A 24-color metaphase-based radiation assay discriminates heterozygous BRCA2 mutation carriers from controls by chromosomal radiosensitivity.

Numerous allelic variants identified in the familial breast cancer and DNA repair genes BRCA1 and BRCA2 are of unknown impact on protein function or clinical relevance, referred to as unclassified variants (UCV). Lymphocytes from pathogenic BRCA1/2 mutation carriers exhibit an increased level of chromosomal damage after irradiation. We established a radiation assay for the discrimination of pathogenic BRCA2 variants versus controls based on the level of chromosomal damage upon irradiation (p < 0.001). As a consequence, lymphocytes from UCV carriers could be separated into two distinct groups with normal or diminished DNA double strand break repair capacity. Our results suggested that all five UCV tested were benign and that one family carried a putative mutation in an as yet undetected DNA-repair gene. Thus, our test may serve as a valuable tool that aids the classification of BRCA2 UCV, but very likely also of BRCA1 UCV or aberrations in other genes involved in the DNA-repair system.