This Month in the *Journal*

Mutant LRP5 Causes High Bone Mass, *by Little et al.* (*p. 11*)

Currently, the factors involved in traits inherited in a Mendelian fashion are much simpler to unravel than those with a complex inheritance pattern. Thus, although the Mendelian traits may be rare, the identification of the relevant genes could have critical implications for our understanding of more-common but more-complex genetic diseases. Little et al. have identified a unique family that segregates high bone mass as an autosomal dominant trait. The trait was discovered by radiography. "Affected" individuals are clinically normal, and their bones have normal shape and outer dimensions; however, they have a bone mass that is ~5 SDs above the mean for the general population. Little et al. were able to limit the critical region that had previously been identified on chromosome 11q12-13 and found a G171V missense mutation in *LRP5*, a member of the LDL-receptor–gene superfamily. At the 2001 annual meeting of The American Society of Human Genetics, mutations in *LRP5* were also reported to cause osteoporosis pseudoglioma syndrome, of which low bone mass is a main component (see the Gong et al. 2001 reference cited by Little et al.), thereby proving Johnson et al.'s (1997; see the reference cited by Little et al.) hypothesis that the diseases are allelic. Beyond the fact that LRP5 is involved in Wnt signaling, the role of this protein in the determination of bone mass is unclear; however, these results define a new pathway likely to play a role in the attainment of peak bone mass and, therefore, could be an important pathway for our understanding of osteoporosis, a much more common and a genetically more complex disorder.

22q Segmental Duplications, *by Bailey et al.* (*p. 83*)

Segmental duplications in the human genome have resulted in repetitive sequences that make both assembly of the genome and analysis of chromosome structure difficult. A greater understanding of these duplications could help us to overcome some of these problems and could also help us to understand better how duplications can be associated with genetic disease. The completion of the chromosome 22 sequence enabled Bailey et al. to systematically study segmental duplications across the q arm of this chromosome, in a much more detailed fashion than previously had been possible. More than 10% of chromosome 22q is duplicated, much more than had been believed on the basis of chromosome-painting studies, so it appears that many of the changes occur on a smaller scale than can be detected by the painting technique. The distribution of the duplications across the chromosome is not uniform. Interchromosomal duplications are concentrated within the most centromeric and telomeric regions, whereas intrachromosomal duplications are found in the proximal third of the chromosome arm. Comparisons with other primates allowed the authors to study the evolution of the duplications. It appears that segmental duplication has been an ongoing process throughout recent primate evolution, and there are several human-specific duplications. The most recent duplication has been localized to the most centromeric position of chromosome 22q, whereas more-divergent duplications are within a more distal part of the pericentromeric region. The authors therefore propose that, possibly through a mechanism involving the alpha-satellite repeats, blocks of sequence integrate next to the centromere and that, as more integrations occur, the previously inserted sequence is pushed to a more distal location in the pericentromeric region. As has been proposed, the segmental duplications show evidence that they may provide a mechanism for the creation of new genes; 11 novel or modified transcripts resulted from the chromosome 22q duplications.

The Map Problem, *by DeWan et al.* (*p. 101*)

With the release of a draft human-genome sequence, it has become possible to compare the genetic order of genome-scan markers to the physical order, on the basis of the assembled DNA sequence. DeWan et al. have done just that and present comparisons of Marshfield panels 9 and 10 to both the Human Genome Project–Santa Cruz and the Celera human-genome databases. Although the great majority of marker orders were found to be consistent with the physical map, there were some disagreements. The marker order of 2%–5% of the markers, depending on which marker set and which genome database were compared, were inconsistent with the genetic order. Genetic markers whose order was inconsistent with a physical map were generally located closer to gaps in the genome sequence than were markers whose order was consistent with the physical map. For most of these inconsistencies, the genetic-map order matches the physical order found in the other genome database. Furthermore, the marker order usually has a likelihood ratio >3 (the difference between the base-10 likelihoods for the Marshfield map and the second most likely order), suggesting that the genetic-map order, rather than the sequence order, is correct in many cases when there are inconsistencies.

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These results suggest that the genome sequence may be useful for confirmation of genetic-marker orders but that there are obviously still assembly errors in the genome databases; using both genome databases can help to eliminate some of these discrepancies. Additionally, the authors suggest that likelihood ratios >3 should be used as an additional criterion to support the genetic-marker order. A web site maintained by the authors will provide updated lists of the genetic and physical marker–order discrepancies, as well as information on genetic-map distances, physical-map positions, and likelihood-ratio support for the genetic maps.

Stepwise Procedure for Polymorphisms within a Gene, *by Cordell and Clayton* (*p. 124*)

How does one know that the association between a genetic polymorphism and a disease is due to a direct effect of the polymorphism and is not simply due to the fact that it is in strong linkage disequilibrium with the etiological polymorphism? Cordell and Clayton propose a stepwise logistic regression procedure for evaluation of the relative importance that genetic variants have for a phenotype of interest. This approach is applicable to both case/control and family data sets. Some of the proposed strategies use haplotypes, and these strategies can be used to fit models for the full genotype- and haplotype-interaction effects of a locus. Other strategies are designed for the analysis of genotype effects only, thereby avoiding the need to determine haplotypes in the data set. This allows the full use of available families, rather than just those for which haplotypes can be determined. The regression approach makes it possible to examine the effect at a locus, conditional on the alleles present at other loci, without assuming particular values for these alleles. This allows a high degree of flexibility for the testing of a wide variety of null hypotheses.

Ancient Origins of Ethiopians and Khoisan, *by Semino et al.* (*p. 265*)

In studies of the history of humans in Africa, the relationships between certain populations have not been clear. Semino et al. make use of the large number of Y-chromosome biallelic markers that have recently become available, and they study the relationships between Ethiopians and other African populations. An African-specific haplogroup is present in all of the groups of Ethiopians and Khoisans studied, and this confirms that they share an ancestral paternity. However, the Ethiopian and Khoisan samples possess different haplotypes within this haplogroup, consistent with a long period of separated evolution following the split between these populations. This haplogroup in the Ethiopians and Khoisans is virtually absent in the other African groups, which may mean that these other groups derived from a more recent ancestral population, which had a long period of differentiation before its expansion. Semino et al. have also identified haplogroups that probably entered the Ethiopian populations from Asia, representing a back-migration. This work will help to clarify the patterns of Y-chromosome variation in Africa.

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