Mexican American Admixture Mapping Panel, *by Tian et al.* (***p. 1014***)

Latino Admixture Map, *by Price et al.* (***p. 1024***)

Genomewide Admixture Mapping Panel for Hispanic/Latino Populations, *by Mao et al.* (***p. 1171***)

The Hispanic/Latino American population is the largest minority population in the United States. The people are descendents of European, Native American, and African populations, so are considered to be admixed. Admixture mapping can be used for such a group to identify genetic variants that are associated with diseases that are more prevalent in one founding population than they are in another. If a founding population has a high genetic disease risk, then it is assumed that the disease alleles in subsequent admixed populations will be associated with genomic segments from the at-risk founding population. To effectively distinguish which regions of an admixed genome come from which founding population, it is necessary to have a genomewide set of markers that are found at different frequencies in each population. Tian et al., Price et al., and Mao et al. have approached this matter in somewhat different fashions, to assemble such a panel of informative markers. These panels will serve as critical tools in the endeavor to search for new disease genes by use of admixture mapping in Hispanic/Latino American populations.

SLC26A4 ***Transcription Control in PS-EVA,*** *by Yang et al.* (***p. 1055***)

Pendred syndrome (PS) and a type of nonsyndromic hearing loss with enlarged vestibular aqueduct (EVA) are both caused by mutations in *SLC26A4*. Although family evidence supports recessive inheritance of PS and EVA, a large proportion of affected individuals carry only a single known mutant allele. A possible alternative mechanism for the development of these diseases was suggested by work with mice deficient for the transcription factor *Foxi1*. These mice do not express *Slc26a4,* and they demonstrate hearing loss with EVA, so it was predicted that activation by FOXI1 would also be required for proper *SLC26A4* expression in humans. Yang et al. examined the noncoding regions of *SLC26A4* in a large number of PS/EVA–affected families, in many of which only one or no known mutation had been identified. In nine families, the authors found a single nucleotide change in the promoter region that was expected to disrupt a consensus binding site for FOXI1. The authors then demonstrated that this mutation significantly reduced the ability of FOXI1 to bind to the promoter and to activate *SLC26A4* expression. The interaction between the two genes was further elucidated by the identification of patients in the group who had mutations in *FOXI1*. These mutant FOXI1 proteins were also unable to effectively activate *SCL26A4*.

Detection of Multifactor Interactions, *by Lou et al.* (***p. 1125***)

There is increasing evidence that it is important to consider gene-gene and gene-environment interactions when searching for the causative factors of complex diseases. Because detection of such interactions by use of methods designed to study a single factor at a time can fail and/or be computationally unfeasible, multifactor approaches have been developed. One such algorithm, the multifactor dimensionality reduction method (MDR), is more computationally tractable than are other approaches, but it has been restricted by limitations, including its inability to handle covariates and be applied to continuous traits. Lou et al. addressed these issues in their development of a generalized form of MDR (GMDR), which increases the flexibility and application of the method. Their simulations demonstrate the increased accuracy achieved with the consideration of covariates. The GMDR was also applied to genotyping data from a study searching for an association between four candidate genes and nicotine dependence. Although the independent main effects of SNPs in two of the genes were nonsignificant, a significant interaction between the two genes was identified.

Causes of Skewed X Inactivation, *by Muers et al.* (***p. 1138***)

In general, X-chromosome inactivation (XCI) is expected to occur at random in unaffected females, so that the number of cells expressing the maternal X chromosome is roughly equal to the number expressing the paternal X chromosome. In situations of X-linked disease, the inactivation is often significantly skewed in carriers, such that expression of the X chromosome without the disease mutation is preferred. Female carriers of one such disease, ATR-X syndrome, have skewing in several tissue types, and Muers et al. were interested to find out the mechanism behind the altered X-chromosome expression. Using a mouse model of Atrx deficiency, the authors set out to determine whether the skewing was the result of a fundamental dysfunction of the XCI process, a selection step early in embryogenesis that affected all subsequent cells,

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or tissue-specific selection that occurred later in development. By following the ratio of XCI in developing embryos, the authors observed that, by late gestation, skewing increased in a cell-specific manner. Additional analysis of the skewing in the hematopoietic system revealed that, although cell selection occurred early in the establishment of the stem cell population, an absence of skewing if the expression of Atrx was abolished postnatally suggested that Atrx was not necessary for adult hematopoiesis.

DYT1 *Intragenic Modification of Susceptibility, by Risch et al.* (*p. 1188*)

A recurrent GAG deletion mutation in *DYT1* is the most common cause of primary torsion dystonia (PTD), a disorder involving a wide range of focal or generalized dystonia. Although the mutation is necessary for the development of PTD, the penetrance of the mutation has been estimated to be ~30%. This has led to the hypothesis that modifying factors must contribute to the eventual phenotype expression. Risch et al. decided to look at how other sequence variants within *DYT1* might affect the functional consequences of the GAG deletion. The GAG mutation is thought to cause disease by producing a dysfunctional *DYT1* gene product that causes inclusions of endoplasmic reticula in vitro. A second variant in *DYT1* has recently been identified that also has this effect in cell culture, but, interestingly, the presence of the two variants together results in the formation of fewer inclusions. With this observation in mind, the authors measured the frequency of *DYT1* variants in GAG carriers with PTD and in those carriers without PTD. They discovered that the previously described SNP, in line with its ability to modify the inclusion effect of the GAG mutation in vitro, was more frequent in carriers without a PTD phenotype. Although this variant was rare and could not explain the reduced penetrance of the GAG deletion in its entirety, the measurement of its effect is expected to significantly add to the genetics-counseling information available for those who carry the SNP.

This Month on the Cover

In 1908, Godfrey Harold Hardy (Science 28:49–50) and Wilhelm Weinberg (Jahreshefte des Vereins für vaterländische Naturkunde in Württemberg 64:368–382) each independently determined an expression to represent the stability of allele and genotype frequencies within an ideal population. Hardy-Weinberg equilibrium predicts that allele frequencies will remain constant over time. This equilibrium applies to loci in populations that are not affected by inbreeding, migration, small population size, assortative mating, natural selection, or mutation. The Hardy-Weinberg equation, $p^2 + 2pq + q^2 = 1$, denotes the frequency of allele A with the variable "p" and denotes the frequency of allele a with the variable "q." For a population meeting the criteria for Hardy-Weinberg equilibrium, the genotypic frequency of AA should equal p^2, the frequency of Aa should equal $2pq$, and the frequency of aa should equal q^2. On the cover, the frequencies of the three genotypes of a biallelic locus in Hardy-Weinberg equilibrium are graphed versus the frequency of allele a. Special thanks to Andrew Kirby for assistance with the image.

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