This Month in the *Journal*

For this issue of *The American Journal of Human Genetics,* Dr. Miron Baron has contributed a review article on the genetics of schizophrenia (p. 299). In it, he summarizes the genetic regions that have been implicated in this disorder, and he also discusses the challenges associated with the identification of genetic loci that are involved in a complex, psychiatric disorder.

Wild-Type Huntington Reduces Apoptosis, *by Leavitt et al. (p. 313)*

Polyglutamine expansions, intracellular aggregates, and neuronal cell death—these are all characteristic of Huntington disease; but what is the pathological mechanism? Through use of transgenic mice expressing human huntingtin (htt), Leavitt et al. think they've found a clue. The authors bred mice that express mutant human htt in the absence of endogenous mouse htt. These mice are infertile, and this infertility is associated with testicular degeneration and, in the spermatids and Sertoli cells, abnormal intracellular protein aggregates and mislocalized actin filaments. The authors believe that the mutant phenotype is a downstream consequence of a massive increase in apoptosis in the spermatogenic cells of these mice. The phenotype can be rescued through the expression of normal levels of wild-type mouse htt in the transgenic mice, thereby contradicting the hypothesis that mutant htt has a toxic gain of function. The results instead suggest that the abnormalities seen in mice expressing mutant htt are a consequence of the loss of normal htt activity, which the authors believe is antiapoptotic.

PRX *Mutations Cause Recessive DSN,* *by Boerkoel et al. (p. 325)*

The recent finding that *Prx* knockout mice develop a severe demyelinating neuropathy has led Jim Lupski and his colleagues to hypothesize that the human orthologue of *Prx* is mutated in some human inherited myelinopathies. *Prx* encodes periaxin, a protein that is thought to be involved in stabilization of the myelin sheath of axons. Human *PRX* maps to chromosome 19q13.3-q13.2, within a genetic interval that has recently been mapped for autosomal recessive myelinopathy. Genetic sequence from 168 patients with peripheral neuropathy revealed that 3 had mutations in *PRX*. These mutations lead to the loss of the acidic domain in the carboxy terminal portion of periaxin. Although the consequences of this loss are not yet known, the authors propose that the domain may mediate a protein-protein interaction that is essential for periaxin function and that mutations in the other components of this interaction may also be associated with neuropathies.

Genomic Divergences among Hominoids, *by Chen and Li (p. 444)*

Estimates of the sequence divergence between human and nonhuman primates have largely relied on DNA hybridization data and sequence data from a limited number of genetic regions. To make more-accurate estimates of this sequence divergence, Chen and Li have obtained DNA sequence from several intergenic, nonrepetitive regions and have compared them between humans, chimpanzees, orangutans, and gorillas. Noncoding regions are not subject to natural selection in the same way that coding regions are, so they should provide a more accurate and general picture of evolution. The average sequence divergence between humans and chimpanzees was found to be 1.24% ± 0.07%, a substantially lower estimate than had previously been calculated, possibly because repetitive sequences have been excluded from Chin and Li's calculations. The data were also used to estimate the effective population size of the common ancestor of humans and chimpanzees, which was approximately five to nine times larger than the estimate of the long-term effective population size for humans. These results indicate that there has been a significant reduction in the effective population size in the human lineage since we diverged from chimpanzees.

Brain mtDNA D-Loop Variants, *by Chinnery et al. (p. 529)*

Last year, *Science* published a report, by Michikawa et al. (see the References list in Chinnery et al.), suggesting that point mutations in the mtDNA control region appear with normal advancing age. These data are intriguing because it has been postulated that accumulation of mtDNA mutations might play a role in the aging process. Concerned with the role of mtDNA mutations in the aging of the brain, Chinnery et al. have examined this phenomenon in brain tissue. In neither normal, aged brains nor brains from patients with neurodegenerative disease did they detect any of the mtDNA control-region mutations that were observed by Michikawa et al. in cultured skin fibroblasts. Perhaps this is due to the fact that Chinnery et al. used primary tissue in their experiments. They suggest that, in culture, selection for the

0002-9297/2001/6802-0001$02.00

variant mtDNA molecules may lead to the appearance of mutations, as reported by Michikawa et al. Whatever the reason for the discrepancy, it appears that, on the issue of mtDNA mutations and aging, the jury is still out.

Inheritance of mtDNA Heteroplasmy, *by Brown et al.* (*p. 533*)

It is pretty much impossible to predict the likelihood that a woman who carries a heteroplasmic mtDNA point mutation will bear a severely affected child, because of the fact that these women transmit variable amounts of mutant DNA to their offspring. Since we do not yet understand the mechanism of transmission of heteroplasmic mtDNA to the offspring, we cannot estimate what proportion of mutant mtDNA a child will carry. To better understand heteroplasmic mtDNA transmission, previous studies included comparisons, between mothers and their children, of the mutant load, as measured in blood samples. Although these studies provide useful information, the results could be complicated by ascertainment bias, since families are identified through affected individuals, and by the fact that mutant load can change with age (see Chinnery et al. 2000*c* in the References list of Brown et al.). To look at mtDNA transmission more directly, Brown et al. measured the mutant load in primary oocytes from a woman who carries the A3243G mtDNA mutation. The frequency distribution of mutant load in the oocytes is binomial and centered around the mean. Because this distribution is not skewed, Brown et al. conclude that selection for or against the mutant mtDNA sequences is not occurring but, rather, that the level of mutant mtDNA in the oocytes is determined by random genetic drift. This work provides the first look at mtDNA transmission in the absence of ascertainment bias, and it puts us on the road to being able to provide accurate genetic counseling for women with heteroplasmic mtDNA mutations.

KATHRYN BEAUREGARD
Deputy Editor