This Month in the *Journal*

This month, the focus in both of our ongoing series, "Insights from Model Systems" and "Human Genetics '97," is on dynamic aspects of chromatin. Feil and Kelsey (p. 1213) discuss chromatin as a carrier of epigenetic information in genomic imprinting. They describe the use of experimental techniques developed by mouse embryologists to address the mechanisms of imprinting in mouse and human cells. Robertson and Jones (p. 1220) discuss the multiple roles of DNA methylation in tumorigenesis. DNA methyltransferase, they argue, not only alters the expression of tumor-suppressor genes at several levels but may also affect the activity and the cell-cycle regulation of DNA repair in precancerous cells. Finally, Choo (p. 1225) discusses latent centromeres, DNA structures that lack the repeat sequences found in normal centromeres but that can be activated to form neocentromeres. Once activated, these structures serve as nucleation sites for spindle formation, allowing chromosome fragments to segregate normally during cell division.

Human* CAC, *Cloning and Mutation Detection, *by Huizing et al.* **(*p. 1239*)**

Mutations in any of the genes involved in mitochondrial β-oxidation of fatty acids cause defects in ketone-body formation during fasting, and they may lead to coma and death in infancy. Huizing et al. have provided the first molecular description of a defect in *CAC,* which encodes the transporter protein that provides substrate fatty acids to the oxidative enzymes in the mitochondrial matrix. Huizing et al., who cloned the rat CAC cDNA, now report the sequence of its human homologue. They also identify a homozygous point mutation in *CAC* in a girl who, unlike other known CAC-deficient individuals, survived the neonatal symptoms of impaired β-oxidation. It is possible that her survival and subsequent good health are the result of her carrying a relatively mild *CAC* allele with some residual, but undetected, carrier activity.

***Novel Alleles of* CCR5,** *by Carrington et al.* **(*p. 1261*)**

The common Δ32 mutation in the chemokine-receptor gene *CCR5* is found disproportionately among long-term survivors of HIV infection. The CCR5 protein is expressed on macrophages, where it serves as a coreceptor for HIV in the early, macrophage-tropic (M-tropic) stage of infection. Cells homozygous for Δ32 are resistant to M-tropic isolates of the virus, and even heterozygosity is associated with delayed onset of AIDS. In a set of ~1,400 individuals at risk for AIDS, Carrington and colleagues have now identified 16 novel polymorphisms in the *CCR5* gene, of which 1 is a probable null allele and 13 are expected to lead to subtle changes in protein sequence. None of these polymorphisms were found in the homozygous state, but four were found along with the Δ32 allele in compound heterozygotes. The authors suggest that one or more of these rare sequence variants may be associated with delayed or restricted HIV progression.

Splicing Defects in the* COL3A1 *Gene, *by Schwarze et al.* **(*p. 1276*)**

In Ehlers-Danlos syndrome type IV, dominant mutations in the *COL3A1* gene disrupt the synthesis and deposition of type III procollagen, and several tissues are prone to rupture in affected individuals. Approximately a third of the known mutations in this gene affect splicing. Schwarze and colleagues have identified point mutations in 33 splicing-defective alleles of *COL3A1*. These mutations are widely scattered throughout the gene, but virtually all of them affect splice-donor sites and lead to single-exon skipping. As with other collagen genes, exons in *COL3A1* encode units of multiple Gly-X-Y repeats and remain in the same reading frame. Exon skipping, therefore, does not introduce premature-termination codons, so the altered mRNAs are not susceptible to nonsense-mediated decay. Schwarze et al. find that misspliced mRNAs and the proteins that they encode do, in fact, accumulate in fibroblasts and cause abnormal synthesis of type III collagen. The authors suggest that most splice acceptor–site mutations would have different molecular consequences. Clinical or biochemical ascertainment criteria, they speculate, exclude those mutations that create null alleles of *COL3A1*.

NF2 *Gene in Schwannomatosis,* *by Jacoby et al.* **(*p. 1293*)**

Jacoby et al. argue here, on both clinical and genetic grounds, that neurofibromatosis 2 (NF2) and schwannomatosis, two conditions that involve Schwann-cell neoplasias and the tumor-suppressor gene *NF2,* should be considered distinct disorders. Unlike NF2, schwannomatosis typically spares the vestibular nerves, and, whereas germ-line transmission of a mutation in *NF2* is the rule in NF2, schwannomatosis is usually sporadic. Somatic loss of heterozygosity (LOH) provides the "second hit" in NF2, as expected when a tumor-suppressor gene is involved. In schwannomatosis, even when LOH

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in *NF2* is observed in tumors, the other mutation in the gene may vary among the tumors found in a single individual. Jacoby et al. find that, within an affected family, point mutations occur preferentially on one inherited allele, with somatic loss of the other allele. They suggest that a novel disease mechanism operates in schwannomatosis, whereby one allele of *NF2* is specifically subject to—or is unable to repair—spontaneous somatic mutations.

Point Mutation in Hair Roots, *by Bendall et al.* (*p. 1303*)

Bendall and coworkers have examined the distribution of a novel mtDNA polymorphism in different tissues from a heteroplasmic family. In three heteroplasmic individuals in this group, the proportion of polymorphic mtDNAs varies widely among hair roots, whereas blood and buccal cells show consistent levels of heteroplasmy. The authors suggest that the variability seen in hair roots reflects their independent development from a small number of progenitor cells in early fetal life; the heteroplasmy seen in blood and buccal cells, on the other hand, reflects an average of a large number of stem cells. This unexpected level of somatic variegation suggests that mtDNA partitioning should be viewed as a dynamic process occurring at least through early fetal development.

PAH ***Genotypes: HPA Phenotypes,*** *by Kayaalp et al.* (*p. 1309*)

Because genetic and clinical screening of newborns for phenylketonuria (PKU) has become standard practice in much of the world, the phenylalanine hydroxylase gene, *PAH,* is among the most widely studied of human disease genes, and PKU represents a textbook example of a simple Mendelian recessive disorder. However, Kayaalp et al., who have assembled data on the disease phenotypes associated with *PAH* genotypes, now dispute this view. Most phenotypes can be predicted from the enzymatic activity seen when the corresponding alleles are expressed in cultured cells, but, as the authors emphasize, some genotypes are associated with surprisingly mild or severely variable disease phenotypes. Thus, Kayaalp et al. argue that the PKU phenotype is subject to modification by other factors—and, possibly, by other genes. Their data also raise concerns about enzyme-activity studies that are performed in transfected cells.

Segregation Analysis of Recurrent Depression, *by Marazita et al.* (*p. 1370*)

The study by Marazita and colleagues on unipolar depression is one of several in this issue that highlight the promise and the frustrations of studying the genetics of complex psychiatric disorders. These investigators focused on 50 probands with early-onset recurrent unipolar depression (UPD) and on their families, because these probands are expected to show relatively clear inheritance of affective disease. Because hereditary factors might predispose either to UPD specifically or to affective diseases in general, Marazita et al. analyzed their data separately with either a narrow or a broad conception of affected status. In each case, the data are fully consistent with a genetic influence on affective disease, but a model incorporating ordinary Mendelian assumptions about transmissibility is favored only with the broad definition of affected status.

Linkage of Positive Symptoms of Schizophrenia, *by Brzustowicz et al.* (*p. 1388*)

Linkage of schizophrenia to a susceptibility locus on 6p has been found in some studies but has been disputed in others. Brzustowicz et al. have reexamined this issue, and they suggest here that the diagnostic categories applied to this disorder may be at fault for some of this confusion. Applying two different categorical definitions of schizophrenia, they failed to find linkage to 6p in a set of 10 large families. However, observing that the symptoms of schizophrenia may segregate in families even when categorical diagnoses do not, the authors followed positive and negative measures of schizophrenia separately as quantitative traits. They found that positive features, those associated with psychotic behaviors, were significantly linked to markers on 6p. A quantitative-trait locus mapping to this region may affect the severity of psychosis, whereas other features of the disease may be subject to other influences.

Linkage of Bipolar Disorder to Chromosome 18, *by McMahon et al.* (*p. 1397*)

Bipolar affective disorder (BPAD) comprises several conditions, including bipolar disorders I and II. McMahon and coworkers, along with several other groups, have previously reported linkage of BPAD to a broad region of 18q. Now, working with a set of 30 newly ascertained pedigrees, McMahon et al. find strong evidence of linkage to a 14-cM region that overlaps slightly with the previously identified region. However, a parent-of-origin effect that was seen before is not as obvious in the present data, and it remains uncertain whether the 14-cM region is identical to the locus mapped before or to a proposed bipolar I locus reported by another group.

JOHN ASHKENAS
Editorial Fellow