Williams-Beuren duplication

Williams-Beuren syndrome (WBS) is caused by nonallelic homologous recombination on chromosome 7q11.23, leading to a microdeletion. WBS is a neurodevelopmental disorder with characteristic cardiovascular, cognitive and behavioral features. Perhaps the most notable aspect of the phenotype is that such individuals have excellent expressive language skills relative to their overall intellectual ability. Martin Somerville and colleagues now describe an individual who has an exact duplication of the 1.5-Mb WBS region and, remarkably, exhibits a severe delay in expressive language (*N. Engl. J. Med.* 353, 1694–1701; 2005). Analysis of single-copy microsatellite markers showed that the proband carries three alleles. Two of the alleles were inherited from his mother and apparently arose *de novo* as a result of meiotic interchromosomal recombination. Five of the six genes examined in the duplicated region showed increased expression. Some abnormalities found in individuals with the WBS microdeletion are not seen in the individual with the duplication, whereas others, including the relative strength in expressive language, exhibit the opposite phenotype. The authors suggest that one or more dosage-sensitive genes in the WBS duplication may join *FOXP2* as a key point of entry for understanding the genetic basis of language acquisition. *AP*

Reexamining CCR5Δ32 selection

The CCR5Δ32 variant of the chemokine receptor CCR5, which mediates HIV entry, has been associated with copy number–dependent HIV resistance. Studies of this variant, present in higher frequencies in European populations, have also provided an interesting example of presumed recent natural selection. Previous studies dated the mutation to near 700 years and have suggested positive selection. A new study presented by Pardis Sabeti, Eric Lander and colleagues (*PLoS Biol.* **3,** e378; 2005) now suggests that the CCR5Δ32 mutation is significantly older—an estimated 5,000 years—and finds no evidence for positive selection. The current study examines 70 SNPs nearby on chromosome 3 and compares these with genome-wide SNPs in 168 immune-related genes. The study, which included individuals from European-American, Chinese and African populations, found that CCR5 variants appeared at similar frequencies both within and between these populations. The pattern of linkage disequilibrium (LD) surrounding CCR5Δ32 was also similar to that observed near other variants found at similar frequencies. Although studies including larger numbers of individuals and other populations are desirable, these findings are consistent with neutral evolution at CCR5Δ32, and they show the importance of examining selection in the context of genome-wide variation. *OB*

MeCP2 and splicing

MECP2 mutations underlie Rett syndrome, an X-linked neurodevelopmental disorder marked by loss of acquired language and motor skills and other distinct behavioral features. MeCP2 binds to methylated DNA and acts as a transcriptional repressor, but the underlying disease mechanisms remain unresolved. New work by Huda Zoghbi and colleagues (*Proc. Natl. Acad. Sci. USA*, published online 26 October 2005; doi:10.1073/pnas.0507856102) now suggests an unexpected role for MeCP2 in the regulation of RNA splicing. Using coimmunoprecipitation and mass spectrometry, the authors identified the Y box–binding protein YB-1 as an interaction partner of MeCP2. This interaction, which occurred only in the presence of RNA, was shown to regulate splicing of a CD44 reporter minigene. To identify *in vivo* targets of MeCP2, the authors used a custom microarray to monitor alternative splicing in the cerebral cortex of *Mecp2* mutant mice and found significant changes in splicing patterns in the mutant animals. Included among the genes showing altered splicing was *Dlx5*, a homeobox gene previously identified as a direct target of MeCP2 transcriptional silencing. These findings suggest dual roles for MeCP2 in transcriptional repression and RNA splicing. *KV*

Histone variant surveyed

The nucleosomes that compact nuclear DNA into chromatin are formed of histone proteins. In addition to the four canonical histone proteins, there are also variant histones that have specialized roles in chromatin biology. Now, three studies report profiling studies of the H2A.Z histone variant in yeast. Bradley Cairns and colleagues (*Cell* **123**, 219–231; 2005) used chromatin immunoprecipitation (ChIP)-chip to identify H2A.Z-occupied sites in open reading frames and intergenic regions; Hiten Madhani and colleagues (*Cell* **123**, 233–248; 2005) used ChIP-chip to profile H2A.Z across chromosome III at 20-bp tiling resolution; and Luc Gaudreau, François Robert and colleagues (*PLoS Biol.* **3**, e384; 2005) surveyed H2A.Z using ChIP-chip at 300-bp genomic tiling resolution. All three studies found promoter-specific localization of H2A.Z at inactive (repressed) genes, and, owing to differing experimental approaches, each study reported unique findings. Cairns and colleagues reported that gene activation promotes H2A.Z loss, but absence of H2A.Z results in attenuation of activation, suggesting that H2A.Z can facilitate activation. Using their high-resolution approach, Madhani and colleagues demonstrated that H2A.Z-containing nucleosomes commonly flank the nucleosome-free region at promoters, and they identified nucleotide sequences necessary for H2A.Z deposition. Finally, Gaudreau, Robert and colleagues showed that H2A.Z-containing promoters have distinct patterns of nucleosome positioning. These studies bring to light interesting possible roles for H2A.Z in transcriptional regulation and chromatin biology. *EN*

Genetically indistinguishable SNPs

Interpreting results of genetic association studies requires proper understanding of the fine-scale structure of linkage disequilibrium (LD) in human populations. As a step toward this goal, Lon Cardon and colleagues (*Genome Res.* 15, 1503–1510; 2005) report an analysis of genetically indistinguishable SNPs (giSNPs) based on high-density genotyping of roughly 30,000 SNPs on chromosome 20 in four different population samples. Cardon and colleagues observed that roughly 50% of SNPs examined had at least one SNP partner in perfect LD in a given population sample. Most giSNP clusters were short (<20 kb) and fell within traditional haplotype block boundaries, but roughly one-third of these clusters were intermingled with SNPs showing incomplete LD, sometimes spanning multiple haplotype blocks. The observed distribution of giSNPs deviated significantly from patterns simulated using a standard coalescent model, suggesting that giSNP distribution patterns in human populations are influenced by mechanisms that are not well approximated by the standard coalescent model. The existence of these long-range giSNP clusters indicates that caution should be exercised when using tag SNPs and haplotype data to infer the location of disease-associated variants in genetic association studies. *KV*

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