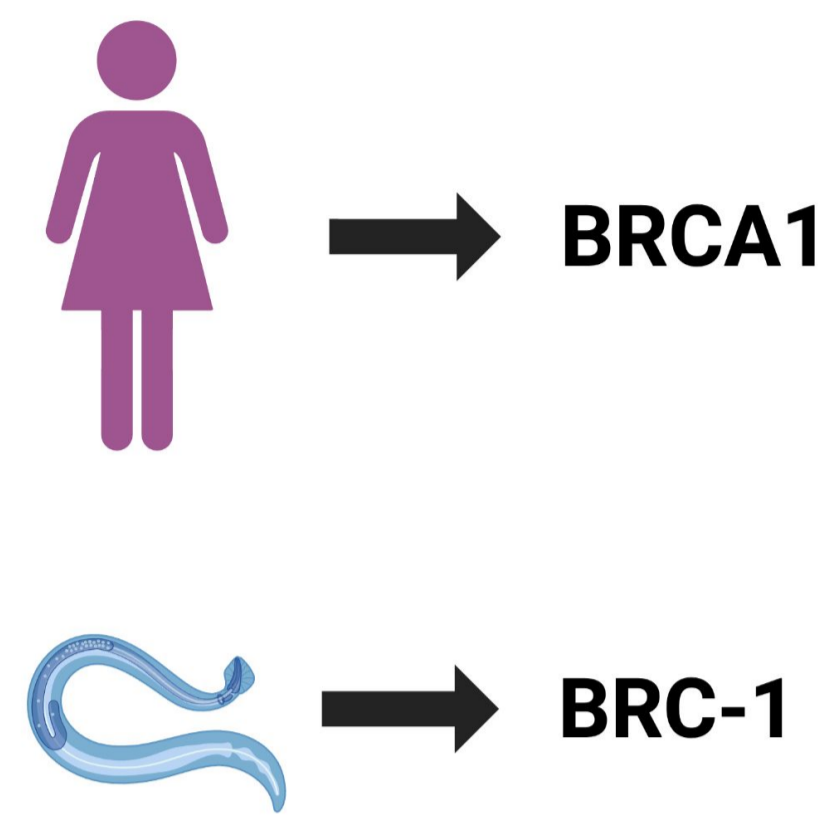


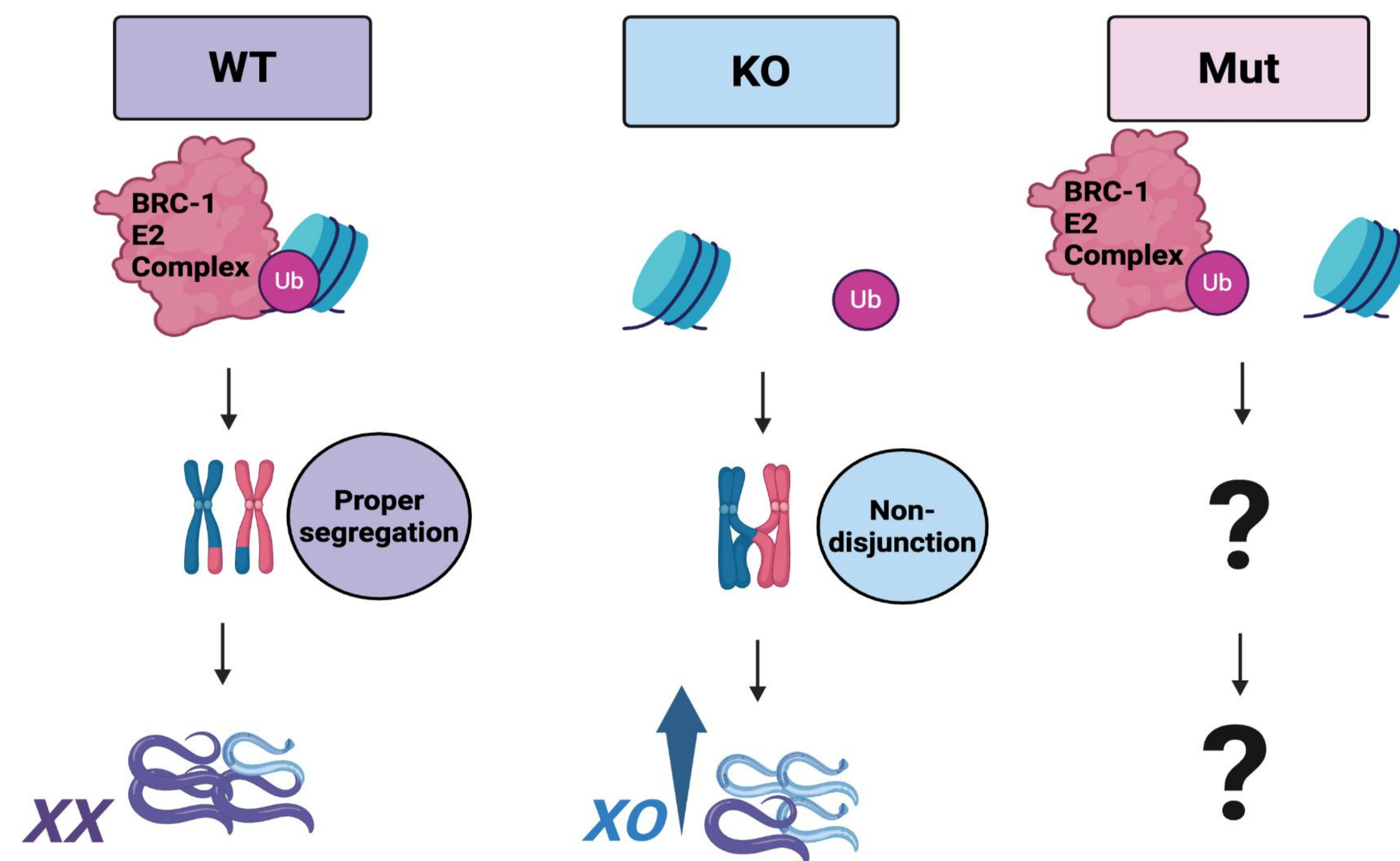


## Introduction



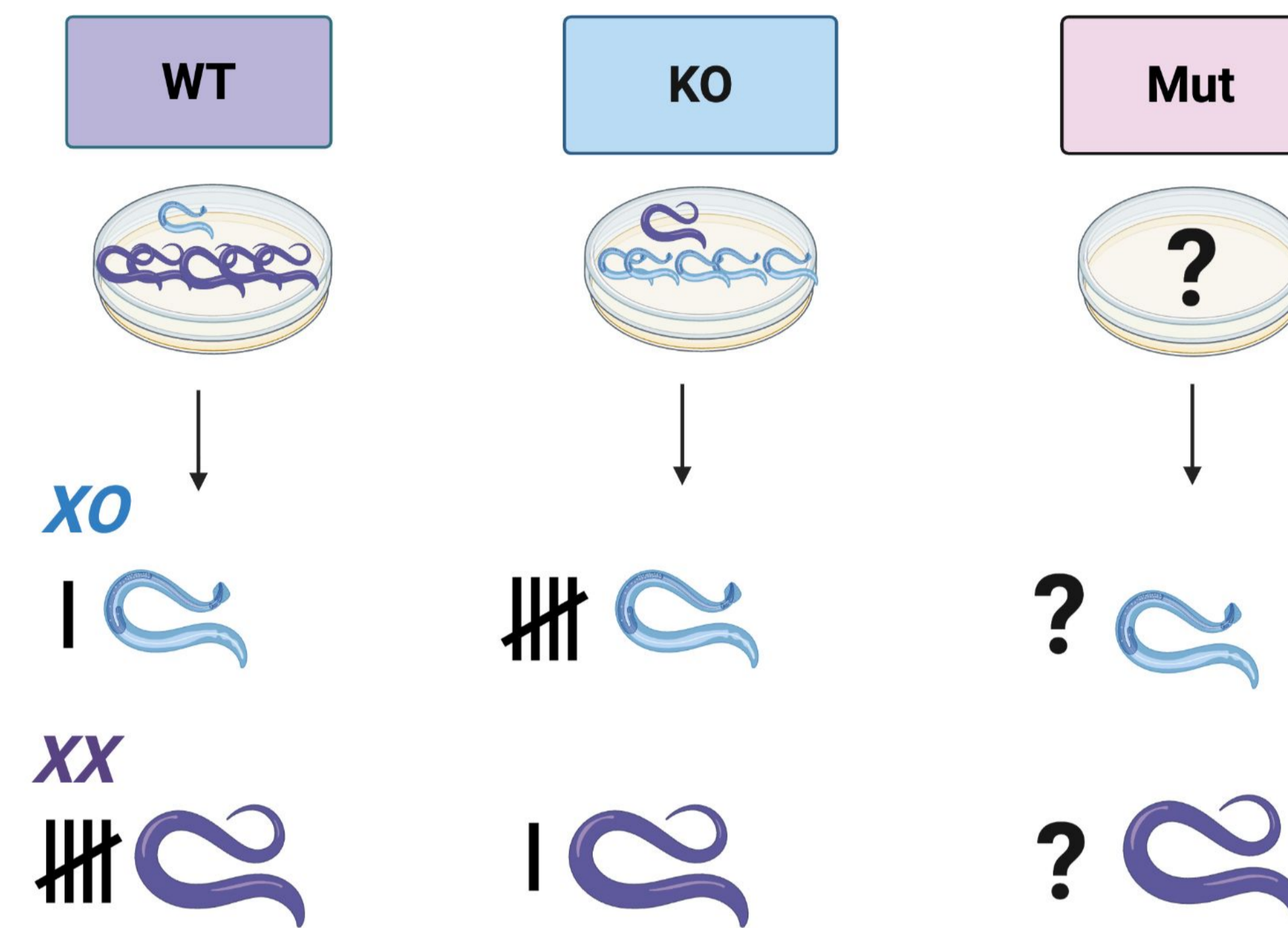
BRCA1 is a protein strongly associated with breast and ovarian cancer. Its *C. elegans* homolog, BRC-1, shares key roles in DNA damage repair and chromatin stability, making the worm a useful model for studying how BRCA1 disruptions contribute to cancer development.

Does nucleosome ubiquitylation of BRC-1 impact proper meiotic crossover in *C. elegans*?



**Above:** Meiotic crossover involves double-stranded break (DSB) formation and proper repair. BRC-1 helps coordinate repair of these lesions to support accurate chromosome segregation. Proper repair is needed to prevent chromosome nondisjunction during meiosis. In *C. elegans*, BRC-1 contributes to DNA damage repair during meiotic recombination. One of the functional domains of BRC-1 mediates nucleosome ubiquitylation, a modification that regulates chromatin accessibility at sites of DNA damage. However, it is unclear whether this specific enzymatic activity is required for successful crossover formation and proper chromosome segregation. N2 wild type worms display functional BRC-1 and proper X chromosome segregation, resulting in primarily XX hermaphrodites. Conversely, the BRC-1 *xoe4* knockout strain lacks the BRC-1 protein and exhibits increased X chromosome nondisjunction, producing a higher frequency of XO males. The *syb5376* mutant strain retains the BRC-1 protein but lacks nucleosome ubiquitylation activity. This specific strain allows us to determine whether nucleosome ubiquitylation of BRC-1 function particularly contributes to proper meiotic crossover and X chromosome segregation. This leads to the question: Does BRC-1 nucleosome ubiquitylation impact proper meiotic crossover in *C.elegans*?

## Quantifying male proportions across three strains



**Above:** To determine X chromosome nondisjunction, we quantified the proportion of males (XO) and hermaphrodites (XX) in three *C. elegans* strains: WT, KO, and Mut. These worms were examined using a light microscope at 2.5X magnification. For each strain, approximately 30 worms per plate were examined and counted, classifying each worm by phenotype (male vs hermaphrodite). Phenotypes are determined by morphological differences in the body shape and tail end of worms. Hermaphrodites display a visible vulva and embryos in the mid-body with a straight, tapered tail. Males exhibit no vulva and a thinner body with a curved tail. For each of the strains, n=1500 total worms were counted. Proportion of males was calculated as total males divided by total worms counted per strain.

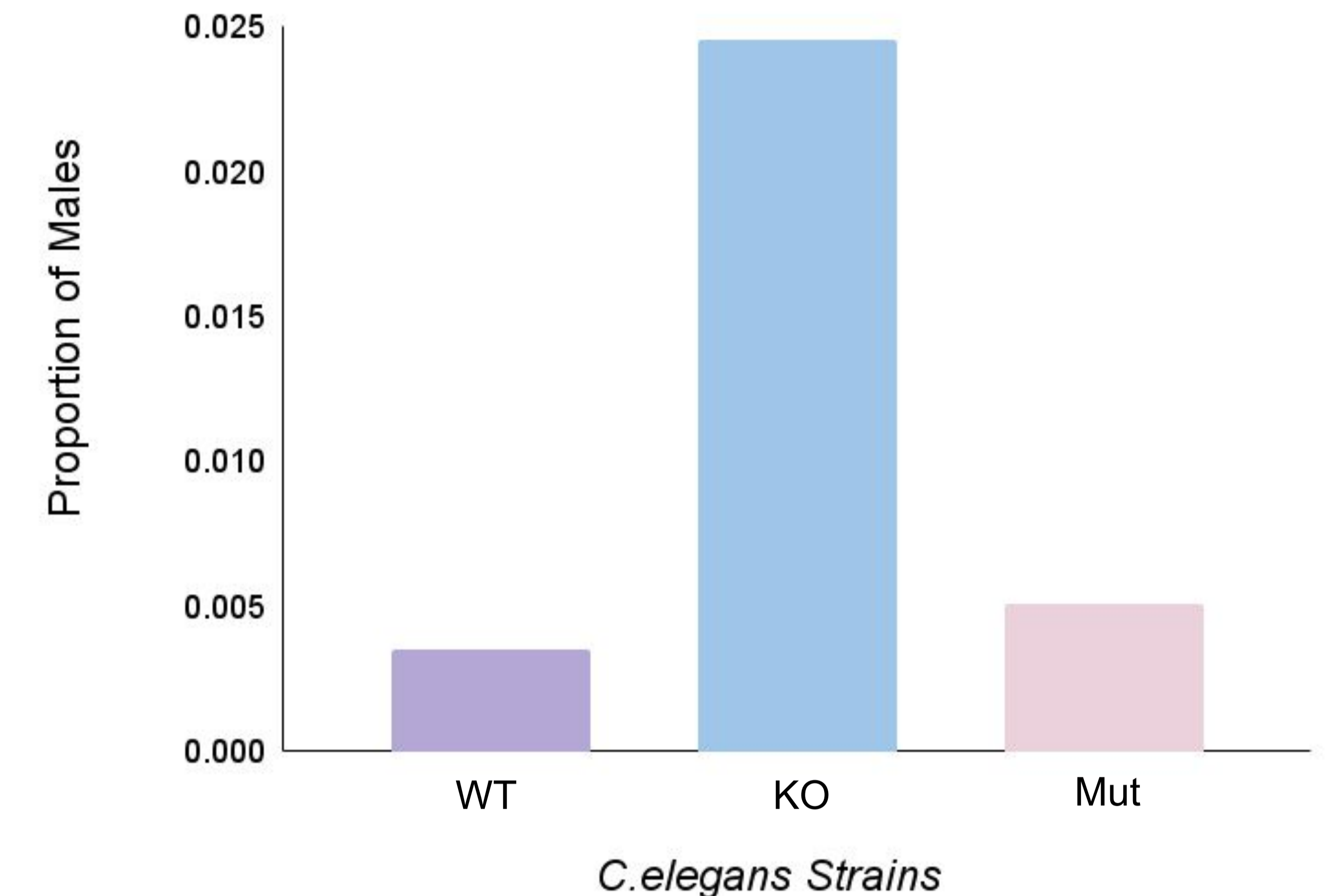
## Objectives

- Explore how the enzymatic function of BRC-1, nucleosome ubiquitylation, disrupts proper meiotic crossover in *C. elegans*.
- Explore how specific changes in nucleosome ubiquitylation function observed across three strains (WT, KO, Mut) impact meiotic crossover.
- Determine proportion of males across all three strains.
- Further *C.elegans* as a model for understanding genetic inheritability of breast and ovarian cancer risk.

## Funding & Thank You

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## Improper nucleosome ubiquitylation of BRC-1 displays an intermediate effect on meiotic crossover



**Proportion of males measured across WT, KO, and Mut *C.elegans*.** Loss of BRC-1 nucleosome ubiquitylation function in *C. elegans* mutant (right) leads to a statistically higher proportion of males than in wild-type (left), but a lower proportion of males than in knockout (middle). Therefore, mutants exhibit an intermediate effect as a result of loss of BRC-1 nucleosome ubiquitylation function. **More data is being collected.**

## Conclusions & Future Directions

- Nucleosome ubiquitylation, an enzymatic function of BRC-1, is a factor in driving proper meiosis crossover.
- However, nucleosome ubiquitylation is **not** the **only** function of BRC-1.
- Ongoing research would look at other phenotypes of BRC-1 such as nucleosome ubiquitylation ability to drive sensitivity to chemotherapy and its effect on ROS levels.

## Citation

Li, Q.; Saito, T. T.; Martinez-Garcia, M.; Deshong, A. J.; Nadarajan, S.; Lawrence, K. S.; Checchi, P. M.; Colaiacovo, M. P.; Engebrecht, J. The Tumor Suppressor BRCA1-BARD1 Complex Localizes to the Synaptonemal Complex and Regulates Recombination under Meiotic Dysfunction in *Caenorhabditis Elegans*. *PLoS Genet* **2018**, *14* (11), e1007701. <https://doi.org/10.1371/journal.pgen.1007701>.