Biomarkers in breast cancer

DELETIONS AT 1P13.3 IS ASSOCIATED WITH SIGNIFICANTLY ADVERSE PROGNOSIS IN BREAST CANCER

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Integrating both chromosomal deletions/amplifications with sequencing alterations is increasingly important in the determination of key prognostic drivers of outcome in breast cancer (Leary 2008, Curtis 2012). We introduce a novel computational approach, Gene Set Outcome Analysis, to determine biologically relevant prognostic gene signatures in regions with frequent deletion or amplification events identified by TCGA. Differential expression of mRNA in these regions is used as a proxy for deletions or amplifications. Gene signatures from each region were evaluated using log-rank test comparing high and low gene expression groups split by cohort mean.

In total, 37,665,870 signatures constrained to 54 deleted and 29 amplified regions were tested for overall survival in Metabric Discovery ER+ (n = 788) resulting in 3,965,340 gene signatures with p-value < .001. The Metabric Validation ER+ cohort (n = 706) was used as a replication study where 2,005,011 signatures have a p-value < .01 in 18 deletion and 7 amplification regions. The best gene signature from each region that validated in the replication study, were evaluated in Super Cohort ER+ (n = 643) for distant metastasis-free survival resulting in 5 deletion and 2 amplification regions with p-value < .01. The best overall gene signature is found in region 1p13-1p21, where samples with lower expression of [GSTM2, CD2, CHI3L2, GSTM3, CELSR2] is associated with poor outcome in Metabric discovery ER+ (HR = 2.7 p = 4.6E-12 q = 2.04E-06), Metabric validation ER+ (HR = 2.4 p = 9.2E-11) and Super Cohort ER+ (HR = 2.2 p = 3.6E-06). The gene signature [GSTM1, CD2, CHI3L2, GSTM3, CELSR2] is equally prognostic indicating the potential importance of aberrations at 1p13.3, specifically Glutathione S-transferase genes (GSTM1-5). The deletion of GSTM1 is common in Caucasian and African-American populations with allele frequencies of 0.225 and 0.407 (Roodie 2004, Sprenger 2000) and is an active research topic in breast cancer. Our findings suggest that deletion of GSTM1, GSTM2 and GSTM3 may result in loss of function that is prognostic. Identification of deletion and amplification events that are prognostic in breast cancer can be used in forward genomics to guide treatment.

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