This Month in Genetics

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Privacy Protection for GWAS Participants

Changes are afoot to the National Institutes of Health (NIH) policy on the availability of data from genome-wide association studies (GWAS). Beginning this year, the NIH had instituted a policy that summary data from all NIH-funded GWAS be submitted to an open-access repository to facilitate data sharing. As of the end of August, this policy was put on hold, and all previously submitted aggregate results from GWAS studies were removed from the NIH's open-access databases. This reversal is due to the publication of a paper by Homer et al. reporting a method of determining whether an individual's genomic data are part of a larger set of SNP microarray data. The fear is that someone could glean personal health information, such as a person's disease status, with this technique if one could place a particular person in the "case" or "control" group of samples in a GWAS. Lest any research participants be overly concerned, let it be noted that one would need to get an individual's high-density genotype data from another source in order to use this method; such a thing is unlikely to happen outside the research setting at this point. Nonetheless, for the time being, aggregate GWAS data will only be available in controlled-access databases so that the privacy of research participants is ensured. Undoubtedly, the NIH's policy toward GWAS data will evolve as the implications of this technique are examined.

Homer et al. (2008). PLoS Genetics 4, e1000167. 10.1371/journal.pgen.1000167.

Preventing Statin-Induced Myopathy

Statins are widely prescribed drugs that reduce low-density lipoprotein (LDL) cholesterol levels. Although statins lower the risk of a cardiovascular event, they are sometimes, albeit rarely, associated with myopathy. During the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial, which aims to identify the most efficacious dose of simvastatin, more than 100 of the 12,000 participants experienced myopathy brought on by the drug. The vast majority of these cases occurred in people taking the higher of the two drug dosages in the trial. The SEARCH collaborative group used a genome-wide association study to identify genetic factors associated with this adverse event and found one SNP that explained more than 60% of the cases of myopathy in their study. This SNP resides in *SLCO1B1*, which encodes the transporter that mediates uptake of the statins into the liver. In fact, it appears that the myopathy risk allele in *SLCO1B1*, which is quite common, may be associated with higher statin blood concentrations that, in turn, cause myopathy. Although further research is needed to cement the role of *SLC01B1* in statin-induced myopathy, reduced cardiovascular risks may need to be balanced with the risk of myopathy when the statin dosage for a particular patient is being determined. *SLCO1B1* genotype may eventually ensure that we get the maximum benefit from these drugs by allowing us to restrict the prescription of high statin doses to people at the lowest risk of an adverse event.

The SEARCH Collaborative Group (2008). New Engl. J. Med. 359, 789–799. 10.1056/NEJMoa0801936.

A Molecular Link between Obesity and Fertility

We tend to think of obesity as a simple energy problem whereby too much fuel is taken in and not enough is expended. But on a molecular level, obesity can also be thought of as a signaling defect that has additional consequences, including reduced fertility. The adipocyte-derived hormone leptin is a key signal that maintains the energy balance. If you wipe out leptin signaling, you get obese, infertile mice. Leptin regulates the STAT3 pathway, but clearly, there are other leptin-mediated pathways because mice that lack leptin-induced STAT3 signaling, although obese, are also fertile. Altarejos et al. report that the Creb1-Crtc1 pathway is central to both the energy balance and fertility-associated effects of leptin signaling. Crtc1 acts downstream of leptin and enhances Creb1's induction of genes involved in appetite and in fertility. Mice that lack *Crtc1* are obese, hyperphagic and totally infertile. Many obese humans are leptin resistant; they don't appropriately reduce their appetite and increase their energy expenditure in response to increased energy stores. Altarejos et al. propose a hunt for genetic variation in *CRTC1* that may contribute to the propensity for obesity in humans. This pathway also could form the basis for attempts at pharmacologic intervention to moderate obesity and its associated effects on fertility.

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Altarejos et al. (2008). Nature Medicine. Published online August 31, 2008. doi:10.1038/nm.1866.

How Do I Love Thee?

I'd like to think my husband married me for my brain or my keen sense of wit, but did he instead stick around because he has a particular allele of the gene for the vasopressin receptor 1a (*AVPR1A*)? Pair bonding in voles is influenced by arginine vasopressin (AVP), and variation in the 5′ region of the gene for its receptor, V1aR, is known to affect social behavior and partner preference in voles. This gave Wallum et al. the idea to determine whether variation in human *AVPR1A* might influence social behavior. Data for their research comes from the Twin and Offspring Study in Sweden, which collected detailed measurements of marital relationships in twin pairs and their spouses. They found evidence that, in males only, variation in a repeat polymorphism in the 5′ flanking region of *AVPR1A* is associated with measurements of partner bonding and the likelihood of marital crisis. Although all couples in this study were required to be in long-term relationships, men homozygous for the 334 allele at this polymorphism were almost half as likely to be married as those lacking this allele. It doesn't seem very romantic to me to boil down love and bonding to a single gene, but Wallum et al. argue that *AVPR1A* alone may influence these social behaviors. In answer to the question, "How do I love thee?," perhaps we should be counting *AVPR1A* as one of the ways.

Wallum et al. (2008) Proc. Natl. Acad. Sci. 105, 14153–14156. 10.1073/pnas.0803081105.

Methylcytosine Double Flip

We geneticists know that Watson-Crick base-pairing is the key to faithful DNA replication, but it is less clear how the epigenetic marks on DNA are maintained with high fidelity. The maintenance DNA methyltransferase DNMT1 is the enzyme that does the job, but it is its binding partner UHRF1 that gives DNMT1 a high specificity for hemimethylated DNA. Three recent papers in *Nature* illustrate how UHRF1 gets its specificity. Each reports a high-resolution crystal structure for UHRF1 bound to DNA. It turns out that this protein is the first nonenzyme that uses a base-flipping mechanism in its interaction with DNA. The 5-methylcytosine in hemimethylated DNA flips out of the double helix and into a binding pocket of the SRA domain of UHRF1. The tight interaction with the flipped-out base explains the specificity of UHRF1 for hemimethylated DNA. This pocket binds unmethylated DNA nonspecifically, whereas full methylation of DNA perturbs the interaction. DNMT1 probably also flips a base out when it binds DNA, but steric hindrance prevents UHRF1 and DNMT1 from doing this trick at the same time. Arita et al. propose that UHRF1 first uses a base flip to identify hemimethylated DNA. It then recruits DNMT1, which subsequently flips a cytosine to facilitate the transfer of the epigenetic mark to the daughter DNA strand.

Avvakumov et al. (2008). Nature. Published online September 3, 2008. 10.1038/nature07273.

Arita et al. (2008). Nature. Published online September 3, 2008. 10.1038/nature07249.

Hashimoto et al. (2008). Nature. Published online September 3, 2008. 10.1038/07280.