Genetics 210
Problem Set 3
Due: May 17, 2012 to gene210.stanford@gmail.com

Part A:
For the following questions, please refer to the assigned reading for Tim Assimes's lecture (April 12th) titled "CVD2011a" (PMID: 21378988)
Note: Please limit responses to 2-3 sentences.

1) According to the article, do GWAS-identified variants explain a large proportion of coronary artery disease (CAD) risk? What do they state is the typical range for a variant associated with CAD?

No they do not; taken together, the known variants explain a small proportion of the predicted genetic risk. The known CAD common variants have odds ratios of 1.1-1.3

2) What additional steps were required in order to perform the GWAS on the South Asian cohort? Why was this not necessary for the European cohort?

PCA was necessary in order to adjust for population substructure in the regression analysis for the East Asians. This was not necessary due to the lack of significant population substructure within Europeans.

3) Figure 3 lists the novel SNPs that were discovered and validated by replication. Which of these SNPs had the highest p-value (look at the "Discovery+Replication" p-value, not the "Discovery" value)? To what phenotype has the risk allele of this SNP been previously linked?

rs1412444 in LIPA (lyosomal acid lipase gene). The risk allele of this SNP has been strongly linked with increased expression level of LIPA mRNA in circulating monocytes.

4) The authors initially performed the analysis by separating the cohort into European and South Asian groups. In the end, do the authors find any susceptibility variants with material differences in effect size or allele frequency between South Asians and Europeans? Why is that?

No they do not, however this may be limited by the fact that current SNP chips are biased towards Europeans and don't capture many important South Asian variants.

Part B:

Previous lectures have touched on some of the issues surrounding GWA studies (e.g. Tim Assimes on cardiovascular disease). One such issue is the question of missing heritability of complex diseases. For example, recent research into the genetics of height estimates a heritability of roughly 80%, but so far GWAS have only been able to explain 5% of the phenotypic variation.

1) List 3 possible explanations for the missing heritability of complex disease from traditional GWA studies. Assume the studies use conventional DNA chips containing tag SNPs for common polymorphisms. Assume that a standard gene association test was used for analysis, such as the one used for the class gene association experiment. Similar to height, assume that the GWA study can only explain a small proportion of the heritability of the complex trait. (Please answer the following in no more than 4-5 sentences.)

Answers will vary

2) For each of the three explanations from part 2, propose an experiment or method of analysis that could go beyond the results obtained from a standard GWA study. For each case, explain how your approach could find additional heritability that was previously missed by the standard GWAS approach. (Please answer the following in no more than 4-5 sentences per experiment.)

Answers will vary