This Month in the *Journal*

Admixture mapping is an approach to gene mapping that makes use of population-specific variation in a trait. The basic idea is to look for association of locus ancestry with the trait in populations that are admixed (i.e., that are derived from mixing of the populations that show differences in the trait). This month in the *Journal,* Paul McKeigue describes recent advances in admixture mapping, including statistical methods and appropriate marker sets, that are making this type of approach increasingly feasible. This approach is attractive because it should be more powerful and should require fewer markers than many traditional gene-mapping methods. However, there are still some challenges in the use of these methods, as Dr. McKeigue explains. He further addresses the types of traits and populations for which these methods will be most useful.

Our second review article this month is by Dirk Kleinjan and Veronica van Heyningen; in it, they discuss long-range control of gene expression. Especially for genes with complex expression patterns, *cis* regulatory elements can lie at great distances from the transcriptional unit. These elements can serve different functions, such as providing a docking site for DNA-binding proteins or controlling chromatin structure in the region. Several examples of long-range control of expression are given, and the methods for finding these elements are discussed, as are implications of the identification of these elements, in terms of both understanding how genes are regulated and what the elements mean for mutation screens.

Genetic Analysis of* AR *and Prostate Cancer, *by Freedman et al.* **(*p. 82*)**

Several studies have looked for association between variation in the gene for the androgen receptor (AR) and risk of prostate cancer, and many of these have yielded positive results. *AR* is a biologically plausible candidate gene because androgens are important for the progression of prostate cancer, and antiandrogens are routinely used in its treatment. However, some researchers do not find evidence of this association, and, in the studies with positive results, there hasn't been a consistent model for the genotype-phenotype correlation. This led Freedman et al. to systematically evaluate variation in *AR* in a multiethnic case-control study comprising >4,000 subjects. Freedman et al. report no association in this sample. A polymorphism of particular interest in *AR,* because of its effect on AR function, is a CAG repeat in the coding region. Freedman et al. found no evidence of association of this repeat with risk of prostate cancer using any previously described model of genotype-phenotype correlation. There was also no association of prostate cancer risk with common SNPs or common haplotypes in AR, nor was there evidence of protein-altering mutations in the case sample. Thus, if the *AR* locus has any effect on prostate cancer risk, Freedman et al. think the effect must be either very small or present in only a subgroup of patients.

0002-9297/2005/7601-0001$15.00

Analysis of Meiosis in Human Fetal Oocytes, *by Lenzi et al.* **(*p. 112*)**
Trisomy 21 Maternal Age and Recombination, *by Lamb et al.* **(*p. 91*)**

Two papers in this issue examine the association of meiotic errors in oocytes with chromosomal aneuploidy. The authors of both papers believe that recombination in female germ cells is a key factor in nondisjunction in these cells, but they use different approaches to examine this more carefully.

Lenzi et al. used human female oocytes to study regulation of recombination during meiosis. They report a high degree of variability between oocytes in the number of MLH1-MLH3 foci, which are thought to mark the areas where mature crossover structures between homologous chromosomes will form. A reduced ability to form the proper structures in some oocytes would have consequences for recombination and, ultimately, proper chromosome segregation during meiosis.

Rather than look at oocytes directly, Lamb et al. examined recombination patterns in trisomy 21 cases of maternal meiosis I origin. They were specifically interested in the relationship between maternal age and increased incidence of chromosomal aneuploidy. Although no significant differences were observed across maternal age groups—in terms of the overall amount of recombination on the nondisjoined chromosomes 21—they did find age-dependent differences in the placement of these exchanges. For example, the youngest maternal-age group had the highest proportion of recombinations in the telomeric region, which are more likely to predispose to nondisjunction. With increasing maternal age, the distribution of recombination events associated with trisomy 21 became more similar to that of a sample with normal chromosome segregation. Lamb et al. postulate that there are different risk factors for trisomy 21 at different maternal ages. In younger mothers, this appears to be the presence of recombination patterns that are more susceptible to chromosome 21 nondisjunction. In older women, an increase in recombination-

independent risk factors for nondisjunction leads to the maternal-age effect.

Malic Enzyme and Epilepsy Susceptibility, *by Greenberg et al.* **(***p. 139***)**

A locus on chromosome 18 was implicated elsewhere in common forms of adolescent-onset idiopathic generalized epilepsy (IGE). This locus appears to have involvement in at least three forms of common IGE—juvenile myoclonic epilepsy, juvenile absence epilepsy, and epilepsy with generalized tonic-clonic seizures—whereas other loci involved in common IGE seem to be more specific to a certain seizure type. Greenberg et al. looked for association of IGE with genes in the chromosome 18 region and report a haplotype in the gene encoding malic enzyme 2 (*ME2*) that confers risk for IGE to homozygous carriers, compared with all other genotypes. ME2 is an enzyme that is indirectly involved in synthesis of GABA, one of the main inhibitory neurotransmitters in the CNS. This led the authors to develop a model in which a common underlying factor in many cases of adolescent-onset IGE might be variation, in *ME2,* that affects GABA synthesis in brain and leads to a change in the threshold for cortical excitability. Alteration of the threshold could increase the susceptibility of those individuals to seizures triggered by mechanisms that are at least partly governed by variation in the genetic regions that show linkage to more-specific seizure types. If this model is true, it would help to explain the phenotypic variability for common IGE that is present even within affected families.

Mapping of QTL for Telomere Length, *by Vasa-Nicotera et al.* **(***p. 147***)**

Telomere length is an important determinant of cellular senescence. In proliferating somatic cells, telomeres shorten with age, and this shortening has been associated with age-related disorders, such as cardiovascular disease and arthritis. Because of this association with aging and the implications of telomere length in cancer, Vasa-Nicotera et al. wanted to look for QTLs involved in the determination of telomere length. This seemed a plausible proposition, because, although the telomere length in a particular person is fairly characteristic, there is variation in telomere length between people, and that trait has been estimated to have high heritability. In fact, the authors' results were promising. They used Southern blots to measure telomere restriction-fragment lengths from leukocytes. These measurements were then used as a quantitative trait in a genome scan. Vasa-Nicotera et al. found significant linkage to a locus on chromosome 12 that contains the *DDX11* helicase gene. This is an obvious candidate gene, because other helicases are known to have roles in telomere maintenance. A preliminary analysis with markers in *DDX11* did not provide evidence for an association with telomere length, but the authors are currently pursuing a more detailed analysis of this gene.

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