#### PHARMACOGENETICS

# A better pill to swallow?

Have you taken a medicine that hasn't worked, leaving a headache or some other ailment to linger on? Well, pharmacogeneticists have been telling us for some time that this apparent ineffectiveness of certain medicines might have its roots in how we metabolize drugs, but there has been little hard evidence to support this claim. However, proof now comes from a recent study, which has discovered single nucleotide polymorphisms (SNPs) that affect the activity of a key metabolic enzyme and that occur at different frequencies in people from different ethnic groups.

This study, published in Nature Genetics, focused on the key enzymes involved in drug detoxification, the cytochrome P450 (CYP), and specifically the CYP3A, family. CYP3A activity is the sum of the activity of several genes, including CYP3A5, the expression of which varies substantially in a minority of Caucasians. The CYP3A proteins metabolize and inactivate many drugs, including cancer chemotherapeutics, immunosupressants, steroids and HIV inhibitors - other CYP3A substrates include carcinogens and oestrogen. Kuehl et al. have now found that a SNP in a CYP3A5 intron leads to aberrant splicing of CYP3A5 and a truncated non-functional CYP3A5 protein. This is important because the full-length CYP3A5 product accounts for over 50% of total CYP3A activity, making it a principal component of the CYP3A complex. And their finding that African-Americans express higher levels of the full-length CYP3A5 allele than Caucasians implies that this ethnic group is less likely to experience dose-related drug toxicities that arise from inefficient drug clearance.

Kuehl *et al.* point out that studies such as theirs show that individual variation in drug metabolism can be easily determined for drugs that are metabolized by enzymes with well-defined and testable functions. But identifying SNPs that affect drug metabolism has been a barrier to progress in this field. How could this be done more efficiently in the future? The authors envisage that DNA from patients with known drug metabolism disorders could be screened against SNP databases as a way to identify novel loci of pharmacogenetic interest.

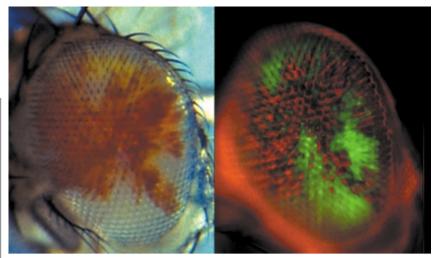
#### References and links

ORIGINAL RESEARCH PAPER Kuehl, P. et al. Sequence diversity in CYP3A promoters and characterization of the genetic basis of polymorphic CYP3A5 expression. Nature Genet. 27, 383–391 (2001)

Magdalena Skipper

FURTHER READING Roses, A. D. Pharmacogenetics and the practice of medicine. Nature 405, 857–865 (2000)





In some cells in the eye, a GFP reporter gene near heterochromatin is expressed (green cells, right), but the adjacent *white* gene, which produces red pigmentation, is silenced (white cells, left), implying that gene promoters might respond individually to the repressive effects of heterochromatin. Reprinted from *Cell* **104**, 839–847 © (2001), with permission from Elsevier Science.

GENE EXPRESSION

## Heterochromatin opens up

The transcriptional activity of a gene can be affected by its location in the genome. This phenomenon has been noted in many transgenic experiments and is also relevant to human disease, for example when the genomic location of a gene is altered by a chromosomal rearrangement. Position effects that reduce transcriptional activity can be mediated by heterochromatin - a compact and transcriptionally inert form of chromatin — which can silence genes placed within or near it. But position effects are not all-or-nothing phenomena, as genes seem to vary in their susceptibility to silencing by heterochromatin. Ahmad and Henikoff have now found a possible explanation for this variation, by showing that increased levels of a transcriptional activator for a gene that is silenced by heterochromatin can counteract the silencing effect.

Position effects were first discovered by *Drosophila* geneticists, who observed that mutations at certain positions in the fly genome give rise to mosaic phenotypes, the precise patterns of which vary between flies. To describe this phenomenon, they coined the term 'position effect variegation' (PEV). PEV reflects the incomplete silencing effect of heterochromatin and provides an opportunity to investigate factors that influence whether a gene is 'on' or 'off'.

Ahmad and Henikoff studied PEV in flies using a transgenic construct comprising two genes — a *white* gene that allows PEV to be easily visualized by variation in eye pigmentation, and a gene that expresses green fluorescent protein (GFP) under the control of the Gal4 transcriptional activator. The construct was located near a heterochromatic region and showed typical PEV. The authors then investigated whether altering the level of the Gal4 activator could affect the silencing of the construct's genes.

The results showed a clear effect not only on the GFP gene but also on the adjacent *white* gene — when Gal4 levels were increased, the degree of heterochromatic gene silencing was reduced. This led the authors to propose that PEV reflects a bistable equilibrium — a balance between the compact heterochromatic state and a more open conformation that is transcriptionally competent. The activator seems to promote the switch from the silent to the open state, which can extend beyond the gene that contains the binding sites for the activator.

But the conclusions go further. Although the effect of the activator can spread to the adjacent *white* gene, this is not always the case. In some flies, the *white* and GFP genes which are only 2 kb apart — can be in different transcriptional states (see picture). This leads to the intriguing idea that heterochromatin might have an unsuspected fine structure, and might not be a block of uniform inactivity as generally supposed.

Mark Patterson

### References and links ORIGINAL RESEARCH PAPER Ahmad. K. &

Henikoff, S. Modulation of transcription factor counteracts heterochromatic gene silencing in *Drosophila*. *Cell* **104**, 839–847 (2001) **WEB SITE** Steven Henikoff's lab