

Gene-set Analysis For Gene-Gene Interactions Using Gene-Trait Similarity Regression

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Introduction

Gene-set analysis has drawn great attention in recent genome-wide and sequence-based association studies. While most gene-set methods have concentrated on detecting genetic main effects, here we focus on methods for studying gene-gene (GxG) interactions. The gene-set GxG method we present focuses on quantitative traits and uses pairwise genetic similarity as a tool to aggregate marker information.

Objective

- Develop a framework for incorporating gene-gene interaction effects in similarity-based methods.
- Propose a series of tests to suit different purposes
 - test for detecting GxG interactions
 - test for detecting marginal main effects for one gene adjust by the other gene
 - joint test for detecting the overall association induced either by genetic main effects or by GxG interactions.

Model

Similarity Model:

$$E(Z_{ij}|X, G) = b_1 S_{ij}^1 + b_2 S_{ij}^2 + b_{12} S_{ij}^{12}$$

Z_{ij} : Trait similarity between i th and j th individual

S_{ij}^1 : Genetic similarity for Gene 1

S_{ij}^2 : Genetic similarity for Gene 2

S_{ij}^{12} : Interaction between Gene 1 and Gene 2

Variance Component Model:

$$Y_i = X_i \gamma + G_i^1 + G_i^2 + G_i^{12} + e_i$$

Y_i : Trait value for i th individual

G_i^l : genotype for i th individual on gene l

$$G_i^j \sim N(0, \tau_l S^l)$$

Connection: $b_l = \tau_l$

Score Test

$$\text{Interaction test: } T_{G \times G} = Y^T P_{12} S_{12} P_{12} Y$$

$$\text{One Gene test: } T_G = Y^T P_j S_j P_j Y, j=1 \text{ or } 2$$

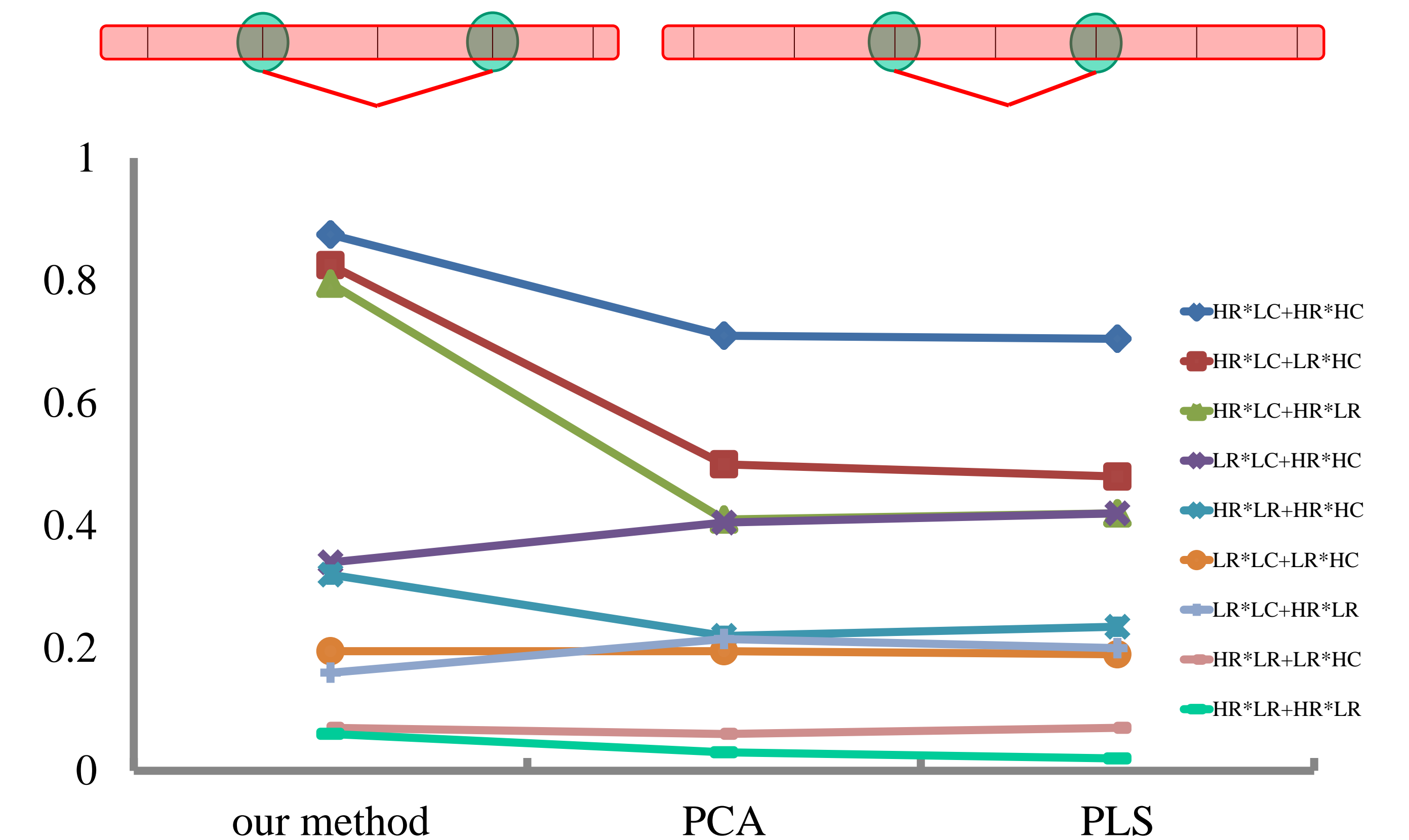
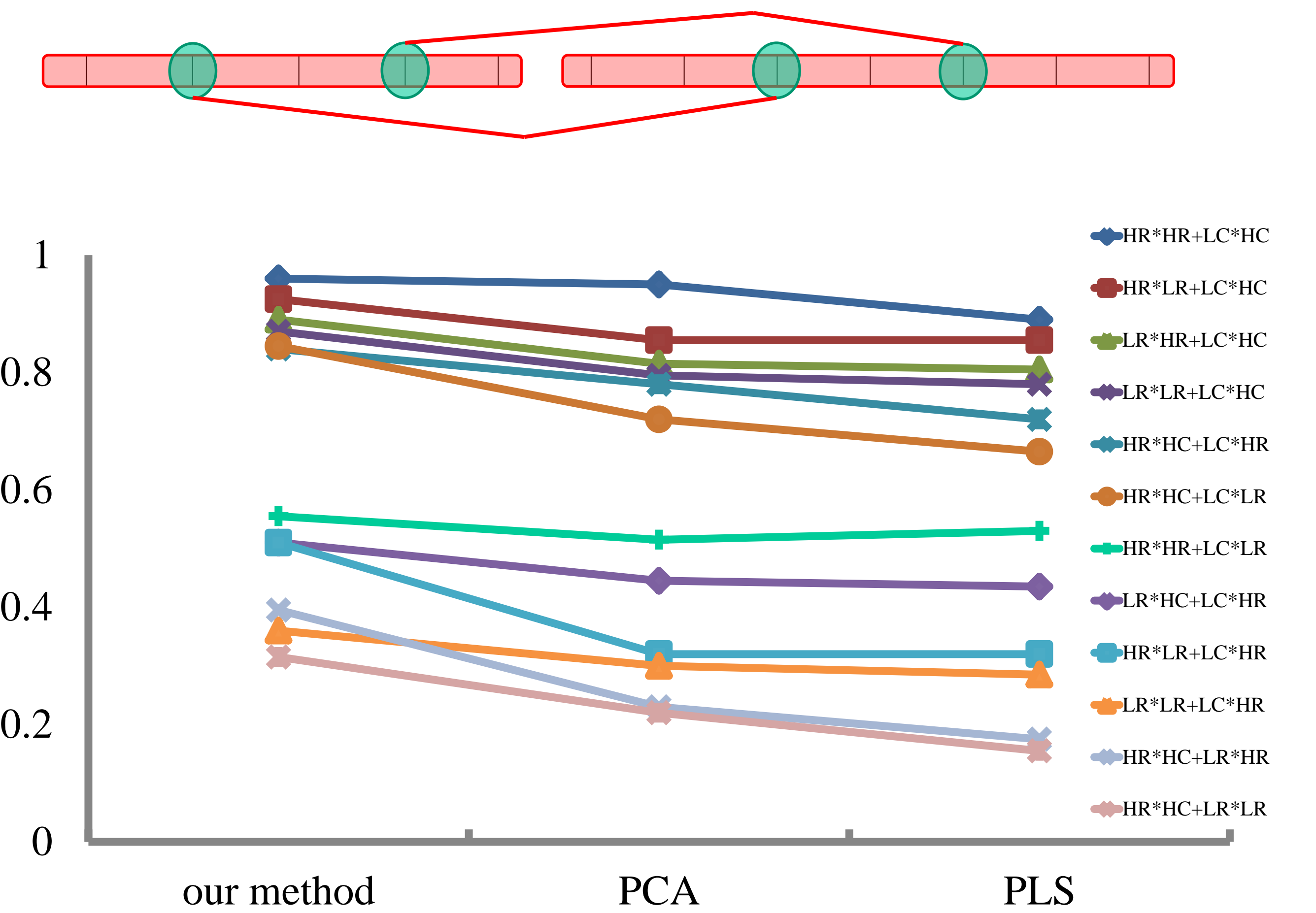
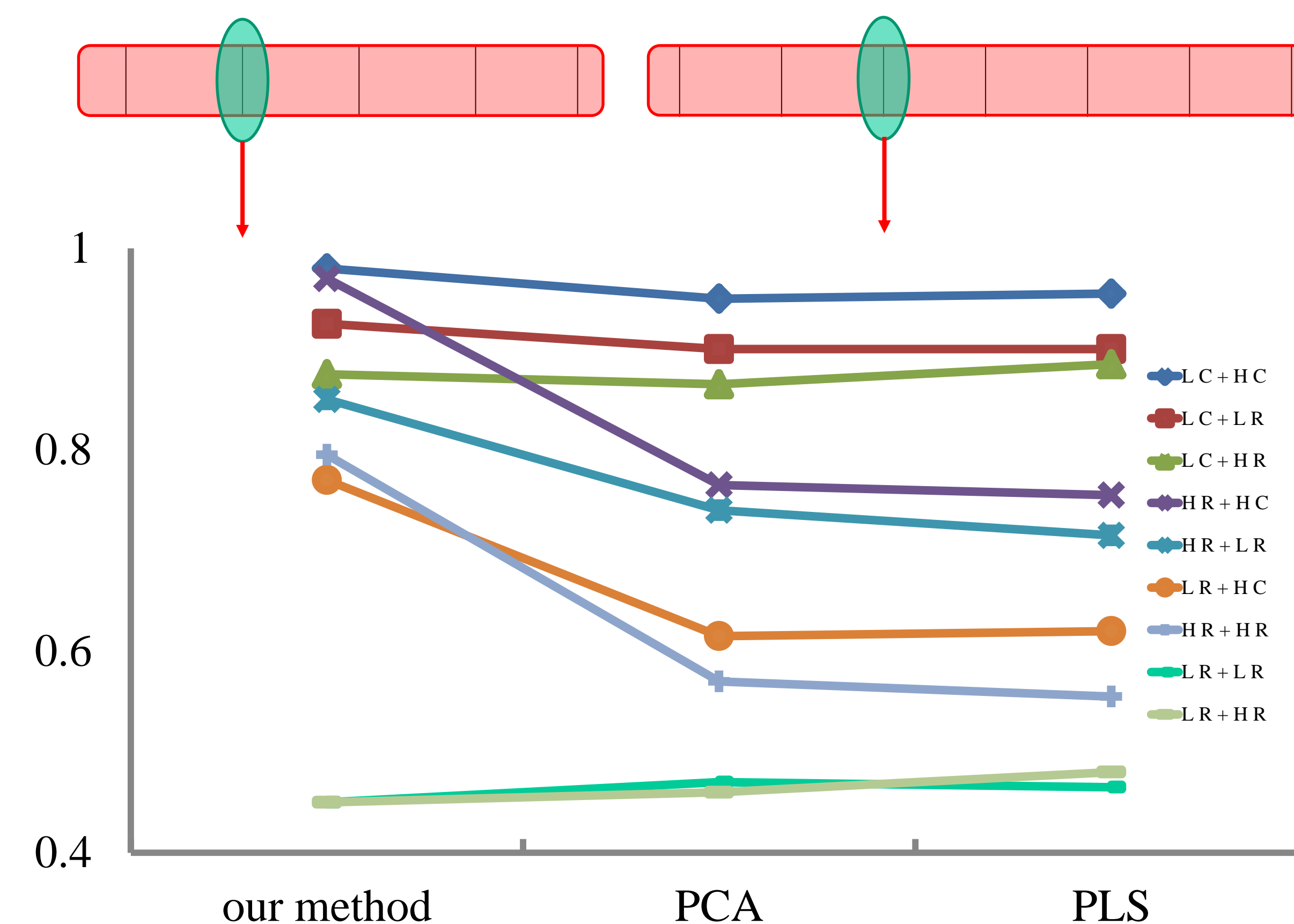
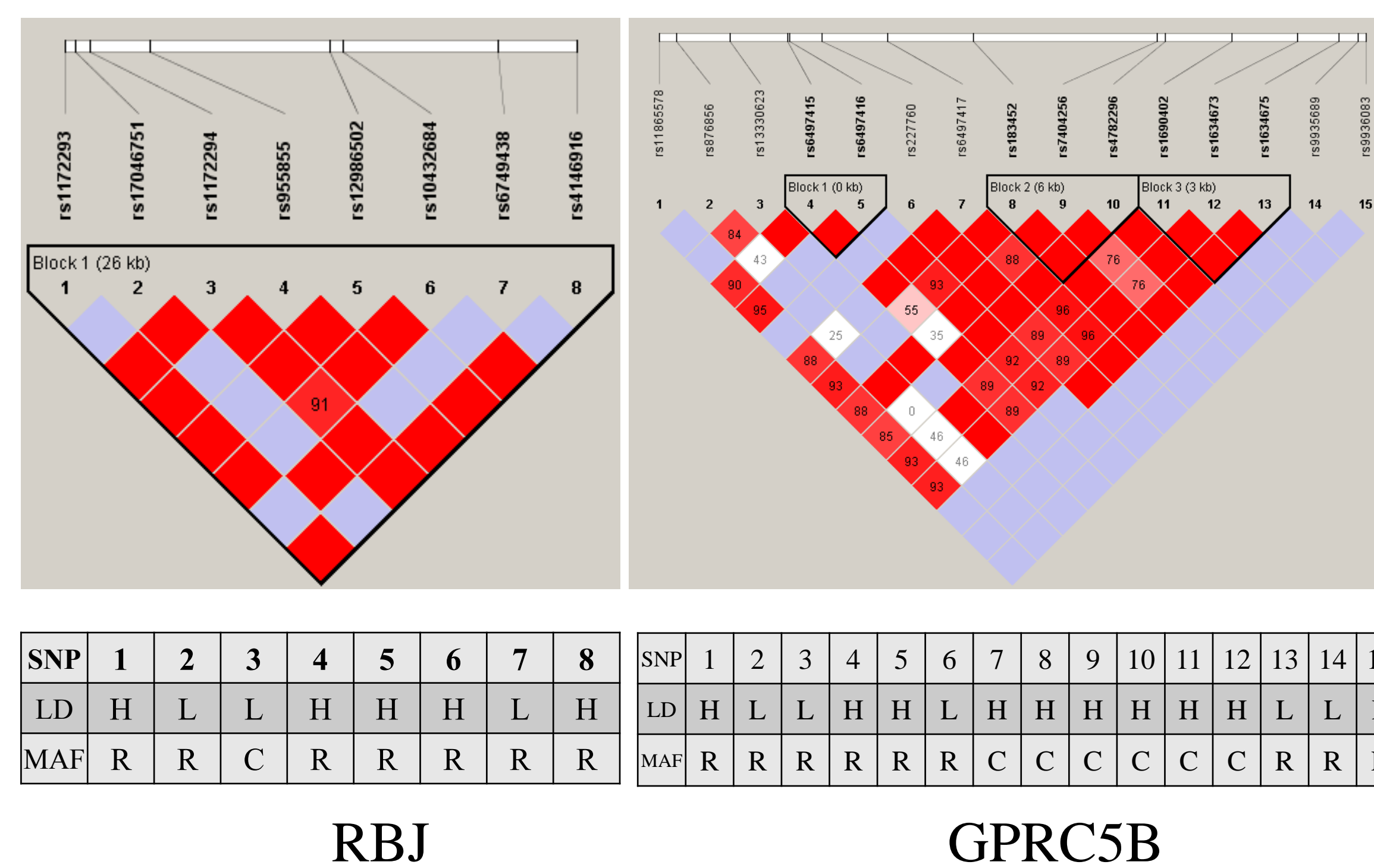
$$\text{Joint Test: } T_{\text{joint}} = Y^T P_0 S_0 P_0 Y$$

Where P is the projection matrix under different null hypothesis.

These test statistics follow a weighted χ^2 distribution.

Simulation

- Based on 2 Candidate genes for BMI
- Consider 2 factors: LD and MAF
- Compare with PCA and PLS



Summary

- On average, our method is better than PCA and PLS.
 - the bigger the MAF, the larger power
 - the higher LD, the larger the power
- When the casual SNP is in Low LD, and the MAF is quite small, our method does not perform as good as the other two methods test for detecting GxG interactions
- Further Study
 - Apply the method to real data
 - Extent the method to Genome wide research