This Month in Genetics

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Pharmacogenetic Help for Outliers

In the United States alone, tens of millions of prescriptions for the anticoagulant warfarin are written each year, and it is among the top ten drugs in terms of the number of associated serious adverse events. One of the problems with warfarin is that the appropriate dose can vary by a factor of ten among patients, so achieving the optimal dose for an individual takes time and careful monitoring. Genetic variation influences the variability in dosage requirements, and pharmacogenetic information is even included on the warfarin product label, but large trials demonstrating that a pharmacogenetic approach predicts warfarin dosage requirements better than other algorithms has been lacking. The International Warfarin Pharmacogenetics Consortium used a large retrospective analysis that included more than 5000 patients on warfarin therapy to develop a pharmacogenetic algorithm that uses genotype information at *CYP2C9* and *VKORC1*. For the 54% of people that needed an intermediate warfarin dose, the pharmacogenetic algorithm did no better than a fixed-dose approach at dose prediction. This makes sense given that the fixed dose was derived from the appropriate therapeutic dose in an average group of patients. Where the pharmacogenetic algorithm did excel was in the tails of the dose distribution; it significantly improved dose prediction in the groups of patients requiring a high or low dose of warfarin, compared to a clinical algorithm that didn't incorporate genetic information. The next step in this story will be to determine in a large prospective study whether use of pharmacogenetic information improves clinical end points, including the number of adverse events associated with warfarin therapy.

The International Warfarin Pharmacogenetics Consortium (2009). N. Engl. J. Med. 360, 753–764. 10.1056/NEJMoa0809329.

Major Role for Copy Number Variation in Governing Variability in Gene Expression

It makes sense that the more copies of a genetic sequence you have, the more it might be expressed, but this hypothesis has not been thoroughly tested on a global scale. Two recent papers in *Nature Genetics* explored this idea in mice and found that there is some truth to this idea, but that the relationship of copy number variants (CNVs) to gene expression is more complicated than this. Both papers use multiple mouse strains in attempts to generate comprehensive CNV maps. They then try to correlate the CNVs with tissue-specific gene expression data. In these studies, CNVs contribute to a large proportion of the strain-dependent variation in gene expression, but this doesn't just include the genes that are encompassed by the CNVs, it can include expression of genes that are up to 450 kb away from the CNV breakpoints. In fact, Cahan et al. found that the vast majority of quantitative trait loci for gene expression differences mapped outside of the corresponding CNVs. Henrichsen et al. also found that genes in CNVs tend to be expressed in fewer tissues and to a lower extent than genes that do not vary in terms of copy number. CNVs thus seem to make a substantial contribution to variation in gene expression in mice, both in expected and in unexpected ways.

Cahan et al. (2009). Nat. Genet. Published online March 8, 2009. 10.1038/ng.350; Henrichsen et al. (2009). Nat. Genet. Published online March 8, 2009. 10.1038/ng.345.

Rare Alleles Protect against Diabetes

Much of the research into genetic susceptibilities for complex traits has been based on the idea that common variation will govern susceptibility to common disease. Once you find an association, though, linkage disequilibrium can make it difficult to tease out exactly what the causal variation is. An alternative approach uses the idea that the effects of many rare variants together could also underlie common disease. The problem with finding these rare variants is that it generally takes large resequencing efforts that have only recently become feasible. Nejentsev et al. worked at the nexus of these approaches to find genes that play a role in Type 1 Diabetes (T1D). Starting mostly with candidate genes that contain common T1D-associated polymorphisms, they resequenced to look for rare variation contributing to T1D. They found four rare variants, all in *IFIH1*, that independently lower risk of T1D. Each of these SNPs either truncates the protein, alters a conserved splice site, or changes a conserved amino acid, suggesting that reducing the function of the IFIH1 protein is protective against T1D. Although a common SNP in *IFIH1* had already been associated with T1D, it

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resides in a block of linkage disequilibrium that encompasses three other genes, making it unclear which was relevant. While highlighting *IFIH1* as a gene involved in T1D, this research also illustrates that studies of rare variation can be meaningful for common diseases.

Nejentsev et al. (2009). Science. Published online March 5, 2009. 10.1126/science.1167728.

Mouse Model of a Couch Potato

Variation in *FTO* confers risk of obesity and it appears to do this through overeating—people with the obesity risk allele in *FTO* tend to eat more and to prefer higher fat foods than do people without the risk allele. How a protein that demethylates nucleic acids influences how much we want to eat is something we don't understand. To get a better handle on the physiological role of this protein, Fischer et al. generated Fto-deficient mice. As early as 2 days after birth, the $Fto^{-/-}$ mice start to lag behind their counterparts in terms of body weight, and they go on to have shorter body length and less fat mass than do their wild-type siblings. In contrast to human studies that suggest that FTO influences food intake without influencing energy expenditure, $Fto^{-/-}$ mice seem to be lean because they burn more energy, not because they eat less. You would think this means that the mice are overactive, but, in fact, this extra energy expenditure is seen despite the fact that $Fto^{-/-}$ mice are less active than their wild-type sibs. Eating fatty food while losing weight without having to exercise? Sounds like a drug company's fantasy to me.

Fischer et al. (2009). Nature. Published online February 22, 2009. 10.1038/nature07848.

Role for Neutrophils in Cystic Fibrosis-Associated Lung Disease

Clearly, mutations in *CFTR* are necessary and sufficient to cause cystic fibrosis (CF). But why do some people have very severe lung disease, whereas others are more mildly affected? Even if one controls for *CFTR* mutation, there is significant heritable variation in the severity of lung disease. To pin down what these modifiers might be, Gu et al. did a case-control association study with a sample in which everybody had CF because of a homozygous ΔF508 *CFTR* genotype. Their "cases" had severe lung disease and were compared to "controls" with milder lung disease. Their results place neutrophil function central to the variability in lung disease in CF. The gene they pulled out of their study, *IFRD1*, encodes a transcriptional coregulator that is upregulated during terminal differentiation of neutrophils. In people without CF, polymorphisms in this gene are associated with variation in effector function of neutrophils. And in mice, neutrophils deficient for IFRD1 are significantly impaired in effector function, and—relevant to the association with CF lung disease—these mice clear *Pseudomonas aeruginosa* more slowly than do their wild-type counterparts and in the context of less inflammation. Although significant improvements in management of CF have been achieved over the past several years, declines in pulmonary function remain a big challenge and the main cause of death for CF patients. The association of CF lung disease with *IFRD1* suggests that neutrophil function might be a potential therapeutic target for CF.

Gu et al. (2009). Nature. Published online February 25, 2009. 10.1038/nature17811.