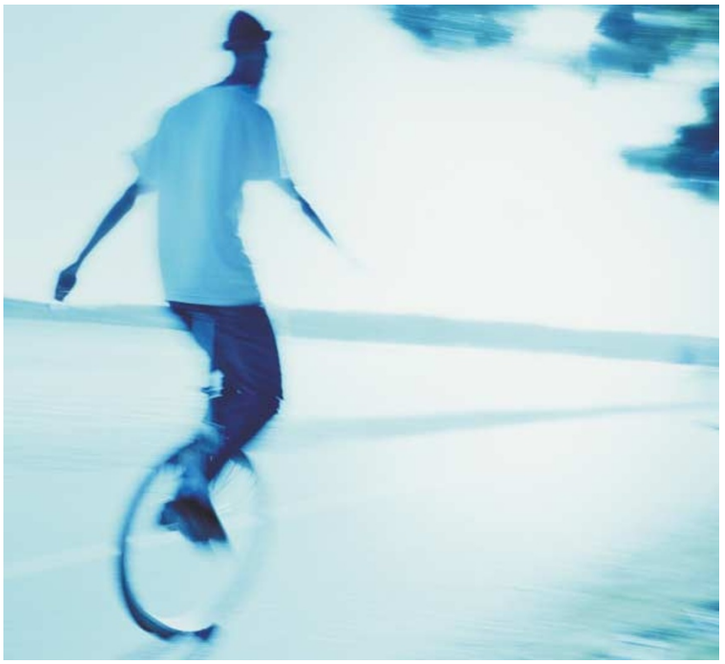
CANCER GENETICS

It doesn't always take two



It takes two, so the song goes, and for genes, this is often so. Recessive disorders, for example, require both copies of a gene to be lost. However, some diseases and traits can occur when one wild-type allele is still present. Now, two papers report that a *BLM* gene mutation — which, when homozygous, causes the recessive, cancer-predisposition disease Bloom syndrome (BS) — surprisingly predisposes mice and humans to intestinal cancer when haploinsufficient. Because BLM is a helicase that maintains genome stability, these papers highlight the crucial role of genome instability in both cancer pathogenesis and predisposition.

Heppner Goss *et al*. generated a new BS mouse model by targeting the mouse *Blm* gene with a mutation (Blm^{Cin}) that causes a premature truncation. This mutation acts as a null allele and simulates a founder mutation (BLM^{Ash}) that is present in 1% of Ashkenazi Jews.

The authors used two approaches to investigate the effect of *Blm* haploinsufficiency on tumorigenesis in these mice. First, they injected them with murine leukaemia virus (MLV). Both wild-type and $Blm^{Cin/+}$ mice developed metastatic T-cell lymphoma on exposure to this virus, but mutant mice died earlier, despite tumour morphology being the same in both sets of mice. Next, they crossed $Blm^{Cin/+}$ mice to Apc^{min} mice — a mouse model of familial adenomatous polyposis coli. (The *min* mutant was chosen because the gastrointestinal (GI) tract is where cancer commonly develops in BS patients.) Double heterozygous mutant mice developed twice as many GI adenomas as did $Apc^{min}/Blm^{+/+}$ animals, and many $Apc^{min}/Blm^{+/-}$ mice had tumours with high-grade dysplasia. Tumours in both $Apc^{min}/Blm^{+/+}$ and $Apc^{min}/Blm^{+/-}$ also showed *Apc* loss of heterozygosity (LOH). In both mutants, *Apc* LOH seemed to occur predominantly through the loss of chromosome 18, where *Apc* is located. However, in some $Apc^{min}/Blm^{+/-}$ tumours, *Apc* loss also occurred through somatic

HUMAN GENETICS

Tracking positive selection

A genome can be thought of as a record of its bearer's evolutionary past. Although some past events might be easy to spot, others, such as recent positive selection — notorious for eluding traditional tests for deviation from natural selection — can be tricky to detect. But help is at hand, for Sabeti *et al.* have now developed a new method, called the long-range haplotype (LRH) test, that can efficiently detect traces of recent positive selection.

The LRH test relies on the relationship between an allele's frequency and the linkage disequilibrium (LD) between that allele and the loci that surround it. If there is no selection, new alleles take a long time to increase in frequency, and recombination around them will ensure that blocks of LD decay over time. By contrast, in the presence of positive selection, young alleles will spread rapidly through the population and will be surrounded by long blocks of LD, as there would not have been the time for recombination to erode them. This sounds simple enough, but recombination frequency is not the same throughout the genome and will therefore affect the speed of LD decay. The LRH test overcomes this problem by having a built-in internal control — different sets of loci in a region under study are compared, and any local discrepancies in the recombination frequency can be adjusted for.

To define the basis of the LRH test, the authors genotyped a collection of closely linked SNPs — a core haplotype — in a small region of the human genome. The decay of LD around each core haplotype was assessed by adding more and more distant SNPs. This allowed them to calculate the probability that any two chromosome segments that carry a given core haplotype are identical by descent. They call this probability 'extended haplotype homozygosity' (EHH), and to find a footprint of positive selection, they simply look for core haplotypes that are frequent and that have high EHH.

Sabeti *et al.* tested their method on two human loci — G6PD and CD40 — that have been implicated in resistance to malaria. LRH passed the test with flying colours. The authors detected long-range LD and high EHH for both loci; in addition, the alleles associated with resistance to malaria were detected as clear core haplotypes only in African populations where malaria is endemic and, therefore, where there is selection for these variants.

Not only is the new method powerful and robust, but also it specifically achieves what other existing tests do not — namely, it detects signs of recent positive selection. Here, it was developed and used in the context of the human genome, but it can be applied to any genome. Moreover, the whole genome can be scanned systematically for signs of positive selection, revealing previously unknown aspects of its history.

Magdalena Skipper

References and links

ORIGINAL RESEARCH PAPER Sabeti, P. C. *et al.* Detecting recent positive selection in the human genome from haplotype structure. *Nature* 9 October 2002 (10.1038/nature01140)

WEB SITE

Whitehead Institute/MIT Center for Genome Research: http://www-genome.wi.mit.edu

recombination. No neoplasias were seen outside the GI tract, and *Blm* LOH was not evident in tumour tissue.

The results of Gruber *et al*. lend further weight to these findings. In a study of 1,244 Ashkenazi Jews with colorectal cancer (CRC), those with CRC were found to be twice as likely to carry the BLM^{Ash} allele as those Ashkenazi Jews without CRC. These findings, and those of Heppner Goss *et al*., indicate that BLM haploinsufficiency might compromise the maintenance of genomic integrity, perhaps by causing an increased mutation rate in heterozygous cells, so speeding their progression to tumorigenesis.

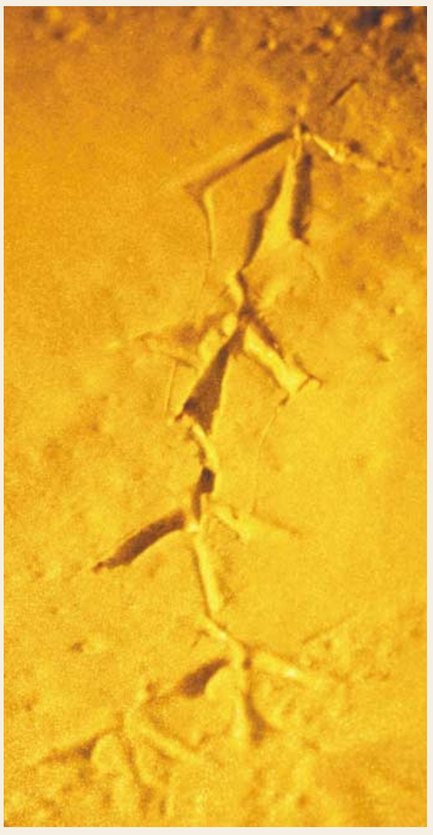
Jane Alfred

References and links

ORIGINAL RESEARCH PAPERS Heppner Goss, K. *et al*. Enhanced tumour formation in mice heterozygous for *Blm* mutation. *Science* **297**, 2051–2053 (2002) | Gruber, S. B. *et al*. *BLM* heterozygosity and the risk of colorectal cancer. *Science* **297**, 2013 (2002)

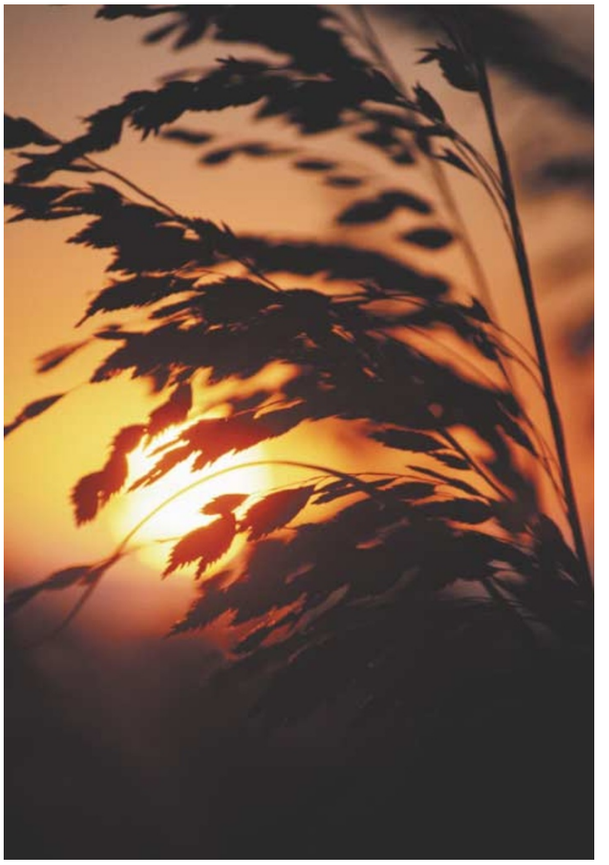
WEB SITE

Joanna Groden's lab: http://www.hhmi.org/research/investigators/groden.html



CIRCADIAN CLOCKS

How plants measure their days



How do some plants know to flower come the long days of summer? Although plant biologists have discovered some of the components of the circadian system that controls this so-called photoperiodic response, they have struggled to understand how both temporal and light information are integrated by plants to control flowering time. Now Marcelo Yanovsky and Steve Kay identify the *Arabidopsis* transcriptional activator CONSTANS (CO) as the point at which this integration takes place. They show, for the first time, that light has a direct effect on the ability of *Arabidopsis* to sense and measure a day's length, in addition to its well-known effects on establishing circadian rhythms.

CO is a key component of the photoperiodic response. Its expression is under circadian control — during short days, its daytime expression levels are low and rise only after sunset, whereas during long days, *CO* mRNA levels start accumulating towards dusk. A direct target of CO is *FLOWERING LOCUS T* (*FT*). Its expression also peaks at dusk during long days, at the time when the rise in *CO* daytime expression coincides with an illuminated part of the day. Could CO function therefore be light dependent?

To investigate this, the authors began by analysing the importance of the circadian control of CO for daylength discrimination in the *Arabidopsis* mutant *toc1*. This mutant flowers early in short days, and was used because its photoperiodic defect is due only to a circadian — and not to a light-response — defect. In *toc1* plants, overall *CO* expression levels remain relatively normal; however, the phase of *CO* expression is significantly advanced under short-day conditions, resulting in the accumulation of high levels of *CO* at the illuminated end of the day. *FT* also accumulates at this time under similar conditions in *toc1*, but not in wild-type, plants, indicating that the earlier shift in *CO* expression induces *FT* expression and that the circadian control of *CO* expression is required for daylength discrimination. Moreover, the high expression of *FT* during short days is probably the molecular defect that underlies the *toc1* phenotype, because the phenotype was abrogated when *FT* was mutated in *toc1* plants.

So, what is the role of light in this response? When the authors assayed *FT* expression in plants that constitutively express *CO*, these plants showed high but rhythmic (peaking at dusk) *FT* expression patterns under long-day conditions. This pattern, however, depended on exposure to light, indicating that CO regulation of *FT* is light dependent. Because *FT* levels are greatly reduced in plants that are mutant for the photoreceptor CRY2, and because these plants have apparently normal *CO* expression patterns, the authors considered it to be a strong candidate mediator of CO's light-dependent regulation of *FT*. In fact, they found that both CRY2 and the photoreceptor PHYA are required for light-induced upregulation of *FT* expression and that this response requires functional CO.

These findings strongly indicate that daylength can regulate flowering time through the coincidence of light — as detected by CRY2 and PHYA — with a particular circadian phase, as manifested by high levels of *CO* expression. Together these events cause a rise in *FT* expression, which triggers flowering. The pathways that control this flowering feat are, however, in need of further illumination.

Jane Alfred

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ORIGINAL RESEARCH PAPER Yanovsky, M. & Kay, S. Molecular basis of seasonal time measurement in *Arabidopsis*. *Nature* **419**, 308–312 (2002)

WEB SITE

Steve Kay's lab: http://www.scripps.edu/cb/kay