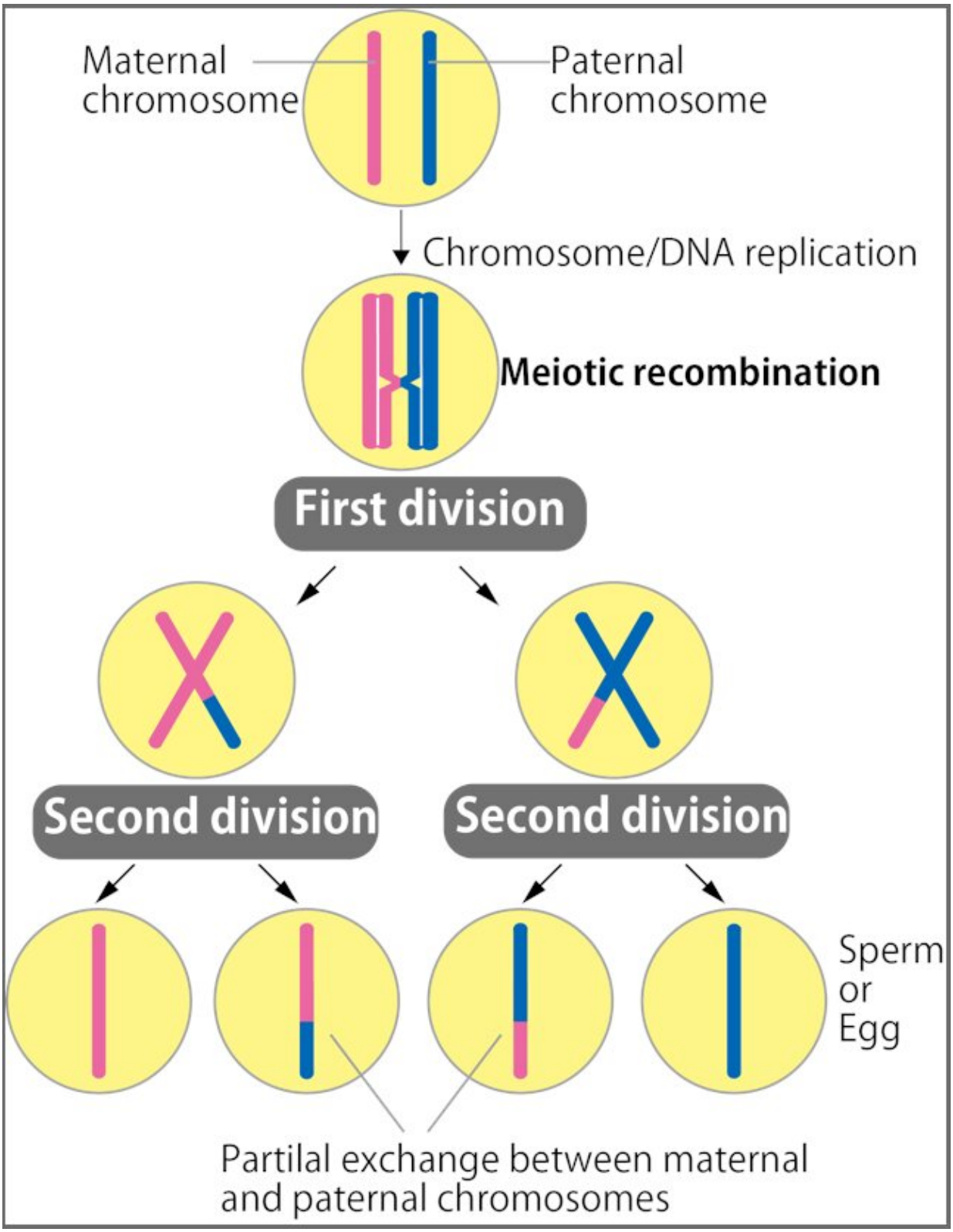
Discovery of a novel gene involved in DNA damage repair and male fertility

June 4 2020



Genetic information is exchanged between maternal and paternal chromosomes

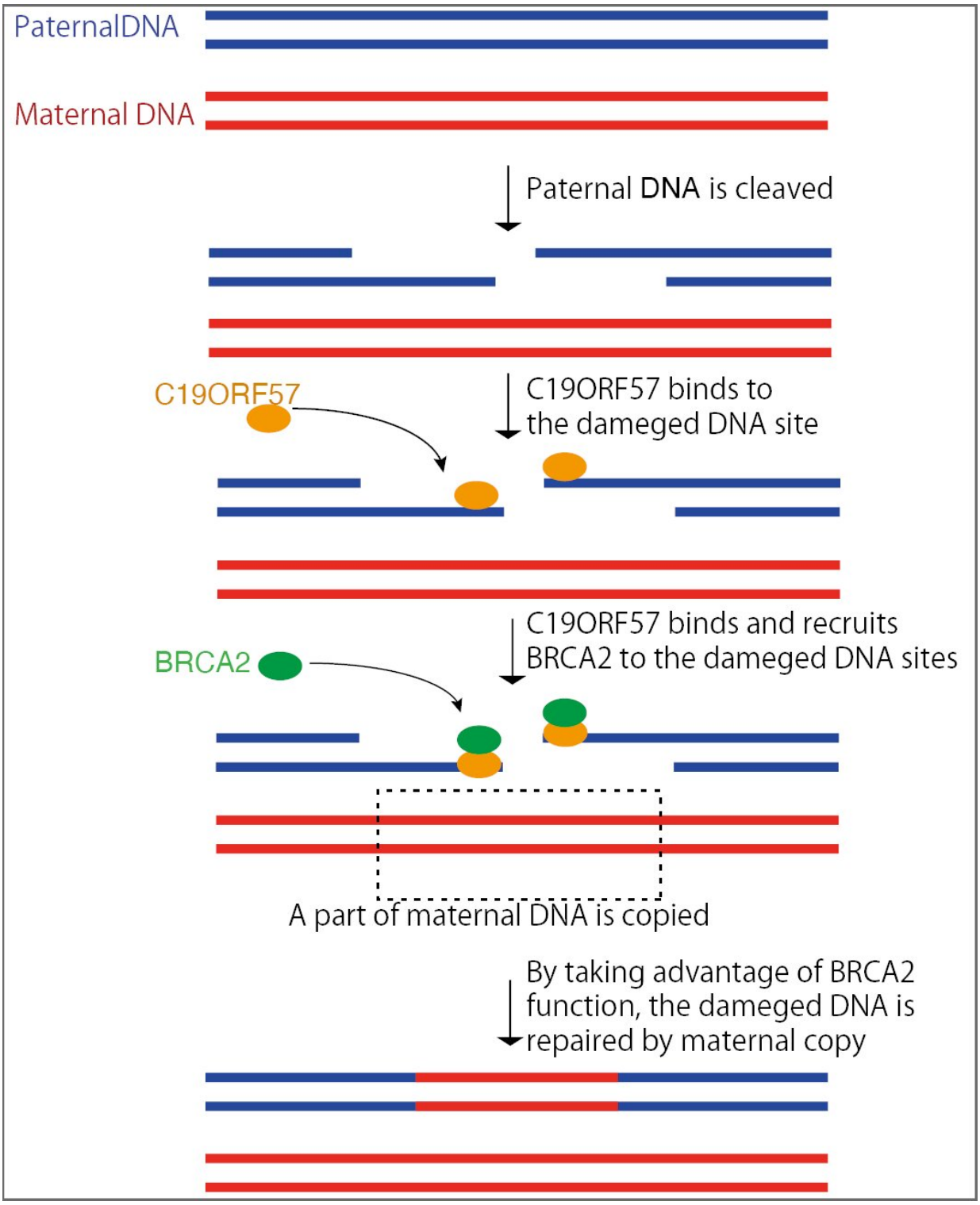
through meiotic recombination. Sperm and eggs receive chromosomes with mixed genetic information, providing genetic diversity in the next generations. Credit: Dr. Kei-ichiro Ishiguro

A research group from the Institute of Molecular Embryology and Genetics (IMEG) at Kumamoto University, Japan has discovered that the gene C19ORF57 plays a critical role in meiosis. The gene appears to be related to the cause of male infertility and could be a big step forward for reproductive medicine.

Meiosis is a specialized type of cell division that generates sperm or eggs. During Meiosis, genetic information is exchanged between maternal and paternal chromosomes through meiotic recombination. This process introduces genetic differences to the next generation.

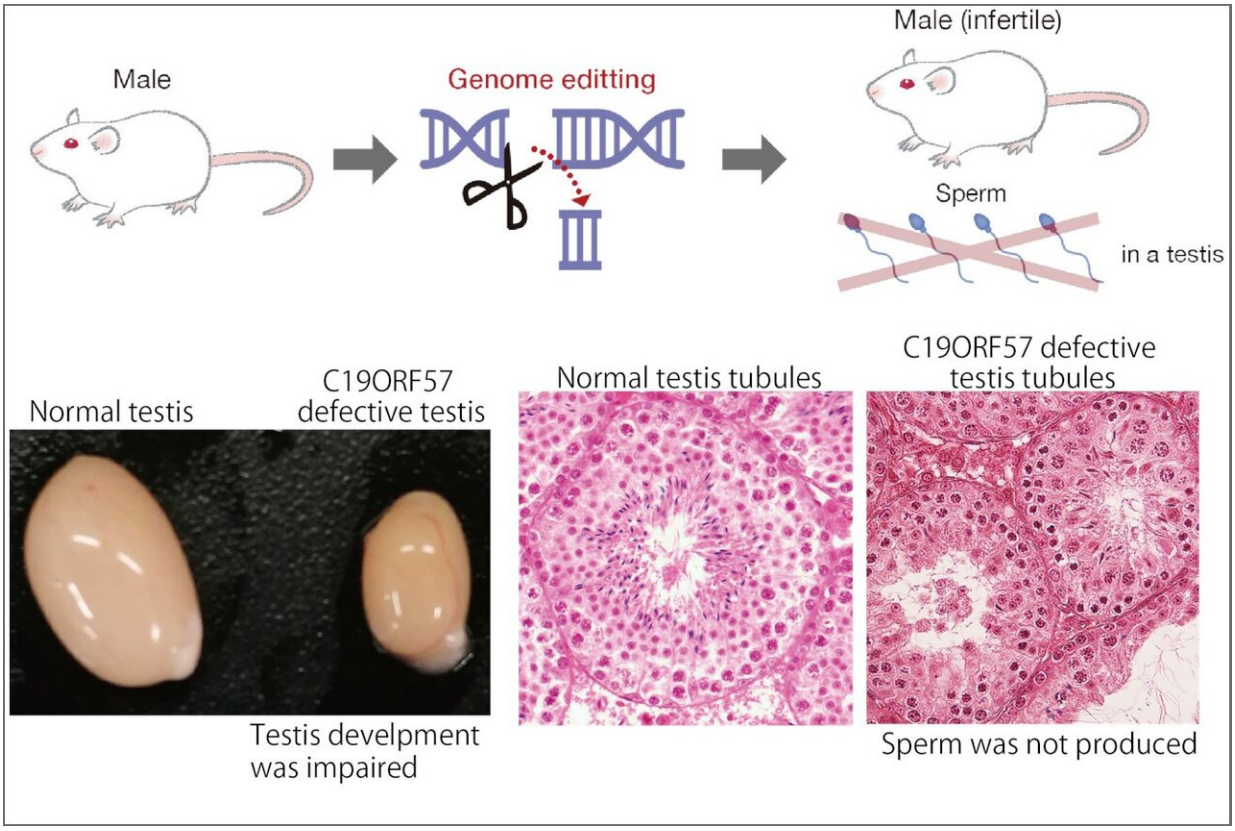
Normally, meiotic recombination is initiated by introducing breaks in the DNA. However, this process is nothing less than DNA damage that is a threat to the cell. Although introduction of DNA breaks is a normal and necessary process to trigger meiotic recombination, these breaks must be repaired immediately. In this study, Drs. Ishiguro and Takemoto discovered a novel gene that plays a crucial role in repairing DNA damage during meiotic recombination.

Previously, the same group discovered the *Meiosin* gene which acts as a switch to turn on meiosis as well as hundreds of other genes in the process. However, the functions of all the other genes have not yet been fully elucidated. The *C19ORF57* gene is one of those controlled by MEIOSIN and its function was unknown until now.



Normally, DNA breaks are introduced at the beginning of meiotic recombination. However, such DNA breaks are a threat to a cell and must be repaired immediately. The newly identified C19ORF57 gene mediates binding

of BRCA2 to damaged DNA sites for repair. Credit: Dr. Kei-ichiro Ishiguro



Reproductive medicine researchers from Kumamoto University (Japan) performed genome editing experiments to verify that the C19ORF57 gene was indeed required for male fertility. When they removed the gene in a murine experimental model, testis were smaller compared to those of normal males, and sperm were not produced in testis tubules, making them infertile. Credit: Dr. Kei-ichiro Ishiguro

The researchers set out to clarify the role of C19ORF57 in meiosis. Using mass spectrometry, the group found that it binds to breast cancer suppressor BRCA2, a protein that is known to play a role in repairing

damaged DNA. This data suggests that C19ORF57 and BRCA2 function together in germ cells.

Further evidence showing cooperation between C19ORF57 and BRCA2 was found through microscopic imaging. The researchers discovered that C19ORF57 goes first to damaged DNA sites and then recruits BRCA2 to the same position on the chromosomes.

Using genome editing technology to artificially inhibit the *C19orf57* gene in mice, researchers found that the male animals became infertile because meiotic recombination did not complete and sperm were not produced. Further analysis of male gonads revealed that the gene plays an essential role in repairing damaged DNA.

There are many unknown causes of human male infertility and this finding potentially reveals a new pathology. Even though these experiments were performed on animal models, the C19ORF57 gene is present in humans. Therapies and diagnostics developed from this research could ensure meiosis quality and decrease the instances of complications.

More information: Kazumasa Takemoto et al, Meiosis-Specific C19orf57/4930432K21Rik/BRME1 Modulates Localization of RAD51 and DMC1 to DSBs in Mouse Meiotic Recombination, *Cell Reports* (2020). DOI: 10.1016/j.celrep.2020.107686

Provided by Kumamoto University