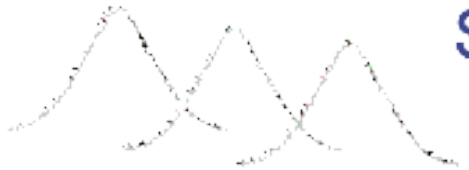

Summer Institute
in Statistical Genetics

2016

Introduction to Genetics and Genomics

3. Association Studies

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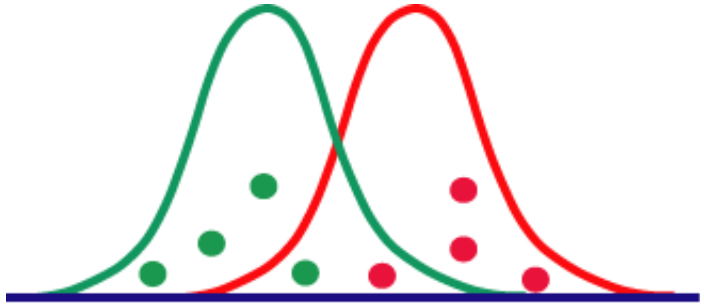
Outline

- General overview of association studies
- Sample results
- Three steps to GWAS:

  primary scan, replication, fine mapping

Principle of Association Studies

Individual	Site	Score
1	A T C C G A	9
2	A C T C G A	8
3	A C C A - G	3
4	T T C A G A	5
5	A T C A G A	2
6	A C C C - G	7
7	T C T A - G	4
8	A T C C G A	8

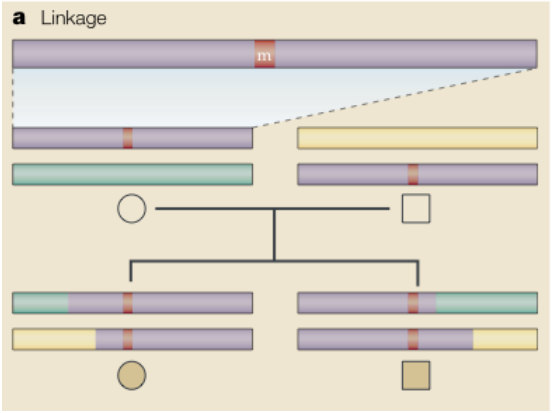


Are the phenotype scores associated with each class of SNP drawn from the same or different distributions ?

Linkage versus Association

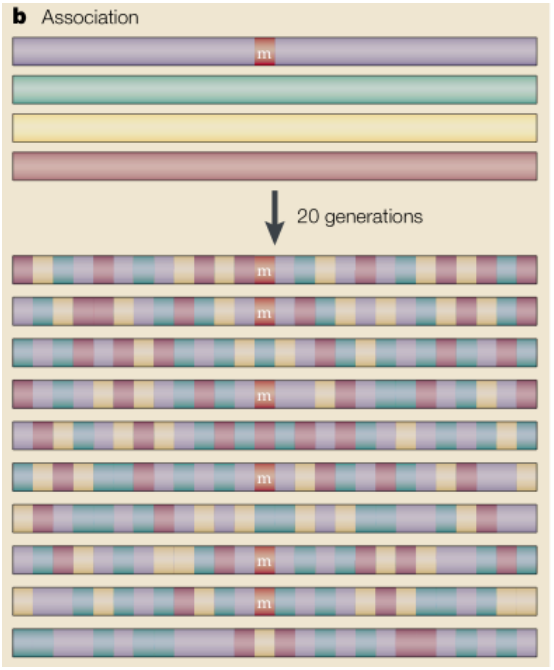
Linkage examines recent recombination events in a pedigree:

- over just several generations
- large chromosomal regions detected
- no information on allele frequency



Association examines historical recombination events in a population:

- basically a 10,000 generation pedigree
- resolution to single genes
- estimates effect size and frequency



Cardon & Bell. 2003. Nat. Rev. Genet. 2:91

Why LD happens

When a mutation occurs, by definition it is only on one chromosome and hence "associated" with the genotypes elsewhere on that chromosome.

Over time, the mutation increases in frequency and becomes a polymorphism. It remains in LD with the genotypes on the chromosome it appeared on.

Eventually recombination breaks up the LD, in proportion to genetic distance.

Measurement of LD

LD is the non-random association of genotypes.

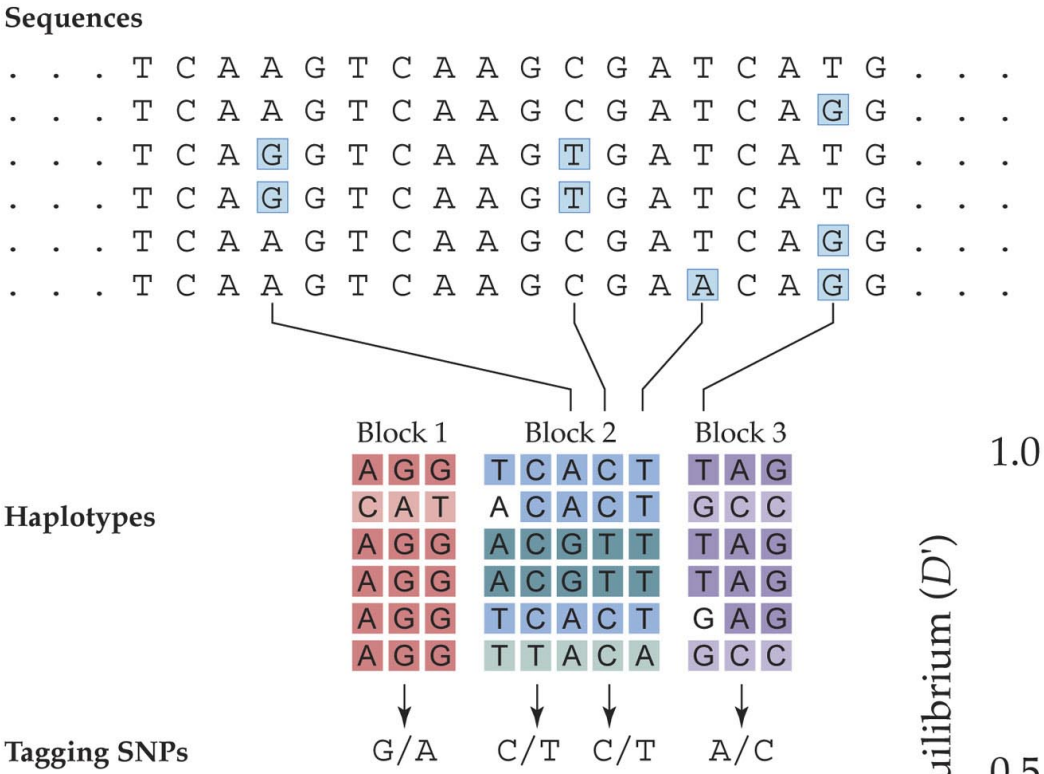
Expected

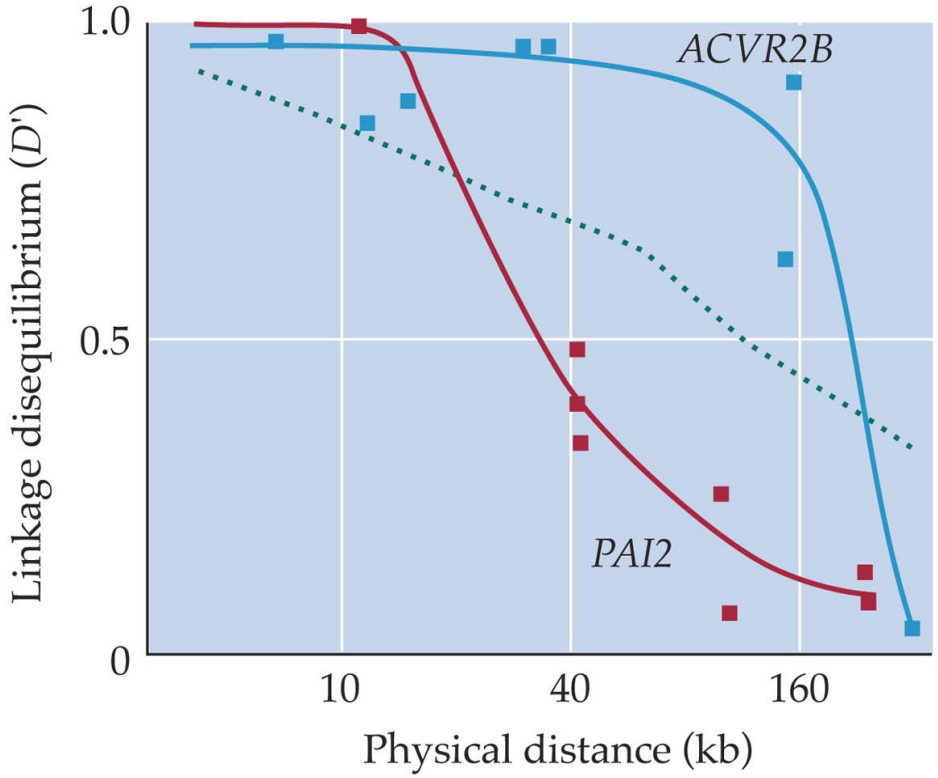
		AA	AG	GG
		24	48	24
TT	24	6	12	6
TC	48	12	24	12
CC	24	6	12	6

Observed

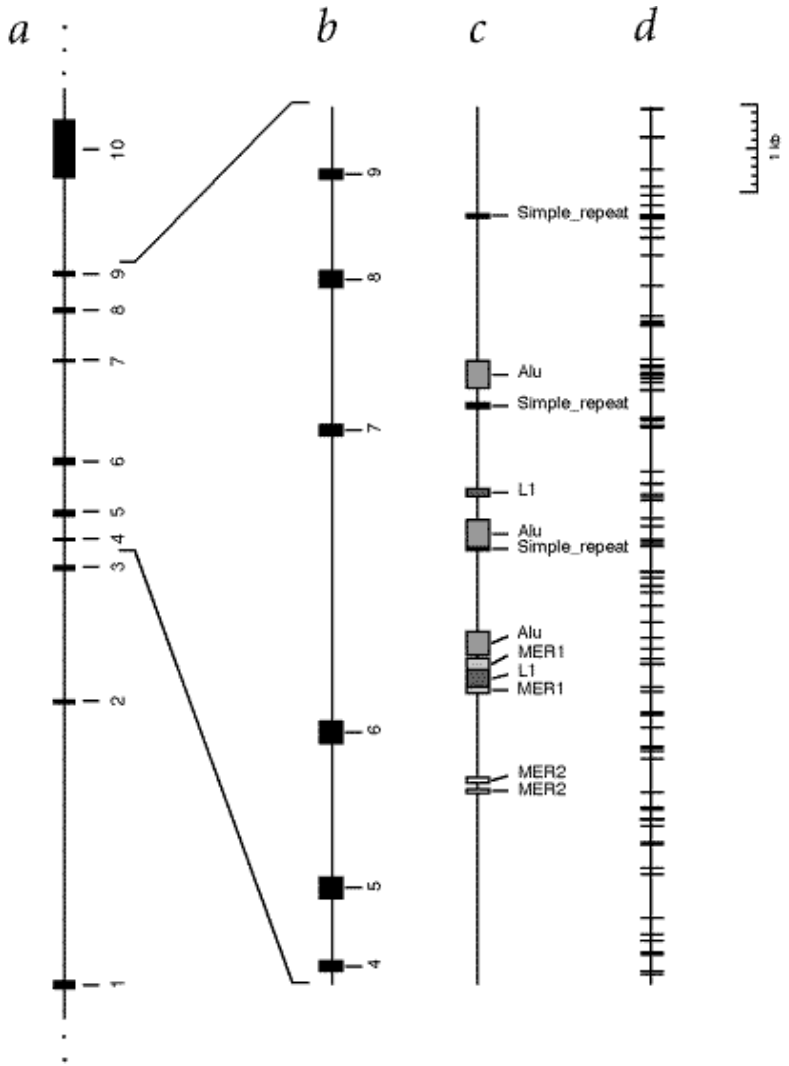
		AA	AG	GG
		24	48	24
TT	24	24	0	0
TC	48	0	48	0
CC	24	0	0	24

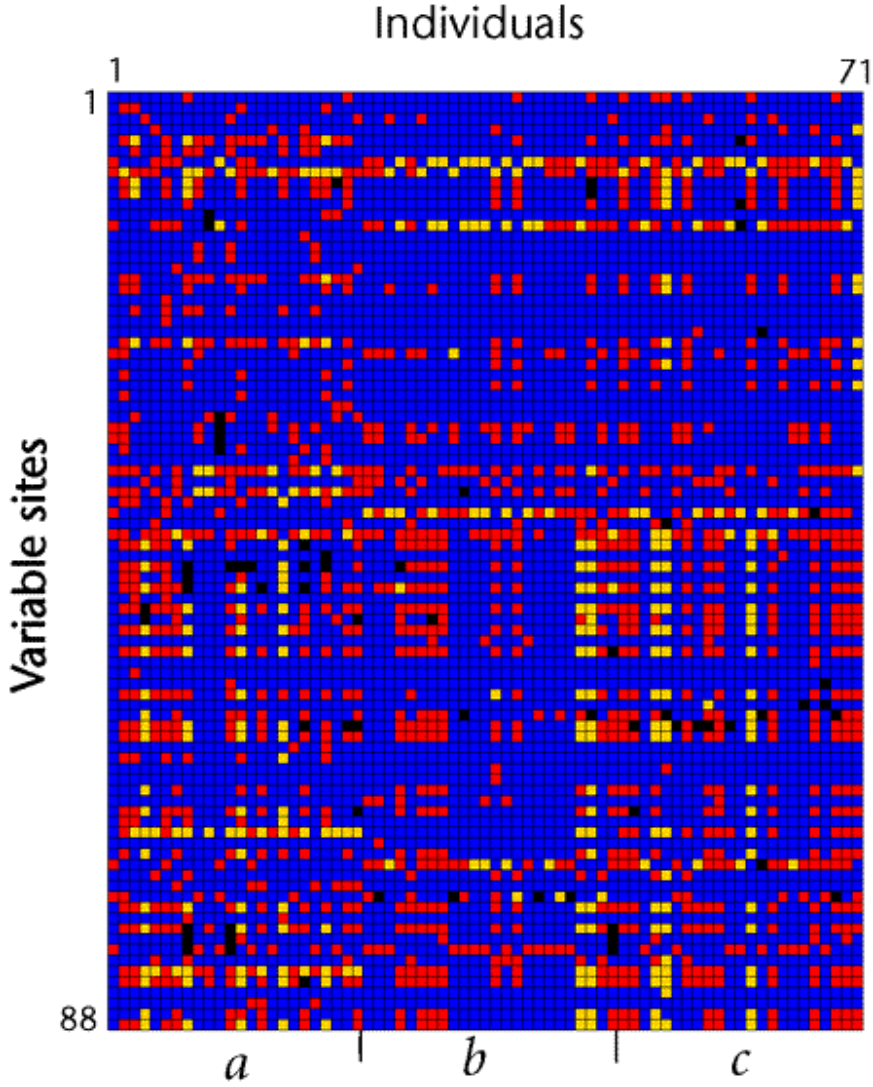
Haplotypes and Tagging SNPs





LPL example

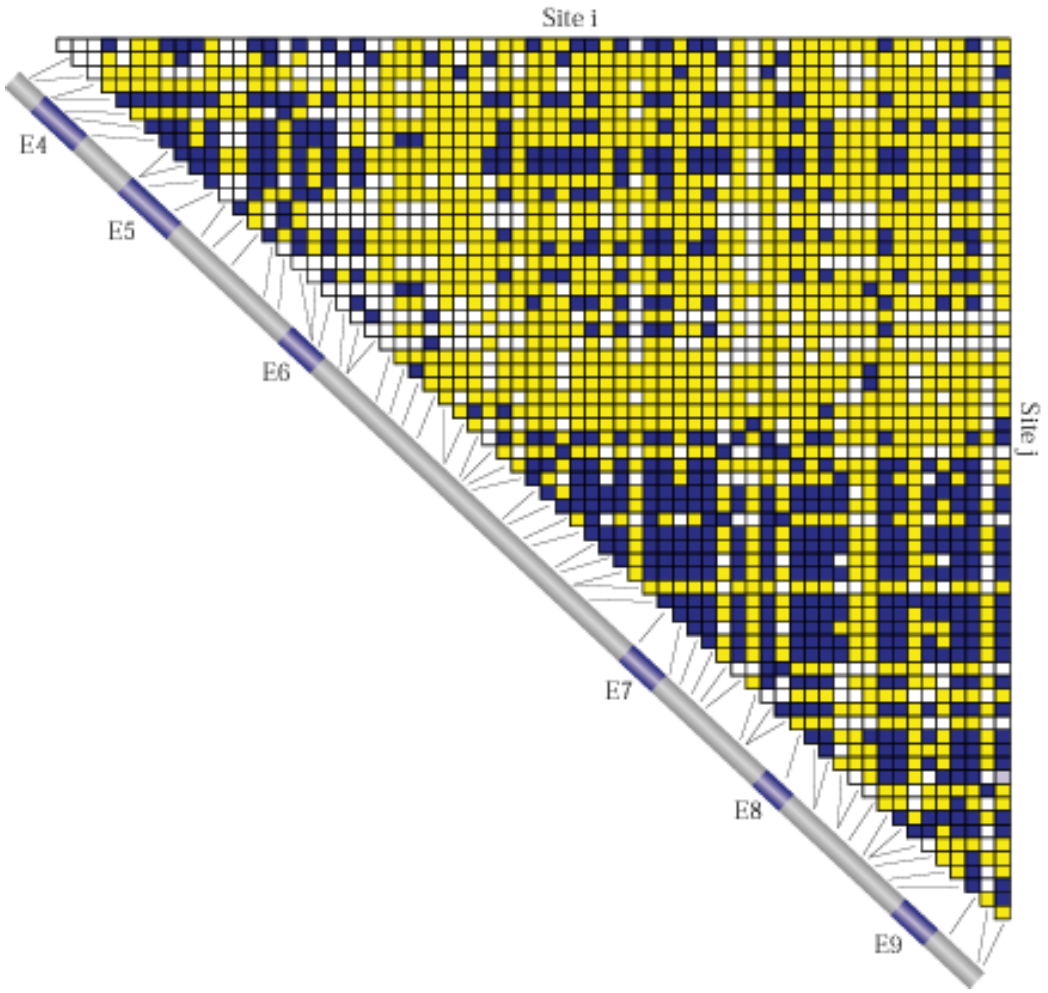




African Finnish

Minnesota

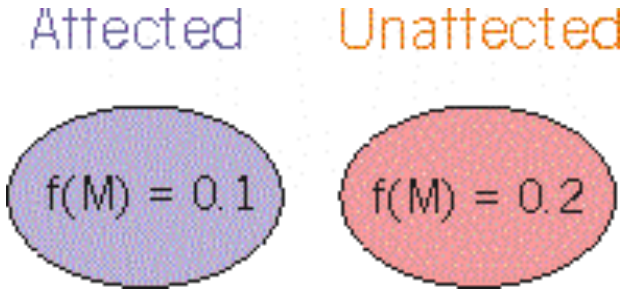
LD plots



Key Parameters for LD Mapping

- Polymorphism: Flies 1/30 bp, 10 x > Human 1/kb
- Haplotype structure/LD:
  Fly LD decays over 200 bp, Human LD decays over 100 kb
- Population structure:
  Panmixia and clinality v. Structure and admixture
- Allele frequencies:
  Much more power for common alleles (infinitesimal model)

Case-Control and TDT designs



	Observed		Expected	
	Allele M	Allele m	Allele M	Allele m
Affected	34	278	61	265
Unaffected	69	256	62	269

$\chi^2 = 14.0$ P <0.001

$\frac{M}{m} \times \frac{M}{m}$

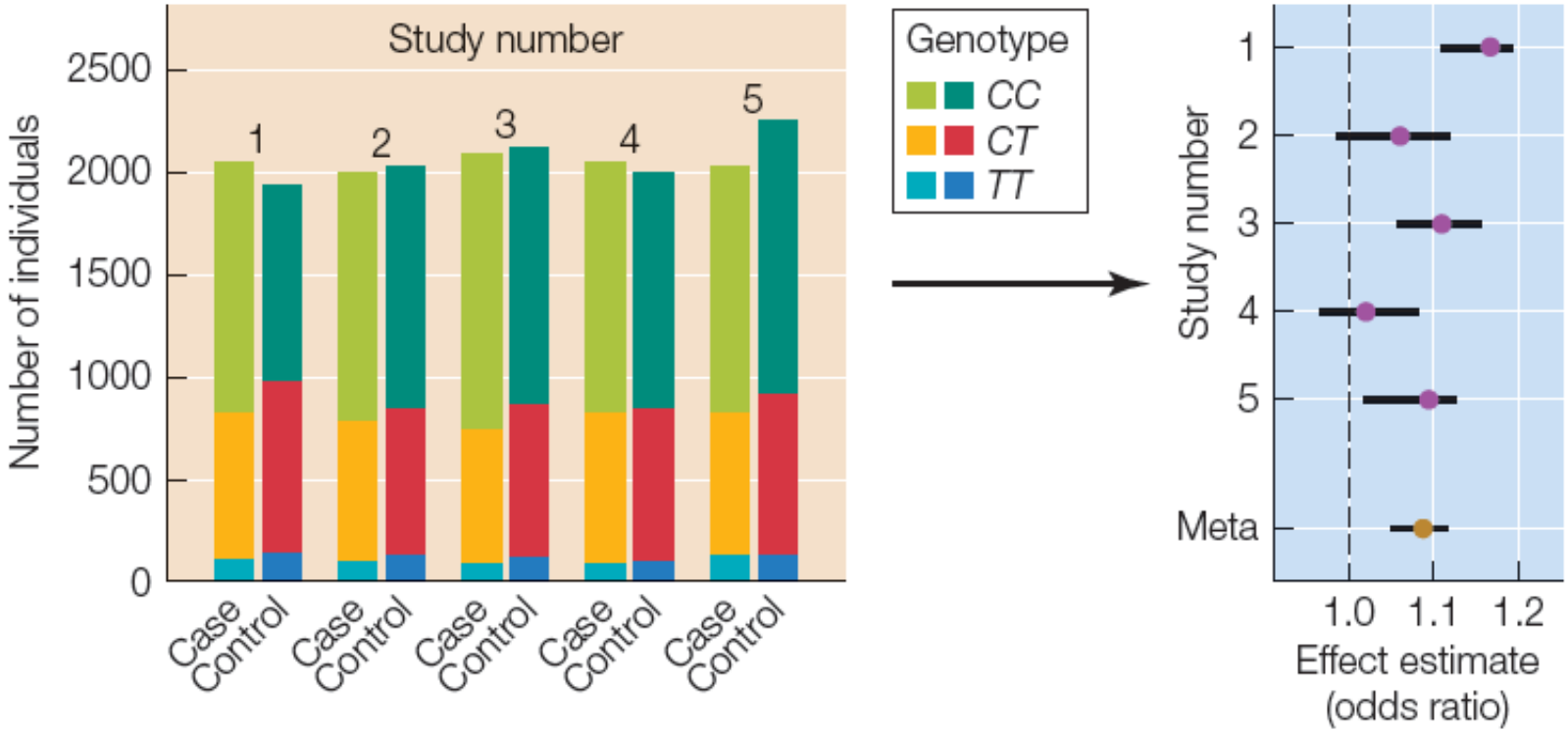
↓

f(M) = 0.63

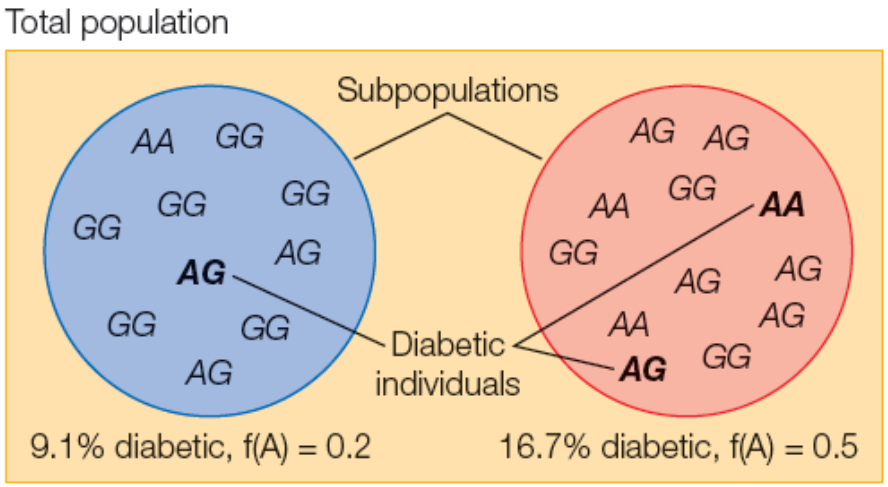
	Transmitted Allele	
	M	m
Observed	78	46
Expected	62	62

$\chi^2 = 8.2$ P < 0.001

Repeatability and Forest Plots



Population Structure



Blue subpopulation

	AA	*AG*	*GG*
Case	80	640	1280
Control	800	6400	12,800
Case/control	0.1	0.1	0.1

Red subpopulation

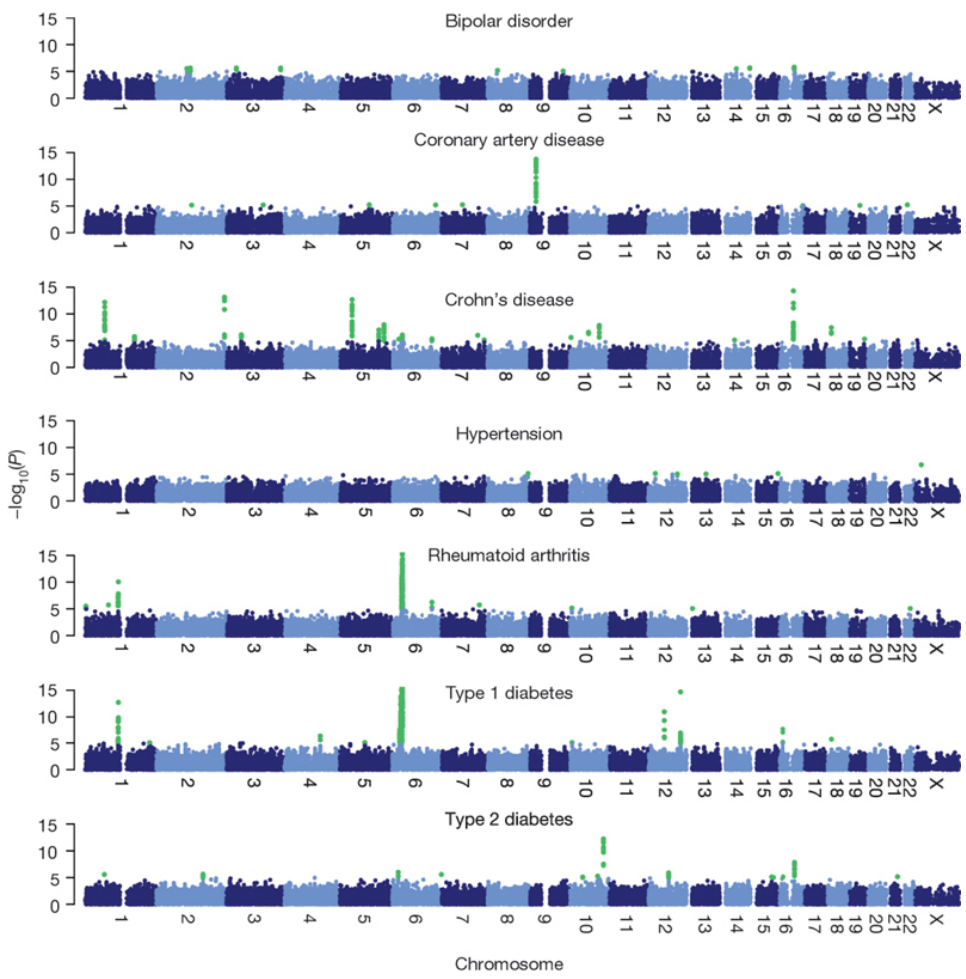
	AA	*AG*	*GG*
Case	200	400	200
Control	1000	2000	1000
Case/control	0.2	0.2	0.2

Total population

	AA	*AG*	*GG*
Case	280	1040	1480
Control	1800	8400	13,800
Case/control	0.155	0.124	0.107

Odds ratio (*A*:*G*) = 1.2 $p = 10^{-8}$

The Genetics of 7 Diseases

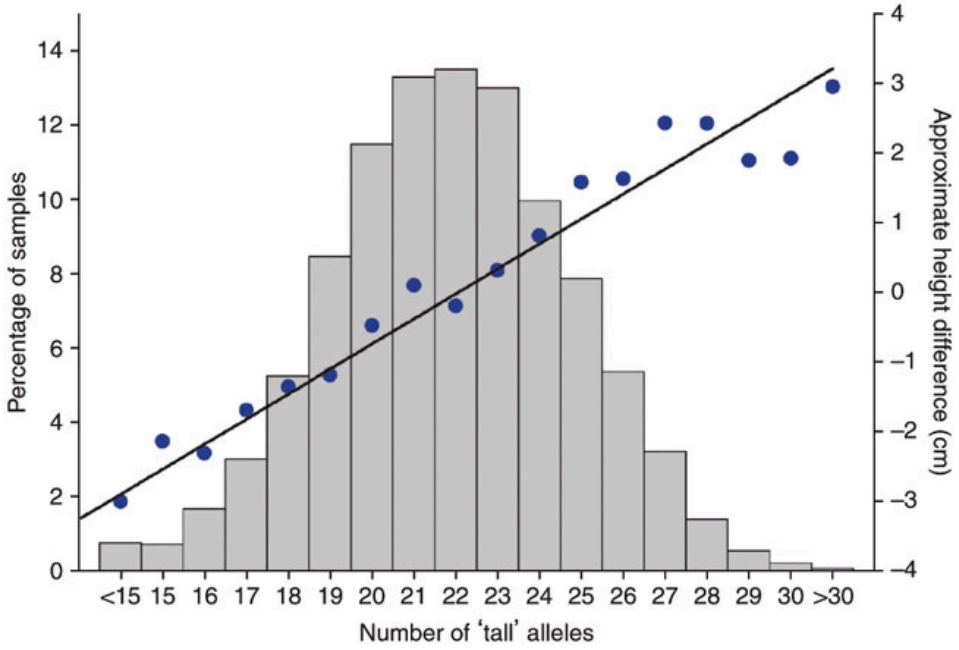


GWAS first appeared 24 months ago, now several new diseases each month

Inflammatory diseases show multiple associations, with some common variants (notably the MHC)

Depression and Hypertension show nothing: likely no variants with a relative risk greater than 1.5

The Genetics of Height



But … they only explain 15% of the variation for height (one fifth of the heritability)

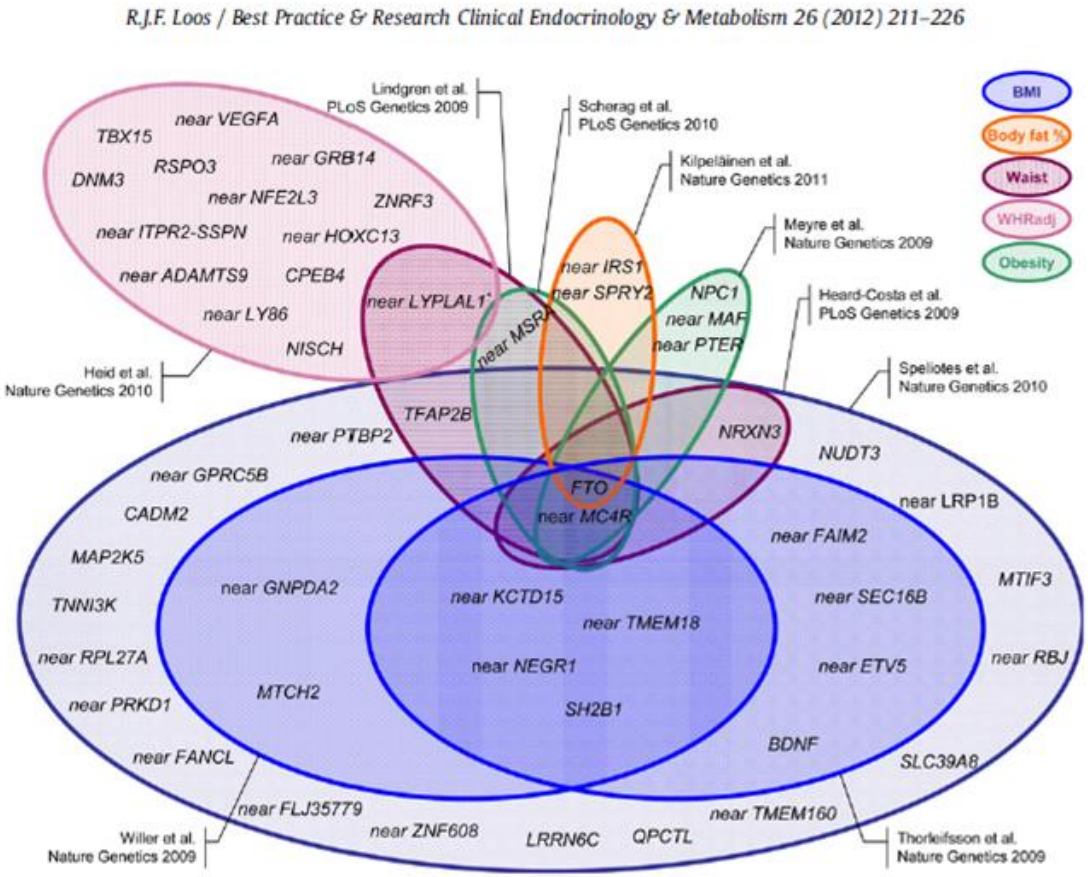
700 loci clearly influence height in combined analysis of 250,000 people

Diverse roles:
Hedgehog signalling
Chromatin structure
Cell cycle regulation
Extracellular matrix deposition

Possible contribution of some of these loci to osteoarthritis, cancer, athleticism

Half the genes have at least two independent associations

The Genetics of Obesity



Heritability of obesity ~ 60%

2/3 Americans BMI > 25

One gene, FTO, is repeatedly associated with BMI, hip circumference and weight, in most human populations

Homozygote classes differ in weight by up to 2 kg

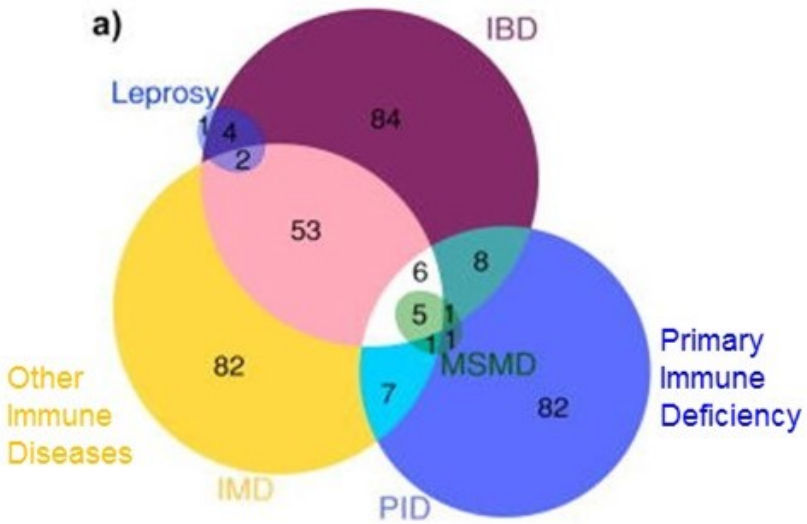
Study of 230,000 people →

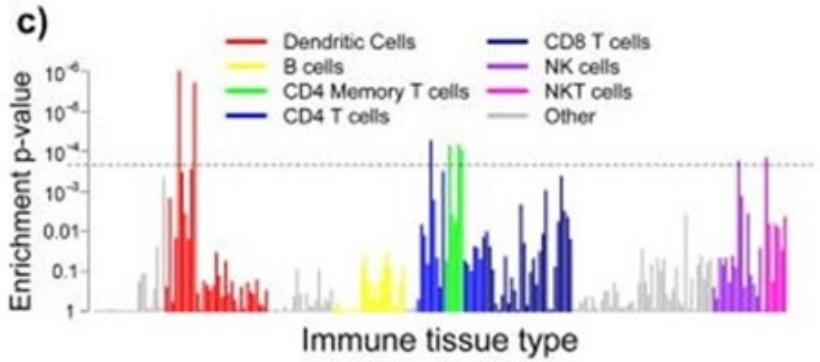
- 49 loci for WHR, many linked to adipose, insulin biology
- 20 loci only in women

Study of 340,000 people →

- 97 loci for BMI, many linked to neuronal function
- Little overlap with WHR

The Genetics of IBD





Inflammatory Bowel Disease affects ~1% of adults either as Crohn's or Ulcerative Colitis

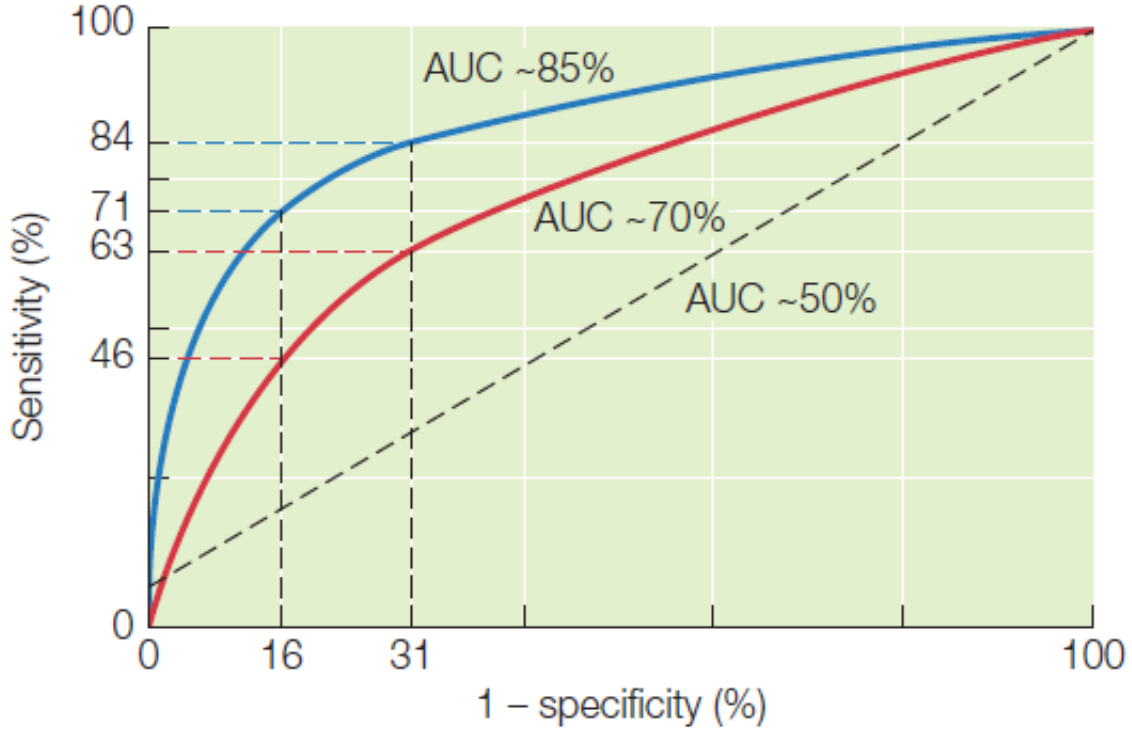
Two genes, IL23R and NOD2, each explain 1% of the variance

Another 160 genes each explain less than 0.25% of it

Strongly overlap with PID and other autoimmune diseases

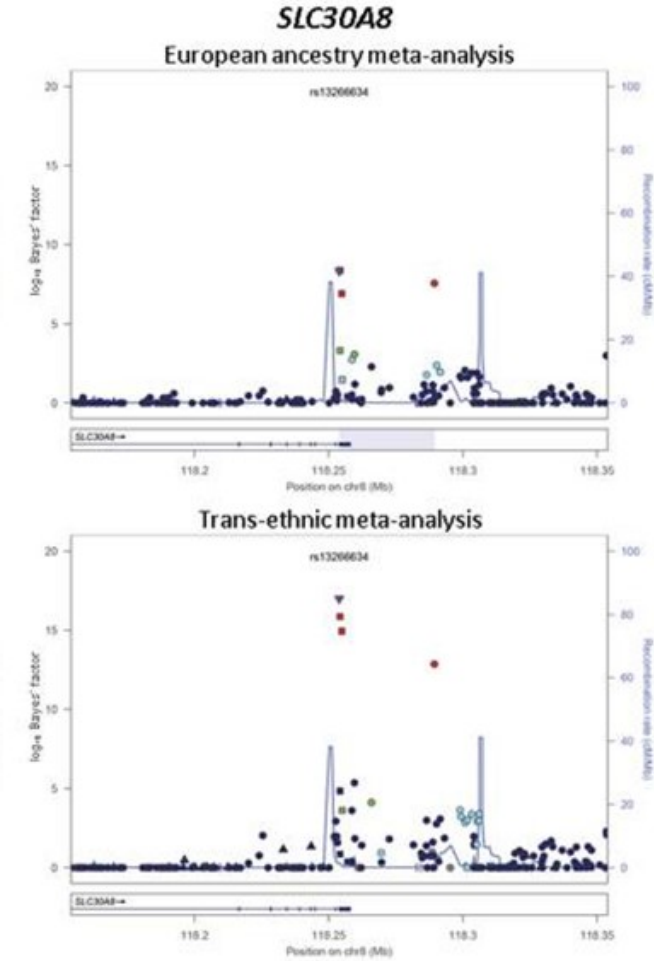
Vast majority are in immune function genes, and ongoing efforts suggest activity in specific immune cell types

Prediction, Specificity, and Sensitivity



	Cases	Controls	
Called positive	True positive (TP), 25	False positive (FP), 215	PPV, (TP/[TP + FP]) = 10.4%
Called negative	False negative (FN), 10	True negative (TN), 1150	NPV, (TN/[FN + TN]) = 99.1%
	Sensitivity, (TP/[TP + FN]) = 71%	Specificity, (TN/[FP + TN]) = 84%	

The Genetics of Type 2 Diabetes



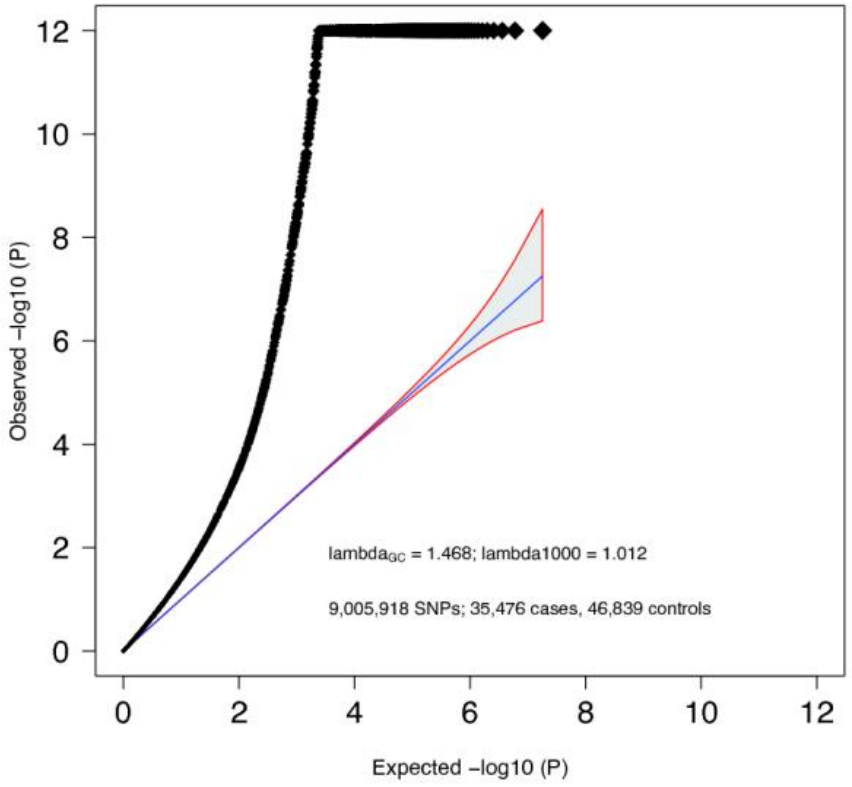
54 established Fasting Glucose or Fasting Insulin loci tend to have pancreatic islet cell functions

23 replicate in African Americans in Trans-ethnic analyses

TCF7L2 is the strongest risk locus for T2D in Caucasians. The ancestral allele is the risk allele: it is found in 90% of Africans, 40% of Europeans, and just 5% of Asians

Considering the top 18 loci:
1% of CAU have >24 alleles
2% of CAU have <12 alleles
They differ 4-fold in odds of T2D

The Genetics of Schizophrenia



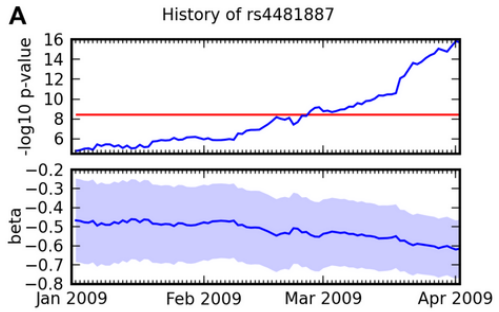
128 independent SNP associations from GWAS of 37,000 cases

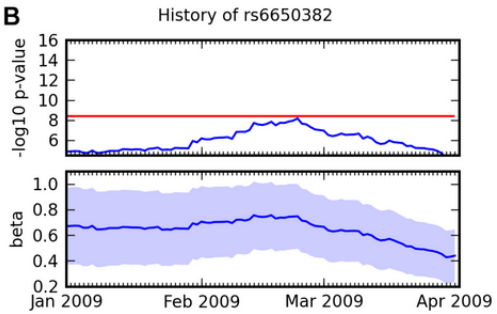
Strong enrichment in genes expressed in certain neuronal cell types or implicated in synaptic transmission

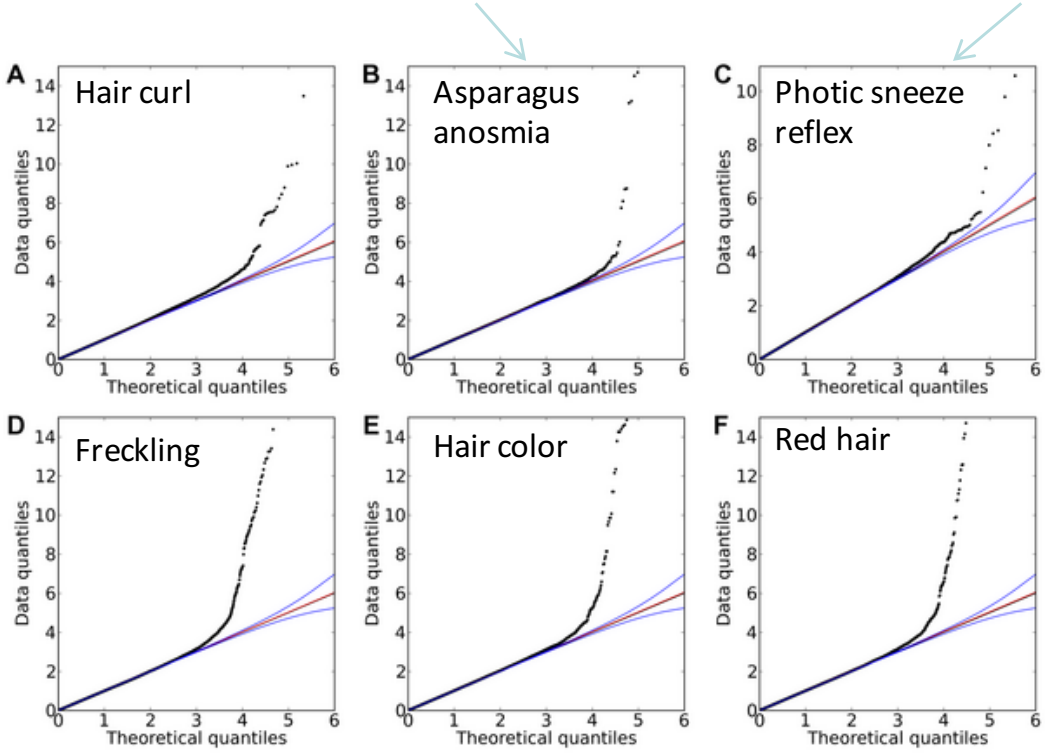
But at least 5% of cases attributable to CNV: copy number variation

3 major chromosomal deletions of >100kb at frequency <1% are almost exclusively found in schizophrenics

23andme studies







Other interesting traits:

Endurance Runner vs Sprinter (30% of people change their answer if they know their ACTN3)

Left vs Right Handedness (nothing striking)

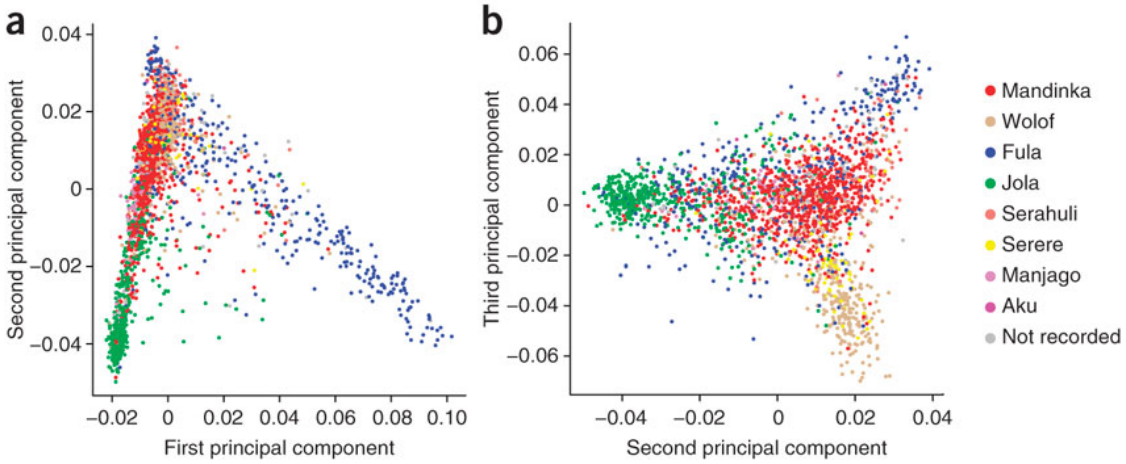
Have you ever needed braces or wisdom teeth surgery?

Breast size (finds breast cancer risk loci)

Hand-clasp dominance …

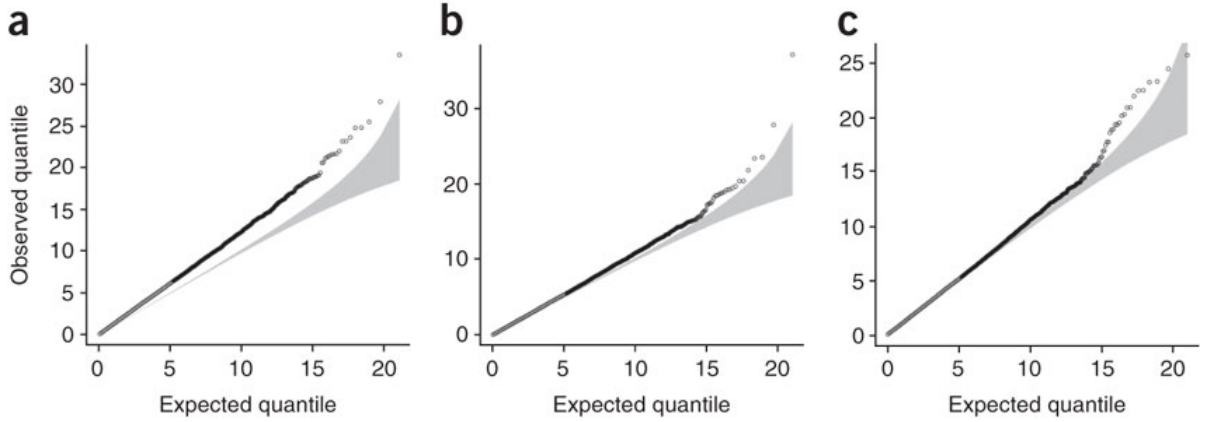
Eriksson et al, (2010) *PLoS Genetics* **6**: e1000993

Genetics of malaria susceptibility



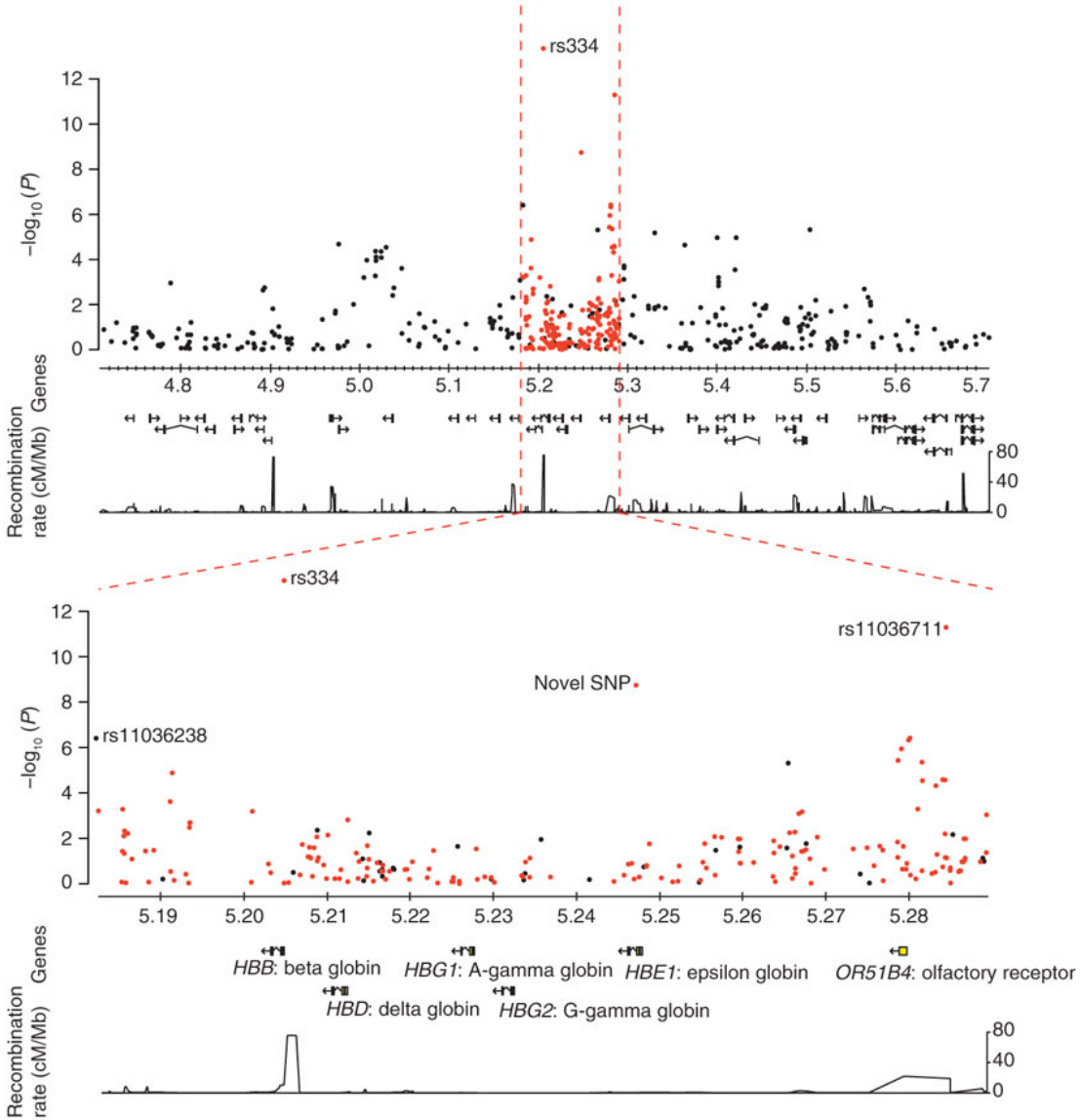
The Gambia

Population structure



Raw Self-report PC adjusted

Imputation and resequencing

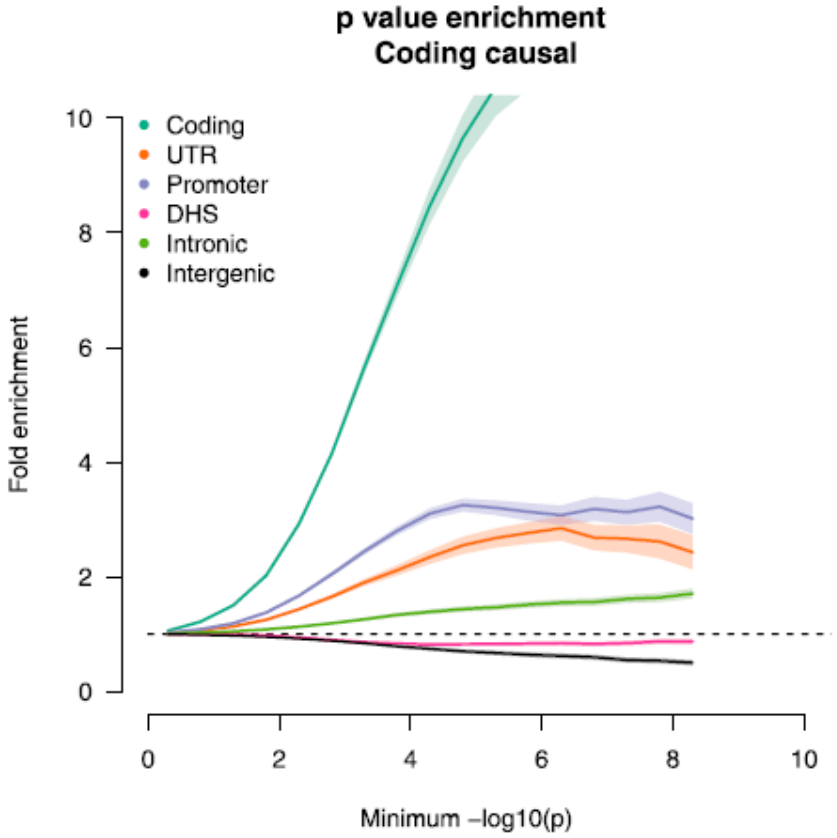


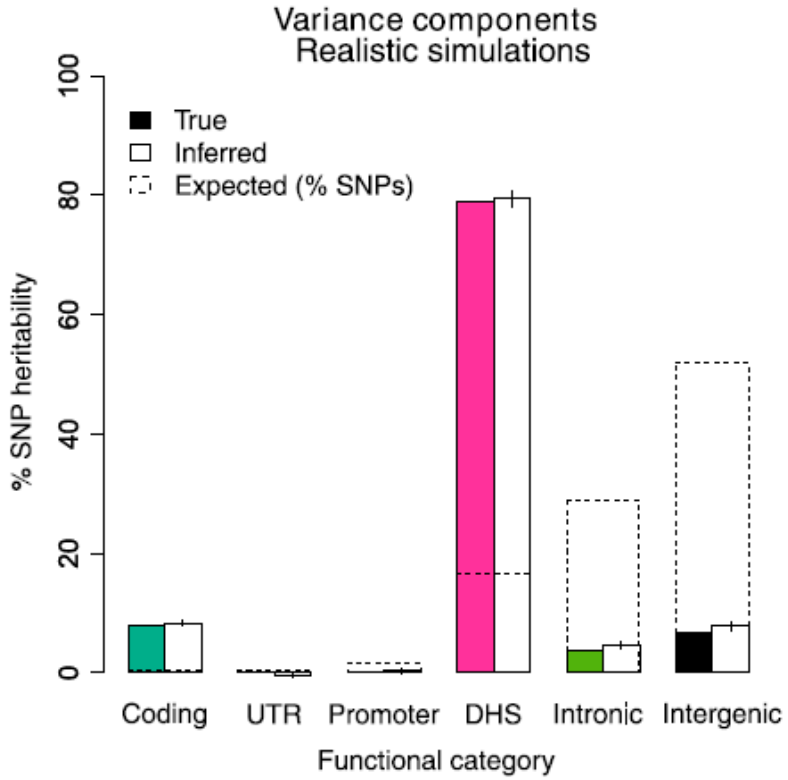
Black SNPs on 550K genotyping panel; red ones imputed after sequencing a subset of participants

rs334 is the *HbS* sickle cell variant that explains 2% of malaria susceptibility

Direct typing rs334 yields NLP > 27! The original hit rs11036238 is not strictly GWAS

Partitioning Heritability





Most GWAS variants are regulatory

Some references

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