This Month in the *Journal*

Genetic Heterogeneity in RSTS, *by Roelfsema et al.* **(***p. 572***)**

Mutations in the gene that encodes CREB-binding protein, *CBP,* cause Rubinstein-Taybi syndrome (RSTS), a disorder characterized by postnatal growth and mental retardation and characteristic facial abnormalities. This transcriptional coactivator has histone acetyl transferase (HAT) activity that facilitates chromatin opening and subsequent gene expression. Although haploinsufficiency for CBP is clearly a mechanism by which RSTS arises, mutations have not been found in all cases. This led Roelfsema et al. to do a careful mutation screen in 92 people with RSTS. Thirty-six *CBP* mutations, ranging from missense mutations to deletions of the entire gene, were identified, and all were predicted to result in loss of CBP's HAT activity. Because *CBP* mutations were not identified in the majority of their sample, Roelfsema et al. decided to screen another gene, *EP300*, which shares homology with *CBP* and also encodes a protein containing a HAT domain. Three inactivating *EP300* mutations were found, the first disease-associated mutations in this gene. All three individuals with *EP300* mutations have a classic RSTS phenotype, so there are no apparent phenotypic differences associated with mutations in this second gene. This work indicates that RSTS is a genetically heterogeneous disorder, and, because mutations still have not been found in more than half of their sample, Roelfsema et al. predict that still more genes are likely to be involved in RSTS.

HapMap and tagSNPs of Human MHC, *by Miretti et al.* **(***p. 634***)**

The MHC region on chromosome 6 has been associated with a variety of phenotypes, particularly those related to autoimmune disease. However, it has been difficult to tease apart these associations because of the high level of linkage disequilibrium (LD) in the area. Miretti et al. report a linkage disequilibrium map with 1.9-kb resolution across >4 Mb of this region, and this has allowed them to propose a set of tagSNPs that will increase the resolution and efficiency of association studies focused on the MHC. The map was generated using >2,000 loci that were genotyped in a CEPH sample. Using these data, Miretti et al. estimate fine-scale recombination rates, define recombination hotspots, identify extended regions of haplotype homozygosity that might suggest positive selection, and find haplotype blocks that cover nearly 82% of the region. The results revealed the presence of one of the longest regions of high LD in the genome, encompassing the olfactory receptor gene cluster. Their data have been deposited to the Web-based database GLOVAR so that they may be more easily viewed and used by other researchers to design future genetic studies of the MHC.

Position Effect of Chromosome Translocation in Campomelic Dysplasia, *by Velagaleti et al.* **(***p. 652***);** *and* ***Translocations ≥900 kb Upstream of* SOX9*,*** *by Hill-Harfe et al.* **(***p. 663***)**

You may recall a recent review article by Kleinjan and van Heyningen in which long-range control of gene expression was discussed. One of the genes they mentioned was *SOX9,* which is mutated in campomelic dysplasia (CD), a skeletal disorder that is often associated with sex reversal in affected males. Rearrangements upstream of *SOX9* have been found in some individuals with CD and have suggested the presence of long-range *cis*-regulatory elements for this gene. In this issue, the regulatory elements are further defined in two articles (by Velagaleti et al. and Hill-Harfe et al.) that describe additional translocation breakpoints in individuals with CD or a related, milder skeletal dysplasia. In three of the cases, the breakpoints mapped ~900 kb upstream of *SOX9*. In the fourth case, the breakpoint was ~1.3 Mb *down*stream of *SOX9* and is the first such breakpoint to be found 3′ to the gene. There are no protein-coding transcripts in the vicinity of these breakpoints that appear likely to contribute to the phenotype, so it is believed that they affect *SOX9* regulation and thus are some of the most distant regulatory elements described to date. Velagaleti et al. use FISH assays to show that the two breakpoint regions are in close spatial proximity to each other and to *SOX9* in interphase nuclei, and they wonder whether this spatial organization facilitates *SOX9* regulation by these elements. They believe that conserved regions near these breakpoints contain *cis*-regulatory elements for *SOX9*, but exactly which sequences are involved and how they work remains to be determined.

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LD and Recombination in Different Populations, *by Evans and Cardon* (*p. 681*)

The basic idea of the HapMap is that it will characterize the distribution of linkage disequilibrium (LD) across the genome, thereby facilitating association studies. One big question is to what extent this information will be transferable between populations. Evans and Cardon address this question through comparisons of fine-scale LD patterns across 10 Mb of chromosome 20q in four samples: one African American, one Asian, and two of European ancestry (from the United Kingdom and from CEPH). The first problem was to decide what LD measure should be used to make these comparisons, and the authors begin with the pairwise measures of LD, D' and r^2. The authors find that, as has been suggested before, D' is likely to confound comparisons of LD between populations because of its sensitivity to marker allele frequencies. In fact, D' measurements in the U.K. and CEPH populations are fairly discrepant, despite their shared ancestry. A better measure appears to be the population recombination rate ρ, which is more robust to these marker parameters and is more closely correlated between populations in general. On a finer scale, the U.K. and CEPH populations show a high degree of correlation for ρ across the region, a finding that suggests that a single HapMap will be useful for populations of similar ancestry. On the other hand, at least for this chromosomal region, there were population-specific highs and lows in ρ that may make multiple haplotype maps necessary to ensure the best possible design of association mapping in different populations.

Genotype-Environment Interactions and Asthma, *by Hoffjan et al.* (*p. 696*)

One current hypothesis about the large increase in incidences of asthma and allergy over the past 50 years is the idea that it results from a reduction in the exposure of kids to dirt and germs that would normally facilitate the development of an appropriately balanced immune response. In support of this hypothesis is the finding that kids who attend day care—and thus are exposed to more infections—are less likely to develop asthma. Hoffjan et al. hypothesize that early environmental exposures interact with a child's genotype to influence the likelihood of asthma and allergy, and they developed the Childhood Onset of Asthma (COAST) study to test this. The authors show that polymorphisms in immune-related genes interact with day care attendance to influence immune phenotypes related to asthma and allergy. Some of the "day care effect" seems to represent the increased number of viral infections in kids who attend day care, but it appears that there must be additional environmental risk factors related to day care that contribute to the gene-environment interaction. These results highlight the importance of taking genes and environmental variables into account jointly in association studies; when they were considered alone, little evidence was found for the influence of either the polymorphisms or day care attendance on the asthma phenotypes.

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