# Week 12 GWAS

Monday, 4 April 2022 8:06 AM

loci of interest → SNP ↔ PHENOTYPE

⇒ TRAITS ARE POLYGENIC
↳ genes are PLEIOTROPIC, EPISTATIC,
multi-allelic

$P = G \times E$
phenotype = genotype × environment

## STATISTICAL TESTS OF ASSOCIATION :

(1) CASE - CONTROL GENOTYPE METHODS

PEARSON'S CHI-SQUARED TEST

Ho : Case & control are from same distribution

eg. {A, G} ⇒ AA, AG, GG

DF = 2

| | AA | AG | GG |
|---|---|---|---|
| CASE | | | |
| CONTROL | | | |

$$X^2 = \sum \frac{(\text{CASE} - \text{CONTROL})^2}{\text{CASE}}$$

(2) Normal approximation to Fisher's exact test ⇒ DOMINANT VS RECESSIVE

→ Ho : Phenotypes (ROWS) and genotypes (COLUMNS) are unrelated

(3) REGRESSION

(3) LOGISTIC

additive model of inheritance

$$y = \beta x + \varepsilon$$

$H_0: \beta_1 = 0$

there is no significant association

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rs 4988235 → bitter taste ability

{A, G}

| | AA | AG | GG | |
|---|---|---|---|---|
| BITTER | | | | |
| YES | 2 | 3 | 7 | 11 |
| NO | 4 | 9 | | |
| | | | | 24 |

COUNT TABLE

| ALLELE | BITTER TASTER | NON-TASTER | TOTALS |
|---|---|---|---|
| A | $2\times2 + 1\times3 = 7$ | $2\times4 + 1\times9 = 17$ | 24 |
| G | $2\times7 + 1\times3 = 17$ | $2\times11 + 1\times9 = 31$ | 48 |
| | 24 | 48 | 72 |

OBSERVED

if A allele is independent of bitter taste

$$P(A \cap \text{BITTER TASTE}) = P(A) \times P(\text{BITTER TASTE})$$

$$P(A) = \frac{24}{72} = 0.333 \Rightarrow P(G) = 0.667$$

$$P(\text{BITTER TASTE}) = \frac{24}{72} = 0.333,$$

$$P(\text{NON\_TASTE}) = 0.667$$

EXPECTED

| | BITTER | NON-TASTER |
|---|---|---|
| A | $P(A) \times P(\text{BITTER}) \times 72 = 0.333 \times 0.333 \times 72 = 8$ | $P(A) \times P(\text{NON-TASTE}) \times 72 = 0.333 \times 0.667 \times 72 = 15.98$ |
| G | 15.98 | 32.04 |

$$X^2 = \sum \frac{(O-E)^2}{E} = \frac{(7-8)^2}{8} + \frac{(17-15.98)^2}{15.98} + \frac{(17-15.98)^2}{15.98} + \frac{(31-32.04)^2}{32.04} = 0.3$$

$df = 1$

R: $1 - pchisq(0.3, 1) = 0.58$

$\Rightarrow$ accept $H_0 \Rightarrow$ A is not significantly associated with bitter taste

ODDS RATIO:

$$P(\text{TRAIT} \mid A) = \frac{P(\text{TRAIT} \,\&\, A)}{P(A)}$$

$$\Rightarrow \text{ODDS}(A) = \frac{P(\text{TRAIT} \mid A)}{1 - P(\text{TRAIT} \mid A)}$$

then

ODDS (A)

$$\text{ODDS RATIO} = \frac{\text{ODDS (A)}}{\text{ODDS (G)}}$$

$$P(\text{TASTER} \mid A) = 7/24 = 0.291$$

$$P(\text{TASTER} \mid G) = 17/24 = 0.709$$

$$\text{ODDS (A)} = \frac{0.291}{1 - 0.291} = 0.41$$

$$\text{ODDS (G)} = \frac{0.709}{1 - 0.709} = 2.43$$

$$\Rightarrow \text{ODDS RATIO} = \frac{0.41}{2.43} = 0.168$$

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non-binary, additive quantitative trait.

eg. LDL cholesterol ; rs 1591147

{A, T}

trait means :

AA mean = 0.02

AT mean = −0.40

TT mean = −2.0

$P(T) = 0.04$ ; $P(A) = 0.96$

SIMPLE ADDITIVE MODEL

mean trait value ~ additively on # of T alleles.

↳ SD's of genotypes are constant.

$$\underline{y} = \underline{\mu} + \underline{x\beta} + \epsilon$$

$y$ = PHENOTYPE [LDL]

$\mu$ = mean of genotype 0 (AA)

$\beta$ = effect of each copy of allele on phenotype.

$\epsilon$ = error $\sim N(0, \sigma^2)$

$x$ = genotype $[0, 1, 2]$ → AA, AT, TT

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FULL MODEL: each genotype has its own mean.

$$y = \mu + x\beta + z\gamma + \epsilon$$

$z$ = indicator if TT or not

[$z = 0$ if not TT, $z = 1$ if TT]

means: (AA : $\mu$, AT : $\mu + \beta$,

TT : $\mu + 2\beta + \gamma$)