This Month in the *Journal*

Efficient Association-Study Designs, *by Li et al.* (*p. 778*)

One of the most important issues that researchers face before starting an association study is deciding which methods are the most cost-effective and powerful. Linkage analyses often use data from multiple family members, but, for association studies, one affected sibling is usually chosen to be compared with unrelated controls. Previous work has demonstrated that the incorporation of all available data can increase power. Here, Li et al. describe a method that can accommodate genotyping data from various sources, including multiple siblings, parents, and unrelated individuals. Using this framework, they then compare study designs and determine which are the most powerful when given the same number of SNP genotypes. The authors evaluate single-locus models as well as scenarios involving multiple genes with varying levels of effect.

HTR2A *and Antidepressant Outcome,* *by McMahon et al.* (*p. 804*)

Patients with major depressive disorder react differently to antidepressant treatment. Whereas some may experience remission, the condition of others does not improve or responds to only one class of drug. McMahon et al. seek to analyze further the genetic basis for this variation. In a screen of candidate genes, they identify an association between *HTR2A,* the gene encoding the serotonin 2A receptor, and patient response to treatment with citalopram. The serotonergic system is believed to play a significant role in the pathophysiology of depression, and the receptor is down-regulated by citalopram. The allele associated with better outcome was found at a higher frequency in whites than in blacks, which may help to explain the racial differences that exist in treatment response.

HTTLPR *in OCD,* *by Hu et al.* (*p. 815*)

The *HTTLPR* polymorphism within the 5′ flanking region of the serotonin transporter gene *HTT* has been frequently studied in association with various neuropsychiatric disorders. *HTTLPR* contains a variable number of repeats; the two most common variants are the long allele of 16 repeats and the short allele of 14 repeats. Traditionally, the polymorphism is considered to be biallelic, with the short allele expressing lower levels of the serotonin transporter than the long allele. Here, Hu et al. closely examine a SNP within the extra repeats of the long allele that renders *HTTLPR* triallelic. One long variant contains an A at this polymorphic site, L_A, whereas the other contains a G, L_G. Hu et al. demonstrate that L_G is bound by the transcription factor AP2 and expresses *HTT* at levels similar to that of the short variant. When all three alleles are considered in an analysis of two independent cohorts, a replicated association is identified between L_A and obsessive-compulsive disorder.

Imprinting and Niemann-Pick Disease, *by Simonaro et al.* (*p. 865*)

Niemann-Pick disease (NPD) is a recessive disorder caused by deficiency of the lipid hydrolase acid sphingomyelinase (ASM). Various lines of evidence have led to the hypothesis that the gene encoding ASM, *SMPD1,* is imprinted. *SMPD1* resides within a cluster of imprinted genes on 11p, and a patient with Beckwith-Wiedemann syndrome due to uniparental disomy of chromosome 11 was previously found to have reduced ASM activity. Also, although there is a correlation between the disease severity of NPD and the level of residual ASM activity, it has been difficult to predict phenotype on the basis of the type of *SMPD1* mutation. Finally, heterozygous NPD carriers sometimes present with signs of the disease. Simonaro et al. evaluate the imprinting status of *SMPD1* by determining which alleles are expressed in patients with ASM-deficient NPD. They determine that only the maternal allele is expressed in each case, because of methylation of the paternal allele. Functional analysis of the maternal variants enables the authors to make genotype-phenotype correlations.

Origins of Inv(10)(p11.2q21.2), *by Gilling et al.* (*p. 878*)

Inv(10)(p11.2q21.2) is a common pericentric inversion that has been identified in a number of populations and that is believed to be nonpathogenic. Because the inversion is so widespread, it was hypothesized that it may have arisen independently in a number of geographic locations. Gilling et al. characterize the breakpoints of the inversion in 20 families from the United Kingdom, Germany, Denmark, Sweden, and Russia, to compare the sequences involved in the chromosomal rearrangement.

No genes are directly disrupted by the inversion and, although there are no obvious sequence motifs at the breakpoints that predispose to chromosomal rearrangement, repetitive elements in the flanking regions might contribute to instability. Surprisingly, the authors find that the sequence of the breakpoints in each of the families is exactly the same. Haplotype analysis revealed that all the inversions are identical by descent, which demonstrates that a single founder event was responsible for the common variant in each of the unrelated families.

This Month on the Cover

In 1952, Alfred Hershey and Martha Chase reported their famous "blender" experiment that demonstrated that DNA, not protein, was the genetic material (J Gen Physiol 36:39–56). They began by labeling the protein coat of bacteriophages with radioactive sulfur and allowing the phages to infect bacteria cells. They then used a blender to dislodge the phage particles from the cells. When they spun down their reactions, Hershey and Chase found that the radioactivity remained in the phage fraction and had not been passed on to the bacteria. In contrast, when the DNA of the phage was labeled instead, the bacteria became radioactive. Special thanks to Lee D. Simon, Rutgers University, for the micrograph.

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