This Month in the *Journal*

This month in the *Journal,* we present a review article by Karl Pfeifer on the mechanisms of genomic imprinting (p. 777). This article outlines current knowledge on the imprinting process, with emphasis on both the human 11p15.5 region, which is associated with Beckwith-Wiedemann syndrome and Wilms tumor, and the 15q11-q13 region, which is associated with the Prader-Willi and Angelman syndromes. Dr. Pfeifer explains in detail how a cell might use a methylation imprint as both a positive and a negative signal for transcription.

Also included in this issue are two invited editorials. In the first (p. 788), Stephen Mount cautions that, even as mapping of the human genome nears completion, researchers are still limited in their ability to predict gene structure. Especially as gene annotation becomes more automated, researchers will need to be aware of the exceptions to the rules for genetic-structure predictions. In the second invited editorial (p. 793), Rando Allikmets discusses the role of the ABC transporter *ABCR* in retinal disease. *ABCR* mutations lead to a clinically heterogeneous array of phenotypes, including Stargardt disease, autosomal recessive retinitis pigmentosa, and autosomal recessive cone-rod dystrophy. Dr. Allikmets outlines current knowledge on the role of *ABCR* in a variety of retinal disorders and highlights the work of both Rivera et al. (p. 800), who find that mutations in *ABCR* are the major cause of autosomal recessive cone-rod dystrophy, and Maugeri et al. (p. 960), who provide further evidence that sequence variation in *ABCR* is associated with age-related macular degeneration.

TNNT1 ***Gene Mutation in Nemaline Myopathy,*** *by Johnston et al.* **(***p. 814***)**

Amish nemaline myopathy is an autosomal recessive disorder that is very common in the Old Order Amish, with an incidence of ~1/500. This muscular disorder presents as tremors in infants. Progressive muscle atrophy and proximal contractures develop and eventually lead to respiratory insufficiency and death at an early age. Mutations in the genes for three sarcomeric proteins—nebulin, α-tropomyosin, and α-actin—have been associated with nemaline myopathy. To identify the gene involved in the unique Amish form of nemaline myopathy, Johnston et al. performed a genome scan and identified, on chromosome 19, a 2-cM region of interest that included the gene for the sarcomeric protein troponin T. Sequencing of this gene revealed a truncating mutation, E180X, in an affected individual. Although it is not clear whether this mutation would result in nonsense-mediated decay, protein instability, or defective protein activity, loss of the C terminus of the protein would remove the sites of interaction with other components of the troponin complex and would disrupt the coupling of excitation and contraction in muscle fibers.

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Linkage Disequilibrium in the **NF1** ***Gene Region,*** *by Eisenbarth et al.* **(***p. 873***)**

Linkage disequilibrium (LD) is not evenly distributed throughout the human genome, but the reason for this lack of uniformity is unclear. Since the extent of LD has a major impact on genetic-association studies, a greater understanding of the LD distribution would allow more-efficient gene mapping. Eisenbarth et al. have examined LD in the region of the *NF1* gene on chromosome 17q11.2, an area that shows variation in the extent of LD. They have been able to correlate differences in LD with the DNA composition in this region. More specifically, the recombination fraction begins to increase precisely at an isochore-transition boundary. Because isochore class is defined by GC content, the change in recombination is associated with a change in the general DNA composition; a higher recombination fraction is associated with a higher GC content. As the authors point out, if this correlation between LD and isochore structure is a general phenomenon, it will have an impact on the marker density required for genetic-association studies. Markers could be concentrated in the regions with lower LD (high-GC content), thereby increasing the efficiency of these studies.

APOE ***Haplotype Variation,*** *by Fullerton et al.* **(***p. 881***)**

All populations studied to date are polymorphic at the *APOE* locus, which encodes apolipoprotein E. The three common alleles of *APOE*—ϵ2, ϵ3, and ϵ 4—vary in their associated risk for both cardiovascular and Alzheimer disease. Individuals possessing an ϵ4 allele have an increased risk of both diseases, whereas ϵ2 is protective. More-complete examination of the alleles of *APOE* has demonstrated variation within each common isoform, and these data led Fullerton et al. to study further variation of *APOE.* Through careful haplotype analysis, these authors discovered considerable variation in the population-specific distribution of *APOE* haplotypes. This variation provides a potential explanation for the interpopulation differences in association of *APOE* with disease risk. On the basis of the haplotypes, reduced-median networks were created to study the history of

variation at the *APOE* locus. It appears that $\epsilon 4$ is the ancestral allele but that $\epsilon 3$ has risen in frequency during the past 200,000 years. Fullerton et al. hypothesize that this change in allele frequency, as well as a reduction in *APOE* variation, result from the rise of an advantageous mutation that is present in the $\epsilon 2$ and $\epsilon 3$ alleles.

Admixture-Generated Linkage Disequilibrium, *by Wilson and Goldstein* (*p. 926*)

The study by Wilson and Goldstein provides an important bit of information on the relationship between LD and admixture. Ultimately, this provides data on the number of markers necessary for genomewide association studies, an important unanswered question. It has been believed for quite some time that admixture creates LD, and this study is the first to conclusively prove this fact. Using the Lemba population from South Africa, which is a Bantu-Semitic hybrid population, these authors report elevated LD at large genetic distances, as well as increased LD at most genetic distances. This is in contrast to the situation in the putative parental populations, Bantu and Ashkenazi Jews, where LD extends only 0–6 cM. Analysis of allele-frequency differentials between the parent populations shows that, in the Lemba, there is a positive correlation between the differentials and LD, and this demonstrates that LD is generated by admixture. Because LD measurements in different populations and different genetic regions have shown considerable variability, researchers should no longer generalize LD across the genome and between populations. Population-specific measurements of LD, such as this one, will allow more-efficient use of markers in genomewide association studies, and they will also help us to understand better the factors, such as admixture, that affect LD variation.

***Report* (*Mutational Hotspots in mtDNA*),** *by Stoneking* (*p. 1029*)

In attempt to resolve the controversy concerning the origin of the hypervariable sites in human mtDNA, Mark Stoneking has analyzed the evolutionary rates for new mutations at these sites. Although the hypervariable sites have generally been hypothesized to be mutational hotspots, an alternative theory has been proposed—that is, that they may have resulted from ancient mutations that were moved to various mtDNA lineages via recombination. Stoneking has found that new mtDNA mutations occur preferentially at the hypervariable sites, supporting the hypothesis that the sites are mutational hotspots. However, the molecular basis for the increased mutation rate at these sites is unknown.

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