This Month in the *Journal*

Tumorigenesis occurs in multiple steps, of which cellular hyperproliferation is only one early manifestation. Compared with the early steps of tumor induction, the later events—changes in adhesive interactions; loss of contact inhibition; increased capacity to extravasate, to metastasize, and to induce angiogenesis—have received relatively little attention from geneticists. Here we feature three articles on the genetics of cancer outcome. Narod (p. 1) discusses the effects that inherited variation in known tumor-suppressor genes and proto-oncogenes exerts on cancer progression. Hartsough and Steeg (p. 6) focus on nm23-H1, a highly conserved protein that specifically suppresses metastasis but not tumorigenesis. Finally, the progression of disease may depend crucially on a patient's idiosyncratic responses to cancer chemotherapy, as Krynetski and Evans (p. 11) show. They consider the drug-metabolizing enzyme thiopurine S-methyltransferase and show that accurate diagnosis of a genetic deficiency in this enzyme permits the clinician to choose a dose that is effective but that avoids potentially fatal toxicity.

In the "Book Reviews" section, Vieland and Hodge (p. 283) recount the argument of biostatistician Richard Royall in his recent book *Statistical Evidence: A Likelihood Paradigm*. They build from his general model a view that they call "evidentialism," which, they argue, can eliminate some unresolvable disputes in statistical genetics, notably the recent debate on significance levels in genome scans.

Differences between Autosomal and X DNA, *by White et al. (p. 20)*

The silencing of loci on one of the two female X chromosomes correlates both with the formation of heterochromatin in the silenced chromosome and with a shift toward replication later in S phase. This process is incomplete, sparing the pseudoautosomal region of the chromosome as well as some scattered loci that somehow escape X inactivation. When autosomal domains translocate to the X, they become subject to a similar epigenetic modification. The timing of DNA replication in these domains is inconsistent between loci, raising the possibility that efficient silencing depends on some properties of X-chromosome DNA sequences. White and coworkers have isolated an Xq:4q derivative chromosome in a somatic-cell hybrid and have used reverse transcription–PCR to follow expression of translocated autosomal genes in this cell clone. They report here that X inactivation could propagate $\geqslant$100 Mb into the sequence derived from 4q but that 6 of 20 genes and expressed sequence tags tested had escaped inactivation. No simple rule based either on the location of these loci in the translocated region or on the presence of CpG islands in their promoters could account for this pattern of expression.

mtDNA Stop-Codon Point Mutation, *by Hanna et al. (p. 29)*

Hanna et al. present the first evidence for a nonsense mutation in a mitochondrial protein gene. Other point mutations in tRNA genes and in electron-transport–chain protein genes have been associated with progressive muscle disorders such as mitochondrial encephalomyopathy with lactic acidosis and strokelike episodes (MELAS). Premature-termination codons in any of the mitochondrial open reading frames had never been reported, but the subject of this study is heteroplasmic for a stop mutation that maps near a previously identified missense mutation in the gene for a respiratory-complex IV subunit. That missense mutation is known to confer MELAS, and the phenotype of the novel mutation seems to be similar, including both exercise-induced lactic acidosis and adult-onset muscular weakness. The subject's skeletal muscle contains >50% mutant mtDNA, with dramatically more wild-type DNA in cytochrome oxidase (COX)–positive muscle fibers than in COX-negative fibers. Her other tissues are homoplasmic for wild-type mtDNA, and her three children have been spared the disease, suggesting that her germ-line mitochondria are also free of the mutation.

Smith-Lemli-Opitz Syndrome Mutations, *by Wassif et al. (p. 55)*

Smith-Lemli-Opitz syndrome (SLOS) is an inborn error of cholesterol biosynthesis in which the final step of this metabolic pathway, the reduction of 7-dehydrocholesterol, is deficient. Although this biochemical defect emerged several years ago, the genetic basis of this disease has been uncertain. Now, Wassif et al. report the cDNA sequence of the human sterol Δ-7 reductase (*DHCR7*), which they identified by homology to known plant and fungal enzymes. They show that fibroblasts from SLOS individuals and from controls express DHCR7 mRNA and that, as with other gene products that act in this metabolic pathway, mutant and wild-type DHCR7 mRNAs are down-regulated when cellular cholesterol is sufficient for growth. Wassif et al. find four

0002-9297/98/6301-0001$02.00

mutations that affect coding sequences of the reductase gene from three unrelated affected people. That the wild-type cDNA complements their biochemical defect seems to indicate that the metabolic defect is a direct effect of these mutations.

MMR-*Gene Mutations in MTS,* *by Kruse et al.* (*p. 63*)

Muir-Torre syndrome (MTS) and hereditary nonpolyposis colorectal cancer (HNPCC) have been considered distinct conditions, because MTS, by definition, presents with tumors of the sebaceous gland. Still, there is considerable phenotypic overlap between the two disorders, including microsatellite repeat-length instability in tumors and a high incidence of colorectal and endometrial cancers; Kruse and coworkers now indicate that MTS and HNPCC may be considered allelic conditions. Underlying HNPCC are mutations in any of four DNA mismatch-repair genes, and Kruse et al. find two of them, *hMSH2* and *hMLH1,* mutated in 9 of 13 families with sebaceous and colorectal cancers. One of these lesions, a nonsense mutation in *hMSH2,* had been identified previously in a family with HNPCC, raising the question of whether any genetic differences exist between affected families that exhibit sebaceous tumors and those that do not.

PLP-*Gene Duplications in PMD,* *by Woodward et al.* (*p. 207*)

Overexpression of the X-linked proteolipid protein gene (*PLP*) occurs in Pelizeaus-Merzbacher disease (PMD) and in several animal models of this neurological disorder. Two transcripts from *PLP* encode major components of the myelin sheath, and mutations in this gene can lead to defects in oligodendrocyte maturation and to spasticity and death in infancy. Although *PLP* point mutations have been reported to cause PMD, most disease alleles appear to be duplications that leave the gene intact. Woodward and coworkers have characterized four such events by interphase-FISH analysis. They show that, in all cases, the duplication was transmitted to affected boys by their unaffected mothers; this X-linked recessive transmission has been reported before, but it appears to be at odds with the etiology of the disease. In other respects, as the authors note, PMD seems strikingly similar to another hereditary neuropathy, Charcot-Marie-Tooth type 1A, that can arise from duplications in a myelin protein gene. Woodward et al. find that the size of the duplication is different in each family, although its distal end appears to be common, suggesting that these distinct but related aneusomies have occurred independently in the different families.

Mapping of Complex Traits with SNPs, *by Zhao et al.* (*p. 225*)

Single-nucleotide polymorphisms (SNPs) promise to be well suited to DNA chip-based genomic screening once a suitably dense SNP map is available. The first chip designed for this application is expected to allow 2,000 biallelic loci to be scored in a single manipulation. Anticipating the introduction of this technology, Zhao et al. have simulated and attempted to analyze genotype data that might arise from a moderately complex genetic trait, one conferred independently by two linked genes. They examine several statistical parameters that could be calculated, and they find that both linkage and linkage-disequilibrium analyses are successful in mapping the causal loci, although the former is prone to false positives. The most robust such analysis, the authors suggest, may involve a combination of the two parameters. However, they note that this combined estimator might be optimal in part because of the specific family structures, allele frequencies, and other factors that they assumed when simulating their data.

Mapping Genes in Admixed Populations, *by McKeigue* (*p. 241*)

McKeigue has previously argued that recently admixed populations represent an important resource for the mapping of disease loci, because of the strong disequilibrium that is expected between disease genes and linked, parental population-specific marker alleles. His earlier analysis exploited the transmission-disequilibrium test, which depends on parental heterozygosity at marker loci. Because this condition is easily met in populations very soon after admixture, the second generation (equivalent, in a laboratory setting, to the F2 generation in a cross between inbred strains) is most appropriate for this kind of analysis. However, statistical significance drops quickly in later generations and in populations where the number of admixed generations varies. Here, McKeigue suggests an alternative method: conditioning the genotype analysis of an affected individual on the contribution, to that individual's parents, of characteristic founding population-specific markers. This method appears to be robust even when the precise history of intermarriage in a family is unknown.

JOHN ASHKENAS
Editorial Fellow