This Month in the *Journal*

This month in the *Journal,* Norman Arnheim, Peter Calabrese, and Magnus Nordborg contribute a review article on recombination in the human genome. They discuss the importance of deciphering recombination patterns, which may or may not fully explain blocks of linkage disequilibrium, the factors governing resolution and accuracy in recombination maps, and the techniques that can be used to study recombination. Only with a greater understanding of the recombination patterns in a variety of regions will we understand the factors underlying recombination rates.

Genome Scan Meta-analysis: Methods, *by Levinson et al.* **(***p. 17***), *Schizophrenia Genome Scan Meta-analysis,*** *by Lewis et al.* **(***p. 34***), *and* *Bipolar Disorder Genome Scan Meta-analysis,*** *by Segurado et al.* **(***p. 49***)**

Three papers in this issue discuss genome scan meta-analysis (GSMA) and its unbiased application to complex disorders. This method has the advantage that raw data and the precise positional relationships of markers between the original studies need not be known because it places markers within 30-cM bins that are then ranked by linkage scores. In the paper by Levinson et al., simulation studies are used to determine the power of GSMA to detect linkage. These simulations also identify thresholds of significance for application to the actual meta-analyses. GSMA is as powerful as, if not more powerful than, nonparametric linkage methods, partly because the use of bins requires a more modest correction for multiple testing.

Lewis et al. apply the GSMA method to 20 schizophrenia linkage scans in which at least 30 affected case subjects with schizophrenia or schizoaffective disorder were genotyped with markers at 30-cM or finer density. The overall analysis meets three aggregate criteria for linkage, which means that more bins achieved evidence of linkage than expected by chance and suggests that multiple loci are linked to schizophrenia. The only bin that achieves genomewide significance after correction for multiple testing corresponds to chromosome 2p12–q22.1, a region that previously was not considered to be a top candidate region for schizophrenia.

Segurado et al. study bipolar disorder using the GSMA method. They include all known bipolar genome scans with at least 20 affected case subjects. Because major mood disorders coaggregate in families of people with bipolar disorder, they select two primary phenotypic models for use in their analysis. The first includes as affected cases of either BP-I or BP-I and schizoaffective-bipolar disorder (SAB). The second includes BP-I, SAB, and BP-II. A secondary analysis with broader disease models was also performed. Although promising results are identified in several regions, no bins reach a genomewide level of significance in the analysis. This may be due to the much smaller number of pedigrees with bipolar disorder who were analyzed, compared with the schizophrenia study, which decreases the power of the analysis. Simulation studies do suggest the bins that are most likely to be linked to bipolar disorder. The authors plan to update this analysis as additional genome scans are completed.

Selecting SNPs for Association Analyses, *by Meng et al.* **(***p. 115***)**

SNP-selection strategies that maintain the majority of information in a genetic region while limiting the amount of genotyping required will be valuable for association studies. Meng et al. propose a unique SNP-selection method that does not rely on the definition of haplotype blocks. In fact, their method can use genotype data rather than haplotype data. As an added benefit, a sliding-window approach allows them to apply the method to large genetic regions. The goal of their method is to select a subset of SNPs that preserves local haplotype frequencies, thus maintaining haplotype information after marker selection. They compare their method with an extension of the htSNP-diversity method originally proposed by Clayton (see Meng et al. references). Simulations allow them to suggest appropriate sliding-window and sample sizes for use with the methods, and an application to real data from chromosomes 12 and 22 shows that the majority of haplotype information can be maintained while achieving substantial reductions in the number of SNPs that need to be analyzed. Marker selection has a negligible impact on the results of an association study that makes use of the chromosome 22 data, although the authors caution that this may not be true in every case. Meng et al. propose this method as a way to prioritize markers for a first genotyping screen, which can then be followed up with additional markers in the regions of interest.

0002-9297/2003/7301-0001$15.00

Allelic Variation in* COMT *Expression, *by Bray et al.* **(***p. 152***)**

Recent work has found an association between schizophrenia and the gene encoding catechol-O-methyltransferase (*COMT*). Schizophrenia is believed by many to be the result of hyperdopaminergic function, and *COMT* is involved in the metabolism of released dopamine. Bray et al. therefore postulate that *COMT* genotypes that are overrepresented in schizophrenics might be associated with an altered level of *COMT* expression. To determine whether this is true, they quantitate allele-specific expression of *COMT* using mRNA from human brain. Indeed, they do find allele-specific differences in *COMT* expression, including reduced expression of a haplotype that includes the functional Val/Met *COMT* polymorphism and is associated with schizophrenia. Lower relative expression of the schizophrenia-associated allele was also observed for the SNP that was most strongly associated with schizophrenia in the study of Shifman et al. (see Bray et al. references). Although Bray et al. have not demonstrated that these findings translate to protein differences, the results do suggest a nice model wherein reduced expression of *COMT* increases susceptibility to schizophrenia due to increases in dopamine levels.

Unique 3′-End Lesions Cause Fabry Disease, *by Yasuda et al.* **(***p. 162***)**

The gene encoding α-galactosidase A (α-Gal A) is unusual in that it lacks a 3′ UTR and has its polyadenylation signal in the coding sequence. Yasuda et al. report two individuals with Fabry disease, which is caused by a deficiency of α-Gal A, who have mutations altering 3′-end formation of the encoded transcripts. Both mutations are small deletions that cause frameshifts that affect the termination codon. One of the mutations also affects the polyadenylation signal. Although it has been proposed that transcripts lacking a termination codon are degraded by the "nonstop transcript decay" pathway, the transcripts produced in these individuals are stable, possibly due to the unique 3′ structure of this gene. Multiple transcripts are produced from each mutated gene, some shorter than wild type and some longer, that seem to result from alternative polyadenylation site usage and aberrant cleavage site selection. Besides being novel Fabry disease mutations, these deletions also provide further information on 3′-end formation.

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