This Month in the *Journal*

Repair of DNA damage occurs via several pathways that have been conserved, in their basic form, in all eukaryotes. Leadon (p. 1259) begins this month's series on the genetics of human DNA repair with a discussion of transcription-coupled repair. Both nucleotide-excision repair and mismatch repair occur preferentially in transcribed genes—and on the transcribed strand of those genes—and Leadon argues that genes underlying Cockayne syndrome and one form of xeroderma pigmentosum, as well as the breast cancer gene *BRCA1,* help to couple transcription to repair. Petrini (p. 1264) shows that Nijmegen breakage syndrome is a disorder of the double-strand break–repair system, and he compares the function of the human NBS1 protein complex to that of a DNA-repair complex that induces cell-cycle arrest in yeast. Maizels (p. 1270) discusses the need for double strand–break repair and mismatch repair at several steps in the maturation of immune cells. She focuses, in particular, on the recombination events required for immunoglobulin-class switching, for which the Bloom syndrome DNA helicase seems to be required. Bogenhagen (p. 1276) shows that DNA repair of several classes occurs in mammalian mitochondria, despite some premature claims to the contrary. Some nuclear DNA–repair factors are alternatively processed and expressed in the mitochondrion, so defects in the corresponding genes may affect the stability of both the nuclear and the mitochondrial genomes. Finally, Oliver et al. (p. 1282) discuss an unusual intranuclear protein modification, the addition of polymers of ADP-ribose, to chromatin proteins, DNA-repair molecules, and regulators of the cell cycle. This modification, carried out by the protein PARP, is required for base-excision repair. Efficient apoptosis, a physiologically benign form of cell death, requires that PARP be proteolytically inactivated.

***Comprehensive Analysis of* TSC1 *and* TSC2,** *by Jones et al.* (*p. 1305*)

TSC1 and *TSC2* encode hamartin and tuberin, tumor-suppressor proteins that collaborate to repress the growth of hamartomas in the brain and many other tissues. Defects in either of these genes cause tuberous sclerosis (TSC), a clinically variable tumor disorder. Jones and colleagues have performed the largest survey, to date, of familial and sporadic cases of strictly defined TSC, and they now report on the range of mutations in both genes among 120 unrelated people. Among probands in this group who had no family history of TSC, a considerable majority carried mutations in *TSC2,* but defects in *TSC1* and *TSC2* are evenly distributed among familial cases. Jones et al. suggest that *TSC2* defects may lead to more-severe disease and, hence, to a lower probability of the affected person reproducing. The authors describe 42 novel and 38 previously reported lesions in *TSC2* in their group. The 19 known missense mutations and short in-frame deletions, which may be informative in structure/function studies, appear to cluster in several locations within the protein.

COX II Mutation, *by Clark et al.* (*p. 1330*)

Cytochrome c oxidase, also known as "complex IV" of the mitochondrial electron-transport chain, consists of 13 subunits, 3 of which are encoded by the mitochondrial genome. Clark et al. have identified, in a mother and son with progressive ataxia and muscle wasting, a heteroplasmic point mutation in the mitochodrially encoded gene for the subunit II of this complex. Muscle biopsies and PCR analysis of individual muscle fibers show that, in fibers that lack cytochrome c oxidase activity, mtDNA with the point mutation predominates over wild-type mtDNA. This mutation destroys the initiator methionine codon in this gene and appears to block all synthesis of subunit II, although other mitochondrially expressed proteins accumulate at normal levels. Surprisingly, expression of the subunit II mRNA is also specifically reduced in cells carrying a substantial proportion of the mutant mtDNA. Clark and colleagues speculate that the stability of mitochondrial mRNA may be diminished in the absence of translation.

Subtle* SMN1 *Mutations in SMA Patients, *by Wirth et al.* (*p. 1340*)*; and* ***Promoters of* SMN *and* SMNc,** *by Echaniz-Laguna et al.* (*p. 1365*)

Spinal muscle atrophy (SMA) results from lesions in a 5q13 duplicated region that contains two nearly identical copies of at least four genes. Despite this complex structure, it now appears that the critical sequence underlying SMA is the telomeric copy of the *SMN* gene (described as "*SMN1*" by Wirth et al. and as "*SMN*" by Echaniz-Laguna et al.; standard nomenclature in this field would certainly be welcome). Other linked genes, such as the neuronal apoptosis-inhibitory protein (*NAIP*) gene and the centromeric copy of *SMN,* termed "*SMN2*" or "*SMNc,*" have also been suggested to contribute to the condition. The most common cause of SMA is the homozygous deletion of all or part of the telomeric *SMN1* gene, but point mutations in this gene

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are also observed. Wirth and co-workers have refined a quantitative PCR-based assay to determine the number of copies of *SMN1* or *SMN2* per genome. They observe single-copy deletions of *SMN1* in obligate carriers and in compound heterozygotes who bear novel point mutations in their remaining copy of *SMN1*. In one case, Wirth et al. show that a gene conversion has replaced one copy of *SMN1* with *SMN2*, a change that is associated with SMA. All of these results appear to indicate that *SMN2* cannot substitute for *SMN1*, although differences in *SMN2* copy number seem to account for some of the clinical variability among patients with identical *SMN1* genotypes. The nonequivalence of these two nearly identical genes is especially surprising in light of results from Echaniz-Laguna et al., who show here that the promoters of these genes are also quite similar. Sequences derived from upstream regions of *SMN1* and *SMN2* drive expression of a reporter gene equally efficient in cultured cells. The authors suggest that differences in expression level between these genes occur at the posttranscriptional level, perhaps by affecting mRNA stability.

Androgen Receptor in* BRCA1 *Breast Cancer, *by Rebbeck et al.* (*p. 1371*)

The risk of breast cancer due to mutations in *BRCA1* is difficult to predict for an individual woman. Here, Rebbeck et al. consider one potential interacting gene, the X-linked androgen receptor (*AR*) gene, which carries a CAG repeat whose length is inversely correlated with AR-expression level. Because AR function alters breast cancer–cell development in culture, Rebbeck et al. examine the variation of trinucleotide-repeat length in this gene in 304 women with inherited *BRCA1* mutations, half of whom had been diagnosed with breast cancer. Of the several possible correlations that the authors examine, one emerges as statistically significant: As the length of the longer CAG repeat increases (and, presumably, as the expression of the weaker *AR* allele drops), women are at greater risk of early-onset disease. Rebbeck et al. suggest that random X inactivation renders *BRCA1* heterozygotes who carry one weakly expressed AR allele especially susceptible to tumor development. This model predicts that tumors in these women should derive preferentially from clones of cells in which the longer *AR* allele occurs on the active X chromosome.

***Recombination Suppression at* RNU2-BRCA1,** *by Liu and Barker* (*p. 1427*)

“Hot” and “cold” spots for meiotic recombination occur on all chromosomes and account for the differences between physical distances and recombination distances between markers. Here, Liu and Barker define the limits of one of the most extended cold spots, a region of >250 kb surrounding *BRCA1*. Using polymorphisms that cover nearly 2 Mb in this region of 17q, Liu and Barker infer haplotypes for 275 randomly ascertained Caucasians and 34 Asian Americans. For the 250-kb core region, these haplotypes fall into three major groups, and the authors reconstruct a possible evolutionary relationship among the major groups and subgroups. All steps in this pathway result from the accumulation of mutations, and there is no evidence that recombination has occurred across this region during the estimated 4,000 generations that separate Asians from Europeans. Haplotypes over autosomal recombination cold spots might be used much like mitochondrial or Y-chromosome markers, to help deduce historical relations among peoples.

Meiotic Transmission of a Neocentromere, *by Tyler-Smith et al.* (*p. 1440*)

Normal centromeres consist of hundreds to thousands of kilobases of simple repetitive “alphoid” DNA to which at least six specific chromatin proteins, the CENP’s, bind during mitosis. However, cell-culture studies show that alphoid sequence is not essential for centromere function and that CENP-A, -C, and -E can bind to any of a large number of chromosomal loci when “latent neocentromeres” at such loci become activated. Because both acentric and dicentric chromosomes are lost from a population of dividing cells, stable transmission requires that exactly one centromere or neocentromere on a chromosome be active at any time. Tyler-Smith and colleagues observed during routine karyotyping that the Y chromosome of a male fetus lacked a constriction at the usual location but contained a constriction at Yq12. Because this karyotypic feature was also seen in the father and a paternal uncle, Tyler-Smith et al. conclude that the Yq12 neocentromere has been active—and that the normal Y centromere has been inactive—for at least three generations in this family. In cells from this family, the Y-chromosomal alphoid array at the inactivated centromere is unusually short, and CENP-B staining is seen only at the neocentromere. Although the neocentromere appears to function adequately in meiotic chromosome segregation, the presence of 45,X cells among the lymphocytes from the father and uncle indicates that it is not entirely equivalent to the centromere in a normal Y chromosome.

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