Aggregation Analysis, Heritability and Segregation Analysis

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What You'll Learn Today

- **Aggregation & recurrence risk:** Detect familial clustering in binary traits and compute and interpret the recurrence risk ratio.
- **Heritability concepts & estimation:** Partition phenotypic variance and estimate heritability using twin studies.
- **Segregation analysis:** Test Mendelian transmission models (dominant or recessive) using family data, and account for ascertainment bias in study design and interpretation.

Part 1: Given a trait, should we perform genetic studies and under what conditions?

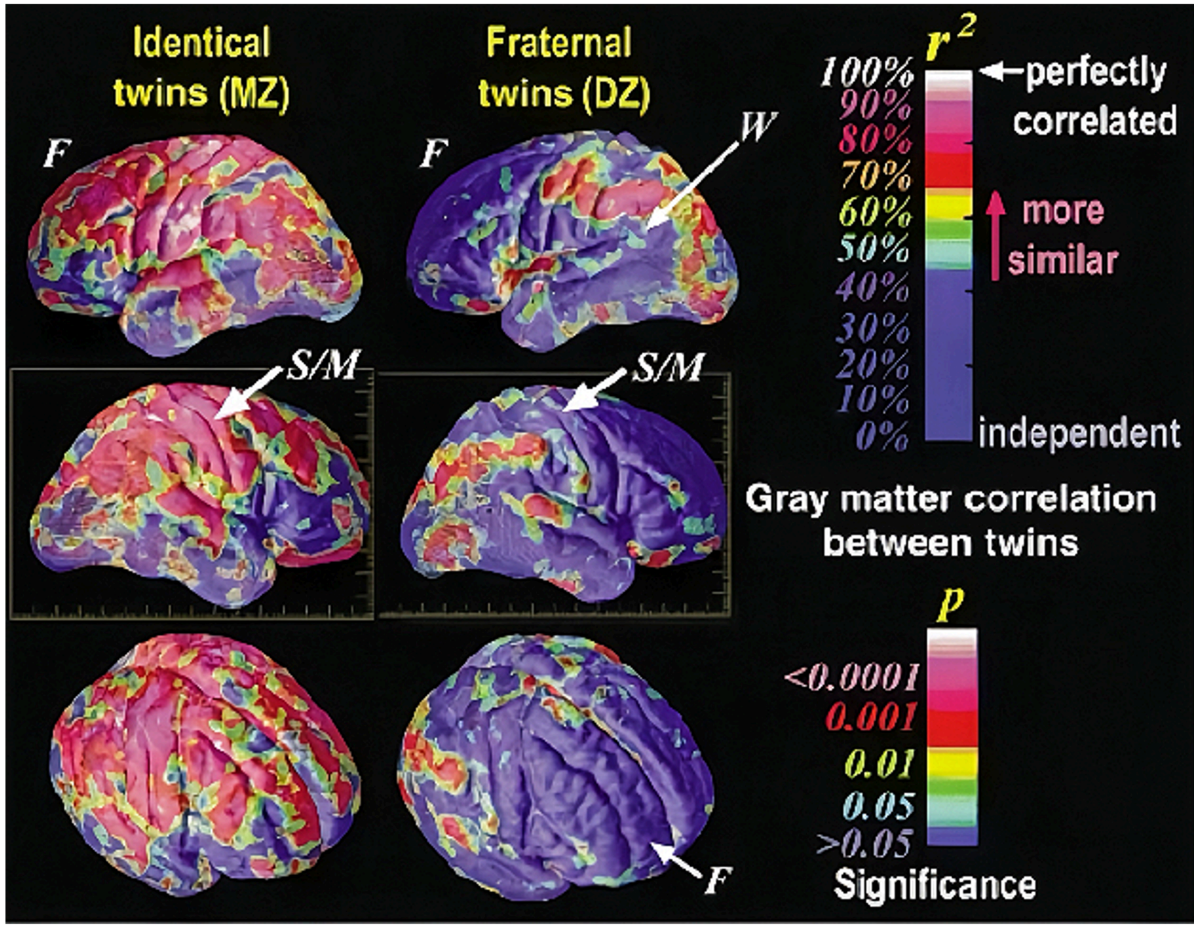
- Most researchers would not undertake a genetic analysis without enough evidence

Problem: Only phenotypes are observed — how to disentangle genes vs. environment?

- Approach: Analyze how similar relatives are to one another for the trait of interest.
  - Strong similarity suggests high genetic contribution (high heritability).
  - Weak resemblance indicates greater environmental effects (low heritability).

Twin Brain Gray Matter Correlation

- Identical twins show much higher gray matter correlation than fraternal twins, highlighting a strong genetic influence on brain structure.



Source: Publicly available from Google Images

Aggregation & Heritability Analyses

- Aggregation analyses – for binary traits
- Heritability analyses – for quantitative traits
- Aim: Demonstrate that diseases or other phenotypes have a **genetic basis** by examining patterns of **phenotypic correlation among relatives** (or clustering within families).
- Approach: Model phenotypic data from families or pedigrees **without using genetic marker data**.
- Developed when genotyping was costly, labor-intensive, and not widely accessible.
- Newer approaches are more popular, e.g. use population GWAS data (without pedigrees) to estimate heritability.

Aggregation Analysis

- Binary traits (e.g. affected/unaffected)
- Core idea: genetic material is inherited in families.
- If the phenotype of interest has a genetic component, the relative of an affected subject will have a higher predisposition to disease than an unrelated subject in the general population, because of the shared genetic material among relatives.

Recurrence Risk Ratio

- Recurrence risk ratio measures the strength of the genetic aggregation among relatives.
- It is defined as a probability ratio which compares the probability of a study subject being affected given that a relative is affected to the general risk in the population (i.e. the prevalence).

$$\lambda_R = \frac{P\left(Y_2 = 1 \mid Y_1 = 1\right)}{K}, \text{ where } K = P(Y = 1).$$

Recurrence Risk Ratio

- We expect that first degree relatives (siblings, parent-offspring pairs) will have a larger recurrence risk ratio than will second or third degree relatives, or mother/father pairs, who will share no genetic material in the absence of inbreeding.

Table 4.1 Observed recurrence risk ratios from a sample of families with schizophrenia. *Source*: Risch (1990a)

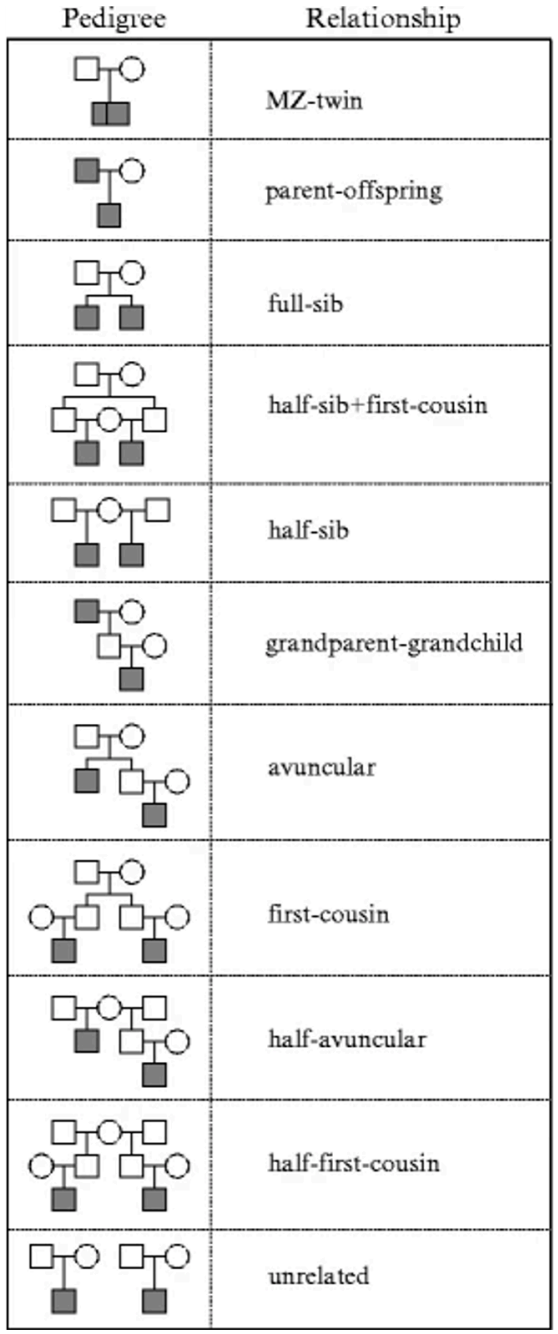
Risk Ratio	λ_O	λ_S	λ_M	λ_D	λ_H	λ_N	λ_G	λ_C
Observed	10.0	8.6	52.1	14.2	3.5	3.1	3.3	1.8

Definitions of subscripts: O = offspring; ; S = sibling; M = MZ twins; D = DZ twins; H = half-sibs; N = niece/nephew; G = grandchild; C = first cousins.

Source: The Fundamentals of Modern Statistical Genetics (Nan Laird & Christoph Lange).

Exercise

- Why might we expect the recurrence risk ratio to be the same for DZ twins as for siblings?
- The observed recurrence risk ratio for DZ twins is bigger than that for siblings. Any possible explanation for that?



Source: Publicly available from Google Images

Explanation

- Monozygotic (MZ) twins should have the highest recurrence risk ratio since they share all of their genetic material, while dizygotic (DZ) twins should have recurrence risk ratios similar to siblings.
- The higher recurrence risk in DZ twins compared to siblings reflects both genetic similarity and greater shared environmental influences.

Estimating the recurrence risk ratio

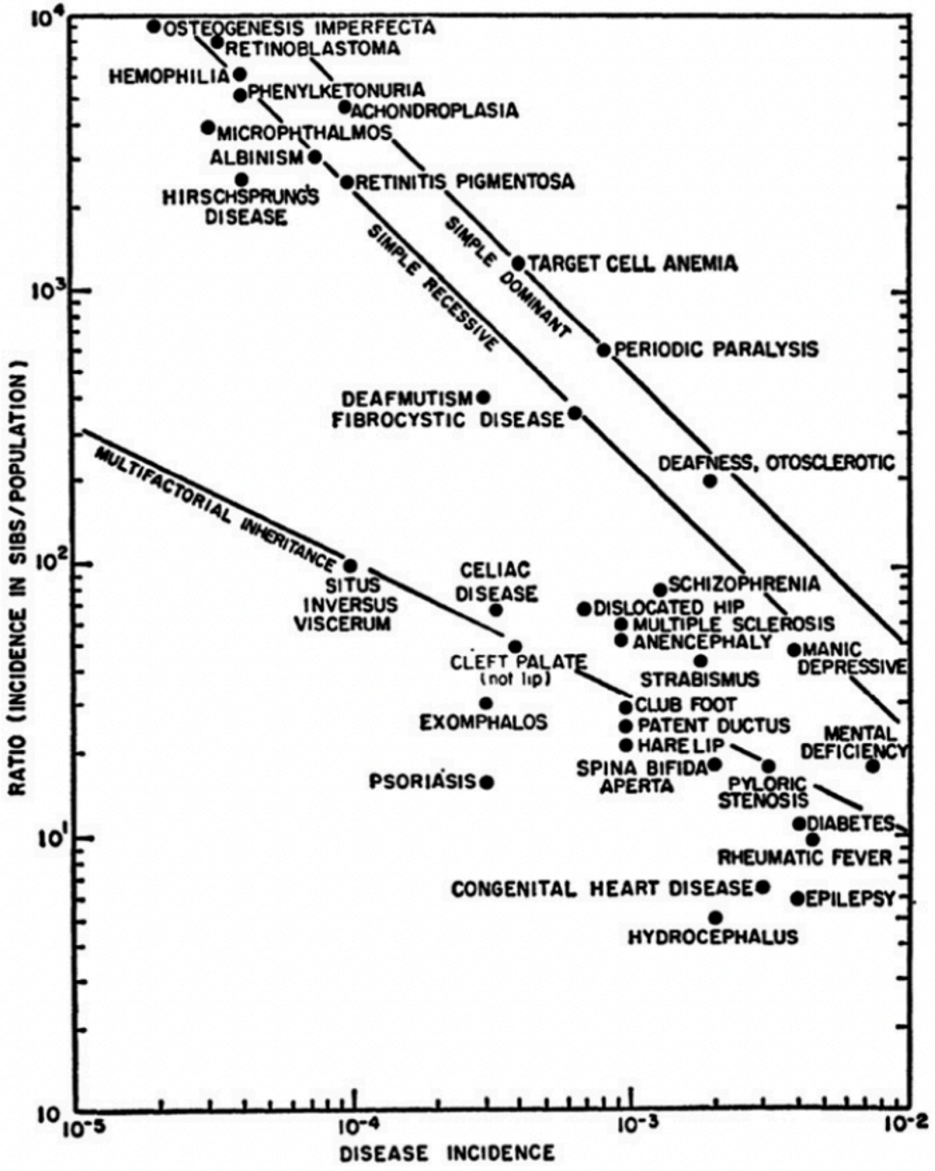
- Obtain a sample of unrelated cases and controls (matched).
- Obtain clinical diagnoses of family disease history, commonly focus on first-degree relatives (i.e. siblings).
- Calculate the proportion of affected siblings among all siblings of the sampled cases: $s_{\text{case}} = P(Y_2 = 1 \mid Y_1 = 1)$.
- Estimating Sibling Recurrence Risk Ratio (λ_s):

$$\lambda_S = \frac{s_{\text{case}}}{K}, \text{ where } K \text{ is the disease prevalence.}$$

- In the absence of K, calculate the proportion of affected siblings among siblings of the controls. If the disease is rare, $s_{\text{controls}} \approx K = P(Y = 1)$.

Recurrence risk ratio

- All monogenic diseases have high recurrence risk ratios.
- The risk ratio for the complex diseases are relatively small.
    - Polygenic basis, environmental influence and incomplete penetrance → Weaker familial clustering



Source: Laird, Nan M., & Lange, Christoph.
The Fundamentals of Modern Statistical Genetics (2011).

Recurrence risk ratio

Question: does $\lambda_R > 1$ prove that the disease has genetic basis?

- Cautions: due to shared exposure to similar environment, it's possible that a disease having no genetic etiology could also show evidence of familial clustering.
    - E.g. flu, infectious disease: $P\left(Y_2 = 1 \mid Y_1 = 1\right)$ for relatives is most likely greater than the population prevalence K, so $\lambda_R > 1$.
- In fact, λ_S for siblings is most likely greater than λ_C for first cousins as well because of the greater amount of shared environment.

Exercise

- Can express recurrence risk ratio as a function of the covariance between two relatives' phenotypes
- Assuming a binary disease, with Y1 and Y2 being two relatives with relatedness R, show that

$$\mathrm{Cov}(Y1, Y2) = P(Y1 = Y2 = 1) - K^* K.$$

- Express λ_R as a function of the covariance and K .

Recurrence Risk Ratio and Disease Model

- Under a simple disease model (i.e. c), the recurrence risk ratio can be readily computed once the penetrance functions and allele frequency are specified.
- Additional technical details for calculating the recurrence risk ratio under a simple disease model are provided at the end of the lecture.

Summary

Aggregation Analysis (for dichotomous traits):

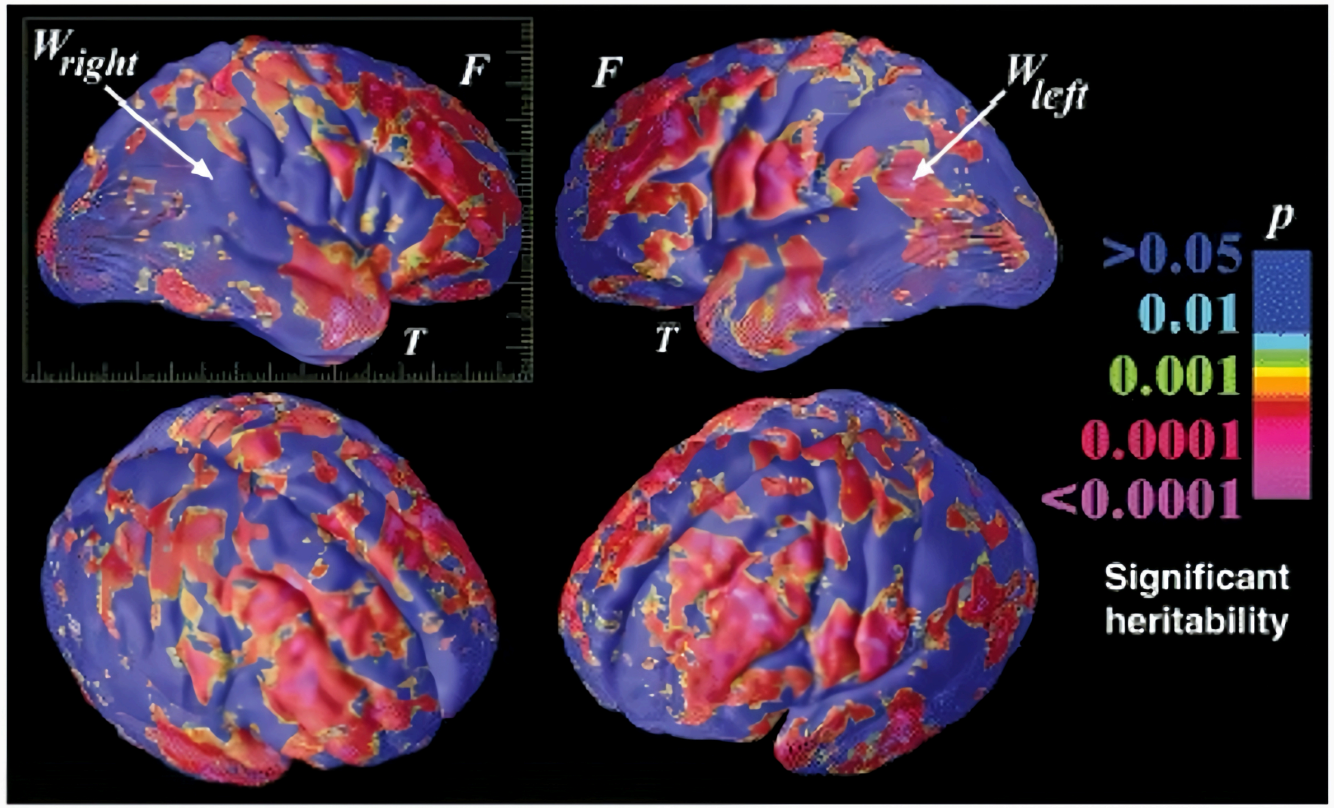
- By estimating the correlation or similarity of a phenotype among family members, one can assess whether a phenotype aggregates in families.
- While a positive result of an aggregation analysis confirms the plausibility of a disease gene, it cannot rule out common environmental effects within families as the origin for the observed correlations.

Heritability

- **Heritability Analysis (for quantitative traits)**: assesses the overall genetic contribution to the variation in the phenotype.
- Example: How much of the variation in height between individuals is due to genetic vs. environmental factors?
    - About 60–80% of the variation in height can be attributed to genetic factors, while 20–40% is explained by environmental influences.

Heritability

- Brain regions for which cortical gray matter distribution is under significant genetic control are shown in red.



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Heritability - Additive Model

- Let's consider the simple additive normal model,

$$Y = \alpha + \beta G + e,$$

  where e captures the effect of environmental (non-genetic) factors.

- What is the total variation in the phenotype Y ?

$$\mathrm{Var}(Y) = \beta^2 \,\mathrm{Var}(G) + \mathrm{Var}(e) + 2\,\mathrm{Cov}(G, e).$$

- If we assume G and e are independent,

$$\mathrm{Var}(Y) = \beta^2 \,\mathrm{Var}(G) + \mathrm{Var}(e).$$

  - Not true in general, but it is a reasonable hypothesis where $\mathrm{Var}(G) \gg \mathrm{Cov}(G, e)$.

Heritability - Additive Model

- Complex traits are typically affected by multiple genes, so

$$Y = \alpha + \sum_m \beta_m G_m + e,$$

$$\mathrm{Var}(Y) = \sum_m \beta_m^2 \,\mathrm{Var}\,(G_m) + \mathrm{Var}(e).$$

- Often we use the following notation to denote the variance partition:

$$V_Y = V_G + V_E.$$

- A natural choice of measure of the genetic contribution (heritability) would be

$$h^2 = \frac{V_G}{V_Y} = \frac{V_G}{V_G + V_E}.$$

Heritability - General Model

- Let's consider a more general model.
- We code $G = 0, 1$ and 2 'additively', but use the following **2 d.f. model**.

$$Y = \mu + aG + dI(G = 1) + e.$$

$$(Y \mid G = aa) \sim N\left(\mu, \sigma^2\right), \mu_0 = \mu;$$

$$(Y \mid G = Aa) \sim N\left(\mu + a + d, \sigma^2\right), \mu_1 = \mu + a + d;$$

$$(Y \mid G = AA) \sim N\left(\mu + 2a, \sigma^2\right), \mu_2 = \mu + 2a.$$

- Different constraints on d lead to different models.
  - Recessive: $d = -a;$ Dominant: $d = a;$ Additive: $d = 0.$

Heritability - General Model

- $Y = \mu + aG + dl(G = 1) + e.$

$$\mathrm{Var}(Y) = a^2 \,\mathrm{Var}(G) + d^2 \,\mathrm{Var}(I(G = 1)) + 2\,\mathrm{adCov}(G, I(G = 1)) + \sigma^2.$$

- We can still use the following notation to denote the variance partition:

$$V_Y = V_G + V_E.$$

- V_Y can be further partitioned into the Additive Genetic Variance V_A and the Dominant Genetic Variance V_G.

$$V_G = V_A + V_D.$$

- Then we will have two definitions of heritabiilty:
  - the broad sense heritability $h^2 = \frac{V_G}{V_Y}$
  - the **narrow sense heritability** (based on the additive variance) $h^2 = \frac{V_A}{V_Y}$

Derivations

G	$I(G)$	with Probability
0	0	$(1-p)^2$
1	1	$2p(1-p)$
2	0	p^2

- Mean and variance of G:

$$E(G) = 2p(1-p) + 2p^2 = 2p.$$
$$\operatorname{Var}(G) = E\left(G^2\right) - (E(G))^2 = 2p(1-p) + 4p^2 - (2p)^2 = 2p(1-p).$$

- Mean of the indicator variable $I = I(G = 1)$:

$$E(I) = 2p(1-p).$$

Derivations

G	$I(G)$	with Probability
0	0	$(1-p)^2$
1	1	$2p(1-p)$
2	0	p^2

- Variance of the indicator variable $I = I(G = 1)$:

$$\operatorname{Var}(I) = E\left(I^2\right) - (E(I))^2 = 2p(1-p) - (2p(1-p))^2.$$

- Covariance between G and I:

$$\operatorname{Cov}(G, I) = E(GI) - E(G)E(I) = 2p(1-p) - 2p2p(1-p) = 2p(1-p)(1-2p).$$

Derivations

- $$\begin{aligned} V_G &= a^2 \operatorname{Var}(G) + d^2 \operatorname{Var}(I(G=1)) + 2\,\mathrm{adCov}(G, I(G=1)) \\ &= a^2 2p(1-p) + d^2\left(2p(1-p) - (2p(1-p))^2\right) + 2ad2p(1-p)(1-2p) \\ &= 2p(1-p)\left(a^2 + 2ad(1-2p) + d^2(1-2p(1-p)\right) \\ &= 2p(1-p)\left(a^2 + 2ad(1-2p) + d^2(1-2p)^2\right) \\ &+ 2p(1-p)\left(d^2\left(1-2p(1-p) - d^2(1-2p)^2\right)\right. \\ &= \frac{2p(1-p)(a+d(1-2p))^2 + (2p(1-p)d)^2}{V_A + V_D}. \end{aligned}$$
- For the simple additive model where $d = 0, V_G = V_A = 2p(1-p)a^2$.

How to estimate Heritability?

- Two ways:
  - Using GWAS data and mixed effect models we can estimate the component of the total phenotypic variance that is explained by genetics.
  - Even without genetic data we can estimate heritability using phenotypic data on relatives.

Heritability Estimation - Twin Study Method

- Twin studies are often used to assess heritability.
    - Identical Twins vs. Fraternal Twins
- Difference in concordance of trait values between identical and fraternal twins can be used to estimate heritability:

$$h^2 = 2(r(MZ) - r(DZ))$$

- Assumes that the resemblance between monozygotic and dizygotic twin pairs due to shared environment is the same – may question this assumption.

Derivations

- Let's consider the normal additive model

$$Y_1 = \mu + aG_1 + e_1, \quad Y_2 = \mu + aG_2 + e_2.$$

- For MZ twins, $G_1 = G_2$, so

$$\operatorname{Cov}(G_1, G_2) = \operatorname{Var}(G) = 2p(1-p)$$

- The phenotypic covariance is then

$$\operatorname{Cov}(Y_1, Y_2) = a^2 \operatorname{Cov}(G_1, G_2) = a^2 2p(1-p) = V_A$$

Derivations

- Because $\mathrm{Var}\left(Y_1\right) = \mathrm{Var}\left(Y_2\right)$, so

$$\mathrm{Var}(Y) = \sqrt{\mathrm{Var}\left(Y_1\right)}\sqrt{\mathrm{Var}\left(Y_2\right)} = V_Y.$$

- Thus

$$h^2 = \frac{V_A}{V_Y} = \frac{\mathrm{Cov}\left(Y_1, Y_2\right)}{\sqrt{\mathrm{Var}\left(Y_1\right)}\sqrt{\mathrm{Var}\left(Y_2\right)}} = \mathrm{Corr}\left(Y_1, Y_2\right) = \rho_{MZ}$$

- **So, why not just collect a sample of MZ twins and using sample estimate of the correlation between Y_1 and Y_2 as the estimate for h^2 ?**

Derivations

- $Y_1 = \mu + aG_1 + e_1, \quad Y_2 = \mu + aG_2 + e_2.$
- $\operatorname{Cov}(Y_1, Y_2) = a^2 \operatorname{Cov}(G_1, G_2)$, assumed that e_1 and e_2 are independent of each other (as well as independent of G_1 and G_2).
- However, e_1 and e_2 independence is highly unlikely. In fact,

  $$\operatorname{Cov}(Y_1, Y_2 \mid MZ) = a^2 \operatorname{Cov}(G_1, G_2 \mid MZ) + \operatorname{Cov}(e_1, e_2 \mid MZ) = \underline{V_A + \operatorname{Cov}(e_1, e_2 \mid MZ)}.$$

Derivations

- What is $\mathrm{Cov}\left(G_1, G_2\right)$ for DZ twins (genetically they are siblings)?

$$\mathrm{Cov}\left(G_1, G_2 \mid DZ\right) = p(1-p).$$

- Thus, for DZ twins we have

$$\begin{aligned}\mathrm{Cov}\left(Y_1, Y_2 \mid DZ\right) &= a^2\,\mathrm{Cov}\left(G_1, G_2 \mid DZ\right) + \mathrm{Cov}\left(e_1, e_2 \mid DZ\right) \\ &= a^2 p(1-p) + \mathrm{Cov}\left(e_1, e_2 \mid DZ\right) = \frac{V_A}{2} + \mathrm{Cov}\left(e_1, e_2 \mid DZ\right).\end{aligned}$$

Derivations

- It is reasonable to assume $\operatorname{Cov}(e_1, e_2 \mid MZ) \approx \operatorname{Cov}(e_1, e_2 \mid DZ)$, so

$$\begin{aligned}
\rho_{MZ} - \rho_{DZ} &= \operatorname{Corr}(Y_1, Y_2 \mid MZ) - \operatorname{Corr}(Y_1, Y_2 \mid DZ) \\
&= \frac{\operatorname{Cov}(Y_1, Y_2 \mid MZ)}{\sqrt{\operatorname{Var}(Y_1)}\sqrt{\operatorname{Var}(Y_2)}} - \frac{\operatorname{Cov}(Y_1, Y_2 \mid DZ)}{\sqrt{\operatorname{Var}(Y_1)}\sqrt{\operatorname{Var}(Y_2)}} \\
&= \frac{V_A + \operatorname{Cov}(e_1, e_2 \mid MZ)}{V_Y} - \frac{\frac{V_A}{2} + \operatorname{Cov}(e_1, e_2 \mid DZ)}{V_Y} \\
&= \frac{1}{2}\frac{V_A}{V_Y} = \frac{1}{2}h^2
\end{aligned}$$

- Thus we can contrast the sample estimates of phenotypic correlation between MZ and DZ twins to estimate the h^2: $\hat{h}^2 = 2\left(\hat{\rho}_{MZ} - \hat{\rho}_{DZ}\right)$.

Details of $Cov(G_1, G_2)$ Calculation

(Unordered) genotype	$G_1 \cdot G_2 =$	with Probability
dd dd	0	NA
dd dD	0	NA
dd DD	0	NA
dD dD	1	$p^2(1-p)^2 + p(1-p)$
dD DD	2	$p^3(1-p) + p^2(1-p)$
DD DD	4	$\frac{1}{4}p^4 + \frac{1}{2}p^3 + \frac{1}{4}p^2$

Details of $Cov(G_1, G_2)$ Calculation

- $\operatorname{Cov}(G_1, G_2) = E(G_1 \cdot G_2) - E(G_1)E(G_2) = E(G_1 \cdot G_2) - (2p)^2.$

- $$E(G_1 \cdot G_2) = p^2(1-p)^2 + p(1-p) + 2\left(p^3(1-p) + p^2(1-p)\right) + 4\left(\frac{1}{4}p^4 + \frac{1}{2}p^3 + \frac{1}{4}p^2\right)$$
$$= 3p^2 + p.$$

- $\operatorname{Cov}(G_1, G_2) = 3p^2 + p - (2p)^2 = p(1-p).$

- **Part 2: After establishing that the trait has a genetic basis, what is the underlying genetic model?**
    - **Segregation analysis**: Tests whether observed inheritance patterns in families fit a specific genetic model.
        - **Segregation ratios**: The proportions of the different genotypes and phenotypes in the offspring of the 6 parental mating types.

6 parental mating type	Offspring Genotype (in Probability)			Offspring Phenotype (in probability)	
	DD	Dd	dd	Affected	Normal
DD x DD	1	0	0	1	0
DD x Dd	1/2	1/2	0	1	0
DD x dd	0	1	0	1	0
Dd x Dd	1/4	1/2	1/4	3/4	1/4
Dd x dd	0	1/2	1/2	1/2	1/2
dd x dd	0	0	1	0	1

Segregation Analysis - Autosomal Dominant Disease

- Segregation analysis determines whether segregation ratios are consistent with expectations of autosomal dominant or recessive transmission.
- Autosomal Dominant Disease: A is the mutant allele and a is the normal allele (i.e. A is rare).

$$p(AA \mid \text{ affected }) = \frac{p^2}{p^2 + 2p(1-p)^2} = \frac{p}{2-p} \approx \frac{p}{2}.$$

- Design: use a random sample of matings between affected (assumed to have genotype Aa) and unaffected individuals (aa).
- Data: observe n offspring in total, among which n_{Affected} offspring are affected by the disease.

Segregation Analysis - Autosomal Dominant Disease

Questions of interest

- Estimation: what is the segregation ratio p ?
- For autosomal dominant disease, an offspring of mating type $Aa \times AA$ has probability $p = 1/2$ of being affected.
- Hypothesis testing: can we reject the H_0 that $p = p_0 = 1/2$?

Segregation Analysis - Autosomal Dominant Disease

- $n_{\text{Affected}} \sim \text{Bino}(n, p)$.
- Important Question to ask: two affected sibs are independent of each other?
    - Mendelian transition from parents to one sib is independent of that of the transition to another sib.
    - However, if there are contributing covariates, then affected siblings are not independent due to common shared environmental effect.
- MLE: $\hat{p} = \frac{n_{\text{Affected}}}{n}$.

Segregation Analysis - Autosomal Dominant Disease

- Hypothesis testing - Likelihood Ratio Test.

$$
\begin{aligned}
T =& 2(I(\hat{p}) - I(\tilde{p})) = 2\left(I(\hat{p}) - I\left(p_0\right)\right) = 2\sum \text{ observed } \times \log \frac{\text{observed}}{\text{expected}} \\
=& 2\left(n_{\text{Affected }} \log\left(\frac{n_{\text{Affected}}}{np_0}\right) + \left(n - n_{\text{Affected }}\right) \log\left(\frac{n - n_{\text{Affected}}}{n\left(1 - p_0\right)}\right)\right) \\
=& 2\left(n_{\text{Affected }} \log\left(\frac{\hat{p}}{1/2}\right) + \left(n - n_{\text{Affected }}\right) \log\left(\frac{1 - \hat{p}}{1/2}\right)\right) \sim \chi_1^2
\end{aligned}
$$

Notes

Other tests:

- Binomial exact test.

$$\text{p-value } = 2P\left(r \geq r_{obs}\right) \text{ if } r_{obs} \geq n/2, \text{ or } = 2P\left(r \leq r_{obs}\right) \text{ if } r_{obs} < n/2.$$

- Normal approximation to Binomial test (with or without continuity correction).

$$r \sim N(np, np(1-p)).$$

- Pearson χ^2_r test.

Notes

- A few notes on likelihood ration test and Pearson χ_r^2 test.
- The proof of $X = 2 \ln \left\{ \frac{L_{H_1}(\hat{\theta})}{L_{H_0}(\hat{\theta})} \right\} \approx \chi_r^2$ is based on the Taylor's expansion w.r.t. θ.
- Pearson χ^2 test is a large sample approximation to $2 \ln \lambda$, an approximation which depends only on the restricted MLE of θ under the null hypothesis. This may be easier to calculate than LRT which requires unrestricted MLE. However, in many complex situations, only likelihood approach is applicable.
- Subject to regularity conditions, the two tests have approximately the same power function for large samples (large-sample equivalence). In that case, we may choose the test that is most convenient computationally.

Segregation Analysis - Autosomal Recessive Disease

- **Uncertain genotype problem**: A specific mating type may not be selected on the basis of the phenotype of the parents:
    - Unaffected individuals can be dD or dd
- **Sampling issue**: How to select families? What is the correct ascertainment procedure?

Segregation Analysis - Autosomal Recessive Disease

- **Example**: interested in the segregation ratio for mating type $dD \times dD$ (predicted to have $p = 1/4$ under the autosomal recessive model).
  - For a pair of unaffected parents, three possible mating types:

$$dd \times dd, Dd \times dd \text{ or } Dd \times Dd$$

  - Propose: **select families (both parents unaffected) with at least one affected offspring**.
  - Rationale: $dd \times dd$ or $Dd \times dd$ mating types do not produce affected offsprings. Thus **only $Dd \times Dd$ mating type will be selected**!

Segregation Analysis - Autosomal Recessive Disease

- **Problems of the above ascertainment procedure**
  - **Will all matings with the $Dd \times Dd$ type be randomly selected?**
  - An offspring of $dD \times dD$ mating type has probability of $1/4$ being affected.
  - Such sampling procedure may miss those $dD \times dD$ families that have no affected offspring just by chance (also depending on the size of a family).
  - The proportion of affected tends to be overestimated based on this sampling scheme.
    - e.g. All families have only one child. If we require at least one affected offspring, then all offsprings in the selected sample will be affected!

Segregation Analysis - Autosomal Recessive Disease

- Statistical remedy: need to take into account of the "**incomplete selection**" of a mating type in segregation analysis. **Ascertainment procedure** should be clearly defined and accounted for (advanced stat gene topic).
    - Glidden and Liang (2002). Ascertainment adjustment in complex diseases. Genetic Epidemiology.
    - Comments by Epstein (209-213), by Burton (214-218), and by Glidden (219-220) in the same issue of Genetic Epidemiology.

Segregation Analysis - Beyond the Simple Model

- Interpretation of deviation from Mendelian segregation ratios.
  - More than one causal locus.
  - Incomplete penetrance.
  - Other characteristics of complex traits/diseases such as heterogeneity, environmental effect and gene-environment interactions.

Summary

- **Aggregation analysis** (for binary traits): If a trait has a genetic basis, relatives of affected individuals show higher risk than the general population.
    - Measured by recurrence risk ratio (λ), which decreases with degree of relatedness (MZ > DZ $\approx$ siblings).
    - Aggregation cannot rule out shared environment as an explanation.
- **Heritability estimation** (for quantitative traits): Decomposes phenotypic variance into genetic (additive A, dominance D) and environmental components.
    - Methods include twin studies (contrast MZ vs. DZ correlations under equal-environment assumption) and GWAS-based mixed models.

What's next: 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.

Types of tests

- SNP: categorical variable with three genotypes
- Possible tests:
  - 2-DF tests that compare all three genotypes.
  - 1-DF tests : some assumption (e.g. monotonicity) about disease and genotype.
- We assume a case-control design: r cases, s controls, $n=r+s$ total sample size.

Additional Details

- We present the technical details for calculating the recurrence risk ratio within a simple Mendelian recessive disease model.

P(Y, G) for Nuclear Families

- (A, a): two alleles of a biallelic marker
- $G = \{aa, aA, AA\}$ with coding (0, 1, 2)
- p: allele frequency of A

Offspring

- (X_1, X_2): genotypes for siblings 1 and 2
- (Y_1, Y_2): phenotypes for siblings 1 and 2

Parents

- (P_1, P_2): genotypes for parents with (g_1,g_2) denote their observed values

Joint Distribution of Y and G

- The probability density for the offspring phenotypes and genotypes, and the parental genotypes is:

  $$f(y_1, y_2, x_1, x_2, g_1, g_2) = f(y_1|x_1)f(y_2|x_2)f(x_1|g_1, g_2)f(x_2|g_1, g_2)f(g_1)f(g_2).$$

  - Assuming HWE also implies random mating, so that the parental genotypes are independent:

    $$P\left(P_1 = g_1, P_2 = g_2\right) = f\left(g_1, g_2\right) = f\left(g_1\right)f\left(g_2\right).$$

  - The genotypes of the offspring are independent conditional on the parental genotypes, and each follows Mendel's first law.

    $$f\left(x_1, x_2, g_1, g_2\right) = f\left(x_1 \mid P_1, P_2 = g_1, g_2\right)f\left(x_2 \mid P_1, P_2 = g_1, g_2\right)f\left(g_1\right)f\left(g_2\right).$$

Joint Distribution of Y and G

- For simplicity, we make the assumption of **phenotypic independence**.The phenotypes of individuals in the pedigree are independent of each other, given their genotypes.

$$f\left(y_1, y_2 \mid x_1, x_2, g_1, g_2\right) = f\left(y_1 \mid x_1\right) f\left(y_2 \mid x_2\right).$$

- Let's assume:
  - A very simple Mendelian recessive model of $f_0 = f_1 = 0$ and $f_2 = 1$.
  - Note that $Y = 1$ implies genotype is AA.
  - The relationship between two individuals is full-sib.
  - Allele frequency of A is p.

Recurrence Risk Ratio and Disease Model

- **We can show that** $P\left(Y_{\text{Sib of } Y} = 1 \mid Y = 1\right) > P(Y = 1)$.
- $P(Y = 1) = P(AA) = p^2$.
- $P\left(Y_2 = 1 \mid Y_1 = 1\right) = \frac{P(Y_1=1, Y_2=1)}{P(Y_1=1)}$.
- $$\begin{aligned} P\left(Y_1 = 1, Y_2 = 1\right) &= P\left(X_1 = AA, X_2 = AA\right) \\ &= P\left(X_1 = AA, X_2 = AA, P_1 = AA, P_2 = AA\right) \\ &+ P\left(X_1 = AA, X_2 = AA, P_1 = AA, P_2 = Aa\right) \\ &+ P\left(X_1 = AA, X_2 = AA, P_1 = Aa, P_2 = AA\right) \\ &+ P\left(X_1 = AA, X_2 = AA, P_1 = Aa, P_2 = Aa\right) \\ &= 1 \cdot 1 \cdot p^2 \cdot p^2 + 2\left(\frac{1}{2} \cdot \frac{1}{2} \cdot p^2 \cdot 2p(1-p)\right) + \frac{1}{4} \cdot \frac{1}{4} \cdot 2p(1-p) \cdot 2p(1-p) \\ &= p^4 + p^3(1-p) + \frac{1}{4}p^2(1-p)^2. \end{aligned}$$

Recurrence Risk Ratio & Disease Model

- $$P\left(Y_2 = 1 \mid Y_1 = 1\right) = \frac{P\left(Y_1 = 1, Y_2 = 1\right)}{P\left(Y_1 = 1\right)}$$
$$= \frac{p^4 + p^3(1-p) + \frac{1}{4}p^2(1-p)^2}{p^2} = p^2 + p(1-p) + \frac{1}{4}(1-p)^2$$
$$= p^2\left(1 + \frac{(1+3p)(1-p)}{4p^2}\right) > p^2 = P\left(Y_1 = 1\right).$$

Recurrence risk ratio & Disease Model

- $f_0 = P(Y = 1 \mid G = aa)$, $f_1 = P(Y = 1 \mid G = Aa)$, $f_2 = P(Y = 1 \mid G = AA)$. ($f_0 = f_1 = 0$ and $f_2 = 1$).
- $$\lambda_R = \frac{P\left(Y_2 = 1 \mid Y_1 = 1\right)}{K} = \frac{P\left(Y_2 = 1, Y_1 = 1\right)}{P\left(Y_1 = 1\right)K} = \frac{P\left(Y_2 = 1, Y_1 = 1\right)}{P(Y = 1)^2}.$$
- Denominator:

$$\begin{aligned} K = P(Y = 1) &= \sum_{x=0,1,2, \text{ or } aa,aA,AA} P(Y = 1, X = x) \\ &= \sum_{x=0,1,2} P(Y = 1 \mid X = x)P(X = x) \\ &= f_0(1-p)^2 + f_1 2p(1-p) + f_2 p^2. \end{aligned}$$

Recurrence risk ratio & Disease Model

- Numerator:

$$
\begin{aligned}
P(Y_2 = 1,\ Y_1 = 1) &= \sum_{x_1,x_2,g_1,g_2 \in \{0,1,2\}} P\big(Y_2 = 1, Y_1 = 1, X_1 = x_1, X_2 = x_2, P_1 = g_1, P_2 = g_2\big) \\
&= \sum_{x_1,x_2,g_1,g_2 \in \{0,1,2\}} f(y_1 \mid x_1)\, f(y_2 \mid x_2)\, f(x_1 \mid g_1, g_2)\, f(x_2 \mid g_1, g_2)\, f(g_1)\, f(g_2) \\
&= \sum_{g_1,g_2 \in \{0,1,2\}} f(g_1)\, f(g_2) \left\{ \sum_{x_1 \in \{0,1,2\}} f(y_1 \mid x_1)\, f(x_1 \mid g_1, g_2) \cdot \sum_{x_2 \in \{0,1,2\}} f(y_2 \mid x_2)\, f(x_2 \mid g_1, g_2) \right\}.
\end{aligned}
$$

- Thus given values for the penetrance functions and the allele frequency, the recurrence risk ratio is easily computed.
- The affected two sibs must have genotype AA, so $x_1 = x_2 = 2$. In return, both parents must carry at least one copy of Aa, so $g_1 \neq 0$ and $g_2 \neq 0$. All these make the number of summations substantially smaller.

What questions do you have about anything from today?