This Month in the *Journal*

Robin E. Williamson[1]

mtDNA and the Peopling Of the Americas

Fagundes et al., 583
Although it is generally accepted that the Americas were the last continents to which *Homo sapiens* were introduced, the timing and location of this peopling are contended. Early mtDNA haplogroup data from Native Americans has been in support of a single migration from Asia, but other evidence has pointed to multiple later migrations. Additionally, there is disagreement about the size of the founding group that peopled the Americas and whether it was subject to a strong or moderate bottleneck. Earlier studies of Native Americans have focused on data from only the control region of the mtDNA. Because it has been found that such sequences can be limited and unreliable, Fagundes et al. analyze the complete mtDNA coding sequence of Native Americans from all major haplogroups. Their analyses support a single-migration scenario with a moderate bottleneck followed by expansion.

Scientific Basis Of Genomic Profiles

Janssens et al., 593
One of the reported goals of identifying associations between genetic alleles and complex disease is that a personalized assessment of risk could result from testing which variant a person possesses at those loci. Companies are hoping to benefit from data generated from genetic association studies by offering such tests to the public. There is some concern that, because the odds ratios of identified risk factors are so low, such analyses can be misleading and even harmful. Additionally, many reported associations may not be real or may not have an equal effect in all populations. Replication and meta-analyses are required to ensure that the associations between variants and disease risk are real. Janssens et al. assess the scientific basis for the genetic-variant testing that is currently commercially available. They look at seven companies that, combined, offer tests for 69 different polymorphisms in 56 different genes. The authors report that many of the tests are not supported by significant associations in meta-analyses.

Analyzing Distantly Related Individuals

Albers et al., 607
Linkage analysis of distantly related affected individuals can be a powerful strategy for identifying loci involved in complex diseases with incomplete penetrance. One difficulty in such studies is that exact determination of the identity-by-descent sharing probabilities is intractable in large pedigrees, and approximating methods via Markov chain Monte Carlo sampling can be time-consuming and complex. Additionally, as denser SNP data becomes available for these analyses, it becomes increasingly important to take linkage disequilibrium (LD) into account, and most current methods are unable to allow for correlation between markers. Albers et al. develop a method that simplifies the approximation of linkage statistics in large pedigrees with distantly related affected individuals. The accuracy of the new method, as implemented in the program ALADIN, is evaluated on data from small pedigrees for which exact computation is feasible. The authors also compare ALADIN to other approximation methods using data from larger pedigrees. ALADIN is found to be more accurate and efficient than other methods, particularly when used on large pedigrees and when accounting for LD.

SCARB2, Epilepsy, and Glomerulosclerosis

Berkovic et al., 673
Action myoclonus-renal failure syndrome (ARMF) is an autosomal-recessive disorder characterized by renal failure and progressive neurological symptoms. Because the disease is lethal and has an age of onset at 15–25 yr, there are not any large pedigrees to study for gene identification based on linkage strategies. Berkovic et al. use homozygosity-mapping techniques in three unrelated affected individuals to identify a candidate disease region on 4q13-q21. Of the 66 known genes at this locus, approximately half were known to be expressed in the brain and in the kidney. To further pare down this list, the authors predict that the gene mutated in ARMF would be downregulated in affected tissues. Gene-expression comparison between patient cells and control cells reveals that *SCARB2* expression is decreased in ARMF. *SCARB2* mutations are found in ARMF patients, as well as in obligate carriers from one of the original ARMF families. The authors also compare the human phenotype with that of mice deficient for *Limp2* (the *SCARB2* mouse ortholog) and describe similarities and differences.

Epigenomic Profiling In Major Psychosis

Mill et al., 696
Major psychosis is a term used to encompass the conditions of schizophrenia and bipolar disorder. Although

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a great deal of effort has been expended in the search for genetic variants that are associated with these disorders, very few significant associations have been identified. Certain observations, such as the fact that environmental effects cannot account for the lack of concordance of disease in monozygotic twins and parent-of-origin effects, have led to the prediction that epigenetic factors may be involved in the development of major psychosis. Because epigenetic changes can be tissue specific and can lead to gene misregulation, they can affect phenotype in a dynamic manner independent of genetic variants or mutations. Previous studies have analyzed the methylation status of certain genes thought to be involved in schizophrenia and/or bipolar disorder, but here Mill et al. perform a genome-wide scan of epigenetic variation in the frontal cortex of cases and controls. The authors identify a number of regions that show significant differences in methylation profile, and they discuss the gene-ontology categories that are implicated to be involved in the etiology of major psychosis.