Germline mutations in breast and ovarian cancer pedigrees establish RAD51C as a human cancer susceptibility gene.

Abstract:
Germline mutations in a number of genes involved in the recombinational repair of DNA double-strand breaks are associated with predisposition to breast and ovarian cancer. RAD51C is essential for homologous recombination repair, and a biallelic missense mutation can cause a Fanconi anemia-like phenotype. In index cases from 1,100 German families with gynecological malignancies, we identified six monoallelic pathogenic mutations in RAD51C that confer an increased risk for breast and ovarian cancer. These include two frameshift-causing insertions, two splice-site mutations and two nonfunctional missense mutations. The mutations were found exclusively within 480 pedigrees with the occurrence of both breast and ovarian tumors (BC/OC; 1.3%) and not in 620 pedigrees with breast cancer only or in 2,912 healthy German controls. These results provide the first unambiguous evidence of highly penetrant mutations associated with human cancer in a RAD51 paralog and support the 'common disease, rare allele' hypothesis.