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Gene amplification in breast cancer – looking for the molecular mechanisms

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Amplification of genes in breast cancer cells was shown to be coordinated in the majority of cases assuming the presence of common undisclosed mechanism underlying intrachromosomal gene amplification process.

Overexpression and amplification of the *HER-2/neu* gene is observed in 20–30% of breast cancer cases and predicts more frequent relapse and shorter survival time. However, the initial events and molecular mechanisms of chromosomal aberrations in the region around *HER2/neu* as well as the precise boundaries of amplified regions remain to be obscure. This study was an attempt to define the boundaries of amplified chromosome 17q12-q21 region around *HER2/neu* gene. Structural peculiarities of amplification boundary regions were investigated by various techniques.

Gene dosage analysis was performed for several genes located around *HER2/neu* gene in 154 breast cancer tissue samples. The copy number of the *ppparbp, her2/neu, znfn1a3 Casc3* and *top2a* genes were analyzed by comparative *TaqMan* real time PCR. Fifty six samples (36 %) were found to be *her2/neu*-amplified ($N_{HER2/neu} \geq 1{,}5$), the boundaries for HER2-containing amplicons were mapped.

Observed results suggest that similar positions of amplified region boundaries in different breast cancer samples are not accidental and may be related with the DNA structural and/or sequence peculiarities of boundary regions. Trying to find "special" sequences at the amplicon boundaries, we performed the analysis of sequence flexibility in the region *TBC1D3– HER2/neu – TOP2A* using the TwistFlex program. The analysis revealed several high flexible sequences in *SOCS7, FBX047, HER2/neu* and *ZNFN1A3* genes. The locations of amplified region boundaries in 30% of cases were inside *ZNFN1A3* gene. Organization of DNA sequence and nucleotide composition of *FlexZNF-1* and *FlexZNF-2* were similar to AT-rich islands of common fragile site (FS). Sequences of *FlexZNF-1* and *FlexZNF-2* have strong potential to form secondary structures according to the analysis by Mfold software (GCG Wisconsin Package^{TM}).

Thus, the analysis of DNA sequence in *TBC1D3–HER2/neu – TOP2A* region revealed the existence of two flexible sequences in the *ZNFN1A3* gene sequence with the strong potential to form stable secondary structures which may affect normal DNA replication at these sites and result in DNA double strand break appearance. The location of *FlexZNF-1* and *FlexZNF-2* strongly coincided with the location of amplified around *HER2/neu* gene fragment boundaries observed by real time PCR analysis.

This observation indicates involvement of *Flex* sites in the process of intrachromosomal DNA amplification.

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