Detecting Associations Between Rare Genetic Variants and Quantitative Traits

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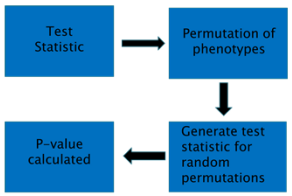
1: Introduction

- A single nucleotide polymorphism(SNP) represents a difference in a single DNA nucleotide of an individual.
- In order to understand genetic diseases and complex traits, it is important to identify the genetic regions associated with these diseases and traits.
- Here we present a way to locate possible genetic regions associated with individuals experiencing chemotherapy-induced peripheral neuropathy.

2:Method Design

- Look at the covariance between the genotypes of individuals at a SNP, and a vector containing information on each individual's phenotype, or trait value.
- We summed the covariance over 50 SNPs to calculate the p-value of a window of 50 SNPs.
- Correlations between the window and the trait associated with the disease can be made in comparing p-values and the predetermined significance levels.



- Calculation of P-value:
- Initially we created a test statistic which was:

$$V = \Sigma_{j \in A} D_j^2 \text{ or } V = \Sigma_{j \in A} |D_j|$$

where: $D_j = \text{cov}(X_j, Y)$

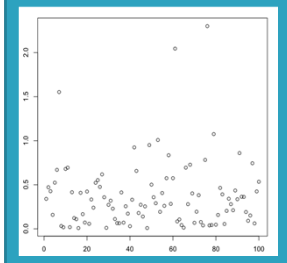
X_j is the genetic location
& Y is the collection of individuals

- We generated 1000 random test statistics.
- We decided how likely our test statistic is to be random.
- P-value is the probability over all possible samples, that the test statistic would be that value or more extreme than that value.

3: Simulations

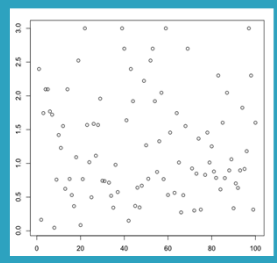
- Simulated 3 different sets of genotypes and corresponding phenotypes:
  - A genotype that had no effect on the individual's phenotype. (Null association)
  - A genotype that increases the individual's phenotype. (Risk association)
  - A genotype that at certain locations increases the individual's phenotype and at other locations decreases that phenotype. (Both association)

Figure 1. Null Association



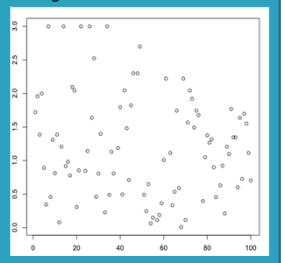
Graph of all the p-values from Null Association Genotypes

Figure 2. Risk Association



Graph of all the p-values from Risk Association Genotypes

Figure 3. Both Association



Graph of all the p-values from Both Association Genotypes

Method Validation

- Compared our methods to a test already being used:
  - SKAT:
    - Test for association between a set of rare (and common) variants and continuous/dichotomous phenotypes using kernel machine methods.[1]
  - A taller graph represents an accurate method.
    - Our method performed similarly to SKAT.

Method Validation

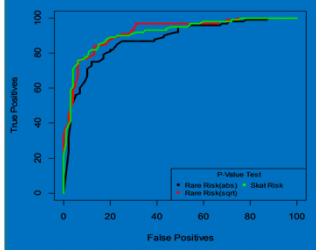


Figure 4A. P-Value Comparison of Our P-values(Risk Association Abs & Risk Association Sqr) vs. SKAT P-values(Risk Association)

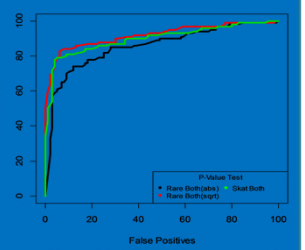


Figure4B. P-Value Comparison of Our P-values(Both Association Abs & Both Association Sqr) vs. SKAT P-values(Both Assocation)

4: Data Analysis

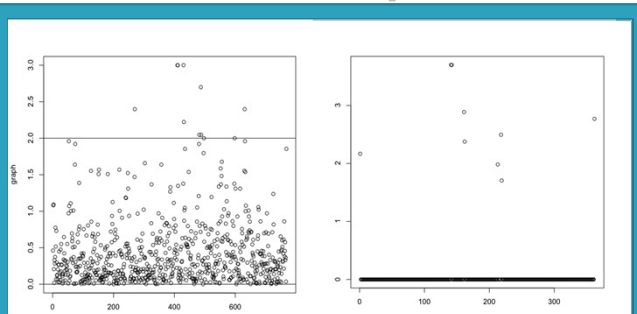


Figure 5. Graph of all p-values from Chromosome 1 with 1,000 permutations.

Figure 6. Graph of significant p-values from Chromosome 1 with 10,000 permutations.

To illustrate the use of our method on real data, we analyzed individuals with chemotherapy-induced peripheral neuropathy.

5: Conclusion

- We developed a method that accurately finds regions that may be associated with diseases and complex traits.
- We found 80 locations that are nominally significant at the 0.05 level. Further testing is needed to determine significance at the genome-wide level.
- We have developed a method that will work well when a particular region contains single nucleotide polymorphisms that put the person at risk, in addition to polymorphisms that protect them from a certain quantitative phenotype.

Citations

[1].Michael C. Wu, Seunggeun Lee, Tianxi Cai, Yun Li, Michael Boehnke, Xihong Lin, Rare-Variant Association Testing for Sequencing Data with the Sequence Kernel Association Test, The American Journal of Human Genetics, Volume 89, Issue 1, 15 July 2011,

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