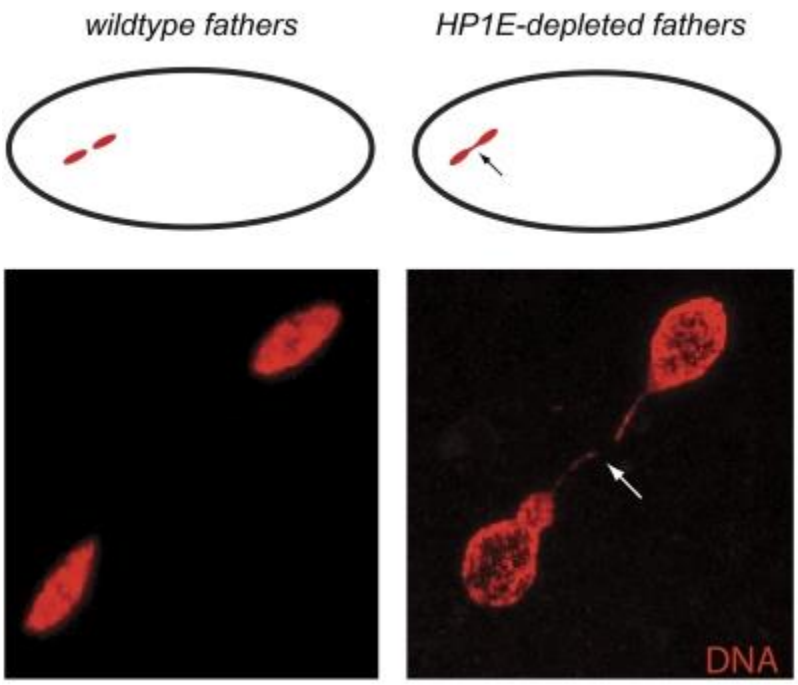
# HP1E leaves a lasting impression on paternal chromosomes

Aug. 17, 2015

**GE Zentner**




Fluorescent imaging of DNA reveals the presence of a chromatin bridge (indicated by an arrow) in PEL embryos fathered by HP1E-depleted males.

*Image from the publication*

The cells of most animals contain two copies of each chromosome. Notable exceptions are egg and sperm cells, which contain only one copy of each chromosome. Thus, when an egg fuses with a sperm during fertilization, the resulting zygote contains two copies of each chromosome, one maternal and one paternal. During development, each chromosome will duplicate and be segregated many times during mitosis. The first zygotic division is notably complex, as both maternal and paternal chromosomes must go through drastic and different reorganization of their chromatin structures. Paternal DNA is packaged with proteins called protamines, which condense DNA more tightly than the histone proteins used by the egg to condense maternal DNA. Thus, paternal chromosomes must decondense, exchange these protamines for histones, recondense, and then recondense in time to for paternal and maternal chromosomes to divide in synchrony in the zygote. While previous work has shown that maternal proteins, provided by the egg, are involved in facilitating the protamine-to-histone transition in the resulting zygote, it is much less clear how paternal proteins participate in this process.

Previous work by postdoctoral fellow Dr. Mia Levine (now Assistant Professor of Biology at the University of Pennsylvania) and colleagues in the laboratory of Dr. Harmit Malik (Basic Sciences Division) demonstrated that a particular protein involved in the formation of condensed, transcriptionally silent chromatin (heterochromatin), called heterochromatin protein 1E (HP1E), is only expressed in testes. Dr. Levine hypothesized that HP1E, given its testis-restricted expression and the well-known roles of HP1 family members in chromatin organization, was a strong candidate for a paternal protein that could influence the exchange of protamines for histones. Dr. Levine, along with research technician Ms. Helen Vander Wende, thus studied the role of HP1E during paternal genome reorganization. Not only did they find that HP1E is essential for successful completion of the first zygotic mitosis, but that the protein itself is not present during this mitosis. Instead, HP1E epigenetically primes paternal chromosomes for future faithful completion of mitosis.

To dissect the role of HP1E during sperm maturation, the authors first examined the pattern of HP1E expression in testes. They found that HP1E was localized to paternal chromosomes only during the zygotic exchange of protamines for histones, and not in mature sperm. As HP1 proteins are well-known organizers of heterochromatin, the authors asked if loss of HP1E might preferentially alter the expression of heterochromatic genes. This analysis showed that 100% of heterochromatic genes altered by HP1E knockdown increased in expression, consistent with the general transcriptional silence of heterochromatin.

The authors next assessed the role of HP1E in male fertility by generating HP1E-depleted male flies, which displayed prominent sterility. However, HP1E-deficient fathers produced motile sperm capable of transferring to females, fertilizing eggs, and initiating embryogenesis. Rather, all but 0.5% of the embryos sited by HP1E-depleted fathers failed to hatch due to a chromosomal defect called a chromatin bridge, which results from incomplete chromosome segregation, followed by further defects in subsequent mitoses. Thus, HP1E is a paternal effect lethal (PEL) gene, meaning that the genotype of the father influences the phenotype of the offspring.

To further understand the requirement of HP1E for the fidelity of chromosome segregation, the authors followed the dynamics of paternal DNA prior to the first zygotic telophase. Paternal DNA from PEL embryos completed the protamine-to-histone transition, recondensed, migrated toward maternal DNA, and entered the first mitosis just as in wild-type embryos. However, paternal DNA failed to condense in synchrony with maternal DNA and failed to separate along the mitotic spindle, instead forming chromatin bridges.

While tracking the fate of DNA from HP1E-depleted fathers, the authors noted that only a portion of the paternal genome is susceptible to HP1E deficiency. Based on their observation that HP1E

depletion upregulates heterochromatic genes, they hypothesized that the regions of the genome most vulnerable to HP1E loss might be long stretches of heterochromatin. To test this, they performed fluorescent *in situ* hybridization (FISH) analysis of heterochromatic regions on all five fly chromosomes in PEL embryos. The Y chromosome, which is completely heterochromatic, was trapped as a chromatin bridge in 94% of PEL embryos, while the maternal X was never bridged. Autosomes were trapped at frequencies intermediate to those of the sex chromosomes.

This work shows not only that HP1E is required for proper zygotic mitosis, but that it exerts this effect transgenerationally; that is, it is not present during the first mitosis but instead primes paternal chromosomes for faithful segregation in zygotes by acting earlier during sperm development. Given that the heterochromatic Y chromosome was frequently trapped in chromatin bridges, it appears that HP1E somehow primes heterochromatic regions of the genome for proper condensation for the first zygotic mitosis.

"Paternal effect lethal genes like HP1E provide a means to investigate the mysterious process of chromatin remodeling that prepares sperm chromatin to re-engage in mitosis. They also reveal the important role of such remodeling factors to coordinate mitosis between maternal and paternal chromosomes, even in the absence of cellular checkpoints that would normally police this coordination," said Dr. Malik.

Levine MT, Vander Wende HM, Malik HS. 2015. Mitotic fidelity requires transgenerational action of a testis-restricted HP1. *eLife* 4:e07378.

See also: Levine MT, McCoy C, Vermaak D, Lee YC, Hiatt MA, Matsen FA, Malik HS. 2012. Phylogenomic analysis reveals dynamic evolutionary history of the *Drosophila* heterochromatin protein 1 (HP1) gene family. *PLOS Genet* 8:e1002729.

Funding for this work was provided by the National Institutes of Health, the Howard Hughes Medical Institute, and the G. Harold and Leila Y. Mathers Foundation.