Heart disease risk variants

Two groups report variants on chromosome 9p21 associated with increased risk of heart disease. Kari Stefansson and colleagues (*Science*, published online 3 May 2007; doi:10.1126/science.1142842) performed a genome-wide association study of 1,607 Icelanders with myocardial infarction and 6,728 controls with no history of coronary artery disease (CAD). They found strong association with three SNPs on 9p21 and replicated the association in four additional myocardial infarction case-control studies. They also found a significant association with CAD after removing myocardial infarction cases. Jonathan Cohen and colleagues (*Science*, published online 3 May 2007; doi:10.1126/science.1142447) performed a three-stage genome-wide association study to look for variants associated with coronary heart disease (CHD). They found two SNPs on 9p21 significantly associated with CHD across all three stages and replicated the association in three additional study groups. The linkage disequilibrium block on 9p21 harboring the risk variants includes *CDKN2A* and *CDKN2B*, whose products are important in regulating proliferation, senescence and apoptosis. Notably, the same region was recently found to be associated with increased risk of type 2 diabetes, which should help intensify efforts to define the mechanisms by which variants in this region contribute to risk of common diseases. ***KV***

Circadian rhythm goes into *overtime*

Generation of circadian oscillations in mammals involves a negative feedback loop consisting of transcriptional activation of the *Period* (*Per*) and *Cryptochrome* (*Cry*) genes by CLOCK/BMAL1 protein complexes, followed by repression of *Per* and *Cry* transcription by PER/CRY protein complexes. Now Joseph Takahashi and colleagues (*Cell*, published online 26 April 2007; doi:10.1016/j.cell.2007.04.030), Patrick Nolan and colleagues (*Science*, published online 26 April 2007; doi:10.1126/science.1141138) and Michele Pagano and colleagues (*Science*, published online 26 April 2007; doi:10.1126/science.1141194) have identified a new player, FBXL3, in this regulatory loop. The papers authored by Takahashi and Nolan identified long-period mutants, named *overtime* and *after-hours*, using ENU mutagenesis screens. Genetic mapping showed that *overtime* and *after-hours* are missense alleles of the *Fbxl3* gene. FBXL3 is a member of the F-box family of proteins that confer substrate specificity to ubiquitin ligase complexes. Functional studies showed that FBXL3 is involved in regulation of CRY protein stability; when this function is impaired by the *overtime* or *after-hours* mutation, CRY protein stability is increased, and the transcriptional repression phase of the cycle is elongated. In a complementary effort, Pagano and colleagues identified CRY proteins through a search for substrates of the FBXL3-containing ubiquitin ligase complex. *EN*

Silkworm coloration gene

Cocoons of the silkworm *Bombyx mori* obtain their coloration through dietary uptake of natural pigments, including carotenoids and flavonoids. Mapping studies have identified 15 genetic loci influencing silkworm cocoon and fiber color. Kozo Tsuchida and colleagues (*Proc. Natl. Acad. Sci. USA* **104**, 8941–8946; 2007) now report the identity of the *Yellow blood* (*Y*) locus, a classical mutant defective in uptake of carotenoids. The authors previously noted that the colorless hemolymph strain, $+^{Y}$, had an insertion of a non-LTR retrotransposon and a partial deletion of *CBP*, which encodes an intracellular carotenoid-binding protein. In the current study, the authors characterized the locus fully and found that $+^{Y}$ had, in addition to the retrotransposon insertion and partial gene deletion, a deletion of an adjacent duplicate copy of *CBP* called *Y*-a. They then generated transgenic silkworms expressing *CBP* in the midgut using the *GAL4/UAS* system and found that the transgenic larvae had significantly higher levels of the carotenoid lutein, as well as yellow pigmentation in the region of the middle silk gland and cocoons with a yellowish color. These data identify CBP as an important mediator of carotenoid uptake and establish the feasibility of modulating silk fiber color through transgenics. *KV*

doublesex and the XY body

During prophase I of male meiosis in mammals, X and Y chromosomes pair at the pseudoautosomal region, and the unpaired portions of each chromosome form the XY body, a specialized transcriptionally silenced chromatin domain. Now David Zarkower and colleagues show that DMRT7, encoded by a mammalian homolog of the *doublesex* gene of *Drosophila*, associates with the XY body and is necessary for the successful completion of male meiosis in mice (*PLoS Genet.* **3**, e62; 2007). The authors first determined that although *Dmrt7* is expressed in the fetal gonads of both sexes, it is expressed in adult testis but not in adult ovary. The timing of expression coincides with the onset of the pachytene stage, and DMRT7 is preferentially localized to the XY body in pachytene spermatocytes. The authors created a targeted deletion of *Dmrt7* that showed that *Dmrt7* is required for male gametogenesis. *Dmrt7*-null testes contain cells arrested in pachynema that subsequently undergo apoptosis. However, XY bodies form, and transcriptional silencing occurs normally in *Dmrt7*-null cells. Examination of rare *Dmrt7*-null 'escape' cells that complete pachynema uncovered abnormalities in chromatin modification marks such as HP1β and H3K9 di- and trimethylation. This work identifies an interesting new player in meiotic sex chromatin regulation. *EN*

Cilia and Sonic hedgehog signaling

Cilia have a role in mediating Hedgehog signaling. Tamara Caspary and colleagues report a new mouse ciliary mutant that provides insight into the link between ciliary structure, Sonic hedgehog (Shh) signaling and patterning of the neural tube (*Dev. Cell* 12, 767–778; 2007). As part of a recessive ENU screen, the authors identified the *hennin* (*hnn*) mutant, which has an open neural tube in the head and caudal spinal cord. An assessment of dorsal-ventral patterning of the neural tube in *hnn* embryos with a variety of markers for motor neurons uncovered an expansion of motor neuron progenitors. Whereas wild-type embryos have a steep ventral-to-dorsal gradient of Shh signaling in the neural tube, *hnn* embryos have a shallower gradient, as well as constitutive activation of Gli activators (effectors of Shh signaling) at low levels. Mapping of the mutation in *hnn* embryos identified a splicing defect in the gene encoding the small GTPase Arl13b. Scanning electron micrographs of *hnn* nodal cilia show that they are shorter and have disruptions of the outer doublet microtubules. The authors conclude that normal structure of the ciliary axoneme is required for the translation of different levels of Shh into the appropriate level of downstream Gli activators. ***AP***

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