

Niarchou et al, Nature Human Behaviour (2022)

DCEG Statistical Genetics Workshop

Basic GWAS Analysis

September 20th, 2023
Aubrey K Hubbard, PhD, MPH

Questions from last lecture?

Poll: PollEv.com/cmurray492



Course Website and Discussion Page Links!

- Course Website [here](#)
- Github Discussion Page [here](#)

Outline

- Genetic Epidemiology Intro
- Motivation for genetic studies
- Quality Control/Assurance

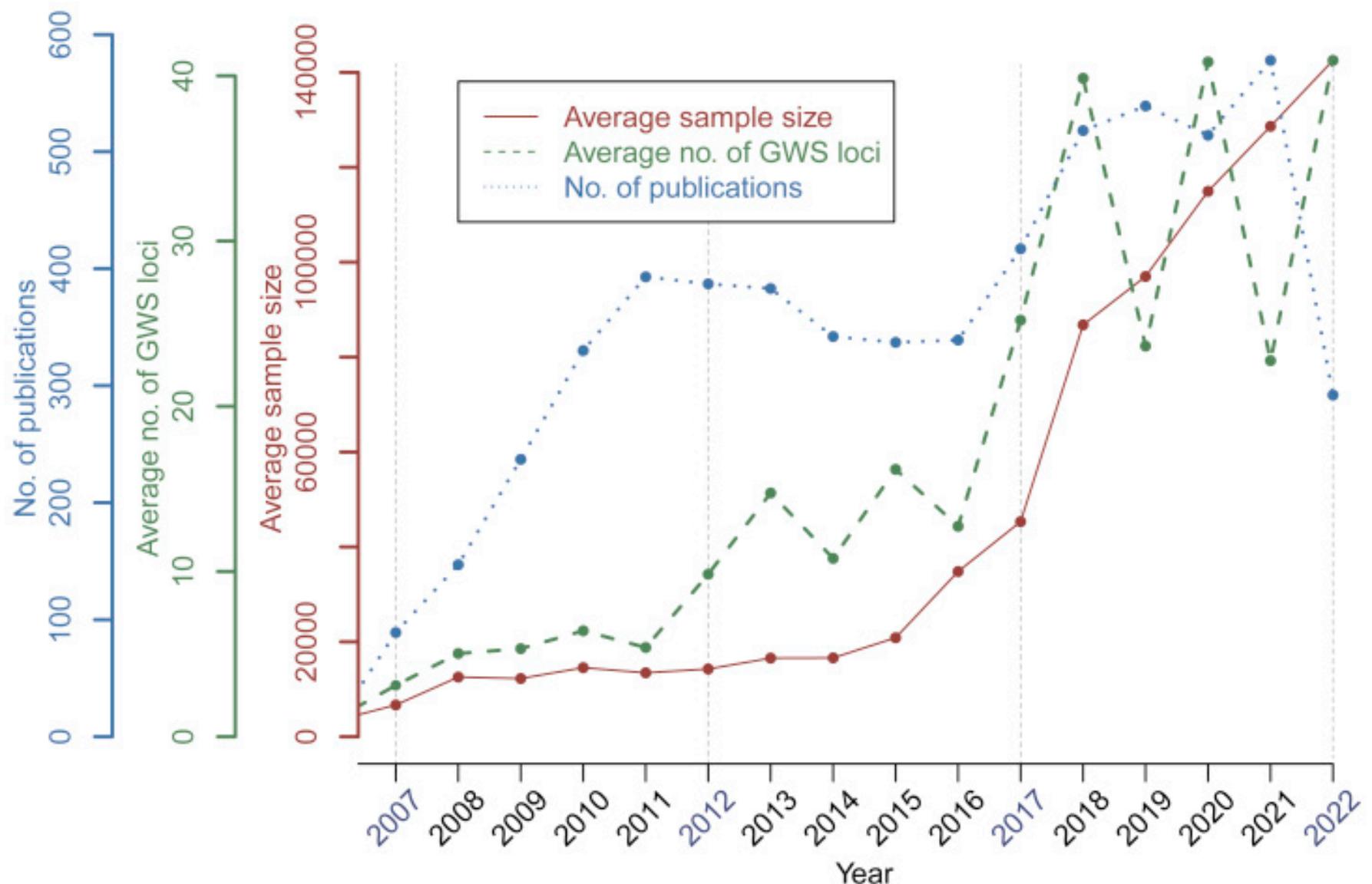
Lecture #1

- Statistical Analysis
- Visualization and Post GWAS QC
- Meta-Analysis
- Annotation & Reporting

Today

Quick GWAS Reminders

Sample Size: Bigger is Better!



GWAS results are not always transferable to other groups

- Genetic differences affect the distribution of allelic variants between groups and environmental differences can alter their effects within groups on traits and disease risk.
- The transferability of GWAS results across populations depends on many factors such as:
 - Allele frequencies
 - Linkage disequilibrium
 - Epistasis
 - Gene-environment interaction

There is a lack
of diversity in
GWAS
studies.

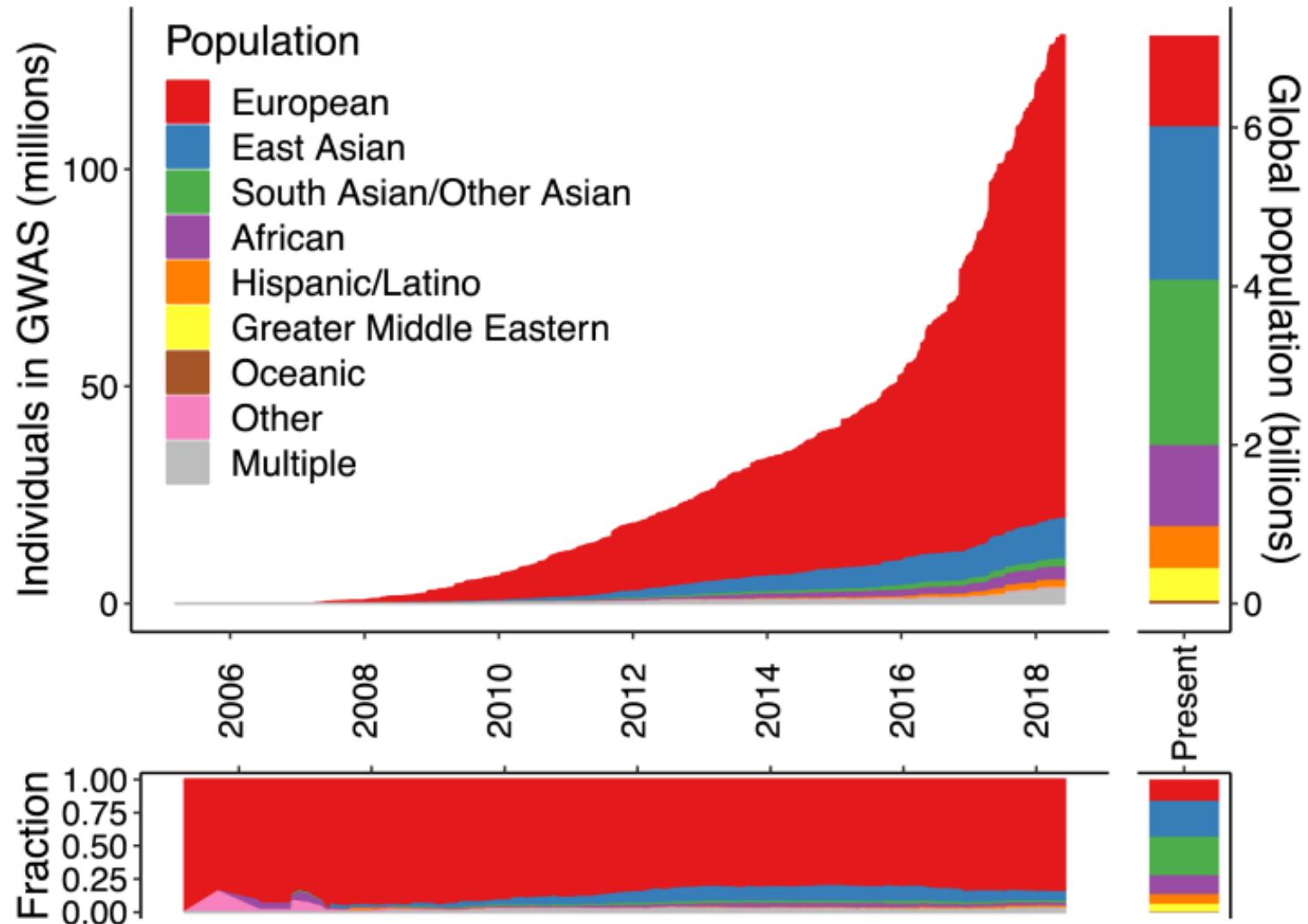
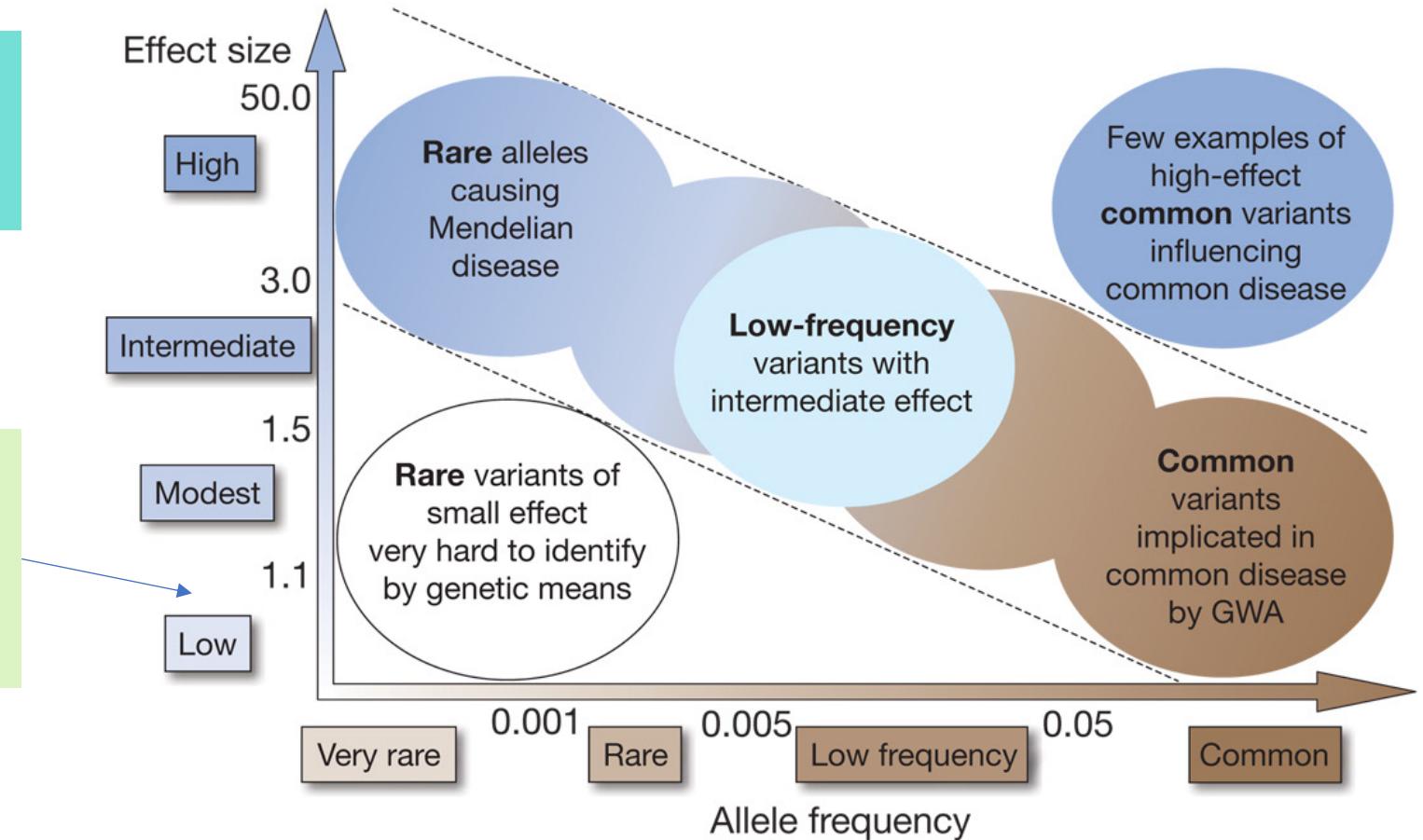


Figure 1. Ancestry of GWAS participants over time compared to the global population.
Cumulative data as reported by the GWAS catalog⁷⁶. Individuals whose ancestry is “not reported” are not shown.

GWAS are used for common variation

GWAS Power Calculations are a function of effect size, allele frequency and sample size.

Common variants have smaller effect sizes which means large sample sizes are necessary to detect them!



Stay Tuned for Rare Variant Analysis Week #5

How to conduct a GWAS

General GWAS Steps

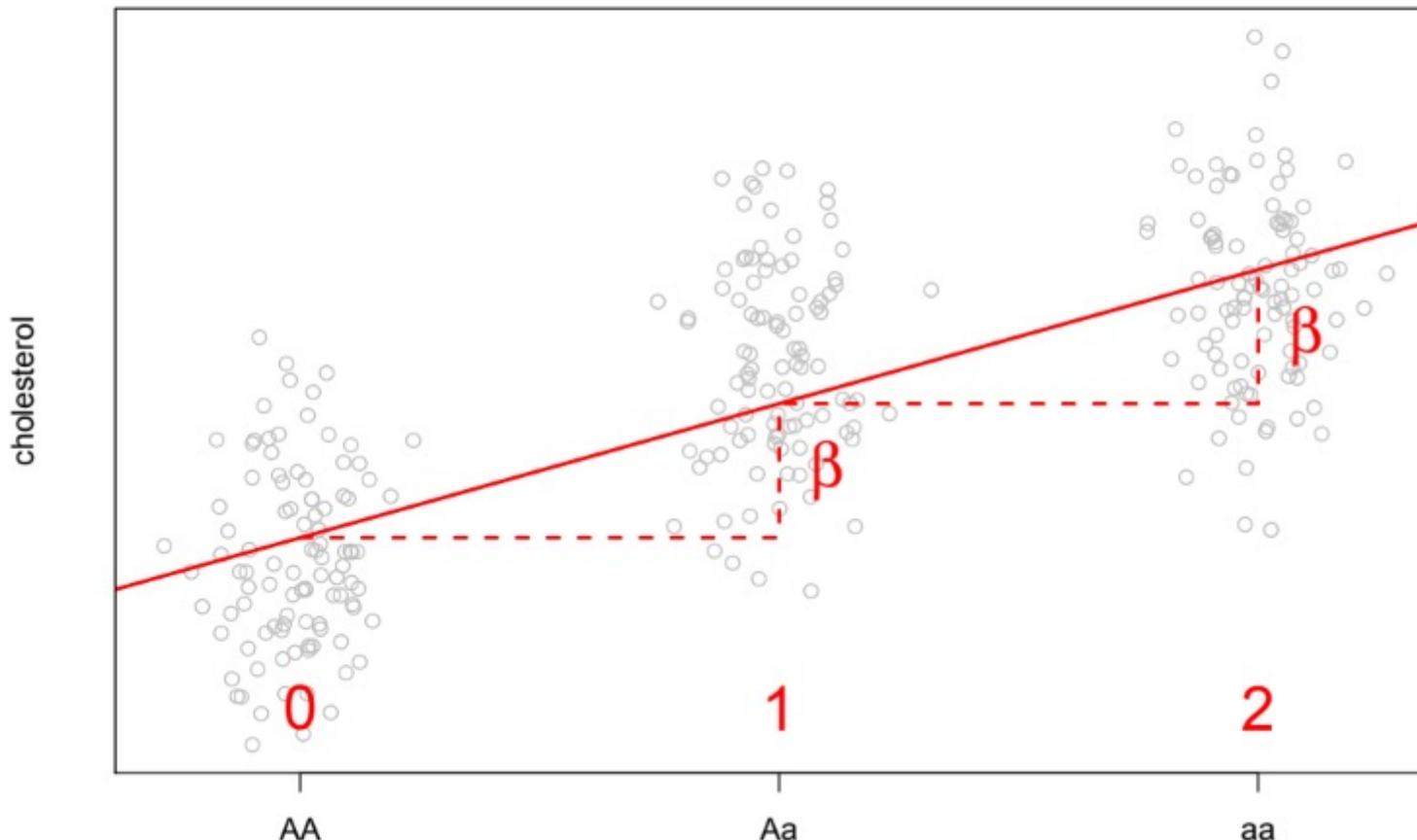
- Data collection, QC, cleaning and Imputation ←Last Practical
- Association Analysis
 - Perform Statistical analysis to identify SNPs associated with the phenotype of interest
 - Adjust for covariates that may confound your association
- Multiple testing correction
 - Control for Type I Error
- Results Visualization and Interpretation
 - Quantile-Quantile Plots, Manhattan Plots, Regional Plots
 - Available webtools
- Post GWAS Follow-up ←More to come in later lectures! Stay tuned

Linear Regression

- Quantitative Traits
 - Height, BMI, cholesterol
- Like standard linear regression
 - estimates the β
 - Include a single genetic marker (e.g., a SNP) as predictor in the model plus other relevant covariates (age, sex, pcs for ancestry)
 - May want to transform highly skewed variables as this is still linear regression!

Additive SNP modeling

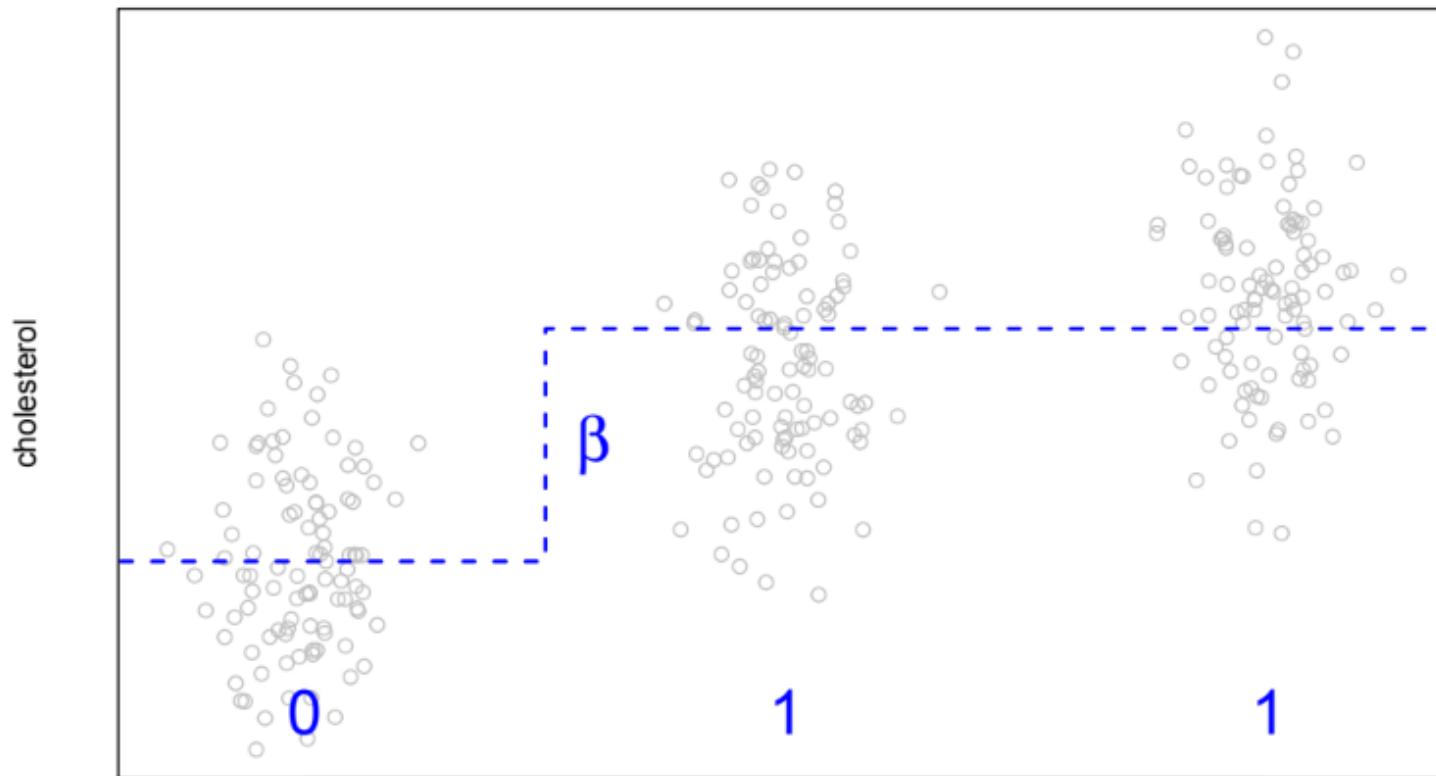
$$y = \beta_0 + \beta \times \#\text{minor alleles}$$



Regress # of effect alleles on outcome

Dominant SNP Model

$$y = \beta_0 + \beta \times (G \neq AA)$$



Recessive Model counts only the non-effect allele

In general: we count alleles additively

- Range from 0-2
- This is the default in many programs
 - Some programs have options to specify dominant or recessive models
- Regress outcome on allele “dosage” with imputed variants
 - Still ranges from 0-2
 - Efficient incorporation of imputation uncertainty in regression estimate standard errors
 - Important: Check how the software you use handles imputation certainty
 - More on imputation to come

Logistic Regression

- **Binary Traits**
 - Disease status
- Estimates an **odds ratio**, describing (averaged over the whole population) how the odds of the event are **multiplied**, per 1 allele (additive) effect
- For example,
 - OR of a T allele is 1.22: an individual with one T allele at that loci has a 22% greater odds of event

Survival Analysis

- “Time-to-event” outcomes
 - Time to Death
 - Time to remission
 - progression-free survival after intervention
 - Important in Cancer Survivorship and Late effects
- Potential packages include: gwasurvivr, genipe, SurvivalGWAS_SV and GWASTools
- Convergence, model assumptions, computationally intensive are all potential pitfalls

Linear/Logistic Mixed models (LMMs)

- Mixed effects regression models are popular statistical models to analyze correlated data with multiple sources of variance
 - Many programs deploy them for both Quantitative and Binary Traits
- Increased use in analyzing genome-wide association studies (GWAS)
- Pose some computational challenges that they pose
- Have utility in dealing with **population structure** and **genetic relatedness**

GWAS
Programs –
This is a
Continually
evolving area

PLINK

SNPTEST

GENESIS

BOLT-LMM

REGENIE

SAIGE

FastGWA-GLMM

Covariates

What goes into the model?

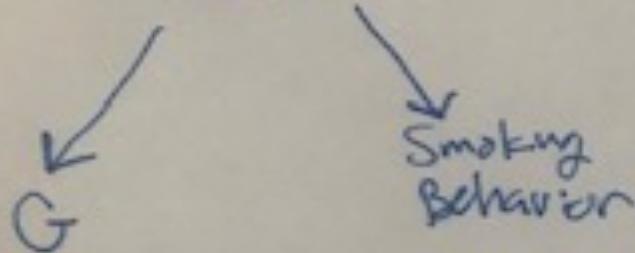
- Consider using **DAGs** (directed acyclic graphs)
- Do **not** throw all the variables available into the model as covariates



DAGs

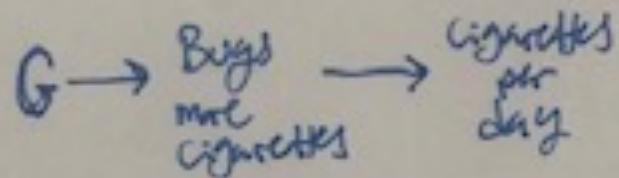
- A way to draw your causal assumptions
- Covariates that are **potential confounders** (and therefore should be in your model) are **common causes** of both the genotype and phenotype
- Covariates that are **on the causal pathway** should **not** be adjusted for
 - This could attenuate or eliminate detection of an association
- Covariates that are **common effects** of the genotype and phenotype will induce bias (**collider bias**) when placed into models

History
Social and Demographic Factors



Confounding

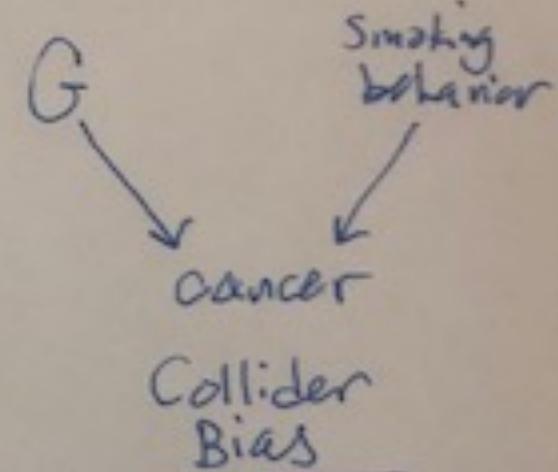
Confounding



associations are
Socially Contingent

(e.g. policies to make cigarettes more inaccessible)

Associations are
Socially Contingent



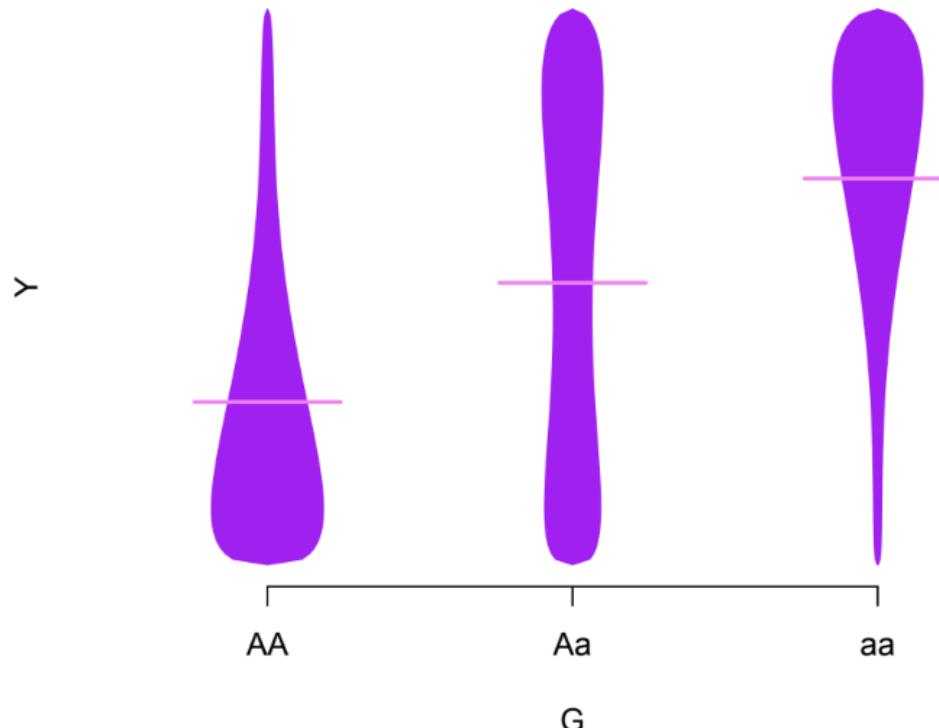
(e.g. studying the G-Smoking behavior association in a lung cancer case-control study)

Collider Bias

Adjusting for “heritable covariates” can also induce non-causal associations.

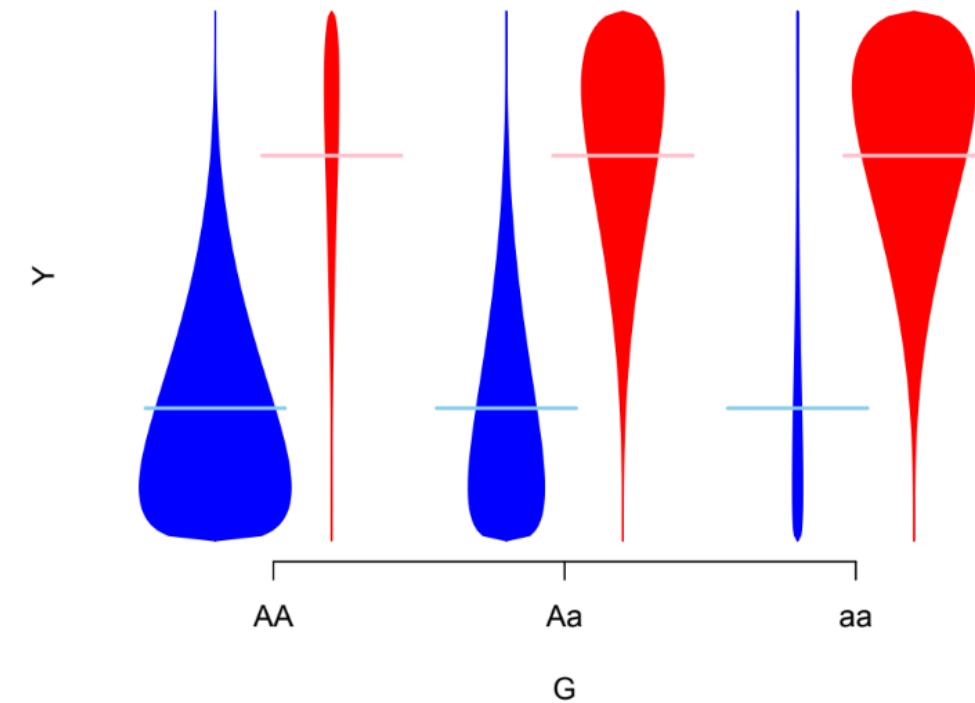
Population Stratification is a common source of confounding in GWAS

Population with a real association between phenotype (Y) and genotype (G)



These signals should be found by regression

Association between phenotype (Y) and genotype (G) varies by ancestry group (red vs. blue)



This effect is ***population stratification*** – a form of confounding.

Claiming Statistical Significance

Multiple Testing Correction for Type I Error Control

- Different statistical procedures accounting for multiple testing have been used in the genome-wide setting:
 - Bonferroni correction
 - false discovery rate procedures
 - permutation based-approaches
 - Bayesian approaches

Multiple Testing Correction: Why 5×10^{-8} ?

- Bonferroni would be overly conservative
- This threshold was derived from the number of estimated independent tests (given LD patterns)
- LD patterns differ are:
 - Ancestry specific!
 - LD patterns differ across ancestry
 - Allele frequency specific!
 - Common variants are much more likely to be highly correlated, inclusion of rarer markers may lead to false positives

GWAS Visualization

Quantile-Quantile plots (QQplots)

- Essential tool for detecting problems in GWAS!
- In GWAS, QQ plots display the quantile distribution of observed p-values (on the x-axis) vs. the quantile distribution of expected p-values
- Under the null hypothesis, p-values follow a uniform distribution
 - In GWAS, it is expected most markers will **not** be associated with the trait

QQ plots: How to Construct them for GWAS

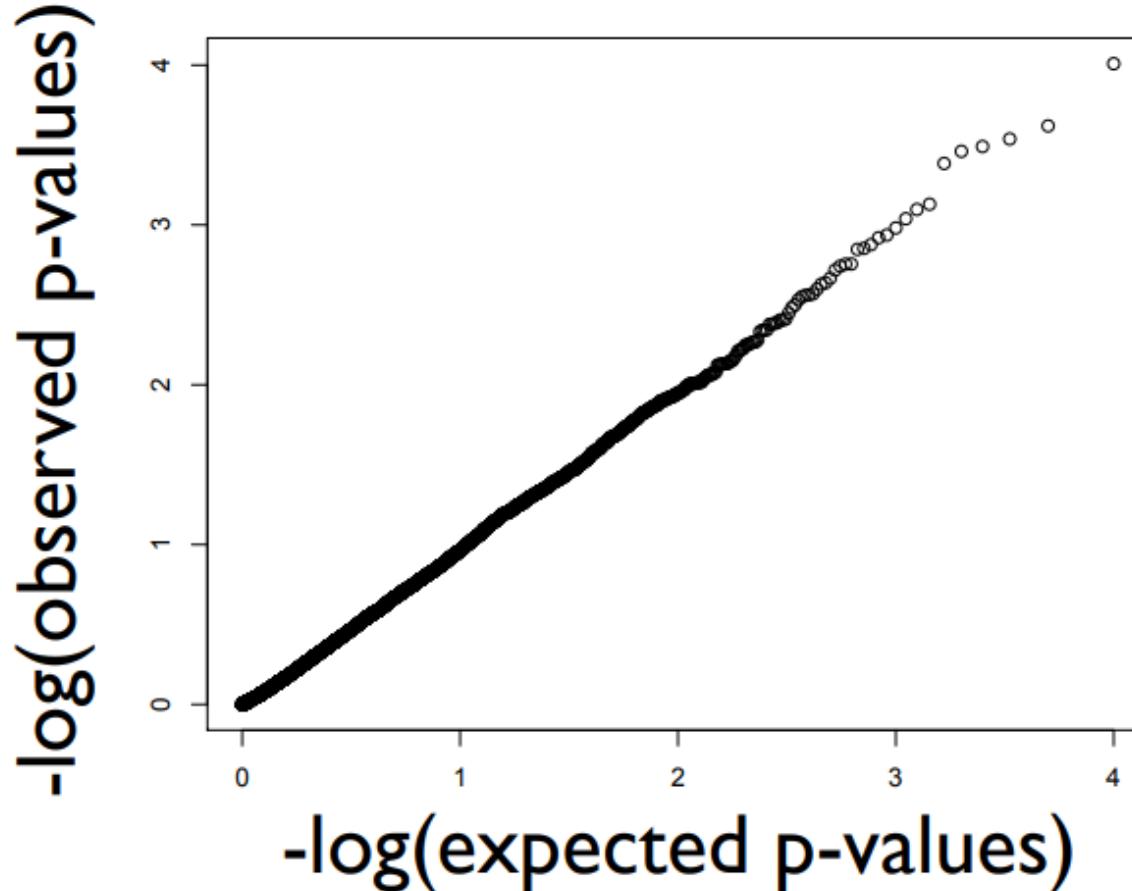
- You performed N tests, take the $-\log(\text{base } 10)$ of all the p-values from each marker and put them in rank order from smallest to largest
- Create a vector of N values evenly spaced from 1 to $1 / N$ (how do we do this?), take the $-\log$ of each of these values and rank them from smallest to largest
- Take the pair of the smallest of values of each of these lists and plot a point on an x-y plot with the observed $-\log$ p-value on the y-axis and the spaced $-\log$ value on the x-axis
- Repeat for the next smallest pair, for the next, etc. until you have plotted all N pairs in order
- Do not worry, we will do this in the practical using R!

Lambda (λ): Related to QQ plot

- λ_{GC} = “genomic control inflation factor” = median (observed chi-squared statistic)/median (theoretical chi-squared under the null)
- This should be close to 1
 - inflation ($\lambda > 1.1$)
 - indicates that most tests are **systematically more significant** than the expected distribution
 - Usually due to lack of control of **population stratification** and unknown **family relationships**
 - Polygenic signals can also cause an inflated lambda! **Stay tuned for LD Score Regression!**
 - deflation ($\lambda < 0.9$)
 - indicates that most of the points are systematically less significant than the expected distribution
 - A common cause of deflation is that markers are assumed to be independent from each other and they are not, which is common when a linkage mapping population is used for GWAS.

QQ plots: No detectable GWAS hits

In a correctly performed GWAS where there ARE NO causal polymorphisms, the QQ plot will be a line:

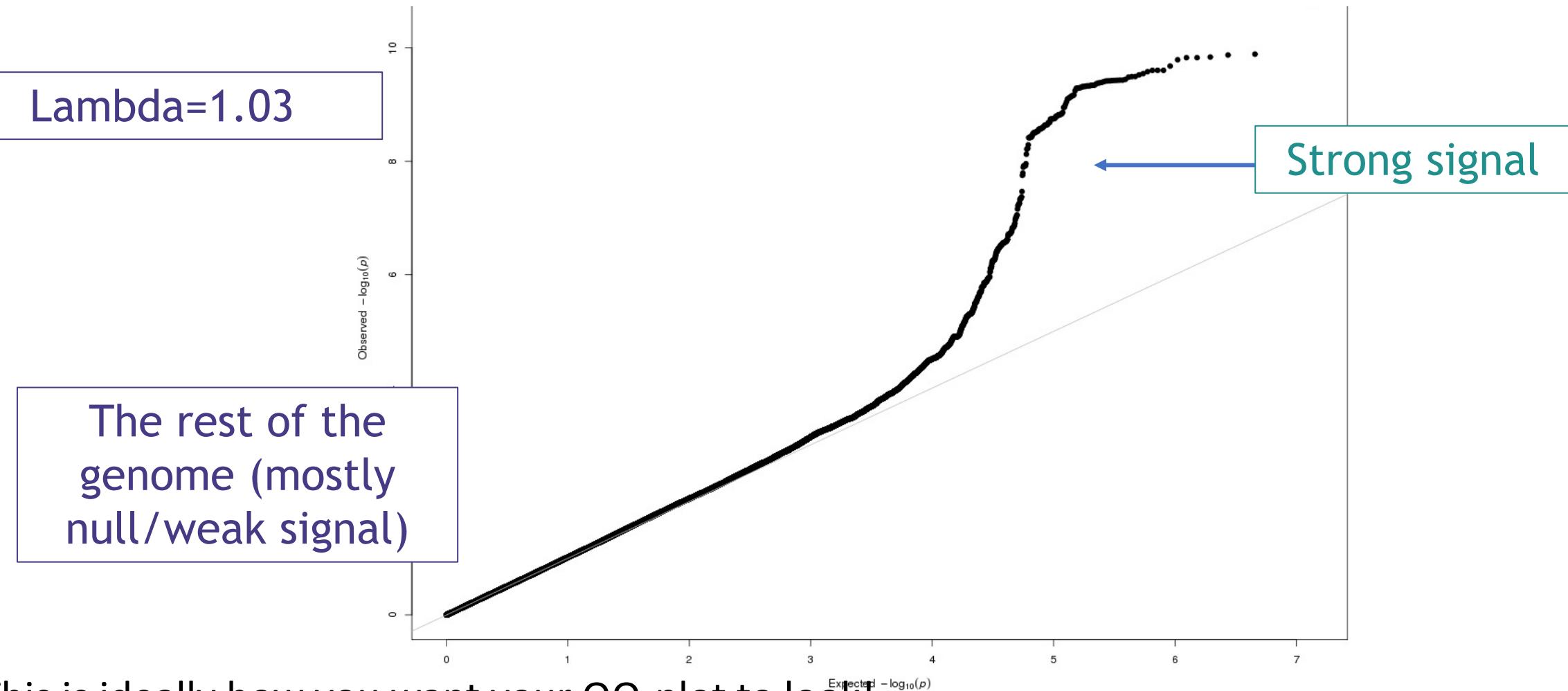


Note: If you do not have power to detect causal polymorphisms, GWAS may be correct and this will also be your result!

Lambda here is close to 1

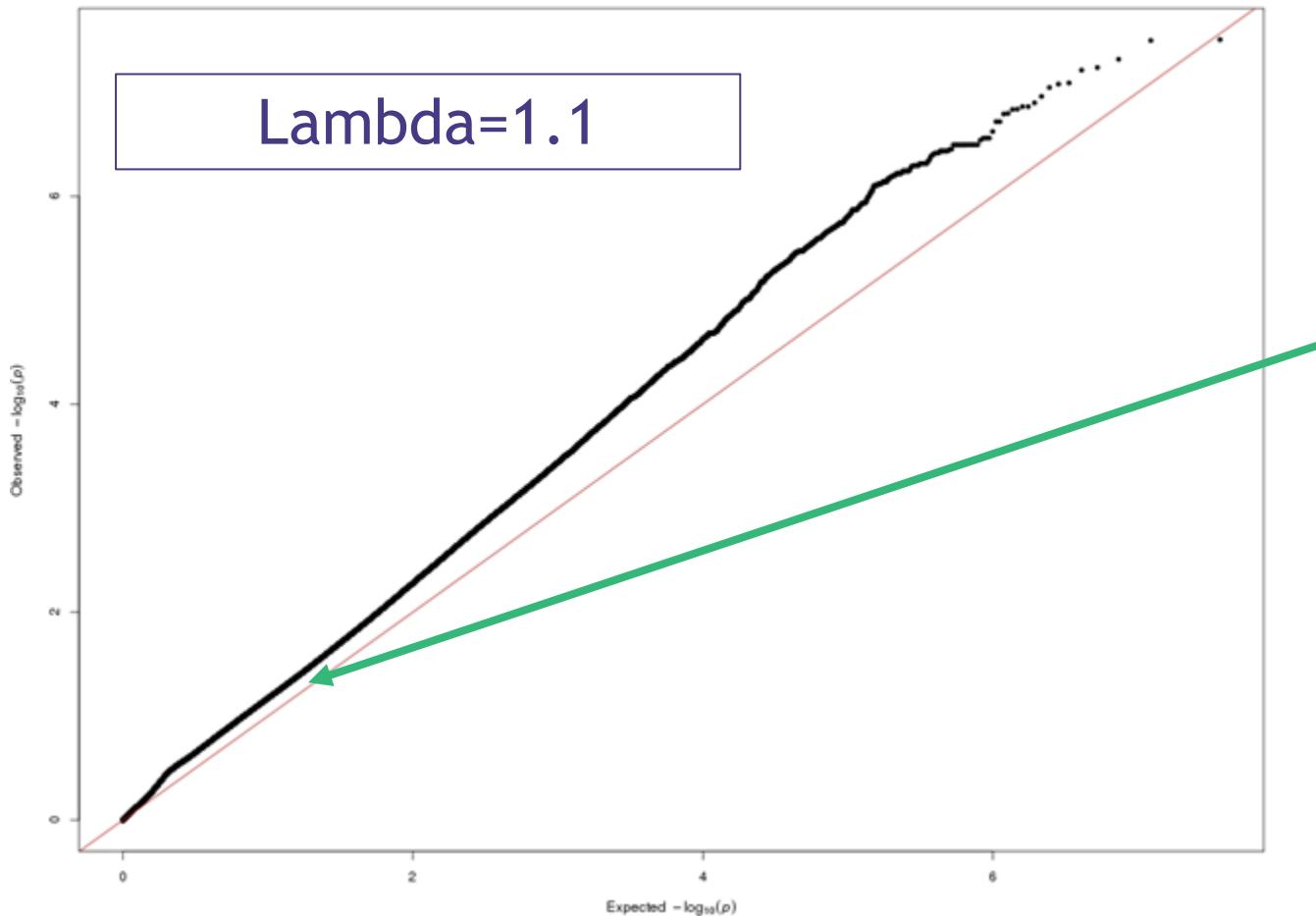
QQ plot for GWAS with significant associations

In a correctly performed GWAS where there ARE causal polymorphisms, your QQ plot will be a line with a tail at the end:



This is ideally how you want your QQ-plot to look!

QQ plot with inflation: Be wary



- Inflation!: Early separation of the expected from the observed means many moderately significant P values are more significant than expected under the null hypothesis.
- Rarely due to thousands of true positives; more often due to systematic bias

Manhattan Plots

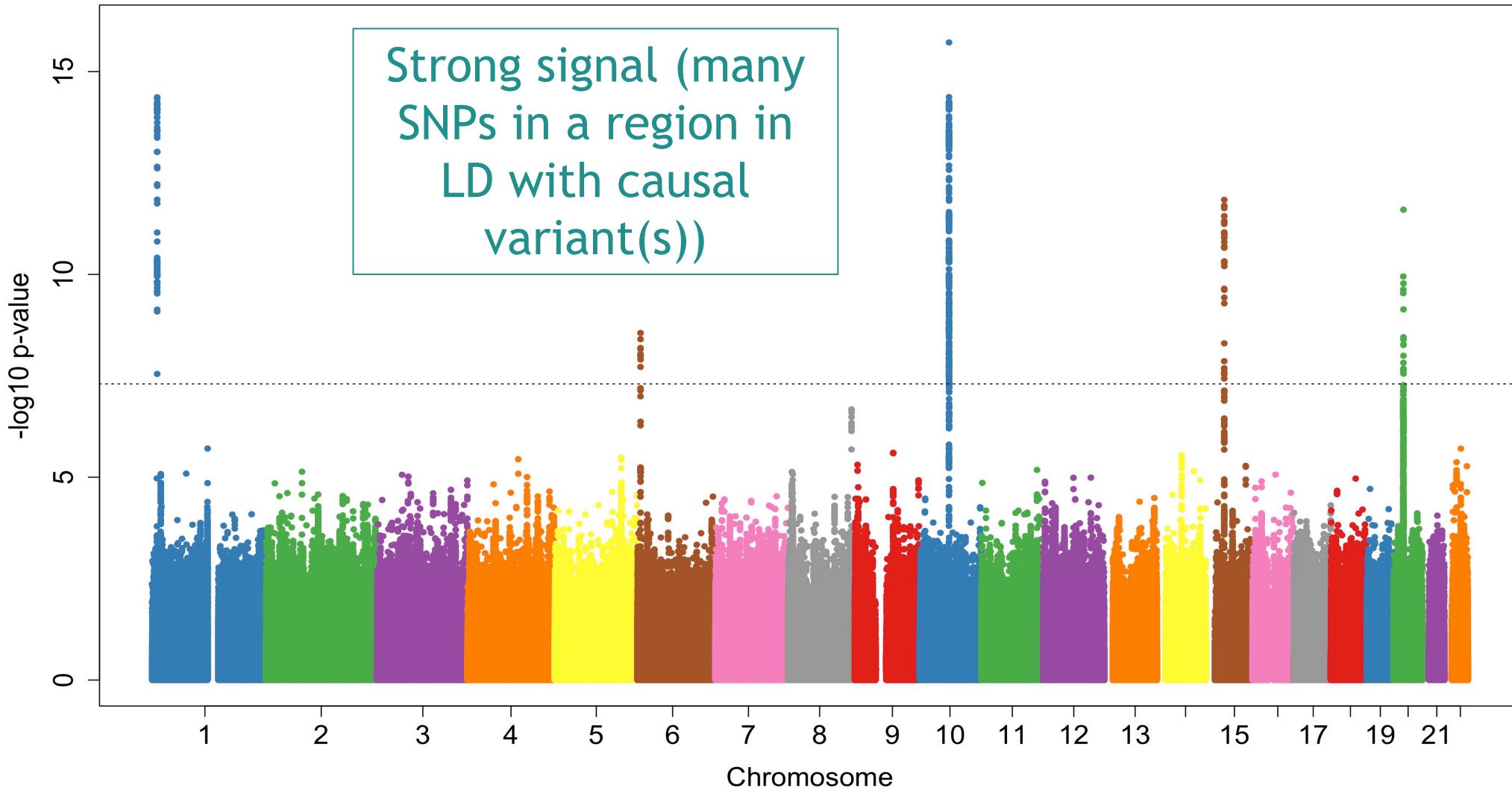
- Plots genomic position and P-value
- Each dot represents a single-nucleotide polymorphism (SNP), ordered on the *x axis* according to chromosome and position
- *y axis* represents their association measured as $-\log_{10}$ transformed *P* values.
- Usually includes a line to mark the genome-wide significance threshold of $P < 5 \times 10^{-8}$

Manhattan Plots - Why Manhattan?

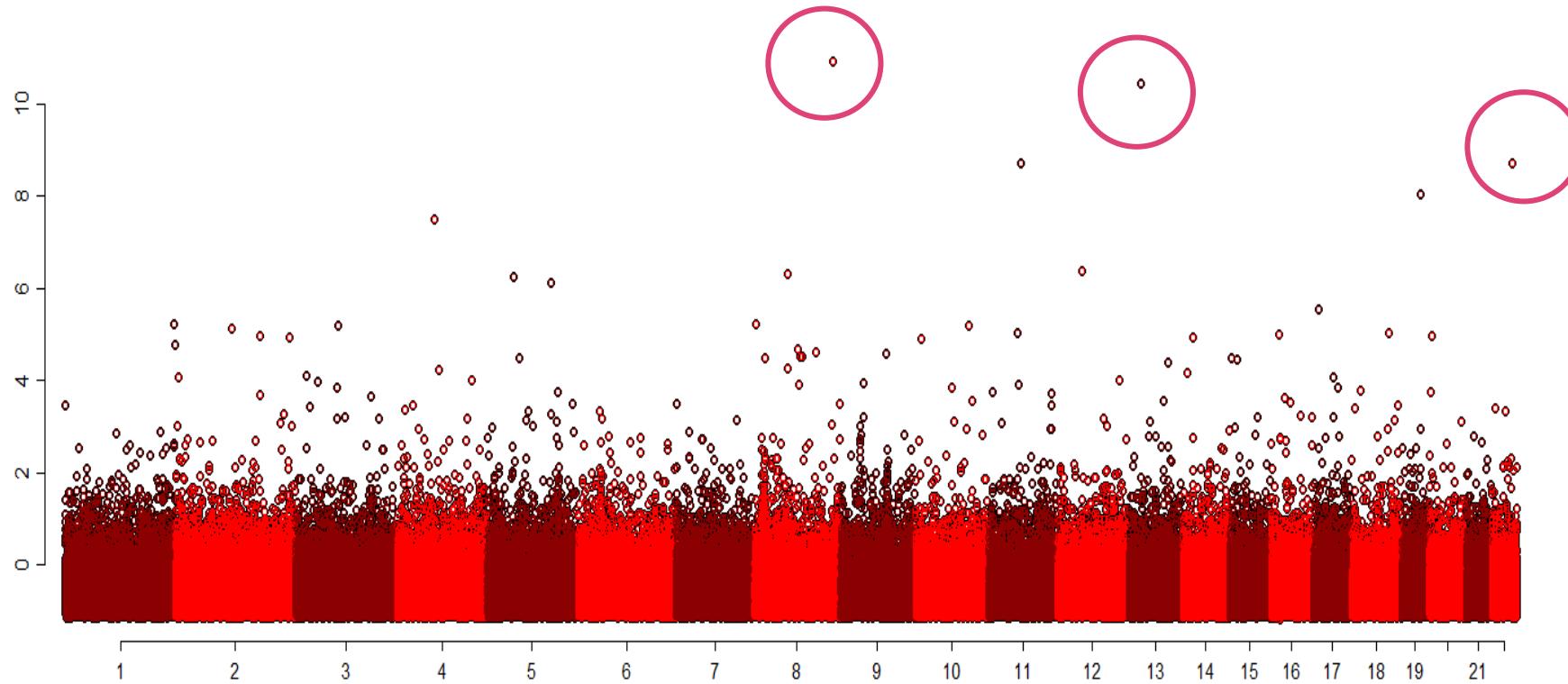


Linkage Disequilibrium!

Manhattan Plots



Manhattan Plots



Remember: There are no stars over Manhattan!

Manhattan Plots: Errors behind the Stars

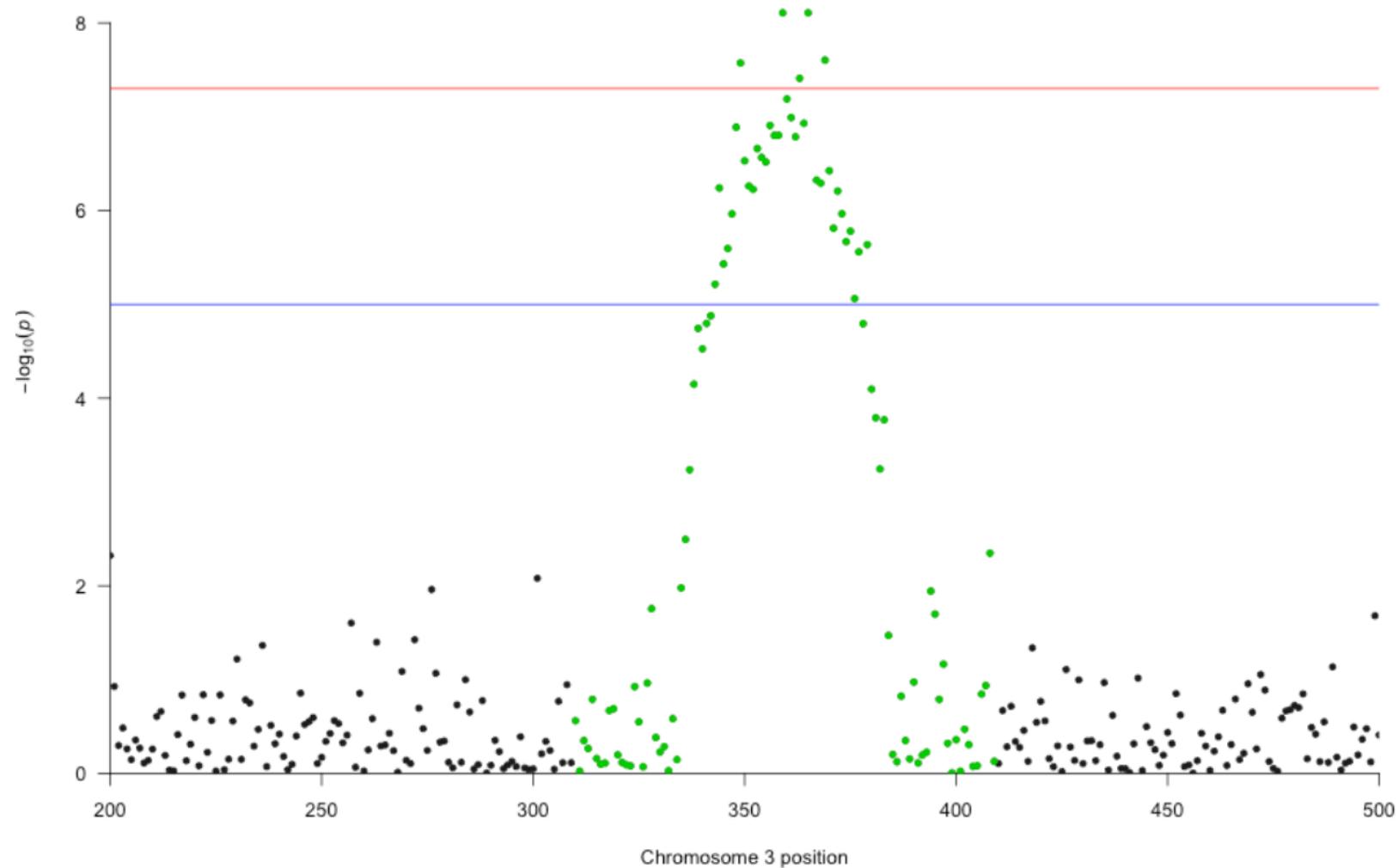


Genetic Signatures of Exceptional Longevity in Humans

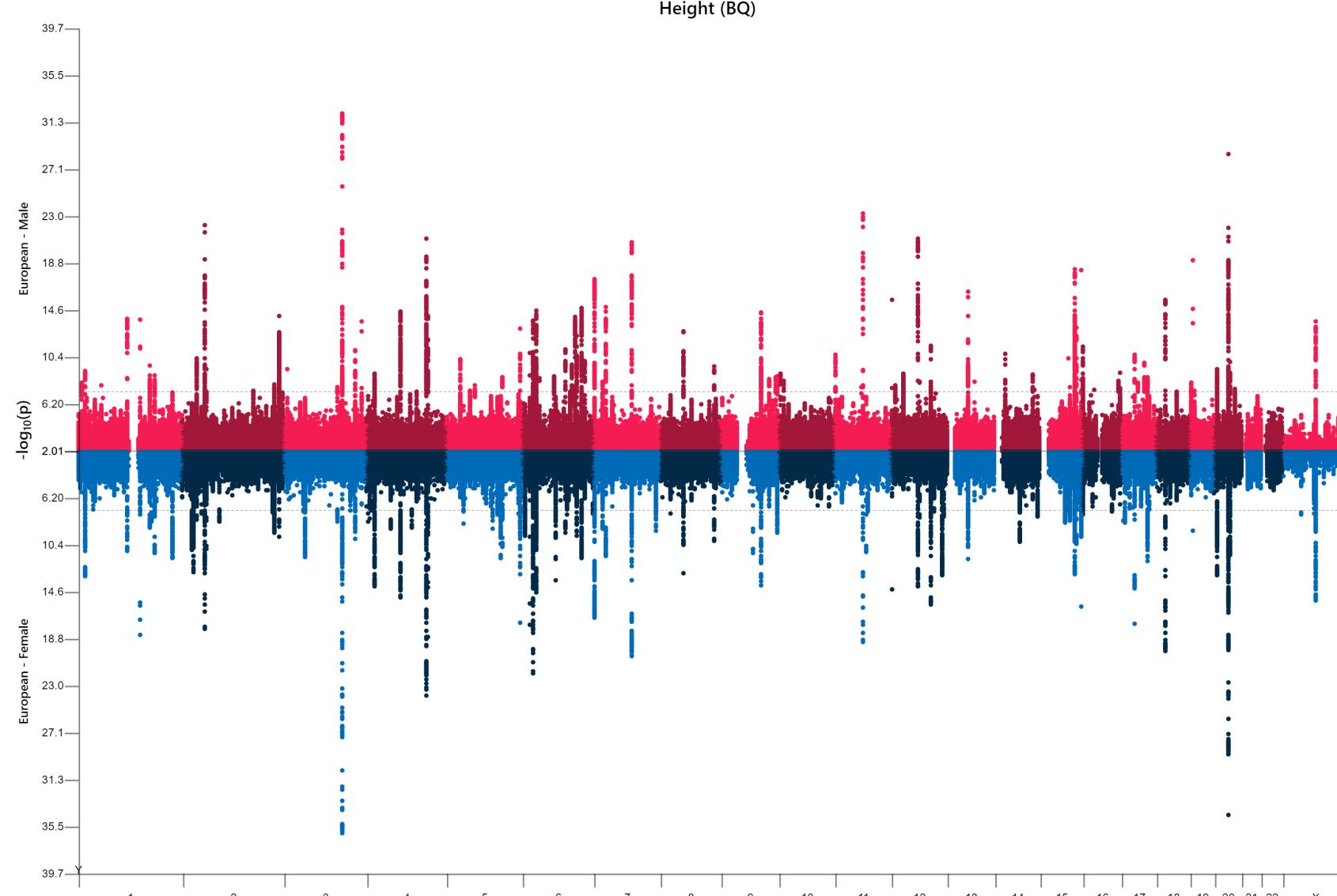
Paola Sebastiani,^{1,*} Nadia Solovieff,¹ Annibale Puca,² Stephen W. Hartley,¹ Efthymia Melista,³ Stacy Andersen,⁴ Daniel A. Dworkis,³ Jemma B. Wilk,⁵ Richard H. Myers,⁵ Martin H. Steinberg,⁶ Monty Montano,³ Clinton T. Baldwin,^{6,7} Thomas T. Perls^{4*}

- Design: centenarian cases (largely from New England) versus public controls (from the web)
- Different DNA collection, preparation, and genotyping protocols (cases genotyped using a newer platform—Illumina 610; controls genotyped using an older platform—Illumina 370)

Regional Plots: Zoomed in Manhattan Plot



Miami Plot: Adult Height Male vs. Female

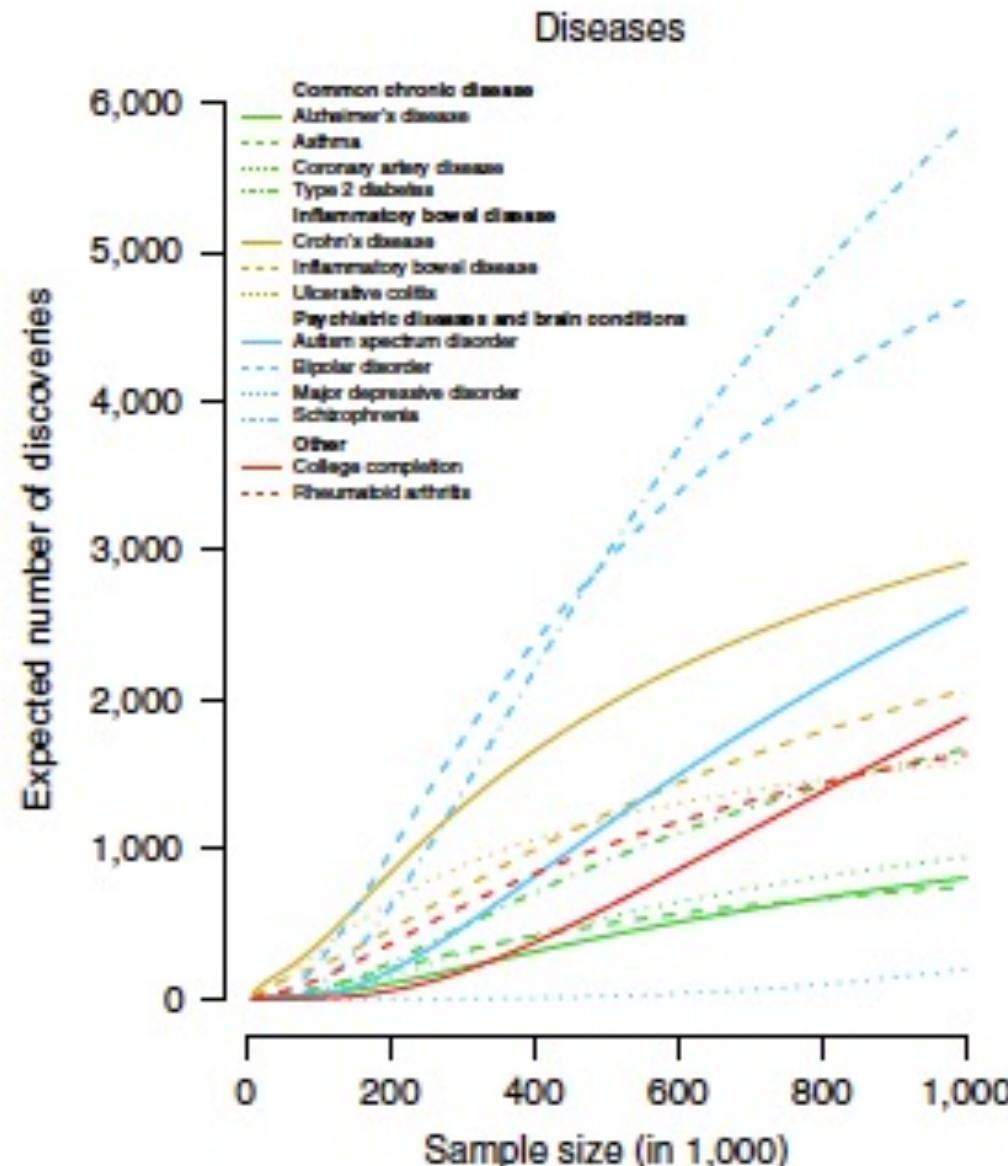
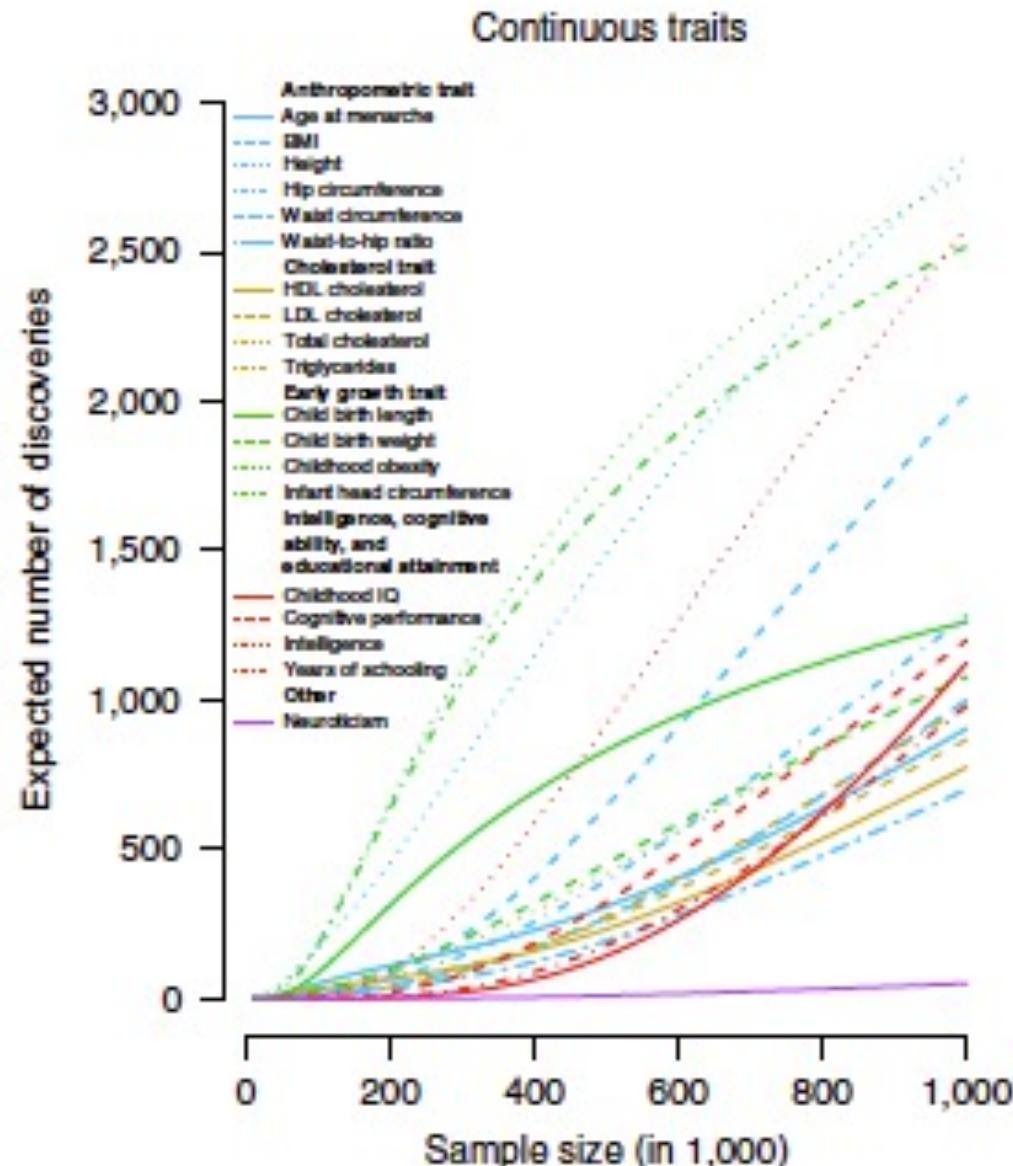


Meta-Analysis (& Imputation too)

Meta-analysis is the combining of the results of many studies

- Motivation
 - Sample Size
 - Leveraging LD differences
 - While conducting GWAS in relatively homogenous samples
 - Limits on sharing individual level differences
 - Federated analysis

Reminder: Very large sample sizes are needed to discover most susceptibility SNPs



assuming 1:1 case:control ratio

Meta-analysis: Large sample size Implications

- No single study can provide the necessary sample size to discover most susceptibility loci for complex human traits
 - Collaboration is a must!
 - A “mega analysis” (pooling individual level data) is often practically infeasible...
 - ...but meta-analysis (combining summary statistics) is quite feasible (with potentially little loss of information)
- While biases in reasonably-well designed and analyzed GWAS may be small (e.g. due to unadjusted confounding), in such large sample sizes, these small biases become important

Imputation

- Makes meta-analysis possible!
- The shared ancestry of chromosomes in a population results in haplotype stretches shared by different individuals. Making use of these shared haplotype stretches, and thereby accounting for the correlation of alleles at nearby markers (linkage disequilibrium, LD), statistical algorithms can make inferences about unobserved alleles
- Meta-analysis required to account for cross-platform differences

Imputation for cross-chip comparisons, e.g. for meta-analysis of SNP associations

All 1KGP SNPs



Illumina SNPs



Affymetrix SNPs



Overlap SNPs



Imputation for cross-chip comparisons, e.g. for meta-analysis of SNP associations

All 1KGP SNPs



Illumina SNPs



+ Imputed SNPs!

Affymetrix SNPs



Overlap SNPs



Imputation outputs & uses

Input: genotyped 2000 samples, 550K SNPs

+ **Reference:** HapMap 60 samples, 2.6M SNPs or 1000G 2504 samples, >85M variants

+ **Imputation = Output:** imputed 2000 samples, 2.6M/85M SNPs

Output data format: probability of each (unobserved) genotype; expected value of each genotype (allele “dosage” ranging from 0-2); most likely (ML, unobserved) genotype (“hard call”)

Will all imputed SNPs provide a reliable estimates of true genotypes?

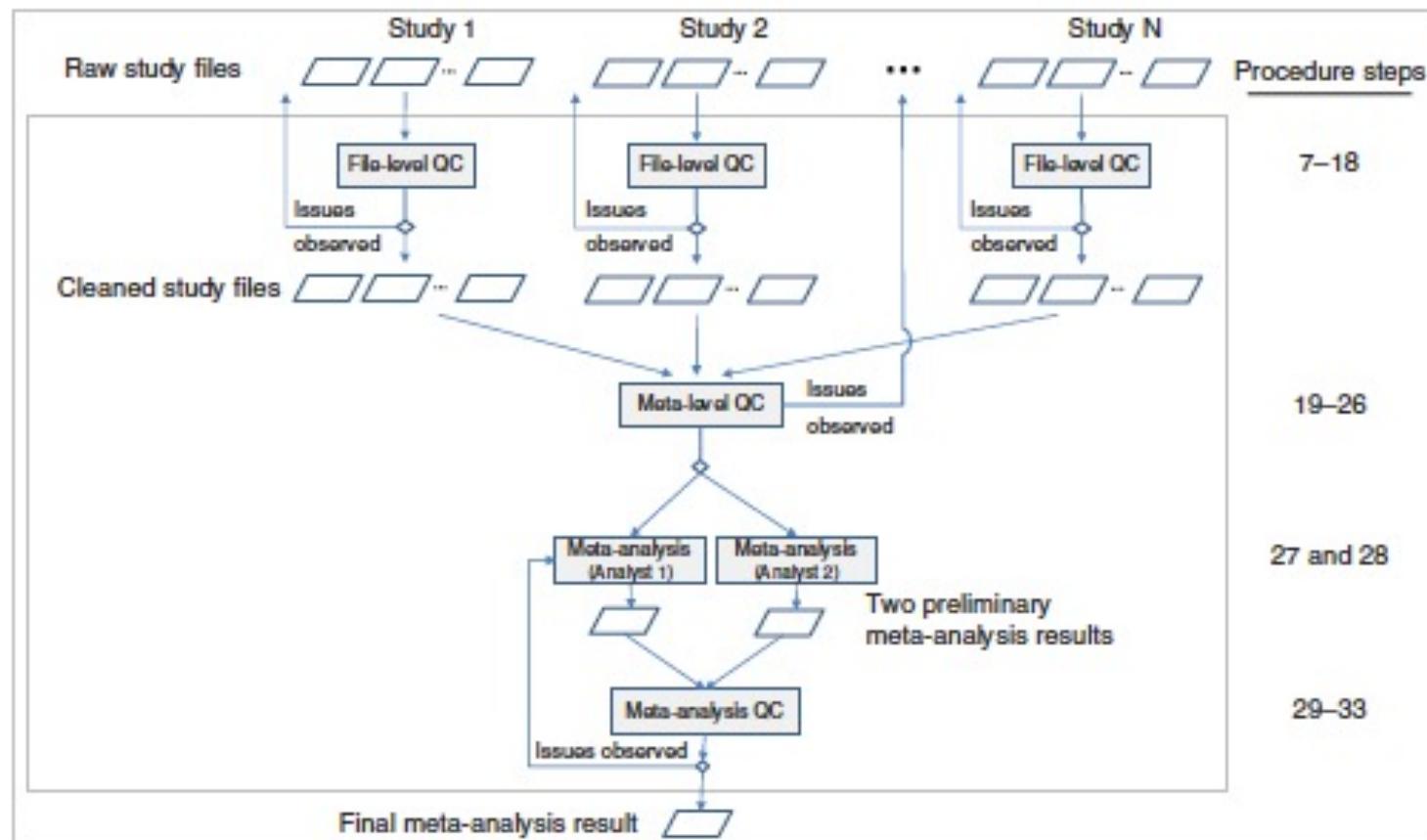
No, but **imputation Rsq** parameter estimates the squared correlation between imputed and true genotypes ($\text{Rsq} = \text{cor}(\text{dosage}, \text{ML})^2$)

How to analyze imputed data appropriately?

Régress outcome on genotype “dosage”— efficient incorporation of imputation uncertainty in regression estimate standard errors.

Quality control and conduct of genome-wide association meta-analyses

Thomas W Winkler¹, Felix R Day², Damien C Croteau-Chonka^{3,4}, Andrew R Wood⁵, Adam E Locke⁶, Reedik Mägi⁷, Teresa Ferreira⁸, Tove Fall^{9,10}, Mariaelisa Graff¹¹, Anne E Justice¹¹, Jian'an Luan², Stefan Gustafsson⁹, Joshua C Randall¹², Sailaja Vedantam^{13–15}, Tsegaselassie Workalemahu¹⁶, Tuomas O Kilpeläinen¹⁷, André Scherag^{18,19}, Tonu Esko^{7,13–15}, Zoltán Kutalik^{20–22}, Iris M Heid^{1,27}, Ruth J F Loos^{23–25,27} & the Genetic Investigation of Anthropometric Traits (GIANT) Consortium²⁶



Software Tools

(handle the tedious bits like making sure reference/non-reference alleles are the same across different studies)

[PLINK](#)

[EASYQC](#)

[METAL](#)

[METASOFT](#)

Meta-analysis: Fixed Effects

- Fixed Effects
 - Assumes error variances are equal across cohorts
 - Combining the contributions of all cohorts allows for a more precise estimation of effect sizes and the significance of effects in GWAS by weighting each individual cohort's results by their sample size or by using the inverse variance method (IVW)
 - IVW Stouffer's Test: ranking approach for differences in scale

Meta-analysis of GWAS stats

- “Fixed effects” meta-analysis rather than “random effects” has been adopted to maximize power, even for signals that are heterogeneous across studies.

$$z_{\text{meta}} = \frac{\langle \beta \rangle}{\langle \text{SE} \rangle}$$

$$\langle \beta \rangle = \frac{\sum_i [\beta_i / (\text{SE}_i)^2]}{\sum_i [1 / (\text{SE}_i)^2]}.$$

$$\langle \text{SE} \rangle = \sqrt{\frac{1}{\sum_i [1 / (\text{SE}_i)^2]}}$$

$$z_{\text{meta}} = \sum_i z_i \times w_i$$
$$w_i = \sqrt{\frac{N_i}{N_{\text{total}}}}$$

Fixed effects meta-analysis based on study-specific estimated regression coefficients and their standard errors. Fixed effects analysis is appropriate since our goal is to test global null (no association in any study).

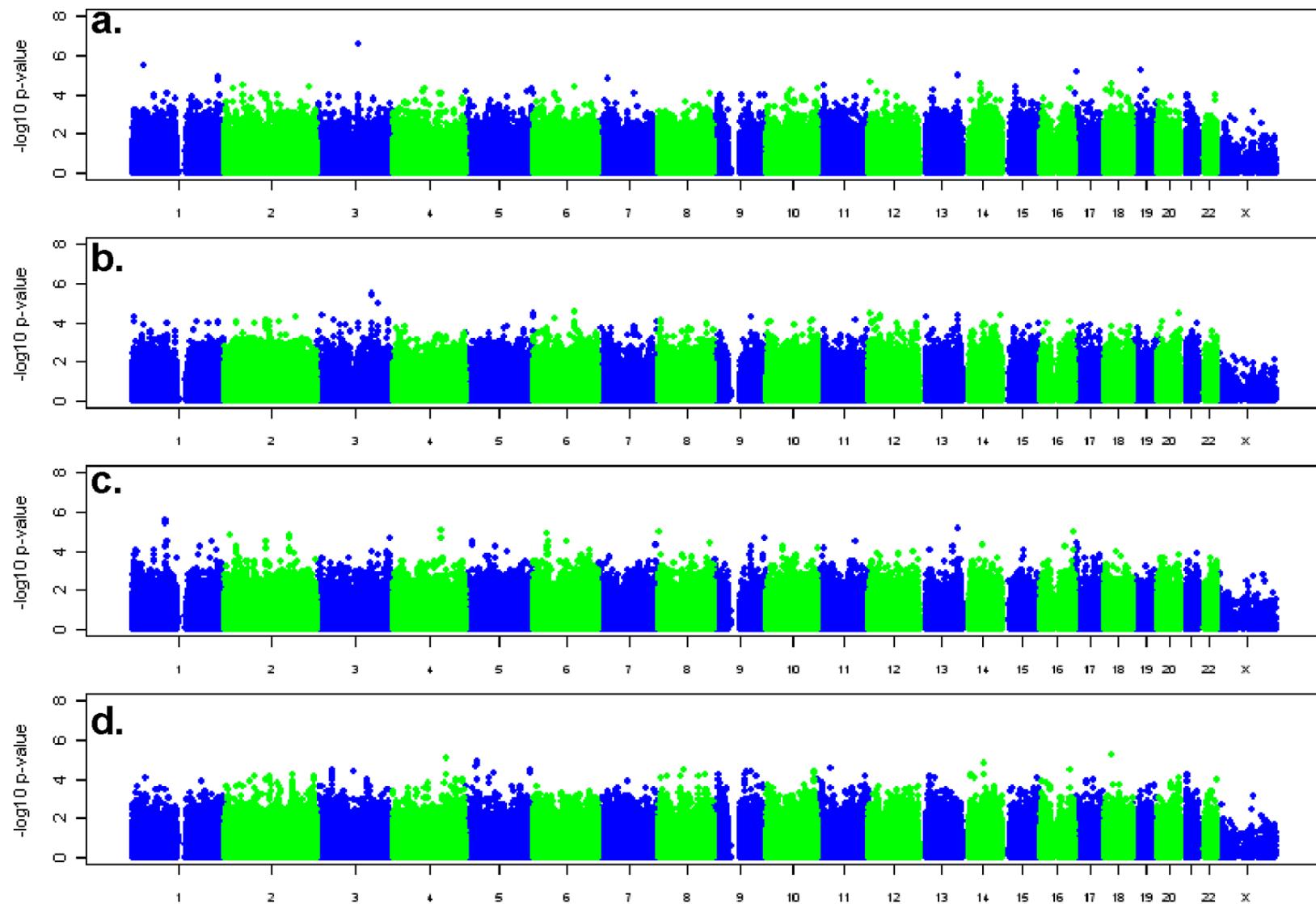
Weighted Z scores (“Stouffer’s method”). Alternative to fixed effects when studies have used different measurement scales (e.g. different methods to quantify a biomarker).

Meta-analysis: Random Effects

- Old methods: DerSimonian and Laird;
 - A variation on the inverse-variance method is to incorporate an assumption that the different studies are estimating different, yet related, intervention effects. This produces a random-effects meta-analysis
 - the standard errors of the study-specific estimates are adjusted to incorporate a measure of the extent of variation, or heterogeneity, among the intervention effects observed in different studies (this variation is often referred to as tau-squared (τ^2 , or Tau^2)).
 - The amount of variation, and hence the adjustment, can be estimated from the intervention effects and standard errors of the studies included in the meta-analysis
- Newer Methods: Han and Eskin **metasoft RE2** and BE
 - Used in Today's Tutorial

Example of increasing sample size via meta-analysis:

- 1) Successively larger iterations of GWAS of smoking behaviors
- 2) Saturated map of Human Height



CPD-continuous

Pack-years

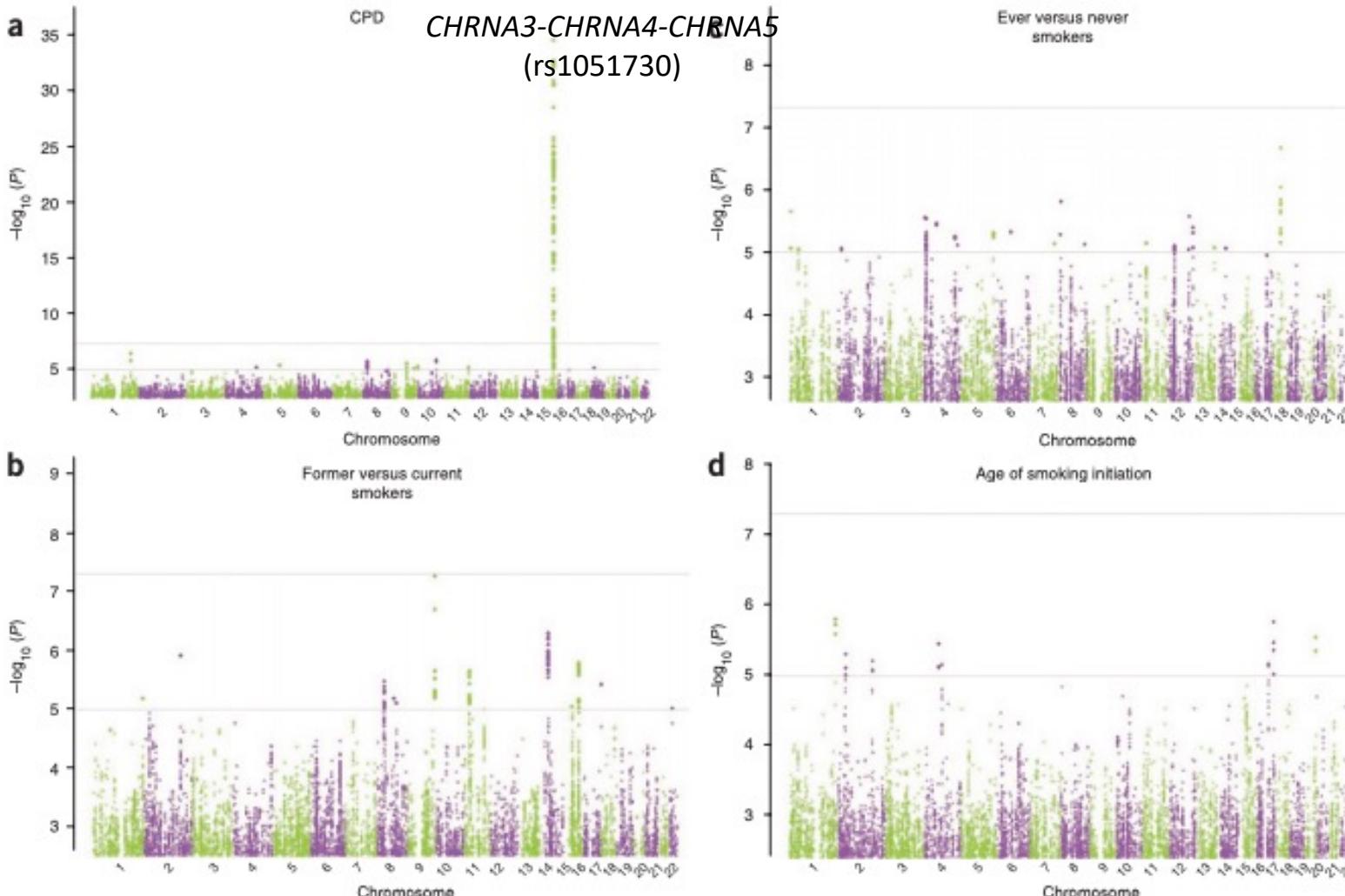
Durations

Age of start smoking

GWAS of smoking behavior: meta-analysis of 2,300 men from PLCO case-control study of prostate cancer and 2,300 women from NHS case-control study of breast cancer

Meta-analysis of smoking GWAS

TAG Consortium (74,503 subjects from 16 studies)



Tobacco and Genetics Consortium (2010) *Nat Genet*
one of three smoking behavior GWAS published in the same issue

Meta-analysis of smoking GWAS

Table 2 Meta-analytic results from three GWAS smoking consortia

SNP	Alleles	TAG meta-analysis					Ox-GSK meta analysis					ENGAGE meta analysis					Combined results		
		Coded AF	n	β	s.e.	P value	n	β	s.e.	P value	n	β	s.e.	P value	n	β	s.e.	P value	
CPD^a: <i>CHRNA3</i>																			
rs1051730	G/A	0.65	38,181	-1.0207	0.086	8.00×10^{-33}	14,952	-1.1593	0.139	8.88×10^{-17}	20,720	-0.9648	0.089	2.15×10^{-27}	73,853	-1.0209	0.056	2.75×10^{-73}	
rs16969968	G/A	0.65	38,181	-1.0150	0.085	4.48×10^{-33}	14,952	-1.1153	0.137	3.72×10^{-16}	20,720	-0.9426	0.089	2.07×10^{-26}	73,853	-1.0029	0.056	5.57×10^{-72}	
CPD^a: in <i>LOC100188947</i>																			
rs1329650	T/G	0.28	38,181	-0.4317	0.091	2.33×10^{-6}	14,952	-0.2568	0.145	7.61×10^{-2}	20,720	-0.3464	0.092	1.73×10^{-4}	73,853	-0.3673	0.059	5.67×10^{-10}	
rs1028936	C/A	0.18	37,284	-0.5545	0.116	1.57×10^{-6}	14,952	-0.2451	0.176	1.65×10^{-1}	20,720	-0.4252	0.113	1.77×10^{-4}	72,956	-0.4464	0.074	1.29×10^{-9}	
CPD^a: <i>EGLN2</i>, near <i>CYP2A6</i>																			
rs3733829	G/A	0.36	38,181	0.3538	0.090	7.67×10^{-5}	14,952	0.0477	0.145	7.43×10^{-1}	20,720	0.4204	0.089	2.90×10^{-6}	73,853	0.3328	0.058	1.04×10^{-8}	
Smoking initiation (ever versus never smokers): <i>BDNF</i>																			
rs6265	T/C	0.21	74,035	-0.0630	0.015	1.72×10^{-5}	34,226	-0.0448	0.022	4.48×10^{-2}	34,762	-0.0762	0.024	1.39×10^{-3}	143,023	-0.0614	0.011	1.84×10^{-8}	
rs1013442	T/A	0.26	74,035	-0.0568	0.014	3.39×10^{-5}	34,226	-0.0386	0.021	6.36×10^{-2}	34,762	-0.0674	0.020	9.60×10^{-4}	143,023	-0.0551	0.010	3.31×10^{-8}	
rs4923457	T/A	0.23	74,035	-0.0600	0.014	2.08×10^{-5}	34,226	-0.0421	0.022	5.05×10^{-2}	34,762	-0.0752	0.024	1.91×10^{-3}	143,023	-0.0586	0.011	3.33×10^{-8}	
rs4923460	T/G	0.23	74,035	-0.0598	0.014	2.22×10^{-5}	34,226	-0.0427	0.022	4.81×10^{-2}	34,762	-0.0734	0.024	2.51×10^{-3}	143,023	-0.0583	0.011	4.08×10^{-8}	
rs4074134	T/C	0.23	74,035	-0.0603	0.014	1.90×10^{-5}	34,226	-0.0421	0.022	5.08×10^{-2}	34,762	-0.0725	0.024	2.81×10^{-3}	143,023	-0.0582	0.011	4.11×10^{-8}	
rs1304100	G/A	0.26	74,035	-0.0557	0.014	4.86×10^{-5}	34,226	-0.0460	0.021	2.62×10^{-2}	34,762	-0.0651	0.022	2.88×10^{-3}	143,023	-0.0554	0.010	4.44×10^{-8}	
rs6484320	T/A	0.24	74,035	-0.0597	0.014	2.04×10^{-5}	34,226	-0.0387	0.021	6.78×10^{-2}	34,762	-0.0723	0.024	2.13×10^{-3}	143,023	-0.0571	0.010	4.91×10^{-8}	
rs879048	C/A	0.23	74,035	-0.0598	0.014	2.28×10^{-5}	34,226	-0.0409	0.022	5.86×10^{-2}	34,762	-0.0728	0.024	2.41×10^{-3}	143,023	-0.0578	0.011	4.94×10^{-8}	
Smoking cessation (former versus current smokers): near <i>DBH</i>																			
rs3025343	G/A	0.84	41,278	0.1177	0.026	5.68×10^{-6}	23,646	0.1295	0.041	1.76×10^{-3}	NA	NA	NA	NA	64,924	0.1210	0.022	3.56×10^{-8}	

All SNPs coded to NCBI Build 36/UCSC hg18 forward strand. Coded allele frequency refers to the allele analyzed as the predictor allele; it is not necessarily the minor allele. For CPD, 174 SNPs followed up across three consortia; 130 exceeded genome-wide significance and the two top SNPs are presented. NA, not available.

^aCPD was analyzed as a continuous variable representing the number of cigarettes smoked per day. Smoking initiation and smoking cessation were analyzed as dichotomous variables, contrasting ever versus never and former versus current smokers, respectively.

Four more loci identified through meta-analysis of three consortia.
(Note: only meta-analyzed “top” 15 SNPs from each study—a missed opportunity! SNPs that are not near the “top” in any individual study can become significant in meta-analysis!)

Association studies of up to 1.2 million individuals yield new insights into the genetic etiology of tobacco and alcohol use

Tobacco and alcohol use are leading causes of mortality that influence risk for many complex diseases and disorders¹. They are heritable^{2,3} and etiologically related^{4,5} behaviors that have been resistant to gene discovery efforts^{6–11}. In sample sizes up to 1.2 million individuals, we discovered 566 genetic variants in 406 loci associated with multiple stages of tobacco use (initiation, cessation, and heaviness) as well as alcohol use, with 150 loci evidencing pleiotropic association. Smoking phenotypes were positively genetically correlated with many health conditions, whereas alcohol use was negatively correlated with these conditions, such that increased genetic risk for alcohol use is associated with lower disease risk. We report evidence for the involvement of many systems in tobacco and alcohol use, including genes involved in nicotinic, dopaminergic, and glutamatergic neurotransmission. The results provide a solid starting point to evaluate the effects of these loci in model organisms and more precise substance use measures.

The GSCAN consortium included >30 studies.

A Saturated map of human height

Meta-analysis identifies 12,111 height-associated SNPs

We performed genetic analysis of up to 5,380,080 individuals from 281 studies from the GIANT consortium and 23andMe.

Annotating GWAS Results

Annotating GWAS Results

REVIEW

10 Years of GWAS Discovery: Biology, Function, and Translation

Peter M. Visscher,^{1,2,*} Naomi R. Wray,^{1,2} Qian Zhang,¹ Pamela Sklar,³ Mark I. McCarthy,^{4,5,6}
Matthew A. Brown,⁷ and Jian Yang^{1,2}

Complex traits are polygenic
Small individual effects, multiple SNPs

Pleiotropy is ubiquitous
Going from association to mechanism is hard
But not impossible, and some translational advances
already

We can construct polygenic scores to predict traits
But the utility of such scores depends on context

Annotating GWAS Results

- Fine-mapping/Co-localization next week!
- Initial Targeted interrogation of external resources may be used to:
 - Ascribe SNPs to protein-coding genes
 - Associate with nearby cell and tissue specific regulatory elements and expression, expression quantitate trait loci (eQTL)
 - Programs include UCSC Genome Browser, GTEx Portal, ENSEMBLE Genome Browser, LDlink, FUMA, etc
 - See Practical!!!

Basic GWAS Analysis Tutorial

Open up Google Colab Notebook 02_GWAS&MetaAnalysis!

Practical and Practical Considerations

- We are not using imputed data!
 - This allows us to do the computation more quickly, however this is not the standard
 - Imputation quality scores are generally filtered out so variants below a certain imputation quality threshold are not used.
 - Some software packages do not use allelic dosage or imputation quality, they may only hard call allele counts
- We are using European samples
 - This is a major limitation of a lot of GWAS to date and a lot of currently available genetic data.
- The inputs have been QC'd for relatedness, genotype missingness, individual missingness, hardy Weinberg equilibrium, heterozygosity
 - Do not embark on a GWAS without QC!
- We are using plink, but there are many other software packages that may be a better fit for your analysis

We have GWAS Results, What now?

- UCSC Genome Browser
<https://genome.ucsc.edu/cgi-bin/hgGateway>
- GTEx Portal
<https://gtexportal.org/home/>
- HaploReg:
<https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php>
- FUMA's SNP2GENE:
- LDlink:
<https://ldlink.nih.gov/?tab=home>
 - Includes a suite of different tools