This Month in the *Journal*

Genetic Disorders of the Skeleton, *by Kornak and Mundlos* (*p. 447*)

This month in the *Journal,* Uwe Kornak and Stefan Mundlos review genetic disorders of the skeleton. Although these disorders have traditionally been grouped on the basis of clinical data, more-recent classification schemes have taken into account molecular data as well. This sometimes results in the grouping of conditions that have a common molecular origin but share little in terms of the clinical phenotype. Kornak and Mundlos use a combination of molecular pathology and development to categorize these disorders into four major groups: disorders affecting skeletal patterning, condensation/differentiation of skeletal precursor structures, growth, and homeostasis. Within each group, they discuss normal skeletal development, including the genes and signaling pathways involved, and the disorders that arise when these processes go awry.

Mouse Models of Miller-Dieker Syndrome, *by Yingling et al.* (*p. 475*)

Jessica Yingling, Kazuhito Toyo-oka, and Anthony Wynshaw-Boris discuss the contiguous gene syndrome Miller-Dieker Syndrome (MDS). This malformation syndrome is associated with a severe grade of lissencephaly—a lack of convolutions in the brain—as well as a characteristic dysmorphic facial appearance and other abnormalities that can include, among other things, epilepsy, heart malformations, and polydactyly. MDS is associated with haploinsufficiency of chromosome 17p13.3. Most cases of isolated lissencephaly sequence (ILS) are also associated with haploinsufficiency in this region. As its name implies, ILS is also characterized by lissencephaly, but at a milder grade than MDS, and it does not include additional malformations. Yingling et al. describe the use of mouse models to tease apart the genes that are involved in these related phenotypes.

Selection on Olfactory Receptor Genes, *by Gilad et al.* (*p. 489*)

The olfactory receptor (OR) gene family is one of the largest in mammalian genomes. These genes are organized in clusters that contain both intact and pseudogenes. Recent evidence indicates that humans accumulate OR gene disruptions at a significantly higher rate than do chimpanzees, suggesting that the OR genes are under different evolutionary forces in the two species. To look further at the human-chimpanzee differences, Gilad et al. study 20 OR genes in humans and chimps and compare them, in terms of variation, with putatively neutral intergenic regions and OR pseudogenes. In both humans and chimps, intact OR genes have significantly lower nucleotide diversity than the intergenic regions and pseudogenes, suggesting that selection is at work on these sequences. However, whereas purifying selection seems to be the likely explanation for the patterns of variation found in the intact OR gene sequences in chimps, it appears that positive selection has driven a subset of alleles to fixation in at least some of the human OR genes. The authors propose that the difference in selective forces between the species may be a result of a decreased reliance on the sense of smell in humans.

Linkage Disequilibrium and Haplotype Blocks, *by Wall and Pritchard* (*p. 502*)

Although the idea of "haplotype blocks" has been a popular one of late, the ability of this type of model to capture the underlying linkage disequilibrium (LD) has not been thoroughly assessed. A haplotype block is a group of consecutive sites that are in complete, or nearly complete, LD with each other. This model implies that if one identifies the haplotype blocks in a region, it would be possible to predict the likely alleles at unobserved sites in the block, and this has implications for association studies. Wall and Pritchard propose three criteria that haplotype blocks should meet, and they assess how well simulated data and three large human data sets fit the haplotype block model. The three criteria are: that most of the sequence should be contained in haplotype blocks (termed "coverage"), that, if two single-nucleotide polymorphisms (SNPs) are in strong LD with each other, they should also be in LD with SNPs between them ("absence of holes"), and that few SNPs should be assigned to more than one haplotype block ("absence of overlapping blocks"). They find that the real data sets violate the "coverage" and "absence of holes" criteria quite substantially and that certain genetic regions show more blocklike LD than others. Simulations indicate that pronounced recombination-rate heterogeneity must exist for data to fit the haplotype block model well. Comparing these simulations with the real data, Wall and Pritchard found that a model where recombination occurs in narrow hot spots is a better match to the observed patterns of LD, suggesting that there is fine-scale variation in recombination rates across the genome. Overall, their results suggest that there will be regional differences in

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how well data fit the haplotype block model. The fit to this model can be improved by increasing marker density, but deviation from the model could have an impact on the use of this concept in the design of association studies.

Transcription and Mutation in Human Genes, *by Majewski* (*p. 688*)

Although mutations are usually detected as base-pair substitutions, mutational forces actually act on single bases, thus raising the potential for strand-specific mutation rates. If the mutation rates of complementary DNA strands are identical, the frequencies of complementary bases should become equal over time (G = C and A = T). Transcription-associated biases in mutation rates have been reported in some organisms, including mammals, and these biases lead to deviations from the G = C, A = T rule. Majewski investigates strand-specific mutational bias in the known human genes, using sequences that should evolve neutrally. It has been suggested that, in mammals, mutational asymmetry might result from transcription-coupled mismatch repair in germ cells. If this theory is correct, one would expect there to be a relationship between the asymmetry of base composition and the expression pattern of genes that are expressed in the germline. To test this, Majewski compares asymmetry in base composition between genes that should be expressed in the germline and those that show tissue-specific expression. Indeed, genes that are expressed in germ cells have a higher average bias in base composition, and this bias increases with the level of gene expression. These results do support the idea that mutational asymmetry in human genes is caused by transcription.

Integrated Haplotype Map of the MHC, *by Walsh et al.* (*p. 580*)

Consistent associations have been found between autoimmune diseases and the MHC region. In addition to the classical *HLA* loci, this 4-Mb region contains many other genes that may influence these associations, yet it has been hard to discriminate between causal variation and the variation that is in LD with it. To tackle this problem, Walsh et al. build a SNP haplotype map of the region and compare it with a high-resolution recombination map generated by Cullen et al. (2002 [see reference in Walsh et al.]). Maps such as this will allow us to better choose the SNPs that will be valuable in association studies of this region, making these studies more cost-effective and efficient. They should also make it easier to zero in on the causal variation involved with different autoimmune diseases. Walsh et al. also use their map to begin to identify SNP haplotypes that can be used as surrogates for HLA typing. As these HLA-predictive haplotypes are further refined through additional genotyping, it may be possible to use high-throughput SNP methods, instead of traditional methods, for HLA typing.

Effects of E-Beam Irradiation on Buccal-Cell DNA, *by Castle et al.* (*p. 646*)

Several large epidemiologic studies use self-collected buccal cells, which are mailed from the participants back to research facilities, as a source of DNA. With the implementation of a plan to sterilize some U.S. mail with irradiation, the effects of electron-beam (E-beam) irradiation on genomic DNA needs to be evaluated. To determine whether this irradiation alters the quantity or quality of recoverable DNA from these samples, Castle et al. collected buccal-cell specimens by expectoration of a mouthwash rinse, split the samples into two aliquots, and exposed one aliquot to E-beam irradiation that simulated the exposure for mail. They found a significant decrease in the yield and quality of DNA extracted from irradiated buccal-cell samples. This may be due, in part, to DNA cross-linking, which is consistent with the increased fraction of DNA that did not migrate into gels in the irradiated samples. They also saw reduced amplification of larger DNA fragments, which may have been caused by DNA cleavage. Although at least some genetic analyses can be performed on these irradiated samples, it seems that amplification of larger DNA fragments and whole genomes may be compromised.

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