Short-limbed dwarfism in dogs

Chondrodysplasia, or short-limbed dwarfism, is a distinctive trait shared by multiple breeds of domestic dogs. Elaine Ostrander and colleagues (*Science*, published online 16 July 2009; doi:10.1126/science.1173275) now show that this phenotype is likely to be caused by an expressed *FGF4* (fibroblast growth factor 4) retrogene that arose once in an ancestral dog population and became fixed in modern breeds through selection. To map the trait's genetic basis, the authors performed a genome-wide association study of 76 distinct breeds, comparing allele frequencies between chondrodysplastic and non-chondrodysplastic dogs, and observed a strong association with a locus on chromosome 18. Additional fine mapping resolved the region of association to a 24-kb segment marked by the insertion of a 5-kb retrogene with 100% identity to *FGF4*. This insertion was present in 19 of 20 breeds with chondrodysplastic features but was absent from 41 breeds lacking this trait. The *FGF4* retrogene is expressed in the articular cartilage of developing and adult long bones, suggesting that the phenotype arises from inappropriate activation of FGF signaling. This proposed mechanism is concordant with observations in humans, where activating mutations in the FGF pathway account for a substantial fraction of chondrodysplasia cases. ***KV***

Restoring transport *in vitro* in cystic fibrosis

Cystic fibrosis (CF) is a recessive genetic disease that results from defects in the *CFTR* gene that perturb the normal regulation of ion transport in the airway epithelium. In those with CF, the airway epithelial cells secrete mucus that is abnormally thick, which eventually leads to obstructive lung disease. Although much effort has been put toward restoring *CFTR* function in affected individuals through gene therapy, clinical trials have achieved limited success. A major obstacle has been developing an efficient method to deliver CFTR to the conducting airway epithelium. Raymond Pickles and colleagues (*PLoS Biol.* **7**, e1000155) have developed a new viral vector to deliver a functional copy of *CFTR* in a culture model of human ciliated airway epithelium. They demonstrate that this approach restores airway surface hydration and mucus transport. Furthermore, the study shows that CFTR expression does not require tight regulation in airway cells and that restoration of transport function to approximately 25% of surface epithelial cells rectifies the physiological defects that lead to lung disease in CF. Further work on this viral vector *in vivo* will be needed to determine the vector's therapeutic potential in delivering functional *CFTR* to the airways of individuals with CF. *PC*

miRNAs and breast cancer stem cells

Cancer stem cells are hypothesized to be self-renewing, with the capacity for generating the diverse cell types that comprise tumors. To identify miRNAs that may regulate breast cancer stem cells (BCSCs), Michael Clarke and colleagues (*Cell* **138**, 592–603; 2009) systematically compared miRNA expression profiles in human BCSCs and nontumorigenic cancer cells. They show that three miRNA clusters are downregulated in normal mammary stem cells, BCSCs and embryonal carcinoma cells. One of the miRNA clusters, miR-200c, suppresses the expression of *BMI1*, a known regulator of self-renewal and differentiation in several types of stem cells. Ectopic expression of miR-200c suppresses cancer cell growth and induces differentiation *in vitro* and also induces differentiation of normal mammary stem cells *in vivo*. The authors found that BCSCs ectopically expressing miR-200c formed fewer tumors than BCSCs not expressing the miRNA cluster, suggesting that miR-200c can regulate the ability of BCSCs to self-renew and proliferate *in vivo*. These results imply that normal stem cells and BCSCs are regulated by common molecular pathways. *PC*

Written by Orli Bahcall, Pamela Colosimo and Kyle Vogan

Second AML genome sequenced

Timothy Ley, Elaine Mardis and colleagues recently reported the first complete sequence of an individual cancer genome (*Nature* **456**, 66–72; 2008) from a subject with acute myeloid leukemia (AML). The same group now reports (*N. Engl. J. Med.* advance online publication 5 August 2009; doi:10.1056/NEJMoa0903840) the sequence of a second AML-derived genome along with follow-up studies to investigate which mutations represent recurrent events in AML pathogenesis. The authors used Illumina technology to sequence the tumor sample and a matched normal skin sample at roughly 20-fold coverage. They then used Sanger sequencing to validate a subset of predicted somatic mutations, focusing on annotated coding regions, RNA genes and conserved noncoding sequences. In addition to finding mutations in *NPM1* and *NRAS*, which have established roles in AML pathogenesis, the authors found a mutation at position 132 of *IDH1*. Notably, similar mutations have been reported to occur at high frequency in malignant gliomas. The authors then screened 187 additional AML samples and found mutations at position 132 of *IDH1* in 8% of tumors, identifying *IDH1* mutations as likely driver events in AML pathogenesis. *KV*

Maize mapping

Michael McMullen and colleagues report a resource for mapping quantitative traits in maize (*Science* 325, 737–740; 2009). The nested association mapping (NAM) population is composed of 4,699 recombinant inbred lines, derived from 25 different families, which were selected to represent the diversity of maize. The genetic map includes 1,106 loci, with an average of one SNP per 1.3 cM, and about 136,000 recombination events. The recombination frequency varied between the 25 families, unfortunately to a level that limited the feasibility of joint linkage-association mapping. In an accompanying paper, Edward Buckler and colleagues report the use of the NAM population to map QTLs for flowering time in maize, examining nearly 1 million plants among four different environments over two years (*Science* 325, 714–718; 2009). Although they find no single QTL with large effects, they observed that many QTLs with small effects contribute to genetic variation in flowering time and that many of these were shared among the families. They also find some evidence for epistatic and gene-environment interactions, although these show only a small contribution to the overall genetic architecture contributing to variation in flowering time. ***OB***