This Month in the *Journal*

Racial and Ethnic Categories in Genetics, *by the Race, Ethnicity, and Genetics Working Group* (*p. 519*)

This month in the *Journal,* the Race, Ethnicity, and Genetics Working Group of the National Human Genome Research Institute provides their view of human genetic variation and how it fits with the complicated concepts of race, ethnicity, and ancestry. They discuss these interactions in terms both of how these concepts relate to studies of population history and of how racial/ethnic categories can be a hindrance or a tool in genetic association studies. Rather than guidelines for the use of race, ethnicity, and ancestry in genetic research, this review provides food for thought, and the Working Group urges researchers to proceed sensitively, with the hope that genetic research will eventually reduce racial and ethnic discrimination.

PTPN22 ***Genetic Variation,*** *by Carlton et al.* (*p. 567*)

Recent reports of the association of *PTPN22* with several autoimmune diseases have provided more concrete evidence that there may be common risk alleles underlying at least some forms of autoimmune dysfunction. R620W was first identified as the risk allele in this gene, an idea that is supported by functional data showing that the minor allele affects binding of PTPN22 to its partner, Csk. This SNP has been the focus of several subsequent studies, but it has not been demonstrated to be the sole risk factor for autoimmune disease in this gene. To dissect *PTPN22* further, Carlton et al. sequenced the coding regions of 48 individuals with rheumatoid arthritis (RA) and selected putative functional and tagging SNPs to genotype in two independent RA case-control samples. The W620 risk allele was found on a single haplotype that differed from a second haplotype at that SNP only. Of these two haplotypes, only the one carrying W620 showed association with RA, which indicates that none of the other SNPs marking those haplotypes conferred risk of the phenotype. However, R620W alone does not fully account for *PTPN22*-associated risk of RA in these samples; three additional SNPs were consistently associated with RA independent of R620W, although they may not function independent of each other. In conjunction with W620, the risk allele at SNP37 is sufficient to explain the association of *PTPN22* with RA in one of their samples. This study confirms the importance of R620W in risk of autoimmune disease, but it indicates that there is additional variation in this gene, including SNP37, that also makes a contribution.

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Combined Genomewide Linkage of BP, *by McQueen et al.* (*p. 582*)

Several genome scans for bipolar disorder (BP) have been performed, but, as with many other complex traits, consistent replication of linkage signals has been lacking. To summarize the results from these studies, one can do a meta-analysis, an approach that has yielded some promising results in the past. McQueen et al. wondered whether they could extract more power still from the individual genome scans if they combined the raw genotype data instead of the results of the individual BP scans. Combining the data in this way allowed them to control for some of the potential sources of variability between studies, such as differences in disease classification. With data from >5,000 individuals from 11 studies, they achieved genomewide significance at loci on chromosomes 6q and 8q, neither of which was significant in the individual scans or in the previous meta-analyses for BP. Although this type of study takes a large amount of collaborative effort, it appears that this can be a powerful way to look at genome-scan data from many sources, even when the individual scans haven't provided consistent results between them.

XPNPEP2 ***Associated with Angioedema-ACEi,*** *by Duan et al.* (*p. 617*)

Millions of people take angiotensin I–converting enzyme inhibitors (ACEi) for the treatment of cardiovascular disease. A small percentage of these individuals will develop a potentially fatal adverse reaction to these drugs called "angioedema." Unfortunately, we can't yet identify the people at risk of this complication. Because lower plasma aminopeptidase P (APP) activities have been reported in people with a history of angioedema associated with ACEi therapy (AE-ACEi), Duan et al. wondered whether they could find QTLs regulating APP activity that might then give them a way to determine genetic risk of AE-ACEi. Through use of eight affected families, they found linkage of plasma APP activity to a marker within *XPNPEP2,* a gene that encodes the membrane-bound form of APP. On closer examination of this gene, Duan et al. found that one family carried a truncating deletion in *XPNPEP2,* whereas a variant allele at a SNP upstream of *XPNPEP2* was present in seven of the families. This SNP association accounts for most of the linkage signal to the *XPNPEP2* region, and, in a

separate case-control sample, it is associated with AE-ACEi. These results could be an entrée into pharmacogenetics for ACEi. At this point, however, it is clear that low APP levels do not explain all cases of AE-ACEi, so—even if these results are replicated—genetic testing for *XPNPEP2* variation will not identify everyone who is vulnerable to AE-ACEi.

Sex and Recombination Levels, *by Lynn et al.* (*p. 670*)

Recombination is a common and necessary part of the mechanisms that ensure proper segregation of homologous chromosomes during meiosis. Although the process is incompletely understood, recognition of the factors that affect recombination rates and patterns is helping to elucidate how recombination is regulated. It is known that the frequency and location of exchange events in males is different than that in females. In an effort to understand these sex-specific variations, work has been done in *Drosophila* and in the medaka fish to examine whether it is the genotype or the sexual environment of the cell that is important in determination of how recombination will proceed. Lynn et al. evaluate the question further by studying the situation in mice with unusual sex-chromosome compositions. These included sex-reversed XY female mice, which were generated through transfer of a Y chromosome from *Mus domesticus poschiavinus* to a C57BL/6J background, as well as XO females that were generated on the same background. It is observed that recombination in sex-reversed females, as well as in females with an XO genotype, occurs at the same rate and in similar patterns as for normal females. Of note, recombination of meiotic chromosomes in males with the special Y chromosome resembles that of normal males. These data demonstrate that the regulation of recombination is primarily dependent on the phenotypic sex of the mice and is not due to their genotype.

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