Association testing I

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$ echo "Data Sciences Institute"
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What You'll Learn Today

- Set up the regression models or table-based tests and choose appropriate genotype codings.
- Interpret effect sizes, uncertainty, and evidence to make clear claims about variant–trait links.
- Recognize key assumptions, power drivers, and the role of LD so you can judge how much to trust a finding.

Association Testing

- **Objective**: establish association between a trait of interest and a genetic marker.
- Study designs: case-control, case-cohort, population-based design.
- Unrelated subjects or **population-based designs**: easy to collect so possible to achieve large sample sizes as in GWAS.
- **Family-based designs**: robust to population stratification, more difficult to collect. Also hard to collect for late-onset diseases.

Overview

- For **a quantitative trait** Y: simple linear regression models to detect association between Y and G:

$$Y = \alpha + \beta G + e, e \sim N\left(0, \sigma^2\right).$$

- Coding of G: 1 d.f. additive (or dominant, recessive) model or 2 d.f. genotypic model.

$G =$	**aa**	**Aa**	**AA**
Additive	0	1	2
Dominant	0	1	1
Recessive	0	0	1
Genotypic	"0"	"1"	"2"

Overview

- **1 d.f. model**: $Y = \alpha + \beta G + e, e \sim N\left(0, \sigma^2\right).$
  - The test of no association is equivalent to $H_0 : \beta = 0.$

- **Genotypic (2 d.f.) model**: $Y = \alpha + \beta_1 D_1 + \beta_2 D_2 + e, \quad e \sim N(0, \sigma^2).$
  - $D_1 = I(G = Aa), D_2 = I(G = AA).$
  - $H_0 : \beta_1 = \beta_2 = 0.$

- **Extended model** (includes environment, other SNPs, interactions):

$$Y = \alpha + \beta G + \gamma E + \delta G x E + e, e \sim N\left(0, \sigma^2\right).$$

Association Analysis for Binary Trait

- For a binary trait Y: $Y = 1$ denotes for being affected/cases, and $Y = 0$ for unaffected/controls
- SNP: categorical variable with three genotypes (Aa, aa and AA)
- Genotype frequency differ between cases and controls only at the DSL or markers that are in LD with the DSL
- How do we detect association between Y and G ?
    - **Compare frequency differences between cases and controls**
    - **Use regression framework** to unify analysis (QTL + binary traits, with covariates and interactions)

Association Testing (2 df test)

- Observed genotype counts at a marker under the study for r cases and s controls.

	aa	Aa	AA	Total
Cases	r_0	r_1	r_2	r
Controls	s_0	s_1	s_2	s
Total	n_0	n_1	n_2	n

- Most general test: nothing is assumed about the relationship between disease and genotype.

$$H_0 : P(Y = 1 \mid AA) = P(Y = 1 \mid Aa) = P(Y = 1 \mid aa)$$
$$H_A : \text{ At least one inequality holds}$$

Contingency Table - Pearson's Homogeneity Test

- Assume we have independent observations from I multinomial distributions, each of which has J categories, e.g. $I = 2$.

	$X = 0$	$X = 1$	$\dots$	$X = J - 1$	**Total**
Cases	r_0	r_1	$\dots$	r_{J-1}	r
Controls	s_0	s_1	$\dots$	s_{J-1}	s
Total	n_0	n_1	$\dots$	n_{J-1}	n

- Our goal is to test whether the multinomial distributions for the two groups are identical.

$$H_0 : \pi_{1j} = \pi_{2j} \equiv \pi_j, \quad j = 0, 1, \dots, J-2.$$

Pearson's Homogeneity Test

- Test Statistic

$$T = \sum \frac{(O - E)^2}{E} \sim \chi^2_{(I-1)(J-1)}.$$

- E： expected counts under the null hypothesis of homogeneity using pooled estimate $\tilde{\pi}_j = \frac{n_j}{n}$.
- df $= (I-1)(J-1)$: number of independent counts $(I(J-1))$ - the number of independent parameters estimated under the null from the data $(J-1)$.

Association Testing (2 df test)

	aa	Aa	AA	Total
Cases	r_0	r_1	r_2	r
Controls	s_0	s_1	s_2	s
Total	n_0	n_1	n_2	n

- Two df Pearson test of independence:

$$\chi^2 = \sum (O - E)^2 / E.$$

- Sum is over all six entries. e.g. $\mathrm{E}[\text{ Case \& aa }] = (r \cdot \mathrm{n}_0)/\mathrm{n}$.

Association Testing (1 df test)

- For example:

	aa	Aa	Total
Cases	r_0	r_1	r
Controls	s_0	s_1	s
Total	n_0	n_1	n

$$T = \frac{\left(r_0 - \frac{rn_0}{n}\right)^2}{\frac{rn_0}{n}} + \frac{\left(r_1 - \frac{rn_1}{n}\right)^2}{\frac{rn_1}{n}} + \frac{\left(s_0 - \frac{sn_0}{n}\right)^2}{\frac{sn_0}{n}} + \frac{\left(s_1 - \frac{sn_1}{n}\right)^2}{\frac{sn_1}{n}} \sim \chi^2_1.$$

Association Testing - Dominant model

	aa	Aa or AA	Total
Cases	r_0	$r_1 + r_2$	r
Controls	s_0	$s_1 + s_2$	s
Total	n_0	$n_1 + n_2$	n

- Dominant model:

$$H_0 : P(Y = 1 \mid AA) = P(Y = 1 \mid Aa) = P(Y = 1 \mid aa)$$
$$H_A : P(Y = 1 \mid AA \text{ or } Aa) \neq P(Y = 1 \mid aa)$$

- Replace r_1 with $r_1 + r_2$ with 1 df chi-square test.
- Optimal when the true disease model is dominant but not for recessive.

Exercise

- Recessive model:

	aa or Aa	AA	Total
Cases	$r_0 + r_1$	r_2	r
Controls	$s_0 + s_1$	s_2	s
Total	$n_0 + n_1$	n_2	n

Association Testing - Additive Model

- We can also test for association using **allele counts**.
- $H_0 : p_{cases} = p_{controls}$

	a	A	Total
Cases	$2r_0 + r1$	$r_1 + 2r_2$	$2r$
Controls	$2s_0 + s_1$	$s_1 + s_2$	$2s$
Total	n_a	n_A	$2n$

- Assumptions: samples are independent both within each group (cases and controls) and between groups. Under this assumption, allele count data can be modeled using two independent binomial distributions.

Estimating Effect Sizes - Risk Ratio (RR)

- A natural measure of effect size is relative risk ratio: $RR = \frac{P(\text{ disease} \mid \text{exposed })}{P(\text{ disease} \mid \text{unexposed })}$.
- Exposure = genotype; recessive model: AA vs (Aa, aa).
- In **case–control** or **genotype-ascertained samples**, group risks are **distorted**.
- Therefore **RR cannot be validly estimated** from those designs.

Odds Ratio

- Odds Ratio are used to approximate the relative risk (RR) for case-control or case-cohort sampling.
- OR compares odds: $\frac{P(D|E)/(1-P(D|E))}{P(D|\bar{E})/(1-P(D|\bar{E}))}$.
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	Disease (+)	Disease (–)	Total
Exposed	a	b	a+b
Unexposed	c	d	c+d

$$OR = \frac{a/c}{b/d} = \frac{ad}{bc}.$$

- When the outcome is rare, $\mathrm{OR} \approx \mathrm{RR}$.

Inference of ORs

- $OR = \frac{a/c}{b/d} = \frac{ad}{bc}$.
- Log(OR) approximately normal.
- Variance:

$$\mathrm{Var}[\log(OR)] \approx \frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}.$$

- 95% CI:

$$\exp\left(\log(OR) \pm 1.96 \cdot \sqrt{\mathrm{Var}[\log(OR)]}\right).$$

Limitations of Previous Tests

- Work well only for simple binary traits without major environmental influence
- Do not easily adjust for covariates (e.g., age, sex, ancestry)
- Population stratification can confound results if unadjusted
- Stratified analyses are one workaround, but not always sufficient

Properties of OR

- Let $\pi_1^* = P(\text{ case } \mid Aa)$ and $\pi_2^* = P(\text{ case } \mid \text{ aa })$.
- Let $\pi_1 = P(\text{ Aa } \mid \text{ case })$ and $\pi_2 = P(\text{ Aa } \mid \text{ control })$.
- We have the following result that links the two quantities:

$$\frac{\text{odds}(\text{ case } \mid Aa)}{\text{odds}(\text{ case } \mid aa)} = \frac{\pi_1^*}{1-\pi_1^*} \Big/ \frac{\pi_2^*}{1-\pi_2^*}$$
$$= \frac{\pi_1}{1-\pi_1} \Big/ \frac{\pi_2}{1-\pi_2} = \frac{\text{odds}(\text{ Aa } \mid \text{ case })}{\text{odds}(\text{ Aa } \mid \text{ control })}.$$

Details of the derivation

$$\frac{\text{odds}(\text{ case } \mid Aa)}{\text{odds}(\text{ case } \mid \text{ aa })} = \frac{\pi_1^*}{1-\pi_1^*} \Big/ \frac{\pi_2^*}{1-\pi_2^*} = \frac{P(\text{ case } \mid Aa)}{1-P(\text{ case } \mid Aa)} \Big/ \frac{P(\text{ case } \mid aa)}{1-P(\text{ case } \mid aa)}$$

$$= \frac{P(\text{ case } \mid Aa)}{P(\text{ control } \mid Aa)} \Big/ \frac{P(\text{ case } \mid aa)}{P(\text{ control } \mid \text{ aa })} = \frac{P(\text{ case }, Aa)P(\text{ Aa })}{P(\text{ control }, Aa)P(Aa)} \Big/ \frac{P(\text{ case }, aa)P(aa)}{P(\text{ control, aa })P(aa)}$$

$$= \frac{P(\text{ case }, Aa)}{P(\text{ control, } Aa)} \Big/ \frac{P(\text{ case, a })}{P(\text{ control, aa })}$$

$$= \frac{P(\text{ Aa } \mid \text{ case })P(\text{ case })}{P(\text{ Aa } \mid \text{ control })P(\text{ control })} \Big/ \frac{P(\text{ aa } \mid \text{ case })P(\text{ case })}{P(\text{ aa } \mid \text{ control })P(\text{ control })}$$

$$= \frac{P(\text{ Aa } \mid \text{ case })}{P(\text{ aa } \mid \text{ case })} \Big/ \frac{P(\text{ Aa } \mid \text{ control })}{P(\text{ aa } \mid \text{ control })}$$

$$= \frac{P(\text{ Aa } \mid \text{ case })}{1-P(\text{ Aa } \mid \text{ case })} \Big/ \frac{P(\text{ Aa } \mid \text{ control })}{1-P(\text{ aa } \mid \text{ control })} = \frac{\pi_1}{1-\pi_1} \Big/ \frac{\pi_2}{1-\pi_2} = \frac{\text{odds}(\text{ Aa } \mid \text{ case })}{\text{odds}(\text{ Aa } \mid \text{ control })}$$

Regression Framework: Extending to Covariates & Traits

- Use Generalized Linear Models (GLMs):

$$g(E[Y \mid X]) = \alpha + X\beta$$

- Link function g depends on trait type:
- Binary traits (logistic):

$$\log \frac{E[Y \mid X]}{1 - E[Y \mid X]} = \alpha + X\beta$$

- Continuous traits (linear):

$$E[Y \mid X] = b_0 + Xb_1$$

- $X =$ coded genotype (additive, dominant, recessive, etc.)

Regression Framework

- Tests genetic effect:

$$H_0 : b_1 = 0$$

- Inference via likelihood ratio test, Wald test, or score test
- Key advantage: allows easy adjustment for covariates (age, sex, ancestry, etc.)
- Flexible framework for analyzing both binary and continuous traits

Remarks

- For logistic regression, the **estimated coefficient** β is equal to the $\log(\text{OR})$ (for the corresponding model)
- For continuous outcomes, the coefficient β represents differences in means by genotype group
    - For recessive model, β is the mean phenotype for the AA group - mean phenotype for Aa or aa group
    - For the additive model, b1 is the mean increase in phenotype with each additional allele.

Interpretation of Logistic Regression

- Consider logit of μ as a linear function of X.

$$\mu(X) = E(Y \mid X) = P(Y = 1 \mid X))$$

$$\text{logit}(P(Y = 1 \mid X)) = \text{logit}(\mu(X)) = \log \frac{\mu(X)}{1 - \mu(X)} = \alpha + \beta X$$

$$\implies P(Y = 1 \mid X) = \frac{\exp(\alpha + \beta X)}{1 + \exp(\alpha + \beta X)},$$

$$P(Y = 0 \mid X) = \frac{1}{1 + \exp(\alpha + \beta X)}.$$

Interpretation of Logistic Regression

- What is the **interpretation of the parameters, α and β**?

$$\text{logit}(\mu(X)) = \log \frac{\mu(X)}{1-\mu(X)} = \alpha + \beta X.$$

- For individuals carry genotype aa, $X = 0$:

$$\text{logit}(\mu(X=0)) = \alpha.$$

- Thus,

$$\alpha = \text{logit}(\mu(X=0)) = \log\left(\frac{\mu(X=0)}{1-\mu(X=0)}\right) = \log\left(\frac{P(Y=1 \mid aa)}{1-P(Y=1 \mid aa)}\right)$$

is the log-odds of being affected/case for genotype aa.

Interpretation of Logistic Regression

- For individuals carry genotype Aa, $X = 1$:

$$\text{logit}(\mu(X = 1)) = \alpha + \beta.$$

- Thus,

$$\beta = \text{logit}(\mu(X = 1)) - \text{logit}(\mu(X = 0)) = \log\left(\frac{\mu(X = 1)}{1 - \mu(X = 1)}\right) - \log\left(\frac{\mu(X = 0)}{1 - \mu(X = 0)}\right)$$

$$= \log\left(\frac{P(Y = 1 \mid Aa)}{1 - P(Y = 1 \mid Aa)}\right) - \log\left(\frac{P(Y = 1 \mid aa)}{1 - P(Y = 1 \mid aa)}\right) = \log\left(\frac{\pi_1^*}{1 - \pi_1^*}\right) - \log\left(\frac{\pi_2^*}{1 - \pi_2^*}\right)$$

$$= \log\left(\frac{P(Aa \mid Y = 1)}{1 - P(Aa \mid Y = 1)}\right) - \log\left(\frac{P(Aa \mid Y = 0)}{1 - P(Aa \mid Y = 0)}\right) = \log\left(\frac{\pi_1}{1 - \pi_1}\right) - \log\left(\frac{\pi_2}{1 - \pi_2}\right).$$

Interpretation of Logistic Regression

- β is the log-odds ratio of being affected/case for individuals with genotype Aa ($X = 1$ copy of allele A) compared with being affected/case for individuals with genotype aa ($X = 0$ copies of allele A)
- β also equals to the log-odds ratio of having genotype Aa among cases compared with having genotype Aa among controls.

Logistic Regression Likelihood

- Probability of outcome:

$$P\left(Y_i = 1 \mid X_i = x_i\right) = \frac{\exp\left(\alpha + \beta x_i\right)}{1 + \exp\left(\alpha + \beta x_i\right)},$$

$$P\left(Y_i = 0 \mid X_i = x_i\right) = \frac{1}{1 + \exp\left(\alpha + \beta x_i\right)}.$$

- Compact form (for $y_i = 0$ or 1):

$$P\left(Y_i = y_i \mid X_i = x_i\right) = \frac{\exp\left((\alpha + \beta x_i) y_i\right)}{1 + \exp\left(\alpha + \beta x_i\right)}.$$

- Assuming independence:

$$P\left(Y_1 = y_1, \ldots, Y_n = y_n \mid X_1 = x_1, \ldots, X_n = x_n\right) = \prod_{i=1}^{n} P\left(Y_i = y_i \mid X_i = x_i\right).$$

Logistic Regression Likelihood

- Likelihood function:

$$L(\alpha, \beta) = \prod_{i=1}^{n} \frac{\exp\left((\alpha + \beta x_i) y_i\right)}{1 + \exp\left(\alpha + \beta x_i\right)}.$$

- Log-likelihood:

$$l(\alpha, \beta) = \sum_{i=1}^{n} \left[(\alpha + \beta x_i) y_i - \log\left(1 + \exp\left(\alpha + \beta x_i\right)\right)\right].$$

- Estimation:
  - Parameters α, β obtained by Maximum Likelihood Estimation (MLE)
  - No closed-form solution $\rightarrow$ need iterative methods (Newton-Raphson, Fisher scoring, etc.)

Logistic Regression Likelihood (More Advanced)

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	aa	Aa	Total
Cases	r_0	r_1	r
Controls	s_0	s_1	s
Total	n_0	n_1	n

- Results for β are identical to the ones derived from a 2×2 table for $\log \mathrm{OR}$.

$$\hat{\alpha} = \log\left(\frac{r_0}{s_0}\right), SE(\hat{\alpha}) = \sqrt{\frac{1}{r_0} + \frac{1}{s_0}},$$

$$\hat{\beta} = \log\left(\frac{r_1 s_0}{r_0 s_1}\right), SE(\hat{\beta}) = \sqrt{\frac{1}{r_0} + \frac{1}{r_1} + \frac{1}{s_0} + \frac{1}{s_1}}.$$

MLE Derivation Details (More Advanced)

- Note that $r_0 : Y = 1, X = 0, r_1 : Y = 1, X = 1, s_0 : Y = 0, X = 0,$ $s_1 : Y = 0, X = 1$. We can simplify the log likelihood:

$$I(\theta) = I(\alpha, \beta) = \sum_{i=1}^{n} \log \left(\frac{\exp\left((\alpha + \beta x_i) \cdot y_i\right)}{1 + \exp\left(\alpha + \beta x_i\right)} \right)$$

$$= r_0 \cdot \log \left(\frac{\exp(\alpha)}{1 + \exp(\alpha)} \right) + r_1 \cdot \log \left(\frac{\exp(\alpha + \beta)}{1 + \exp(\alpha + \beta)} \right)$$

$$+ s_0 \log \cdot \left(\frac{1}{1 + \exp(\alpha)} \right) + s_1 \cdot \log \left(\frac{1}{1 + \exp(\alpha + \beta)} \right)$$

$$= r_0 \alpha - r_0 \log(1 + \exp(\alpha)) + r_1(\alpha + \beta) - r_1 \log(1 + \exp(\alpha + \beta))$$

$$- s_0 \log(1 + \exp(\alpha)) - s_1 \log(1 + \exp(\alpha + \beta))$$

$$= r\alpha + r_1 \beta - n_0 \log(1 + \exp(\alpha)) - n_1 \log(1 + \exp(\alpha + \beta)).$$

MLE Derivation Details (More Advanced)

- Obtain the score functions

$$\frac{\partial I(\theta)}{\partial \alpha} = r - n_0 \frac{\exp(\alpha)}{1+\exp(\alpha)} - n_1 \frac{\exp(\alpha+\beta)}{1+\exp(\alpha+\beta)}$$

$$\frac{\partial I(\theta)}{\partial \beta} = r_1 - n_1 \frac{\exp(\alpha+\beta)}{1+\exp(\alpha+\beta)}.$$

MLE Derivation Details (More Advanced)

- Calculate the MLE

$$\frac{\partial I(\theta)}{\partial \alpha} = 0, \frac{\partial I(\theta)}{\partial \beta} = 0 \Longrightarrow$$

$$r - n_0 \frac{\exp(\hat{\alpha})}{1 + \exp(\hat{\alpha})} - r_1 = 0 \Longrightarrow \exp(\hat{\alpha}) = \frac{r_0}{s_0} \Longrightarrow \hat{\alpha} = \log \frac{r_0}{s_0}$$

$$\frac{\exp(\hat{\alpha} + \hat{\beta})}{1 + \exp(\hat{\alpha} + \hat{\beta})} = \frac{r_1}{n_1} \Longrightarrow \exp(\hat{\alpha} + \hat{\beta}) = \exp(\hat{\alpha}) \cdot \exp(\hat{\beta}) = \frac{r_1}{n_1 - r_1} = \frac{r_1}{s_1}$$

$$\Longrightarrow \exp(\hat{\beta}) = \frac{r_1}{s_1} / \frac{r_0}{s_0} = \frac{r_1 s_0}{r_0 s_1} \Longrightarrow \hat{\beta} = \log \frac{r_1 s_0}{r_0 s_1}.$$

- Variance calculation involves the second derivatives and the Fisher's information.

Logistic Regression Inference

- How would we perform a formal hypothesis test of

$$H_0 : \beta = 0$$

- Wald test would be identical to the test derived for testing $\Delta = 0$

$$T = \left(\frac{\hat{\beta} - 0}{SE(\hat{\beta})} \right)^2 \sim \chi^2_1.$$

$$\hat{\beta} = \log \left(\frac{r_1 s_0}{r_0 s_1} \right),$$

$$SE(\hat{\beta}) = \sqrt{\frac{1}{r_0} + \frac{1}{r_1} + \frac{1}{s_0} + \frac{1}{s_1}}.$$

Logistic Regression Inference

- LRT

$$T = 2\left(\log\left(L_{H_1}(\hat{\alpha}, \hat{\beta})\right) - \log\left(L_{H_0}(\tilde{\alpha}, \beta = 0)\right)\right) \sim \chi^2_1.$$

- $\tilde{\alpha} = ?$

$$H_0 : \beta = 0,$$

$$\log\left(\frac{\mu(X)}{1 - \mu(X)}\right) = \alpha.$$

$$L(\theta) = L(\alpha, 0) = \prod_{i=1}^{n} \frac{\exp\left((\alpha) \cdot y_i\right)}{1 + \exp(\alpha)}$$

Logistic Regression Inference

$$I(\theta) = I(\alpha, 0) = \sum_{i=1}^{n} \log\left(\frac{\exp\left((\alpha) \cdot y_i\right)}{1 + \exp(\alpha)}\right)$$

$$= r \cdot \log\left(\frac{\exp(\alpha)}{1 + \exp(\alpha)}\right) + s \cdot \log\left(\frac{1}{1 + \exp(\alpha)}\right)$$

$$= r \cdot \alpha - n \cdot \log(1 + \exp(\alpha))$$

$$\frac{\partial I(\theta)}{\partial \alpha} = r - n \cdot \frac{\exp(\alpha)}{1 + \exp(\alpha)}$$

$$\frac{\partial I(\theta)}{\partial \alpha} = 0 \Longrightarrow \tilde{\alpha} = \log\frac{r/n}{(n-r)/n} = \log\frac{\mu}{1-\mu}$$

- This is not surprising since r/n is a pooled estimate of $\mu = P(Y = 1)$ regardless of the value of X.

Logistic Regression Inference

- Score test involves the score function and the Fisher's information evaluated under the null hypothesis that $\beta = 0$.

$$T = S(\tilde{\alpha}, \beta = 0)' I(\tilde{\alpha}, \beta = 0)^{-1} S(\tilde{\alpha}, \beta = 0) \sim \chi_1^2.$$

- Note that the CI for OR is derived from the CI for $\log \mathrm{OR}$, e.g. $95\% \mathrm{CI}$ for OR is

$$(\exp(\hat{\beta} - 1.96 SE(\hat{\beta})), (\exp(\hat{\beta} + 1.96 SE(\hat{\beta})))$$

Exercise

- The data below come from the study by Knowler et al. (1988), on the association between IDDM type 2 and a haplotype from the GM system human immunoglobulin G. These data include all individuals in a sample of 4,920 Native Americans of the Pima and Papago tribes. In this example, think of the GM haplotype as just an allele at a suspected DSL.

GM haplotype	# subjects	$\#(\%)$ with IDDM
Present	293	$23(7.9)$
Absent	4627	$1343(29.0)$

Exercise

- We can reformulate the data:

GM haplotype	affected/case $(\%)$	unaffected/control	Total
Present, D	$23(7.9)$	270	293
Absent, d	$1343(29.0)$	3284	4627
Total	1366	3554	4920

- We are interested in comparing 7.9% with 29%.

Power and Significance

- Power $1-\beta$: probability of detecting an effect when it truly exists.
- Significance level α : probability of false positive (rejecting H_0 when true)
Effect	Detect	Not Detect
True	$1-\beta$	β
False	α	$1-\alpha$
- Goal: minimize α and maximize $1-\beta$.

Power Estimation

- Many genetic association tests follow a normal or chi-squared distribution
- Under H_1 : distribution becomes noncentral chi-squared with noncentrality parameter (NCP) λ
- For a test statistic T :

$$\text{- } H_0 : E(T) = df \left(\text{ central } \chi^2 \right)$$
$$\text{- } H_1 : E(T) = df + NCP \left(\text{ noncentral } \chi^2 \right)$$

How to Increase Power

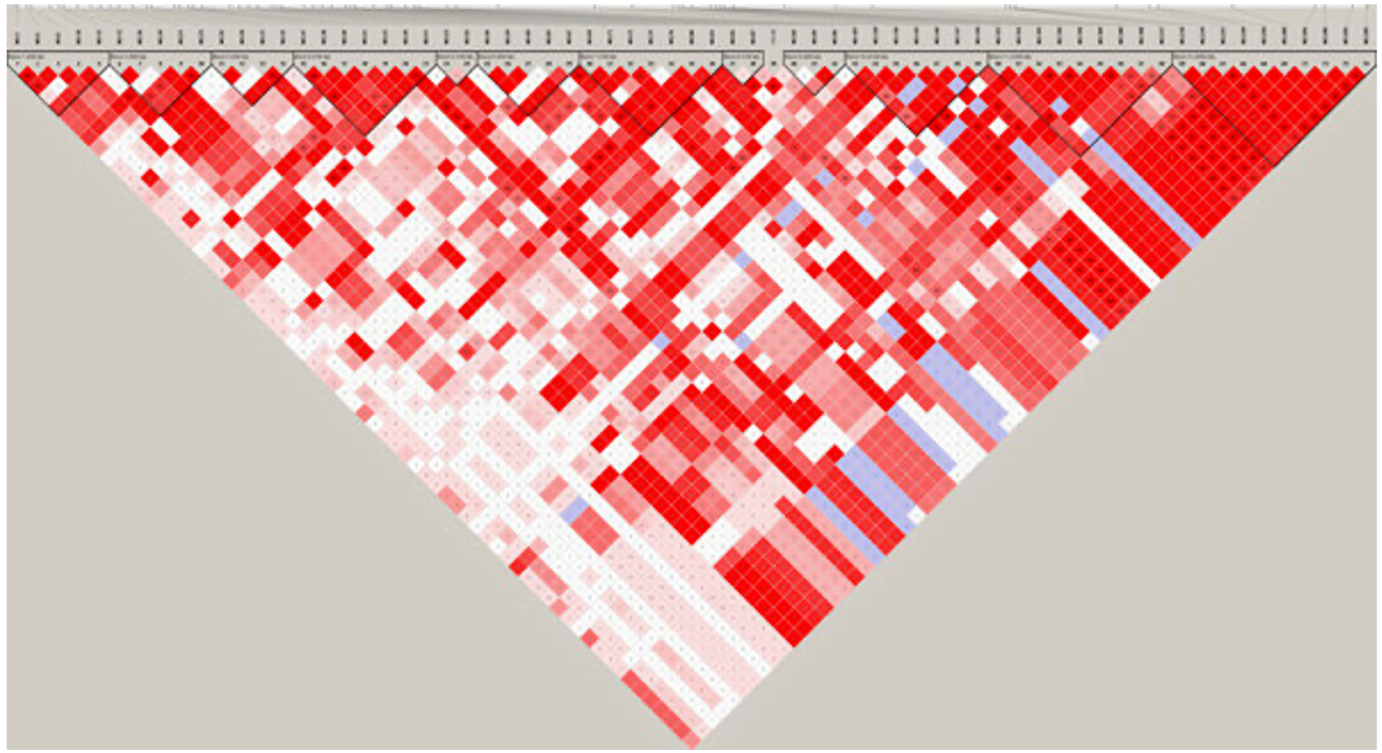
- Example (allelic test at a SNP): true effect size $a = \log(OR)$, risk allele frequency f and proportion of cases $\phi = r/n$.
- The noncentrality parameter:

$$NCP \approx 2\phi(1-\phi)na^2 f(1-f)$$

- Increase sample size n
- Increase effect size a (e.g., extreme case selection)
- Adjust case/control ratio ϕ

Linkage Disequilibrium (LD)

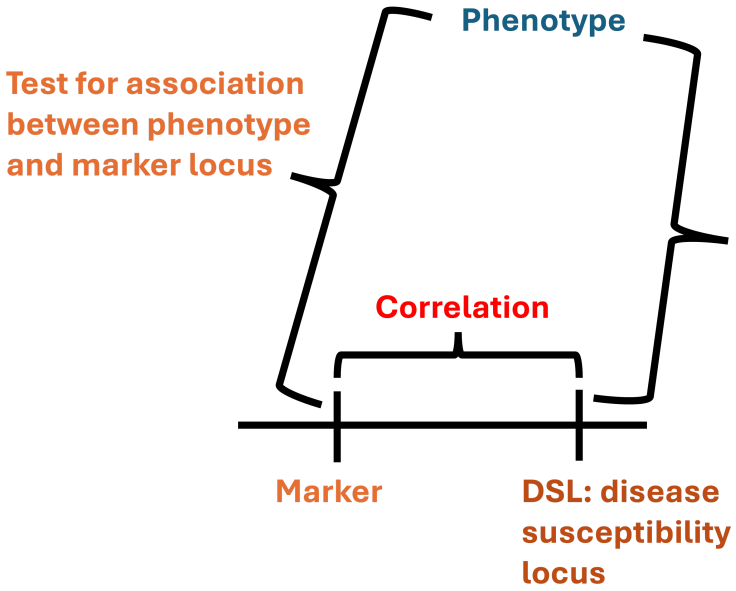
- LD is commonly measured using the Pearson correlation (ρ) between genotypes at two markers



Source: Publicly available from Google Images

Indirect Association

- We usually test genetic markers, not the actual causal mutation
- A marker may be correlated with the true disease-causing variant → indirect association
- Linkage disequilibrium (LD) between a marker and the causal variant creates an observed association with the phenotype



Source: Created by Fan Wang

International HapMap Project

- Multinational project launched at the end of the Human Genome Project
- **Main goal:** provide data to estimate **linkage disequilibrium (LD)** across populations
- DNA samples collected from 4 groups:
  - 30 Yoruba trios (Nigeria)
  - 30 CEPH trios (European ancestry)
  - 45 Japanese (Tokyo)
  - 45 Han Chinese (Beijing)

International HapMap Project

- Data: SNP genotypes for 270 individuals + allele frequencies in each population
- Provides standard LD measures (e.g., ρ^2)
- Impact: reduced the number of SNPs needed for GWAS
    - From ~10 million SNPs → ~500,000 tag SNPs

SNP Microarrays

- **SNP:** single nucleotide polymorphism (usually biallelic: A/a)
- SNP arrays detect common variants (≥5% frequency) in a population
- Nearby SNPs are correlated → ~300K–600K tag SNPs capture most variation
- Modern platforms cover >1 million SNPs to map common variation

LD Varies by Population

- LD patterns differ across populations
- Example:
  - LDlink tool
  - SNP pair: *rs146366639* and *rs6661489*

What's Next

- Population substructure in association studies
- Association analysis in family designs

What questions do you have about anything from today?