Silencing of genes mapped on 7q are candidates to be associated with multiple primary tumors including triple negative breast cancer

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BACKGROUND: The presence of multiple primary cancers (MPCs) has been related to environmental, therapies and genetic factors. A great percentage of patients with MPCs and family history of cancer are suspected to have a hereditary cancer predisposition syndrome. However, only a small proportion of these cases are explained by mutations in high-penetrance genes, suggesting the involvement of undiscovered genes in cancer predisposition.

HYPOTHESIS:Copy number variations (CNVs) and copy-neutral loss of heterozygosity (cnLOH) can affect tumor suppressor genes (TSGs) and oncogenes, encompassing new candidates genes related to a high risk of cancer development.

METHODS:We used a high-resolution microarray platform to investigate germline genomic alterations in two unrelated patients with MPCs showing in common triple negative breast tumors and absence of germline mutations in the *BRCA1*, *BRCA2* and *TP53* genes. We also assessed, the mother of one patient, four children and the breast cancer sample of one proband.

RESULTS:Large genomic rearrangements on chromosome 7q, over 40Mb involving the same region, were found in both patients: one with mosaic loss (80% of cells) and the other with cnLOH as a result of maternal allele duplication. The four children evaluated showed no alterations on 7q. The patients shared 330 genes in common on 7q22.1-q34, including several TSGs previously related to breast cancer risk and five imprinted genes (*COPG2IT1*, *MEST*, *CPA4*, *MESTIT1* and *KLF14*). The analysis of the triple negative BC from one patient revealed a mosaic gain of 7q in a similar region involved in the germline cnLOH. The maternal allele duplication involving imprinted genes in one case and the deletion in the same region mapped on 7q in the other patient are events leading to silencing of genes. The involvements of TSGs and imprinted genes mapped on 7q have the potential to be associated with MPCs risk and also with cancer progression. To our knowledge, this is the first description of patients with MPCs, including triple negative breast cancer, harboring constitutive large alteration on 7q.