Genetic Inference

ASHG: Epistasis and the Missing Heritability

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As if no time has passed at all since the sunny shores and lost laptops of the American Society of Genetics 2009 meeting, ASHG2010 has rolled around, this time in Washington DC. As always, I'm going to be trying to write a few thoughts on the conference every day, though this year it may be split between here and Genomes Unzipped.

I'll also be semi-live-tweeting (wifi coverage is patchy), so you can get up-to-the-minute details of all the talks on my twitter feed (@lukejostins), or from other tweeps via the hashtag #ASHG2010.

EPISTASIS AND MISSING HERITABILITY

As Daniel observed on Twitter, I very nearly had a heart attack when Eric Lander, in his Distinguished Speaker's talk about the Human Genome Project, said that the "missing heritability" is probably all down to Epistasis (i.e. interactions between variants). His argument was that GWAS had low power to detect gene-gene interactions, and therefore there could be lots hanging around that count account for the unexplained variance.

This is a fallacy, and a big one. The power to detect interaction between any two variants is indeed very low, but the power to assess the effect of interactions as a class is very high; instead of inferring lots of interactions, you can merely infer a single parameter, the expected degree of interaction. Eric's statement is like saying that because you cannot see a tree from a mile away, you won't know that there is a forest there.

People have indeed set out to infer the degree of gene-gene interaction in complex disease. In a PLoS Genetics paper a few years back David Clayton demonstrated that there is actually very high power to detect deviation from simple multiplicity. He showed that there is evidence for some interactions in Type I Diabetes, but that these effects are almost entirely driven by the very strong HLA signal. If we look at normal variants, there is very little interaction at all.

We can go one better. David Clayton's paper calculated the predictive power (in the form of the AUC) of a logistic regression model with and without interaction terms for type 1 diabetes. Naomi Wray recently published a paper showing how you can convert between the AUC and the proportion of heritability explained, and, even better, produced an online calculator for doing exactly that.

Plugging David AUCs into Naomi's calculator tells us that the non-HLA variants explain 10% of the heritability of Type I Diabetes. If we include interactions, this increases to 11% of the heritability. So, while epistasis exists, and increases the proportion of heritability explained, the increase is nowhere near enough to account for the