This Month in the *Journal*

This month in the *Journal,* there is a discussion of Schork and Greenwood's recent paper (*AJHG* 74:306–316), which claimed that NPL methods have an inherent bias against linkage detection when there are uninformative relative pairs in the sample. As you can see in our Letters to the Editor, some of our readers do not feel that "bias" is the appropriate term for the effect described by Schork and Greenwood. Those readers also emphasize that many nonparametric methods do not exhibit this "bias."

TRD and Allele Sharing, *by Lemire et al.* (*p. 571*)

Allele-sharing methods for gene mapping test for deviations from Mendelian segregation. Linkage to a trait locus can be one explanation for this deviation, but there can also be trait-independent transmission-ratio distortion (TRD). Although TRD is not generally taken into account, Zöllner et al. (2004 [*AJHG* 74:62–72]) recently found it to occur in many regions across the genome. This could have implications for use of allele-sharing methods, which generally are not robust to TRD and therefore could yield false-positive results in affected regions. Lemire et al. were aware of this possibility, so, when they found evidence of an asthma locus on chromosome 6 in a region known to be subject to TRD, they were wary. They knew that TRD should affect allele sharing in phenotypically concordant and discordant sib pairs in the same manner but that true trait-dependent linkage should not. To exploit this idea, Lemire et al. developed an allele-sharing test, S_{ad}, that is less sensitive to TRD because it combines allele-sharing information from affected sib pairs and phenotypically discordant relative pairs; true linkage should be apparent as excess allele sharing in the former but not in the latter. The results of this test on the asthma data set are consistent with TRD in the chromosome-6 region, which implies that the authors were right to be cautious in their interpretation of this result.

Mutation History of the Roma/Gypsies, *by Morar et al.* (*p. 596*)

The Roma (Gypsies) are believed to have an Indian origin, but the history of this population is not well documented. Currently, there are many endogamous subgroups of Roma whose identities are based on various social and linguistic factors. The groups share a common genetic history, as evidenced by ancestral Y chromosome and mtDNA lineages and the presence of shared founder mutations. Morar et al. wondered whether these mutations could be used to glean more information about the relationships between and the histories of the Roma subpopulations, so they genotyped a large number of Roma individuals for five such mutations and surrounding markers to construct haplotype genealogies. Genetic support for the historical relationship between the Roma and people from the Indian subcontinent was provided by a congenital myasthenia syndrome–associated haplotype that was found in both populations. This mutation, along with another that causes hereditary motor and sensory neuropathy–Lom, was widely dispersed in the Roma and was presumed to have been present in the founding Roma population. This made it possible to use coalescence estimates to date the founding of the Roma population to ~32–40 generations ago. Other mutations were specific to subgroups of the population, which highlights the differentiation of these subgroups and indicates that they arose after the Roma population fragmented. There was little evidence of gene flow between the subgroups, which suggests that endogamy was put in practice soon after these subgroups arose. In addition to revealing information about the history of the Roma, the authors believe the internal differentiation within the greater Roma population can be used to fine map traits. One could start by crudely mapping a trait in extended families from a single Roma group. From there, a sample of diverse Roma groups could be used to identify shared regions of linkage disequilibrium that may contain the founder mutation.

Sequence-Based Linkage Analysis, *by Furman et al.* (*p. 647*)

Recently, there has been much debate concerning the relative usefulness of SNP versus STR maps for genome-wide linkage analysis. Furman et al. propose a slightly different approach that doesn't make use of the currently available maps but instead is a sequence-based approach in which polymorphisms are simultaneously discovered and genotyped in each pedigree in the study. The information content that can be gleaned from resequencing short, contiguous segments of DNA at various intervals across the genome was determined via simulations, and the authors found that a set of sequence blocks of 500–1,000 bp at 1-Mb intervals provides information content similar to that of a SNP map of a similar density or to that of a 10-cM STR map. Data from chromosome 19 proved that a similar level of information content could be achieved with real sequence. Although perhaps not yet competitive for general genome-scan applications, the

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sequence-based approach does have unique advantages. It uses every sequenced variant as a marker, regardless of its heterozygosity, and thus increases the pool of available variation. The fact that it does not depend on only available markers means it can meet the specific map-resolution and information-content requirements of a particular study. The authors suggest that this method might be useful currently in fine-mapping situations or to identify rare variants that could be used to track chromosomal regions in large pedigrees. As sequencing technologies develop and become less expensive, this method may be more generally useful for genome scans.

MAPT *in Parkinson Disease,* *by Skipper et al.* **(*p. 669*)**

The H1 haplotype of the tau gene (*MAPT*) has been associated with Parkinson disease (PD) and with disorders characterized by aggregation of the four-repeat tau isoform. Evidence suggests that the H1 haplotype can be broken down into subhaplotypes, which could be helpful for more detailed studies of the association of H1 with PD. To do this, Skipper et al. first replicated the association with H1 in a sample of 200 people with PD. H1-specific SNPs were identified and were used to define H1 subhaplotypes, some of which were specific for either the case or the control group. A sliding-window analysis allowed the authors to focus the association with PD on an ~90-kb interval that includes exons 1–4 of *MAPT.* Skipper et al. speculate that genetic variation in or near this region affects *MAPT* expression or splicing and that this in turn modifies risk of PD.

Resistin SNP Induces Type 2 Diabetes, *by Osawa et al.* **(*p. 678*)**

Resistin is an insulin antagonist that is secreted by adipocytes. When it was discovered, researchers hoped that it would provide a mechanistic link between obesity and type 2 diabetes (T2DM). Whereas manipulation of the resistin gene (*Retn*) in mice indicates that it has effects on insulin resistance and on blood glucose levels, the picture in humans is less clear. Osawa et al. studied polymorphisms in the 5′ flanking region of *RETN,* and they report a role for the *RETN* polymorphism −420G→C in T2DM. In their Japanese case-control sample, individuals homozygous for −420G were at increased risk of T2DM. Electrophoretic mobility shift assays indicated that proteins found in adipocyte extracts bind to the G but not to the C allele of this SNP, and additional experiments revealed these proteins to be Sp transcription factors. This difference in transcription-factor binding is thought to enhance *RETN* promoter activity, which translates into higher serum-resistin levels in diabetic individuals homozygous for −420G, thus providing a molecular link between resistin and T2DM.

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