

Interactions in Genetic Association Analysis

Statistical interaction occurs between two factors if their combined effect is different than what would be expected based on their individual separate effects. In genetics, differences in risk or mean phenotype between genotypes vary according to the exposure (interacting) variable.

Simple example: Phenylketonuria (PKU) is a genetic defect that causes severe intellectual disability only in the presence of dietary phenylalalanine. Every baby is tested for this trait to see if they need a special diet.

Modeling Statistical Interaction

We need a model to form an expectation for the joint effect, which we can use to define the interaction. The definition of interaction relies on some specification of non-interactive effects.

Let G_i be the genotype for person i , and E_i be an environmental factor for a person i

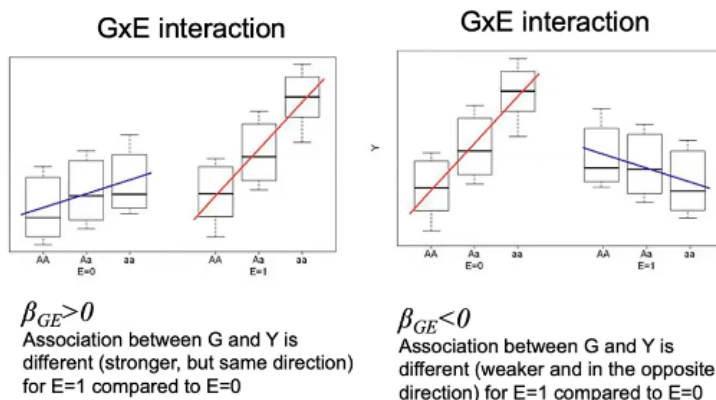
- For continuous outcome Y , linear regression model:

$$E(Y_i) = \beta_0 + \beta_G G_i + \beta_E E_i + \beta_{GE} G_i E_i$$

- For binary outcome Y , logistic regression model:

$$E(\text{logit}(Y_i)) = \beta_1 + \beta_G G_i + \beta_E E_j + \beta_{GE} G_i E_i$$

$H_0: \beta_{GE} = 0$; No interaction, the measure of association β_G between the distribution of the phenotype Y and the genotype G does not depend on E .



- Model interaction is always written as a departure from additive effects
- For both logistic and linear regression, this translates to departure from additivity of effects
- For logistic regression
 - Interaction == departure from additivity of log(ORs)
 - This is the same as departure from multiplicative OR effects
 - Interaction in logistic model is multiplicative interaction on the scale of the odds ratio
 - $OR_{GE} \neq OR_G * OR_E$
 - $OR_{G,E=1} \neq OR_{G,E=0}$

Example logistic model with interaction (CP = cleft palate):

$$E(\text{logit}(Y_i)) = \beta_1 + \beta_G G_i + \beta_E E_i + \beta_{GE} G_i E_i$$

Y=1 → phenotype=cleft palate (case) Y=0 → control
 G=1 → TGF α polymorphism present G=0 → absent
 E=1 → mom is a smoker E=0 → non-smoker

β_E : log-odds ratio of CP for E=1 vs E=0 when G=0

β_G : log-odds ratio of CP for G=1 vs G=0 when E=0

$\beta_E + \beta_{GE}$: log-odds ratio of CP for E=1 vs E=0 when G=1

$\beta_G + \beta_{GE}$: log-odds ratio of CP for G=1 vs G=0 when E=1

So there are 2 interpretations of β_{GE} :

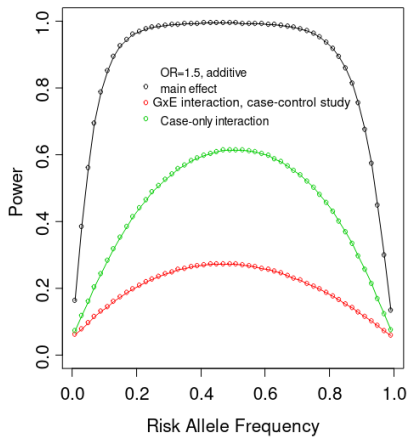
1. The difference between the Environment logOR when G = 1 vs when G = 0
2. The difference between the Genotype logOR when E = 1 vs when E = 0

The odds ratio of exposure to non-exposure is $\exp(\beta)$, or the increased odds of disease at the locus for each additional allele is $\exp(\beta)$ times smaller for exposure group than non-exposure group.

- Overall we define β_{GE} is the difference between the observed $\ln(\text{OR})$ and the $\ln(\text{OR})$ expected when the G and E act additively
- When $\beta_{GE} = 0$ ($\exp(\beta_{GE}) = 1$):
 - no departure from additivity
 - the genotypic OR in the two groups E = 1 and E = 0 are the same
 - the environment odds ratios in the two groups G = 1 and G = 0 are the same

If there is interaction, we should not use summary measures (OR & genotypic means) for the marker or the environmental factor alone. We may improve power to identify genes and SNPs by *testing within subgroups of the interacting exposure*, or just testing for interaction.

- When independence assumption is met, case-only design is much more powerful than case-control logistic regression test of interaction



Limitations

- Provides non information about main effects
- The interaction estimate can be biased if the assumption of G-E independence is violated

Two-Stage Screening Procedure

As we've seen GxE tests have poor power compared to the main effect tests, as the multiple testing problem is more serious. One way to improve power is to do fewer tests, which gives a smaller multiple testing correction and thus larger significance level.

For example, a genome wide test for smoking and SNP interaction power will be very low, as we are usually accounting for > 2.5 million SNPs, so we would need to use a multiple testing correction like $\alpha = 5 \times 10^{-8}$

Screen procedures are one way to choose which GxE tests to do. A screening procedure gives us a way to select only a small subset of the SNPs $m \ll M$ to test for G-E interaction. So, we adjust for m SNPs instead of M SNPs, making significance α/m instead of α/M .

The tricky part is the screening procedure **must be independent** of the G-E interaction test in order to maintain α , also the screening test needs to be good at identifying variants that are likely to have a G-E interaction.

- Stage 1: screen all GWAS SNPs to identify the subset for which there is likely to be a GxE interaction
- Stage 2: Test for interaction only for the m SNPs that passed the stage 1 screening
- Use the same data set for stages 1 and 2, this is different than discovery replication 2 stage design which use independent data sets
- Procedures for screening:
 - Main effect screen - stage 1 screen based on main effects of genotype
 - If the SNP is not associated with the outcome phenotype it does not pass stage

- SNP-E screen - Stage 1 screen based on SNP-E association
 - If the SNP is not associated with E it does not pass stage 1
 - Appropriate only for case-control samples

Kooperberg LeBlanc Stage 1 (Main G Effect Screening)

Y = phenotype (continuous, binary, or censored survival)

G = binary 0-1 genotype (or additive 0,1,2)

E = binary 0-1 environmental variable

Test $H_0: \beta=0$ in the appropriate model. E.g.:

$$E(Y) = \beta_0 + \beta G$$

$$E(\text{logit}(P(Y=1))) = \beta_0 + \beta G$$

Perform test using all data (E = 0 and E = 1)

- When a GxE interaction exists, except crossover interactions, there will be some evidence of G-Y association in at least some E subgroups(s)
- When the association is strong, it can also be detected marginally in all exposure groups combined
- First stage screening will identify the SNPs more likely to show interaction
- First stage marginal G-Y association test is approximately independent of second-stage interaction test, so significance is preserved
- Most SNPs are not strongly marginally associated with Y so will be removed from consideration of interaction
- Works with cohort data, any phenotype
- Power is lower when the G-Y association is in a different directions in different E strata

Murcray Stage 1 (SNP-E Screening)

Y = phenotype (binary)

G = binary 0-1 genotype (can use additive 0-1-2 as well)

E = binary 0-1 environmental variable

Test $H_0: \beta=0$ in the model:

$$\text{logit}(P(E=1)) = \beta_0 + \beta G$$

This test is only performed with cases and controls combined.

- If there is no G-E association in the population, interaction exists when there is evidence of G-E association in cases
- When this association is strong, it can also be detected in cases and controls combined
 - Assumes cases are $\sim 1/2$ the sample

- If cases are a small part of of sample, this screen won't work properly (not independent of GxE test)
 - Most SNPs will not be associated with E
 - First stage "screening" test will identify SNPs likely to exhibit multiplicative interaction with E on case status
 - First-stage marginal G-R association test is approximately independent of second-stage interaction test, so the significance level for stage 2 corrects only for the stage 2 tests performed
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