ALLERGY, GENETICS

TRUE, FALSE, TRUE, FALSE, TRUE, FALSE, FALSE

29.01.2010

While <u>some of my earlier co-workers</u> continue to praise the achievements of GWAs, <u>some</u> <u>other earlier co-authors</u> now show that the common variants thrown on the current GWA chips are leading to false associations (politely called "synthetic" associations)

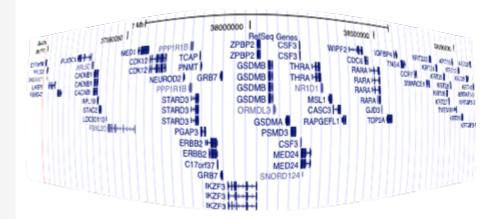
We propose as an alternative explanation that variants much less common than the associated one may create "synthetic associationsâ€☐ by occurring, stochastically, more often in association with one of the alleles at the common site versus the other allele. Although synthetic associations are an obvious theoretical possibility, they have never been systematically explored as a possible explanation for GWAS findings. Here, we use simple computer simulations to show the conditions under which such synthetic associations will arise and how they may be recognized. We show that they are not only possible, but inevitable... by occurring, stochastically, more often in association with one of the alleles at the common site versus the other allele. Although synthetic associations are an obvious theoretical possibility, they have never been systematically explored as a possible explanation for GWAS findings. Here, we use simple computer simulations to show the conditions under which such synthetic associations will arise and how they may be recognized. We show that they are not only possible, but inevitable...

The proof comes with a sickle cell anemia study

For sickle cell anemia, a total of 179 SNPs reached genome-wide significance (p<5 \tilde{A} —10 \hat{a} '8), encompassing an ~2.5-Mb region on chromosome 11p15.4 ... The region contains dozens of genes and dozens of visually discernable LD blocks in HapMap YRI population. The top association signal (rs7120391, p = 1.1 \tilde{A} —10 \hat{a} '136) is 9 kb from OR51V1, which is very near the causal gene, HBB ... Clearly, highly significant association signals can travel across multiple LD blocks to distant genomic regions.

I share the view that these modest associations emerging from genome-wide associations maybe more important as anticipated (for being pointers to rare variants of much larger effect) while it is currently impossible to discern true and false associations.

Regarding <u>my problem mit ORMDL3</u> 2.5 Mb seems to be a huge distance even spanning more genes than I anticipated – so IKZF3 may be still in the race but also many other genes there. Welcome back in the linkage era!



Back to <u>rare & common</u> variants: a new <u>PNAS paper</u> remains sceptical

A model is investigated in which mutations that affect a complex trait [...] also affect fitness because the trait is a component of fitness or because the mutations have pleiotropic effects on fitness. The model predicts that the genetic variance, and hence the heritability, in the trait is contributed by mutations at low frequency in the population, unless the mean strength of selection of mutations that affect the trait is very small or weakly selected mutations tend to contribute disproportionately to the trait compared with strongly selected mutations. Furthermore, it is shown that each rare mutation tends to contribute more to the variance than each common mutation. These results may explain why most genome-wide association studies have failed to find associations that explain much of the variance. It is also shown that most of the variance in fitness contributed by new nonsynonymous mutations is caused by mutations at very low frequency in the population. This implies that most low-frequency SNPs, which are observed in current resequencing studies of, for example, 100 chromosomes, probably have little impact on the variance in fitness or traits.[...]

let's see!

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