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Tumor Biology - Tumor Heterogeneity / Molecular Subclassification

High Resolution Comparative Genomic Hybridization (CGH) Indicates That Genomic Profiles Are Very Heterogeneous for HER2 and TOP2A in FISH-Amplified Human Breast Cancer Specimens.

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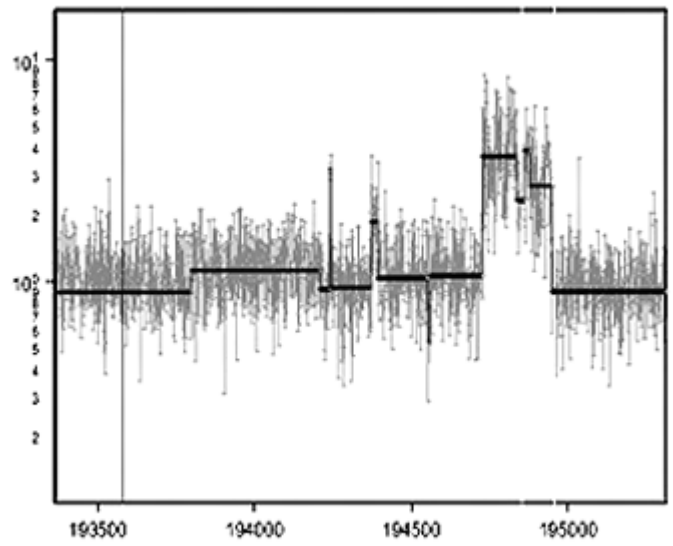
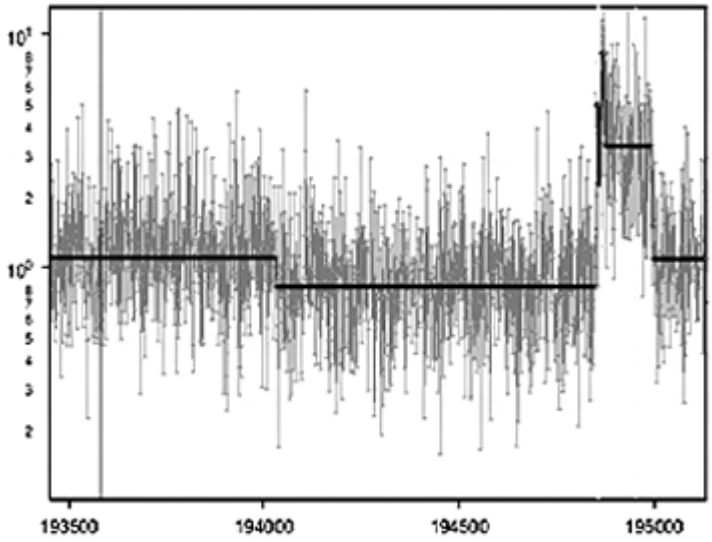
Background: Clinical studies relating TOP2A and HER2 status by FISH and response to specific drug therapies, including anthracyclines, have yielded inconsistent results. The discordance across studies appears to reflect, in part, the well-documented limitations of FISH testing, including the use of large FISH probes to evaluate the relatively small genes of interest. However, it is also likely that the dichotomization of gene status into "amplified" or "non-amplified" categories inadequately describes complex changes across the gene areas of interest. Identification and delineation of specific amplification-deletion patterns in this region may be of significant clinical interest and could provide deeper insight into mechanisms of drug resistance. Consequently, we selected a subset of HER2 and TOP2A amplified specimens (by FISH) from an ongoing study of CGH, and examined individual amplification-deletion patterns by CGH.**Methods:** 471 consecutive, archived, formalin-fixed paraffin-embedded, >1cm, HER2 2+ and 3+ by immunohistochemistry primary breast cancer specimens diagnosed between January 2000 and 2006 were selected. HER2 status was evaluated by FISH at MSKCC and CGH at Cold Spring Harbor Laboratory (CSHL) for all 471 specimens in a double-blinded experiment and clinical correlates evaluated. TOP2A status was also evaluated by FISH at MSKCC and CGH at CSHL in the subset of 64 HER2 2+ by IHC, HER2 FISH-positive specimens. Individual genome profiles by CGH were examined for 20 HER2 and TOP2A FISH co-amplified specimens.**Results:** 45 specimens had results available for analysis, 20 of which were amplified for both HER2 and TOP2A by FISH. By CGH: 6/20 (30%) were not amplified for HER2 or TOP2A; 4/20 (20%) had homogeneous amplification of HER2 and TOP2A; 8/20 (40%) had HER2 > TOP2A amplification; and 2/20 (10%) had TOP2A > HER2 amplification. Individual genome profiles around HER and TOP2A were examined by CGH. Marked heterogeneity was observed across specimens.



MSK197



Conclusions: CGH at the genome level suggests that current dichotomization strategies for classifying HER2 and TOP2A status appear to incompletely describe and represent the heterogeneity of genomic lability in these regions. The dichotomization of gene amplification results by FISH may contribute to the discordance demonstrated in reported some clinical studies. Studies exploring clinical correlates are underway.

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