This Month in the *Journal*

Robin E. Williamson[1]

Predicting HLA Alleles from SNP Data

Leslie et al., page 48
The HLA locus has been implicated in a number of diseases, but studies assessing an association between phenotypes and HLA alleles can be difficult and expensive because of the complexity of the region. Evidence has suggested that, in contrast to HLA typing using traditional methods, genotyping of SNPs that tag the HLA alleles could be less expensive and more efficient. But, using such SNP-tagging techniques is complicated by the large number of carefully chosen SNPs that would need to be used to successfully proxy for all the HLA alleles, many of which are rare and/or found on diverse haplotype backgrounds. Leslie et al. suggested a method based on identical-by-descent assumptions in which SNPs throughout the region are typed and used to compare a chromosome with unknown HLA alleles with a database of known alleles. The authors demonstrated how this method can be advantageous over other technologies and discussed ways to optimize performance through SNP selection. The sensitivity and specificity achieved by the method was evaluated with SNP data from two individual datasets.

OSMR Mutations in Lichen Amyloidosis

Arita et al., page 73
Primary localized cutaneous amyloidosis (PLCA) is characterized by itchy, hyperpigmented, and thickened skin. Most cases of PLCA are sporadic, but a few familial cases do exist, and linkage studies have identified significant familial PLCA (FPLCA) loci. Here, Arita et al. mapped FPLCA in a large Brazilian pedigree to 5p13.1-q11.2 and, after screening candidate genes thought likely to be involved in skin disease, identified a missense mutation in the gene encoding oncostatin M receptor β, *OSMRβ*, in the affected members. The involvement of *OSMRβ* mutations in FPLCA was further corroborated with the identification of a second mutation in two other families. Two ligands—OSM and IL-31—of the receptors have effects on pathways within keratinocytes, and functional work here revealed that the cultured keratinocytes of affected individuals had a decreased response to treatment with the proteins. The involvement of *OSMRβ* in the etiology of a familial itchy skin disease identifies new pathways involved in the itching process.

Genome-wide Association of CVD Biomarkers

Wallace et al., page 139
There is evidence that genetic variation may influence an individual's biochemical profile and that these quantitative traits can serve as biomarkers or risk factors for disease. Because the identification of polymorphisms that associate with these traits can be more straightforward than measurement of an association between a variant and the disease itself, such quantitative trait analysis can be very rewarding. Wallace et al. performed a genome-wide association analysis for 25 biochemical variables in three large population datasets. The authors identified variants within the gene encoding the solute carrier family 2 member 9, *SLC2A9*, that affected serum-urate levels in all three groups. An individual's elevated level of serum urate was linked previously to the development of hypertension, coronary artery disease, and other metabolic disorders. Additionally, the authors also confirmed loci that were previously known to be associated with lipid traits. Of note, the significance of the association of one of these SNPs with LDL levels was recognized here because of freely available data posted by another study. The same allele was also recently reported to be associated with coronary disease.

Polynesian Origins from Genome-wide Data

Kayser et al., page 194
A great deal of information can be learned about the ancestors of a population and their migration route by genetic analysis. Studies are traditionally done with DNA from the mitochondria and from the Y chromosome. As expected, such work focuses on either the maternal genetic background of a group with the mtDNA or the paternal history with the Y chromosome. In some cases, the results of the two different analyses can sharply contrast, and it is difficult to assess the total admixture contributions to that population. Many groups have sought to determine the genetic origins of the Polynesian people, and they have concluded that the mtDNA is predominantly from East Asia and the Y chromosome data is mostly from Melanesia. This disparity has led to interesting hypotheses about how people from East Asia migrated to Polynesia through New Guinea and Melanesia, where males were added to their group. Although such information is very significant and useful, it does not help to determine the contribution of the ancestral

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populations to the entire genome of the Polynesians. Here, Kayser et al. compared autosomal markers from the Polynesians to those of the Han Chinese and Papua New Guineans and reported that the genetic background of the Polynesians is 79% East Asian origin and 21% Melanesian origin.

Nature of mtDNA Deletions in Neurons

Reeve et al., page 228

Previous work has demonstrated that somatic mtDNA deletions accumulate through clonal expansion in the tissues of aging humans. Such a phenomenon has also been observed in the neurons of patients with neurodegenerative diseases. Reeve et al. sought to determine whether these deletions were characteristically similar to deletions in patients with multiple deletions as well as to those in patients with single pathogenic mtDNA deletions. Neurons carrying these deletions can be identified through the assessment of a biochemical defect of the enzyme cytochrome c oxidase (COX). Individual COX-deficient neurons were isolated, and the location and size of each mtDNA deletion was determined. Analysis of the deletion breakpoints revealed that all types of deletions were most likely to be flanked by direct perfect repeats and that the distribution of the breakpoints was similar whether or not they occurred within repeat sequences. These shared characteristics suggest that the different types of mtDNA deletions are created through a shared mechanism.