This Month in Genetics

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LETM1 Identified as a Mitochondrial Calcium Transporter

I would expect that in response to the question "What are mitochondria?" most of us would blurt back, "The powerhouse of the cell." But beyond this obvious function, mitochondria are also very important as intracellular calcium repositories that participate in calcium signaling. The mitochondria can use this link to regulate the activity of their energy-generating enzymes. Mitochondria have been known for a while to possess tightly regulated calcium transporters, but these proteins have been characterized on a functional level only; their identities have been unknown. That is, until a genome-wide RNAi screen allowed Jiang et al. to identify *Letm1* as a mitochondrial Ca^{2+}/H^{+} antiporter. This transporter brings Ca^{2+} into the mitochondria in exchange for H^{+}, and experiments in liposomes indicate that this is a one-to-one exchange and that this process is electrogenic. Besides going beyond our simple definition of the function of mitochondria, the identification of *Letm1* as a mitochondrial calcium transporter is important for an additional reason: the human homolog, *LETM1,* is deleted in nearly all patients with Wolf-Hirschhorn syndrome. The pathogenesis of this subtelomeric deletion syndrome, which includes mental retardation, epilepsy, growth delay, and a characteristic facial appearance, has been unclear. Perhaps the identity of *LETM1* will lead to increased understanding of the etiology of this disorder.

Jiang et al. (2009). Science 326, *144–147. 10.1126/science.1175145.*

Should Everybody Have Access to GWAS Data?

Last year, Homer et al. published in PLoS Genetics a paper (PLoS Genet. *4*, e1000167) that led some researchers and policy makers to question the wisdom of making data from genome-wide association studies (GWASs) publicly available. The Homer et al. paper suggested that if you had a person's individual genotype data, you could determine whether their DNA was present in a mixed sample from which only marker allele frequencies were known. In terms of a GWAS, the fear is that somebody could take a person's genotype information and then figure out whether they were in the case or the control sample in a publicly available GWAS data set. Inferences about the person's disease status could then be made. As the GWAS came into vogue, the National Institutes of Health had a two-tiered access policy for GWAS data. In level 1, summary information and aggregate genotype data, including marker allele frequencies by case-control status, were made publicly available. In level 2, individual-level data on study participants were made available only to qualified researchers who submitted an application for access. In response to the Homer et al. paper, modifications to this policy were rapidly implemented, in which aggregate genotype data were removed from public access. In a recent issue of PLoS Genetics, three articles explore the ramifications of the work by Homer et al. In the first article, several researchers contribute their views on how policy changes and research should proceed from here. Their suggestions range from setting an internationally agreed upon code of conduct for scientists working with genome data to granting wide access to the genomic data with the understanding by research participants that full disclosure of their genetic information will be made. A research article by Visscher and Hill and another by Braun et al. put Homer's metric to the test to determine its power and limitations.

P3G Consortium et al. (2009). PLoS Genet 5, *e1000665. 10.1371/journal.pgen.1000665.*

Visscher and Hill (2009). PLoS Genet 5, *e1000628. 10.1371/journal.pgen.1000628.*

Braun et al. (2009). PLoS Genet 5, *e1000668. 10.1371/journal.pgen.1000668.*

Comparing Results from Two Direct-to-Consumer Personal Genome Scans

Whether we argue about how the currently marketed direct-to-consumer (DTC) genome scans are regulated or about whether they should even be able to provide this service, the fact is that several such scans are available and have already been used by thousands of people. There are many decisions that go into turning a saliva sample into a set of risk calculations, which leaves me to wonder how well the risk calculations agree among DTC companies. Now, I need not wonder any longer—in the October 8 issue of *Nature*, which has a focus on human genetics, Pauline Ng et al. sent samples from the same set of five individuals to both 23andme and Navigenics and compared the risk analyses performed by both companies. Because both companies pull data from the publicly available results of genome-wide association studies, it is not surprising that their risk calculations agree for several

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DOI 10.1016/j.ajhg.2009.10.021.

diseases. For other diseases, though, the two companies don't agree even in the direction of the relative risk for all individuals. This is in large part due to differences in the criteria for the selection of genetics markers included in the risk calculations, but it does highlight how much we have to learn about genetic contributions to common diseases, and it leaves me wary as to how much the average consumer appreciates about these risk predictions. Ng et al. propose a set of recommendations that they think personal genomics companies would be wise to follow, including the idea that the companies should make clear to consumers the fraction of disease risk that the genotyped markers can explain, which for many disorders is very little. The authors also argue for research monitoring how personal genome scans alter consumer behavior and how well these approaches actually predict disease risk in prospective studies.

Ng. et al. (2009). Nature 461, *724–726. 10.1038/461724a.*

The Location and Role of Human CNVs

Genome-wide association studies (GWASs) were never designed to find all of the genetic variation that contributes to complex diseases. Nevertheless, the fact that the results coming from these studies account for only a small fraction of trait variation in most cases is rather disappointing. In a recent issue of *Nature*, Manolio et al. explore some of the potential sources of this "missing heritability," which range from undetected rare variants to inflated heritability estimates. Copy number variation (CNV) could be another underappreciated contributor to trait variation, and Manolio et al. call for further exploration of the role of CNV in complex disease. A resource that will greatly aid this exploration is the most complete map of human copy-number variants (CNVs) that has been published to date, which was created by Conrad et al. Their goal was to create a map of all CNVs of 1 kb or larger, and they estimate that they ultimately found 80%–90% of those with a minor allele frequency greater than 5%. However, an analysis by Conrad et al. indicates that most of their CNVs are well-tagged by SNPs, and so they suggest that existing GWASs have already indirectly looked at associations with these CNVs. On the basis of this finding, Conrad et al. don't view common CNVs as a main contributor to the missing heritability problem.

Conrad et al. (2009). Nature. Published online October 7, 2009. 10.1038/nature08516.

Manolio et al. (2009). Nature 461, *747–753. 10.1038/nature08494.*

Role for siRNAs in Chromosome Segregation

The kinetochore is a complex assembly of proteins to which the spindle fibers attach and subsequently pull the chromosomes to opposite poles during anaphase. During the cell cycle, the chromosomes should align at the metaphase plate and the kinetochores should be oriented to the opposing spindle poles. Claycomb et al. identify a small RNA-based system that is crucial for this process and for proper chromosome segregation in *C. elegans*. They find a class of small RNAs, called 22G-RNAs, that are antisense to more than 4000 protein-coding genes in the *C. elegans* genome and are associated with the Argonaute protein CSR-1. Rather than regulating gene expression, the 22G-RNAs appear to target CSR-1 to genomic loci that are distributed fairly uniformly along the chromosomes. These euchromatic domains support the proper alignment of the kinetochores through a mechanism that is as yet undefined. Without CSR-1, chromosomes don't align properly at the metaphase plate and the kinetochores don't orient to opposite poles. van Wolfswinkel et al. identified another crucial component of this system. They found that CDE-1 uridylates the 3′ end of the CSR-1-associated siRNAs, thereby destabilizing them. In the absence of CDE-1, these siRNAs are overexpressed, and this loss of function is also associated with defects in chromosome segregation. Granted, unlike mammals, *C. elegans* centromeres are spread along the length of the chromosome rather than localized to one distinct area, but the conservation of CDE-1 throughout the animal kingdom suggests this siRNA-based system for regulation of chromosome segregation may be more widespread.

Claycomb et al. (2009). Cell 139, *123–134. 10.1016/j.cell.2009.09.014.*

van Wolfswinkel et al. (2009). Cell 139, *135–148. 10.1016/j.cell.2009.09.012.*

This Month in Our Sister Journals

Low Uptake of Genetic Services for Lynch Syndrome Assessment

"If you build it, they will come" might have worked in baseball, but what about genetic testing? If you develop a genetic testing protocol and identify patients who might benefit from this analysis, will patients accept the referral? This probably wasn't the question that South et al. hoped they were going to address when they explored an approach to identifying people with colorectal cancer who might be at risk of Lynch syndrome. However, it was one of the more striking results of their study. Lynch syndrome predisposes affected individuals to visceral cancers, particularly colorectal cancer (CRC), and is caused by a defect in DNA mismatch repair (MMR). These defects

can be detected through the absence of MMR proteins in a tumor sample and/or the instability of microsatellite sequences. Because only a minority of CRCs are due to Lynch syndrome, clinical criteria have been used for selecting which tumors are appropriate for the evaluation of MMR defects. South et al. felt that this approach could lead to underdiagnosis of Lynch syndrome, so they decided to explore the feasibility of evaluating all CRCs for the expression of MMR proteins as a way of detecting Lynch syndrome. Immunohistochemical staining of four MMR proteins was performed on all 270 CRC cases that were diagnosed over a two-year period at the Ohio State University Medical Center. Of the 57 cases in which the tumor lacked staining for one or more MMR proteins, further evaluation indicated that 34 of these might benefit from a genetics consultation, and the affected individuals were contacted. Surprisingly, only nine of these individuals kept their appointments with the genetics clinic to discuss the possibility of further testing for Lynch syndrome, and two of these individuals were ultimately diagnosed with Lynch syndrome, which is a minority of the expected number of cases in this sample. From a scientist's point of view, the identification of Lynch syndrome is important in that it can affect the clinical management of CRC and also has implications for cancer risk in the family members of affected individuals. The low uptake of genetic consultation in this sample indicates that we need to look at how we deliver, and how patients receive, this information to identify the barriers to uptake of genetic evaluation.

South et al. (2009). Genet. Med. 11, *812–817. 10.1097/GIM.0b013e3181b99b75*.

Promiscuous Proteins

The formation of amyloid fibrils is associated with several disease states. A classic example is β-amyloid in Alzheimer disease, but various other proteins have the capacity to form these aggregates under certain conditions. Although we don't fully understand how this happens, we do know that once the aggregation of the amyloid protein starts, or is seeded, the process really takes off. Not only can one amyloid protein seed its own amyloid aggregation, there can be cross-seeding of other amyloid proteins into fibrils. Ross et al. used yeast prions, which are infectious amyloid forms of normal yeast proteins, as a model system to study cross-seeding of amyloid formation. They looked at the Ure2p transition to [URE3] prions and found that cross-seeding might be more widespread than previously suspected. If they took a fragment of Ure2p and scrambled up the pieces so that they had a totally different amino acid order, this scrambled sequence could still prime [URE3] formation in a mechanism that involved direct interaction between the scrambled protein sequence and the wild-type protein. Because the amino acid composition, and not the primary protein sequence, was important for amyloid seeding, the authors used a simple algorithm to search the yeast proteome for protein fragments with a composition similar to that of the Ure2p prion domain. Of the five protein fragments that were most similar to the Ure2p prion domain, four of them could cross-seed [URE3] formation, hinting that there is much more promiscuity in seeding amyloid formation than we were aware of. Strikingly, the efficiency of the cross-seeding, which was previously thought to be low, was actually almost as high as that of the homologous Ure2p prion domain. We don't yet know whether the same type of cross-seeding occurs in humans, but if it does, this could help further our understanding of the process by which amyloid aggregates initiate.

Ross et al. (2009). Genetics. Published online September 14, 2009. 10.1534/genetics.109.109322.