This Month in the *Journal*

Genetic Structure and Race/Ethnicity, *by Tang et al.* **(***p. 268***)**

Population structure is a concern in case-control association analyses, especially with samples from the United States, where there is so much mixing between populations. This mixing potentially can lead to hidden population structure and can confound the results of these studies. The work by Tang et al. should allay some of these fears by providing more information on the determinants of population structure. In a large sample recruited in the United States and Taiwan, Tang et al. find that there is a very high correspondence between group membership that is based on self-identified race/ethnicity and membership that is based on genetic-cluster analysis. That is to say that the major racial/ethnic categories (white non-Hispanic, black non-Hispanic, Hispanic, and East Asian) in the study corresponded almost completely with the four genetic clusters that were generated on the basis of genotypic information. Further, when they compared white or African American non-Hispanic subpopulations from different recruitment sites around the United States, they did not find significant allele-frequency differences. Thus, the impact of sampling these populations from different geographic locations is likely to be fairly modest. For a comparison of linkage maps for these populations, please see the article by Jorgensen et al., who used data from the same study, the Family Blood Pressure Program.

Natural Selection on Chimpanzee* CCR5,** *by Wooding et al.* **(p. 291***)**

The chemokine receptor CCR5 is important for local control of the immune response, but it is more notorious for its role as a coreceptor for HIV infection of leukocytes. Variation in *CCR5* has been associated with HIV susceptibility, and, in fact, the *CCR5*-Δ*32* allele in humans is associated with slowed disease progression or near-complete resistance to HIV infection in the heterozygous and homozygous states, respectively. Wooding et al. are interested in the fact that, although chimpanzees can be infected with HIV and simian immunodeficiency virus (SIV) through a CCR5-dependent mechanism, they rarely develop immunodeficiency as a result of these infections. This led to the hypothesis that variation in *CCR5* in chimpanzees might play a role in resistance of these animals to HIV/SIV–mediated disease. Wooding et al. approach this problem from an evolutionary standpoint and assess the patterns of *CCR5* variation in wild-born chimpanzees, compared with other chimpanzee loci as well as with the human locus. Genetic diversity is typically higher in chimpanzees than in humans, but Wooding et al. found that the opposite is true at the *CCR5* locus. Several lines of evidence—based on the patterns of variation at *CCR5*—point to the fact that a selective sweep occurred at this locus in chimpanzees, whereas balancing selection is evident in humans. Although the precise target for selection in *CCR5* has not yet been teased out, the different patterns of *CCR5* variation in chimpanzees compared with humans suggest that functional variants are lying therein. Until they are identified, their role in resistance to HIV/SIV–mediated disease remains plausible but unclear.

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Epigenetic Influences in FRAXA Deletions, *by Edamura et al.* **(***p. 302***)**

It is perhaps curious that there is negligible postnatal somatic trinucleotide-repeat instability associated with the fragile X syndrome locus (*FRAXA*) and that repeat expansions are limited to maternal transmissions. Edamura et al. used a cell-culture system to identify factors governing the instability of the *FRAXA*-associated CGG repeat. In this system, they put the SV40 origin of replication into a construct containing a CGG repeat and *FRAXA*-flanking sequence and assessed the length of the repeat tract after replication. They found replication-dependent deletions in the repeat tract and were able to assess the effects of different parameters on this repeat instability. In addition to repeat size, instability was affected by the position of the repeat relative to the origin of replication, the presence of CpG methylation, and whether the repeat was on the leading or lagging strand. The authors emphasize the role of epigenetic modification in the modulation of *FRAXA*-repeat instability and propose a model to correlate their findings with empirical observations for *FRAXA*-repeat instability.

SLC25A22 ***Mutation in Neonatal Epilepsies,*** *by Molinari et al.* **(***p. 334***)**

Molinari et al. present evidence that impaired mitochondrial-glutamate import can lead to severe epilepsy. The family they studied included four affected siblings with a severe neonatal epilepsy featuring a characteristic electroencephalogram pattern. Each of them was homozygous for a missense mutation in *SLC25A22,* which encodes a glutamate transporter that moves glutamate from the cytosol into the mitochondrial matrix. The as-

sociation of this gene with the phenotype is supported by the findings that fibroblasts from the affected individuals fail to oxidize glutamate normally and that the mutant protein, when reconstituted into liposomes, is defective for glutamate transport and exchange activities. During development, *SLC25A22* expression is limited largely to the brain and is seen in areas relevant for myoclonic seizures. A pathogenic mechanism for this mutation is not clear, but the authors speculate that impaired glutamate transport into the mitochondria might alter glutamate metabolism in glial cells. These cells are involved in the clearance of synaptically released glutamate, the major excitatory neurotransmitter in the brain.

***Constitutional Disruption of* HMGA2,** *by Ligon et al.* (*p. 340*)

Disruptions of *HMGA2* have been found in several types of benign tumors, including lipomas and uterine leiomyomas. The high-mobility–group (HMG) proteins are involved in regulating gene expression, but the more specific function of HMGA2 is still the subject of speculation. The report by Ligon et al. may provide insight into its function, with the identification of an individual who has a constitutional disruption of *HMGA2* due to an inversion. This inversion truncates *HMGA2* and does not appear to result in a fusion transcript with another gene. The phenotype of this boy provides hints that HMGA2 might be involved in growth control and adipogenesis, because he shows extreme somatic overgrowth and multiple lipomas, a phenotype that is similar to previous descriptions of mice expressing truncated HMGA2. This individual also has advanced endochondral bone and dental ages, which suggests that HMGA2 might also have a role in the development of these tissues.

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