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Breast cancer risk and germline genomic profiling of women with neurofibromatosis type 1 who developed breast cancer.

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Abstract

NF1 mutations predispose to neurofibromatosis type 1 (NF1) and women with NF1 have a moderately elevated risk for breast cancer, especially under age 50. Germline genomic analysis may better define the risk so screening and prevention can be applied to the individuals who benefit the most. Survey conducted in several neurofibromatosis clinics in the United States has demonstrated a 17.2% lifetime risk of breast cancer in women affected with NF1. Cumulated risk to age 50 is estimated to be 9.27%. For genomic profiling, fourteen women with NF1 and a history of breast cancer were recruited and underwent whole exome sequencing (WES), targeted genomic DNA based and RNA-based analysis of the NF1 gene. Deleterious NF1 pathogenic variants were identified in each woman. Frameshift mutations because of deletion/duplication/complex rearrangement were found in 50% (7/14) of the cases, nonsense mutations in 21% (3/14), in-frame splice mutations in 21% (3/14), and one case of missense mutation (7%, 1/14). No deleterious mutation was found in the following high/moderate-penetrance breast cancer genes: ATM, BRCA1, BRCA2, BARD1, BRIP1, CDH1, CHEK2, FANCC, MRE11A, NBN, PALB2, PTEN, RAD50, RAD51C, TP53, and STK11. Twenty-five rare or common variants in cancer related genes were discovered and may have contributed to the breast cancers in these individuals. Breast cancer predisposition modifiers in women with NF1 may involve a great variety of molecular and cellular functions.

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