IL23R variants and IBD

A team of scientists, led by Judy Cho, reports results from a genome-wide association scan for variants associated with Crohn disease (CD), a common form of inflammatory bowel disease (IBD) (*Science*, published online 26 October 2006; doi:10.1126/science.1135245). For their initial scan, the group analyzed 567 individuals with ileal CD and 571 matched controls of non-Jewish European ancestry using the Illumina HumanHap300 platform. Of the three most strongly associated markers, two were located in *CARD15*, a known risk locus for CD, and one was located in *IL23R*, which encodes a subunit of the receptor for the proinflammatory cytokine IL-23. The group subsequently replicated this association in an independent ileal CD case-control study of individuals of Jewish ancestry and in an independent family-based study. The *IL23R* variant identified in the initial scan is a coding variant associated with reduced risk of IBD. However, a preliminary analysis of other common variants in the region suggests that there are multiple variants in the region independently associated with risk of, or protection against, IBD. These results, coupled with prior evidence showing that IL-23 overexpression results in severe chronic inflammation in mice, identify this pathway as a rational target for therapeutic intervention in IBD. *KV*

Transcript stability and inflammation

The expression of proinflammatory cytokines is known to be tightly regulated and can result in septic shock when aberrant. One key point of control in their expression is mRNA stability, mediated by AU-rich elements (AREs) in the 3′ untranslated regions, which promote transcript instability. Jin-Yu Lu and colleagues now show that mice lacking one of the ARE-binding proteins, Auf1, have elevated expression of TNFα and IL-1β and are highly susceptible to endotoxic shock (*Genes Dev.*, published online 3 November 2006; doi 10.1101/gad.1467606). Lu *et al.* challenged *Auf1*-null mice with bacterial lipopolysaccharide endotoxin, which stimulates a systemic inflammatory response. While most of the wild-type mice survived the challenge, the *Auf1*-null mice had severe endotoxemia and a fivefold increase in mortality. The elevated levels of TNFα and IL-1β were due to abnormal stabilization of their mRNAs. Interestingly, the stability of the mRNA encoding IL-6 was not altered, possibly owing to a different array of AREs in its 3′ region. Finally, Lu *et al.* showed that the administration of neutralizing antibodies to TNFα and IL-1β could protect the *Auf1*-null mice from endotoxic shock. The authors suggest that some proportion of human inflammatory disease might have its origin in defects in this post-transcriptional control of the inflammatory response. *AP*

Circadian loci interactions

Drosophila mutants that show circadian rhythmicity in conditions of constant light give insight into the mechanism of synchronization between the internal circadian clock and the environment. The Cryptochrome, Timeless and Jetlag proteins are known to regulate this synchronization. When investigating a mutant strain, called *Veela*, which maintains rhythmicity in constant light, Ralf Stanewsky and colleagues uncovered interactions between natural genetic variants and mutations in circadian loci (*Proc. Natl. Acad. Sci. USA*, published online 26 October 2006; doi:10.1073/pnas.0606675103). Mapping placed *Veela* close to the *Timeless* gene; however, sequence analysis did not uncover any *Timeless* mutations. But the authors noticed that *Veela* flies had the *ls* allele of *Timeless*. Wild-type *Drosophila* strains carry either the *ls* or the *s* allele; the *ls* allele produces a form of Timeless that is less susceptible to light-induced degradation. Since the *ls* allele cannot itself explain the *Veela* phenotype, the authors next looked at the nearby *Jetlag* gene, which is close to, but outside of, the *Veela* interval, and found a coding mutation. The authors suspect that the combination of the *ls* allele of *Timeless* with the *Jetlag* mutation causes the *Veela* phenotype, and their mapping stocks confirmed that crossovers that combined the *Jetlag* mutation with the *s* allele of *Timeless* led to a normal phenotype. *EN*

Research Highlights written by Orli Bahcall, Emily Niemitz, Alan Packer and Kyle Vogan.

Departures from HWE

Daniel Schaid and colleagues have developed a new method of testing for departures from Hardy-Weinberg equilibrium (HWE) useful for population samples consisting of groups of varied ancestries (*Am. J. Hum. Genet.*, published online 3 November 2006). Commonly used methods independently evaluate HWE within individual group strata in a population sample by an exact test and then use the lowest *P* value among these for a global test; however, such analyses can be limited by small sample numbers in each stratum, which may not be sufficient to detect deviations from HWE. In comparison, the current approach concurrently analyzes SNP genotypes over all strata in the population. In an advance over recent methods with similar goals, this provides an exact stratified test, avoiding several possible biases introduced with approximate stratified tests based on allele frequencies. Initial applications to both HapMap and Perlegen data sets showed that the method had greater power, reaffirming the usefulness of combining testing over multiple strata as well as using an exact stratified test. These data sets, each with small sample sizes from individual groups, provide an ideal test of this new method to detect departures from HWE that might have been missed by earlier analyses, and refines the use of these resources in association studies. *OB*

Hominid admixture and adaptive traits

Last year, Bruce Lahn and colleagues reported that a common class of haplotypes at *MCPH1*—a gene previously implicated in the regulation of brain size—is distributed broadly through the human population in a pattern consistent with recent positive selection (*Science* **309**, 1717–1720; 2005). In a follow-up study, Lahn and colleagues (*Proc. Natl. Acad. Sci. USA*, published online 7 November 2006; doi:10.1073/pnas.0606966103) present new evidence suggesting that this broadly distributed D haplogroup was introgressed into the human population through a rare interbreeding event with an archaic hominid lineage. By resequencing a 29-kb region spanning exons 4–9 of *MCPH1* in 89 individuals, Lahn's group discovered that the D and non-D haplogroups comprise two distinct and deeply divided clades. Based on their analysis, they estimate that the two lineages became separated 1.1 million years ago and remained reproductively isolated until 37,000 years ago, when the D allele was introduced into the population of anatomically modern humans and subsequently rose to high frequency through positive selection. If correct, these findings suggest that rare hominid admixture events might have served to introduce beneficial alleles that contributed to the adaptive evolution of modern humans. *KV*