familial cancer

GENOMIC ALTERATIONS IN PATIENTS SHOWING MULTIPLE PRIMARY TUMORS AND FAMILY HISTORY OF CANCER

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Aim: Multiple primary tumors (MPT) are a major cause of mortality and morbidity among patients that have survived after the treatment of a first cancer. It has been proposed that after the first primary tumor, high risk of a subsequent tumor could be associated with radiotherapy used as treatment for the first cancer. Other potential risk factors include unhealthy lifestyle, genetic predisposition, aging, environmental determinants or an interaction between these factors. However, an association between the presence of MPT and family history of cancer in cases without clinical and molecular evidence of a known hereditary cancer syndrome is rarely described.

Methods: Genomic DNA from 12 patients with at least two primary tumors and without mutations on TP53 was evaluated by CytoScan HD Array (Affymetrix). Chromosome Analysis Suite (ChAS) software v.2.0.1 was used considering at least 50 markers for gains; 25 for losses and a minimum of 5Mb for cnLOHs. Data from 1038 phenotypically healthy individuals (Affymetrix) and from Database of Genomic Variants were used as reference. Only alterations found in <1% (rare) or never described (new rare) in the reference population were considered.

Results: All cases, except one, presented a family history of cancer. Five cases developed MTP after radiotherapy and only one was located in the same treated area. It was detected 67 rare and 15 new rare genomic alterations encompassing 5,906 genes: 17 losses, 29 gains, and 36 cnLOH. X chromosome presented the higher number of alterations. Two patients with breast cancer presented a large deletion/cnLOH on 7q21. Enrichment analysis revealed 1275 genes associated with breast cancer (p= 0.001), which was diagnosed in 6 patients and their family members (all negative for BRCA1/2 or TP53 mutations). cnLOHs accounted for 44% of all the alterations.

Conclusions: A significant proportion of cases (11/12) presented family history of cancer and the patients were not submitted to radiotherapy (7/12). We demonstrated the presence of rare genomic alterations in patients with MPT suggesting their involvement in the MPT development. cnLOH may arise as a new mechanism associated with the risk to develop MPT.

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