WEB WATCH

Lessons in histology

- http://eulep.anat.cam.ac.uk/

Pathbase — a database of normal and transgenic mouse histology — is the kind of resource that developmental geneticists have been waiting for. Having engineered a specific mutant, mouse geneticists often lack the necessary expertise that is vital for the accurate analysis of mutant phenotypes. Well, Pathbase is here to help.

The database can be searched — for example, by tissue or by the type of pathology. You can navigate around Pathbase using a simple menu, which also includes links to other useful sites and even information on pathology courses. By following a simple set of instructions, individuals who have completed a free registration can contribute images and pathology descriptions to Pathbase. There is also a bulletin board, called pathology forum, to which comments or questions can be submitted.

The project is curated by an international consortium of pathologists and veterinarians whose goal is also to develop standard histopathology and anatomy nomenclature. Although Pathbase is still being improved, it already contains useful data and in the future it might even include other organisms.

Magdalena Skipper

Correcting the record

- http://www.francisgalton.com/

If you're gasping in horror at the decision to devote this column to someone who pursued and defended eugenics, then this study of Sir Francis Galton in 11 PDF files could teach you a thing or two. Galton was a practical innovator, introducing the modern weather map, human fingerprinting, twin studies and coining the nature–nurture distinction. His statistical innovations laid the foundation for all social science. All in all, a true Victorian polymath.

Tanita Casci

GENETIC DISEASE

Twin-track approach to fragile X

About 8 years ago, the fragile X syndrome gene *FMR1* was shown to encode an RNA-binding protein, but its physiological function has remained elusive. The most popular theory is that FMR1 regulates translation because it is associated with polysomal RNA. However, until now, there has been little information on the RNA targets that are bound by FMR1. Two papers in *Cell* report complementary studies aimed at finding such targets, and both converge on a small set of transcripts — encoded by genes involved in several aspects of neuronal function — that represent very strong candidates for regulation by FMR1.

The study by Victoria Brown, Peng Jin and colleagues involved two microarray experiments. In the first, mRNA isolated from mouse brain was compared with mRNA that had been immunoprecipitated with an FMR1 antibody, the aim being to find mRNA that was bound to FMR1. Of the >25,000 genes screened, 432 were identified that were enriched by immunoprecipitation. The second study compared polysomal RNA from fragile X with control human cell lines. The authors reasoned that if FMR1 regulates translation by binding to polysomal RNA, the absence of FMR1 in the fragile X cell lines should lead to differences in the abundance of specific polysome-associated RNAs. In this experiment, >35,000 genes were compared, and 251 showed substantial differences in abundance between the polysomal RNA fractions of the fragile X and control cell lines. A partial comparison of the sets of genes revealed 14 that were identified in both experiments, and could therefore be targets for regulation by FMR1.

The second paper reports a biochemical approach to finding the optimal RNA target sequence for FMR1. After several rounds of selection from a pool of random RNA sequences, Jennifer Darnell *et al.* identified an RNA molecule that bound to FMR1 with high affinity. They then defined the minimal sequence required for binding, and concluded that FMR1 requires a specific RNA structure called a G quartet, which is present in only a small percentage of transcripts.

HUMAN GENETICS

C major variations

Every year, malaria affects half a billion people and kills up to 3 million of them. For ~10,000 years, malaria has put the human genome under considerable selective pressure to evolve natural ways of resistance — the sickle cell haemoglobin (HbS) variant being a classic example. But other haemoglobin variants have been described and some, such as haemoglobin C (HbC), have been implicated in resistance to malaria. Until recently, the link has been tenuous, but Modiano and colleagues now provide conclusive evidence that, when homozygous, HbC confers substantial resistance to this devastating disease.

HbC is a common West African haemoglobin variant in which glutamic acid at position 6 has been mutated to lysine but, unlike the HbS mutation, this substitution does not affect the molecule's affinity for oxygen. Following inconclusive reports about the role of HbC in resistance to malaria, Modiano *et al.* re-examined the issue by looking at HbC frequency among 4,348 children in West African Burkina Faso. The authors found that HbC frequency was markedly reduced in 835 children who had been hospitalized with malaria; moreover, only one of these indivduals was homozygous for HbC. Its frequency in the sick population indicates that, when heterozygous, HbC could account for a 29% reduction in the relative risk of clinical malaria and 93% when homozygous — compared to 70% reduction among HbS carriers.

Given the very high level of protection that HbC bestows on homozygous individuals, and the lack of obvious adverse effects among HbC carriers, Modiano and colleagues suggest that the allele is likely to rise in frequency among Africans, and will perhaps even replace the HbS variant in Africa. But because its protective effects mainly manifest themselves in homozygotes, the spread of the allele is likely to be slow. It will also be useful to