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Accurate prediction of *BRCA1* and *BRCA2* heterozygous genotype using expression profiling after irradiation induced DNA damage

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Germline mutations in the *BRCA1* and *BRCA2* genes predispose women to an increased risk of breast and ovarian cancer. Both genes have important roles in DNA damage repair and have been implicated in gene expression regulation. In this study the differential gene expression changes following radiation-induced DNA damage in healthy cells from *BRCA1/2* mutation carriers has been compared with non-carrier controls using high-density microarray technology.

Short-term primary fibroblast cultures were established from skin biopsies from 10 *BRCA1* and 10 *BRCA2* mutation carriers and 10 controls, all of whom had previously had breast cancer. The cells were subjected to 15 Gy ionizing irradiation to induce DNA damage. RNA was extracted from all cell cultures pre-irradiation and at 1 hour post-irradiation. For expression profiling 15 K spotted cDNA microarrays manufactured by the Cancer Research UK cDNA Microarray Facility were used. Statistical feature selection was used with a Support Vector Machine (SVM) classifier to determine the best feature set for predicting *BRCA1* or *BRCA2* heterozygous genotype. To investigate prediction accuracy a non-probabilistic classifier (SVM) and a probabilistic classifier (a Gaussian Process classifier) were used. These both achieved 90-100% accuracy, in the task of distinguishing *BRCA1* and *BRCA2* mutation carriers from non-carriers following radiation induced DNA damage, an effect which could not be achieved without irradiation.

We conclude that after irradiation induced DNA damage, *BRCA1* and *BRCA2* mutation carrier cells have a distinctive expression phenotype and this may have a future role in predicting genotypes with application to clinical detection and classification of mutations.