

HIGHLIGHTS

WEB WATCH

Mining mutants

To prepare for the flood of new alleles being generated by large-scale mutagenesis screens, and by the mouse community more generally, the Mouse Genome Database (MGD) is restructuring its existing mutant allele data and is incorporating new controlled phenotype vocabularies. The goal is to improve user search tools to allow phenotypic data to be found, analysed and compared at many levels of resolution — from sequence changes to organismal traits.

To do this, MGD is extracting certain types of information (such as a mutant's strain of origin) from existing, unstructured data in MGD and is organizing it into separate, searchable fields. Another aspect of this effort is a new Allele and New Mutant Submission Form, which allows researchers to submit information about a known allele or new mutant, such as how it was generated, its mode of inheritance, its molecular basis and its phenotype on different strain backgrounds. Each allele receives an MGD accession number that provides it with a unique identifier within the database.

MGD is also working with many of the new mutagenesis centres to obtain mutant information through direct data downloads. The aim is to provide an information resource on new phenotypes and alleles and, through links to the mutagenesis centres themselves, to provide access to detailed phenotypic data on individual mice and to information on how mouse strains can be obtained. Original data contributions and updates from the community will also be key to MGD's ability to develop new and more flexible search tools.

Janan Eppig, The Jackson Laboratory, USA

EPIGENETICS

Satellite tools

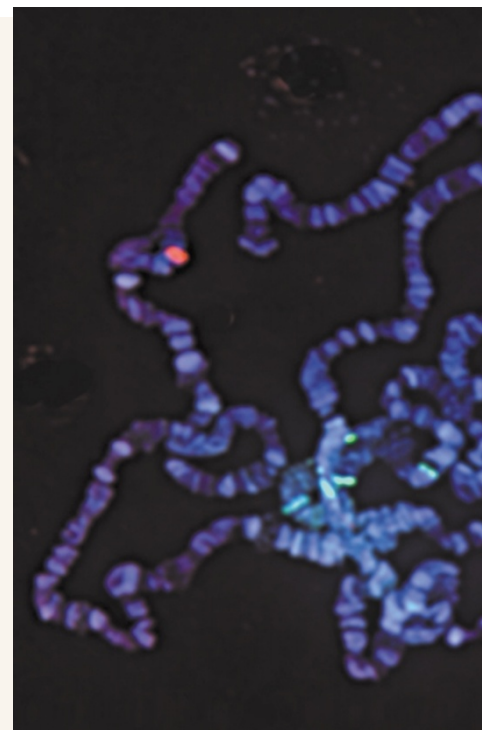
Satellite DNA is mysterious. It comprises an array of short tandem-repeat sequences, and is associated with an inactive type of chromatin — heterochromatin. The function of satellite DNA is unclear, although there is evidence that it plays a role in the structural organization of the nucleus. To understand satellite DNA better, we need tools to manipulate it. Two papers published by Ulrich Laemmli's laboratory demonstrate how sequence-specific drugs can be used to study satellite DNA. And the effects of the drugs on the heterochromatic state of satellite DNA have some surprising phenotypic consequences.

The sequence-specific drugs are polyamides that comprise a short chain of aromatic amino acids able to bind the minor groove of DNA in a sequence-specific manner. Several such compounds were made and shown to bind specifically to different classes of *Drosophila* satellite DNA, depending on the sequence of the basic repeat unit. By labelling the drugs with a fluorescent tag, the

different minisatellites could be visualized within cells. (For example, minisatellites are highlighted in red and cyan in the stained polytene chromosomes in the image.)

Binding of the polyamide drug to satellite DNA causes significant changes to the conformation of the heterochromatin — the chromatin 'opens up', and becomes more accessible to enzymes such as topoisomerase II and endonucleases. The authors then went on to ask whether drug treatment would reactivate a gene silenced under the influence of heterochromatin.

They did this by examining the effects of polyamides on *Drosophila* mutants subject to position effect variegation (PEV) — mutants caused by the juxtaposition of a gene and a heterochromatic region. In some cells, the heterochromatin spreads and silences the adjacent gene in that cell and its progeny. The resulting organism is a mosaic of wild-type and mutant tissue. Two PEV mutants were tested. When *white-mottled* flies were fed



Courtesy of Ulrich Laemmli and Armand Schrupf.

the polyamide drug, which had no effect on wild-type flies, the phenotype was suppressed. This is the expected result — the drug leads to a more open heterochromatin conformation next to the *white* gene, so the gene is less likely to be silenced by heterochromatin spreading. When the second PEV mutant was treated with a polyamide drug, the effects were more surprising.

This mutant, *brown^{Dominant}* (*bw^D*), is caused by a large insertion of heterochromatic satellite DNA (labelled red in the image) in the *brown* gene. The fascinating

HUMAN GENETICS

Regulating cholesterol by A,B,C

Cholesterol, like other sterols, is an essential component of our cell membranes. However, high cholesterol intake and absorption can cause ill health, and so the body has evolved ways to regulate its absorption

from our diet. A striking exception to this occurs in sitosterolemia, a rare, recessive human disorder that causes increased intestinal absorption of dietary sterols, including plant sterols and cholesterol, and premature coronary heart disease. Now, researchers have discovered two novel ATP-binding cassette (ABC) transporter genes that are mutated in sitosterolemia sufferers.

The genes were identified by a combined microarray and candi-

