This Month in the *Journal*

Power to Map QTL in General Pedigrees, *by Yu et al.* (*p. 17*)

There are several different methods that have been proposed for quantitative-trait–loci (QTL) analysis. How, then, should one decide which method to use? To help researchers make this decision, Yu et al. compared regression and maximum-likelihood methods for different family structures. The emphasis was on nuclear families consisting of several siblings and arbitrary general pedigrees. Four methods were considered: the Haseman-Elston (HE) and Visscher-Hopper (VH) regression methods, a maximum-likelihood variance-components method, and a novel regression method (SR) proposed by Sham et al. (2002) (see reference in Yu et al.) for general pedigrees. Theoretical derivations have been used in the past to compare the power of different methods. To do this, assumptions are made about the distributions of the test statistics that, if true, would mean that the relative power of different tests can be determined through calculations of the expected test statistic under the alternative hypothesis of linkage. Yu et al. show that, when the family size is large, test statistics from regression-based methods do not follow the assumed distribution. This makes conclusions regarding relative power based on average test statistics inaccurate. Instead, Yu et al. advocate the use of empirical power for comparisons between the QTL-mapping methods. This type of comparison shows that, in contrast to what has been suggested elsewhere on the basis of theoretical calculations, the SR method is not necessarily more powerful than the variance-components methods for large sibships and general pedigrees.

Cladistic Linkage Disequilibrium Mapping, *by Durrant et al.* (*p. 35*)

To take advantage of the reams of data that can be gained from high-throughput genotyping in population-based samples, Durrant et al. propose a novel disease-gene–mapping method, based on cladistic analysis, that can be used for whole-genome scans, fine mapping, or candidate-gene studies. The idea behind this method is that disease chromosomes that share a mutation should have a more recent common ancestor—and therefore should be more similar—than control chromosomes. This similarity is quantified on the basis of the proportion of matching markers within sliding windows of SNPs and is expressed as a cladogram that is constructed to minimize haplotype diversity within clades. Under the null hypothesis of no association, the haplotypes in each cluster in the cladogram have an equal chance of being carried by a case or by a control. Durrant et al. developed two haplotype-based logistic regression analyses based on this idea and used simulations to show that the power of each is greatly increased, in a variety of situations, over that for a single locus-based test of association. In addition, by use of a real data set of cystic fibrosis cases and controls, their method assigned the strongest signal of association to a window of markers centered very near to the ΔF508 mutation, the most common in the sample. Through use of this type of analysis, genotypes at unlinked markers can be incorporated as covariates to control for population stratification, which is a general concern in case-control studies. Currently, this cladistic approach uses a Bonferroni correction to control for multiple testing, on the basis of the number of windows and the partitions of haplotypes in the cladogram. The power of the approach might be increased even further through use of less conservative correction procedures.

Whole-Genome Scan Using SNP Arrays, *by John et al.* (*p. 54*)

There is a lot of excitement surrounding the possibility that SNP-based linkage studies may be faster and more powerful than microsatellite-based ones because of the development of high-throughput SNP-genotyping technologies and dense SNP-based maps. The question now is: will this prediction hold true? You might remember an article by Middleton et al., in our May issue (Am J Hum Genet 74:886–897), in which a SNP-based genome scan for bipolar disorder yielded more-precise linkage information than did a microsatellite-based scan on the same sample. In this issue, John et al. report similar results from a comparison of the two approaches to find loci involved in rheumatoid arthritis. Moreover, they tested several possible explanations for the discrepancies in results, including differences in the genotyping error rates, the maps used in the analyses, and the information content of the marker sets. The factor with the largest effect proved to be the higher information content of the SNP array, compared with the microsatellites. This work adds to the evidence that SNP-based linkage analysis will be a useful approach for gene mapping. John et al. also show that this type of data can be used as a springboard to association studies. They used their SNP maps to define haplotype blocks in the HLA region, which had the strongest evidence of linkage to arthritis in the genome scans. Directly under the peak of linkage,

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they found significant association of a haplotype with disease.

Long-Term ERT for Fabry Disease, *by Wilcox et al.* **(***p. 65***)**

Early reports of the success of enzyme replacement therapy for Fabry disease were based on a 20-wk phase 3 clinical trial and 6-mo open-label extension study that evaluated treatment with recombinant human α-galactosidase A (Fabrazyme). Because of the resultant renal failure that uniformly develops in untreated patients, therapy for this disorder has focused on the renal pathology, with clearance of accumulated globotriaosylceramide (GL-3) to normal levels in the microvascular endothelium as the desired endpoint. During the first 6 mo of the extension study, the vast majority of treated patients showed clearance of accumulated GL-3 from the kidney and other tissues, such as the skin and heart. However, the majority of patients seroconverted within the first few weeks of treatment, and this raised concerns regarding the long-term efficacy of this therapy. Wilcox et al. now report that patients in the extension study have continued to exhibit normal mean plasma GL-3 levels and have sustained clearance of GL-3 from capillary endothelium for 30–36 mo, despite the high prevalence of seroconversion. Adverse events associated with this therapy have generally been mild and tolerable and severe events few. Overall, the continued safety and sustained success of enzyme-replacement therapy on the basis of measures of GL-3 is encouraging. The next step is to assess its effect on clinical outcomes of Fabry disease, such as stroke and cardiovascular events. A Fabry Disease Registry has been established to follow patients over the long term in order to make these assessments possible.

Mutation of Human* BMP15 *Gene, *by Di Pasquale et al.* **(***p. 106***)**

Since the 2000 report by Galloway et al. (see reference in Di Pasquale et al.) that mutations of *Bmp15* in sheep were associated with increased ovulation in the heterozygous state and with severe infertility in the homozygous state, several groups have attempted to find infertility-associated *BMP15* mutations in women. Di Pasquale et al. have finally found one, in two sisters with hypergonadotropic ovarian failure. This heterozygous missense mutation was inherited from the unaffected father and is located in a conserved region encoding the propeptide region of the BMP15 protein, a member of the transforming growth factor–β (TGF-β) superfamily. This propeptide region is proteolytically cleaved to produce an active, mature form of the protein, but the processing does not occur normally with the mutation. The mutant protein also does not stimulate growth and proliferation of granulosa cells in culture, as it should, and, in fact, it abrogates the stimulating effect of the wild-type protein when the two proteins are added to granulosa cells in equal amounts. These results suggest that BMP15 is required for the progression of folliculogenesis in humans and that mutations in this gene may be an explanation for some cases of female infertility. Its location on the X chromosome hints that haploinsufficiency for *BMP15* could at least partly explain the ovarian dysgenesis associated with Turner syndrome.

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