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This Month in the *Journal*

This month's "Human Genetics '97" series focuses on the genetics of somatic tissues, specifically the extent and consequences of genomic instability in the soma. It is widely appreciated that somatic loss of heterozygosity (LOH) can cause tumor development when a tumor-suppressor gene is affected, but the frequency of LOH at other loci is more difficult to observe. Tischfield (p. 995) discusses multiple genetic and epigenetic mechanisms that could lead to allele-specific suppression of gene expression in somatic cells, and he describes an experimental system that allows these events to be studied in primary cell culture. Qian and Germino (p. 1000) discuss polycystic kidney disease, which is associated with LOH in the *PKD1* gene, and they argue that LOH may be a disease mechanism in many cases in which dominant inheritance is coupled with sporadic incidence.

Writing in the series "Insights from Model Systems," St. John and Xu (p. 1006) discuss somatic LOH from the perspective of *Drosophila* biology, where it serves as a carefully constructed tool for genetic analysis. By inducing mitotic recombination in engineered strains of flies, developmental geneticists can identify and study fly tumor-suppressor genes. The genes identified may be familiar as homologues of human tumor suppressors, such as *RB*, or may be identified first in the fly and only later in human cells, as with *lats*. In either case, they point to an astonishing degree of conservation of the biochemical pathways that regulate cell growth in animals only distantly related to us.

MMAC1 *Mutations in Early-Onset Breast Cancer,* *by Tsou et al. (p. 1036)*

Individuals with Cowden syndrome (CS) are subject to numerous benign growths as well as to breast cancer and other malignancies. One gene, *MMAC1,* is mutated in CS pedigrees and in many spontaneous tumors. *MMAC1* encodes a protein phosphatase that acts in vitro on phosphotyrosine or on phosphoserine or phosphothreonine in target substrates; the physiological substrates of MMAC1 are unknown. Tsou et al. report that they have identified three novel mutations in this gene, in families with early or bilateral breast cancer. However, they found no evidence that *MMAC1* mutations are common among women who develop breast cancer at an early age. Furthermore, Tsou et al. found no coding-sequence mutations in 23 CS families for whom linkage to the *MMAC1* locus had never been established. On this basis, they suggest that CS is genetically heterogeneous. As other genes related to this disease are identified, a biochemical pathway may emerge by which this protein phosphatase regulates cell growth.

Low-Penetrance Retinitis Pigmentosa, *by McGee et al. (p. 1059)*

At least eight loci are associated with dominantly inherited retinitis pigmentosa, and two of these loci, RP9 and RP11, show incomplete penetrance. McGee et al. have analyzed the inheritance of this condition in three extended families that show linkage to RP11. They argue that, where sibships show divergent phenotypes (presence or absence of disease), a modifier locus may account for the difference. One modifier appears to be associated with the RP11 allele derived from the parent who did not transmit the disease allele. The authors suggest that polymorphic alleles that lead to high expression of a wild-type protein could suppress the effects of an otherwise dominant mutant allele. Other models for interallelic interaction or for second-site suppression are also possible.

Aberrant Splicing of the Human AR, *by Brüggenwirth et al. (p. 1067)*

Karyotypic males with defects in the androgen-receptor gene (*AR*) fail to develop normal male genitalia and typically present either with ambiguous genitalia or as apparently normal, but infertile, females. *AR* encodes a ligand-activated transcription factor with a phosphorylation state that correlates with DNA binding activity. Brüggenwirth et al. report on a family with an unusual form of androgen insensitivity, whose members have no defect in their exonic or splice-junction sequences in *AR*. Affected people in this family express an AR of nearly normal size that fails to be maximally phosphorylated or to bind target DNA, in vitro. The authors identified a mutation in an intron, within a splice-acceptor sequence, and they characterized the altered mRNAs derived from this mutant allele. The lesions in the AR protein are subtle, but they affect its zinc finger domain, which mediates DNA binding.

Puerto Ricans with Hermansky-Pudlak Syndrome, *by Hazelwood et al. (p. 1088)*

Underlying the various symptoms of Hermansky-Pudlak syndrome (HPS) are defects in several membrane-bound organelles in diverse cell types: Melanosome abnormalities lead to oculocutaneous albinism, a lack of dense

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bodies in platelets compromises blood coagulation, and an accumulation of ceroid lipofuscin in lysosomes in alveolar macrophages is associated with fibrotic lung disease. One gene for this syndrome, *HPS,* has been cloned, and common disease alleles are known, including one 16-bp deletion that is common in Puerto Rico. Hazelwood et al. show that two Puerto Rican individuals with HPS lack this common allele. Indeed, they appear to express wild-type HPS mRNA and, instead, may carry a mutation at an entirely different locus. The suggestion that HPS is genetically heterogenous is consistent with the existence of at least 12 genes that cause similar conditions in the mouse.

TRYP1 ***Mutations in ROCA,*** *by Manga et al.* (*p. 1095*)

Oculocutaneous albinism (OCA) among southern African Blacks is distinctive in that the tyrosinase-negative form (OCA1) is unknown, whereas other forms, such as rufous OCA (ROCA or OCA3), are relatively common. Manga et al., by studying nine South African families, have now linked ROCA to the gene for tyrosinase-related protein 1 (*TRYP1*). They identify two common mutations in this gene and report that most albinos in this group are either homozygotes or compound heterozygotes for these mutations. In one family with a pigmentation phenotype similar to that for ROCA but with still lighter hair, they found mutations in *TRYP1* and in the *P* gene, which is associated with OCA2. The authors discuss this genetic interaction and its parallels with interactions seen between mouse pigmentation genes.

De Novo Rearrangements in SMA, *by Wirth et al.* (*p. 1102*)

Unlike dominant conditions, in which the sporadic incidence rate provides a ready measure of mutation rate, the mutation rate at recessive-disease loci is not commonly measured. Rather, this rate is usually derived from incidence rates in populations believed to be at equilibrium. Now, Wirth et al. have identified de novo rearrangement rates for the spinal muscular-atrophy locus. This locus contains two inverted, nearly identical repeats of ~500 kb, and biallelic loss or inactivation of the telomeric copy of the *SMN* gene in this region leads to spinal muscular atrophy. Wirth et al. report that de novo rearrangements occur mostly during spermatogenesis and are found in 7 of 340 families with this disease. The mutation rate that they have deduced is in good agreement with the rate calculated from equilibrium incidence levels.

Linkage of Paget Disease of Bone to 18q, *by Cody et al.* (*p. 1117*)

Cody et al. argue that two autosomal dominant bone diseases, Paget disease of the bone and familial expansile osteolysis (FEO), represent allelic disorders. Both conditions present with bone lesions, and, in both, osteoclasts appear to carry viral inclusions in their cytoplasm and nuclei, probably indicating infection by a paramyxovirus. FEO leads to debilitating disease in the limbs, which may be spared in Paget disease, and it presents at an earlier age. Cody et al. describe a family with Paget disease in which the condition is linked to 18q, where FEO maps. In this pedigree, a single outlier, who is symptomatic but who lacks the disease haplotype, complicates this argument.

Laboratory Policies for Testing of Children, *by Wertz and Reilly* (*p. 1163*)

Wertz and Reilly have surveyed diagnostic genetic laboratories to determine how they respond to requests for two controversial kinds of testing—those that determine a child's predisposition to untreatable illnesses that arise only later in life and those that determine, in a minor too young to face reproductive decisions, carrier status for a recessive condition. Of 105 such laboratories, a slight majority appear to recognize a responsibility to regulate such testing, in that they have refused—at least once—to test a child. In addition, many labs report that they have been contacted by physicians concerned about the appropriateness of such tests. Wertz and Reilly note that policy statements from groups involved with Huntington disease have influenced policy decisions by laboratories, and they suggest that similar statements from other groups could help standardize testing policy for other conditions as well.

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