Important discoveries are sometimes so neat and satisfying that, in retrospect, they seem obvious. So it is with the finding described by Howlett et al. (1) on page 606 of this issue. These authors disclose that the inheritance of two defective copies of the BRCA2 breast cancer susceptibility gene (2) can lead to Fanconi anemia (FA) (3), a complex disorder characterized by congenital abnormalities, progressive bone marrow failure, and cancer susceptibility.

Homozygous carriers of BRCA2 mutations inherit a high risk of developing breast cancer (up to 85%) and other cancers such as ovarian and pancreatic. No developmental or other obvious defects have been noted in these individuals. The BRCA2 protein is thought to be important in the repair of DNA damage by homologous recombination, at least in part by regulating the activity of RAD51 (2). Cells lacking BRCA2 inaccurately repair damaged DNA, leading to gene mutation and progression of tumors, and are particularly sensitive to DNA cross-linking agents.

Most patients with FA present within the first decade of life with bone marrow failure and cancer, typically acute myeloid leukemia and squamous cell carcinoma, usually of the head and neck (3). This is accompanied by congenital abnormalities such as growth retardation and skeletal defects (microcephaly and absent radii or thumbs), kidney defects, and abnormal skin pigmentation. The heterogeneity of the disease leads to difficulties in making a firm clinical diagnosis, and therefore the cellular hypersensitivity to DNA cross-linking agents such as mitomycin C that these patients exhibit is used as the gold standard diagnostic tool.

FA is a recessively inherited disorder that can result from mutation in at least eight individual genes (3). Apart from genes B and D1, these have all been isolated previously and encode diverse proteins, many of which interact within a cellular complex related to the maintenance of genomic stability.

Howlett et al. (1) show that one of the previously unidentified FA genes, FANCD1, is in fact BRCA2. The cellular consequences of homozygosity for BRCA2 mutation—spontaneous chromosome instability and hypersensitivity to DNA cross-linking agents—are similar to those in cells derived from FA patients. This prompted the authors to determine the sequence of the BRCA2 gene in FANCD1 patients. One individual with FA carried two different truncating mutations in BRCA2 typical of those that cause susceptibility to breast cancer when heterozygous. Individuals carrying two BRCA2 mutations have not been reported before, and this result was surprising as it was thought likely that this combination of mutations would be lethal. An explanation for this finding might be suggested, however, by previous work on BRCA2 knockout mice. Mice homozygous for mutations that eliminate most of the BRCA2 gene do die early in embryogenesis, whereas those with apparently milder (“hypomorphic”) mutations can survive to adulthood (4, 5). It is intriguing that these mice have some phenotypes that are reminiscent of FA, including small gonads, skeletal defects, and sensitivity to DNA cross-linking agents (4, 5). It is possible therefore that only hypomorphic BRCA2 mutations lead to FA, whereas stronger mutations are lethal during embryogenesis. The final piece of evidence implicating BRCA2 in the pathogenesis of FA is the partial rescue of sensitivity to mitomycin C of a FANCD1 cell line by introduction of a wild-type BRCA2 gene (6). Although this result, in itself, is open to alternative interpretation, taken together with the genetic data, it provides a persuasive argument for the role of BRCA2 mutation in FA.

Preliminary evidence is also presented by the authors for a role of BRCA2 mutation in another FA complementation group, FANCB, although this requires additional confirmation.

This is not the first link between FA and breast cancer susceptibility. Another FA complementation group protein, FANCD2, can interact and colocalize with BRCA1 (6). Moreover, both FANCD2 protein and BRCA1 can be phosphorylated by ATM, itself recently implicated in susceptibility to breast cancer (7, 8). Thus, it seems that the pathways disrupted in FA and breast cancer susceptibility are intimately connected on several levels (see the figure).

So if BRCA2 can be an FA gene, could other FA genes be new BRCA genes? Little evidence could be found in previous studies for an excess of cancers in relatives of FA patients (9). Nevertheless, this work could not take into account the existence of multiple genes for FA; if only some behaved like BRCA2, the analysis would be negative. It would be particularly interesting to examine FANCD2, with what appears to be a central role in the pathway (see the figure). Doubtless the new work by Howlett et al. (1) will stimulate considerable interest in readdressing the issue of cancer susceptibility in FA heterozygotes.

Only a small proportion of the cases of FA, which in itself is rare, is caused by BRCA2 mutation. But the importance of this finding is that it connects two previously different bodies of work on DNA repair. Doubtless this will fuel progress into understanding both breast cancer and FA.

The authors are at The Breakthrough Breast Cancer Research Centre, The Institute of Cancer Research, London SW3 6JB, UK. E-mail: elisa@icr.ac.uk

References
1. N. G. Howlett et al., Science 297, 606 (2002); published online 13 June 2002 [10.1126/science.1073834].
5. V. P. Yu et al., Genes Dev. 14, 1400 (2000).

Published online 13 June 2002; 10.1126/science.1074482
Include this information when citing this paper.