Predominance of pathogenic missense variants in the RAD51C gene occurring in breast and ovarian cancer families.

Abstract:
RAD51C was defined by Meindl et al. in 2010 as a high-risk gene involved in hereditary breast and ovarian cancers. Although this role seems to be clear, nowadays there is controversy about the indication of including the gene in routine clinical genetic testing, due to the lower prevalence or the absence of mutations found in subsequent studies. Here, we present the results of a comprehensive mutational screening of the RAD51C gene in a large series of 785 Spanish breast and/or ovarian cancer families, which, in contrast to the various subsequent studies published to date, includes the functional characterization of suspicious missense variants as reported in the initial study. We have detected 1.3% mutations of RAD51C in breast and ovarian cancer families, while mutations in breast cancer only families seem to be very rare. More than half of the deleterious variants detected were of missense type, which highlights their significance in the gene, and suggest that RAD51C mutations may have been so far partially disregarded and their prevalence underestimated due to the lack of functional complementation assays. Our results provide new evidences, suggesting that the genetic testing of RAD51C should be considered for inclusion into the clinical setting, at least for breast and ovarian cancer families, and encourage re-evaluating its role.
incorporating functional assays.