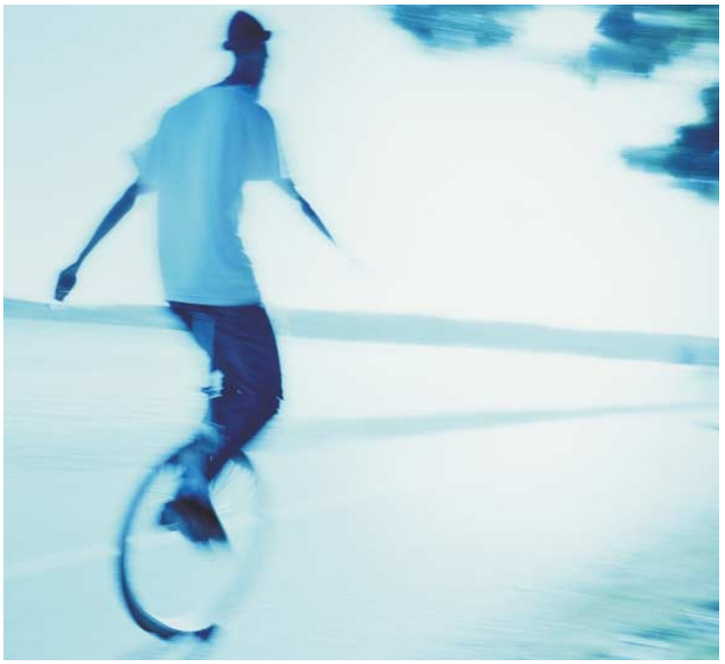
CANCER GENETICS

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.

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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