This Month in *The Journal*

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The XQTL Test in Family-Based Designs

Zhang et al., page 431

Methods to test for association with markers on the X chromosome differ from those dealing with autosomal loci because the X chromosome undergoes differential inheritance in males versus females and is subject to dosage compensation. In addition, the analysis of qualitative traits is handled differently than the analysis of quantitative traits. Although algorithms to look for association between X-linked markers and qualitative traits as well as linkage methods to identify X-linked quantitative trait loci (QTL) have been developed, tests for X-linked QTL are less common. Here, Zhang et al. develop a test to identify X-linked QTL by using family samples. The test, called XQTL, is extended to two-marker haplotype analysis and is able to handle multiple offspring and missing genotype and phase information. The authors use simulations to compare XQTL to current methodology and show that XQTL has higher power with or without missing parental genotypes. XQTL is then used to evaluate whether variants in the monoamine oxidase genes, *MAOA* and *MAOB*, are associated with the age at onset of Parkinson disease.

DPP6 in IVF

Alders et al., page 468

Idiopathic ventricular fibrillation (IVF) is the uncoordinated contraction of cardiac muscle of the ventricles without a known cause. These patients have no identifiable structural heart disease or known repolarization abnormalities. Currently, IVF can be diagnosed only after the occurrence of a sudden cardiac death or an aborted sudden cardiac death. A family history of IVF is present in up to 20% of IVF patients, indicating a genetic component to this condition. Because IVF can result in sudden death, identifying presymptomatic risk factors is of critical importance. By using three distantly related families in which several members died suddenly or were successfully resuscitated, Alders et al. identify a conserved haplotype on 7q36. They find that a portion of this haplotype shared in seven additional IVF patients, allowing the authors to limit the haplotype to a region of interest approximately 1.5 Mb that encompasses only one annotated gene, *DPP6*. A common mutation in *DPP6* is found in all patients with the shared haplotype. *DPP6* encodes a putative subunit of potassium channel complexes, dieptidyl-pepidase 6, strengthening its candidacy for association with IVF. These data indicate that there is indeed a genetic component to IVF development and provide hope for earlier risk assessment.

A Duplication within a *BMP2* Regulatory Element

Dathe et al., page 483

Brachydactylies are a collection of disorders that involve abnormal development of the phalanges. Many types of brachydactyly are caused by disruption of the bone morphogenetic protein (BMP) pathway, and it has been established that the BMP pathway contains a variety of transmembrane receptors and ligands that control morphogenesis. One type of brachydactyly, BDA2, is characterized by shortening of the middle phalanges of the second and fifth finger. Mutations in BMP proteins have been identified in some patients with BDA2, but the etiology of other cases remains unclear. Dathe and colleagues study two families with a variable but penetrant BDA2 phenotype. After disruption of the known genes is excluded, genome-wide linkage analysis identifies a locus on 20p. The locus includes the promising candidate, *BMP2*, but initial sequencing efforts of the genes in the linkage region fail to identify any obvious mutations. The authors then examine the genomic region surrounding the BMP2 coding sequence in one family and find a small duplication about 110 kb downstream. An overlapping duplication is identified in the second family. The authors predict that the microduplications are causing BDA2 by disrupting the regulation of *BMP2* expression. To examine this hypothesis, a transgenic mouse model is created with a highly conserved sequence from within the duplication. Transgene expression overlaps with that of *Bmp2* limb expression, suggesting that the sequence is involved in regulating the *Bmp2* expression in those tissues.

Genome-wide Linkage Screen of Familial PD

Gao et al., page 499

Linkage analysis is one way to uncover regions of the genome associated with a certain trait or disorder. Unlike a genome-wide association study (GWAS), which is used to associate particular SNPs with disease, a genome-wide linkage study (GWLS) is used to associate larger chromosomal

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regions > with disease. Further studies are then necessary to limit the region(s) to the responsible gene(s). In this month's issue, Gao et al. conduct a GWLS to detect genomic regions that associate with Parkinson disease (PD). PD is a neurodegenerative disorder for which there currently is no cure. Although there is evidence that PD does have a genetic component, decisive data is lacking. Gao and colleagues conduct linkage analysis on 174 PD families. Their findings indicate that a region on chromosome 18 containing 76 annotated genes and another locus on chromosome 3 containing 90 genes are associated with PD, particularly under a dominant model of inheritance. Future studies will aim to pinpoint the gene(s) within these regions that contribute to PD pathology.

The p53 Pathway and Natural Selection

Shi et al., page 534

The transcription factor p53 is a major regulator of several cellular pathways and is a key player in coordinating the proper cellular stress response. The expression of p53 is regulated by a number of proteins, and one of its main inhibitors is MDM2. MDM2 expression is also regulated by p53; the interplay between the two proteins is integral to cellular homeostasis. This regulation has been shown to be influenced by SNPs within the genes. Given that the variants affect the cellular stress response, researchers have predicted that the alleles may be under selective pressures. This hypothesis is supported by the observation that the alleles are found at different frequencies across different ethnic populations. Previous work has found that the variation coincides with latitude and UV exposure, but population differences among the groups studied confounded the results. To focus on the environmental effects alone, Shi and colleagues look for signs of selection within homogeneous populations that live across an extreme range of latitudes. They report that the p53 allele has undergone selective pressure because of changes in winter temperature, but not in response to UV exposure. In contrast, the MDM2 variant showed signs of selection only because of UV exposure. This evidence suggests that the two alleles were not coselected for.