Efficient dimension-reduction technique for the joint analysis of correlated phenotypes

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Multivariate phenotypes

- Complex diseases
  - Interest in analyzing multiple intermediate phenotypes instead of association between genetic variants and disease labels

- Joint analysis
  - Pleiotropy
  - Correlated phenotypes
Goals

- Dimension-reduction technique which can handle high-dimensional phenotypes
- Computational efficiency
Principal components of explained variance

\[ \mathbf{Y} = (Y_1, \ldots, Y_p) \]
Two-stage approach to PCEV

\[
\{Y_{11}, \ldots, Y_{1p_1}\}, \ldots, \{Y_{q1}, \ldots, Y_{qp_q}\} \quad \overset{\text{Maximize heritability}}{\longrightarrow} \quad X
\]

\[
\tilde{Y}_1, \ldots, \tilde{Y}_q \quad \overset{\text{Maximize heritability}}{\longrightarrow} \quad X
\]
PCEV computation
Testing for association between multivariate phenotypes and covariates

- Wilks’ test (appropriate only when $p < n$)

- Perform PCA on the phenotypes, retain a certain number of components (less than $n$), perform PCEV on the components, and use Wilks’ test

- Permutation test
Type I error rate
Power

One-stage

Two-stage
Data analysis

- 993 healthy individuals who served as controls for the Assessment of Risk of Colorectal Tumors in Canada (ARCTIC) cohort

- Each gene was analyzed separately
  - Multivariate phenotype: methylation values for CpG sites contained in the gene and in the promoter region
  - Covariate: cigarette smoking (binary)
Comparison of univariate approach and PCEV

AHRR, F2RL3 and GPR15 have previously been identified by Bretling et al. (AJHG, 2011)
Variable importance

- We can rank the contribution of each phenotype to the association using *variable importance*:

\[
VIMP := \text{corr}(w^TY, Y_j)
\]
Variable importance and univariate p-value

The multivariate association of F2RL3 seems to be driven mainly by one CpG site.
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- Thomas Hudson

Thank you