β-defensins and pigmentation

The melanocortin 1 receptor (Mc1r) plays a key role in regulating pigment-type switching in vertebrates, with its activation promoting synthesis of a dark pigment called eumelanin and its inhibition promoting synthesis of a lighter pigment called pheomelanin. Although much of the natural variation in mammalian coat color is explained by variant alleles of *Mc1r* or of *Agouti*, which encodes an inhibitory ligand for Mc1r, a recent mapping study in dogs identified another locus, termed *K*, with marked effects on pigmentation. Now, Greg Barsh and colleagues (*Science*, advance online publication 18 October 2007; doi:10.1126/science.1147880) show that the *K* locus encodes a member of the β-defensin family of antimicrobial peptides. The evidence, which includes genetic mapping and mutation analysis in dogs, transgenic studies in mice and biochemical assays in heterologous cell lines, suggests that the product of the *K* locus promotes eumelanin production by binding directly to Mc1r and acting as a competitive inhibitor of Agouti. This unexpected link between β-defensins and the melanocortin pathway highlights the utility of genetic mapping for revealing biological functions and suggests that diversity within the β-defensin gene family may have been driven, in part, by selection related to pigmentation. *KV*

Coverage and power

Michael Eberle, Sarah Murray and colleagues at Illumina present an analysis of the coverage and power of two new whole-genome genotyping platforms, HumanHap550 and HumanHap650Y (*PLoS Genet*. **3**, e170; 2007). SNP selection for these platforms was guided by HapMap data; the HumanHap550 panel was designed for coverage of European (CEU) and Asian (CHB+JPT) HapMap sample populations, whereas in the HumanHap650Y panel, an additional 100,000 common African (YRI) tag SNPs were added to increase coverage in this sample population. The authors estimate the coverage of, and power to detect genetic associations using, these panels, following on previous studies reported in this journal (*Nat. Genet.* **38**, 659–662; 2006; *Nat. Genet*. **38**, 663–667; 2006). They estimate that these platforms cover a majority of common variation in the genome, and also estimate the power to detect genetic associations to complex traits assuming single disease loci of moderate risk or multiple loci. They estimate that with a sample size of 1,000 cases and 1,000 controls, these panels have ~80% power to detect single disease loci of moderate risk (RR ~1.8–2.0). Increasing sample sizes to 10,000 cases and 10,000 controls, under some scenarios, could allow for detection of single loci with lower relative risks (RR ~1.2–1.3). *OB*

SHANK3 mutations and autism

Disease-associated mutations in the gene encoding the synaptic scaffolding protein SHANK3 were recently found in three families affected with autism-spectrum disorder, or ASD (*Nat. Genet.* **39**, 25–27; 2007). In support of these findings, Steve Scherer and colleagues (*Am. J. Hum. Genet.* **81**, 1289–1297; 2007) now report the identification of similar alterations in *SHANK3* in three unrelated subjects with ASD. Scherer and colleagues screened 400 individuals with ASD for sequence or copy number changes in *SHANK3* by direct sequencing or array-based intensity analysis. The changes they found included a *de novo* missense mutation and two *de novo* deletions encompassing *SHANK3*, all of which were uniquely present in the affected probands. Collectively, the frequency of *de novo* and likely pathogenic changes in *SHANK3* discovered among the ASD-affected subjects examined in these two studies was approximately 1%, which the authors suggest may be high enough to warrant testing in a clinical diagnostic setting. These findings strengthen the link between *SHANK3* mutations and ASD and add to a growing body of literature implicating proteins involved in synaptic transmission, including neurexins, neuroligins and synaptic scaffolding proteins, in the etiology of this disorder. *KV*

Three-ring circuit

Mesodermal development in the sea urchin embryo is probably the best-established system for studying the functioning of *cis*-regulatory sequences in the context of gene regulatory networks. Joel Smith and colleagues now report a dissection of a key subcircuit that governs dynamic changes in gene expression during the blastula stages of sea urchin embryogenesis (*Science* **318**, 794–797; 2007). The blastula-stage sea urchin embryo consists of a series of torus-like layers of cells. Smith *et al.* focus on a gene regulatory subcircuit involving *otx*, *wnt8* and *blimp1* that dynamically directs transcription of the latter two factors in inner, and then outer, rings of cells. In the inner tier of cells, Groucho-Tcf initially represses zygotic *blimp1* and *wnt8* expression. A small amount of maternal *blimp1* initiates *wnt8* expression, activating β-catenin, which, in concert with ubiquitously expressed Otx, activates zygotic *blimp1* expression. Wnt8 diffuses to the middle torus, where Wnt-dependent signals again cooperate with Otx to drive *blimp1* expression, while Blimp1 shuts off its own expression in the inner torus via autorepressive *cis*-regulatory sequences. This third iteration of this process results in *blimp1* expression in the outer ring of cells alone. For this subcircuit, "its design ordains its function". *AP*

Cinnamon and GARField

The NHGRI has supported 'light' 2× coverage whole-genome sequencing for 26 mammals, 17 of which have now been assembled and released. This light sequence coverage for phylogenetically diverse species has been intended as a cost-effective means to identify highly conserved sequence elements. Stephen J. O'Brien and colleagues at the NCI, Agencourt Bioscience and the Broad Institute now report the initial genome sequence of a domestic cat, *Felis catus* (*Genome Res.* 17, 1675–1689; 2007), the latest in this series of low-coverage genome sequencing. The inbred Abyssinian domestic cat, named Cinnamon, was sequenced using a whole-genome shotgun approach at 1.9× coverage. The light coverage of the current cat genome was able to capture about ~65% of euchromatic sequence; however, the depth of annotation was improved through a comparative approach to annotated genome assemblies of six mammals (human, chimpanzee, mouse, rat, dog and cow). Through alignment to these other genome sequences, the study identified 20,285 feline gene candidates and 133,499 conserved sequence blocks (CSBs), and constructed a set of 339 homologous synteny blocks (HSBs) in the cat genome. The NCI-GARField (Genome Annotation Resource Field) browser, found at http://lgd.abcc.ncifcrf.gov, hosts the ordered assembly and provides a searchable guide to the assembled feline genome. *OB*

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