

# Hotheaded healer

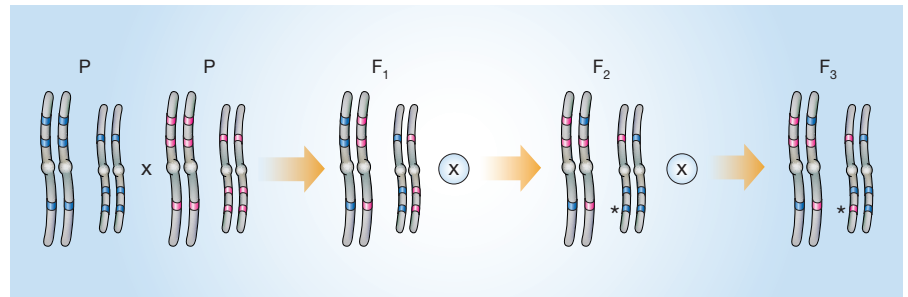
Detlef Weigel and Gerd Jürgens

A previously unknown way of reversing genome-wide sequence changes in DNA has been revealed by an analysis of plants carrying mutations in a gene called *HOTHEAD*. The mechanism remains a mystery.

Variety is the spice of life. This adage applies as much to genetic material as to anything else — if DNA were static, there would be no change over time and no evolution. Everything in moderation, though, to use another proverb. Most random changes in DNA (mutations) are harmless, because much of our DNA has no essential function. Nevertheless, of all possible mutations, the ones that are detrimental far outnumber those that might have a positive effect. Unwanted changes in DNA, which occur quite often, can have disastrous consequences and lead to all sorts of diseases. How, then, does the genome heal itself? Lolle and colleagues<sup>1</sup> have just had the first glimpse of a novel mechanism that does just that. They report their findings on page 505 of this issue.

The genome has sophisticated tools for correcting mutations every time a cell replicates its DNA in preparation for cell division<sup>2</sup>. This machinery, which discovers incorrect copying or damage in the DNA, is essential for avoiding the accumulation of unwanted mutations during our lifetime. There is nothing mysterious about this process, as it uses the intact DNA strand as a template for correcting mistakes on the broken or damaged strand. But can the genome also detect mutations that have become 'fixed', where the DNA sequence on both strands has changed? Reversion of fixed mutations is less unusual than one might suppose, but it generally relies on the original DNA still being present. For example, transposons, which are essentially parasitic sequences of DNA, may insert into a gene and disrupt its activity. But if the transposon is precisely excised, and the host DNA stuck back together, the gene reverts to its normal state.

More intriguing are cases in which fixed changes revert to the original sequence without an apparent template. For example, in microbes, revertants that confer some sort of physiological response can be easily selected from large numbers of individuals. Thus, although mutations back to the original sequence are rare, on the order of one in a billion per site and per generation, the large population size makes the isolation of revertants possible. There is even evidence that stress increases the frequency at which revertants occur<sup>3</sup>. Amazingly, precise reversion events have also been described in humans<sup>4</sup>. Unfortunately, it is unclear whether these



**Figure 1** Reversion in *hothead* plants. Two parents (P) with different DNA sequence variants at several positions (colour-coded) in the genome are crossed. In subsequent generations (F<sub>1</sub> and F<sub>2</sub>), plants are allowed to self-fertilize (indicated by a circled cross). In the F<sub>3</sub> generation, there is reversion (asterisk) to a sequence originally present in the grandparent, but not in the immediate parent. This has been observed for several sites at surprisingly high frequency in the *hothead* mutant.

events are more frequent than expected by chance.

By contrast, there is no doubt that the reversion rates observed by Lolle and colleagues<sup>1</sup> in the plant *Arabidopsis* cannot be explained by random mutations. The authors' spectacular discovery started with a mutant called *hothead*, in which various organs are fused. What made *hothead* special was not its morphological defects but the finding that several independent mutant strains yielded apparently normal progeny at a high frequency (a few per cent). Lolle and colleagues show that this is due to precise reversion that restores the original DNA sequence. They ruled out several trivial explanations: the reversion is not due simply to a drastic increase in mutation rate, and it could not have been caused by gene conversion, where a related gene from elsewhere in the genome is used as a template. Nor is the reversion specific to the *HOTHEAD* gene or to harmful mutations, as the authors show by using hybrids carrying innocuous sequence changes at several other sites in the genome (Fig. 1). They find that *hothead* mutant progeny at later generations can recover DNA variants that have come from one of their great-grandparents, even if their immediate parent did not contain the variant.

Why does reversion occur so frequently in *hothead* mutants? The *HOTHEAD* gene itself does not seem to encode a protein with an obvious connection to DNA repair<sup>5</sup>, so the authors speculate that the high reversion frequency may indicate a response to some sort of elevated metabolic stress. Another fascinating question is what template the cell uses to restore the original DNA sequence.

From the authors' experiments it seems unlikely that the template is a cache of extrachromosomal DNA. Rather, it may well be an unknown species of RNA. This is not unreasonable, as DNA and RNA can be copied back and forth precisely<sup>2</sup>, and RNA molecules can, for example, guide dramatic DNA sequence changes in some organisms<sup>6</sup>. An obvious candidate would be messenger RNA, which is an intermediate molecule involved when the DNA sequence is being translated into protein. However, the sequence reversions observed by Lolle and colleagues are not restricted to those parts of the genome that are normally copied into messenger RNA.

Many experiments to explore this mechanism of unorthodox inheritance, which can skip several generations, come to mind. But it seems a safe bet that the isolation of secondary mutants that have lost the ability to produce healthy progeny will provide helpful clues.

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