This Month in *The Journal*

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Keeping It Together to Avoid Tearing It Apart

Prakash et al., page 743

Thoracic aortic aneurysms and dissections (TAAD) occur when the walls of the aorta break down, enlarge, and can eventually rupture. The good news about TAAD is that surgery can fix the problem; the bad news is that there are few, if any, ways to know that a problem exists before it is too late. Most cases of TAAD are sporadic, but familial cases do exist, and a number of loci have been identified. In those families in which gene mutations have been identified, the disrupted genes are involved with the contractility or the adhesion of smooth muscle cells. This has led to the hypothesis that the disruption of such pathways is likely to be associated with increased risk of TAAD. In this issue, Prakash et al. perform genome-wide analyses to identify copy-number variants (CNVs) that are significantly associated with increased risk of TAAD. The authors look for CNVs that are enriched in their datasets of patients with sporadic TAAD and familial TAAD. A number of loci are implicated in their analysis, and their assessment of the functions and pathways of the genes involved provide additional support for the hypothesis that genes disrupted in TAAD are involved in the maintenance of the extracellular matrix, cell adhesion, and vascular smooth cell contractility.

I'll Take Mine Rare

Liu and Leal, page 790

The SNP arrays used for genome-wide association analyses (GWAS) contain common SNPs that can serve as proxies for genomic regions, but very rare or unique variants are not captured well. GWAS using these chips have identified a number of disease risk alleles, but a large percentage of heritability for these phenotypes remains to be identified. One prediction is that rare variants contribute significantly to disease risk and that these variants can only be identified through the use of more comprehensive sequencing approaches. Sequencing technologies are becoming time-effective and cost-effective enough that it is now feasible to do a large amount of sequencing, either entire genomes or exomes or candidate regions, in tested individuals. There are now several instances in which rare variants that are significantly associated with disease risk have been identified. With the increased use of methodology to search for associations with rare variants, it is necessary to establish the best ways to replicate and confirm these associations. Is it best to resequence in an independent set of cases and controls the entire gene that contains the implicated variant in order to determine the total risk load of rare variants in that gene? Or, is it sufficient to genotype the risk variant already identified in the additional samples? It is surely less expensive to do targeted genotyping, but is that really a rigorous analysis of the region's rare variants that contribute to disease risk? In this issue, Liu and Leal address these questions about how best to assess the replication of associations with rare variants. The authors incorporate information about population genetics and sequencing error rates into their analyses to establish recommendations for following up on significant associations with rare variants.

mtDNA Mutations Might Allow Detection of Prostate Cancer

Kloss-Brandstätter et al., page 802

Prostate cancer follows only skin cancer in the onerous title of most common cancers affecting men. The prostate is a gland that comprises part of the male reproductive system. It is responsible for producing a portion of the seminal fluid. Men with early stages of prostate cancer often have no symptoms. Rather, an enlarged or abnormal prostate is likely to be discovered during the digital rectal exam (DRE), the classic "turn your head and cough" portion of a standard physical examination. Blood tests for prostate-specific antigen (PSA) are also commonplace for men over 40 or 50 years of age. Neither an abnormal prostate gland nor an elevated level of PSA is diagnostic for prostate cancer, but both indicate that further testing is needed. Biopsies are used for actual diagnosis of the cancer. Recognizing the important role that mitochondrial DNA (mtDNA) mutations have been found to play in the development and progression of many types of cancer, in this issue Dr. Kloss-Brandstätter and colleagues sequenced the entire mitochondrial genome in prostate cancer patients to find clues as to why so many men develop the cancer. By examining both the frequency and types of somatic mtDNA mutations in prostate cancer patients, this team is able to identify several genetic changes having clinical significance. Among their exciting findings is an association between somatic tRNA mutations and PSA

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DOI 10.1016/j.ajhg.2010.11.009.

levels at diagnosis. Although prostate cancer is treatable by surgery, radiation, or chemotherapy, it is often fatal. Finding genetic changes associated with prostate cancer and its primary biomarker will potentially help monitor and treat this common deadly disease.

Proliferation Rate Matters

Stark et al., page 829

The HapMap populations have served as a tremendous resource to researchers across the world. The international project was initiated in an effort to help researchers identify genetic variants associated with human disease. In Phase I of the project, samples were collected and genotyped from people from four different populations: Yoruba in Ibadan, Nigeria (YRI); Japanese in Tokyo (JPT); Han Chinese in Beijing (CHB); and CEPH (Utah residents with European ancestry; CEU). The DNA for genotyping these people came from Epstein-Barr-virus-transformed lymphoblastoid cell lines (LCLs). These lines are maintained by the International HapMap Project and distributed to researchers as requested. Last year, the HapMap populations expanded to include more members of these four original populations, and samples from seven additional populations were also collected. Again, LCLs were created and used for DNA extraction and genotyping. And again, these LCLs are maintained and distributed. Despite the unprecedented and largely altruistic information provided by these cell lines, a paper in this week's issue advises caution when comparing data obtained from LCLs arising from the first phase of the HapMap project with those from HapMap Phase III. Stark and colleagues compare the proliferation rate between LCLs of different populations established at different times during the HapMap Project. They find differences both between populations and between lines from the same population established a couple of years apart. These findings do not in any way diminish the contribution of the International HapMap Project, but they do highlight some potential confounding issues regarding genetic studies using these samples.

Sometimes It's the Men, and Sometimes It's the Women

Emery et al., page 848

There has been an ongoing discussion over whether human evolution has been characterized by a female bias, meaning that individual males mated with more than one female, versus a male bias, in which one female has offspring fathered by a number of different males. Determining the human sex ratio through history has traditionally depended on data from mtDNA and the Y chromosome, but newer analyses using whole-genome sequence data have had more power. They also disagree with each other. Some report evidence of a female bias, and others report a male bias. The studies presenting these different views have used different methodologies on different datasets, so it has been suspected that the contradiction in the results might be due to the different approaches used. But, which studies were performed correctly and got the right answer? In this issue, Emery and colleagues report their analyses of the data and conclude that, in a way, both sides are right. The authors examine the same set of data with both methods and evaluate which factors affect the findings. It turns out that when these sex biases occurred makes a difference; one approach is more sensitive to recent biases, whereas the other approach better detects ancestral bias. Emery et al. propose that an ancestral female bias in all human populations and a subsequent male bias in non-African populations is consistent with the results obtained by previous studies and can reconcile some of the reported conflicts.