FGFR2 and breast cancer

Genome-wide association analysis has shown that a haplotype within intron 2 of the *FGFR2* gene is associated with increased susceptibility to breast cancer. Now Bruce Ponder and colleagues investigate the function of the susceptibility allele in the regulation of *FGFR2* gene expression (*PLoS Biol.* 6, e108; 2008). An analysis of *FGFR2* gene expression in tumors homozygous for the susceptibility haplotype or for the common haplotype revealed that the risk haplotype was associated with higher levels of *FGFR2* gene expression. Electrophoretic mobility shift assays for the eight most strongly associated SNPs showed that two SNPs differentially formed protein–DNA complexes. At one SNP, the common allele bound C/EBPβ and the risk allele did not, and at the other SNP, the common allele bound Oct-1 and the risk allele bound both Oct-1 and Runx2. Using a reporter construct, the authors found that the risk allele bound to Oct-1 and Runx2 had stronger transcription stimulating activity than the common allele, whereas the C/EBPβ-bound common allele had higher transcription stimulating activity than the risk allele. The authors concluded that binding to Oct-1 and Runx2 is probably the primary determinant of transcription activity. However, it remains to be determined whether insights into *FGFR2* regulation in breast cancer can be extrapolated to the mechanism of increased risk for tumor formation. *EN*

Neuroblastoma risk variants

John Maris and colleagues (*N. Engl. J. Med.* advance online publication 7 May 2008; doi:10.1056/NEJMoa0708698) report that common variants on chromosome 6p22 are associated with neuroblastoma, a childhood cancer of the peripheral nervous system. The authors carried out a genome-wide association study of 1,032 cases of European ancestry and 2,043 matched controls using the Illumina HumanHap550 BeadChip. In the initial scan, three SNPs on 6p22 passed the threshold for genome-wide significance. Replication studies using three independent sample collections confirmed that the variants on 6p22 were consistently associated with neuroblastoma risk, with a per allele odds ratio of 1.3–1.4. Individuals homozygous for the 6p22 risk alleles were more likely to present with more clinically aggressive forms of the disease and had a lower probability of event-free survival. The risk variants reside in a linkage disequilibrium block containing two genes of unknown function, *FLJ22536* and *FLJ44180*. Although the biological basis for the association remains unknown, this study is the first to establish a role for common variants in the etiology of neuroblastoma, and provides an entry point for understanding how the more clinically aggressive forms of the disease arise. *KV*

Human matrilineal diversity

The degree of genetic structure in populations of early *Homo sapiens* in sub-Saharan Africa is an important question, with implications for our understanding of the modern human dispersal out of Africa 60,000–70,000 years ago (ybp). Doron Behar and colleagues analyzed 624 complete mitochondrial sequences for haplogroup L(xM,N), and report a significant amount of matrilineal structure in early human settlements (*Am. J. Hum. Genet*. **82**, 1130–1140; 2008). Previous work had shown that the L0d and L0k haplogroups account for more than 60% of the contemporary mtDNA gene pool in the Khoisan people of South Africa. Behar *et al*. carried out an mtDNA coalescence analysis showing that, other then very recent (3,000–5,000 ybp) introgressions owing to the expansion of Bantu-speaking peoples from western Africa, the mtDNA gene pool of the Khoisan is in fact almost entirely restricted to L0d and L0k. The authors hypothesize that this split between the L0 and L1′5 clades, which probably occurred 140,000–210,000 ybp, represents a drift-generated divergence of the ancient human population into two small populations. This evidence for early maternal structure in human populations suggests that small groups of early humans remained in geographic and genetic isolation until migrations during the Late Stone Age resulted in the peopling of regions outside of Africa. *AP*

Written by Orli Bahcall, Emily Niemitz, Alan Packer and Kyle Vogan

Darwin's tomatoes

Among Charles Darwin's collections from the Galapagos Islands were two accessions of wild tomato, *Solanum cheesmaniae* and *Solanum galapagense*, which have unique leaf shapes despite their relatively recent divergence. The leaves of *S. cheesmaniae* resemble the relatively simple unipinnately compound leaves of cultivated tomato, whereas the leaves of *S. galapagense* are more complex, with three orders of leaflets. Seisuke Kimura and colleagues report that the leaf complexity phenotype is caused by a 1-bp deletion in a region upstream of a gene called *TKD1* (*Curr. Biol.* **18**, 672–677; 2008). *TKD1* encodes a novel member of the KNOX family of transcription factors, although it lacks a homeodomain. It is expressed in developing leaves, and the variant found in *S. galapagense* is associated with overexpression, suggesting that it is a dosage-sensitive regulator of leaf complexity. The authors note that the phenotype of the classic tomato mutation *bipinnata* resembles the phenotype induced by overexpression of TKD1 in tomato. They then go on to show that an 8-bp deletion in an ortholog of the *Arabidopsis thaliana* gene *SAW* underlies *bipinnata*, and that TKD1 competes with KNOX1 for binding to SAW in *Solanum*. Finally, the authors argue that mutations affecting dosage-sensitive transcription factors such as TKD1 offer a simple mechanism for generating natural variation. *AP*

Preparing for environmental change

The ability of an organism to sense environmental change can prove critical to fitness, and doing so in advance can allow time for preparation. Saeed Tavazoie and colleagues report an *in silico* analysis of how microbial genetic networks may allow for such prediction of environmental changes (*Science* advance online publication 8 May 2008; doi:10.1126/science.1154456). The authors developed a computer program, Evolution in Variable Environment (EVE), which models biochemical networks evolving within complex environments. They carried out simulations allowing for competition and adaptive evolution within nine temporally structured environments. The evolved networks showed a high level of redundancy, but they identified a 'minimal network' of essential nodes. Searching for experimental evidence of predictive capacity *in vivo*, they examined the *Escherichia coli* transcriptional response upon temperature and oxygen changes. They found correlation between gene expression changes after temperature upshift and oxygen downshift intended to model the transition of *E. coli* into a gastrointestinal tract, and showed that these genes were enriched for aerobic respiration functions. When they introduced *E. coli* into a new dynamic environment with temporal changes in temperature and oxygen, the evolved organisms no longer showed correlated transcriptional responses for temperature upshift and oxygen downshift, suggesting that this correlation is environment-specific. *OB*