This Month in the *Journal*

This month in the *Journal,* Beaudet and Jiang (p. 1389) offer their view on the evolution of imprinting. They propose a rheostat model in which imprinted genes are hypervariable in terms of gene and phenotype expression. They theorize that haplotype selective advantage acts on these hypervariable loci to yield rapid, reversible imprinting-dependent evolution. This type of evolution is predicted to provide a selective advantage when variation over a phenotypic continuum can help an organism to adjust to a changing environment.

Evaluation of Chromosome 22 Maps, *by Matise et al. (p. 1398)*

How well do genetic-linkage and radiation-hybrid maps actually reflect the true position of markers, as identified by DNA sequence information? This is a question addressed in the article by Matise et al., who use the "completed" sequence of chromosome 22 to look at the accuracy of nine different genetic-linkage, radiation-hybrid, and integrated maps of this chromosome. Whereas the genetic-linkage and radiation-hybrid maps show similar levels of concordance to the sequence map, with ~78%–80% of markers falling within 500 kb of their assumed correct position, the integrated maps, in general, had fairly poor concordance. The least-dense maps have the highest percentage of markers near their sequenced positions, suggesting that there may be a trade-off in the use of denser marker maps. Four chromosomal regions show marker discrepancies on multiple maps. These regions are all near duplicated genes or DNA segments, which, not surprisingly, may contribute to mapping errors. Comparisons of the genetic and sequence maps also allow the authors to determine that the distribution of recombination for chromosome 22 is significantly different between males and females. Finally, an assessment of two radiation-hybrid maps indicates that radiation-induced breakage is fairly evenly distributed on chromosome 22 and is not concentrated in particular radiation-sensitive sequences.

COL6A3 ***Mutations in Ullrich Congenital Muscular Dystrophy,*** *by Demir et al. (p. 1446)*

Diffuse muscle weakness, proximal-joint contractures, hyperextensible distal joints, and dystrophic muscle fibers are the cardinal features of Ullrich congenital muscular dystrophy (UCMD), in which the onset of symptoms is at birth. Although mutations associated with UCMD have been described in *COL6A2,* the gene encoding the $\alpha 2$ chain of collagen VI, it had appeared that additional genes might also be involved in this disease. Demir et al. looked for regions of homozygosity in a consanguineous family affected by UCMD and identified three potential UCMD loci. Analysis of two additional consanguineous affected families supported linkage of UCMD to chromosome 2q37, in an interval that contained *COL6A3,* a likely candidate gene because it encodes the $\alpha 3$ chain of collagen VI. A homozygous mutation was identified in each of the three families and included a splice-site mutation that leads to an in-frame deletion of 17 residues from the triple-helical domain of the protein, an R465X nonsense mutation that is predicted to truncate the protein after the first two N-terminal domains, and an R2342X nonsense mutation encoding a protein that lacks the C-terminal domain. Curiously, the severity of the genotype did not predict the severity of the phenotype, since the most severely truncating mutation, R465X, was found in a patient with a mild phenotype. Suppression of the predicted effect of R465X appears to be due to alternative splicing of the RNA, which leads to the exclusion of the mutation-containing exon. Immunostaining of muscle and fibroblasts from this patient showed only mildly reduced collagen VI expression, in contrast to the severely affected patient with the R2342X mutation, in whose muscle no collagen VI expression was detected.

Recombination in Human Oocytes, *by Tease et al. (p. 1469)*

Measurements of meiotic recombination in human females have been made only indirectly, through the examination of DNA-polymorphism inheritance in families. Since variation in maternal recombination has been identified as a risk factor for chromosome nondisjunction, a more thorough characterization of this recombination would be helpful to our understanding of how and why nondisjunction occurs. Tease et al. have been able to make direct measurements of recombination in fetal oocytes by staining for MLH1, a mismatch-repair protein. The distribution of MLH1 foci at pachytene matches that of chiasmata at metaphase I, thereby providing a marker for recombination. An average of 70.3 crossovers were found per oocyte at pachytene, although there was considerable variability between cells. The number and distribution of MLH1 foci were determined for chromosomes 13, 18, 21, and X. In addition to a recombination frequency 1.4 times larger than what has been measured in males, an intersex difference in the

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distribution of crossovers was also observed. It had previously been found that, in male germ cells, chiasma tend to form adjacent to telomeres. In contrast, MLH1 foci were rarely observed in these regions in the oocytes. These data indicate a sex-specific difference in the control of recombination. Some chromosomes 18 and 21 lacked an MLH1 focus and presumably would be at higher risk for nondisjunction as meiosis is completed. Although lack of recombination is important for malsegregation of chromosomes 13 and X, neither chromosome lacked an MLH1 focus in any of the oocytes that were classified as normal in this study; however, some oocytes were classified as abnormal because of partial or complete asynapsis of these chromosomes, and the authors suggest that the association of nonrecombinant chromosomes 13 and X with maternal nondisjunction may be derived from these abnormal oocytes.

Human-Chimpanzee Comparison, *by Ebersberger et al. (p. 1490)*

Ebersberger et al. performed a genomewide comparison of human and chimpanzee DNA sequences, using almost 2 Mb of sequence that they obtained from a male chimpanzee. The average sequence difference between the species was 1.24%, identical to what was seen in a previous study, which used a much smaller amount of the chimp genome (see the Chen and Li [2001] reference cited by Ebersberger et al.). Transitions at CpG sites account for 28% of all substitutional differences, although this type of site makes up only 3.5% of the total sequences compared. This means that these sequences are 23 times more likely to show a transition than are nucleotides in a different sequence context. On a larger scale, individual chromosomes showed different levels of divergence, even when the comparisons were restricted to introns and intergenic regions, meaning that these differences are not due to gene-density differences between chromosomes. The authors also attempted to look at the mutation rate in males versus females. The outcome of this analysis varied depending on the nucleotide diversity estimated for the common ancestor of chimps and humans, so it is unclear whether the time that DNA sequences spend in the male and female germlines is the major determinant of the overall evolutionary rate. However, the differences in levels of divergence between the autosomes indicate that there are factors other than the sex-specific differences that influence the accumulation of substitutions in the human genome.

Instability of* FMR1 *Alleles, *by Sullivan et al. (p. 1532)*

Hyperexpansion of a CGG repeat in the 5′ UTR of *FMR1* leads to methylation of a neighboring CpG island, which, in turn, shuts off transcription of the gene. Absence of the *FMR1* gene product, the fragile X mental-retardation protein, leads to the fragile X syndrome phenotype. Although the instability of *FMR1* premutation alleles (those that have $\geqslant$60 CGG repeats) has been well studied, the factors involved in expansion of smaller alleles to the premutation form have not been fully characterized. Sullivan et al. tackle this question through studies of 1,452 parent-child transmissions of common-sized ($\leqslant$39 CGG repeats) and intermediate-sized (40–59 repeats) *FMR1* alleles. Although some previous studies had found that the number of AGG interspersions in the repeat plays a role in repeat instability, Sullivan et al. found that, in their sample, the length of the CGG repeat 3′ to the last interrupting AGG best explains the risk related to repeat structure. In contrast to the instability of maternally inherited premutation alleles, the common-sized and intermediate-sized alleles are more unstable when inherited paternally. The authors propose that this seemingly contradictory finding results from intersex differences in mutational or selection mechanisms.

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