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Hotspots found for chromosome gene swapping

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Crossovers and double-strand DNA breaks do not occur randomly on yeast chromosomes during meiosis, but are greatly influenced by the proximity of the chromosome's telomere, according to research in the laboratory of Whitehead Fellow Andreas Hochwagen. This work may lead to a better understanding of developmental chromosome abnormalities and birth defects.

Meiosis is a type of cell division that produces cells with only one copy of each chromosome—spores in yeast, and eggs and sperm in higher organisms.

During meiosis, chromosome pairs line up in the middle of the cell. The chromosome pairs are then pulled apart, with complete copies of all of the chromosomes ending up at opposite sides of the cell. To ensure that the chromosomes align properly in the middle of the cell, the chromosomes crossover—swap certain sections of genes. Without the crossovers, the chromosomes could misalign and both copies of a chromosome could end up in one cell. When this happens, the cells die or suffer from severe genetic problems, such as Down syndrome.

Before a crossover can occur at a given site, both strands of a chromosome's DNA helix must be broken. About half of these double-strand DNA breaks (DSBs) are processed to form crossovers, and the rest are resealed to restore the original chromosomes. The final number of crossovers is relatively small and scientists have long wondered how cells ensure that even the smallest chromosomes undergo at least one

crossover. Indeed, in almost half of Down's Syndrome cases, chromosome 21, one of the smallest human chromosomes, failed to form a crossover in one of the parents.

In a paper published online in *Current Biology* on November 29, Massachusetts Institute of Technology graduate student Hannah Blitzblau suggests that part of the answer lies in where DSBs are formed. Blitzblau has shown that these DSBs are not scattered randomly throughout the chromosomes, but occur most frequently in a specific band near telomeres, the end caps of chromosomes. When telomeres are spliced into the central part of a chromosome, this DSB "hotspot" effect is still seen at the same distance from the new telomeres.

"This is a simple mechanism for making sure that all chromosomes, even the shortest ones, have the crossovers required for meiosis," says Blitzbau. "If the breaks occurred randomly, the smallest chromosomes often wouldn't have any crossovers."

In addition, Blitzblau showed that DSBs occur at high rates around the central part of the chromosome called the centromere, It was previously thought that DSBs and crossovers rarely occurred in this region.

"This is incredibly surprising," says Hochwagen. "The chromosomes start the crossover process in the centromeres, but divert and reseal the breaks instead."

Some of the earlier research had been done in mutant yeast strains; the Whitehead researchers say that the current work in non-mutant yeast is a more accurate representation of normal processes.

This research will help scientists understand chromosome events leading to infertility and birth defects. In addition, although this work does not touch on why some cells divide improperly, Blitzblau and Hochwagen

anticipate that the technologies developed for this study will allow researchers to identify sites that are sensitive to breaks caused by agents, such as certain cancer drugs. The investigators are adapting the methods used in yeast to map break-sensitive sites in mammalian cells.

Source: Whitehead Institute for Biomedical Research