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A pathway leading to activation of BRCA1

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Fanconi anaemia is a rare inherited disorder that causes children to develop bone marrow failure. Although a bone marrow transplant can cure the anaemia, many patients go on to develop a variety of cancers.

The disorder is brought about by a mutation in any one of seven genes - five of which have been cloned. The proteins produced by these five genes form an enzyme that activates the sixth. Research teams led by Alan D'Andrea, of the Dana-Farber Cancer Institute in Boston, and Markus Grompe, of the Oregon Health Sciences University in Portland, report in the 16 February *Molecular Cell* that they have cloned and identified that sixth gene, called *FANCD2* (Mol Cell 2001, **7:** 241-248). In a second the group also reports that *FANCD2* produces a protein that switches on *BRCA1* (Mol Cell 2001, **7:** 249-262).

Approximately 50% of women with a strong family history of breast cancer have a defective *BRCA1* gene. The protein encoded by *BRCA1* helps repair damaged DNA, but little is known about how *BRCA1* is activated. It seems that the FANCD2 protein becomes monoubiquitinated in response to DNA damage. The ubiquitination serves as a targeting signal that enables FANCD2 to interact with BRCA1. Once bound, the two proteins co-operate in DNA repair.

D'Andrea believes that it may be possible to design a drug that amplifies the effects of FANCD2, thus accelerating the repair work of BRCA1 and reducing the chances that breast cancer will occur in people with a genetic predisposition for it. But, says D'Andrea, "Much work remains to be done before such therapies become a reality."

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