Estimating Penetrance Parameters, *by Zöllner and Pritchard* (***p. 605***)

When an association between a genetic variant and a phenotype is identified, the next step is often to determine the size of the effect of that variant on the phenotype. There are pitfalls involved if this is done using data from the same population in which the association was found, because of the ascertainment effect associated with the selection of that data set. Odds ratios calculated in this fashion are often discovered to be higher than the real effect, and this creates problems in subsequent attempts at replication, because of inflated power expectations. One method for proper determination of the variants' effect is analysis of the association in a completely independent and random group of individuals. However, this can be cost and time prohibitive, so it was a goal of Zöllner and Pritchard to be able to correct for the bias in the original data set. Their proposed method used data about the prevalence of the phenotype in the general population to establish an estimator for the penetrance of the variant. Simulations demonstrated that power calculations with use of odds ratios estimated with their algorithm were more accurate. Additionally, using real data from the original study that demonstrated an association between *PPARγ* and diabetes, the authors were able to properly correct for the ascertainment bias and to determine the effect of the variant more accurately.

Regularized Regression Haplotype Analysis, *by Li et al.* (***p. 705***)

Using haplotype methods in association studies has its advantages, but arguments remain over the best way to choose the haplotypes for analysis. Techniques employing linkage-disequilibrium blocks as guidelines can be limiting, whereas sliding-window strategies can lose a lot of power because of the large number of tests performed. Sliding-window methods with a fixed window length can be problematic when large regions are analyzed, so algorithms using variable-sized windows have been developed. To avoid losing a great deal of power to corrections, efforts have been made to limit the size and number of the windows, but current methods may lead to a loss of sensitivity or can be very time consuming. Li et al. propose a strategy that first predicts maximum window size on the basis of haplotype diversity and sample size and then performs an efficient joint analysis with use of a regularized regression. The regression is able to take into account redundancy and complementariness of the haplotypes, to decrease the effective number of degrees of freedom, and, subsequently, to improve power.

Admixture Mapping of Inflammatory Markers, *by Reich et al.* (***p. 716***)

Circulating levels of inflammatory markers are associated with risk of developing various diseases, including atherosclerosis, myocardial infarction, stroke, and autoimmune disease. Differences in the levels of certain markers have been observed between European Americans and African Americans, so Reich et al. predicted that they might be able to identify genetic loci associated with marker levels through the use of admixture-mapping techniques. In a group of African Americans, they found that the levels of interleukin 6 soluble receptor, IL6 SR, increased with higher amounts of European ancestry, whereas high C reactive protein levels were correlated with the amounts of African ancestry. An admixture scan for association with IL6 SR levels identified a locus on chromosome 1 that contained the gene (*IL6R*) that encodes the interleukin 6 receptor. This gene was of particular interest because its protein, IL6R, localizes to cell surfaces and gets processed to release its soluble form, IL6 SR. Fine mapping with SNPs in the region revealed that IL6 SR levels are associated with an *IL6R* SNP that was expected to interfere with the cleaving of IL6R to IL6 SR.

Etruscan Origins: Novel Clues from mtDNA, *by Achilli et al.* (***p. 759***)

The Etruscans, an ancient population with a unique culture and language, lived in central Italy in the 9th century B.C. They were a highly sophisticated people and differed significantly from other groups that lived in the region. Although it is understood that their demise came about when the region was conquered by the Romans, their origin is a matter of controversy. Some believe that the Etruscans were native Italians who developed into their own group, whereas others support the idea that they were descendants of immigrants who came from the Near East. To gain more insight into this mystery, Achilli et al. chose to study the mtDNA of people living in modern-day Tuscany. This region lies within that settled by the Etruscans and has remained somewhat isolated, so it was hoped that traces of the ancient people might still remain. The authors found that many of the sequences analyzed existed only in the Near East and were not found in surrounding Italy or Europe. These data support the hypothesis that the founders of the Etruscan people were originally from the Near East.

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INI1 ***in Familial Schwannomatosis,*** *by Hulsebos et al.* **(*p. 805*)**

Patients with schwannomatosis develop rare neoplasms called "schwannomas" that are benign and encapsulated. These tumors are also found in people with neurofibromatosis type 2, which is caused by mutations in *NF2*. Somatic mutations in *NF2* have also been identified in the schwannomas associated with schwannomatosis, but linkage studies of schwannomatosis-affected families have suggested that an independent region on chromosome 22 is the causative locus. One gene at this locus, *INI1,* is a tumor-suppressor gene that has been shown elsewhere to be mutated in families in which infants develop malignant rhabdoid tumors. Here, Hulsebos et al. decided to examine whether *INI1* mutations also contribute to familial schwannomatosis, by sequencing the gene in a proband and her father. Both were found to be heterozygous for a germline nonsense mutation in exon 1. Immunohistochemistry of sections of tumors from the patients revealed that some cells were positive for INI1 whereas others were negative, suggesting that loss of heterozygosity in the negative cells contributed to the development of the neoplasm. This mosaic pattern was in contrast to the even staining observed in schwannomas from patients without schwannomatosis.

This Month on the Cover

Mendelian Inheritance in Man (MIM), the ultimate resource describing human genes and genetic disorders, was first published in 1966 by Dr. Victor McKusick (*Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive and X-Linked Phenotypes*. Johns Hopkins University Press, Baltimore). Several print editions followed, until it was eventually published and maintained online. See Dr. McKusick's historical account of the development of MIM and the online version, OMIM, in this month's Perspectives feature "Perspective on MIM/OMIM," starting on page 588. An introduction is provided below by Dr. Arno Motulsky. On the cover, the growth of knowledge compiled through time can be seen by the number of known loci indicated on the X chromosome at three time points: 1975, 1983, and 1998.

Robin E. Williamson
Deputy Editor

This Month in Perspectives

This month's contribution to the "Perspectives" series by Victor McKusick is a "must read" article for human and medical geneticists. Most readers of the *AJHG* are well acquainted with McKusick's comprehensive catalogue of human genes, mutations, phenotypes, and modes of inheritance (Mendelian Inheritance in Man, or MIM). The catalogue has been fully available online (OMIM) for some time and is updated periodically. In January 2007, we reached a score of >17,000 entries and almost 15,000 mutations catalogued on OMIM! Victor furnishes a perspective on the origin and history of this monumental Web resource and provides detailed explanations for the rationale of classifying genes, mutations, and phenotypes, with an emphasis on gene-phenotype relationships. He points out that non-Mendelian genetics—such as chromosomal and epigenetic variation, as well as multifactorial or complex disorders and related susceptibility alleles—are beginning to be included in OMIM. The "Perspectives" article provides a wide-ranging exposition about use of the catalogue for insights into medical and human genetics that, in earlier times, were discussed in the front matter of the periodically published MIM volumes and were read with anticipation by many of us. A book with both old and new content of this sort will be of much interest in the future. Since OMIM continues to be a valuable resource for geneticists and clinically for genetics counselors and helps in teaching and research of genetic diseases, a variety of users (including geneticists who study nonhuman species) will profit practically and conceptually from a careful reading of this "Perspectives" article.

Arno Motulsky