Research explains the role of the gene BRCA1 in DNA repair

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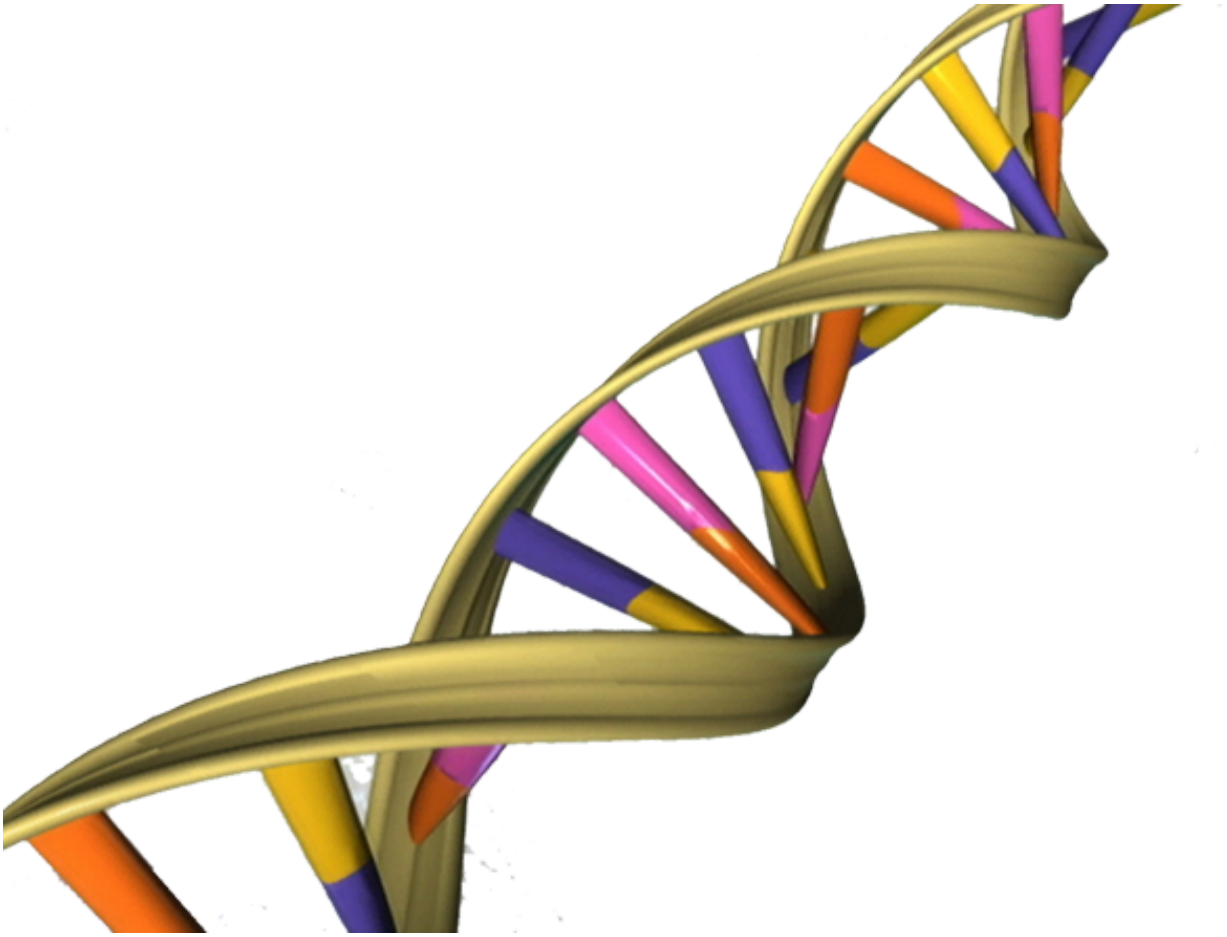

A depiction of the double helical structure of DNA. Its four coding units (A, T, C, G) are color-coded in pink, orange, purple and yellow. Credit: NHGRI

Scientists at the University of Birmingham are a step closer to understanding the role of the gene BRCA1. Changes in this gene are associated with a high risk of developing breast and ovarian cancer.

The research, published in *Nature Structural and Molecular Biology*, explains how the gene encourages the attachment of the protein, ubiquitin, to other proteins and plays a vital role in DNA repair.

Should the results be confirmed by further studies, it is possible that patients with certain genetic changes in BRCA1 could be identified as being at higher risk of breast and ovarian cancer.

The gene BRCA1 makes a protein that can attach ubiquitin, which helps to regulate processes in the body, to other proteins. However little was known about the importance of this activity in DNA repair.

The new research has found that this attachment of ubiquitin by BRCA1, its 'ubiquitin ligase activity', is needed for a specific type of DNA repair that is 'error-free', known as homologous recombination. It is known that cells without this type of DNA repair can develop mutations leading to cancer development. Cells lacking the BRCA1 ubiquitin ligase activity were found to be sensitive to certain DNA damaging agents that need homologous recombination in for repair.

Dr Jo Morris, lead author from the University of Birmingham, explained, "We know that loss of BRCA1 is associated with a high risk of breast cancer, so getting to grips with understanding this gene has been a major aim of breast cancer research. This study may explain why some cancer predisposing mutations are found in the front part of the BRCA1 gene - the part that allows it to function as a ubiquitin ligase."

The team sought to identify how BRCA1 manages to perform the ubiquitin attachment role, and found that it relies on a part of a partner

protein, called BARD1.

Using changed versions of BARD1, and leaving the BRCA1 protein untouched, they were able to identify the attachment function of BRCA1 and show that it is needed for the cell response to, and proper repair of, DNA damage.

Dr Morris added, "Our finding that BRCA1 has several independent functions in DNA repair has implications for treatment. Clinicians are currently worried that breast cancer patients with low or absent BRCA1 may become resistant to therapeutic agents such as Olaparib. Our data show that cancer cells without BRCA1 have more than one "Achilles heel", and so there are more ways to target cancers and therefore to prevent tumours becoming resistant to treatment."

More information: Human BRCA1-BARD1 ubiquitin ligase activity counteracts chromatin barriers to DNA resection, *Nature Structural and Molecular Biology*, DOI: 10.1038/nsmb.3236

Provided by University of Birmingham