This Month in the *Journal*

This month in the *Journal*, Eleanor Feingold (p. 217) discusses regression-based QTL mapping. Because it can be overwhelming to consider the different methods out there, Dr. Feingold attempts to simplify this choice through comparisons of the different statistics, in terms of power and robustness, as well as their individual strengths and weaknesses. Dr. Feingold also explains how the new regression-based method developed by Sham et al. (p. 238), which can handle pedigrees of arbitrary structure, might be a useful alternative.

Stratification in Association Studies, *by Ardlie et al.* **(*p. 304*)**

Difficulties in replicating disease-marker associations have often been blamed on population structure, something that has been feared to give spurious results in association studies in general. Using four real case-control cohorts, Ardlie et al. report that, at least in a well-matched, moderately sized sample, population stratification is probably not as big a problem as has been feared. The samples examined were U.S. whites and African Americans with hypertension and U.S. whites and Polish whites with type 2 diabetes, all with appropriate controls. Ardlie et al. found no evidence of significant population structure, which is detected as an overall difference in marker-allele frequencies between groups, except in the African American sample. The stratification among African Americans was no longer seen if recent immigrants were removed from consideration, thereby removing some of the sample heterogeneity. Despite the lack of detectable population stratification, an attempt to replicate an association between the PPARγ Pro12Ala polymorphism and type 2 diabetes still gave discrepant results between the U.S. and Polish populations. Part of the explanation for this discrepancy may be the difference in power between the samples (which are the same size), due to a difference in the frequency of the risk allele between the two populations. Although this work is encouraging for investigators who use heterogeneous populations in association studies, it is clear that researchers need to be aware of factors, other than population stratification, that may affect the outcome of association studies.

Human Long Interspersed Elements, *by Myers et al.* **(*p. 312*)**

A recently integrated subfamily of L1 long interspersed elements can be distinguished on the basis of a shared sequence within the 3′ untranslated region. Myers et al. use this sequence to extract all members of this L1 subfamily from the human genome sequence, yielding 468 hits. All but one of these sequences are absent from the orthologous position in nonhuman primates, indicating that they inserted after the divergence of humans and apes. Although a little more than half of these L1 elements were fixed present (meaning that every tested individual was homozygous for the presence of the element), the rest were polymorphic and were present at widely different frequencies. Some of the polymorphic insertions are population specific, their frequencies differing by at least 25% between populations. These insertions may prove to be useful markers in future population-genetics studies, because they represent unique events; all individuals possessing a particular L1 element inherited it identical by descent. Furthermore, the ancestral allele is known—it is the absence of the insertion—and this makes it easier to determine the root of phylogenetic trees.

Association between Dysbindin and Schizophrenia, *by Straub et al.* **(*p. 337*)**

Straub et al. report that variation in the gene for dysbindin, *DTNBP1*, is associated with schizophrenia. In a previous study by the same group (see the reference cited by Straub et al.), a genomewide scan, using multiplex families with schizophrenia, identified two linkage peaks on chromosome 6, one at 6p24 and one at 6p22. In the current report, the authors further investigate the 6p22 region, using SNPs and simple-sequence length polymorphisms. Markers and marker haplotypes in this region show an association with schizophrenia, and, because the markers with positive results are largely clustered within *DTNBP1,* this may be the gene underlying the association. Dysbindin is likely to be a component of the dystrophin protein complex, which is found in postsynaptic densities in the brain. This complex is thought to be involved in neuromuscular synapse formation and synaptic signaling. Although, as the authors state, models for the role of dysbindin in schizophrenia are entirely speculative, it is interesting to note that neuropathological evidence shows that there are synaptic changes associated with schizophrenia.

Pericentric Inversion Breakpoints of PTR19, *by Kehrer-Sawatzki et al.* **(*p. 375*)**

Although, on a DNA-sequence level, humans and chimpanzees show only ~1% average sequence divergence, some obvious differences can be observed between cer-

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tain human and chimpanzee chromosomes. These include a chromosome fusion and a few pericentric inversions. Although these differences could provide us with a better understanding of human-chimpanzee differences and the evolution of *Homo sapiens,* they have gone largely uncharacterized. Kehrer-Sawatzki et al. have investigated the pericentric inversion by which chimpanzee chromosome 19 differs from human chromosome 17. The authors cloned and characterized the breakpoints and found that they occurred in regions rich with repetitive elements. A repeat-mediated, nonhomologous recombination method is proposed for this inversion. No gene disruption or obvious difference in gene expression was observed between the species, so the direct effects of this inversion are unclear.

A CHEK2 Variant in Familial Breast Cancer, *by Vahteristo et al.* **(*p. 432*)**

Vahteristo et al. have provided the first confirmation, in two independent samples, of the recently published association between the *CHEK2* 1100delC mutation and breast cancer [CHEK2 Breast Cancer Consortium (2002) Nat Genet 31:55–59]. This inactivating mutation was originally identified in individuals with Li-Fraumeni syndrome, a cancer-susceptibility syndrome that often includes breast cancer, and this finding led researchers to determine whether *CHEK2* might be involved in nonsyndromic forms of breast cancer. As in the article by the CHEK2 Breast Cancer Consortium, the *CHEK2* variant was not found at a significantly higher frequency in a population-based series of individuals with breast cancer than in control individuals. However, when cohorts were selected for a positive family history of breast cancer and a lack of *BRCA1* and *BRCA2* mutations, the frequency of the *CHEK2* variant was increased, even when the case patients had only one affected first-degree relative. The frequency of the *CHEK2* mutation was even higher in a group of individuals with bilateral breast cancer. *CHEK2* 1100delC appears to be a relatively common, low-penetrance allele that may make a significant contribution to familial clustering of breast cancer on a population level, but, as yet, mutation screening for this variant on an individual level will not be useful.

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