This Month in the *Journal*

Epigenetics and Assisted Reproductive Technology, *by Niemitz and Feinberg* **(***p. 599***)**

Recent studies suggest that assisted reproductive technologies (ART) might be associated with epigenetic defects, including Beckwith-Wiedemann and Angelman syndromes. In this issue of the *Journal,* Emily Niemitz and Andrew Feinberg discuss this research, as well as data from animals that support this connection. They go on to suggest steps that should be taken to conclusively demonstrate or refute this association and to accurately calculate the risks associated with ART. This may involve policy changes, such as the addition of questions pertaining to ART procedures to the U.S. Standard Certificate of Live Birth and increased regulation/reporting of culture conditions for human embryo culture. Additional research is also needed to develop an understanding of the mechanisms of this association, if it truly exists.

Haplotype Diversity across 100 Genes, *by Crawford et al.* **(***p. 610***)**

With all the hoopla over haplotype structure and haplotype tagging, Crawford et al. figured it would be useful to do a survey of complete sequence variation in 100 genes to see how well the use of common coding SNPs really captures genetic diversity. In both an African American and a European American sample, they completely resequenced 100 genes related to inflammation and lipid metabolism and inferred haplotypes using PHASE. They found much more diversity than has generally been described in previous studies. Although it was believed that common haplotypes represent the majority of chromosomes, Crawford et al. found that common haplotypes (those with a frequency >5%) represented only 56% of chromosomes in the African American population and 75% of those in the European American population, and only a fraction of the haplotypes inferred were shared between the two populations. There was also a lot of variability in the number and diversity of haplotypes between individual genes. Another popular method for selecting SNPs for use in association studies is to choose biologically plausible candidates from within coding regions. Crawford et al. find that use of coding regions alone also incompletely resolves common haplotypes and haplotype-block structure, regardless of the exact block definition used. The authors suggest that, for many genes, knowledge of complete variation will be needed to best design association studies. This means a lot more sequencing for people, but Crawford et al. feel they have adequately defined the variation in their study, using sample sizes of 23 and 24 for the two populations. As high-throughput sequencing becomes more widely available, this will become more feasible, although still a bit daunting.

Data Mining and Genome Scan, *by Pociot et al.* **(***p. 647***)**

To identify the genes involved in complex traits, Pociot et al. wanted to explore new strategies that could overcome the limitations of traditional types of analyses. They decided to explore the use of data-mining techniques by applying them to a type 1 diabetes (T1DM) data set that previously had been used in a traditional genome scan. The procedure they developed includes decision-tree construction and artificial neural networks and should allow the detection of multiple interacting disease genes. A comparison of the results from the data-mining analyses with those of the original genome scan demonstrates that data mining can detect the strongest observations that have been reported using traditional linkage methods. In addition, the data-mining techniques identified novel T1DM loci and several different interactions between loci. Other benefits over traditional analyses include the identification of combinations of relatively few markers that could predict disease status and the fact that information on unaffected individuals is analyzed and can be used to predict regions harboring protective loci for disease. The authors feel these and other data-mining techniques might be useful ways to uncover the complicated genetic architecture of complex traits.

Power for Genetic Association Studies, *by Ambrosius et al.* **(***p. 683***)**

Power calculations are an important part of designing association studies. The allele frequencies of the SNPs in these studies are usually unknown for the exact sample being tested, so the assumption is often made that the allele frequencies in another population or in a small portion of the sample are equal to that in the full sample of interest. Ambrosius et al. were interested in the effect of this assumption on power estimations. They also explored another potential problem in these power calculations, that variability in sample sizes between different genotype groups is often ignored. Their results show that ignoring these assumptions results in overestimation of power and that, consequently, one would underestimate

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the sample size needed to achieve a certain power when an association study is designed. They propose a Bayesian approach to this problem that takes into account available genotype information and places a prior distribution on the allele frequencies. The authors demonstrate that this approach more accurately estimates power.

Mitochondrial Diversity among the Etruscans, *by Vernesi et al.* (*p. 694*)

The Etruscans settled in Italy between 900 and 800 B.C., bringing civilization and urbanization with them. They are believed to have had a very strong influence on the development of Roman culture, but their origins have been controversial. To look at this genetically, Vernesi et al. gathered samples from 80 skeletons buried in Etruscan necropoleis. Using careful controls, they managed to get reliable mtDNA sequences from 30 individuals. The relatively low internal genetic diversity in the population suggests they shared common ancestry, thereby proving that the Etruscans were not just a culturally related entity. Next, the sequences were compared with those of modern European populations to determine how they might be related. This is actually one of the first studies with enough ancient DNA samples to make these comparisons. They show that the Etruscans are less similar to their modern counterparts than random European populations are to each other. Also, the Etruscans are less like the modern population of Italy than they are like the modern Turks, which suggests a closer evolutionary relationship for the Etruscans and populations of the eastern Mediterranean. Questions remain as to the ultimate fate of the Etruscans, because few Etruscan haplotypes exactly match those in the modern mitochondrial database.

GABRA2 ***Associated with Alcoholism,*** *by Edenberg et al.* (*p. 705*)

Alcoholism is a complex disease that obviously has a strong environmental component but also a genetic one. In a whole-genome scan, the Collaborative Study on the Genetics of Alcoholism (COGA) previously reported linkage to a locus on chromosome 4p near a cluster of genes encoding the $GABA_A$ receptor. GABA is an important inhibitory neurotransmitter in the brain, and it mediates some of the effects of alcohol, including sedation and symptoms related to withdrawal. To look further at the role of this genetic region in alcoholism, Edenberg et al. genotyped 69 SNPs across four $GABA_A$ receptor genes and used them in a pedigree disequilibrium test with the COGA sample. The SNPs in only one gene, *GABRA2*, were consistently associated with alcoholism. The role of *GABRA2* in alcoholism was supported by the fact that multiple SNPs in this gene were also associated with an endophenotype for alcoholism, the beta frequency band of electroencephalography. Unfortunately, the effects of *GABRA2* on alcohol dependence could not be attributed to a particular sequence variation, but the strength of the association, which withstood a conservative correction for multiple testing, and the fact that 43 of 47 consecutive three-SNP haplotypes tested were associated with alcoholism suggest that *GABRA2* does influence susceptibility to alcoholism.

High Percentage of Mutant Osteoblasts in Mosaic Carriers, *by Cabral and Marini* (*p. 752*)

One approach to the treatment of osteogenesis imperfecta is the transplantation of normal mesenchymal precursors. These stem cells are isolated from bone marrow and can differentiate into osteoblasts that will produce normal type I collagen, the structural component of the bone and skin that is defective in affected individuals. To get an idea of whether this will actually work, it will be important to determine the level of wild-type cells necessary to produce normal bone. One way this can be studied is with individuals mosaic for mutations in the collagen I genes. Because the proportion of mutant cells in these people varies from tissue to tissue, it is important to look at bone samples. This is what Cabral and Marini have done in two mosaic carriers of *COL1A1* mutations who were identified because they had affected children. The first mosaic woman was mildly affected and had 50%–73% mutant cells in bone samples. The second, unaffected mosaic woman had 40% mutant cells in a sample from her skeletal system. These findings suggest that normal skeletal function can develop even in the presence of a significant mutation burden in the osteoblasts. An initial goal for the treatment of osteogenesis imperfecta with mesenchymal cell transplants can then be set as the achievement of ~30%–60% normal osteoblasts, although the distribution of the normal cells throughout the skeletal system is also likely to be crucial for proper bone strength.

KATHRYN GARBER
Deputy Editor