How yeast chromosomes avoid the bad breaks

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The human genome is peppered with repeated DNA elements that can vary from a few to thousands of consecutive copies of the same sequence. During meiosis—the cell division that produces sperm and eggs—repetitive elements place the genome at risk for dangerous rearrangements from genome reshuffling. This recombination typically does not occur in repetitive DNA, in part because much of it is assembled into specialized heterochromatin. Other mechanisms that restrain recombination in repetitive DNA have remained elusive, until now.

In a paper published online today in the journal *Nature,* researchers in the lab of Whitehead Institute Fellow Andreas Hochwagen describe a defense mechanism in yeast that shields repetitive DNA from meiotic DNA recombination. According to the work of Hochwagen and his colleagues, the protective repeat-associated heterochromatin makes the DNA segments near the boundary of the heterochromatin particularly vulnerable to inappropriate meiotic recombination. DNA elements surrounding these at-risk border regions are protected from meiotic recombination by a novel system involving the concerted action of two proteins, pachytene checkpoint protein 2 (Pch2) and origin recognition complex subunit 1 (Orc1), which are present in organisms ranging from yeast to humans.

During meiosis an organism's chromosomes pair up, with every pair containing a copy inherited from each of the organism's parents. To match up the chromosomes, the cell breaks both strands of the

chromosomes' DNA in multiple locations, and the chromosomes swap DNA sections that have the same sequence. Later, when the paired chromosomes are pulled apart, each resulting chromosome is a patchwork of maternal and paternal genes. The creation of reshuffled chromosomes assists chromosome assortment into spore, sperm, and egg cells, but it also has a profound effect on evolution, because it produces new genetic variants.

"To me it's always been very confusing why you would break your genome. It's your blueprint," says Hochwagen. "Obviously, it helps you make new variations and combinations of genes, but it's incredibly dangerous and you really need to make sure that it happens the right way."

In repetitive DNA, this system of breaking and swapping is particularly hazardous, as there are many options that a section of repeat DNA could be swapped with. If the wrong repeat is chosen, a chromosome can gain or lose a large chunk of DNA. In humans, such mistakes have been linked to genetic neurological and developmental disorders, including autism spectrum disorders and schizophrenia.

By studying the highly repetitive DNA that makes up yeast's ribosomal DNA (rDNA), Gerben Vader and Hannah Blitzblau, first authors of the Nature paper and postdoctoral researchers in Hochwagen's lab, have determined that yeast's rDNA is protected from inappropriate recombination by two mechanisms. It was previously shown that heterochromatin prevents chromosome breakage in repetitive DNA. But in their paper, Vader and Blitzblau demonstrate that, ironically, the protective heterochromatin renders the transition zone between the repetitive and non-repetitive DNA particularly fragile. The yeast cell buttresses these borders with Pch2 and Orc1, which prevent chromosome breakage across the entire transition zone. In their absence, rDNA frequently gains or loses repeats.

"We had previously seen very little chromosome breakage in large regions close to repetitive DNA," says Blitzblau. "The finding that the borders of heterochromatin are particularly fragile helps us to understand why the cell invests in specifically protecting these regions."

Although the modes of heterochromatin formation vary between organisms, similar strategies may be at work in higher organisms, too.

"In mice and flies repetitive DNA is also packaged into heterochromatin, and there is evidence that very few breaks happen in these regions during meiosis," says Vader. "So it is possible that this type of protection is a general phenomenon."

More information: "Protection of repetitive DNA borders from self-induced meiotic instability" *Nature*, online August 7, 2011

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