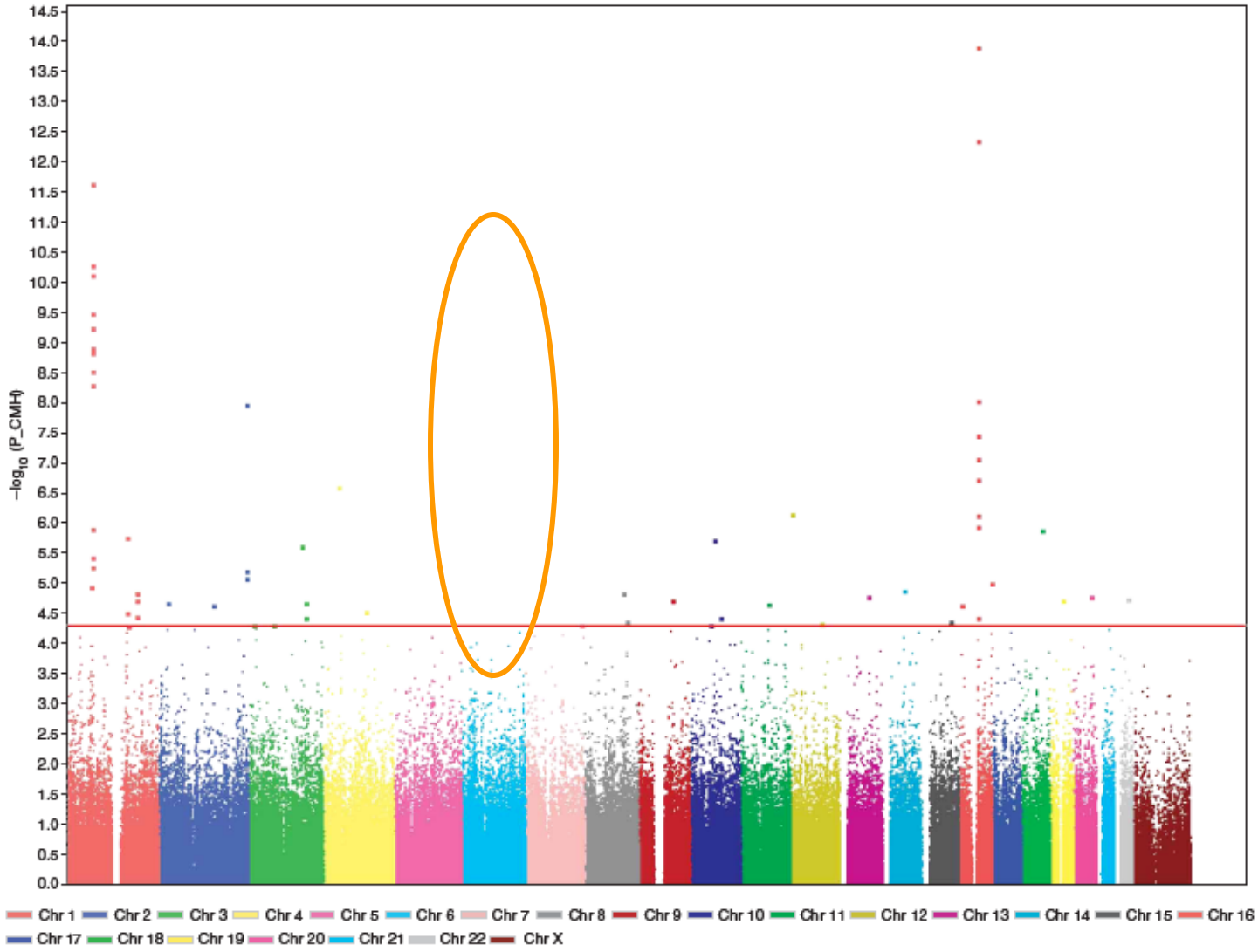



**Figure 1** Genome-wide association results for 946 ileal Crohn disease cases and 977 control samples. Single-marker association results for the combined non-Jewish and Jewish samples using the Cochran-Mantel-Haenszel (CMH) test. Each chromosome is depicted as a different color. The red line indicates the threshold ($P < 5 \times 10^{-5}$) selected to define regions for evaluation in the replication studies. The *P* value thresholds for suggestive and significant associations are $3.28 \times 10^{-6}$ and $1.64 \times 10^{-7}$, respectively, based on a Bonferroni correction for multiple testing. A modest correction factor ($\lambda = 1.056$) is necessary to correct for stratification between cases and controls, but it does not modify the current results.

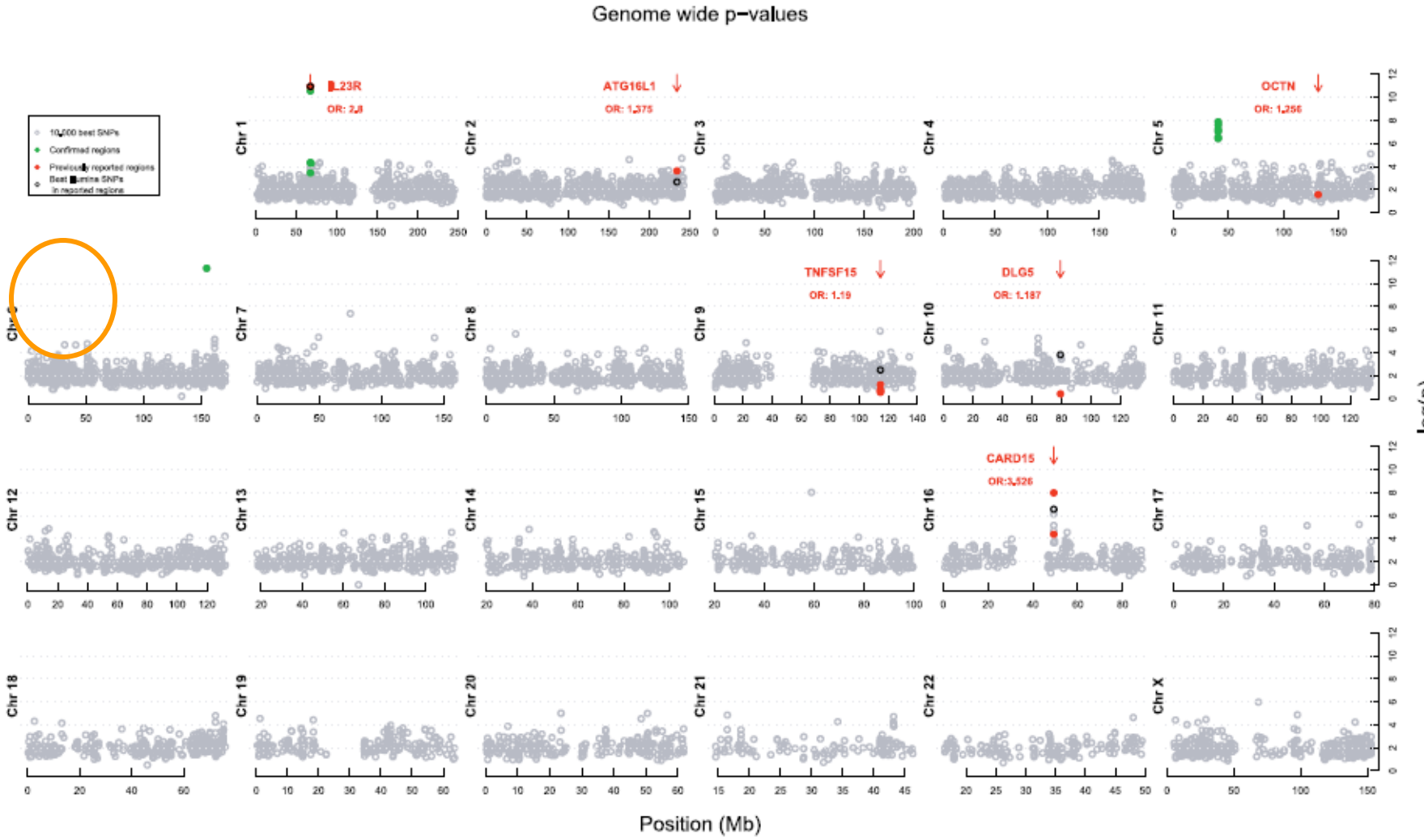



**Figure 1.** Results of the GWA for CD

*p*-values (−log[*p*]) for the 10,000 best SNPs out of 302,451 are shown (gray circles). The position of previously described susceptibility loci are marked by red arrows. The *p*-values obtained in our cohorts with the reportedly associated SNPs/mutations are shown by the red dots, and the corresponding odds ratios are indicated. The *p*-values obtained with SNPs included in the Illumina panel ≤50 kb from these SNPs/mutations are marked by black circles. SNPs genotyped in the confirmation cohort are shown as green dots.

doi:10.1371/journal.pgen.0030058.g001

European Journal of Human Genetics (2002) 10, 259–265

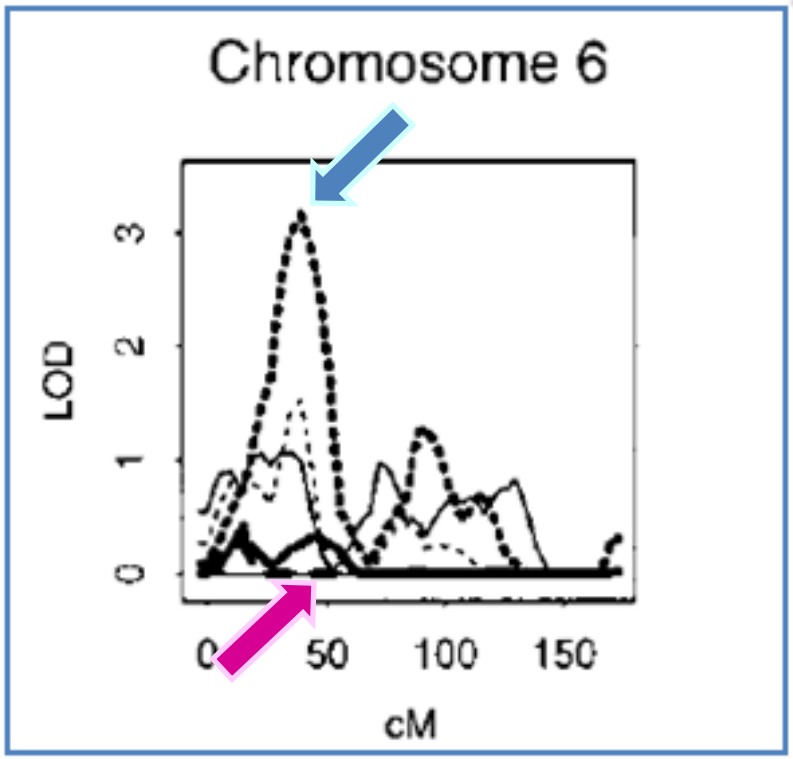
www.nature.com/ejhg

ARTICLE

# Sex stratification of an inflammatory bowel disease genome search shows male-specific linkage to the HLA region of chromosome 6

Sheila A Fisher*,[1], Jochen Hampe[2], Andrew JS Macpherson[3], Alastair Forbes[4], John E Lennard-Jones[4], Stefan Schreiber[2], Mark E Curran[5], Christopher G Mathew[1] and Cathryn M Lewis[1]

*[1]Division of Medical and Molecular Genetics, Guy's, King's and St Thomas' School of Medicine, King's College London, UK; [2]Department of General Internal Medicine, University Hospital Kiel, Christian-Albrechts-University, Kiel, Germany; [3]Division of Medicine, Guy's, King's and St Thomas' School of Medicine, King's College London, UK; [4]St Mark's Hospital, Harrow, UK; [5]DNA Sciences, Fremont, California, USA*


Chromosome 6
LOD
0
1
2
3
0
50
100
150
cM


Chromosome 1
Chromosome 2
Chromosome 3
Chromosome 4
Chromosome 5
Chromosome 6
Chromosome 7
Chromosome 8
Chromosome 9
Chromosome 10
Chromosome 11
Chromosome 12
Chromosome 17
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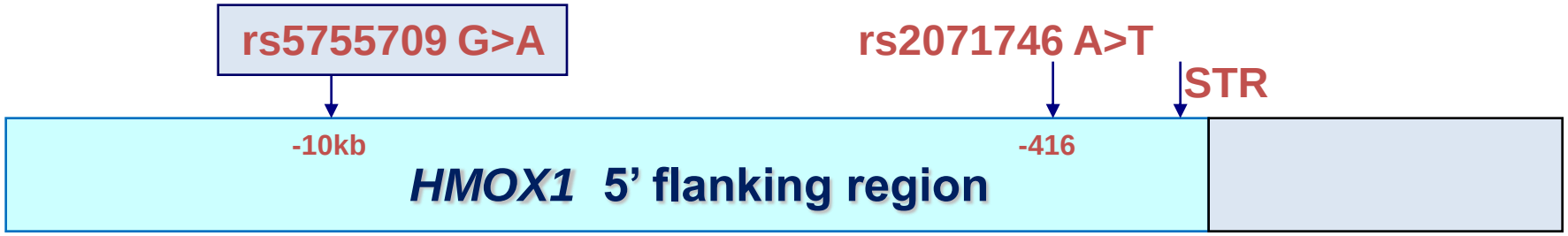
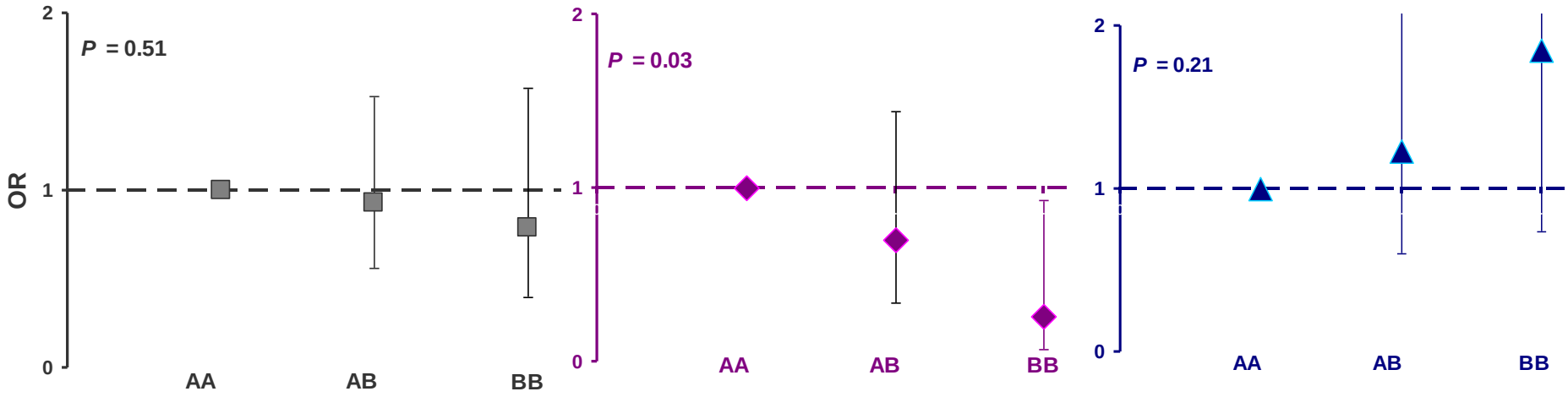
LOD
cM
CD ALL
CD MALE
CD FEMALE
UC ALL
UC MALE
UC FEMALE

# Effect Modification by Gender




***P* (sex) = 0.015**

***P* (sex; case-only) = 0.01**

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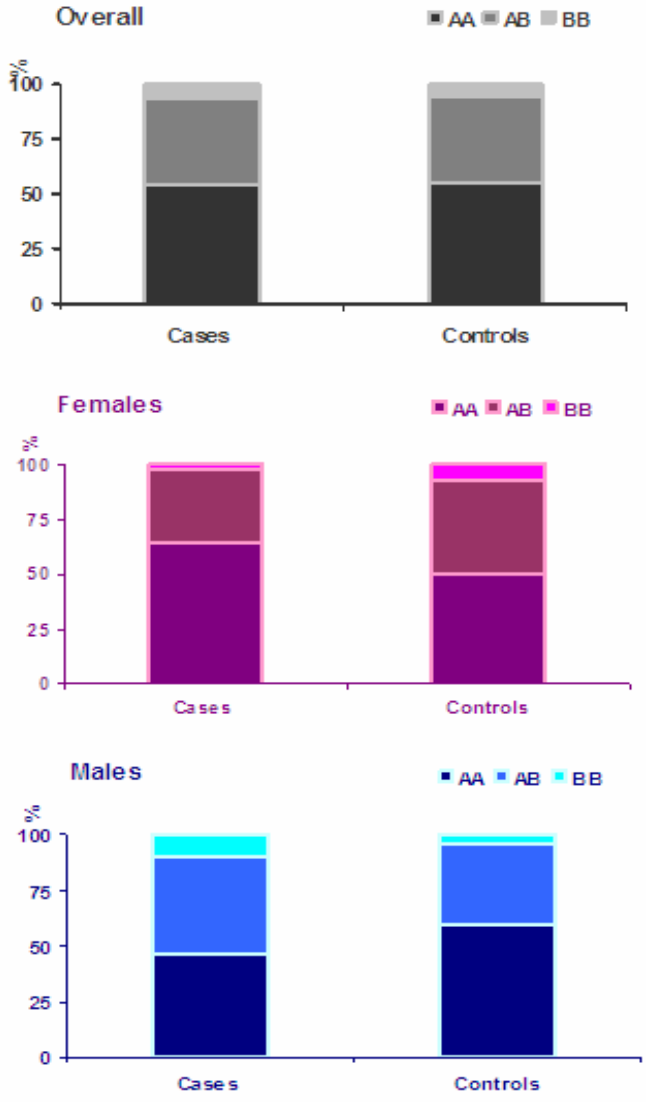
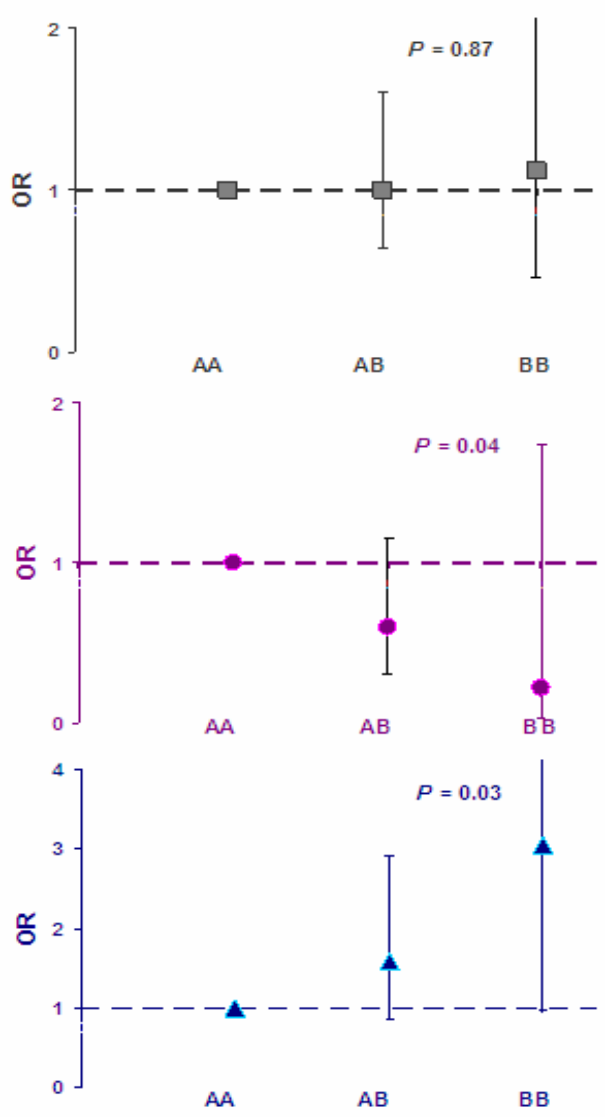
# Effect Modification by Gender

## *NRAMP2* rs422982 Shows Sex-specific Associations




*P* (sex) = 0.008


Saturday, March 29, 2008

**Why do genome-wide scans fail?**

# High technology does not preclude the need for appropriate data analysis

# Childhood ALL Study

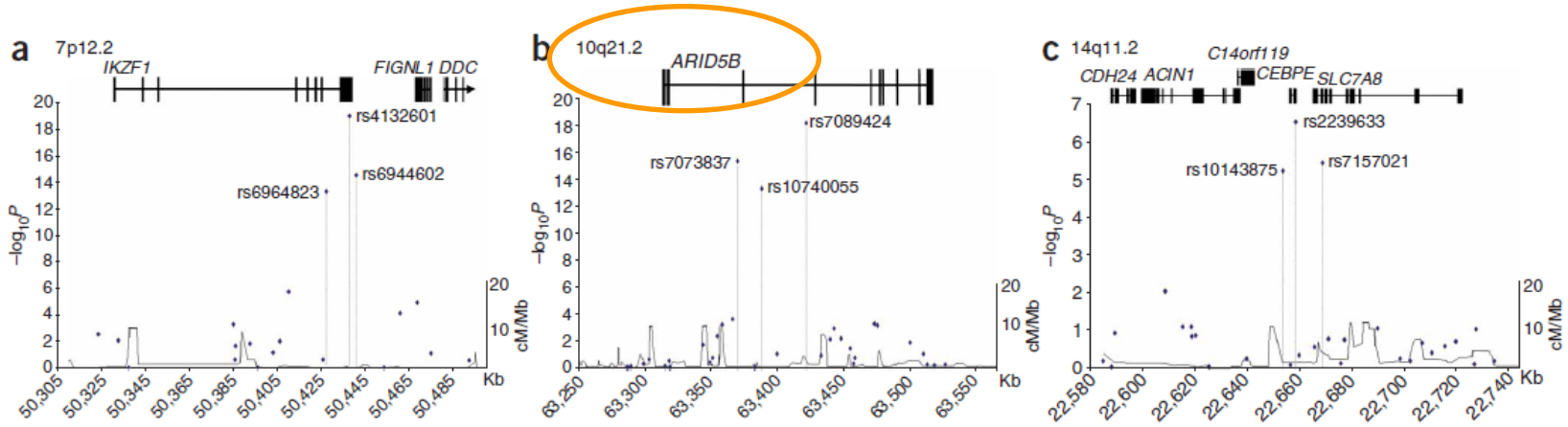


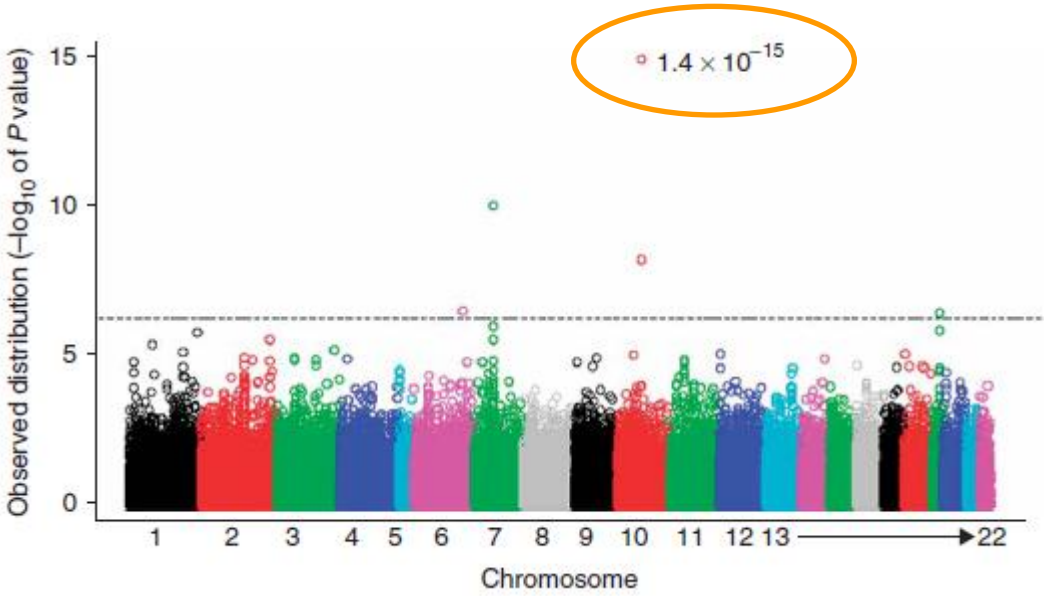

**Figure 1** LD structure and association results for each of the disease-associated regions. (**a**) 7p12.2; (**b**) 10q21.2; (**c**) 14q11.2. Chromosomal positions based on NCBI build 36 coordinates, showing Ensemble (release 48) genes. Armitage trend test *P* values (as $-\log_{10}$ values; left *y* axis) are shown for SNPs analyzed. Recombination rates in HapMap CEU across the region are shown in black (right *y* axis). Also shown are the relative positions of genes mapping to each region of association. Exons of genes have been redrawn to show the relative positions in the gene; therefore, maps are not to physical scale.

Loci on 7p12.2, 10q21.2 and 14q11.2 are associated with risk of childhood acute lymphoblastic leukemia

Elli Papaemmanuil[1], Fay J Hosking[1], Jayaram Vijayakrishnan[1], Amy Price[1], Bianca Olver[1], Eammon Sheridan[2], Sally E Kinsey[3], Tracy Lightfoot[4], Eve Roman[4], Julie A E Irving[5], James M Allan[5], Ian P Tomlinson[6], Malcolm Taylor[7], Mel Greaves[8] & Richard S Houlston[1]

Germline genomic variants associated with childhood acute lymphoblastic leukemia

Lisa R Treviño[1,6], Wenjian Yang[1,6], Deborah French[1], Stephen P Hunger[2], William L Carroll[3], Meenakshi Devidas[4], Cheryl Willman[5], Geoffrey Neale[1], James Downing[1], Susana C Raimondi[1], Ching-Hon Pui[1], William E Evans[1] & Mary V Relling[1]

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# GWAS & Epidemiologic Research

## Germline genomic variants associated with childhood acute lymphoblastic leukemia

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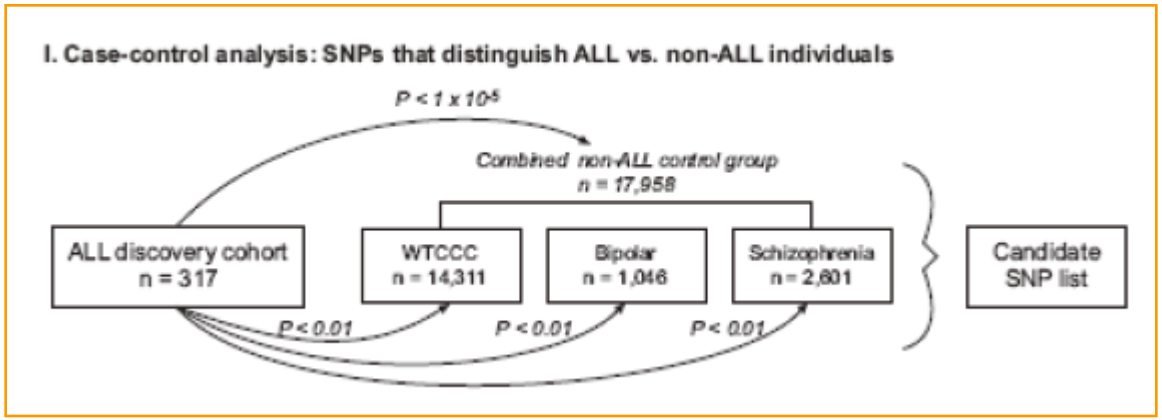


Saturday, March 29, 2008

**Why do genome-wide scans fail?**

# High technology does not preclude the need for good research design


Saturday, March 29, 2008

**Why do genome-wide scans fail?**

# Improvements in GWAS

**Better study design**

**Better data analysis**

***(statistical threshold, epistasis, gender effect)***

**Consideration of the environment**

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Saturday, March 29, 2008

**Why do genome-wide scans fail?**

# Improvements in GWAS

- Next-generation GWAS (1KG)

# Supplementary Tools

- Conventional genotyping methods
- Next-generation sequencing
- Epigenomics

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Genomics 2010+

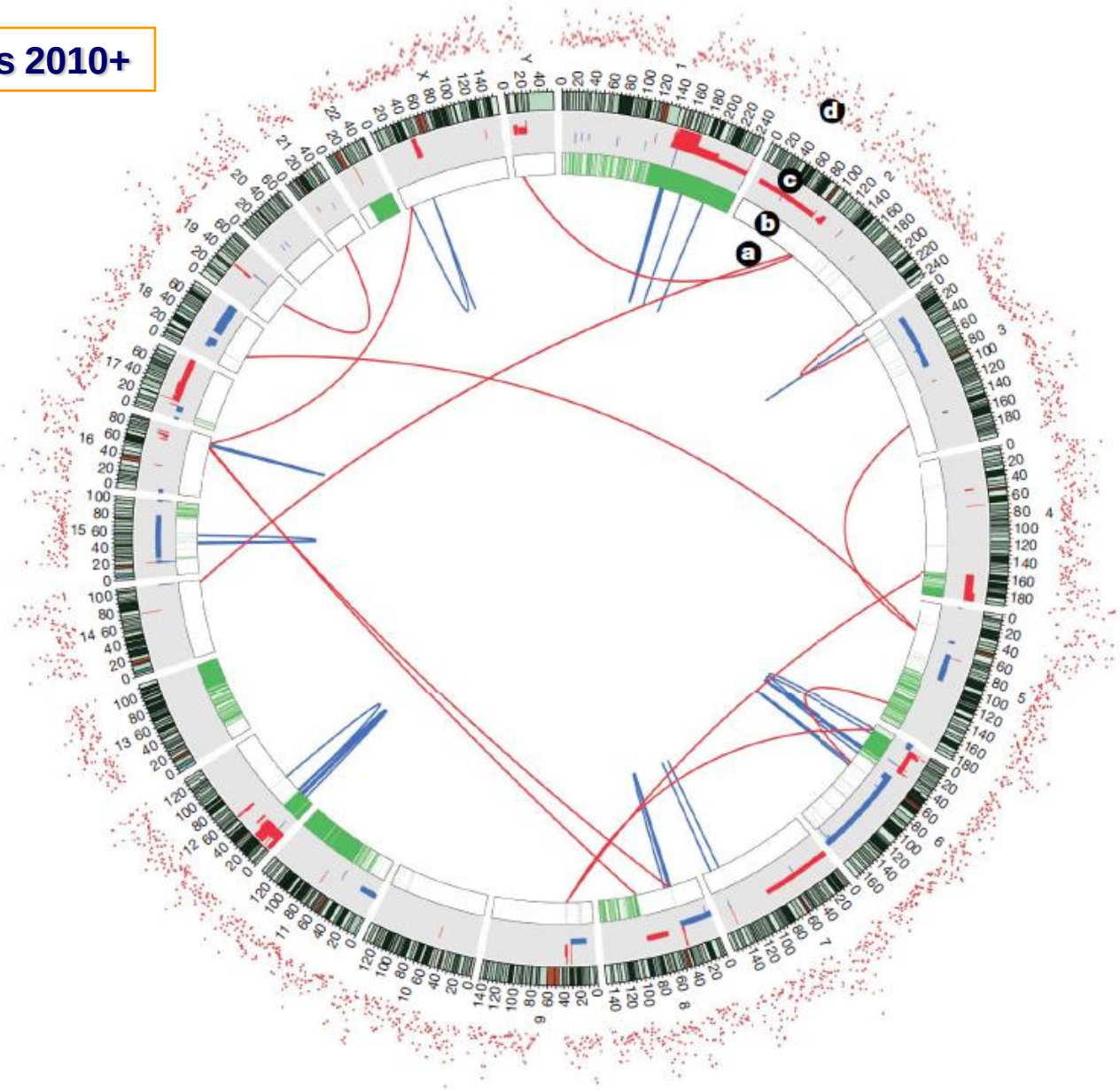


**Figure 1 | The genomic landscape of somatic alterations.** **a–d**, Various types of genomic profiles of the adenocarcinoma sample in this study. **a**, Experimentally confirmed somatic structural variations. Red lines indicate interchromosomal structural variations whereas blue lines represent intrachromosomal structural variations. **b**, Regions of loss of heterozygosity and allelic imbalance are in green and were based on the Affymetrix SNP 6.0 array data. **c**, Copy number profiles were derived from the Agilent array data with red indicating copy number gain and blue representing copy number loss (scale range: 0 to 4 copies). **d**, Each red dot represents the number of high-confidence somatic SNVs in a 1 Mb window. This figure was created using the Circos program[28].

## The mutation spectrum revealed by paired genome sequences from a lung cancer patient

William Lee[1], Zhaoshi Jiang[1], Jinfeng Liu[1], Peter M. Haverty[1], Yinghui Guan[2], Jeremy Stinson[2], Peng Yue[1], Yan Zhang[1], Krishna P. Pant[3], Deepali Bhatt[2], Connie Ha[2], Stephanie Johnson[4], Michael I. Kennemer[3], Sankar Mohan[5], Igor Nazarenko[3], Colin Watanabe[1], Andrew B. Sparks[3], David S. Shames[5], Robert Gentleman[1], Frederic J. de Sauvage[2], Howard Stern[4], Ajay Pandita[5], Dennis G. Ballinger[3], Radoje Drmanac[3], Zora Modrusan[2], Somasekar Seshagiri[2] & Zemin Zhang[1]

nature
Vol 465|27 May 2010|doi:10.1038/nature09004

# Genomics 2011

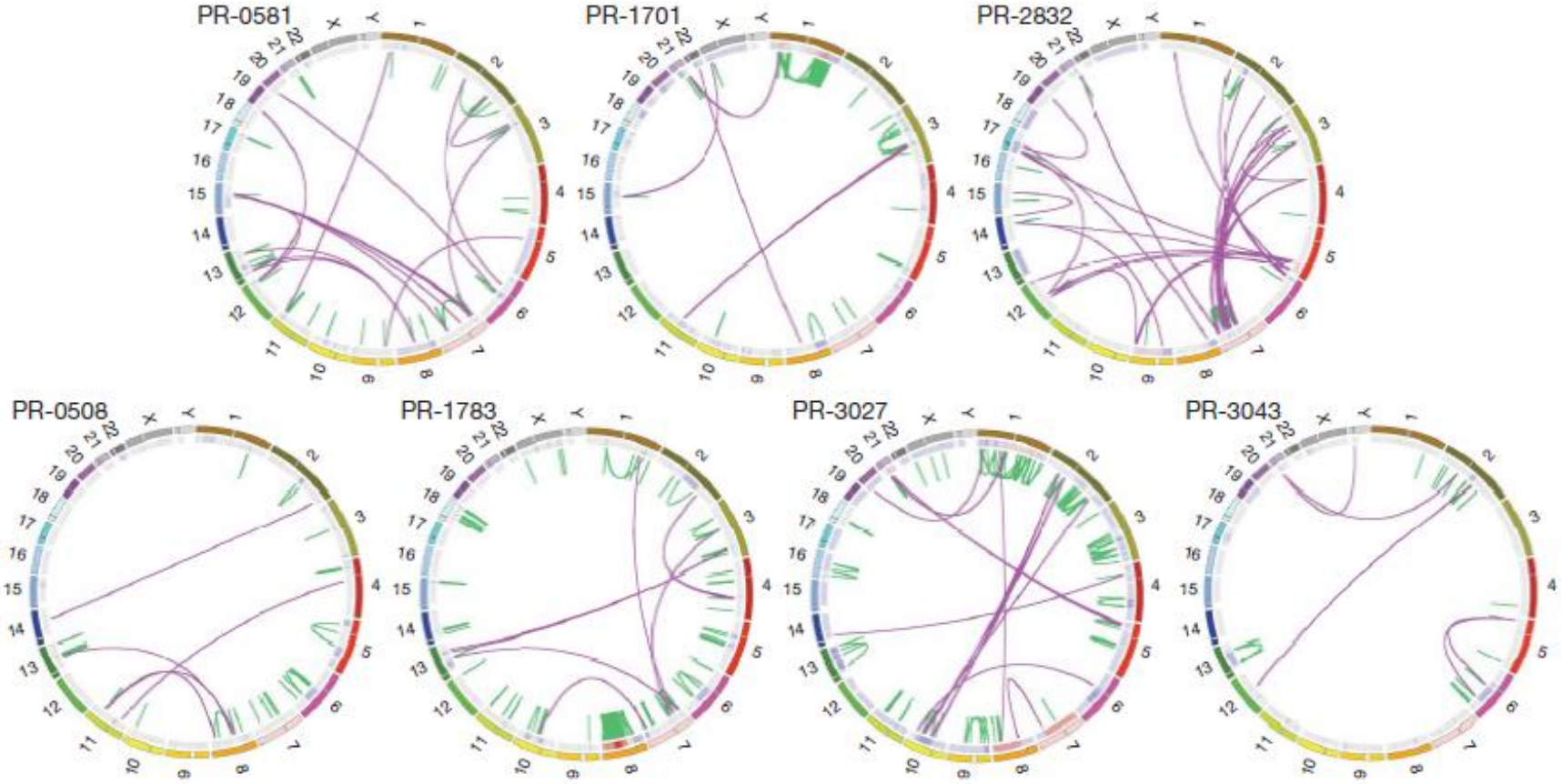


**Figure 1 | Graphical representation of seven prostate cancer genomes.** Each Circos plot[12] depicts the genomic location in the outer ring and chromosomal copy number in the inner ring (red, copy gain; blue, copy loss). Interchromosomal translocations and intrachromosomal rearrangements are shown in purple and green, respectively. Genomes are organized according to the presence (top row) or absence (bottom row) of the *TMPRSS2–ERG* gene fusion.

ARTICLE

doi:10.1038/nature09744

## The genomic complexity of primary human prostate cancer

Michael F. Berger[1]†*, Michael S. Lawrence[1]*, Francesca Demichelis[2,3]*, Yotam Drier[4]*, Kristian Cibulskis[1], Andrey Y. Sivachenko[1], Andrea Sboner[5,6], Raquel Esgueva[2], Dorothee Pflueger[2], Carrie Sougnez[1], Robert Onofrio[1], Scott L. Carter[1], Kyung Park[2], Lukas Habegger[6], Lauren Ambrogio[1], Timothy Fennell[1], Melissa Parkin[1], Gordon Saksena[1], Douglas Voet[1], Alex H. Ramos[1,7], Trevor J. Pugh[1,7,8], Jane Wilkinson[1], Sheila Fisher[1], Wendy Winckler[1], Scott Mahan[1], Kristin Ardlie[1], Jennifer Baldwin[1], Jonathan W. Simons[9], Naoki Kitabayashi[2], Theresa Y. MacDonald[2], Philip W. Kantoff[7,8], Lynda Chin[1,7,8,10], Stacey B. Gabriel[1], Mark B. Gerstein[5,6,11], Todd R. Golub[1,12,13,14], Matthew Meyerson[1,7,8,14], Ashutosh Tewari[15], Eric S. Lander[1,7,16], Gad Getz[1], Mark A. Rubin[2] & Levi A. Garraway[1,7,8,14]

Fig. 1. One-year-old female genetically identical viable yellow agouti mice ($A^{vy}$). Maternal dietary supplementation with methyl donors such as folic acid, choline, and betaine [34] or the phytoestrogen, genistein [32], shifts the coat color of the offspring from yellow to brown, and reduces the incidence of obesity, diabetes, and cancer.

Reproductive Toxicology 23 (2007) 297–307

Review

# Epigenetic gene regulation: Linking early developmental environment to adult disease

Dana C. Dolinoy[a,b,c], Jennifer R. Weidman[a], Randy L. Jirtle[a,b,c,*]

illumina

APPLICATIONS SYSTEMS SERVICES SCIENCE SUPPORT

COMPANY

Products / Infinium HumanMethylation450 BeadChip Kits

## Infinium HumanMethylation450 BeadChip Kits

| | |
|---|---|
| System: | iScan, HiScanSQ |
| Technology: | BeadArray |
| Assay: | Infinium Methylation Assay |
| Applications: | Gene Regulation and Epigenetic Analysis, Sequencing-Based Methylation Analysis |
| Species: | Human |
| Contents: | Each Infinium HumanMethylation450 BeadChip can process 12 samples. Each kit contains BeadChips along with reagents for amplifying, fragmenting, hybridizing, and analyzing DNA methylation in human DNA samples. |

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# Genetic Risk Profiling: Something is Missing

eQTL studies are showing that future visits to the clinic will not be solely based on personalized genomics (that is, genome sequencing) but instead on personalized 'omics', which will combine in-depth analysis of DNA and functional genomics to tell us more about the medical condition of an individual.

From expression QTLs to personalized transcriptomics

*Stephen B. Montgomery and Emmanouil T. Dermitzakis*

# Genetic Risk Profiling: Something is Missing

**No single 'omics' analysis can fully unravel the complexities of disease pathogenesis**

**Genetics certainly does not go far enough**

**Combinatorial complexity of disease development should be taken into account**

# CONCLUSION

**Integromics, including exposomics, will be the most informative omics**

# Genomics and Proteomics in Epidemiology

## *Treasure Trove or "High-Tech Stamp Collecting"?*

*David J. Hunter*

*Epidemiology* • Volume 17, Number 5, September 2006

Epidemiologists should not be seduced by technology into measuring observations for the sake of doing so. Tony McMichael[12] warned us against this when he wrote about the dangers of "high-tech stamp collecting." Epidemiology has been described as "the art of the possible," but there is a difference between the study of the important diseases that are possible to study and the study of what is possible just for the sake of doing so. "Because it is there" (Mallory's answer to the question of why he wanted to climb Everest) is not a good mantra for the epidemiologist. We have to learn what technologies can be usefully applied to which questions rather than applying everything to anything. Inevitably, a certain amount of "stamp collecting" may be required to learn the use (or nonuse) of new technologies. Still, the principles of good study design and adequate sample size must not be forgotten in any drive to generate novel data.

IN THE FUNNY PAGES: "MISTER WONDERFUL," A NEW STRIP BY DAN CLOWES (SORT OF FAMOUS, IN AN UNDERGROUND WAY, FOR "GHOST WORLD" AND "ART SCHOOL CONFIDENTIAL") THAT JUST MIGHT BE THE STRANGEST STORY OF A BLIND DATE EVER ... WELL, EVER TOLD BY A GRAPHIC

The New York Times Magazine

SEPTEMBER 16, 2007 / SECTION 6

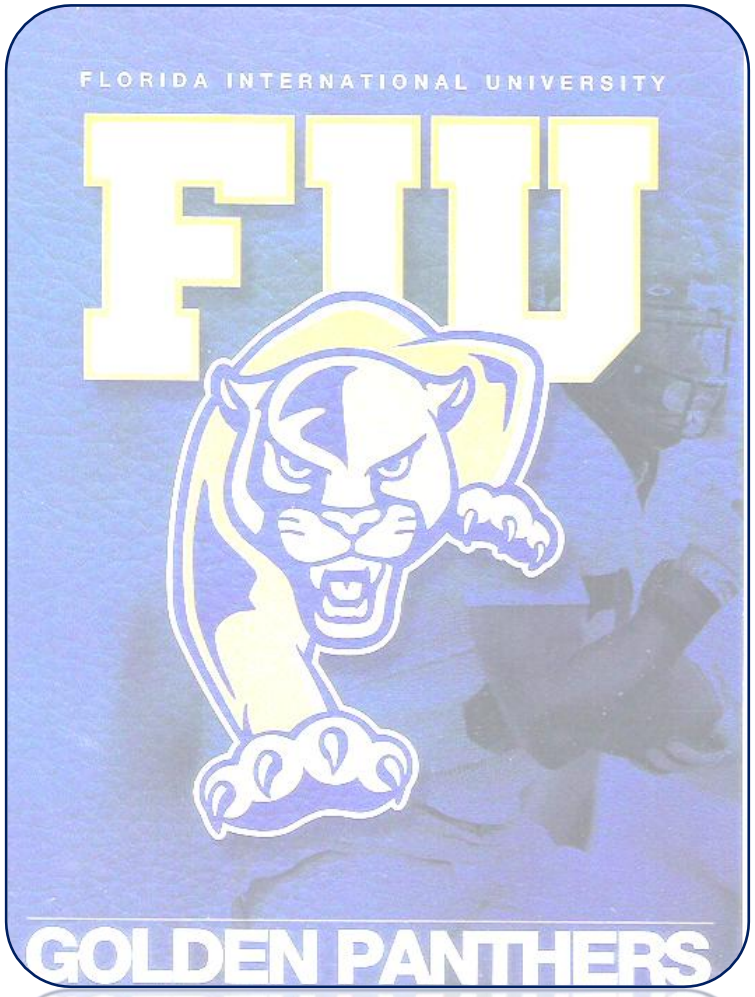
The scandal of poor epidemiological research

*Reporting guidelines are needed for observational epidemiology*

# Unhealthy Science

Why can't we trust much of what we hear about diet, health and behavior-related diseases?

By Gary Taubes





**Sandeep, Amy and Malar**

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- TÜBİTAK

http://www.dorak.info/kusadasi.pdf


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