## Rates of recombination

**Two studies provide new insight into the way recombination is regulated in humans. Although sperm typing studies and LD-based estimates have defined recombination hotspots and shown how recombination rates vary at a relatively fine scale, each approach has limitations. Graham Coop and colleagues now report the use of genome-wide SNP data to localize crossovers to high resolution in an extended pedigree of Hutterites (*Science*, advance online publication 31 January 2008; doi:10.1126/science.1151851). Approximately 60% of crossovers occurred in hotspots that had been inferred from analyses of LD, with a significant amount of heritable variation in the use of particular hotspots between individuals. Progress in identifying the genetic basis of this heritable variation comes from a study by Augustine Kong and colleagues, in which they carried out a genome-wide scan for variants associated with recombination rate (*Science*, advance online publication 31 January 2008; doi:10.1126/science.1152422). The authors identified SNPs associated with recombination rate in a region containing the genes *SPON2* and *RNF212*. The latter is the best candidate, as it is homologous to *ZHP*-3, an ortholog of yeast *CST9* that functions in meiotic recombination and assembly of the synaptonemal complex. Interestingly, these variants have the opposite effect on recombination rate in males and females.** ***AP***

## Handling excess heme

Heme, an iron chelator, is an essential cofactor of hemoglobin and cytochromes. However, excess heme is toxic to cells and must be exported to maintain cellular homeostasis. Janis Abkowitz and colleagues (*Science* **319**, 825–828; 2008) now report the phenotype of mice lacking a key heme export protein, Flvcr. Homozygous *Flvcr* null mice died *in utero* with a deficiency in erthyrocyte production; postnatal deletion resulted in a severe hyperchromic macrocytic anemia marked by a similar defect in erythrocyte maturation. Conversely, Flvcr overexpression in bone marrow cells resulted in a mild hypochromic microcytic anemia, a phenotype consistent with enhanced heme efflux. These data suggest that Flvcr is required to prevent the accumulation of toxic levels of free heme under conditions where its synthesis exceeds cellular demands. Other tissues in *Flvcr*-deleted mice also developed a pronounced iron overload, suggesting that Flvcr serves a similar homeostatic function in non-erythroid cells and is required for maintaining systemic iron balance. The authors speculate that heme toxicity, arising from a transient excess of intracellular free heme, could be a general pathophysiological mechanism underlying other forms of pure red-cell aplasia such as Diamond-Blackfan anemia. *KV*

## Ancestry informative markers

Two new studies examine European American population structure, each reporting a set of ancestry informative markers (AIMs) useful for inferring ancestry and correcting for population stratification in genome-wide association studies (GWAS) conducted in these populations. Alkes Price *et al.* (*PloS Genet.* **4**, e236; 2008) examined individuals of European American ancestry from four recent GWAS of multiple sclerosis, bipolar disorder, Parkinson's disease and inflammatory bowel disease. Using EIGENSOFT, Price *et al.* found the top three principal components correlated with, in order, samples of northwest European, southeast European, and Ashkenazi Jewish ancestry, and report a set of 300 AIMs selected to be informative in distinguishing these three clusters. Chao Tian *et al.* (*PLoS Genet.* **4**, e4; 2008) took a similar approach, analyzing the components of variation using both EIGENSTRAT and STRUCTURE, in individuals from a recent GWAS of rheumatoid arthritis, as well as self-identified European Americans from the New York Cancer Project. Tian *et al.* report a set of 192 AIMs for distinguishing along a north-south cline (ascertained using northern European vs. Ashkenazi Jewish ancestry) and a set of 1,211 AIMs for distinguishing along a west-east cline (ascertained using Irish vs. other northern European ancestry). The authors discuss the use of these AIM panels in the design and analyses of initial GWAS, as well as in follow-on replication studies in independent samples or candidate-gene studies. *OB*

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

## *Pten* and premature ovarian failure

The ovarian follicle contains an oocyte surrounded by granulosa cells. Follicle activation can generate a mature oocyte or lead to follicular degeneration. This process is regulated by extrinsic hormones and also by intrinsic signaling pathways. For example, Kit ligand is produced by granulosa cells and signals through the receptor protein tyrosine kinase Kit, which is expressed at the surface of oocytes. Kit signaling activates the phosphatidylinositol 3-kinase (PI3K) pathway and is essential for follicular development. Foxo3a, a transcription factor and downstream inhibitory target of PI3K signaling, represses activation of the primordial follicle. Now Kui Liu and colleagues show that PTEN, a negative regulator of PI3K, has an important role in suppressing follicular activation (*Science* **319**, 611–613; 2007). The authors engineered oocyte-specific deletion of *Pten* using the Cre-lox system. Females with deletion of *Pten* had a maximum of one normal-sized litter and became infertile by 12–13 weeks of age. By postnatal day 8 they had large ovaries with an increase in activated follicles; activation of the pool of primary follicles led to follicle depletion and premature ovarian failure. The authors report enhanced PI3K signaling in *Pten*-deficient isolated oocytes. This study shows the role of the PTEN–PI3K pathway in regulation of follicular activation and oocyte growth. *EN*

## Cohesins linked to CTCF

**Cohesins, in addition to their well-established role in mediating sister chromatid cohesion prior to mitotic segregation, are thought to play key roles in regulating expression of genes critical for normal development. A study by Matthias Merkenschlager and colleagues (*Cell* 132, 422–433; 2008) now suggests that cohesins mediate these noncanonical functions via interactions with CTCF, a site-specific DNA binding protein implicated in the maintenance of chromatin boundaries. To gain insight into cohesin function, the authors transduced mouse cell lines with an epitope-tagged version of the cohesin subunit Rad21, and then carried out chromatin immunoprecipitation coupled with hybridization to tiling arrays covering 3% of the mouse genome. A 12-nucleotide CTCF-binding motif was found to be enriched among the Rad21-bound sequences. Further comparison of chromatin immunoprecipitation data for Rad21 and CTCF showed that 70% of binding sites were shared by the two proteins. In transfection assays, knockdown of Rad21 impaired CTCF-dependent insulator function; conversely, knockdown of CTCF disrupted positioning of Rad21 on chromatin. These findings provide insights into the developmental phenotypes associated with mutations in cohesin subunits, such as those seen in Cornelia de Lange or Roberts syndrome.** ***KV***