This Month in Genetics

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It Goes Straight To My Head

Over the past several years, considerable success for the treatment of lysosomal-storage disorders has been gained through the use of enzyme-replacement therapy (ERT). One of the major advances that led to the first available therapy, for Gaucher disease, was efficient targeting of recombinant glucocerebrosidase to macrophages via the mannose receptor. This is achieved by the removal from the enzyme of terminal sugars in order to expose mannosyl residues. Most of the currently used recombinant lysosomal enzymes have mannosyl and mannose-6-phosphate residues that use the corresponding receptors for uptake from the plasma. A key remaining issue with ERT for lysosomal-storage disorders is the fact that the therapeutic enzyme cannot cross the blood-brain barrier to ameliorate the central nervous system effects associated with some of these disorders. In the hope that it might increase delivery across the blood-brain barrier, Grubb et al. attempted to increase the bioavailability of recombinant enzyme in a mouse model of mucopolysaccharidosis type VII (MPS VII) through avoidance of uptake by the mannose or mannose-6-phosphate receptors. They modified the relevant enzyme, β-glucoronidase (GUS), by chemical inactivation of terminal sugars and showed that this increased the plasma half-life in treated mice from 11.7 min to 18.5 hr. In several tissues, higher levels of enzyme were achieved in mice given the modified GUS compared to the unmodified enzyme. Most notable was the brain, in which enzyme levels equivalent to almost 8% of the wild-type level were achieved. In hippocampal neurons of MPS VII mice treated with modified GUS, lysosomal accumulations were virtually eliminated, whereas the accumulations were unaffected by treatments with the unmodified enzyme. It is as yet unclear how the modified GUS is getting across the blood-brain barrier, but these results suggest that improvement of the neurological manifestations of lysosomal-storage disorders may be within our grasp.

J.H. Grubb et al. PNAS 105, 2616-2621, 10.1073/pnas.0712147105.

Shades Of White

Everybody seems to be a geneticist nowadays. Any phenotype that has a whiff of heritability is a target for a genetic association study. But experience has shown that this rush to find genetic variation that contributes to complex traits has resulted in many false-positive associations. One source of these false-positive results is population stratification, or the presence of allele frequency differences between two groups that is based on differences in population history. To limit false associations due to population stratification, researchers often require that all individuals participating in their study self-identify themselves as belonging to a particular group, such as "white" or "African American," members of which would presumably share a similar ancestral background. Research over the past couple of years has shown that distinguishing samples in this fashion does not fully avoid population stratification and that, even within white European samples, population structure exists. Ancestry informative markers (AIMs) are genetic markers that are selected to find population structure so that it can be properly controlled. Sets of AIMs have previously been proposed for use in European populations, but they have tended to be very large sets of markers that would be appropriate for use in whole-genome studies, rather than replication studies that require limited genotyping. Tian et al. and Price et al. have each used large collections of European American samples to demonstrate that the population structure observed in Europe is also found in this group. As previously noted for European samples, there is a north-south cline of ancestry in Europe and a less distinct east-west cline, and the Ashkenazi Jewish population separates out as a distinct group, regardless of geographic location. Each group proposes small sets of AIMs that lack the high genotyping burden of previously proposed marker sets but can still distinguish European population substructure and provide appropriate control to avoid spurious genetic associations. An accompanying Perspective article by the two research groups suggests which AIM sets might be appropriate in different situations.

A.L. Price et al. (2008). PLoS Genet. 4, e236, 10.1371/journal.pgen.0030236; C. Tian et al. (2008). PLoS Genetics 4, e4, 10.1371/journal.pgen.0040004.

The Future Is Now

Most of us have heard about or even spouted off on the promise of pharmacogenetics and pharmacogenics and

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the idea that, in the future, doctors will genotype individuals for a series of markers that can predict drug efficacy as well as adverse events. Over the past few months, this promise is becoming reality. This summer, the anticoagulant warfarin became the first widely prescribed drug to include genetic testing in its label information because of the wealth of data that variation in *CYP2C9* and in *VKORC1* influences the response to warfarin. Now Mallal et al. have provided crucial data that support the use of prospective genetic screening prior to prescription of the widely used antiretroviral drug abacavir. Approximately 5% of people who receive abacavir have a hypersensitivity reaction to the drug, and this can even be life-threatening. The HLA-B*5701 allele has been reported in several studies to be highly associated with this reaction. As part of the PREDICT-1 study, Mallal et al. did a double-blind, prospective, randomized study to determine the effectiveness of prospective genotyping for HLA-B*5701 in reducing hypersensitivity reactions to abacavir. One difficulty with studies of the hypersensitivity reaction is that it tends to be overdiagnosed—even individuals not taking abacavir have been diagnosed with an abacavir-hypersensitivity reaction in some studies. To address this issue, the authors used a skin-patch test to immunologically confirm hypersensitivity reactions in their sample. The authors found that screening for HLA-B*5701 and withholding abacavir from this subset of the sample completely eliminated immunologically confirmed hypersensitivity reactions. Although nearly 39% of HLA-B*5701 carriers in the nonscreened group tolerated abacavir for the observation period, prescreening for this allele identifies a group of individuals at the greatest risk for a reaction to abacavir. Ordering this pharmacogenetic test prior to prescription of abacavir may be standard of care in the near future.

S. Mallal et al. (2008). NEJM 358, 568–579.

About Face

In Treacher Collins syndrome (TCS), haploinsufficiency for *TCOF1*, which encodes Treacle, causes deficiencies in migrating neural crest cells that ultimately cause craniofacial defects. Because *TCOF1* haploinsufficiency causes insufficient ribosome biogenesis, previous work had proposed that this ribosome deficiency directly caused neuroepithelial apoptosis and the resulting lack of appropriate neural crest cell production. Jones et al. attempted to understand the pathogenic process of TCS more clearly by using a mouse model for the disease and found that p53, rather than ribosome, deficiencies are the key to TCS. Microarrays of embryonic mice revealed several p53-responsive genes that were upregulated in $Tcof1^{+/-}$ embryos, compared to wild-type, a result that led the authors to discover higher p53 protein levels in the $Tcof1^{+/-}$ embryos. Working with the hypothesis that $Tcof1^{+/-}$ causes p53 activation of downstream targets, they treated pregnant mice with the p53 inhibitor pifithrin-α and found that it brought neuroepithelial apoptosis in $Tcof1^{+/-}$ embryos to levels more closely resembling those of wild-type embryos. Provided it was given long enough during the pregnancy, this treatment also rescued the craniofacial defects in $Tcof1^{+/-}$ pups. Genetic reductions in p53 had similar effects. Although the TCS-like phenotype was rescued by manipulations of p53, the production of mature ribosomes was unaffected, excluding this $Tcof1^{+/-}$-associated feature as directly causing the craniofacial anomalies associated with TCS and incriminating p53 and its targets in TCS pathogenesis. Although p53 manipulation in mice rescued the obvious defects in $Tcof1^{+/-}$ mice, these manipulations were performed very early in embryogenesis, making it difficult to translate these findings directly into treatment of humans. Now that p53 and its targets are the culprits in this disease, this work does, however, provide us with many new avenues of therapy to explore.

N.C. Jones et al. (2008) Nat. Med. 14, 125–133.

Recombination See-Saw

The recombination rate varies across chromosomes, among individuals, and between the sexes. This process must be tightly regulated because errors can have severe consequences, including chromosomal rearrangements and nondisjunction. But what factors are involved? Kong et al. approached this question through a genome-wide association study using more than 3000 individuals for whom they had recombination-rate estimates. In males, three SNPs in the same area of chromosome 4p16.3 were the only ones that achieved genome-wide significance, and the same three SNPs were associated with recombination rates in females. However, the associations with these SNPs were in opposite directions in the two sexes; the haplotype associated with a decrease in the genome-wide recombination rate in males is associated with an increased recombination rate in females. Evolutionarily, this creates a see-saw effect whereby when the female recombination rate is up, the male recombination rate goes down and the overall average recombination rate in the population stays fairly similar. Two genes are found in the block of linkage disequilibrium represented by the associated haplotype. *RNF212*, a putative ortholog of a gene involved in recombination in *C. elegans*, is believed to be the relevant gene for the association, but functional studies have not yet been performed.

A. Kong et al. (2008) Science. Published online January 31, 2008. 10.1126/science.1152422.