This Month in the *Journal*

Robin E. Williamson[1]

Local Ancestry in Admixed Populations

Sankararaman et al., page 290
As a result of the fact that association studies using cases and controls are based on allele-frequency differences, any background differences between the cases and controls can result in false-positive associations with the phenotype studied. One way to handle this confounding by population substructure is to first measure its effect and then correct for it. This correction increases in complexity if the samples studied are from recently admixed populations. Such recent mixing breaks the genome into segments that may each have allele frequencies based on different ancestral populations. Being able to determine the ancestry of each locus would increase the ability of admixture mapping to identify genetic associations. Sankararaman et al. develop local ancestry in admixture populations (LAMP) to infer the ancestry of each locus on a genome-wide scale. They demonstrate on HapMap data how LAMP is more accurate and efficient than other methods used to infer locus-specific ancestral information. LAMP also has the added advantage of being applicable even if the ancestry history of a population is unknown.

The *BMP4* Gene and Eye, Brain, and Digit Anomalies

Bakrania et al., page 304
A locus for anophthalmia-microphthalmia (AM) was previously identified at 14q22-q23, and *OTX2* mutations were found in patients with microphthalmia and retinal dystrophy. However, a more complex phenotype of AM found in conjunction with hypopituitarism and digit anomalies was also linked to the same region, and *OTX2* was determined not to be a good candidate gene for that disease. Because of the known functions of *BMP4*, another gene located at 14q22-q23, Bakrania et al. suspected that disruption of the gene could be responsible for the complex AM phenotype. The authors screen patients with ocular defects, and *BMP4* mutations are found in a number of them, including several with digit anomalies. In animal models, *Bmp4* had been shown previously to interact with members of the Hedgehog (*Hh*) pathway, so Bakrania et al. perform expression analyses in sections from human eye, brain, and hand plate and demonstrate that the gene expression in humans supports a similar relationship between the genes. The authors then check their patients with the *BMP4* mutations for variants in members of the *Hh* signaling pathway and find sequence changes that are expected to increase the severity of the observed phenotype.

Ridge Regression for Genetic Associations

Malo et al., page 375
As genotyping technology improves, the ability to identify significant association between genetic variants and phenotypes also improves. However, because of the high correlation between typed SNPs and SNPs in LD with them, it is difficult to determine which SNP(s) is in fact responsible for the measured association. Regressional analysis can be used to identify a causal SNP if multiple independent variables are assessed, but traditional methods cannot be applied if the variants are in strong LD with each other. Malo et al. develop a technique that incorporates ridge-regression procedures to allow for moderate to strong LD between markers. The authors use simulations to compare their method to more traditional techniques and measure how well each can parse out which SNP(s), out of a group of correlated SNPs, is causally associated with a phenotype. The authors also apply the methods to SNP data from the *CHI3L2* region to demonstrate how accounting for LD between markers can greatly affect the outcome of association analysis.

Genome-wide Association of Iris Color; *HERC2* Intron 86 and Eye Color

Kayser et al., page 411 Sturm et al., page 424
Eye color in humans is a polygenic trait for which a locus on 15q11.2-q12 has been identified. Variants in *OCA2*, a gene within that region, were previously found to be associated with blue versus nonblue eye color. Here, two groups use different techniques to search for additional SNPs that play a role in determining iris color. Kayser et al. perform a genome-wide association study and genome-wide linkage study in datasets from the Netherlands. As expected, the strongest linkage peak is at 15q13.1 and encompasses the region including *OCA2*. Association analysis identifies markers in *OCA2* and *HERC2*, the gene directly upstream of *OCA2*. Likewise, Sturm et al. use a fine-mapping approach in subjects of European origin and also identify an association between eye color and

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variants in *HERC2*. The SNPs within *HERC2* are found to have an independent effect and not to be in LD with the *OCA2* alleles previously determined.

Warfarin Pharmacogenetics in Jewish Groups

Scott et al., page 495

Warfarin is an important anticoagulant, but its use is complicated by the fact that dosing requirements are variable and overdosing is dangerous. Variants in *CYP2C9* and *VKORC1* that are associated with a patient's response to warfarin have been identified. Here, Scott et al. look at the frequencies of these alleles in Ashkenazi and Sephardic Jews in an effort to determine which variants would best serve as markers for predicting warfarin sensitivity in these populations. The authors find that most of the people they studied would benefit from dose prediction based on their genotype at *CYP2C9* and *VKORC1*. In addition, a variant identified to confer resistance to warfarin, but not customarily assessed in warfarin testing, is found to override the effects of other sensitivity alleles. This suggests that the analysis of this additional resistance allele would add to the predictive capabilities of the screening.