Several genes involved in the DNA damage response and in maintaining genomic stability have emerged as breast cancer susceptibility genes. These include BRCA1 and BRCA2, as well as other genes with smaller contributions to breast cancer aetiology, such as TP53, CHEK2, and ATM. Germline mutations in BRCA1 and BRCA2 increase sensitivity to DNA damage and decrease cellular capacity to repair double strand DNA breaks through homologous recombination. Interestingly, DNA damage induces activation of ATM (ataxia-telangiectasia mutated), which performs a central role in relaying signals that orchestrate DNA repair. People with heterozygous nonsense mutations in ATM appear to display increased susceptibility to breast cancer. Besides rapidly phosphorylating BRCA1, activated ATM also phosphorylates p53 and CHEK2 (CHK2, hCDCS1), which have been implicated in breast cancer predisposition. Germline mutations in TP53 or CHEK2 cause Li-Fraumeni syndrome, a multiple cancer phenotype syndrome, which features early onset breast cancer. Recently, it was found that germline mutations in CHEK2 also increase the relative risk for breast cancer outside the Li-Fraumeni syndrome. Given the emerging relationship of impaired DNA damage response and breast cancer susceptibility, we hypothesised that other genes in this pathway might be candidate cancer susceptibility genes.

Histone H2AX (H2AFX, OMIM 601772) is such a candidate gene. H2AX is a minor variant of the highly conserved histone H2A that is part of the histone octamer in the core of the nucleosome. It differs from H2A by having a longer carboxy-terminal tail that contains an SQE motif, a consensus site for phosphorylation by PI3K related kinases such as ATM, ATR, and DNA-PK. Following DNA damage, ATM phosphorylates H2AX at serine 139 (part of the SQE motif) and phosphorylated H2AX (γ-H2AX) seems to localise specifically at sites of damage. More importantly, several proteins involved in DNA repair including BRCA1, BRCA2, Rad51, and Mre11 are recruited to sites of γ-H2AX. Two other independent lines of evidence derived from model organisms support the notion that H2AX plays an important role in the DNA damage response and in chromosomal stability. Phosphorylation of S129 of Saccharomyces cerevisiae H2A (homologous to S139 in human H2AX) is necessary for efficient processing of DNA repair and is proposed to cause alteration of chromatin structure that facilitates repair. Mice lacking H2AX are sensitive to radiation, are growth retarded, and their cells display high levels of ionising radiation induced chromosomal instability. Thus, although the exact function of H2AX is still unknown, it is clear that it plays a role in the DNA damage response.

To establish if germline H2AX mutations are present in breast cancer families, DNA samples were obtained from 101 unrelated breast cancer patients.

METHODS AND RESULTS
Each of these patients was from a family with three or more cases of breast cancer. These families were selected because they have previously been tested for the presence of germline mutations in BRCA1 and BRCA2 using the protein truncation test (PTT) and no mutations were found. There were, on average, 4.2 cases of breast cancer per family (range 3 to 11) with an average of 3.0 cases of breast cancer in first degree relatives per family (range 2 to 9). Seventeen of the families also contained cases of ovarian cancer. For each family, a single patient affected with breast cancer was studied, with a mean age of diagnosis of 47 years (range 24 to 72 years).

The H2AX gene contains a single exon with 432 nucleotides. The coding sequence of the H2AX gene was evaluated by direct sequencing of a 561 bp fragment amplified using the following primers: F5′-CGTCTGTGTCTAGTTGAGC-3′ and R5′-TGAGGGCGGTGGTGGCTTTA-3′. No mutations or sequence variants were found in the 101 patients.

DISCUSSION
Our results suggest that germline H2AX mutations are unlikely to be common in families with familial breast cancer. Furthermore, the absence of polymorphic variation in this gene precludes the possibility that missense variants within the coding region of H2AX are associated with breast cancer risk in the population as a whole. It is, of course, possible that rare disease causing mutations in H2AX exist, and these might be uncovered in a larger study.

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Absence of constitutional H2AX gene mutations in 101 hereditary breast cancer families

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