Human Recombination Hotspot Detection, *by Li et al.* **(*p. 628*)**

Recombination occurs throughout the genome at specific sites, termed "hotspots," that separate genomic DNA into regions of high linkage disequilibrium (LD). An understanding of where these hotspots occur not only provides insight into the mechanisms behind recombination but may also affect association studies that incorporate LD. Sperm-typing techniques can be used to look at recombination on a fine scale, but they are experimentally intensive and slow. To make the search for hotspots more efficient, researchers have developed computational means to predict recombination hotspots from population genotype data. The algorithms vary in their approach and differ in their ability to correctly identify hotspots, their need for phased data, their false-positive rate, and their computational cost. Previously, when the recombination site predictions of the top detection methods were compared with the hotspots identified experimentally by sperm typing, the most accurate technique was the slowest and was unable to handle unphased data. Here, Li et al. develop TWPLL (truncated, weighted pairwise log-likelihood), a method that is faster and can be applied to phased and unphased data. After demonstrating the speed and accuracy of TWPLL, the authors use their method on the ENCODE regions to predict new hotspots.

Bayesian Haplotype Analysis, *by Morris* **(*p. 679*)**

In the search for associations between polymorphisms and complex diseases, many methods analyzing multilocus haplotypes are being developed and used. There has been a tendency among researchers to use these algorithms to fit their data to multiplicative models but to ignore dominance effects, because of concern over the penalties associated with additional testing. Here, Morris presents an approach that accommodates dominance effects and allows for the identification of associations that would not have been observed if a nonmultiplicative model had not been incorporated. He expands on his earlier development of a method that uses common ancestry to cluster marker SNP haplotypes, via a Bayesian partition model, into clades, in an effort to minimize lost information. Comparisons of the new algorithm, GENEBPMv2, with other methods demonstrate how power can be gained, without too much cost, by allowing for dominance. The usefulness of this approach is presented with an analysis of genotype data of *CYP2D6,* a gene involved in drug metabolism.

HLA-B Matching Increases Schizophrenia Risk, *by Palmer et al.* **(*p. 710*)**

The etiology of schizophrenia is considered to be complex, with susceptibility to the disease being influenced by genetic and environmental factors. Previous studies have suggested that complications during pregnancy may contribute to the risk of a child's developing neurodevelopmental disorders. One such complication, Rhesus incompatibility, occurs when maternal antibodies are produced against paternal red-blood-cell antigens. This maternal response can cause significant risk to the developing fetus. In contrast, studies of the human leukocyte antigen (HLA) locus support the hypothesis that the production of maternal antibodies to paternal HLAs may actually improve the chances of a healthy pregnancy. Palmer et al. therefore predicted that if the maternal HLA alleles match those of the developing fetus, complications may arise that would increase the risk of schizophrenia in the child. The authors searched for an association between HLA matching and the risk of schizophrenia-related disorders and found significant evidence that matching of HLA-B alleles increases the risk of schizophrenia in female offspring.

Two Founding Events for* LRRK2 *G2019S, *by Zabetian et al.* **(*p. 752*)**

The G2019S mutation in *LRRK2* is a frequent cause of autosomal dominant Parkinson disease in populations of European descent. A number of studies that have looked at probands from Europe, the Middle East, and North Africa have found the mutation on a single founder haplotype. When analyses were then done to estimate the time since the most recent common ancestor, it was difficult to reconcile the time with the known historical data of the populations involved. To learn more about the region and to potentially resolve the discrepancies associated with the evolution of the G2019S mutation, Zabetian et al. reassessed the polymorphisms in the region and chose five new markers to evaluate in a new set of cases and controls. These studies revealed two distinct haplotypes that are predicted to have arisen from two independent founders. The authors also used their new data to recalculate how long ago the families with haplotype 1 may have shared a common ancestor. The approach they used yields a time that more easily fits with the migrational patterns of the people studied.

SAMD9 Mutation in NFTC, *by Topaz et al.* **(*p. 759*)**

Familial tumoral calcinosis (FTC) is a life-threatening condition characterized by the deposition of calcified tumors.

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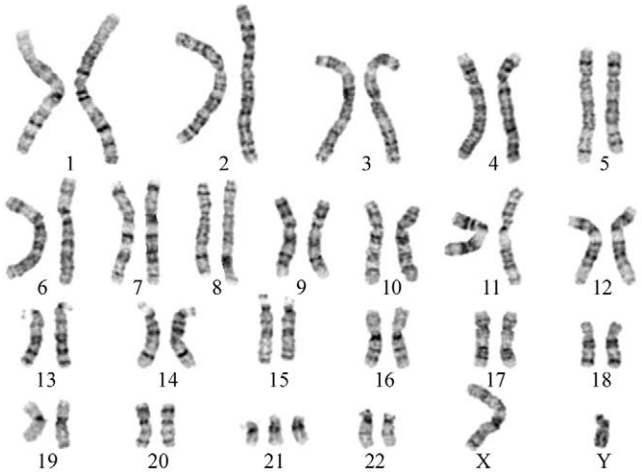
When associated with hyperphosphatemia, FTC is caused by mutations in *GALNT3* or *FGF23,* but Topaz et al. describe five FTC-affected families with normal phosphate levels and no mutations in either of the known disease genes. Gene-mapping studies led to the identification of an *SAMD9* mutation that segregated in the affected individuals of all five analyzed families. The function of the protein encoded by *SAMD9* has not yet been elucidated, but the mRNA is expressed in a number of tissues, including skin. Expression of the *SAMD9* transcript was found to be elevated in patient fibroblasts, as well as in cells transfected with mutant *SAMD9*. The authors studied the effect of the mutation at the protein level by creating fusion proteins with green fluorescent protein. Whereas the wild-type protein localized to the cytoplasm, no mutant SAMD9 was observed. It is thought that a major difference between the normophosphatemic (NFTC) and hyperphosphatemic (HFTC) forms of FTC involves the way the calcinosis is acquired. There are indications that NFTC develops as a response to inflammation or injury and that HFTC is a result of deposits forming because of improper calcium and phosphate metabolism. The differences between the two forms of the disease may help to determine the function of *SAMD9*.

This Month on the Cover

In 1959, Jerome Lejeune et al. published their chromosomal analysis of nine children with Down syndrome and noted that each had 47 chromosomes instead of the normal 46 (C R Hebd Seances Acad Sci 248:1721–1722). The recognition of the association between the extra chromosome and Down syndrome is often considered a critical moment in the dawn of clinical cytogenetics. Recall from the March *AJHG* 2006 cover that the manuscript reporting



that normal cells have 46 chromosomes had just been published in 1956 by Tijo and Levan (Hereditas 42:1–6). On the cover, the presence of an extra copy of chromosome 21 in a patient's cell determines that he or she has Down syndrome. Here, the same chromosomes are organized into a numbered karyotype, so that the patient's three copies of chromosome 21 can be easily observed. Special thanks to Joana Carvalho Da Costa and Azra H. Ligon, Brigham and Women's Hospital, Department of Pathology, Clinical Cytogenetics Laboratory, Boston, for the metaphase and karyotype images.

Robin E. Williamson
Deputy Editor