Reconstructing Genetic Ancestry Blocks in Admixed Individuals, *by Tang et al.* (***p. 1***)

Population admixture results in the segregation of alternating lengths of ancestral chromosomes into ancestry blocks. It is crucial to account for this substructure when using populations for association studies, and the blocks can be used as additional data in admixture mapping. The need to correctly determine the ancestry of loci in the genome has resulted in the creation of multiple methods. Traditionally, these methods infer ancestry with use of a hidden Markov model (HMM), but, because a large number of studies are now making use of increased marker density, the HMM can be confounded by background linkage disequilibrium (LD). To allow for the lack of independence between a dense set of markers, Tang et al. developed a new method, Markov–hidden Markov model, which is implemented in their program SABER. When used on phased data, the new algorithm can be used to predict ancestry blocks. With unphased data, the method yields diploid ancestry blocks. The advantage of accounting for background LD when estimating ancestry was showcased in simulations on dense SNP data.

High Incidence of Later-Onset Fabry Disease, *by Spada et al.* (***p. 31***)

As medical advancements are presenting new ways to treat genetic diseases, it becomes more important to improve screening and diagnosis. One such example is Fabry disease, an X-linked disorder caused by a deficiency in α-galactosidase A (α-Gal A), which causes the accumulation of globotriaosylceramides in blood vessels. The disease has been estimated to affect 1 in 50,000 individuals. Although classic cases present in early childhood, an increasing number of patients who experience cerebrovascular, cardiac, and renal difficulties later in life have been linked to α-Gal A. In an effort to improve screening and to better understand the prevalence of the deficiency, Spada et al. tested the enzyme activity in 37,104 Italian neonates. Mutation screening of those in whom a deficiency was identified reveals that the incidence may, in fact, be closer to 1 in 31,000. Closer examination of the families of these neonates revealed that many of the grandparents are affected, a few of whom died because of complications of their undiagnosed disease. The identification of these affected individuals is especially important, since enzyme-replacement therapy is being developed as an effective means to treat the disease. This possibility of treatment makes it even more critical that those with the disease be effectively identified.

Epigenetic Variation in Germ Cells, *by Flanagan et al.* (***p. 67***)

It is becoming increasingly well accepted that DNA methylation differences are a significant source of genetic variability. Although abnormal methylation patterns have been associated with disease, a large amount of normal variation may occur within and between individuals. Many studies have investigated this normal epigenetic variation between the somatic tissues of individuals, and, here, Flanagan et al. examined the epigenetic differences in germ cells. They began by comparing the methylation status of the promoter regions of several disease-related genes in the sperm of healthy males. They then used CpG microarrays to make further comparisons. Overall, there appeared to be a high level of both intra- and interindividual variability. Some of the differences were subtle, whereas other involved loci were "on" in some samples and "off" in others. A significant amount of variation was ascribed to an age effect that was observed when the age of the donor males was incorporated as a covariate. Although it is unclear whether these genes will retain their epigenetic status after fertilization, the effects of this variability are important to consider in conjunction with DNA sequence changes.

POF1B ***Mutation in POF,*** *by Lacombe et al.* (***p. 113***)

Proper ovarian development requires two copies of many genes on the X chromosome. For this reason, women with monosomy X or disruptions of critical ovarian genes can suffer from premature ovarian failure (POF). Two regions important for ovarian development, POF1 and POF2, have been identified on the basis of cases of women with POF who also had X-chromosome abnormalities. Here, Lacombe et al. describe a consanguineous Lebanese family in which several of the female members have POF. Linkage analysis identified a POF locus on Xq21 within the POF2 critical region. Disruption, by chromosomal translocations, of two genes within the locus, *diaphanous* and *POF1B,* had been identified elsewhere in women with POF. On screening these two candidates in the family, the authors identified a homozygous missense mutation in *POF1B* in all affected women. Women heterozygous for the mutation are not affected. Sequence homology analysis revealed that the C terminus of the POF1B protein is a myosin tail. To determine how the missense mutation might affect the function of the uncharacterized POF1B, the authors evaluated the ability of the mutant protein to bind to actin. The binding strength of the variant POF1B is decreased fourfold in comparison with that of wild-type POF1B.

Am. J. Hum. Genet. 2006;79:i–ii. 0002-9297/2006/7901-0001$15.00

This Month on the Cover

Sickle-cell anemia was the first disease for which a connection was made between an abnormal protein and phenotype. Linus Pauling was working on hemoglobin in 1945 when he heard about the characteristics of red blood cells in sickle-cell anemia. Previous work by Irving Sherman had already demonstrated that the cell shape was related to oxygen levels (Sherman IJ [1940] Bulletin of the Johns Hopkins Hospital 67:309–324). Combining this data with an interest in hemoglobin structure, Pauling et al. went on to show, in 1949, that patients with only abnormal hemoglobin protein had sickle-cell anemia, whereas those with an equal mix of abnormal and normal protein had sickle-cell trait (Pauling L, Itano HA, Singer SJ, Wells IC [1949] Science 110:543–548). Special thanks to Dr. James G. White, University of Minnesota, for the scanning electron micrograph.

Robin E. Williamson
Deputy Editor