This Month in the *Journal*

This month in the *Journal,* Cecilie Löe Licht, Tinna Stevnsner, and Vilhelm Bohr present a review article on Cockayne syndrome group B (CSB). This premature aging syndrome is a deficiency of transcription and DNA repair, and it is caused by mutations in the *CSB* gene. This review focuses on the many different roles of CSB, including involvement in transcription by RNA pol I, II, and possibly III; transcription-coupled nucleotide excision repair; and base-excision repair. The multifaceted nature of this protein and its involvement in basic processes help to explain the multisystemic presentation of Cockayne syndrome.

MDR1 *and Inflammatory Bowel Disease,* *by Brant et al.* **(***p. 1282***)**

Genomewide scans for inflammatory bowel disease (IBD) have indicated linkage to a region on chromosome 7q. Located within this region is the *MDR1* gene, which encodes the membrane transporter P-glycoprotein-1. Because *mdr1*-deficient mice develop colitis, this gene has been of interest for IBD, and a recent study reported association of the 3435T variant of *MDR1* with the IBD ulcerative colitis (UC) but not Crohn disease (CD). Brant et al. sequenced this gene in several patients with IBD and chose three exonic SNPs that they used in both a case-control study and a family-based association study for IBD. They report association of both CD and IBD with the Ala893 allele of *MDR1,* which has a significantly lower transporter activity than the other alleles of this SNP. In contrast to the previous study by Schwab et al. (2003 [see reference in Brant et al.]), no association between 3435T and UC, CD, or IBD was observed. The Ala893 IBD-risk allele was found at the same frequency in Jewish control individuals as in white, non-Jewish subjects, a finding not unexpected by Brant et al. because of the higher prevalence of IBD in the Jewish population. With these results, evidence is building that *MDR1* could be the second major gene for IBD, after *Card15/Nod2*. Although transport of pharmacologic agents via the P-glycoprotein has been studied extensively, a greater understanding of the endogenous substrates for this protein may be needed before a potential role of this protein in IBD can be determined.

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Crossover Preference in SMS-REP, *by Bi et al.* **(***p. 1302***)**

In several genomic disorders, low-copy repeats (LCRs) act as substrates that mediate nonallelic homologous recombination (NAHR). One of these disorders is Smith-Magenis syndrome, the majority of cases of which are caused by a common 4-Mb interstitial deletion that is flanked by highly homologous LCRs called "SMS-REPs." To determine whether the specific sequences within the SMS-REPs influenced the position of the NAHR, Bi et al. performed breakpoint analyses on somatic cell hybrids that contained the common deletion allele. Although the deletion-associated breakpoints were distributed throughout the region of homology between the distal and proximal SMS-REPs, half of the 16 hybrids had breakpoints in a 12-kb region within the *KER* gene cluster. This same hotspot was implicated in 3 of 13 cases with the reciprocal product of the SMS deletion, dup(17)(p11.2p11.2). This interval contains several fragments of perfect identity and is flanked by a set of inverted repeats. Although the role of these sequences in the NAHR has not been determined definitively, the authors propose that these features may promote NAHR within the hotspot, possibly through formation of a hairpin structure by the inverted repeats. This work supports the previous suggestion that chromosome environment, not just sequence itself, dictates the site of strand exchange in recombination.

Marker Informativeness for Inference of Ancestry, *by Rosenberg et al.* **(***p. 1402***)**

Inference of ancestry can be useful in a variety of types of genetic studies, including admixture mapping and population genetics. Rosenberg et al. aim to increase the efficiency of marker selection for use in ancestry inference by proposing new measures for marker informativeness of ancestry. These measures are robust to the input data set and can accurately determine whether a locus is among the most informative, which is proven to be a useful indicator of the ability of a marker to infer ancestry. When these measures are applied to randomly chosen markers, microsatellites are found to be more informative than SNPs. A general pattern of correlation for informativeness between geographic regions can be found, with the exception of Oceania and America. This correlation suggests that a panel of generally informative markers could be useful. Rosenberg et al. have begun to create such a panel through use of their informativeness measures. These markers can be used,

for instance, to test for population stratification in case-control association studies. If population structure is found, the markers can then be used to control for this stratification in structured-association methods. Overall, this work suggests a scheme for making decisions about the markers used in studies of ancestry.

Allelic Variation in L1 Retrotransposition, *by Lutz et al.* (*p. 1431*)

Two alleles of the L1 retrotransposon L1.2 have been isolated, L1.2A and L1.2B. L1.2B retrotransposes in cultured cells at 16-fold higher frequency than L1.2A, although the alleles differ at only three nucleotides. Two of these differences result in differences at the amino acid level, and the sequence of L1.2A differs from the consensus of a highly active ("hot") L1. On the basis of the activity of L1.2A/L1.2B chimeras, it became clear to Lutz-Prigge et al. that the S1259L polymorphism is responsible for 80% of the difference in retrotransposition activity between the two L1.2 alleles, whereas I1220M accounts for the remaining 20%. How these small sequence differences translate to large differences in activity is not clear. These data predict that L1 allelic heterogeneity could influence the probability, within individuals, of having a new retrotransposition event that could lead to a disease-causing mutation.

SVA Elements, *by Ostertag et al.* (*p. 1444*)

Not only can L1 retrotransposons mobilize and lead to disease-causing insertions, but the L1 machinery can also be used by nonautonomous retrotransposons, such as *Alu* elements, for their own mobilization. Ostertag et al. wanted to determine the origin of a mobile element that inserted into the α-spectrin gene in a family with hereditary elliptocytosis, and they discovered an additional retrotransposing element that seems to fit this second category. The inserted sequence was the result of an SVA-mediated transduction event. The authors isolated and characterized the full-length SVA precursor of this insertion and realized that SVA insertions contain some of the hallmarks of retrotransposition by the L1 machinery, such as ending in a poly A tail directly following a poly A signal and possessing flanking L1-like target site duplications. The recent α-spectrin insertion studied here suggests that SVA elements are currently active. In fact, SVA elements have been the source of at least two other disease-causing insertions, one in *BTK* and one in *fukutin*. Ostertag et al. estimate that there are >2,000 full-length SVA elements in the genome. These elements show little sequence divergence, indicating that they have evolved recently. In addition to being a potential source of disease-causing insertions, these recently evolved elements may be useful as markers for phylogenetic studies.

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