Anticoagulant pharmacogenetics

Warfarin is a widely used anticoagulant monitored using an intermediate endpoint calculated as the ratio of an individual's clotting time to the population mean (INR). However, the stable warfarin dose to achieve a given INR can vary by a factor of 10 among individuals. Now the International Warfarin Pharmacogenetics Consortium (*New Engl. J. Med.* 360; 753–764; 2009) have generated predictive algorithms based on a set of retrospective studies totaling 4,043 subjects receiving a stable dose of warfarin and with an INR of 2 to 3. The consortium validated the models on retrospective studies of a further 1,009 individuals undergoing warfarin therapy. The algorithms incorporated either clinical variables only or clinical variables plus *CYP2C9 *1,*2 *3* genotypes and at least one from a set of seven *VKORC1* SNPs. The pharmacogenetic algorithm identified more stable doses achieving the target coagulation than did the clinical model when applied to the outlying tails, that is, the 46.2% of the population requiring less than 21 mg or more than 49 mg per week to achieve the desired INR range. The limitations of the study are that it deals with a clinical endpoint, and eventually the study will need to consider the frequency of adverse events, such as thromboembolism and bleeding, and environmental factors. ***MA***

Ascl2 and intestinal stem cell fate

Hans Clevers and colleagues recently showed that *Lgr5* expression specifically marks an intestinal stem cell (ISC) population located at the crypt base in mice. In a follow-up study (*Cell* **136**, 903–912; 2009), Clevers and colleagues now identify Ascl2, a transcription factor with homology to *Drosophila* Achaete-scute complex proteins, as a key upstream regulator of *Lgr5* in ISCs. The authors purified *Lgr5*-expressing cells from isolated mouse crypts and used expression profiling to identify genes specifically enriched in these cells. By *in situ* hybridization and immunohistochemistry, they found that, within the mouse intestine, Ascl2 is expressed exclusively in *Lgr5*-positive ISCs. Forced expression of Ascl2 throughout the intestinal epithelium resulted in an expansion of *Lgr5* expression and conversion of villus epithelium to a crypt-like fate. Conversely, conditional deletion of *Ascl2* from the intestine resulted in rapid loss of *Lgr5* expression, accompanied by an increase in apoptotic cells and crypt fission. They further showed that ASCL2 binds directly to the *LGR5* promoter by performing chromatin immunoprecipitation studies in a human colorectal cancer cell line. Collectively, these data show that Ascl2 has an essential role in maintaining *Lgr5*-positive stem cells at the crypt base. *KV*

Rare variants in T1D

John Todd and colleagues report a resequencing study to identify rare variants associated with type-1 diabetes (T1D) (*Science* published online, doi: 10.1126/science.1167728; 5 March 2009). The authors selected ten candidate genes for resequencing within pooled DNA samples from among 480 T1D cases and 480 healthy controls and resequenced 144 target regions, covering a total of 31 kb within exons and regulatory regions of these genes. They identified 212 SNPs, 179 of which classified as rare with a minor allele frequency of <3%. These variants were tested for association with T1D by comparison of allele frequencies in DNA pools of cases and controls, confirming previous associations with common SNPs and identifying new associations with rare SNPs in *IFIH1*. The *IFIH1* SNPs were replicated in a further 8,379 T1D cases and 10,575 controls, as well as in 3,165 families. Logistic regression analyses showed that four rare variants identified in *IFIH1* were associated with T1D independently of each other, and independent of a common nonsynonymous SNP in *IFIH1* previously identified within a GWAS study. Previous T1D GWAS have reported an association at the 2q24 locus, including *IFIH1* as one of several candidate genes, and this follow-on study now points to *IFIH1* as a causative gene. *OB*

Written by Myles Axton, Orli Bahcall, Lily Khidr & Kyle Vogan

Cracking the common cold

Human rhinovirus infection is a major cause of upper and lower respiratory tract disease, and is responsible for an estimated half of all asthma attacks. Claire Fraser-Liggett and colleagues now report genome sequencing and phylogenetic analyses based on all available isolates of human rhinovirus (HRV) (*Science* published online, doi: 10.1126/science.1165557; 4 February 2009). Previous studies have drawn on a reference collection of 99 human rhinovirus strains, including HRV-A and HRV-B serotypes, isolated from affected individuals over the course of two decades. The authors now sequence at 6× coverage 80 of the previously unsequenced strains within this reference collection, as well as 10 new field samples recently acquired from individuals with a cold. These full genome sequences, together with seven recently identified HRV-C isolates from individuals with influenza-like symptoms, were used as the basis for phylogenetic analyses. The phylogenetic trees generated here show significant differences to previous ones based on capsid sequences, highlighting the importance of obtaining full-length genome sequences from large numbers of clinical isolates. They report a new clade D within HRV-A, which may represent a fourth species, and also find evidence that recombination has a greater role in generating HRV diversity than previously suspected. *OB*

Drivers of colorectal cancers

The design of targeted therapeutics for human colorectal cancers (CRC) is dependent on the ability to distinguish alterations that are causal in tumor formation and progression from those that have little or no effect on tumor growth. To identify novel drivers of CRC, David Largaespada and colleagues (*Science* published online, doi:10.1126/science.1163040; 26 February 2009) catalogued genes with common insertion sites (CIS) generated in tumors harvested from a gastrointestinal (GI) tract-specific transgenic mouse model that exploits the transposition of a mutagen catalyzed by Sleeping Beauty (SB) transposase. Comparison of mouse CIS genes with human genes that are mutated, amplified, deleted or aberrantly expressed in CRC, listed in the Catalog of Somatic Mutations in Cancer database (COSMIC), or known cancer genes identified by the Cancer Genome Project, revealed a significant overlap of mouse candidate genes and human genes that are altered in cancer. The authors identified 15 CIS genes that are most likely to cause CRC by virtue of being classified in at least three out of the five aforementioned categories. Five of these genes are validated human CRC genes and three are highly implicated in human CRC, but the remaining seven represent new candidate CRC genes that, on the basis of their functions in DNA stability, p53-induced apoptosis and Wnt signaling, could potentially be drivers of CRC. ***LK***