PLANT GENETICS

Taking after Grandma

People often talk about characters — hair colour, a hooked nose, a talent for the trombone — missing a generation. This is simply the result of recessive genes acting on complex traits. However, Susan Lolle, Robert Pruitt and colleagues now report in *Nature* that, for the plant *Arabidopsis thaliana* at least, this can be quite literally true.

The *A. thaliana HOTHEAD* (*HTH*) gene encodes an enzyme related to the glucose-methanol-choline oxidoreductases. Recessive mutant alleles produce flowers with fused sepals, petals, stamens and carpels. However, around 10% of the progeny from crosses between homozygous mutant *hth* parents revert to a normal phenotype.

Many trivial explanations, such as contamination, could produce this result, but Lolle and colleagues carefully excluded each of these. Instead they found that the sequence of one, and occasionally both, of the *hth* alleles had reverted to the wild type in the phenotypically normal progeny. Such precise correction could not result from random mutation, however a search for related sequences in the genome that could function as a source of corrective recombination drew a complete blank.

This unusual process is not limited to changes in the *HTH* gene. In third-generation plants that were derived from crosses between two different *Arabidopsis* ecotypes, as many as 1 in 25 of the ecotype-specific marker genes had sequences that were not present in the parents' genome, but only in their grandparents'. Such deviations from conventional inheritance were only seen in homozygous *hth* mutant backgrounds, irrespective of the precise mutant allele that was present.

To explain this curious phenomenon, the authors propose that the sequence of some, or perhaps even all, plant genes is passed down through the generations independently of the conventional genome, but in a form that can be used to correct changes when they arise. Such a corrective mechanism could be triggered by metabolic stresses, for example. No such system is currently known, indeed it would defy the tenets of Mendelian genetics, but one possibility is that it involves RNA. Double-stranded RNA molecules that are responsible for gene silencing can persist through several generations in *Caenorhabditis elegans*, and the ability of RNA to function as a template for modifying DNA is well established.

Many plants have been responsible for fundamental discoveries in genetics: Gregor Mendel's wrinkled peas or Barbara McClintock's variegated ears of maize, to name but two. The *hothead* mutants of *A. thaliana* could be destined for similar notoriety for uncovering an emergency back-up to the genome.

Christopher Surridge,
Senior Editor, Nature

References and links

ORIGINAL RESEARCH PAPER Lolle, S. J. *et al.* Genome-wide non-Mendelian inheritance of extra-genomic information in *Arabidopsis*. *Nature* 24 March 2005 (doi:10.1038/nature03380)

FURTHER READING Fire, A. *et al.* Potent and specific genetic interference by double-stranded RNA in *Caenorhabditis elegans*. *Nature* **391**, 806–811 (1998)

EPIGENETICS

A shifting balance

Disruption to the normal pattern of imprinting has been implicated in cancer; for example, loss of imprinting (LOI) at the gene insulin-like growth factor 2 (*IGF2*) locus is seen in several common cancers, and the 10% of the population with LOI at *IGF2* have a higher than normal risk of developing colorectal cancer. A recent report by Andrew Feinberg and colleagues shows that epigenetic alterations to *IGF2* promote intestinal tumorigenesis and that a shift towards undifferentiated cell fate might contribute to an increased rate of tumour initiation.

Wanting to understand how epigenetic changes at the *IGF2* locus cause intestinal tumourigenesis, the authors created a mouse model using a deletion of the differentially methylated region (DMR) that regulates *Igf2* imprinting in mice. Female mice that lack the DMR inherit a normal active copy of *Igf2* from their father, but also an abnormally active (imprint-free) copy of *Igf2* from their mother. Crossing these females with adenomatous polyposis coli (*Apc*) mutant males predisposes the resulting offspring to multiple intestinal neoplasia. The authors compared *Apc* mutants carrying a silenced maternal copy of *Igf2* (they called these LOI$^-$ mice) with their *Apc* mutant litter mates (LOI$^+$ mice) that had two active copies of *Igf2*.

Confirming the role of IGF2 in colon cancer, LOI$^+$ mice developed twice as many tumours in the small intestine and colon. Curiously however, LOI$^+$ mice also had longer intestinal crypts — the invaginations in the intestinal epithelium, at the bottom of which stem-cell proliferation occurs. Feinberg *et al.* postulated that this increase in crypt length could be due to a shift in the ratio of differentiated to undifferentiated epithelial cells. Sure enough, LOI$^+$ mice had higher levels of undifferentiated epithelial-cell markers in their small intestines than LOI$^-$ mice. A similar increase was seen in the intestinal epithelium of patients with *IFG2* LOI.

The authors suggest that this shift increases tumour initiation, rather than the rate of tumour progression, and supporting this, they found that LOI$^+$ and LOI$^-$ mice have the same ratio of small to large tumours. It is likely that the shift in normal tissue to a less differentiated state increases the number of cells vulnerable to subsequent genetic alterations. Future work will determine whether epithelial differentiation or LOI itself will be the better predictor of cancer risk.

Jenny Bangham

References and links

ORIGINAL RESEARCH PAPER Sakatani, T. *et al.* Loss of imprinting of *Ifg2* alters intestinal maturation and tumorigenesis in mice. *Science* 24 February 2005 (doi:10.1126/science.1108080)

IN THE NEWS

BIOS – a new way in biotechnology?

- http://www.bios.net
- https://www.bioforge.net

BIOS — Biological Innovation for Open Society — is a project that aims to revolutionize biological inventions by providing alternatives to intellectual property protection.

BIOS was created by CAMBIA, an Australian not-for-profit biotechnology group that was the talk of the media when it published a plant transformation strategy that does not depend on the patented *Agrobacterium*. The new method is protected by an open-source license that allows users to benefit from an invention without the obstacles associated with patent protection, while safeguarding the rights of the inventor.

But there is much more to BIOS. Its extensive web site defines it as "a new initiative […] to extend the metaphor and concepts of Open Source to biotechnology and other forms of innovation in biology".

The Patent Lens part of the web site includes a wealth of information on intellectual property. You can search for patents and find out about intellectual property policies and practices. The Technology Landscape link will take you to documents that describe the state of patent protection surrounding selected key areas of research, although, for now, the focus is mainly on plant biotechnologies. There are even tutorials, for example, on how to read a patent!

BioForge — a new community for biological innovation — is an important part of the BIOS initiative. It is a virtual platform for worldwide collaboration and resource sharing, within the open-source philosophy of BIOS.

If you have an inventive streak in you or had your research options limited by patents, this is the web site for you. Open Source has had a huge impact on the software industry; the time has come to test it in the biotechnology world.

Magdalena Skipper