This Month in the *Journal*

Sex chromosomes operate under a different set of constraints than autosomes. The idiosyncrasies of these portions of the genome owe largely to their existence, for some or all of their history, in haploid form and to the complete absence of recombination over most of the Y chromosome. These features also limit the approaches that can be used to study functional variation on the sex chromosomes. Three papers this month review the significance and the challenges of studying the human X and Y chromosomes. Lau (p. 921) discusses the role of Y-linked loci in cancer genetics, focusing on the putative oncogene *TSPY,* which may be responsible for tumors of the prostate and testes and for gonadoblastoma, an unusual cancer that is found in phenotypic females who carry a Y chromosome. McElreavey and Krausz (p. 928) discuss the azoospermia locus on the Y chromosome, a complex region that is required for male fertility. Finally, Lanasa et al. (p. 934) review the consequences of lethal mutations on the X chromosome. Such mutations might be inferred from skewed patterns of X inactivation in carrier females or from recurrent spontaneous abortions of male fetuses. Such data could make it possible to estimate the prevalence of X-linked lethal alleles in the population.

Mitochondrial tRNA Mutation Causing RP and Hearing Loss, *by Mansergh et al.* **(***p. 971***)**

The combination of progressive hearing loss and retinitis pigmentosa is characteristic of Usher syndromes, a heterogeneous set of autosomal recessive disorders that have been linked to at least eight loci. Mansergh and colleagues have previously reported an extended pedigree in which the Usher symptoms occur in four generations of family members but do not segregate in a recessive pattern. Now, the same group shows that the previously suggested linkage of the condition to an autosomal locus was incorrect—but that a novel mtDNA point mutation appears to segregate with the phenotype in this family. Mansergh et al. note that the disease is matrilineally inherited and that muscle tissue from at least one affected individual contains an abnormal proliferation of mitochondria, as has been seen in other mtDNA mutations associated with progressive diseases. Affected family members—as well as some of the kindred who do not appear to be affected—carry a mitochondrial gene mutation in heteroplasmic form, with the mutant mtDNA representing 10%–95% of the total. This apparent disease mutation, one of several sequence variants that are observed in the family, occurs at a conserved position within a tRNA gene and may act similarly to mutations that have been observed in other disease variants of mitochondrial tRNA genes.

0002-9297/99/6404-0001$02.00

Germ-Line Mosaicism in Tuberous Sclerosis, *by Rose et al.* **(***p. 986***);** ***Fibrillin-1 Germ-Line Mosaicism,*** *by Rentamäki et al.* **(***p. 993***)**

Parental mosaicism is a plausible explanation whenever a dominantly acting mutation arises in a family in a sporadic fashion. Two papers in this issue suggest that germ-line mosaicism—rather than true de novo mutations in gametogenesis—may be at work even in cases in which the parents' somatic tissues exhibit no detectable levels of mosaicism. Rose and colleagues suspected germ-line mosaicism in one of the tuberous sclerosis genes, either *TSC1* or *TSC2,* when they observed seven families each of which included two affected children but had no prior history of the disease. One mutation in *TSC1* and five mutations in *TSC2* are identifiable in blood cells of the affected individuals in these kindreds but not in samples from the unaffected parents. Similarly, Rentamäki et al. show that two sisters with Marfan syndrome share a novel missense mutation in the gene for fibrillin-1, which is not found by PCR methods in any parental somatic tissues. Both of these reports stress that germ-line mosaicism is likely to be miscategorized, in many cases, as de novo mutation and that, for counseling purposes, the recurrence risk to a family with one apparently sporadic incidence of a dominant, high-penetrance disorder should be considered to exceed the population-wide de novo mutation rate.

Genotype-Phenotype Relation and Dominant Negative Isoform, *by Mohammad-Panah et al.* **(***p. 1015***)**

The Romano-Ward (RW) and Jervell Lange-Nielsen (JLN) syndromes both present with cardiac defects, and both conditions arise from mutations in the *KCNQ1* gene. The KCNQ1 RNA is alternatively spliced to encode the KvLQT K^+ channel, which contributes to the repolarization of the cardiac muscle after an action potential, and a truncated isoform of the channel, which inhibits the function of the long isoform. RW alleles cause cardiac arrhythmia as a dominant trait, whereas JLN alleles are associated with mild or no heart defects in heterozygous carriers. Mohammad-Panah and colleagues have expressed mutant and wild-type KCNQ1 cDNAs in transfected cells, in order to probe this dif-

ference in allele interactions. They find that nearly all of the disease alleles, whether associated with RW or JLN, are inactive when expressed in isolation and that, surprisingly, the difference between the two classes of alleles is seen in their effect on short isoform function. Products of the JLN mutant alleles abolish both the channel activity of the long isoform and the channel-inhibitory activity of the short isoform, so they do not interfere with the function of wild-type proteins expressed in the same cell. RW-associated mutations are dominant, it appears, because they encode nonfunctional channels and functional inhibitory subunits.

Multicentric Origin of HFE Mutations *by Rochette et al.* (*p. 1056*)

Hereditary hemochromatosis is among the most common of human genetic diseases. The prevalence of the causal C282Y allele of the *HFE* gene approaches 10% in Europeans, which raises the question of whether this sequence variant affords some selective advantage, at least in the heterozygous state. Rochette et al. now present evidence that will likely fuel more such speculation. These authors screened people of Southeast Asian and Sri Lankan origin for the C282Y allele as well as for the other, lower-penetrance hemochromatosis allele, H63D. They show here, on the basis of haplotype analysis, that the H63D mutation may have arisen as many as four times and that the C282Y mutation has occurred at least twice. Whether these mutations, which alter iron metabolism in carriers and homozygotes, protect against pathogens or some other form of environmental threat is uncertain, but it is interesting to consider whether other functional variants, perhaps ones that do not predispose to hemochromatosis, may have been under positive selection at various times during human evolution.

Relaxed Replication of mtDNA, *by Chinnery and Samuels* (*p. 1158*)

Defects in mtDNA are commonly associated with the diseases of advancing age and, indeed, have been proposed as mechanisms for the physiological changes associated with aging. Chinnery and Samuels now present a mathematical model for changes in the population of mtDNAs in postmitotic cells, and they argue that this model can account for the delayed onset and progressive character of mitochondrial diseases. The authors propose that cells maintain a cell type–specific optimum mtDNA copy number by holding the degradative rate constant and adjusting the frequency at which the average mitochondrial genome replicates. Assuming that cells neither repair mtDNA sequence variations nor divide, this simple model implies that any initial degree of heteroplasmy will fluctuate dramatically within single-cell level but will evolve in a predictable manner in the overall cellular population until all cells have eliminated one or another variant. Applying this model to the presence of deleterious mutations, Chinnery and Samuels find that the rate at which a disease mutation becomes fixed in a subset of the initial heteroplasmic cells depends on several parameters, including the initial mtDNA population size. This theory may account for the finding that nondividing cell types such as muscle and neurons carry many more copies of mtDNA than do shorter-lived cells.

Nile River Valley mtDNA Variation, *by Krings et al.* (*p. 1166*)

The Nile River Valley, extending from the southern Sudan to northern Egypt, represents a tract of hospitable land surrounded by desert, a "long and narrow oasis," in the words of Krings and colleagues. This valley is home to several ancient peoples with distinct cultures and languages, and the extensive historical record documents contacts among them during the past 4,000 years. Here, Krings et al. consider whether these populations have been free, during their history, to travel along the Nile and to intermarry or whether there have been substantial barriers to migration. These authors define a simple three-locus mtDNA haplotype that allows them to distinguish most northern from most southern residents of the valley, so individuals who carry the "northern" haplotype, even if they live in the Sudan, are presumed to be descended from women of the northern Nile River Valley. Krings et al. report, as one would if migration has been unrestricted, two smooth clines of mtDNA sequence variation among present-day residents of this region: variation among mtDNAs of the northern haplotype is most pronounced in the north, and, conversely, mtDNAs of the southern haplotype exhibit the greatest sequence variation among residents of the southern Nile River Valley. Krings et al. conclude that the valley has served as a corridor for migration during recorded time, and they speculate that the mixing that they observe corresponds to known periods of military or political expansion by northern- or southern-dwelling peoples.

JOHN ASHKENAS
Editorial Fellow