# This Month in the *Journal*

For those of us without a statistical background, gene-mapping methods can sometimes be perplexing. To unravel their mysteries, we present two invited editorials. The first, by Dale Nyholt (p. 282), explains the statistical properties of the most popular linkage analysis techniques, with particular emphasis on the variability in the significance of a LOD score, depending on the technique that is used. Next, Jurg Ott and Josephine Hoh (p. 289) provide an overview of statistical methods for both gene mapping and the analysis of microarray data.

Our next two invited editorials provide commentary on articles that are included in this issue. Abel and Casanova (p. 274) discuss the finding, by Greenwood et al. (p. 405), of a tuberculosis-susceptibility locus. They speculate on the likely spectrum of genetic control for tuberculosis and on the ramifications of this finding. The next editorial is by Folstein and Mankoski (p. 278), who pull together the results presented by Lai et al. (p. 357) and Vincent et al. (p. 510). The Vincent et al. article reveals a gene, termed "*RAY1,*" that is interrupted by a translocation breakpoint on chromosome 7q31 in a patient with autism. On an overlapping region of 7q31 is *SPCH1,* which is associated with a severe disorder of speech and language and which, through work by Lai et al., has been narrowed to ~6 Mb. Folstein and Mankoski discuss the possibility that a single gene could be involved in both autism and the speech and language disorder.

***Analysis of SNPs around* APOE,** *by Martin et al.* (*p. 383*)

The use of single-nucleotide polymorphisms (SNPs) as markers for genetic mapping has been touted as the wave of the future, and large initiatives with the aim of identifying hundreds of thousands of SNPs are currently under way. But how effective will SNPs be in identifying the genes involved in complex disorders? Eden Martin and colleagues (p. 383) have performed a study designed to examine this problem, using *APOE* as a model locus. *APOE* is a well-established susceptibility gene for late-onset Alzheimer disease. Using 60 SNPs surrounding *APOE,* in both case-control and family-based analyses, the authors have attempted to collect evidence for association between Alzheimer disease and the already-identified locus. Not only do their results demonstrate that associations can be detected at SNPs near a complex disease gene, but they also suggest how SNPs can be more effectively utilized in this type of analysis. These suggestions include the use of a high density of SNPs and the incorporation of haplotype analysis, which can yield more-significant results than are provided by single-locus tests. Interestingly, there were SNPs in *APOE* that were not highly associated with Alzheimer disease, as well as SNPs in a neighboring gene that did show strong association with the disease. These results highlight the difficulties in definitively identifying the gene associated with a disorder, even when the general genetic region of interest is known, and emphasize the need for a multidisciplinary approach to gene identification. This study will no doubt be very useful as a model for SNP-based association studies of complex disease.

***Trisomic Pregnancy and Menopause,*** *by Kline et al.* (*p. 395*)

The increased risk of autosomal trisomy with advancing maternal age has long been recognized but not understood. Dorothy Warburton has hypothesized that this increased risk is due to depletion of the oocyte pool in older women. This hypothesis, which is tested by Warburton and colleagues in this issue of the *Journal,* predicts that women who have had trisomic pregnancies will undergo menopause at an earlier age, since menopause occurs when the oocyte pool drops below a certain level. In their study sample, Kline et al. found that women whose index pregnancy was a trisomic spontaneous abortion had a lower median age at menopause than did women whose index pregnancy was a chromosomally normal birth or loss. These results fit very nicely with those of a recent *Journal* Report by Freeman et al. (66:1680–1683 [cited by Kline et al.]), who found that women who have either a congenital or surgical loss of an ovary are at an increased risk for a child with Down syndrome (trisomy 21). Both papers are consistent with an association between diminished oocyte pools and trisomic pregnancies and provide support for the Warburton hypothesis that oocytes in a suboptimal state of development can become the dominant follicle in a diminished oocyte pool and that these suboptimal oocytes are more likely to exhibit nondisjunction.

***Chromosome 11 Melanoma Tumor–Suppressor Genes,*** *by Goldberg et al.* (*p. 417*)

Although significant evidence exists for the presence of multiple tumor-suppressor genes on chromosome 11, it has been difficult to delineate the regions involved. Previous research has focused on the identification of homozygous deletions on this chromosome and has


0002-9297/2000/6702-0001$02.00

turned up only one such region, on chromosome 11q23. Goldberg et al. have reasoned that haploinsufficiency of a tumor-suppressor gene might provide a growth advantage to tumor cells, and they have designed a new mapping strategy based on this idea. This method, termed "homozygosity mapping of deletions" (HOMOD), uses the number of homozygous genotypes observed at adjacent loci to determine the probability that a hemizygous chromosomal deletion exists. These researchers have examined melanoma cell lines for extended regions of homozygosity (i.e., homozygosity at more than five adjacent markers) and have used these data to define deletions. Loss of heterozygosity (LOH) studies on melanoma samples were also performed, and the results correlated very well with the regions defined by HOMOD analysis. Together, the HOMOD and LOH analyses identified six small regions of overlapping deletions that better defined the locations of putative tumor-suppressor genes on chromosome 11. HOMOD is a promising method for the further identification of tumor-suppressor genes in human cancers.

***A High Frequency of HV1 Heteroplasmy,*** *by Tully et al.* **(***p. 432***)**

As the only significant noncoding region in the mitochondrial genome, the HV1 locus has been used extensively in studies of human evolution and population genetics, as well as in forensic testing. Although the chance of mtDNA heteroplasmy is high because there are hundreds of copies of mtDNA per cell, a mixed population of mtDNA has not often been observed. Tully et al. have used a sensitive, denaturant gradient gel electrophoresis method (DGGE) to measure the population incidence of HV1 sequence heteroplasmy and have found that it occurs in 13.8% of the individuals examined and at a broad spectrum of sites within HV1. This level of heteroplasmy is much higher than that previously measured. Presumably, this is due to the fact that most heteroplasmic variants occurred at very low proportions that could not be detected by earlier, less-sensitive methods. Accurate measurements of HV1 heteroplasmy, by methods such as DGGE, should allow better estimations of generational mutation rates in the mitochondrial genome, a calculation critical for evolutionary studies using mtDNA.

***Report* (ABCR *Mutations in AMD*),** *by Allikmets and the International ABCR Screening Consortium* **(***p. 487***)**

In a 1997 study, Rando Allikmets and colleagues provided evidence that heterozygous carriers of mutations in *ABCR* are predisposed to age-related macular degeneration (AMD), a very common form of acquired visual impairment in the elderly (see the References list provided in the article by Allikmets and the International ABCR Screening Consortium). However, this association has been controversial and difficult to corroborate. To investigate further the relationship between *ABCR* mutations and AMD, a large, multinational consortium was established. The study presented, in this issue of the *Journal,* by the International ABCR Screening Consortium was designed to eliminate some of the controversy of previous studies, including arguments on population stratification and on statistical corrections. More than 1,200 cases of AMD and a similar number of matched controls were screened, in a masked fashion, for the presence of two of the more common *ABCR* variants, G1961E and D2177N. Carriers of D2177N and carriers of G1961E were found to have three- and fivefold increases in AMD risk, respectively. These data provide substantial evidence for the association between *ABCR* mutations and AMD. They are interesting for an additional reason: the G1961E and D2177N mutations were first identified in patients with Stargardt disease, a recessively inherited degeneration of the macula of the retina, which has an early age at onset. The variants therefore lead to different phenotypes (including a strikingly different age at onset) if they are in a homozygous or a heterozygous state.

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