Variations on a theme I

Perlegen Sciences Inc. has published its eagerly anticipated analysis of common variants in the human genome (*Science* 307, 1072–1079; 2005). David Hinds and colleagues genotyped more than 1.5 million SNPs in 71 Americans of European, African and Asian ancestry. These polymorphisms include those likely to be common across groups, as well as those that are relatively evenly distributed across the genome. The genotyping was reassuringly accurate, with more than 99.5% of the SNP calls concordant with those that have also been genotyped as part of the International HapMap Project. The pattern of linkage disequilibrium (LD) is consistent with the known continuum of diversity from Africans to Europeans to Asians. Hinds *et al*. also observed that regions of extended LD tend to correlate with functional genomic features, suggesting that selection contributes to the overall pattern of variation in the genome. Encouragingly, comparisons with resequenced regions in the Seattle SNP Project revealed that ~73% of the Seattle SNPs would be ascertained by Perlegen's less complete set, based on a stringent threshold for LD. This work therefore represents important progress toward the identification of a set of haplotype-tagging SNPs for genome-wide association studies. ***AP***

Variations on a theme II

The major histocompatibility (MHC) locus is associated with susceptibility to a multitude of autoimmune diseases; therefore, a detailed understanding of the sequence variation in this region is of substantial interest and utility. To this end, Panos Deloukas and colleagues now report a high-resolution linkage disequilibrium map of a 4.5-Mb region of the human MHC (*Am. J. Hum. Genet.* **76**, 634–646; 2005). By increasing the average marker density to one SNP per 1.9 kb, this analysis defines 202 haplotype blocks covering 82% of the region, a considerable increase over the 17 previously defined blocks that covered 25% of the region. This work confirms the known extreme variation in recombination rates across the MHC and the locations of recombination hotspots. The identification of a set of tag SNPs (available at http://www.glovar.org) from the entire set of typed SNPs with a minimum allele frequency of >5% provides a rich resource for MHC association studies. *EN*

Making muscles

The transcription factors at the top of the hierarchy of myogenic differentiation—MyoD, myogenin, MRF4, Myf5 and MEF2—have been known for some time. Alexandre Blais and colleagues have now used a combination of techniques to construct an initial blueprint for the full transcriptional network that these factors trigger (*Genes Dev*. **19**, 553–569; 2005). Blais *et al*. use the well-studied model of C2C12 myoblasts differentiating into myotubes. Through ChIP-on-chip analysis, array-based transcriptional profiling, bioinformatics and literature mining, the authors identify scores of interactions between the myogenic transcription factors and target genes. Notable findings include a large number of targets involved in synapse formation at the neuromuscular junction, confirming that muscles have an intrinsic program for promoting synapse formation. Blais *et al*. also found a large number of targets involved in stress-response pathways, consistent with the increased mitochondrial function and production of free radicals that accompanies muscle contraction. The overall topology of the network is characterized by feedback and feed-forward loops, and multi-input motifs, reflecting combinatorial control of targets by more than one myogenic transcription factor. All told, the data comprise a rich resource for the study of muscle differentiation. *AP*

South Korean H5N1

The highly pathogenic avian influenza strain H5N1 that has been spreading through Asia since December 2003 has caused at least 45 human fatalities. Initial isolates from the 1997 Hong Kong outbreak were the first to document direct transmission of H5N1 viruses from poultry to humans. Jae-Hong Kim and colleagues now report the characterization of H5N1 isolates in poultry from South Korea, which has suffered outbreaks among chickens and ducks since 2003, although no human cases have been identified (*J. Virol*. **79**, 3692–3702; 2005). Phylogenetic analysis showed that the South Korean poultry isolates were avian in origin, containing hemagglutinin and neuraminidase genes of the Gs/Gd lineage commonly shared among the recent Asian isolates, and suggested that some markers may have been fixed in the lineage since 2001. The polymerase gene of the South Korean isolates was unique, however, distinguishing them from isolates able to infect humans. The South Korean isolates were also highly pathogenic in chickens, causing 100% mortality within one day after inoculation, although there was lower mortality in ducks, and none observable in mice. This comparative study characterizing the phylogenetic, biological and pathogenic characteristics of the H5N1 flu isolates is important in further understanding the nature of this spreading epidemic. *OB*

let-7 miRNAs target Ras

let-7* is a well-studied microRNA (miRNA) best known for its role in regulating the timing of seam cell differentiation in *Caenorhabditis elegans*. *let-7* belongs to a large miRNA family conserved from worms to humans. Frank Slack and colleagues (*Cell* 120, 635–647; 2005) now report that several members of the Ras proto-oncogene family are conserved *let-7* targets, providing a mechanistic link between *let-7* miRNAs and cancer. *let-60*, encoding the *C. elegans* ortholog of Ras, and *NRAS*, *KRAS* and *HRAS*, encoding the three human Ras homologs, each contain multiple predicted binding sites for *let-7* miRNAs in their 3′ untranslated regions. Using functional assays in *C. elegans* and human cells, Slack and colleagues show that *let-7* family members negatively regulate Ras expression. They also report that expression of *let-7* miRNAs is frequently reduced in human lung cancers relative to normal adjacent tissue samples, accompanied by a concomitant increase in Ras protein expression. The potential relevance to human cancer is underscored by an earlier report showing that *let-7* overexpression inhibited growth of a lung cancer cell line *in vitro*. The present work adds to the mounting evidence implicating miRNAs as candidate tumor suppressors in humans.** ***KV

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