Complex QTLs for a complex disease

David Samuelson and colleagues report progress in identifying common, low-penetrance susceptibility variants for breast cancer (*Proc. Natl. Acad. Sci. USA* 104, 6299–6304; 2007). The authors had previously identified four QTLs for mammary carcinoma susceptibility in rats. One of these, *Mcs5*, is an allele in the Wistar-Kyoto strain that acts to suppress tumorigenesis in a susceptible Wistar-Furth background. Using congenic lines, they now show that *Mcs5* is a compound QTL in which two elements are required in *cis* to confer the phenotype of tumor resistance. The two elements of the QTL are *Mcs5a*, which consists mostly of intronic sequences of *Fbxo10*, and *Mcs5a2*, which includes intronic and exonic sequences of *Fbxo10*, as well as the first exon of another gene, *Frmpd1*. Transcript levels of each gene were similar in mammary tissue from the two strains, but they were differentially expressed in the thymus (*Fbxo10*) and spleen (*Frmpd1*). Association studies with a combined population of approximately 12,000 women showed that haplotypes from the orthologous human loci are associated with breast cancer risk in opposing directions with marginally significant *P* values and modest odds ratios. The authors suggest that these results underscore the potential genetic complexity of common diseases. ***AP***

Small dogs and *IGF1*

The domestic dog shows considerable size variation—greater than that seen in other canids. In a new study, Elaine Ostrander and colleagues examine the genetic basis for size variation in domestic dogs (*Science* **316**, 112–115; 2007). In 463 Portuguese water dogs (PWD), the authors scanned a 15-Mb interval on chromosome 15 in which two QTLs had previously been found to associate with body size. They found a single peak, within the insulin-like growth factor 1 (*IGF1*) gene. In addition, they found that 96% of these PWD chromosomes carry one of two *IGF1* haplotypes (B and I) and that dogs homozygous for haplotype B had significantly smaller skeletal size and mass than those homozygous for I. Examining SNP variation in 526 dogs from 23 small and 20 giant breeds, they found evidence for a selective sweep near *IGF1* as well as a single *IGF1* haplotype common among all 14 sampled small dog breeds. Finally, they genotyped six tag SNPs, distinguishing the major *IGF1* haplotypes, within 3,241 dogs from 143 breeds, and showed that the SNP 5 A allele is negatively associated with breed mass. *OB*

RAB23 mutations in Carpenter syndrome

Genetic studies in mice have implicated the small GTPase Rab23 as a negative regulator of Hedgehog signaling. Andrew Wilkie and colleagues (*Am. J. Hum. Genet.*, in the press) now show that *RAB23* mutations in humans result in Carpenter syndrome, a recessive disorder marked by craniosynostosis, polysyndactyly and obesity. The authors used linkage analysis and homozygosity mapping to identify a candidate region on chromosome 6 containing 24 annotated genes, including *RAB23*. Sequence analysis in 15 families uncovered biallelic *RAB23* mutations, including nonsense and frameshift alleles, in all affected individuals. In mice, similar nonsense mutations in *Rab23* result in the open brain (*opb*) phenotype, which is marked by exencephaly, polydactyly and embryonic lethality. Although a lumbar myelomeningocele was present in one affected individual with a homozygous *RAB23* mutation, and although digit patterning defects are common features of both the human and mouse phenotypes, there are many notable differences in the phenotypic spectra associated with loss of Rab23 function in the two species. In particular, the craniosynostosis and obesity associated with human *RAB23* mutations demonstrate unexpected roles for this trafficking protein in late embryonic and early postnatal processes, perhaps unrelated to its role as a regulator of Hh signaling. *KV*

H2A.Z and epigenetic memory

The subnuclear localization of DNA has been linked to the regulation of transcription; some genes change location and move to the nuclear periphery upon activation. Now Jason Brickner and colleagues show that in yeast, the histone H2A.Z variant mediates peripheral localization and promotes epigenetic memory of the active state (*PLoS Biol.* **5**, e81; 2007). The authors used an integrated array of lac repressor binding sites as a marker to track the localization of the *INO1* and *GAL1* loci after induction of transcriptional activation or repression by removal or addition of inositol or galactose; the loci are detected by binding of a GFP-tagged lac repressor. This allowed the authors to determine that upon activation, the *INO1* and *GAL1* loci are recruited to the nuclear periphery; this localization persists (after subsequent repression) through cell division. The persistence of the peripheral localization is functional, as it allows enhanced reactivation after switching to activating conditions. Finally, the authors determined that the histone variant H2A.Z is incorporated into promoter nucleosomes upon repression of previously activated loci. In cells lacking H2A.Z, the loci are not retained at the periphery and cannot be rapidly reactivated. This work defines a form of cellular memory based on subnuclear localization mediated by the H2A.Z variant. *EN*

TCF7L2 variants and birth weight

Variants in *TCF7L2* have recently been identified as strong risk factors for type 2 diabetes. Tim Frayling and colleagues (*Am. J. Hum. Genet.*, in the press) now report that the same diabetes risk variants are associated with increased birth weight. The authors genotyped the variants in 15,709 individuals and 8,344 mothers and found that each fetal copy of the type 2 diabetes risk allele was associated with an 18-g increase in birth weight, whereas each maternal copy was associated with a 30-g increase in birth weight. A stratified analysis in 6,044 mother-offspring pairs suggested that the association was driven by the maternal genotype. The authors also analyzed the joint effects of maternal variation in *TCF7L2* and *GCK* (encoding glucokinase), a gene previously associated with variation in birth weight, and found that variants in the two genes contributed additively to differences in birth weight, with similar effects sizes. Based on an analysis of diabetes-related intermediate traits in 10,314 subjects, the authors propose that risk alleles at *TCF7L2* act by reducing maternal insulin secretion, leading to increased maternal glycemia and increased nutrient availability to the fetus. ***KV***

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