Wilms tumor suppressor on the X

Wilms tumor is a pediatric cancer of the kidney thought to be derived from undifferentiated nephrogenic precursors. *WT1*, an autosomal Wilms tumor suppressor gene expressed during kidney development in the renal blastema, is inactivated in 5%–10% of cases, but the genetic events underlying the majority of Wilms tumor cases remain unknown. Daniel Haber and colleagues (*Science*, published online 4 January 2007; doi:10.1126/science.1137509) now report the identification of a gene on the X chromosome that is inactivated in roughly 30% of sporadic Wilms tumors. The gene, discovered through a genome-wide analysis of DNA copy number changes in sporadic tumors, was found to be inactivated in both male and female affected individuals through somatic events (deletions or point mutations) that abrogated function of the single active allele. Like *WT1*, this X-linked gene (*FAM123B*, also called *WTX*) shows a restricted pattern of expression in the developing kidney. Notably, of the 51 tumors screened, none harbored deletions or point mutations in both *WT1* and *FAM123B*, suggesting that inactivation of these key tumor suppressor genes may be mutually exclusive events that define distinct subclasses of Wilms tumor. ***KV***

Synonymous yet functional

The identification of haplotypes or SNPs associated with disease risk or complex traits is a difficult task that is compounded by the challenge of demonstrating effects on gene function. To simplify the task, investigators may narrow their focus to nonsynonymous variants. Two new studies reporting functional effects of synonymous variants give reason to rethink this practice. Haplotypes of the *COMT* gene associate with varying levels of pain sensitivity; synonymous changes associate with the greatest difference in pain sensitivity and COMT enzymatic activity. Through an investigation of the structure of the mRNA encoded by the *COMT* haplotypes, Luda Diatchenko and colleagues demonstrate that the haplotype associated with the lowest enzymatic activity forms the most stable mRNA stem-loop structure and produces the least amount of translated COMT protein (*Science* **314**, 1930–1933; 2006). In addition, a study by Michael Gottesman, Chava Kimchi-Sarfaty, Jung Mi Oh and colleagues (*Science*, published online 21 December 2006; doi:10.1126/science.1135308) reports that a synonymous SNP in *MDR1* results in production of a protein with altered structural properties. The synonymous change introduces a rare codon, which the authors propose results in altered translation rate and protein folding. These studies show how oft-ignored synonymous variants may contribute to biological function. *EN*

Structural interaction network

Protein interaction network (PIN) studies in different organisms have provided a wealth of data, but a clear concern in evaluating these studies is the reliability of the data sets and predicted interactions. A new study by Mark Gerstein and colleagues (*Science* **314**, 1938–1941; 2006) adds a dimension to PINs through structural modeling, intended to increase the reliability of the reported protein interactions. The authors begin with the yeast PIN, first removing low-confidence interactions and then incorporating structural and chemical information on protein interactions. They also apply three-dimensional structural modeling to exclude possible configurations of complexes that appear mutually exclusive and thus narrow the range of possible interactions. Their result is termed the structural interaction network (SIN) and consists of 873 proteins and 1,269 interactions, 438 of which are mutually exclusive. In initial analyses of the SIN, notable properties include a maximum of 14 interaction partners per hub protein, in contrast to earlier interactome studies reporting much higher ranges. They also distinguish between 'multi-interface' hubs that involve simultaneously possible interactions and 'singlish-interface' hubs with mutually exclusive interactions, showing that the former are more likely to be essential and coexpressed and show a lower evolutionary rate. The SIN data set and updates can be found at http://sin.gersteinlab.org. *OB*

Research Highlights written by Orli Bahcall, Emily Niemitz, Alan Packer and Kyle Vogan.

Cilia-driven flow in frogs

Elegant studies in mammalian and fish embryos have revealed a population of motile cilia whose activity produces a leftward flow that induces expression of the *Nodal-Pitx2* left-right (L-R) signaling cassette and determines the subsequent laterality of the internal organs. But despite evidence that the role of the *Nodal-Pitx2* pathway is conserved across all vertebrates, the generality of the cilia-based mechanism upstream of this pathway remains controversial. Now, Martin Blum and colleagues (*Curr. Biol.* **17**, 60–66; 2007) present strong evidence that an equivalent population of motile cilia exists in frogs, suggesting that cilia-driven leftward flow is a conserved mechanism for determining organ laterality in all vertebrates. Using innovative microscopic techniques in *Xenopus laevis* embryos, the authors found that cells of the gastrocoel roof plate project a cluster of monocilia that rotate in a clockwise direction, generating laminar leftward flow that appears shortly before the onset of asymmetric *Nodal* expression. Several key ciliary components previously implicated in L-R signaling, including inversin and polycystin-2, were also localized to the frog monocilia, suggesting that the poorly understood downstream signaling events linking flow to the induction of *Nodal* expression may also be conserved across vertebrates. *KV*

Human eye-color variation

Eye color is a polygenic trait, although a recent estimate suggests that a locus on chromosome 15 including *OCA2* accounts for as much as 74% of the phenotypic variance. David Duffy and colleagues now report that a three-SNP haplotype in the first intron of *OCA2* is responsible for most of this association and indeed is diagnostic for the dominant brown versus the recessive blue eye trait (*Am. J. Hum. Genet.* 80, 241–252; 2007). The authors genotyped 58 SNPs across *OCA2* in a collection of 3,839 adolescent twins, their siblings and their parents and identified eight haplotype blocks. Three SNPs in intron 1 that comprise one of these haplotypes showed the strongest association with blue eye color, with *P* values ranging from 10^{-54} to 10^{-96}. The data suggest that the haplotype TGT acts as a highly penetrant recessive blue eye color allele. It is present in some individuals with green eye color but is never observed in those with brown eyes. Light eye color has been associated with higher risk of melanoma, and the authors propose a study to assess the specific contribution of the *OCA2* intron 1 haplotype in this context. ***AP***