Beyond initial GWAS analysis: two-stage designs, family data, imputation, meta-analysis

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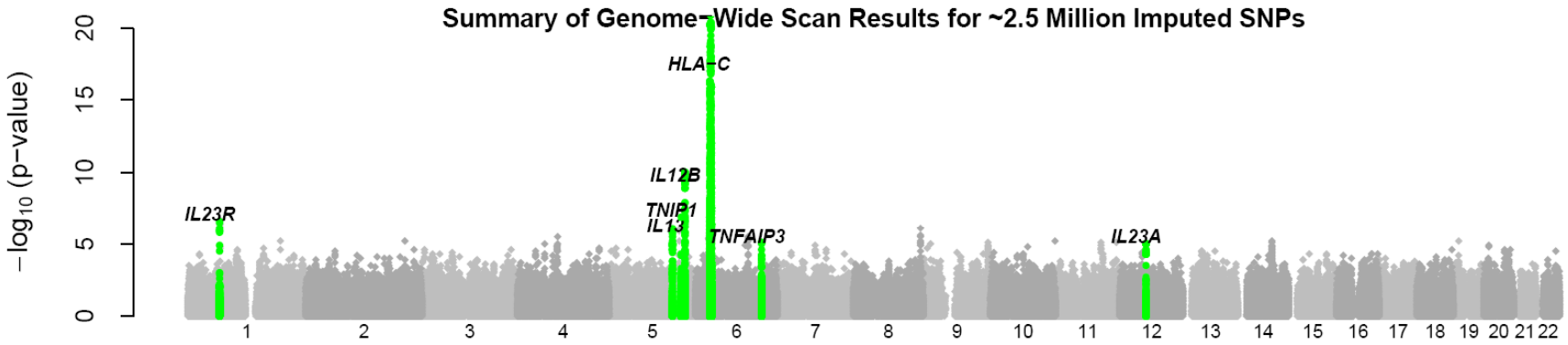
Genomewide Association Studies

- Survey 100,000 – 1,000,000 SNPs in a large set of cases and controls
- Comprehensively survey the genome for common variants of relatively small effect
- Have rapidly increased the catalog of genetic loci implicated in common disorders
  - For example, there are now ~20 loci implicated in type 2 diabetes
- The results are quite a contrast to those of earlier genetic association studies that focused on small numbers of genes and polymorphisms
- Still, much of the genetic variance of these traits remains unexplained.

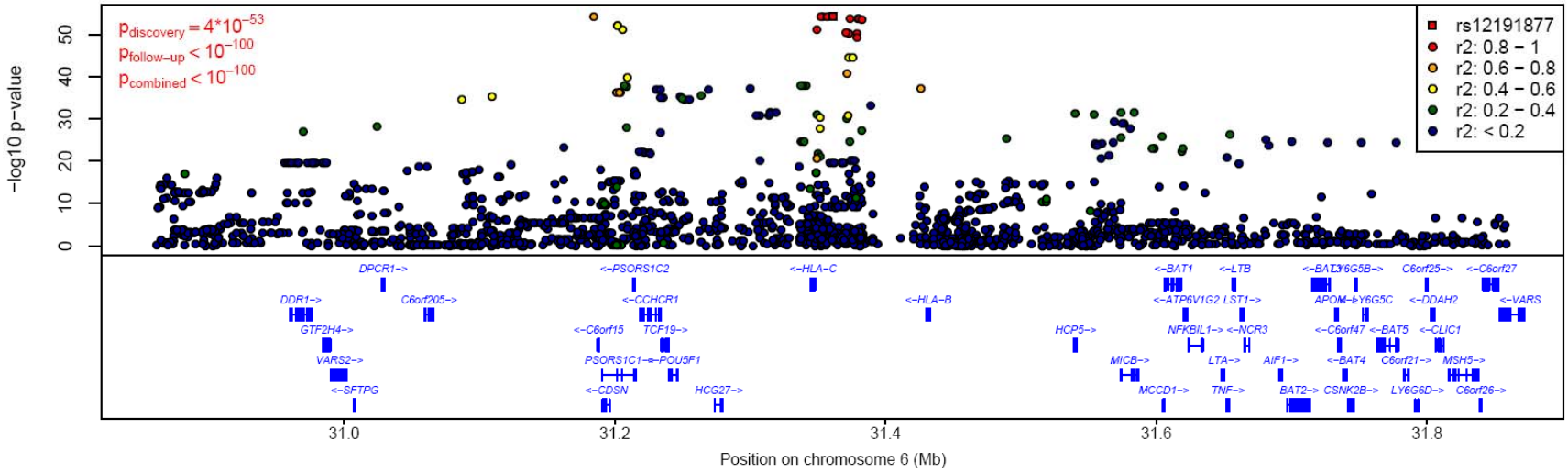
Collaborative Association Study of Psoriasis: Example of a Successful GWAS

- Examined ~1,500 cases / ~1,500 controls at ~500,000 SNPs
- Examined promising SNPs in extra ~5,000 cases / ~5,000 controls
- Outcome: 7 regions of confirmed association with psoriasis



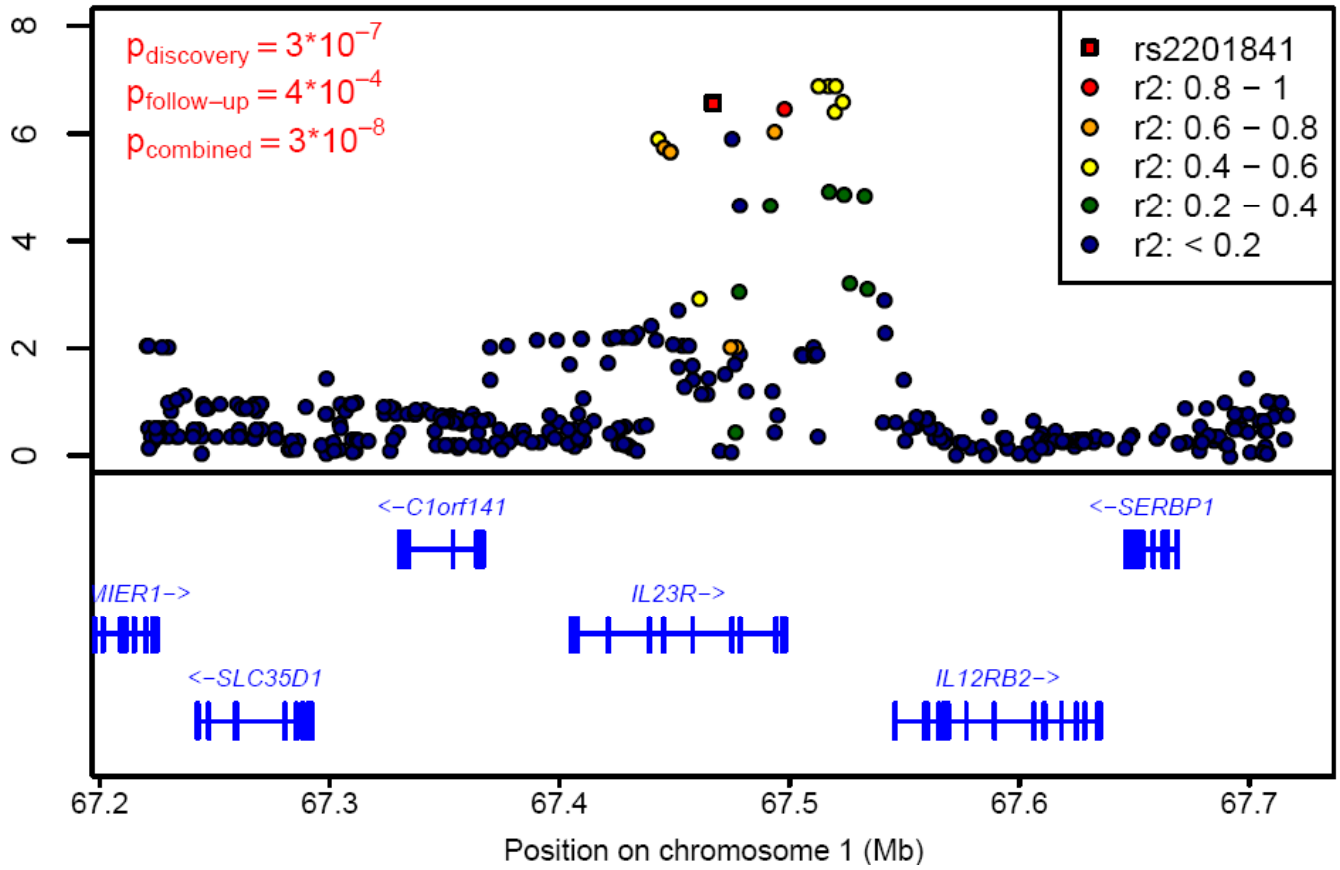
Hits colored in green have $p < 5x10^{-8}$ when evidence from follow-up and original scan is combined

HLA-C



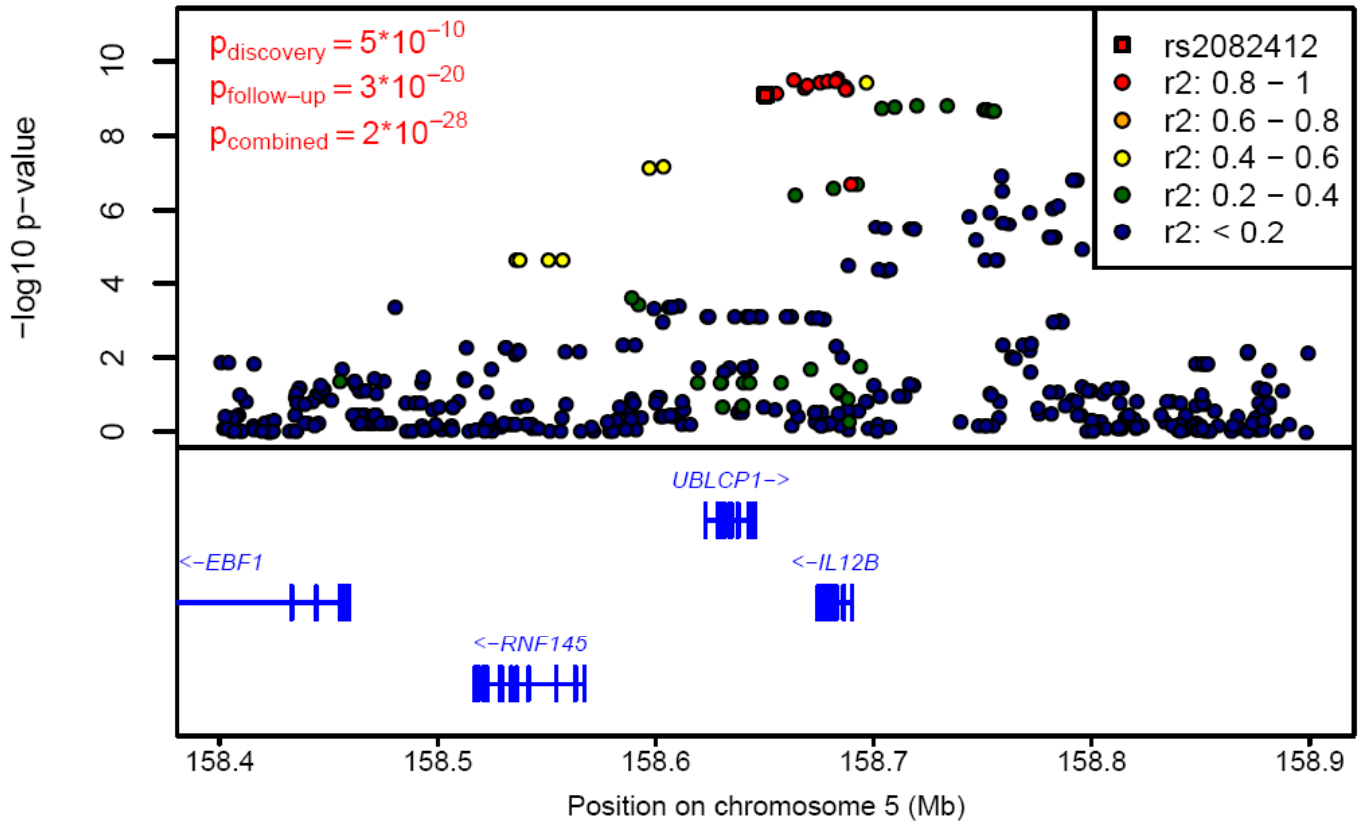
Top psoriasis associated SNPs in **strong linkage disequilibrium with HLA-Cw6**.
Evidence for psoriasis associated SNPs that are far from HLA-Cw6.

IL23R



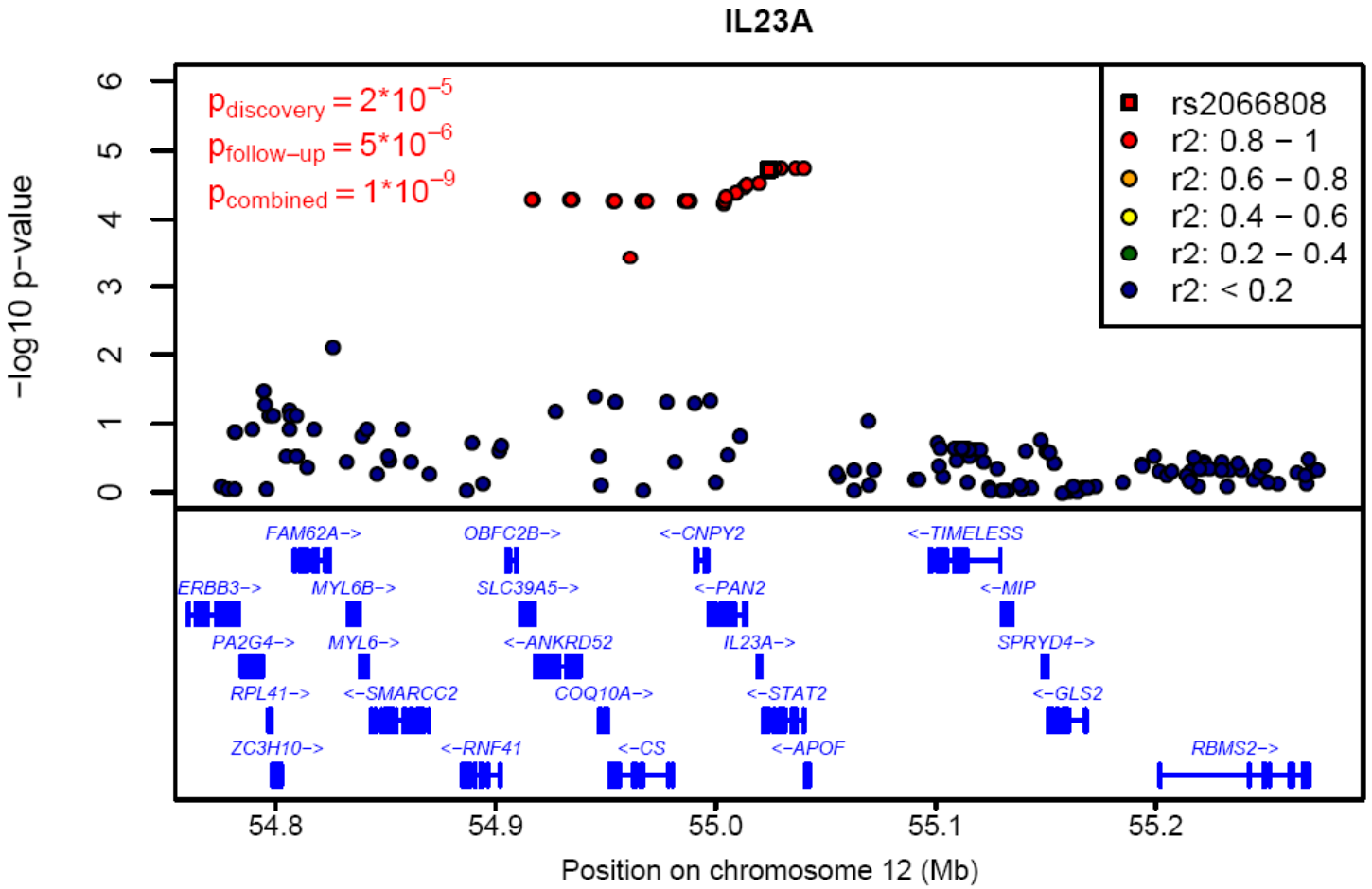
Previously identified locus, psoriasis associated SNPs also **associated with Crohn's**.

IL12B



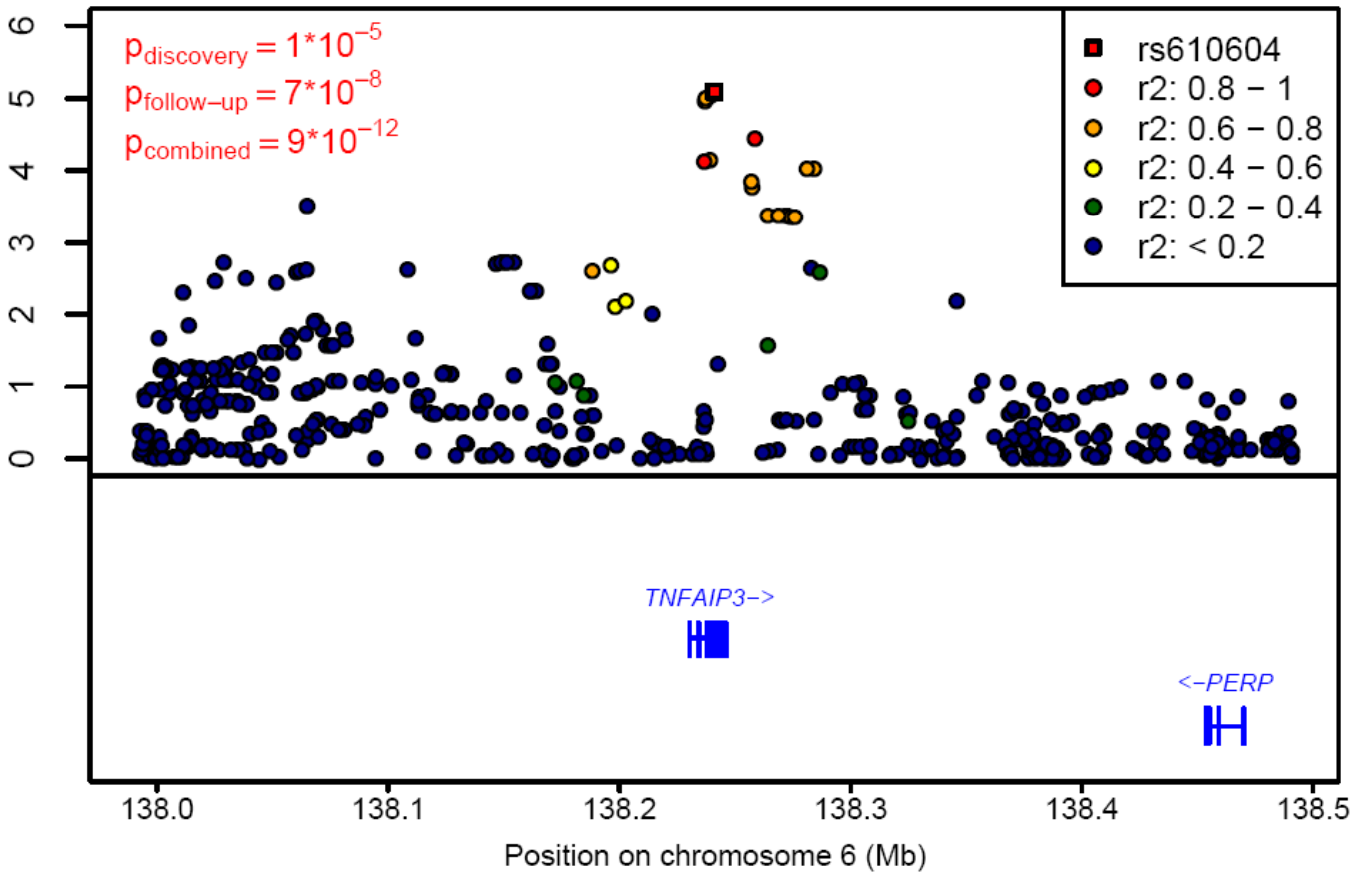
Previously identified locus, psoriasis associated SNPs **associated with Crohn's**.

IL23A



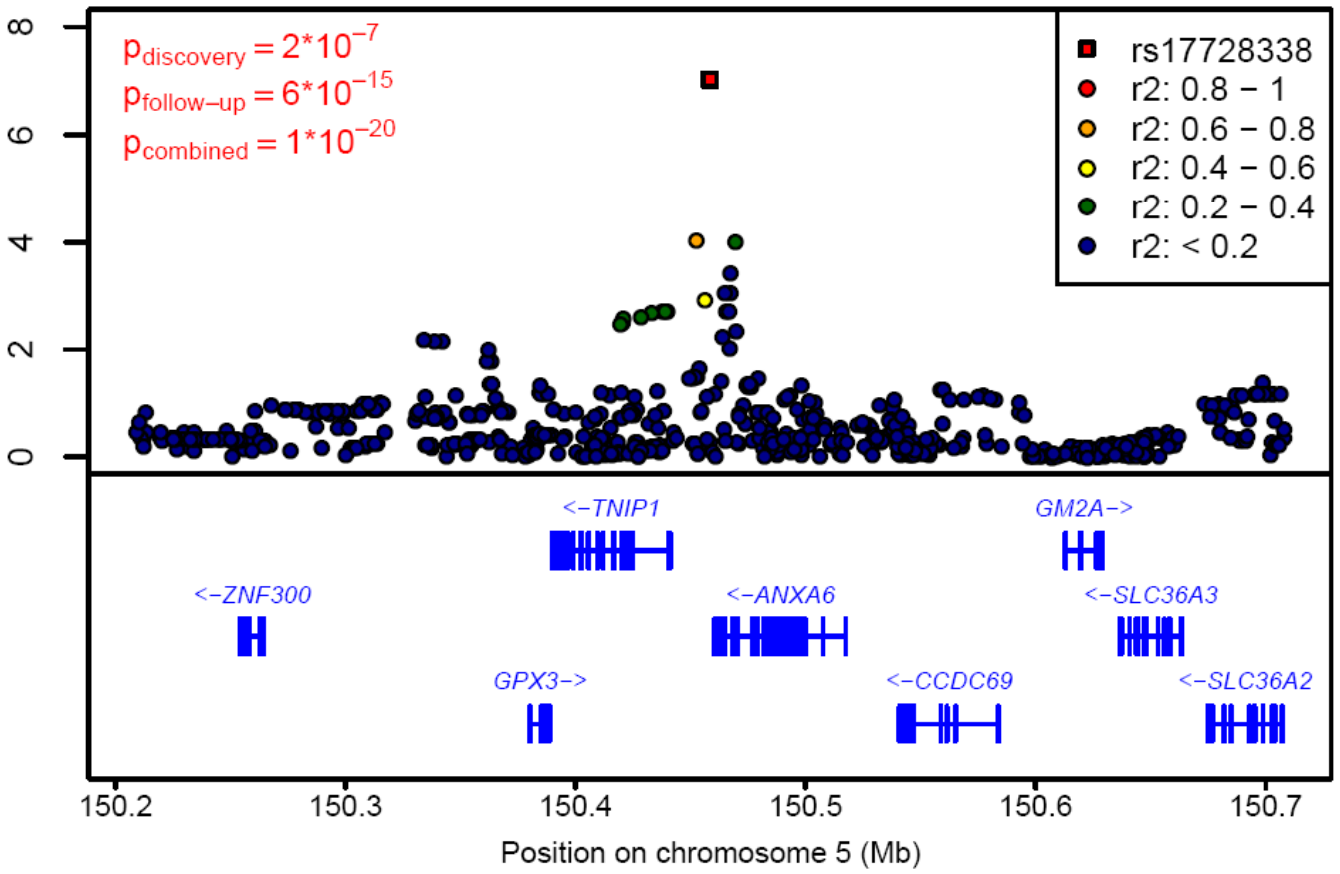
New locus, psoriasis associated SNPs **not associated** with Crohn's.

TNFAIP3



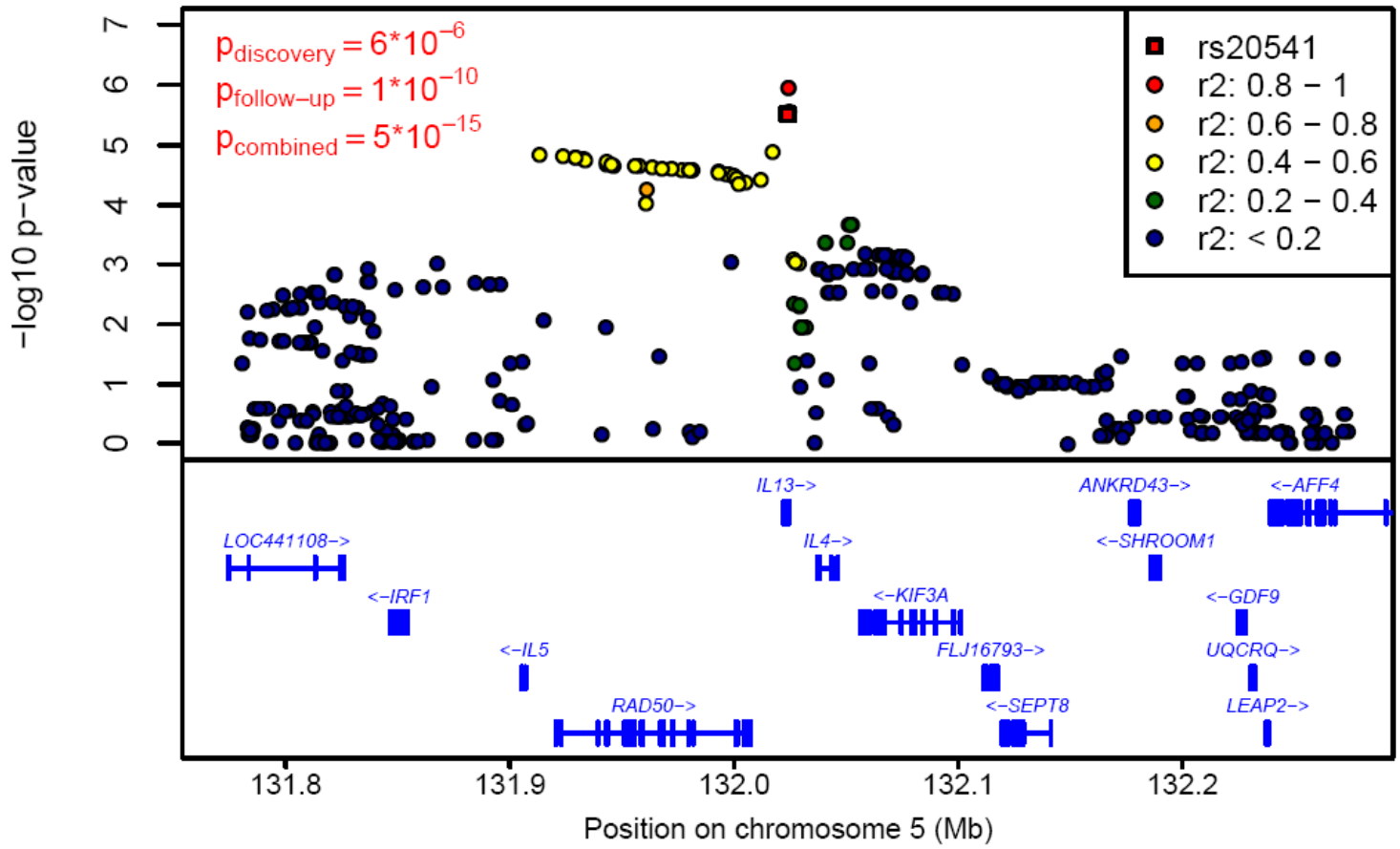
New locus; other SNPs in the locus are associated with lupus and rheumatoid arthritis.

TNIP1



New locus; note potential evidence for independently associated alleles.

IL4/IL13



New locus; IL4 and IL13 are excellent functional candidates.

Psoriasis GWAS: Summary of Replicated Loci

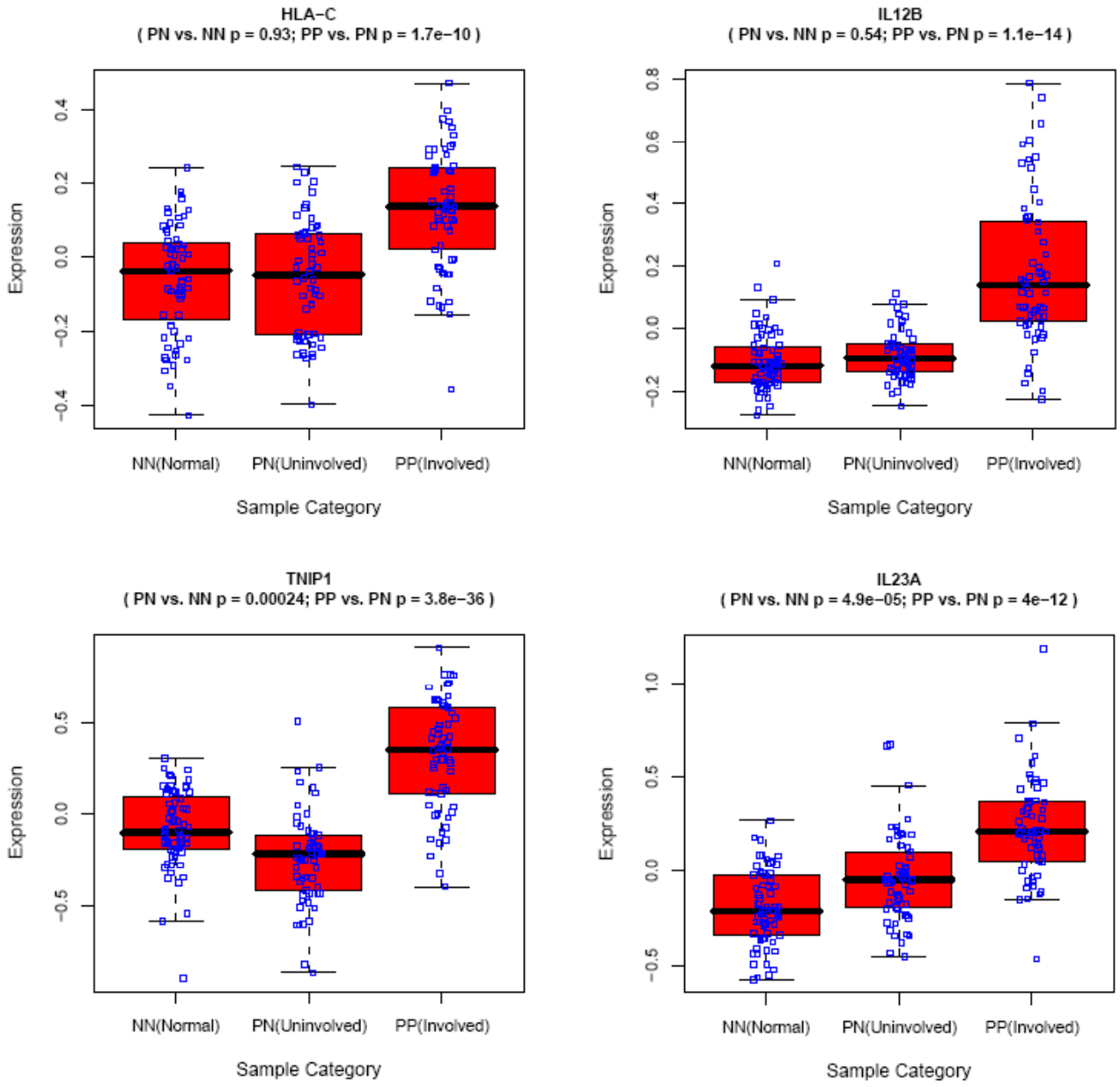
SNP	Alleles	Discovery samples (1,359 cases, 1,400 controls) Frequency[a] Case	Control	OR	*P* value[b]	Follow-up samples (5,048 cases, 5,051 controls) Frequency Case	Control	OR (meta)	*P* value[b] (meta)	Combined *P* value[d]	Notable nearby genes (relative position)[c]
rs12191877	T/C	0.313	0.141	2.79	4×10^{-53}	0.301	0.147	2.64	$<10^{-100}$	$<10^{-100}$	***HLA-C*** **(–13 kb)**
rs2082412	G/A	0.856	0.792	1.56	5×10^{-10}	0.848	0.798	1.44	3×10^{-20}	2×10^{-28}	***IL12B*** **(+24 kb)**
rs17728338	A/G	0.093	0.056	1.72	2×10^{-7}	0.087	0.054	1.59	6×10^{-15}	1×10^{-20}	***TNIP1*** **(–12 kb)**
rs20541	G/A	0.832	0.783	1.37	6×10^{-6}	0.827	0.790	1.27	1×10^{-10}	5×10^{-15}	***IL13*** **(nonsynonymous)**
rs610604	G/T	0.374	0.318	1.28	1×10^{-5}	0.360	0.320	1.19	7×10^{-8}	9×10^{-12}	***TNFAIP3*** **(intronic)**
rs2066808[d]	A/G	0.958	0.931	1.68	2×10^{-5}	0.947	0.932	1.34	5×10^{-6}	1×10^{-9}	***IL23A*** **(+3.7 kb)** STAT2 **(intronic)**
rs2201841	G/A	0.350	0.286	1.35	3×10^{-7}	0.325	0.295	1.13	4×10^{-4}	3×10^{-8}	***IL23R*** **(intronic)**

Multiple hits within a pathway…

- Three of the top replicated hits are for:
  - IL23R (IL-23 receptor) 3×10^{-8}
  - IL23A (IL-23 subunit) 9×10^{-10}
  - IL12B (IL-23/IL-12 subunit) 1×10^{-28}
- Two other replicated hits at:
  - TNFAIP3 (TNFα-inducible protein 3) 9×10^{-12}
  - TNIP1 (TNFAIP3 interacting protein 1) 1×10^{-20}
- Evidence for epistasis among these SNPs?
  - None.

Additional Phenotype Information

- Evaluation of gene expression for ~50,000 transcripts
  - Affymetrix U133 Plus 2.0 Arrays
- Skin biopsies
  - 40 control biopsies (buttock)
  - 40 biopsies of unaffected skin from cases (buttock)
  - 40 biopsies of affected skin from cases (plaque)
- Early assessment of the impact of any associated variants we identify
  - Comparison of control and unaffected skin biopsies particularly interesting

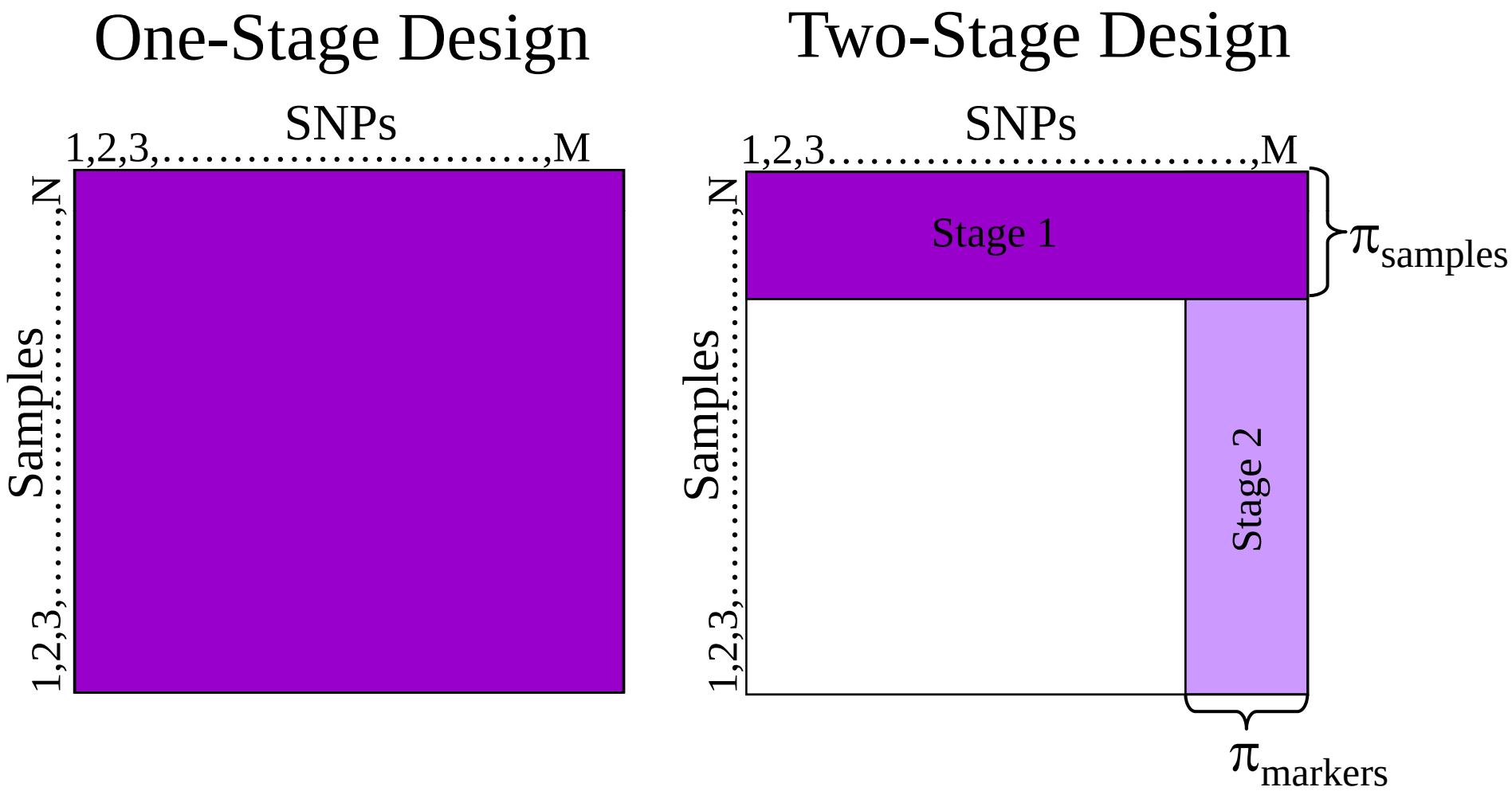


Four of the the functional candidates show increased expression in psoriatic skin.

Other Hits Supported by Our Study

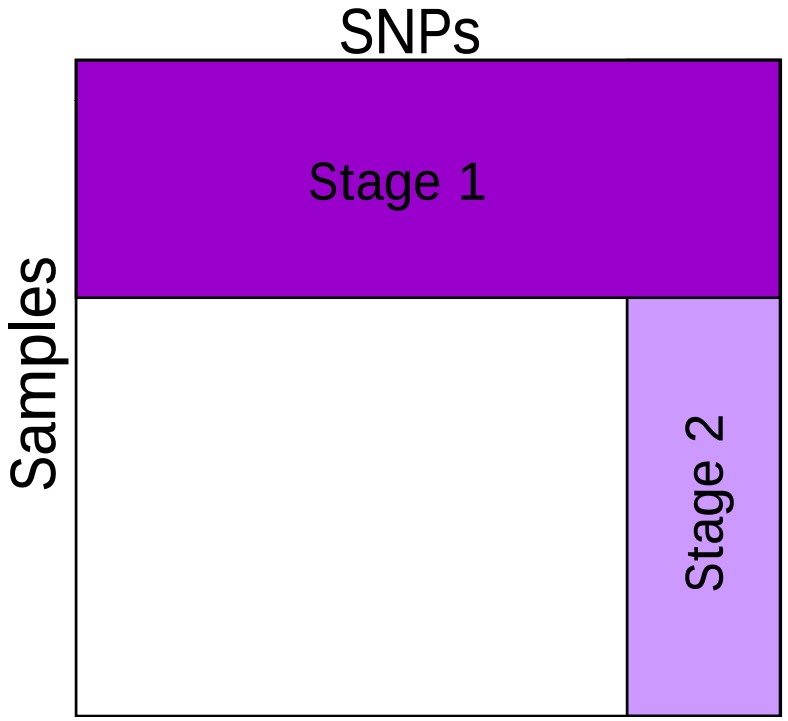
- Support for association with deletion in late cornified envelope region (LCE) identified by Xavier Estivill ($p \sim 0.001$)
- Support for association with ZNF313, a potential regulator of T-cell activation ($p \sim 10^{-4}$)
- Some support for association with IBD5 region

One- and Two-Stage GWA Designs

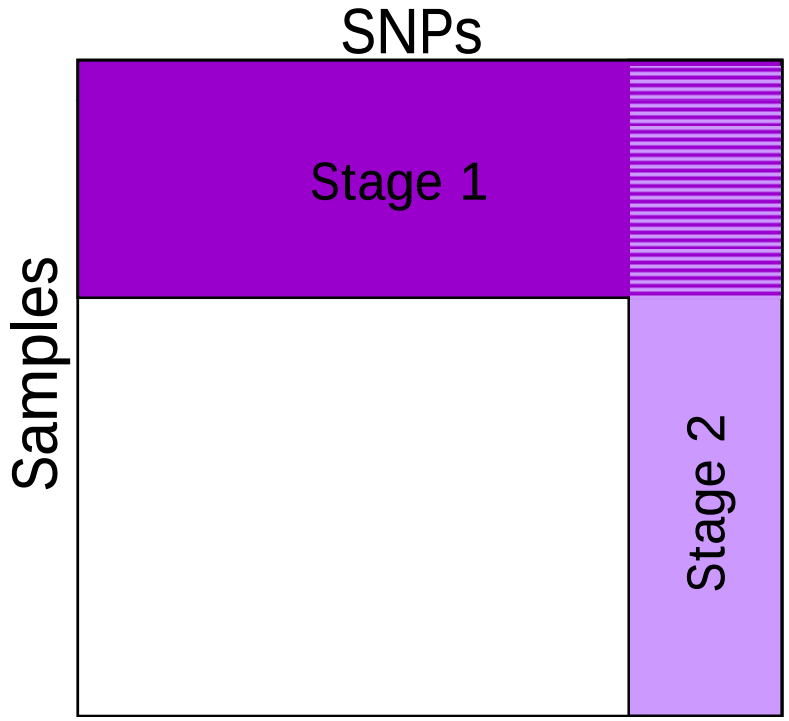


Analyzing Two Stage Designs

Replication-based analysis



Joint analysis



Joint Analysis: Statistics

- The standard test statistic for comparing allele frequencies could be expressed as:

$$z = \frac{\hat{p}_{case} - \hat{p}_{control}}{\sqrt{\left(\hat{p}_{case}(1-\hat{p}_{case}) + \hat{p}_{control}(1-\hat{p}_{control})\right)/2N}}$$

- Based on z_{stage1} and z_{stage2} the joint statistic is:

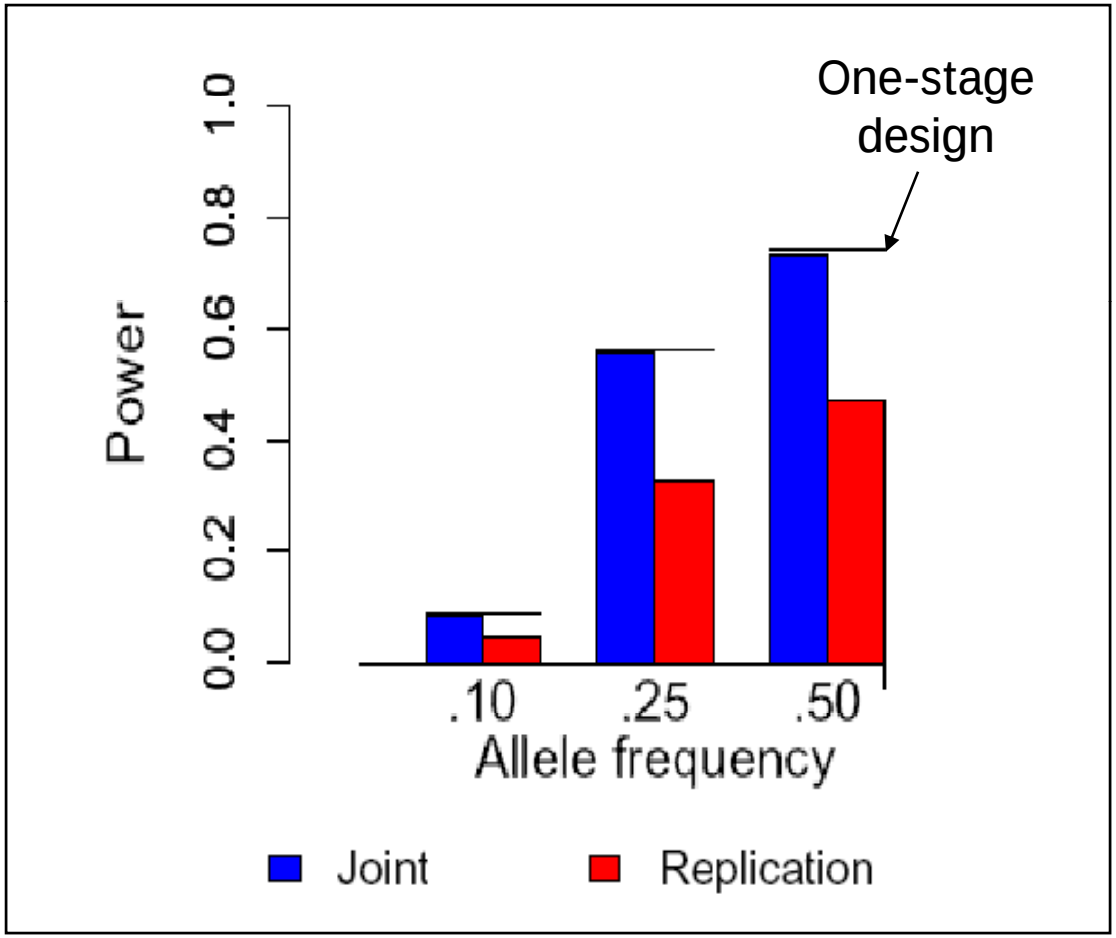
$$z_{joint} = z_{stage1}\sqrt{\frac{N_1}{N_1+N_2}} + z_{stage2}\sqrt{\frac{N_2}{N_1+N_2}}$$

- Note that using z_{joint} will require a more stringent significance threshold than using z_2

Two Stage Design Power

50% of samples typed in phase 1

1% of markers followed up in phase 2



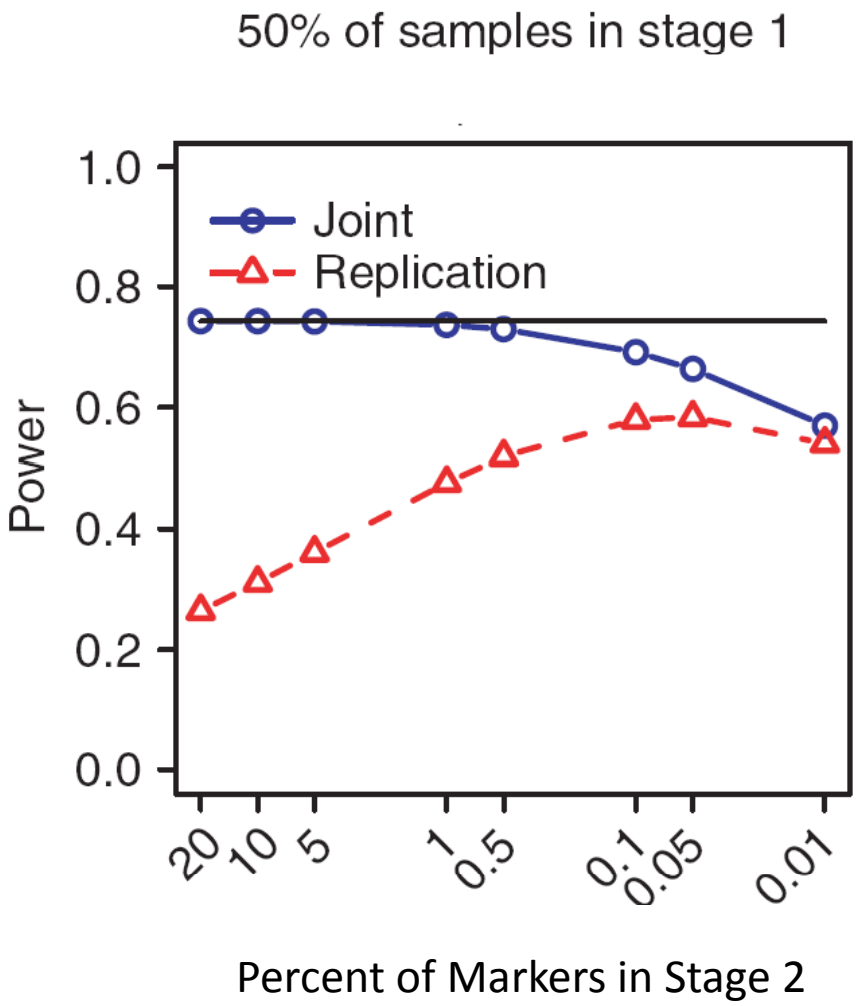
M = 300,000 markers

N = 1000 cases, 1000 controls

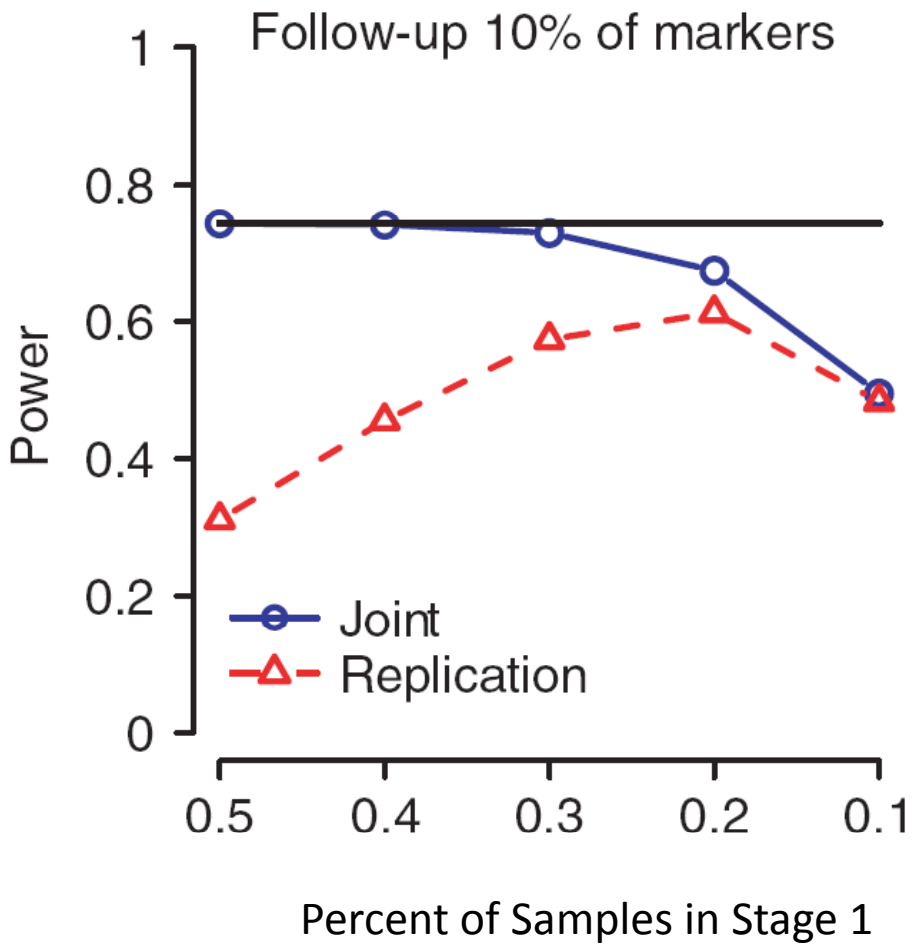
GRR = 1.4 (multiplicative model)

Prevalence = .10

Replication or Joint Analysis: Proportion of Markers Followed Up



Replication or Joint Analysis: Proportion of Samples Followed Up



Multistage Designs

- Genotyping costs can be substantially reduced when staged approach is used

- Typically, cost can be reduced by 40-60% depending on ratio of genotyping costs between stages 1 and 2

- www.sph.umich.edu/csg/abecasis/CaTS
- //workshop/goncaloa/2009/CaTS-setup.exe
- (f:/goncaloa/2009/merlin-examples/)

Beyond the Initial Analysis

- **Things that we already know will work …**
  1. **Imputation of genome scan genotypes in relatives**
  2. **Imputation of HapMap genotypes in everyone**
  3. **Meta-analysis of genome wide scans**
  4. **Contrasting results for scans targeting related traits**

- Things that might work …
  1. Screening for rare variants
  2. Screening for interactions
  3. Focusing on the “right” pathways
  4. Studying copy number polymorphisms

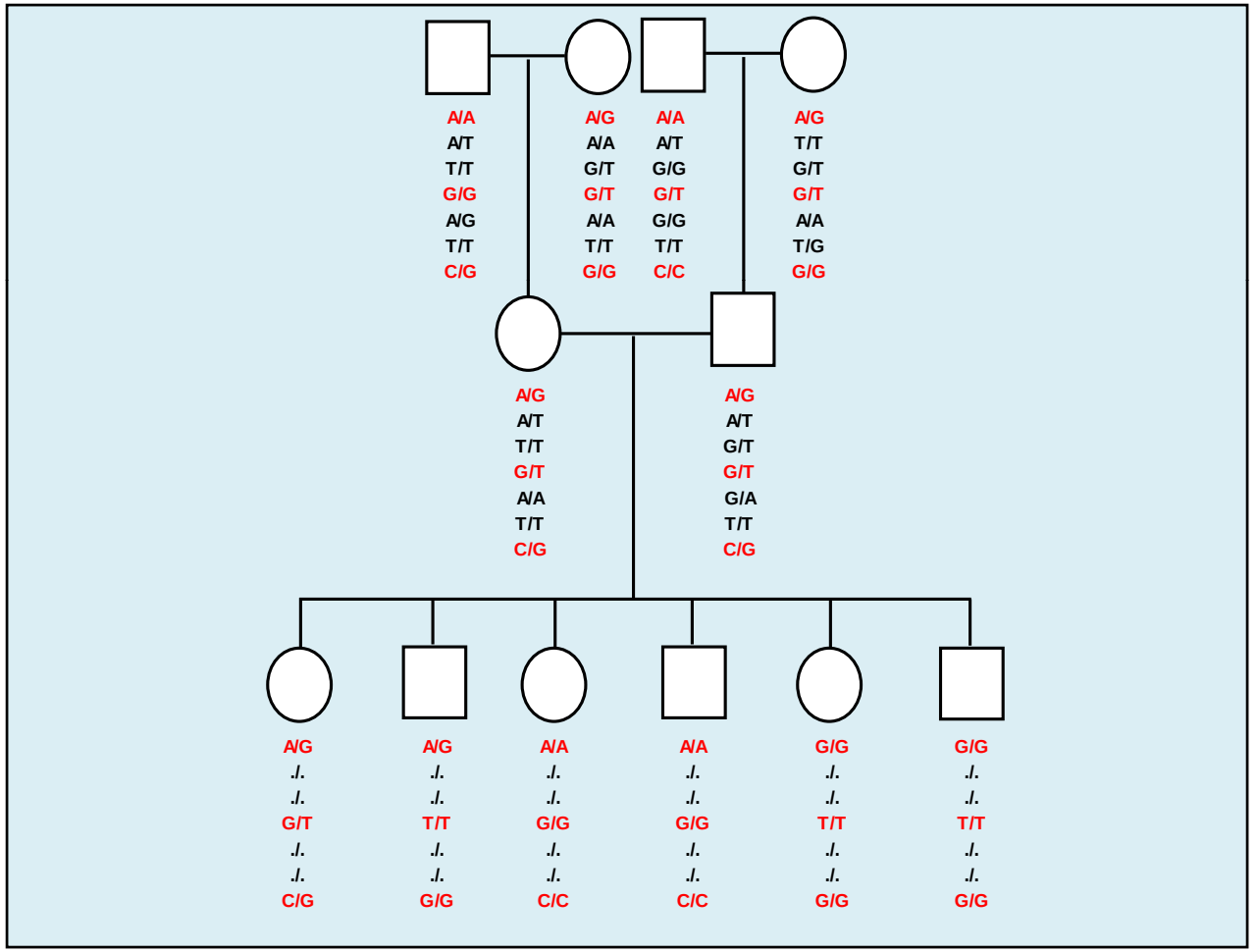
- Things for molecular biologists to do …
  1. Many new targets to investigate

In Silico Genotyping For Family Samples

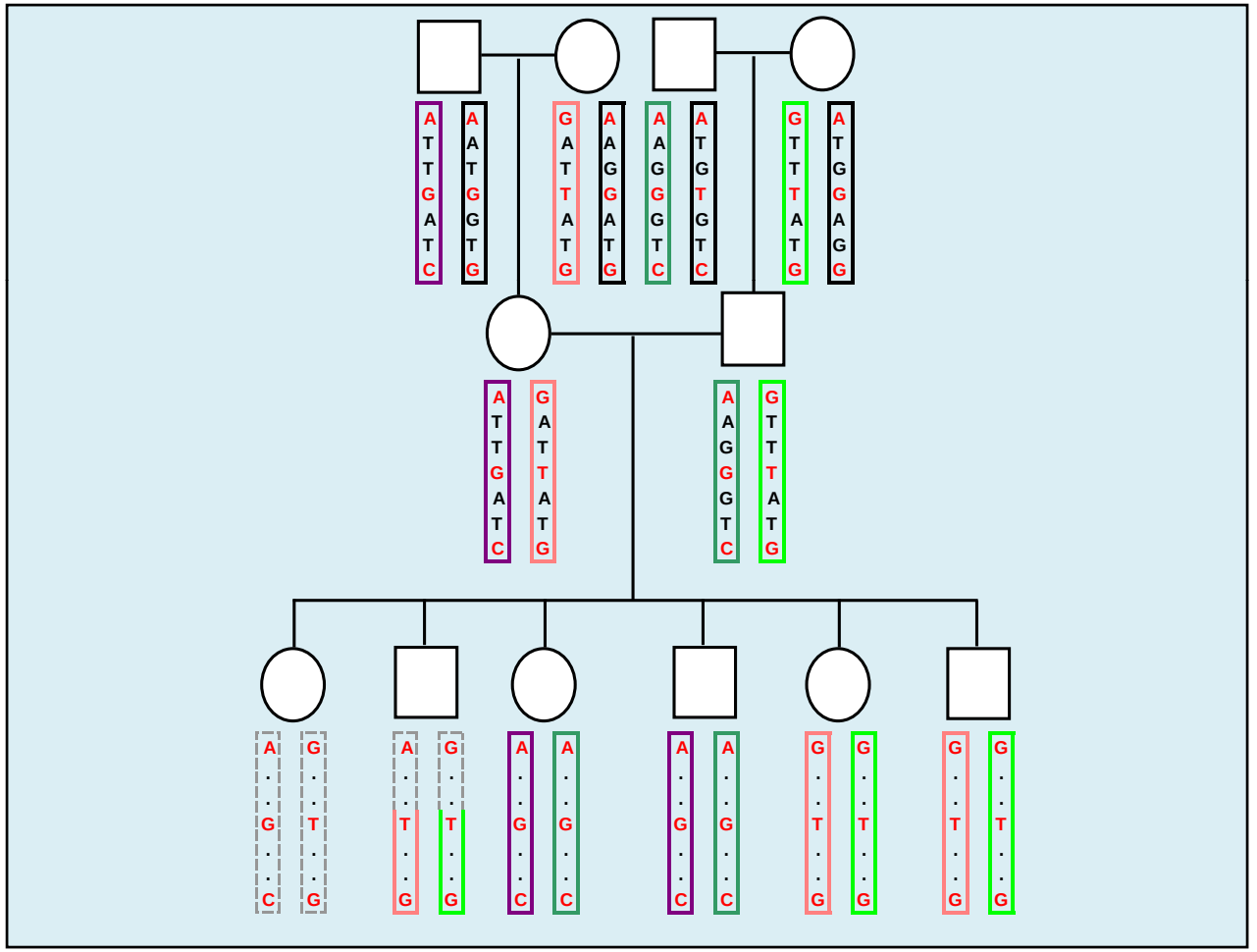
- Family members share large segments of chromosomes
- If we genotype many related individuals, we will effectively be genotyping a few chromosomes many times
- Propagate genotypes obtained in genome wide association study to related individuals
- Propagation can be based just on genetic relationships …
- … but will work better if we first identify shared chromosomal regions in each family using a subset of markers

Burdick et al, *Nat Genet,* 2006
Chen and Abecasis, AJHG, 2007

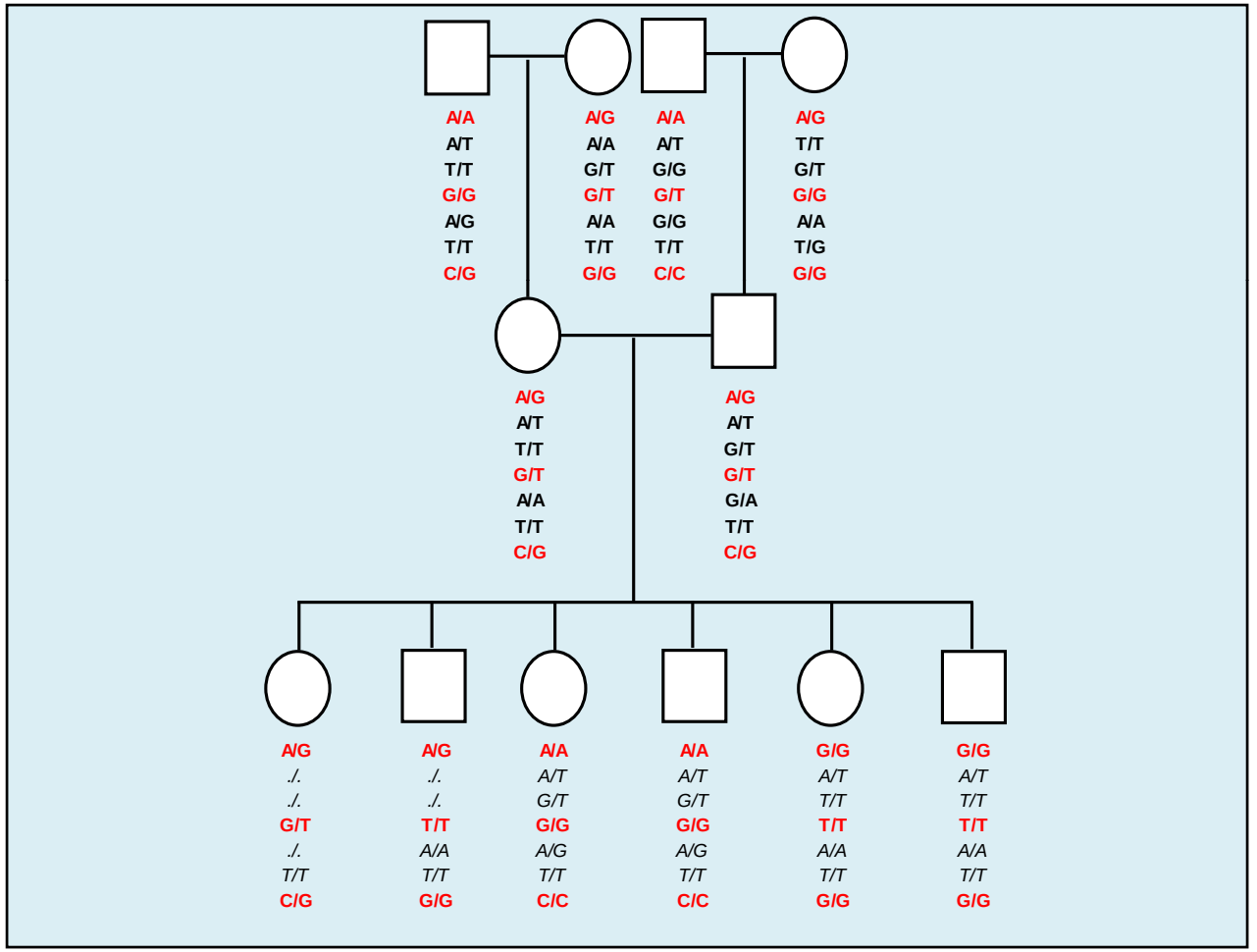
Genotype Inference
Part 1 – Observed Genotype Data



Genotype Inference
Part 2 – Inferring Allele Sharing



Genotype Inference
Part 3 – Imputing Missing Genotypes



Formal Approach

- Consider full set of observed genotypes G
- Evaluate pedigree likelihood L for each possible value of each missing genotype g_{ij}
- Posterior probability for each missing genotype

$$P(g_{ij} = x \mid G) = \frac{L(G, g_{ij} = x)}{L(G)}$$

- Optimally, downstream analyses should use probabilistic genotype assignments rather than a single most likely genotype

Chen and Abecasis, AJHG, 2007

Standard Linear Model for Genetic Association

- Model association using a model such as:

$$E(y_i) = \mu + \beta_g g + \beta_c c + \ldots$$

- y_i is the phenotype for individual i
- g_i is the genotype for individual i
  - Simplest coding is to set g_i = number of copies of allele *'1'*
- c_i is a covariate for individual i
  - Covariates could be estimated ancestry, environmental factors…

- β coefficients are estimated covariate, genotype effects
- Model is fitted in variance component framework

Model With Inferred Genotypes

- Replace genotype score g with its expected value:

$$E(y_i) = \mu + \beta_g \bar{g} + \beta_c c + \ldots$$

- Where

$$\bar{g}_i = 2P(g_i = 2 \mid G) + P(g_i = 1 \mid G)$$

- Association test implemented as score test or as likelihood ratio test
  - Variance component framework to allow for relatedness

- Alternatives would be to
  - (a) impute genotypes with large posterior probabilities; or
  - (b) integrate joint distribution of unobserved genotypes in family

Score Test for Association

- A standard variance component analysis would work …
- … but might be rather slow on a genomewide scale
- We can approximate the result that would be obtained from maximum likelihood estimation using a rapid score test:

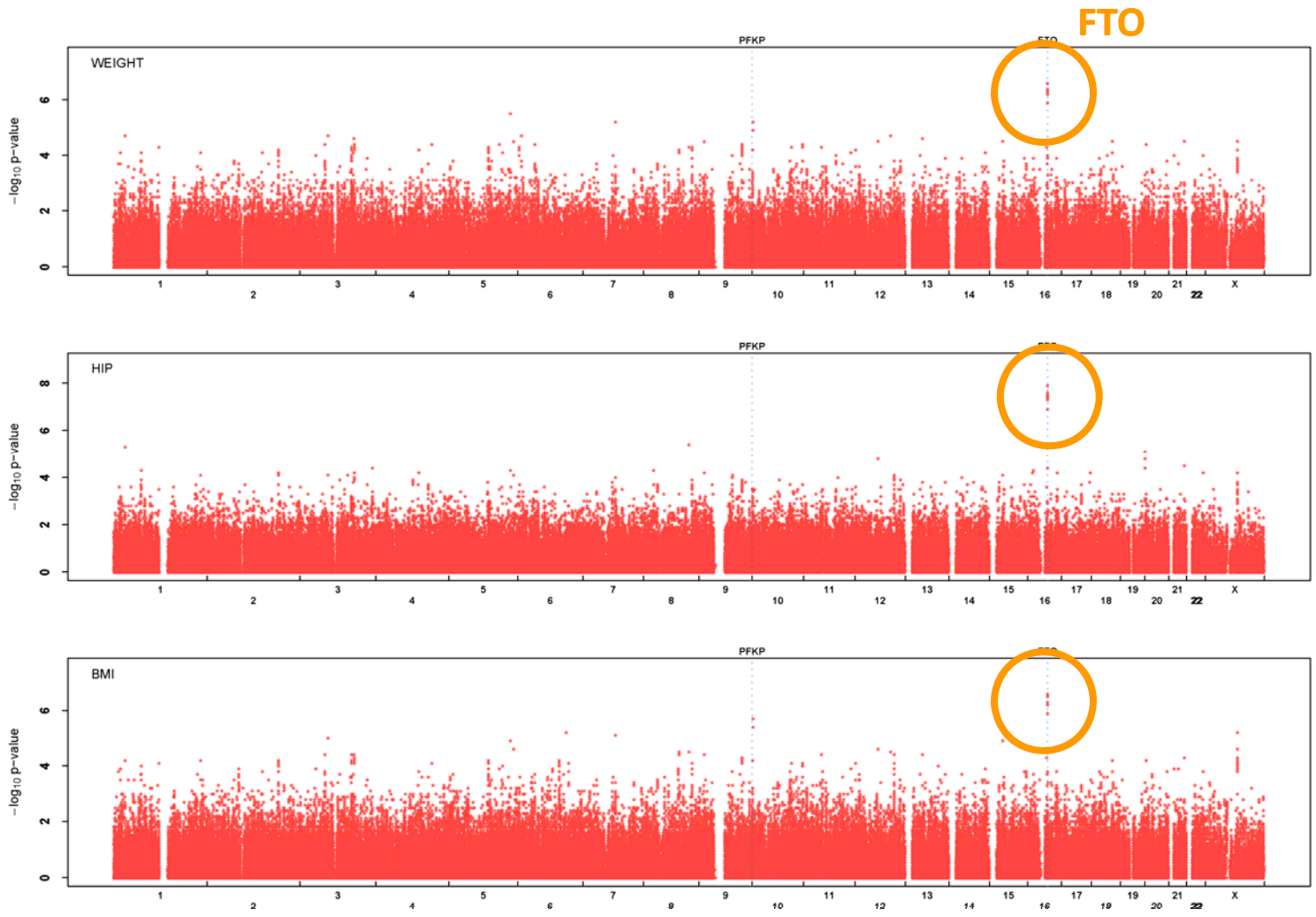
$$T^{\mathrm{SCORE}} = \frac{\left\{\sum_i \left[\bar{g}_i - E(\bar{g}_i)\right]' \left[\Omega_i^{(\mathrm{base})}\right]^{-1} \left[\mathbf{y}_i - E(y_i)^{(\mathrm{base})}\right]\right\}^2}{\sum_i \left[\bar{g}_i - E(\bar{g}_i)\right]' \left[\Omega_i^{(\mathrm{base})}\right]^{-1} \left[\bar{g}_i - E(\bar{g}_i)\right]}$$

- Similar approaches could actually be used for unrelated individuals, provided we can model an appropriate variance-covariance matrix

Quantitative Trait GWAS in Sardinia

- 6,148 Sardinians from 4 towns in Ogliastra
- Measured 98 aging related quantitative traits
- Genotyping:
  - 10,000 SNPs measured in ~4,500 individuals
  - 500,000 SNPs measured in ~1,400 individuals
- So far, we have confidently identified genes involved in traits as disparate as obesity and height, the regulation of cholesterol, uric acid and glucose levels, among others

FTO and Obesity Related Traits



Scuteri et al, PLoS Genetics, 2007

MERLIN Exercise

Imputation within Families, Association

- We will look at the MERLIN tutorial on association analysis

  http://www.sph.umich.edu/csg/abecasis/Merlin/tour/

  //workshop/goncaloa/2009/merlin-examples/

  (f:/goncaloa/2009/merlin-examples/)

- Merlin will fill in missing genotypes based on information on relatives

- Merlin implements two flavors of association testing:
  - The **--assoc** option implements maximum likelihood testing
  - The **--fastassoc** option implements the score test approach

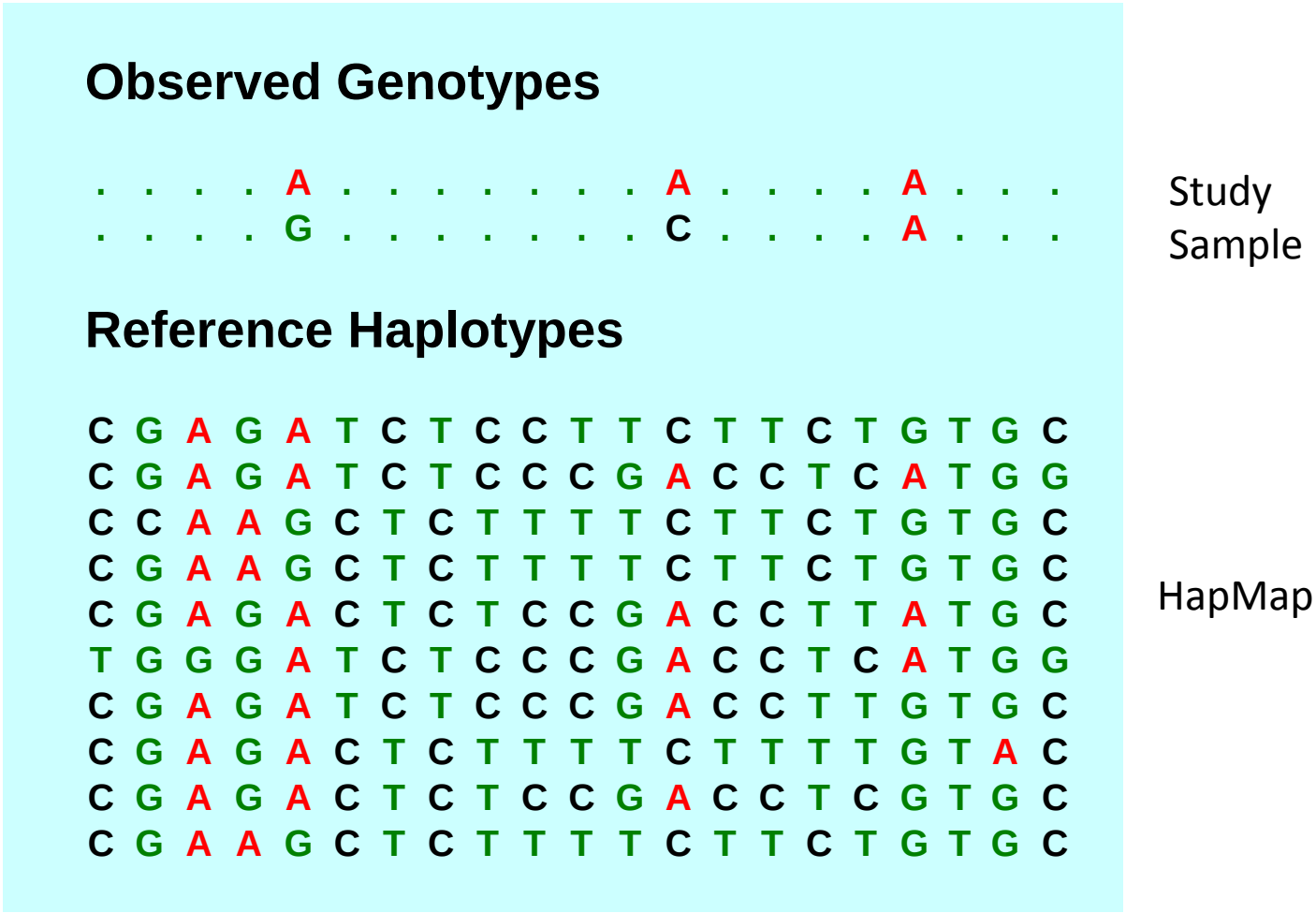
Relatedness in The Context of GWAS

- When analyzing family samples …
- FOR INDIVIDUALS WITH KNOWN RELATIONSHIPS
  - Impute genotypes in relatives, who may be completely untyped
  - Imputation works through long shared stretches of chromosome
- But the majority of GWAS that use “unrelated” individuals…

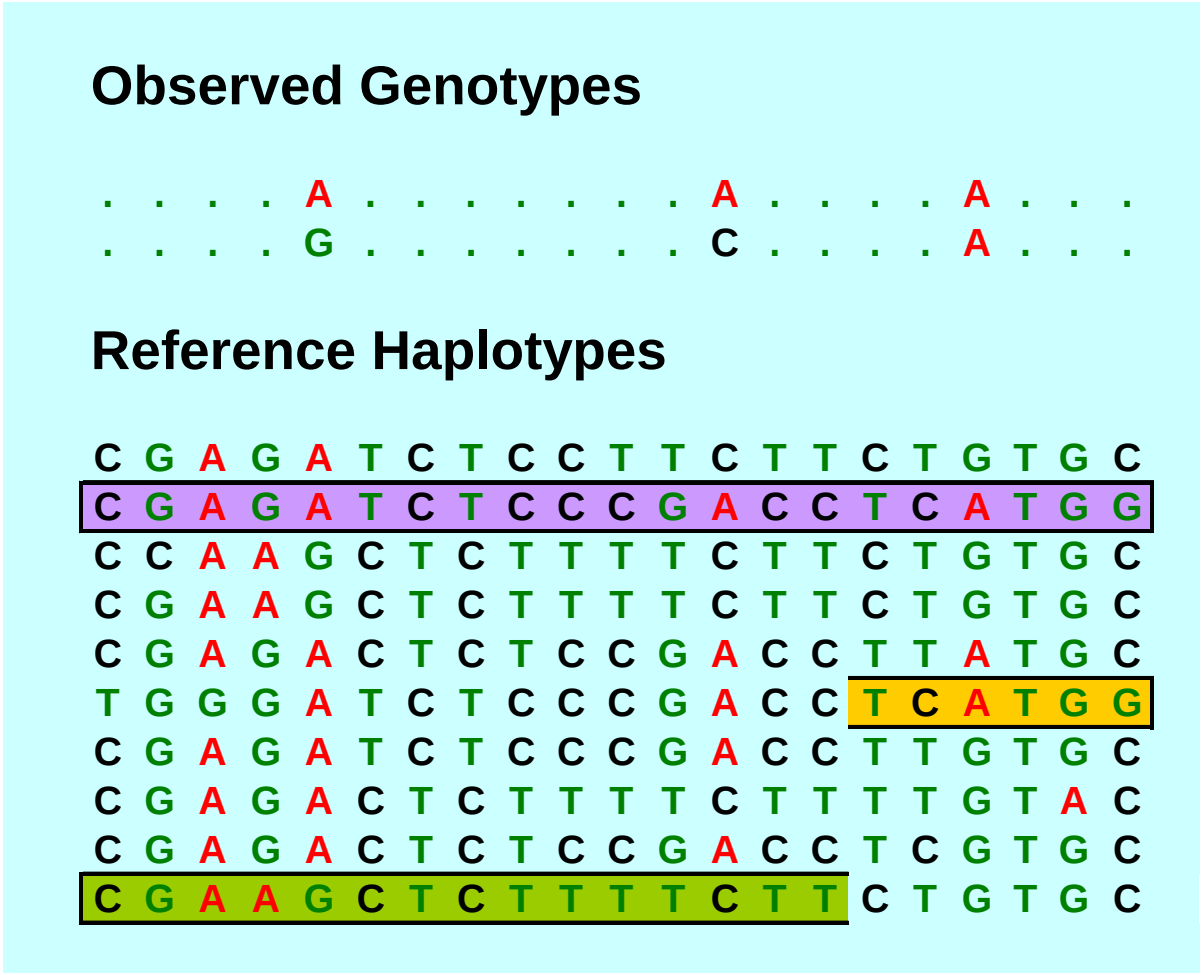
Relatedness in The Context of GWAS

- When analyzing family samples …
- FOR INDIVIDUALS WITH KNOWN RELATIONSHIPS
  - Impute genotypes in relatives, who may be completely untyped
  - Imputation works through long shared stretches of chromosome
- But the majority of GWAS that use “unrelated” individuals…
- FOR INDIVIDUALS WITH UNKNOWN RELATIONSHIPS
  - Impute observed genotypes in relatives
  - Imputation works through short shared stretches of chromosome

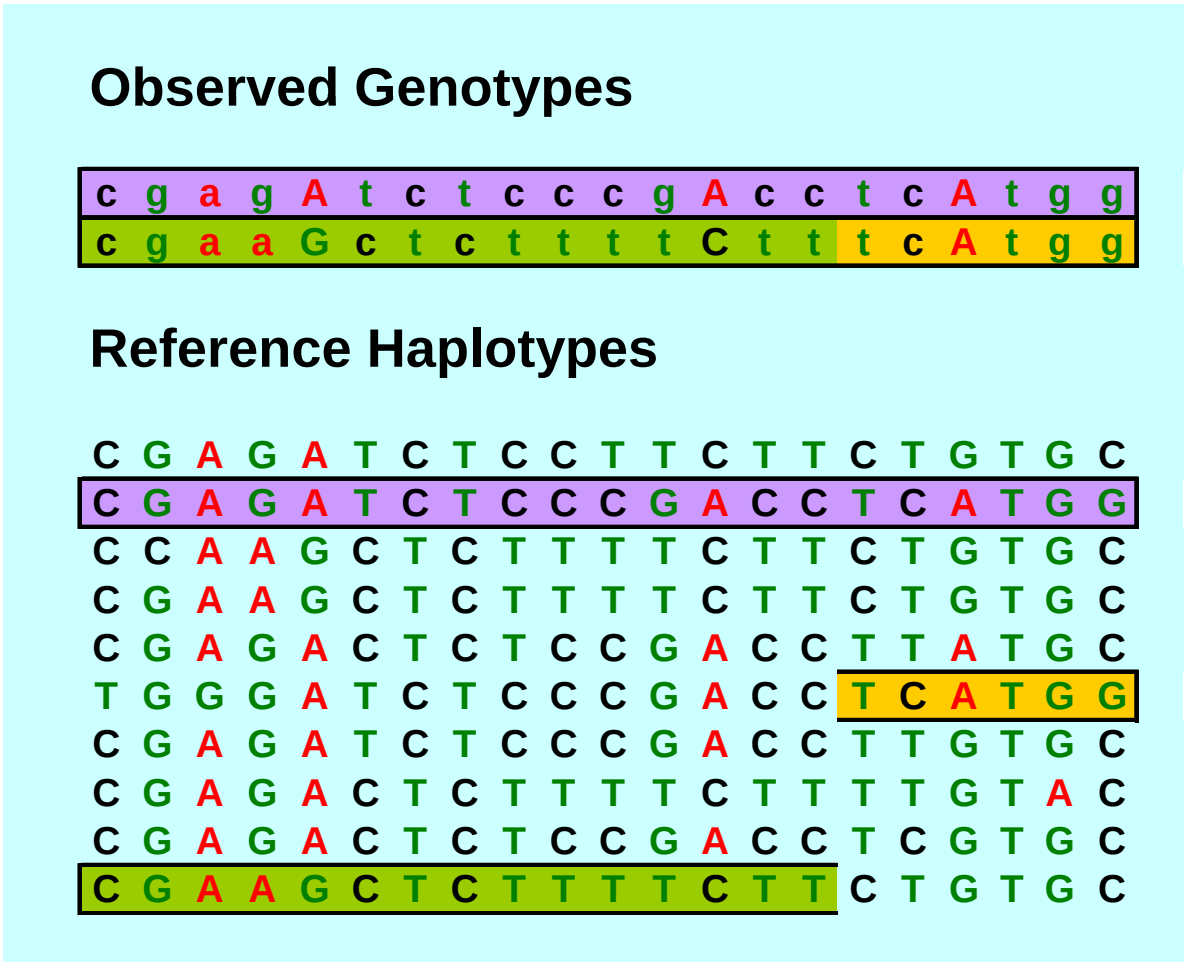
Observed Genotypes



Identify Match Among Reference



Phase Chromosome, Impute Missing Genotypes

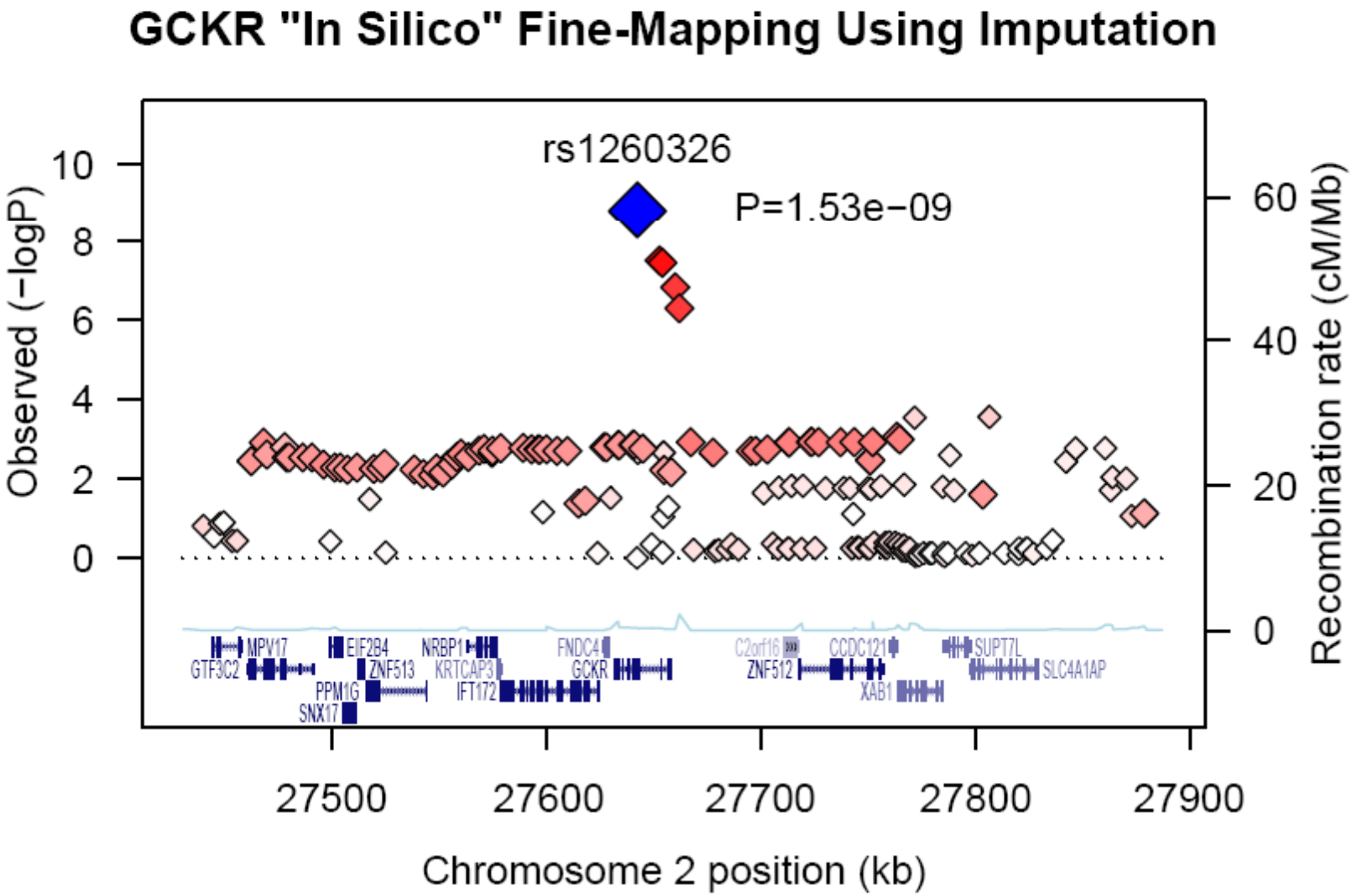


Implementation

- Markov model is used to model each haplotype, conditional on all others
- Gibbs sampler is used to estimate parameters and update haplotypes
  - Each individual is updated conditional on all others
  - In parallel to updating haplotypes, estimate “error rates” and “crossover” probabilities
- In theory, this should be very close to the Li and Stephens (2003) model

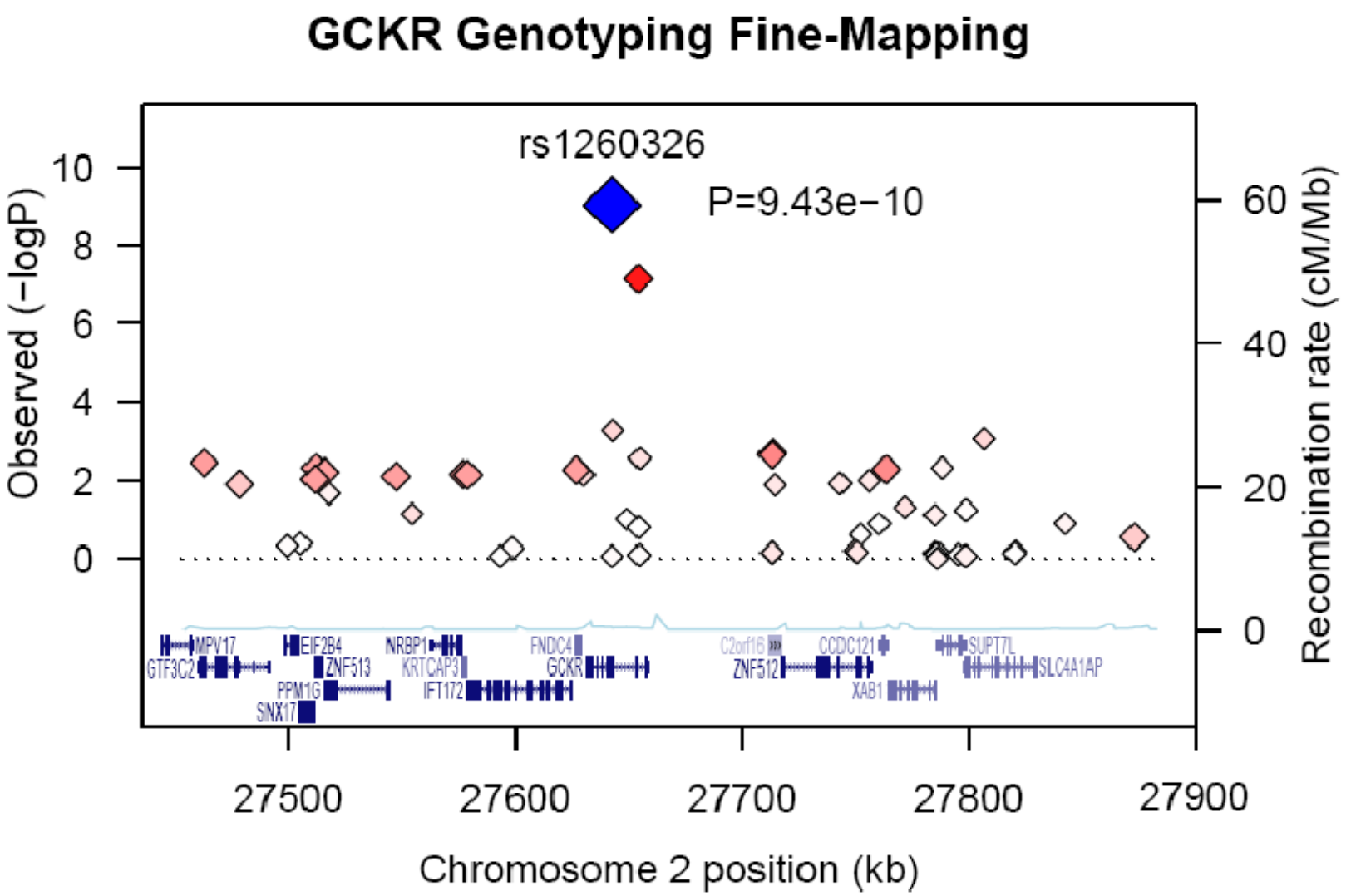
Does Imputation Really Work? Results from One Recent Assessment

- Use 438,670 SNPs to impute 2.5M SNPs in GAIN psoriasis scan
  - Nair et al, *Nature Genetics*, in press
- Re-genotyped ~906,600 SNPs in 90 samples using the Affymetrix 6.0 chip.
- Discrepancy rate of 1.80% per genotype (0.91% per allele).
  - 57,747,244 imputed genotypes compared with Affymetrix calls
  - 661,881 non-Perlegen SNPs present in the Affymetrix 6.0
- Average r^2 between imputed calls and Affymetrix calls was 0.93.
  - r^2 exceeded 0.80 for >90% of SNPs.



Association between triglycerides and GCKR

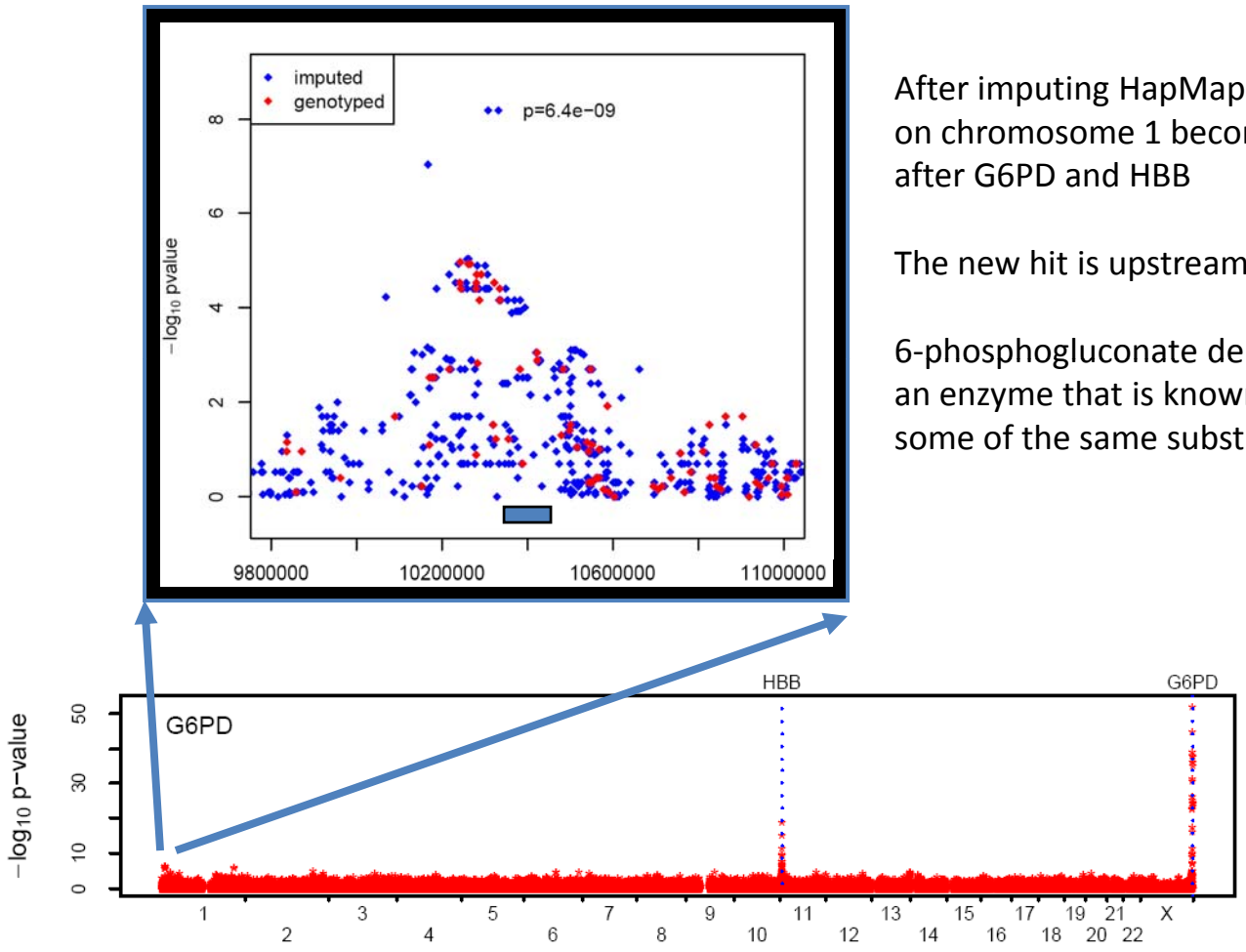
Sekar Kathiresan, DGI, see poster 32



Association between triglycerides and GCKR

Sekar Kathiresan, DGI, see poster 32

Sardinia G6PD Activity Example …

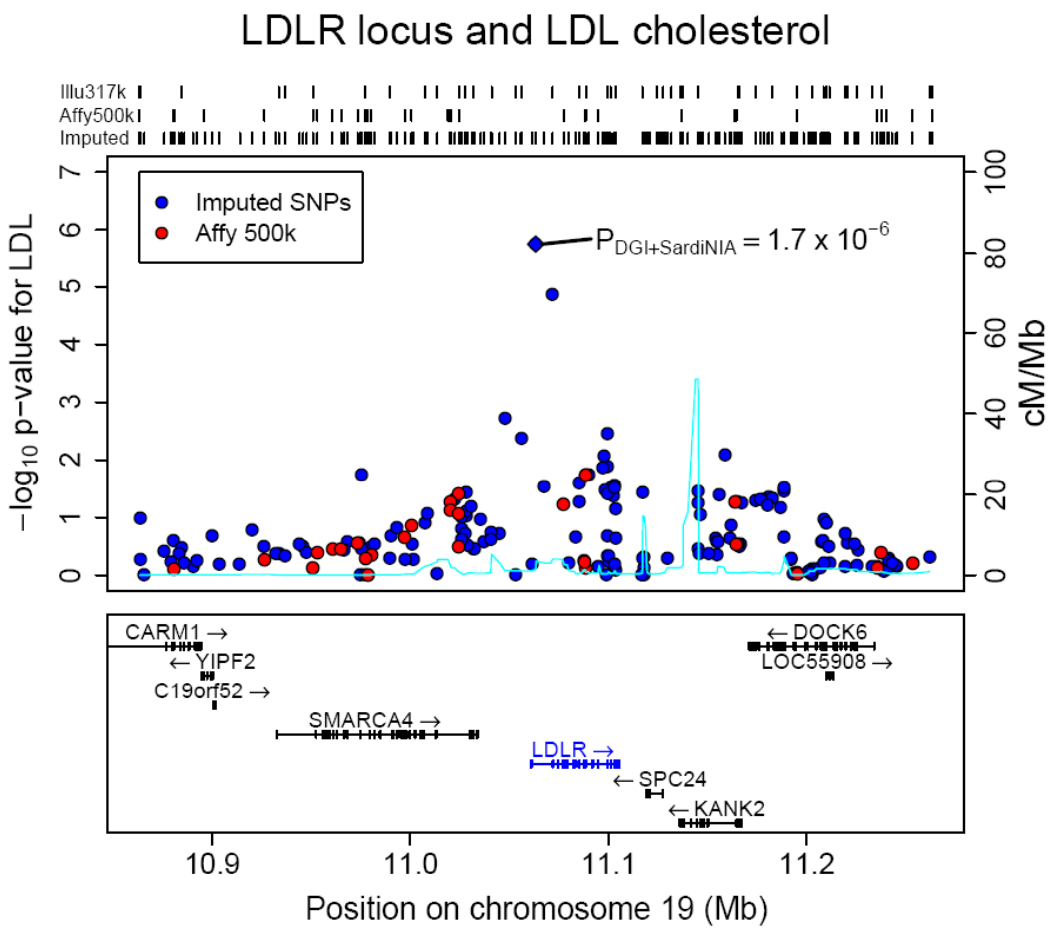


After imputing HapMap SNPs a region on chromosome 1 becomes top hit after G6PD and HBB

The new hit is upstream of 6PGD

6-phosphogluconate dehydrogenase is an enzyme that is known to metabolize some of the same substrates as G6PD

LDLR and LDL example



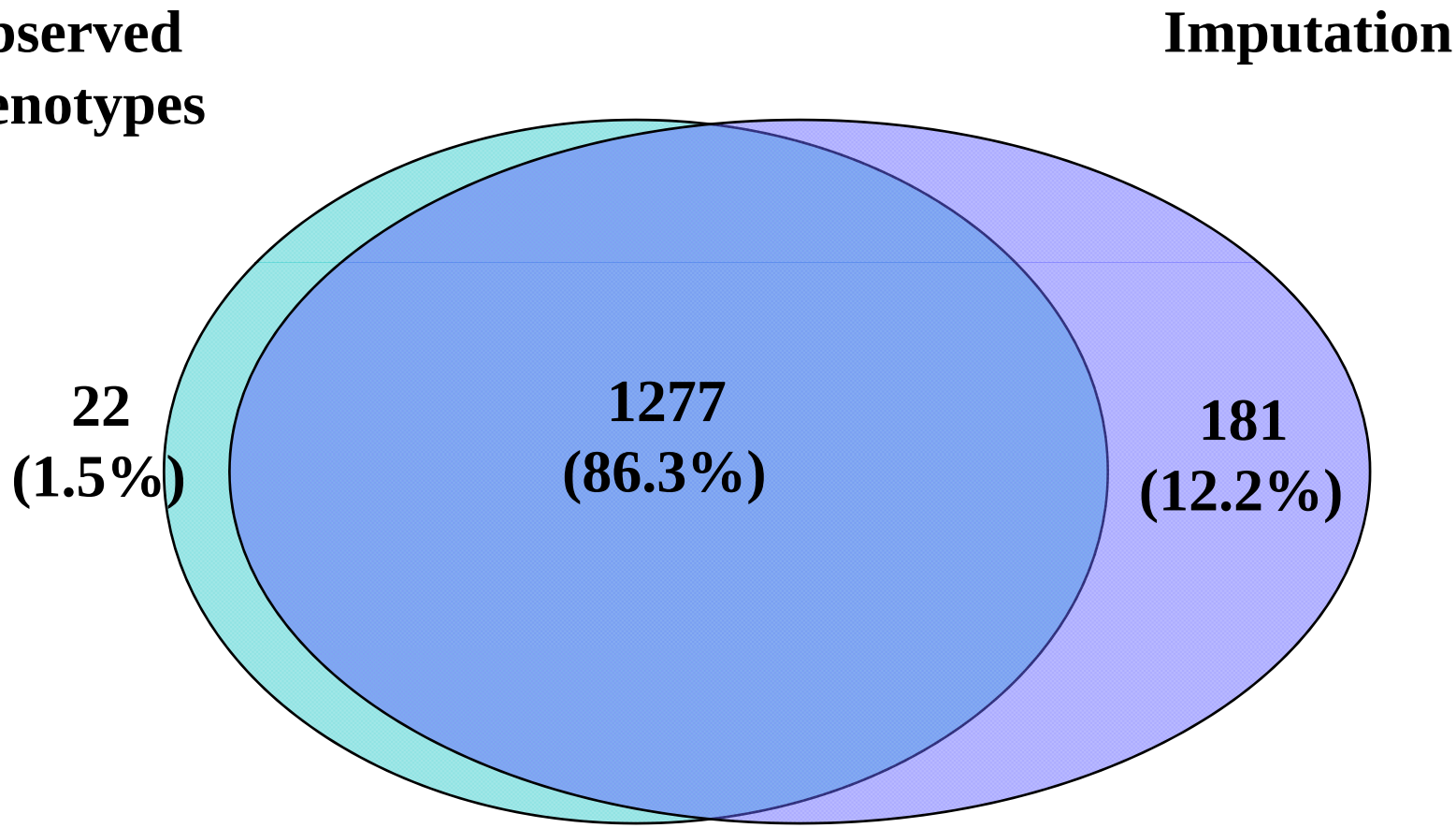
Impact of HapMap Imputation on Power

	Power	
Disease SNP MAF	**tagSNPs**	**Imputation**
2.5%	24.4%	56.2%
5%	55.8%	73.8%
10%	77.4%	87.2%
20%	85.6%	92.0%
50%	93.0%	96.0%

Power for Simulated Case Control Studies.
Simulations Ensure Equal Power for Directly Genotype SNPs.

Simulated studies used a tag SNP panel that captures
80% of common variants with pairwise $r^2 > 0.80$.

For eQTL Mapping, Imputation Increases Number of *cis* eQTL by ~10%



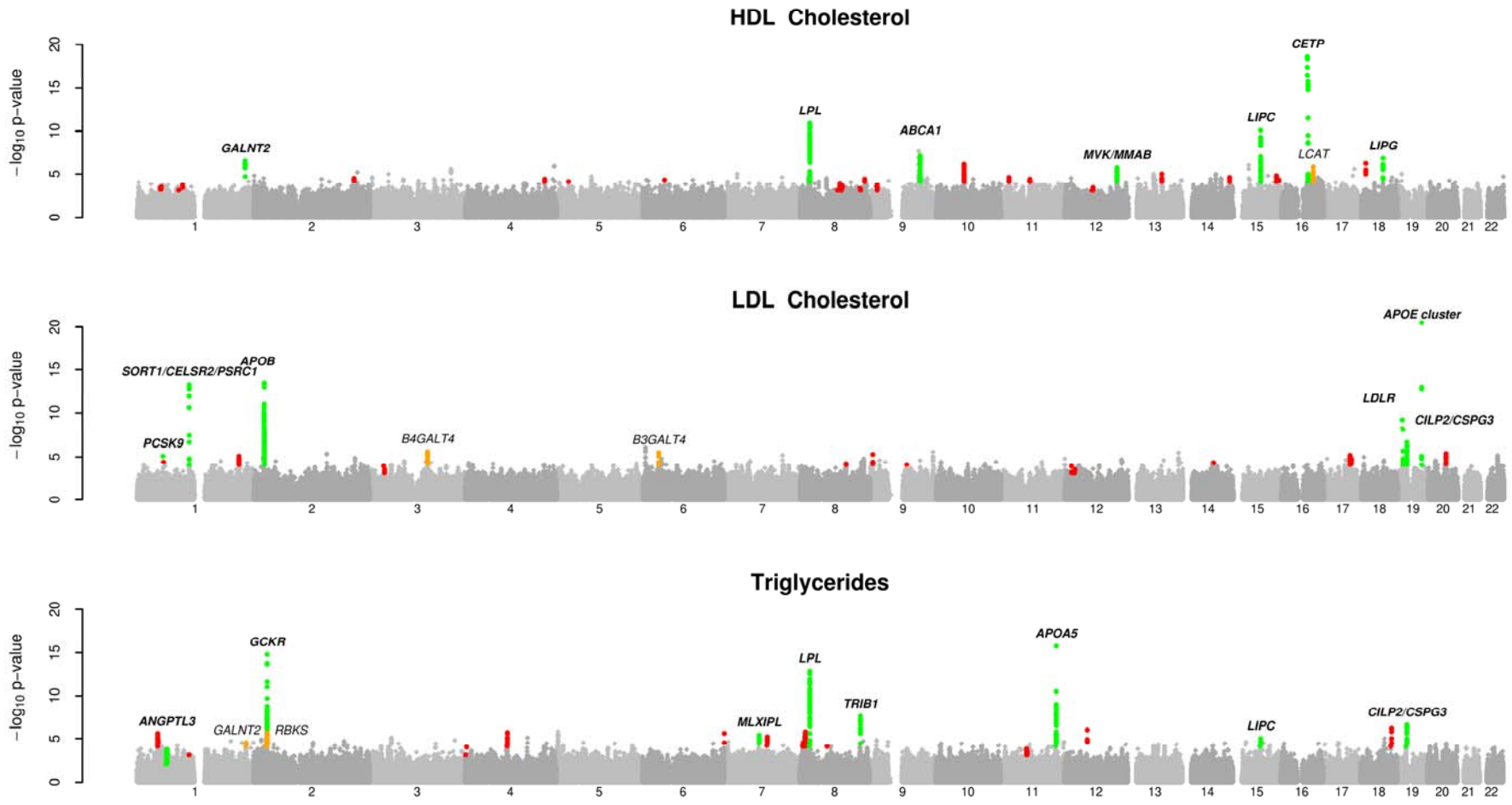
Combining Genomewide Studies: Cholesterol Levels Example

- HDL-Cholesterol, LDL-Cholesterol and Triglycerides
  - Strongly associated with risk of coronary artery disease
  - Important non-genetic factors include diet, statins, age
  - Several previously identified genes
  - Heritability 30-40%

- Our experiment
  - Examine 8,816 individuals from 3 genomewide scans
  - Scans used different marker platforms, combined with imputation
  - Individually, SardiNIA, FUSION and DGI scans had 1-3 hits
  - Confirm findings in >11,500 additional individuals

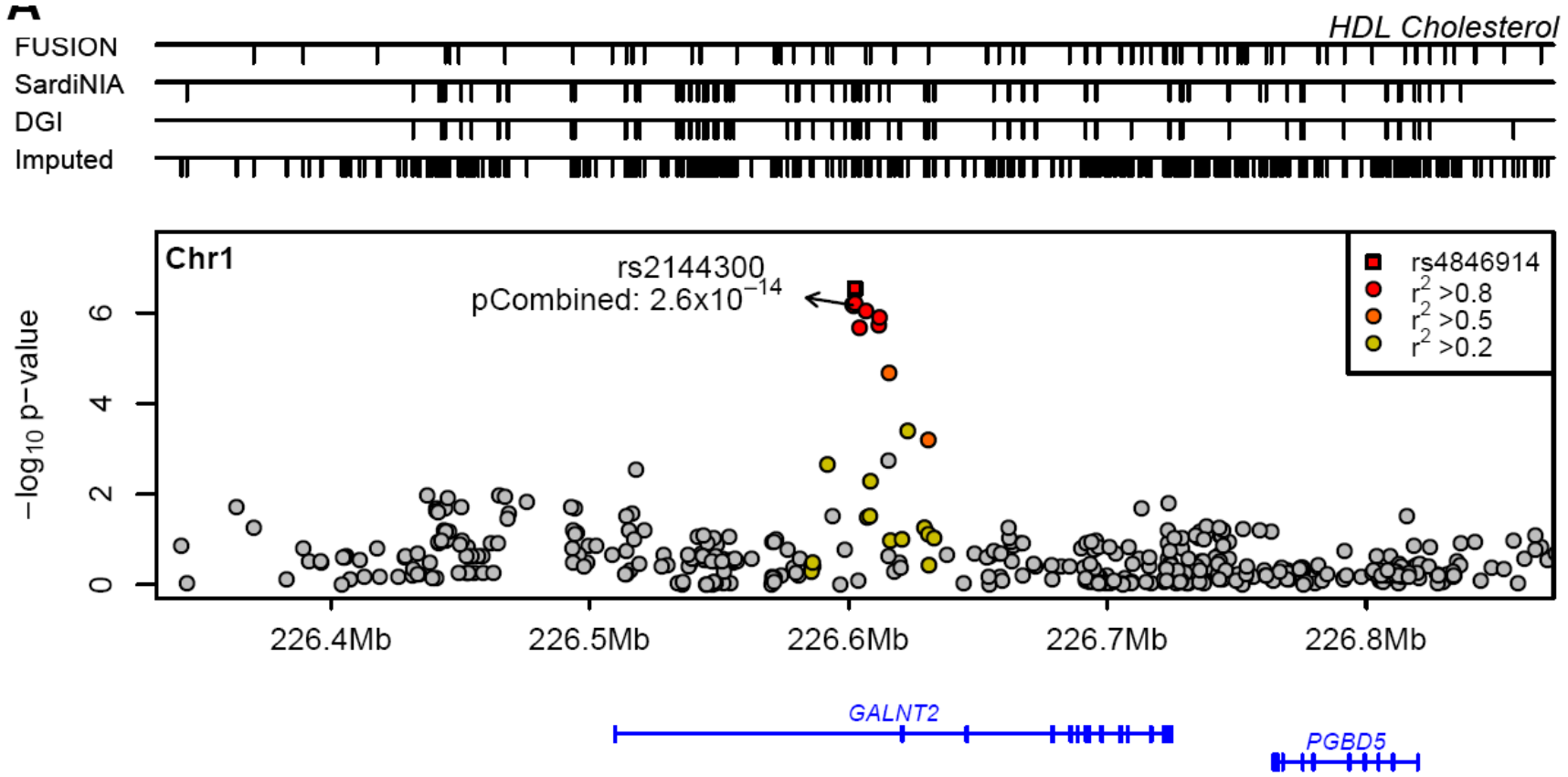
- Identified a total of 18 loci associated with cholesterol at $p < 5x10^{-8}$

What do we learn from meta-analysis? Combined Lipid Scan Results



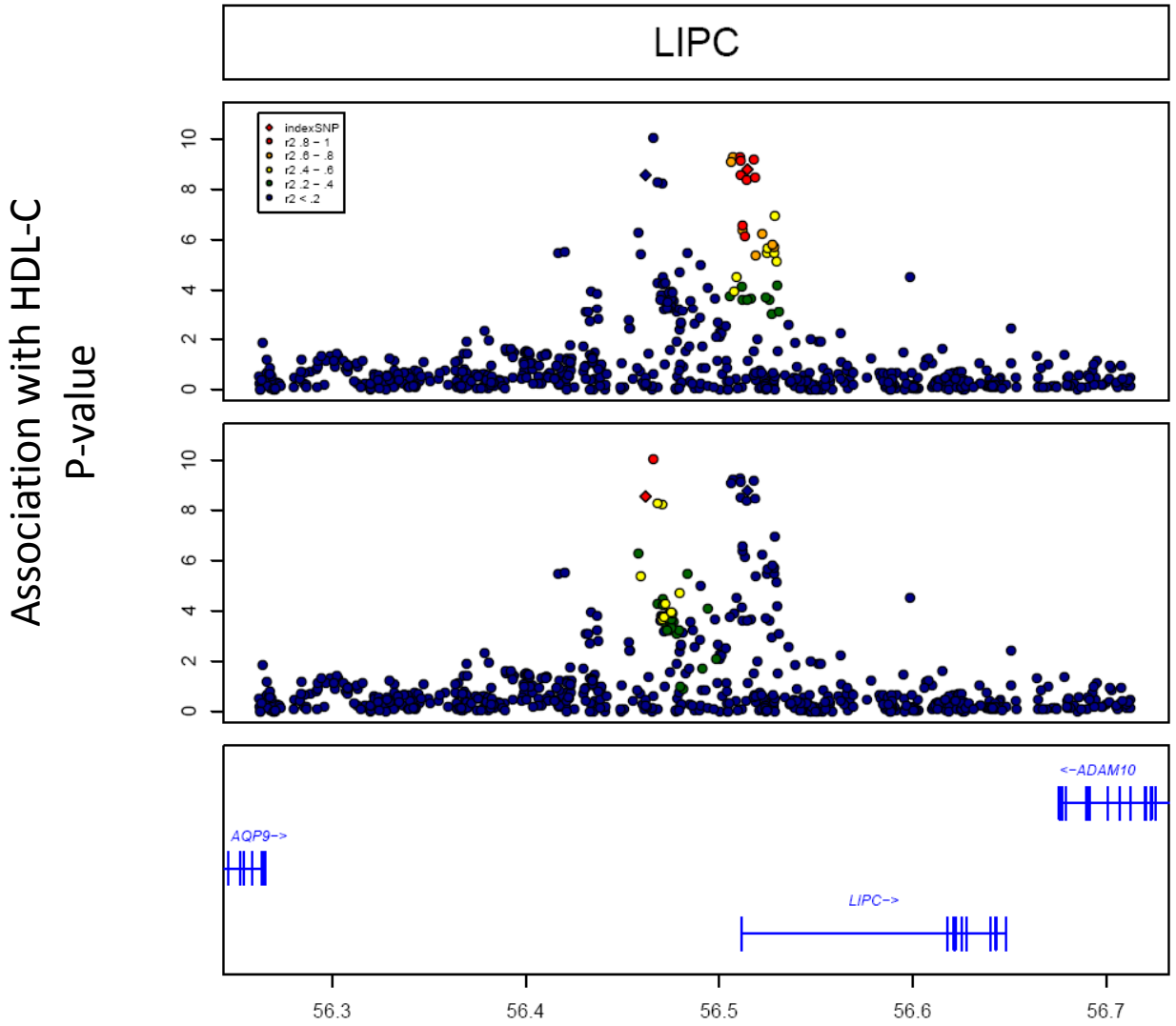
Willer et al, *Nat Genet*, 2008

New HDL Locus



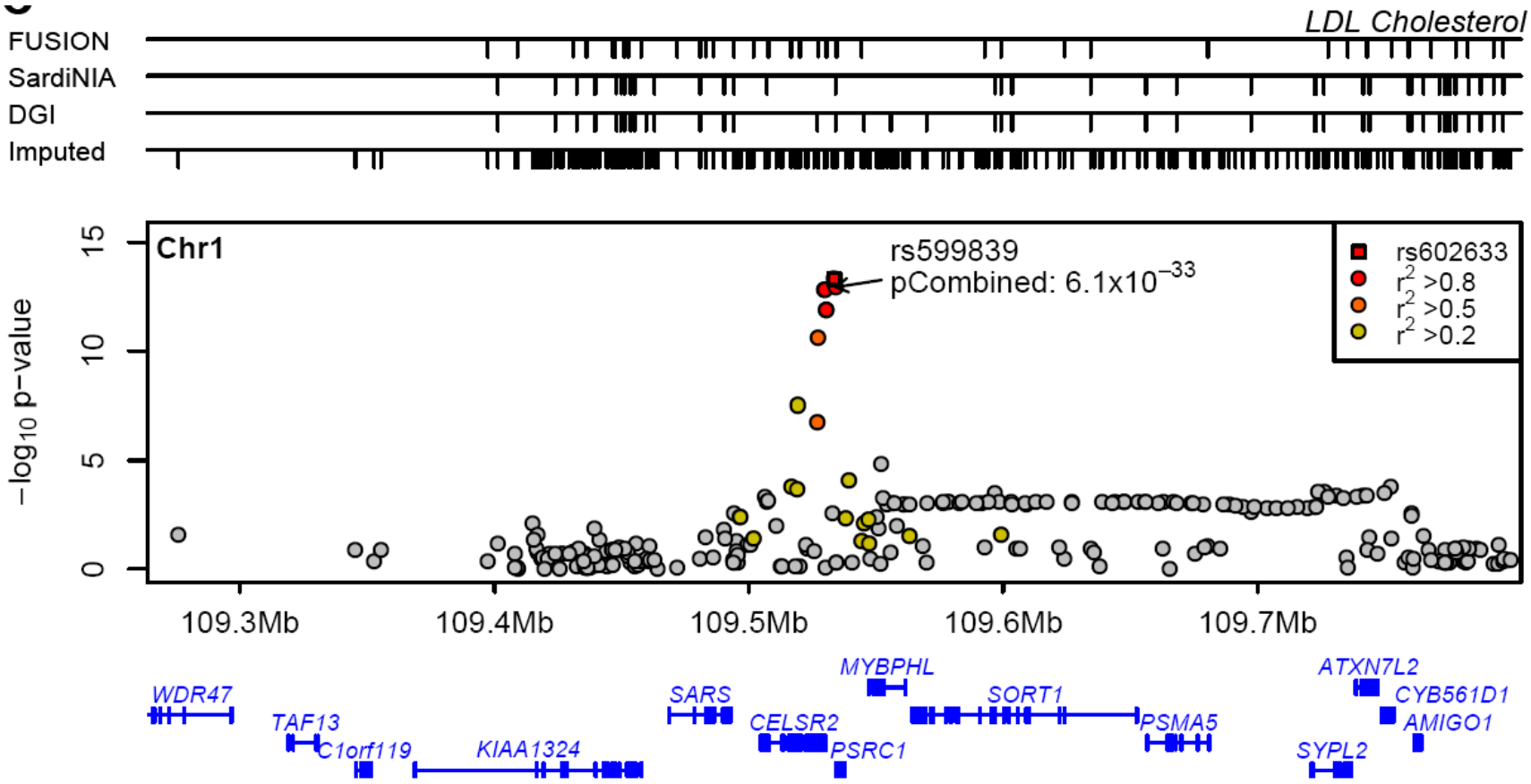
Willer et al, *Nat Genet*, 2008

New HDL Signal For An Old Locus …



What happens when we contrast results with related traits?

New LDL Locus, Previously Associated with CAD



Comparison with Related Traits: Coronary Artery Disease and LDL-C Alleles

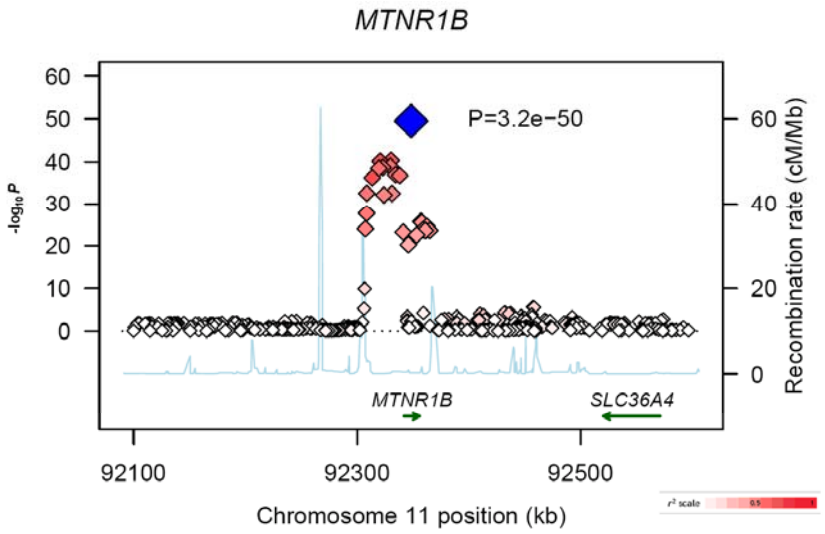
Gene	LDL-C p-value	Frequency CAD cases	Frequency CAD ctrls	CAD p-value	OR
APOE/C1/C4	**3.0×10^{-43}**	**.209**	**.184**	**1.0×10^{-4}**	**1.17 (1.08-1.28)**
APOE/C1/C4	**1.2×10^{-9}**	**.339**	**.319**	**.0068**	**1.10 (1.02-1.18)**
SORT1	**6.1×10^{-33}**	**.808**	**.778**	**1.3×10^{-5}**	**1.20 (1.10-1.31)**
LDLR	**4.2×10^{-26}**	**.902**	**.890**	**6.7×10^{-4}**	**1.29 (1.10-1.52)**
APOB	**5.6×10^{-22}**	**.830**	**.824**	**.18**	**1.04 (0.95-1.14)**
APOB	**8.3×10^{-12}**	**.353**	**.332**	**.0042**	**1.10 (1.03-1.18)**
APOB	**3.1×10^{-9}**	**.536**	**.520**	**.028**	**1.07 (1.00-1.14)**
PCSK9	**3.5×10^{-11}**	**.825**	**.807**	**.0042**	**1.13 (1.03-1.23)**
NCAN/CILP2	**2.7×10^{-9}**	**.922**	**.915**	**.055**	**1.11 (0.98-1.26)**
B3GALT4	**5.1×10^{-8}**	**.399**	**.385**	**.039**	**1.07 (0.99-1.14)**
B4GALT4	**1.0×10^{-6}**	**.874**	**.865**	**.051**	**1.09 (0.98-1.20)**

Data from WTCCC; Willer et al, *Nature Genetics*, 2008

MTNR1B influences glucose levels in non-diabetics and is a new T2D locus

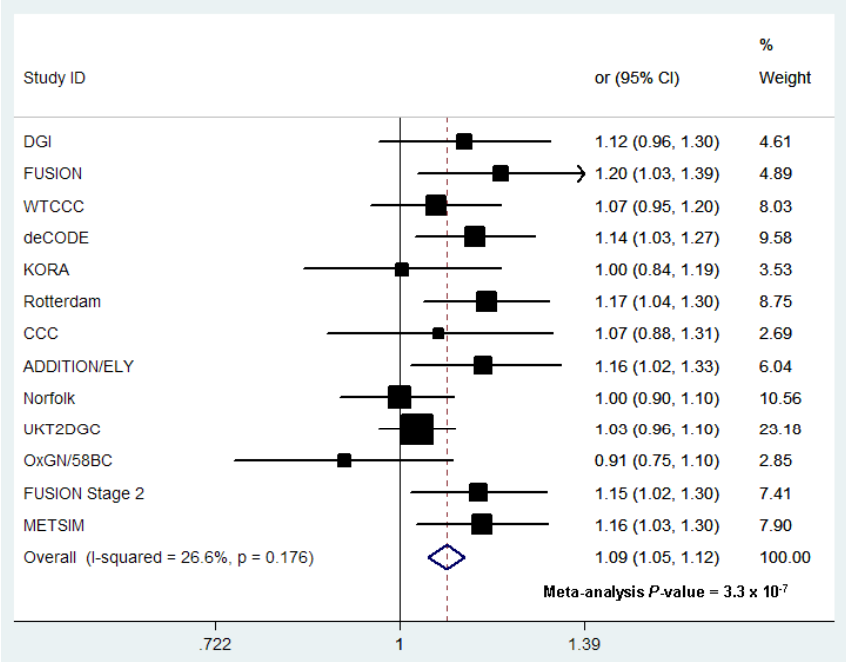
Association with glucose,

36,000 non-diabetics



Association with diabetes,

18,000 cases vs. 64,000 controls

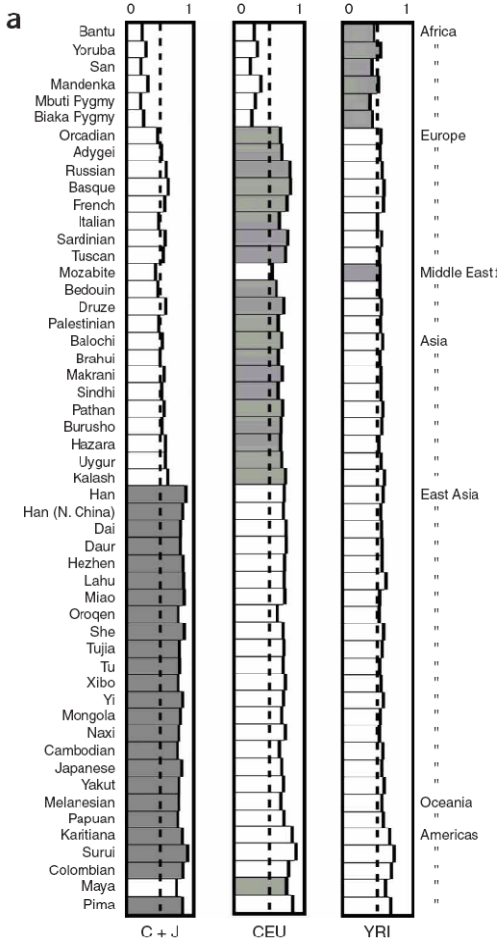


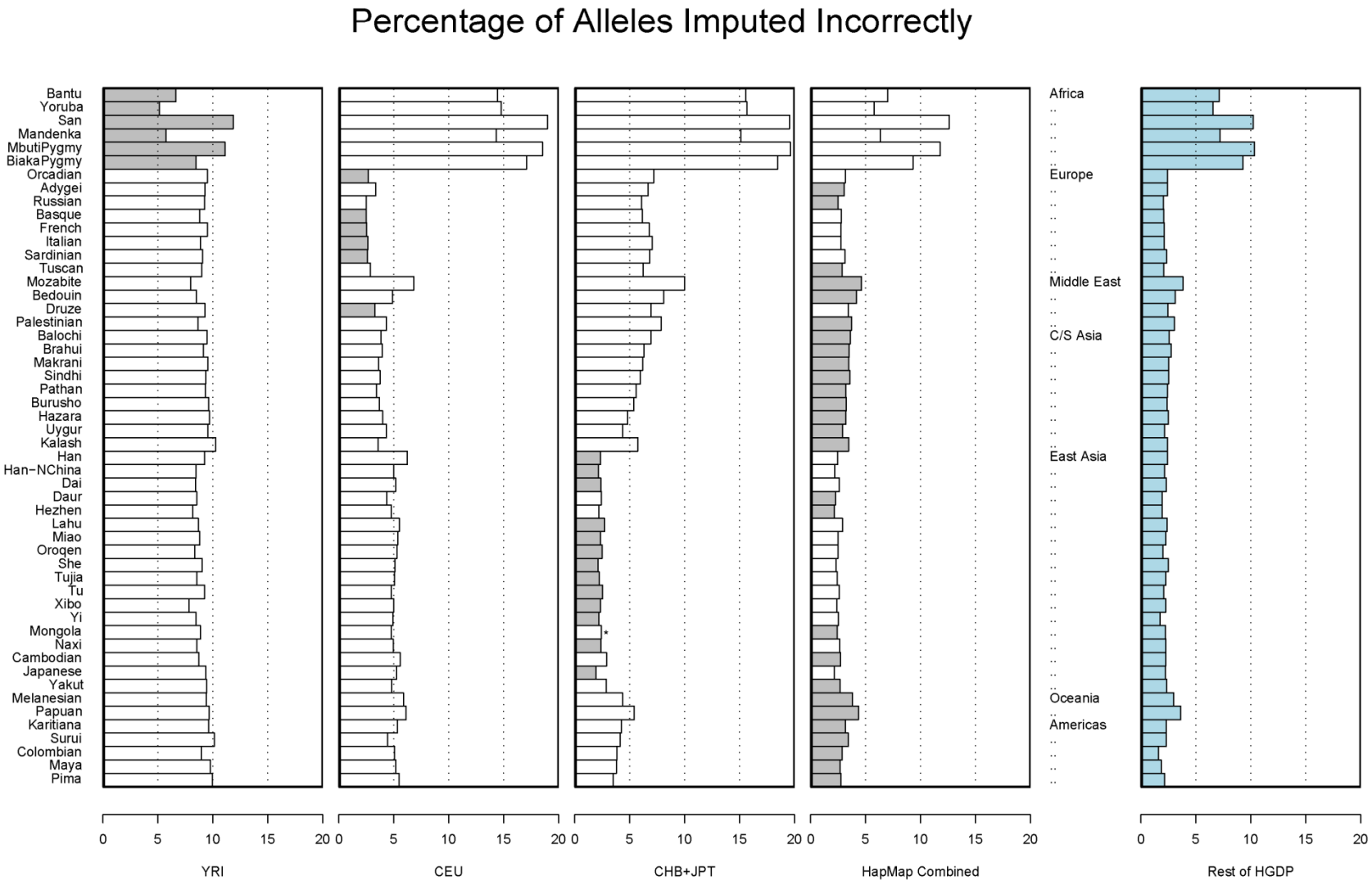
Prokopenko et al, *Nature Genetics*, 2009

Does Imputation Work Across Populations?

- Conrad et al. (2006) dataset
- 52 regions, each ~330 kb
- Human Genome Diversity Panel
  - ~927 individuals, 52 populations
- 1864 SNPs
  - Grid of 872 SNPs used as tags
  - Predicted genotypes for the other 992 SNPs
  - Compared predictions to actual genotypes

Tag SNP Portability





(Evaluation Using ~1 SNP per 10kb in 52 x 300kb regions For Imputation)

Beyond the Initial Analysis

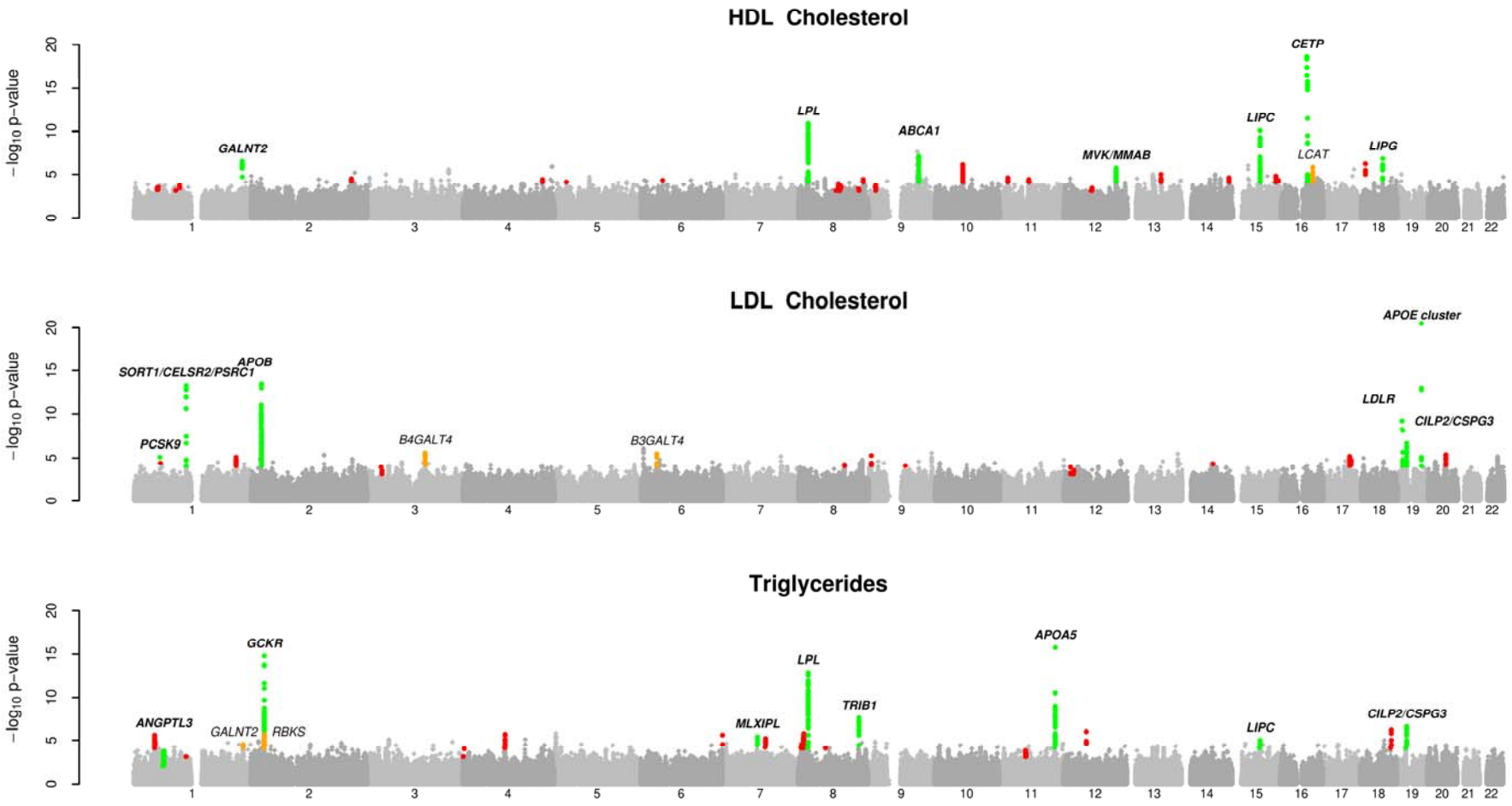
- Things that we already know will work …
  1. Imputation of genome scan genotypes in relatives
  2. Imputation of HapMap genotypes in everyone
  3. Meta-analysis of genome wide scans
  4. Contrasting results for scans targeting related traits

- **Things that might work …**
  1. **Screening for rare variants**
  2. **Screening for interactions**
  3. **Focusing on the "right" pathways**
  4. **Studying copy number polymorphisms**

- Things for molecular biologists to do …
  1. Many new targets to investigate

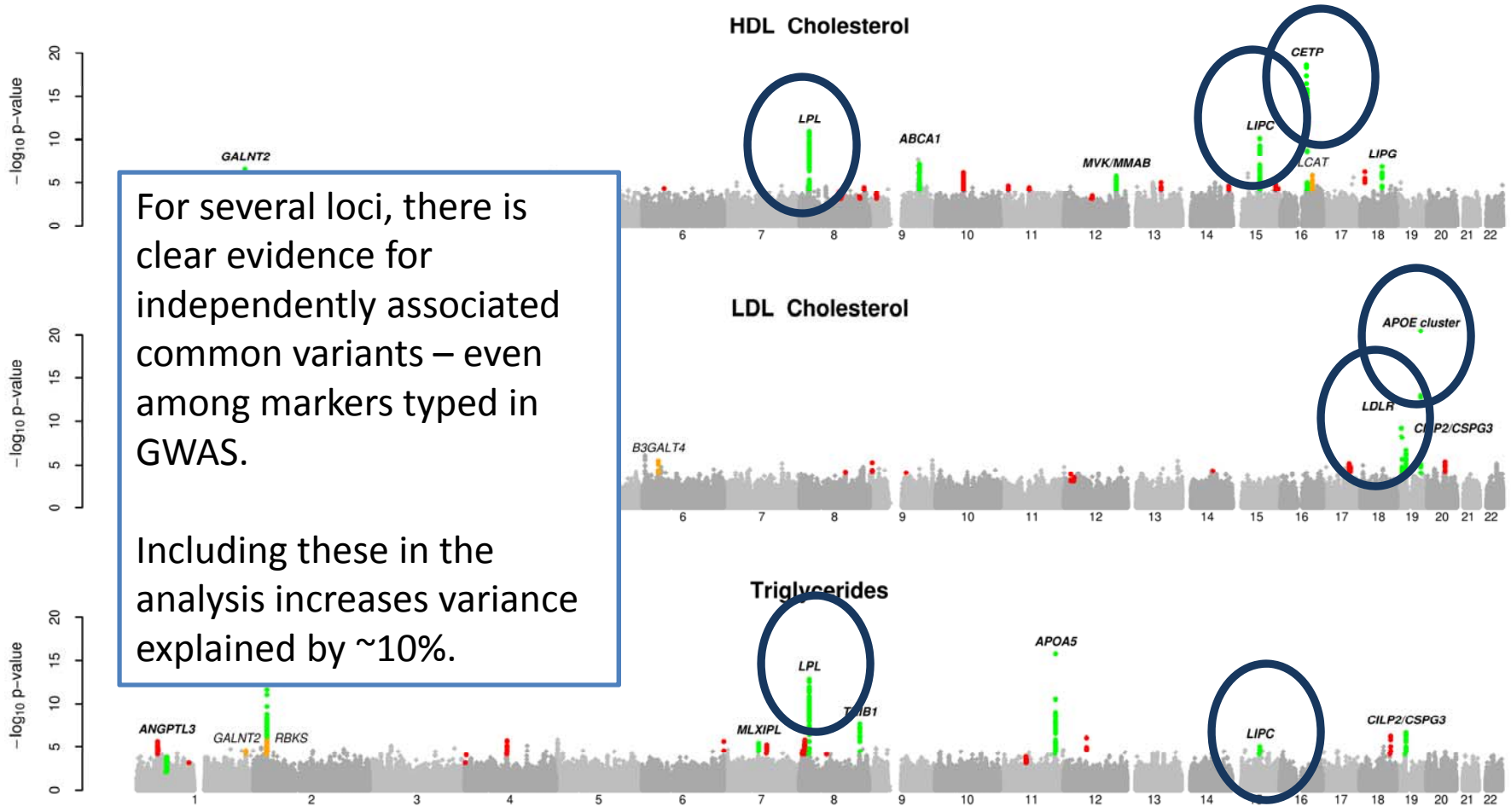
Will GWAS Loci Harbor Additional Variants?

Combined Lipid Scan Results



Willer et al, *Nat Genet*, 2008

Combined Lipid Scan Results

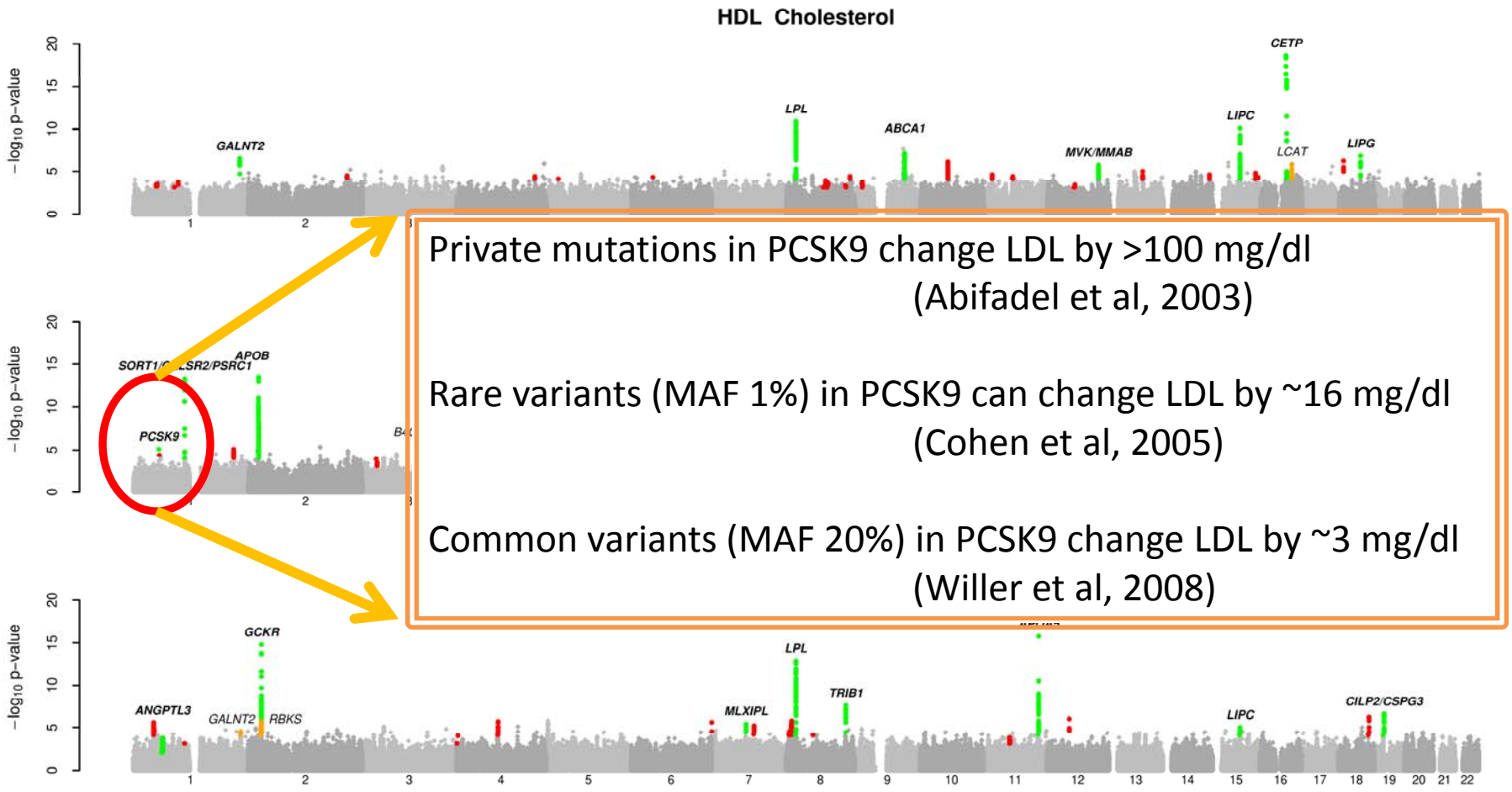


For several loci, there is clear evidence for independently associated common variants – even among markers typed in GWAS.

Including these in the analysis increases variance explained by ~10%.

Willer et al, *Nat Genet*, 2008

Combined Lipid Scan Results



Private mutations in PCSK9 change LDL by >100 mg/dl
(Abifadel et al, 2003)

Rare variants (MAF 1%) in PCSK9 can change LDL by ~16 mg/dl
(Cohen et al, 2005)

Common variants (MAF 20%) in PCSK9 change LDL by ~3 mg/dl
(Willer et al, 2008)

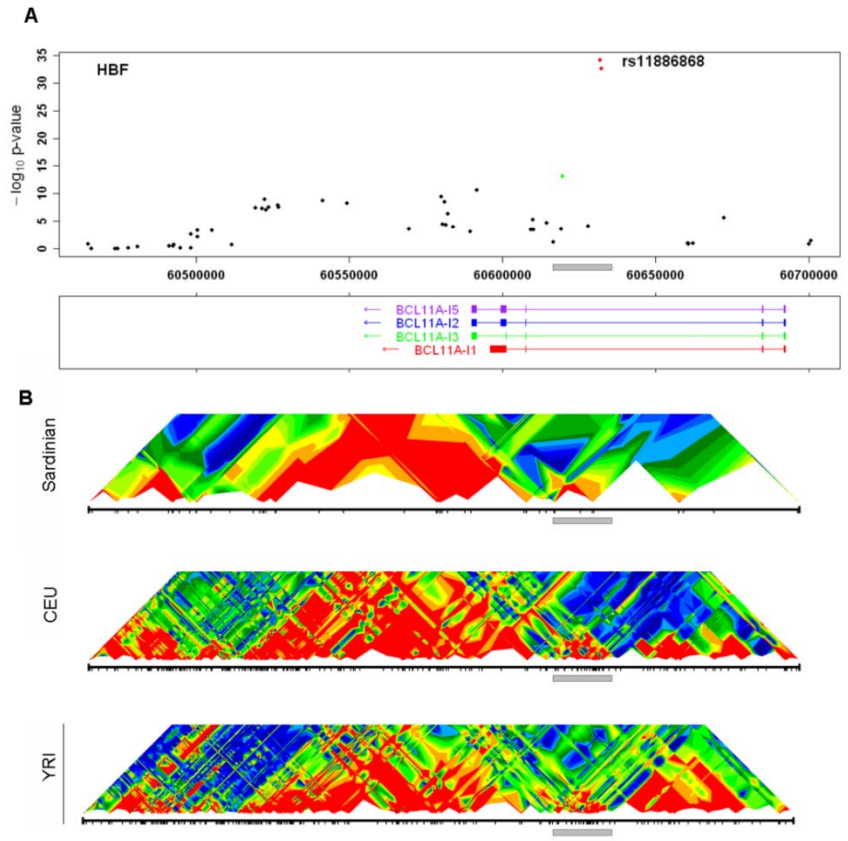
Willer et al, *Nat Genet*, 2008

What about interactions?

Typical Story Parallels Our Psoriasis GWAS:

No evidence for interactions.

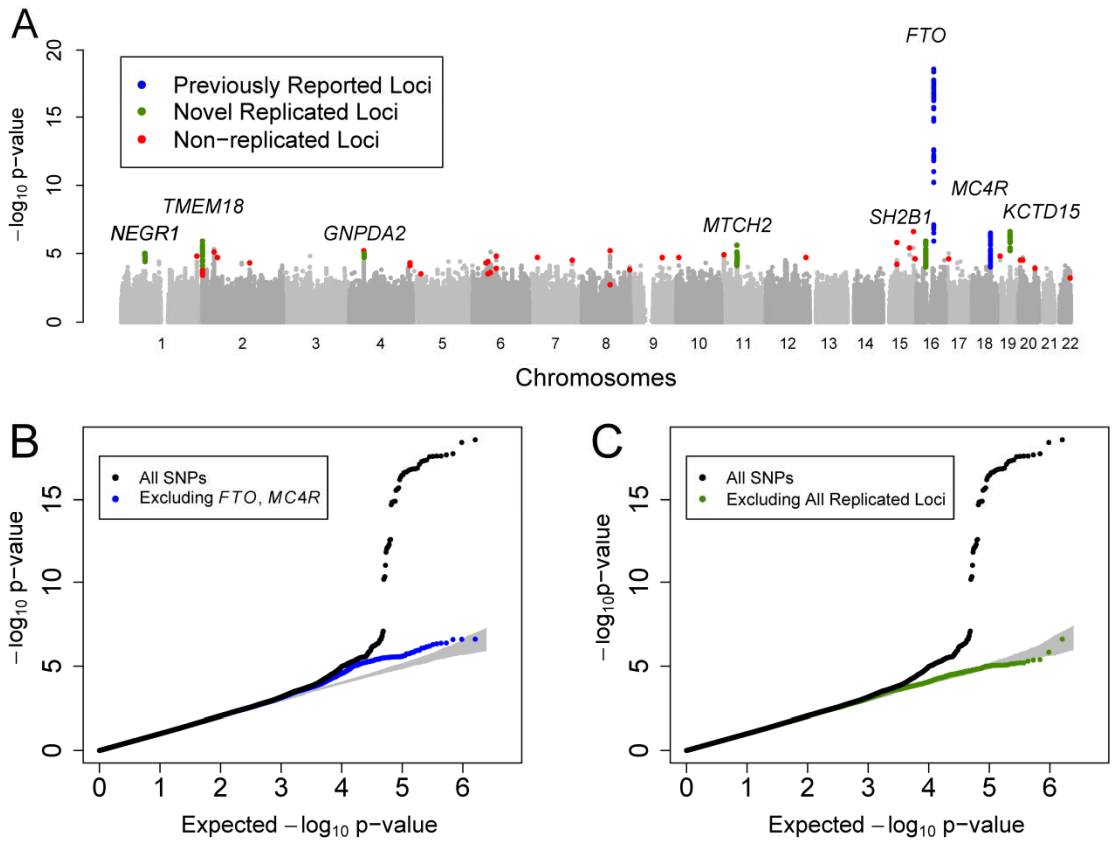
Unusual Story:
BCL11A and Fetal Hemoglobin Levels



- Mapped association of fetal hemoglobin levels in adults and BCL11A variants
- BCL11A variants “rescue” thalassemia phenotype in β-globin null homozygotes
- Uda et al, PNAS, 2008

Focusing on the right pathways…

Genes impacting BMI act in the brain?

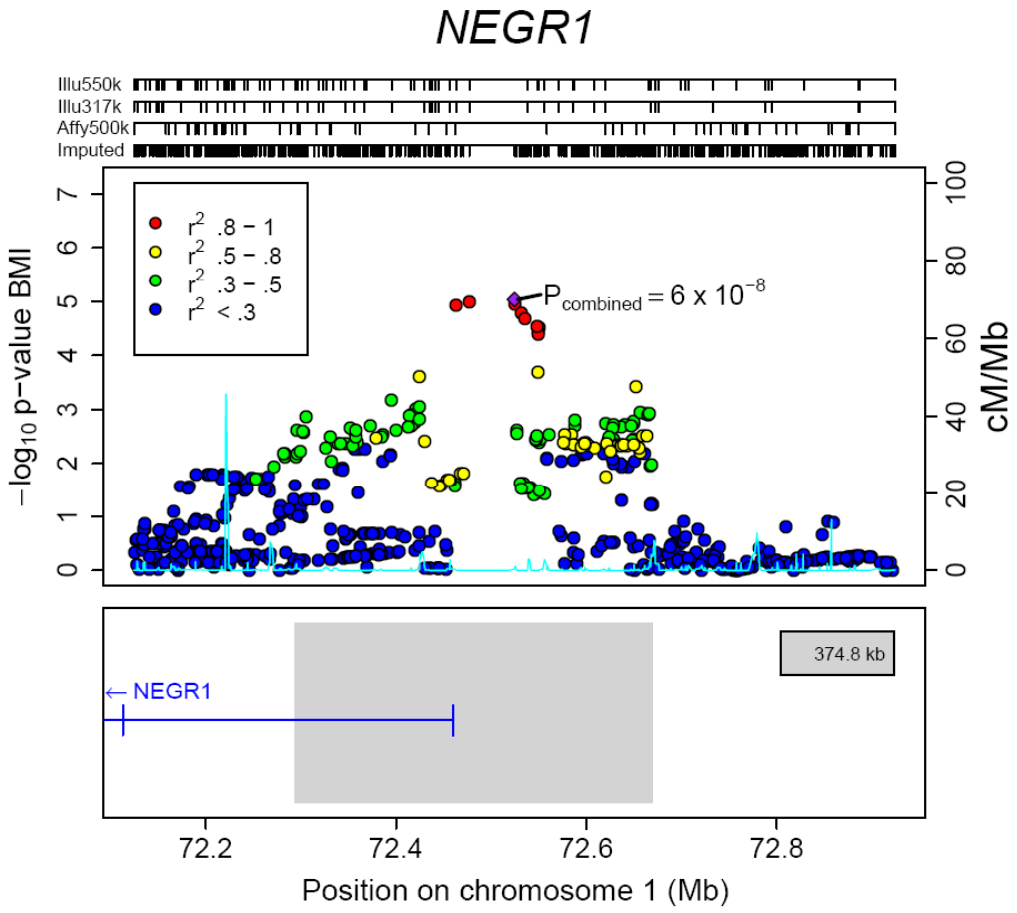


Seven of eight confirmed BMI loci show strongest expression in the brain…

Willer et al, *Nature Genetics,* 2009

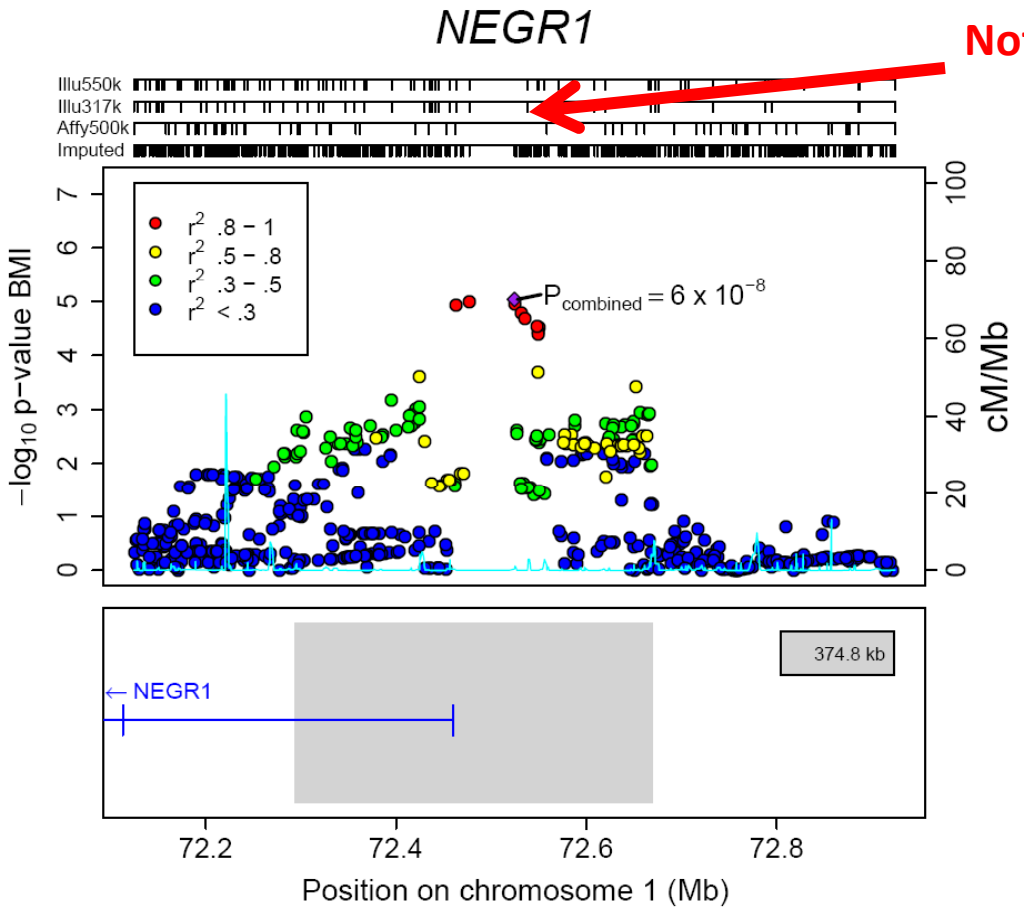
How important is copy number variation?

NEGR1 – BMI Association



Willer et al, *Nature Genetics,* 2009

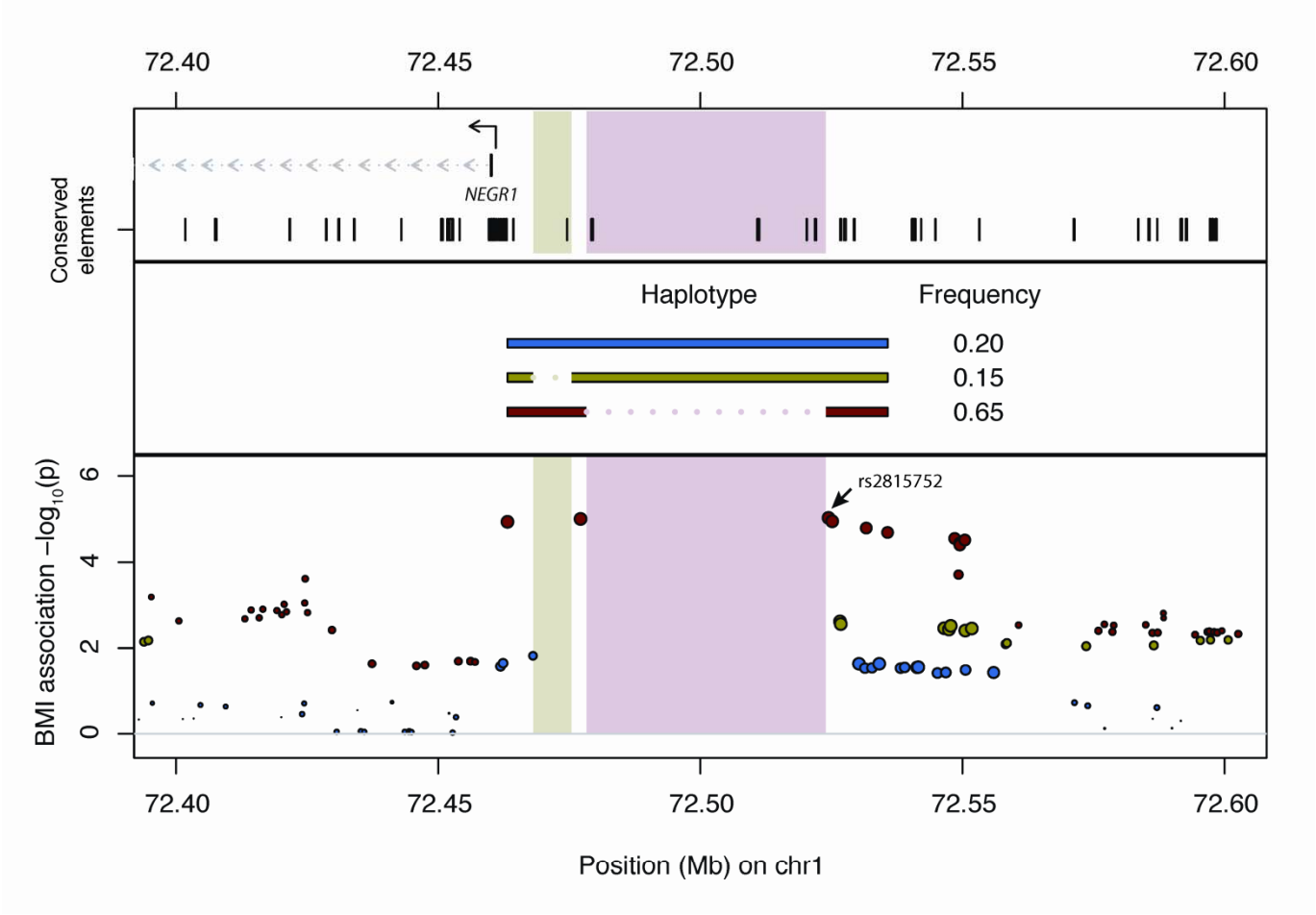
NEGR1 – BMI Association



Note hole in marker panels….

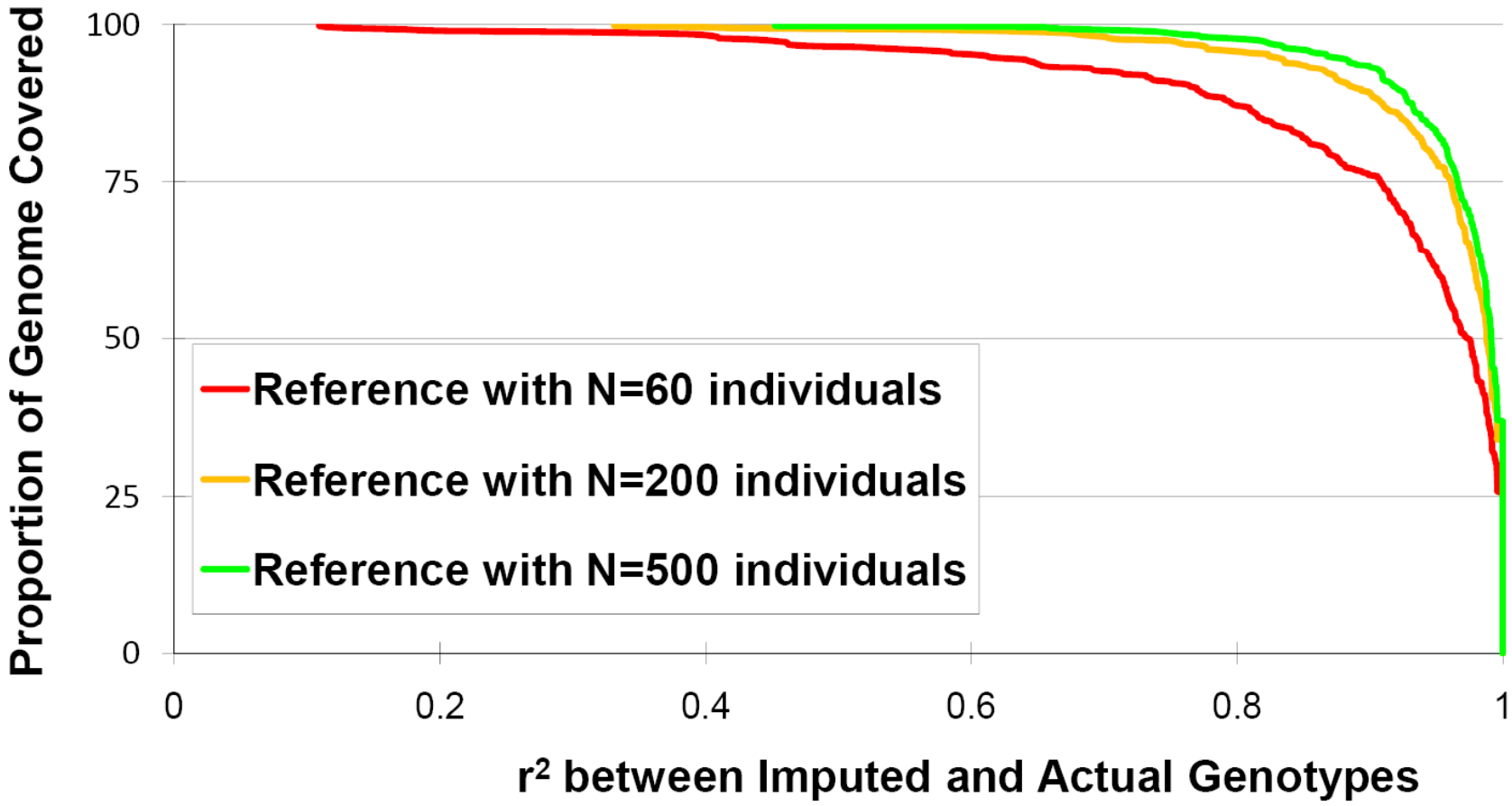
Willer et al, *Nature Genetics,* 2009

Associated Haplotype Carries Deletion



Willer et al, *Nature Genetics,* 2009

How will we do with larger reference panels? Improve Imputation and Power in all GWAS



Increasing reference panels from 60 (HapMap) to 500 individuals (1000 genomes?) should decrease imputation error in GWAS from ~1.4% to ~0.4%.

Genome-wide Scan Reveals Association of Psoriasis with IL-23 and NF-κB Pathways

Rajan P. Nair[1*], Kristina Callis Duffin[2*], Cindy Helms[3*], Jun Ding[4*], Philip E. Stuart[1], David Goldgar[2], Johann E. Gudjonsson[1], Yun Li[4], Trilokraj Tejasvi[1], Binjian Feng[2], Andreas Ruether[5], Michael Weichenthal[6], Dafna Gladman[7], Proton Rahman[8], Steven J. Schrodi[9], Sampath Prahalad[10], Stephen L Guthery[10], Judith Fischer[11], Wilson Liao[12], Pui Kwok[12], Alan Menter[13], G. Mark Lathrop[11], C. Wise[14], Ann B. Begovich[9], John J. Voorhees[1], James T. Elder[1,15#], Gerald G. Krueger[2#], Anne M. Bowcock[3#], Gonçalo R. Abecasis[4#] for the Collaborative Association Study of Psoriasis[16]

- University of Utah
  - Gerald Krueger
  - Kristina Callis
  - David Goldgar
- University of Michigan
  - JT Elder
  - Rajan Nair
  - Phil Stuart
  - Johann Gudjonsson
  - John Voorhees
- Washington University
  - Anne Bowcock
  - Alan Menter
  - Cindy Helms
  - Gonçalo Abecasis
  - Yun Li
  - Jun Ding

Variants in the melatonin receptor 1B gene (*MTNR1B*) influence fasting glucose levels

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Six New Loci Associated with Body Mass Index Highlight a Neuronal Influence on Body Weight Regulation

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