This Month in the *Journal*

Population Genetics of Haplotype Blocks, *by Anderson and Slatkin* **(***p. 40***)**

Several recent studies have attempted to determine the factors that generate haplotype blocks in the human genome. Whereas some results suggest that haplotype block boundaries correspond to recombination hotspots, other studies have concluded that one need not invoke hotspots in a model of haplotype-block generation. Anderson and Slatkin have revisited this problem and have focused on a particular genomic region in which haplotype blocks are definitely present, chromosome 5q31, using dense genotype data from Daly et al. (2001 [see reference in the article by Anderson and Slatkin]). They did a series of simulations under conditions designed to closely mimic the data collection process for the chromosome 5q31 data. They found that the extent of within-block haplotype diversity was consistent with either of two models, one with hotspots in a population of constant size and one with no hotspots and rapid population growth. To distinguish between the two models, they looked at estimates of recombination rates near block boundaries in the simulated and 5q31 data. Because hotspots of intensity sufficient to create haplotype blocks were not evident, these estimates suggest that population growth, rather than the presence of hotspots, is the primary cause of the haplotype blocks in this region. This does not mean that there are not any hotspots in this region but rather that they are not present at most haplotype-block boundaries. Even in regions with recombination hotspots, population growth should be considered as a parameter that can affect the formation of haplotype blocks.

Genomewide Transmission Distortion, *by Zöllner et al.* **(***p. 62***)**

Although little is known regarding transmission distortion in humans, this evolutionarily important phenomenon might actually be widespread. To test this hypothesis, Zöllner et al. did a genomewide study of transmission distortion in a sample of nuclear Hutterite families. They determined whether the fraction of identical-by-descent sharing among siblings exceeded Mendelian expectations. Average genomewide sharing among the sibling pairs in this sample is 50.43%, which is significantly higher than the predicted 50%. The increased sharing is spread across the genome, suggesting many loci are involved, and it is not restricted to a subset of families. Transmission distortion was also observed in two of three additional samples that were examined from other populations. Because average genomewide sharing of maternal and paternal alleles is similar and maternal and paternal sharing patterns are correlated, it appears that viability selection plays a role in the transmission distortion. This result could have implications for gene-mapping studies, because commonly used linkage methods are generally not robust to transmission distortion, leading to increased false positives. The authors suggest that, for large studies, it may be advisable to assess average genomewide sharing in the sample and to use this value as a baseline before assessing excess transmission by use of these mapping methods.

Linkage Disequilibrium–Based SNP Selection, *by Carlson et al.* **(***p. 106***)**

It is generally not feasible or productive to genotype all common variation in a gene of interest when undertaking a population-based case-control study. If a randomly chosen subset of markers is used, one must assume that some of the genotyped markers will be correlated with the genetic variation that actually confers risk for the phenotype under study. The power of these studies depends on the linkage disequilibrium (LD) between the genotyped and risk markers. To increase the efficiency of marker selection, Carlson et al. propose an algorithm that identifies optimized minimal sets of single-nucleotide polymorphisms (SNPs), termed "tagSNPs," using observed LD. To use their method, only a modest number of samples need to be resequenced to define all common SNPs in a candidate gene. The algorithm uses the observed patterns of LD and is designed to ensure that all polymorphisms above a specified frequency threshold are either assayed directly or exceed a specified level of LD, as measured by r^2, with an assayed polymorphism. Carlson et al. tested the algorithm on a set of 100 candidate genes that were resequenced in 24 African Americans and 23 European Americans. In situations in which a single SNP is associated with risk, tagSNPs selected using this algorithm are more powerful than an equivalent number of either haplotype-selected htSNPs or randomly selected SNPs. At a relatively stringent r^2 threshold, the tagSNPs could also resolve the majority of haplotypes in the candidate genes. Although common variation tends to be shared between populations, the algorithm works most effectively if tagSNPs are selected separately for each population.

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Novel Syndrome Due to* MCT8 *Mutations, *by Dumitrescu et al.* (*p. 168*)

Thyroid hormone plays a crucial role in fetal and early postnatal development. Dumitrescu et al. report two families with altered thyroid function in which affected males have neurological abnormalities and delays in motor and mental development, whereas female relatives of the probands have a milder thyroid phenotype but no neurological abnormalities. Both families have abnormalities in the relative serum levels of iodothyronines, and the neurological defects in the males were refractive to normalization of serum thyroid-stimulating hormone levels. The authors turn to *MCT8,* which has recently been characterized as an iodothyronine transporter in rats. The location of *MCT8* on the X chromosome makes it a particularly attractive candidate gene because of the more severe phenotype in males. *MCT8* mutations were found in both families, with the affected males being hemizygous and the affected females heterozygous. The association of thyroid-hormone abnormalities with mutations in *MCT8* provides evidence that thyroid hormones require specific channels for their cellular uptake, a topic that has been under debate for quite some time.

A Repeat Influences Penetrance of 5T Variant, *by Groman et al.* (*p. 176*)

The 5T variant of *CFTR* is defined by a tract of five thymidines in intron 8 that influences inclusion of exon 9 in the processed transcript. Although it is thought to be carried by ~25 million people in the U.S., the significance of 5T is not absolutely clear. Some people who have 5T in *trans* with a severe cystic fibrosis (CF) mutation have nonclassic CF or male infertility due to congenital bilateral absence of the vas deferens, but others are healthy and fertile. A stretch of TG repeats adjacent to 5T correlates with exon 9 skipping and is thought to increase penetrance of 5T. Groman et al. did a collaborative study and found that TG repeat number does influence disease risk. In fact, all individuals in their study who carried TG13-5T and a severe CF mutation in *trans* were affected, whereas TG11-5T was found in 78% of unaffected individuals. These results better cement the idea that TG-repeat testing is valuable for counseling individuals carrying 5T.

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