This Month in the *Journal*

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Corrected Odds Ratios for Genome Scans

Wright et al., 1064
Significant results of genome-wide association scans are subject to what has become known as the "winner's curse," a bias in which the estimate of risk effect is inflated. This complicates follow-up studies because power estimates are made on the basis of effect size; replication studies can turn out to be underpowered. Methods of correcting for this significance bias are under development, and it is the focus of Ghosh et al. to establish an approach that is computationally feasible for genome-wide data and that can be implemented with standard software. Their algorithm is based on odds ratio (OR) calculations and is universal in its application to dominant, recessive, and additive models. The authors use simulations to demonstrate how their various corrected estimators significantly reduce the bias of their measurements. They then use their method to estimate bias-corrected effect sizes for several published associations and report that their estimates more closely match values obtained in follow-up studies.

Genome-wide Association of Expression

Duan et al., 1101
Gene expression can be controlled via variation at expression-quantitative nucleotides (eQTNs) located near to or far from the gene. Because changes in gene expression often have an effect on phenotype, analysis of eQTNs can contribute to the information about genetic association with disease. Recent work has examined, on a genome-wide scale, how genetic variation affects expression in humans. Duan et al. expand upon these studies with a comprehensive evaluation of the effects of eQTNs on expression of transcripts throughout the genome in the CEU and YRI HapMap samples. This analysis reveals thousands of significant associations in both of the populations, and a comparison between the CEU and YRI samples suggests that the ratio of distant to local effects is higher in YRI than it is in CEU. The authors also report that eQTNs in close proximity to the affected gene are found in LD blocks and that, as expected, these blocks are larger in CEU than in YRI. In general, these local eQTN blocks are more likely than distant eQTNs to be common in the two populations. Duan et al. evaluate the regions containing eQTNs and discuss which categories of gene function are most frequently involved.

The Dawn of Human Matrilineal Diversity

Behar et al., 1130
Through the study of mtDNA, research has established that most of the non-African people in the world share one of two clades within the mtDNA phylogeny. The most recent common ancestor of these clades has been localized to sub-Saharan Africa, and it is assumed that the out-of-Africa dispersal originated from this region. Many of the current African populations in the area are a mix of mtDNA branches, and this has led to speculation that a homogeneous distribution accounted for the observed lack of internal maternal genetic structure. However, in some peoples, such as the Khoisan of South Africa, distinct clades dominate and separate the people from surrounding populations. The basis for the prevalence of these mtDNA lineages in the Khoisan people is incompletely understood, so Behar et al. analyze complete mtDNA sequences from related populations to establish the origin and timing of the development of the Khoisan mtDNA structure. The authors conclude that the Khoisan are the source of their most common clades and that the other haplogroups have been recently introduced from other areas. Then, to explain why the two clades are highly prevalent within the Khoisan, Behar et al. develop two hypotheses to explain how different combinations of population division, isolation, and drift could create the conditions to yield the mtDNA structure observed today.

Genome-Wide Association Study for CRP

Ridker et al., 1185 and Reiner et al., 1193, respectively
Evaluating the levels of circulating C-reactive protein (CRP) in healthy individuals can serve as a means of predicting their risk of developing metabolic syndrome, cardiovascular disease, or stroke. Work has focused on establishing which factors affect CRP levels, and evidence supports a role for genetics. Previous studies have identified associations with variants in *CRP* and *APOE*, but these account for only a small portion of the predicted genetic effect. In an effort to identify additional genetic variants associated with plasma CRP levels, Ridker et al. and Reiner et al. perform genome-wide association studies by using thousands of individuals. Strong significant signals are observed with SNPs in *HNF1A*, the gene encoding hepatocyte

[1]Deputy Editor, *AJHG*
DOI 10.1016/j.ajhg.2008.04.007.

nuclear factor-1α. Of particular note, Reiner et al. extend the data acquired from the markers genotyped in their study by using linkage disequilibrium measurements in HapMap data to impute data for untyped SNPs in the *HNF1A* region. They predict that a block of five SNPs is the most significantly associated with CRP levels. One of these five SNPs is typed in the Ridker et al. study and is the *HNF1A* SNP that shows the strongest evidence of association. The authors hypothesize that *HNF1A* variants might affect CRP levels because the *CRP* promoter region contains a binding site for the transcription factor HNF−1α.

ZNF469 Mutations in Brittle Cornea

Abu et al., 1217

People with brittle cornea syndrome (BCS) suffer from a variety of different issues, including a very fragile cornea that is easily damaged, hypermobility of the joints, and hyperlaxity of the skin. Among Israelis, most individuals affected by BCS are Jews of Tunisian descent, and previous work identified a BCS locus on 16q24 in these people. Abu et al. study five Tunisian Jews with BCS and a Palestinian family with six affected members to fine-map the disease region. Of the 50 known genes in the narrowed region, the authors choose to analyze the sequence of the 32 that are known to be expressed in skin fibroblasts. A single base-pair deletion in *ZNF469* is detected in the Tunisian Jews, and a different single base-pair deletion segregates with BCS in the Palestinian family. *ZNF469* is shown to be expressed in the cornea, and its protein's homology to portions of corneal collagens suggests that ZNF469 might be involved in maintaining and/or regulating the complex structures of the cornea. Various other disorders share overlapping features with BCS, and Abu et al. suggest that disruption of *ZNF469* might also be etiologic in some of those diseases.