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Our panel of experts highlight the most important research articles across the spectrum of topics relevant to the field of breast cancer management

Breast Cancer Management

Expert panel: Hitoshi Tsuda, National Defense Medical College, Japan

Przybytkowski E, Lenkiewicz E, Barrett MT *et al.* Chromosome-breakage genome instability and chromothripsis in breast cancer. *BMC Genomics* 15(1), 579 (2014).

The array comparative genomic hybridization (aCGH) analysis is usually performed to clarify regional gain, amplification and deletion of chromosomes. In the present study, the authors focused on the putative chromosomal breakpoints that can cause gene rearrangements by the method combining cell sorting and aCGH and assessed the total number of putative breakpoints per genome, designated as breakpoint instability index (BPI) by using Agilent's ADM-2 algorithm. Although aCGH is not very novel technology, the trial to assay chromosomal breakpoints is timely when the concept of chromothripsis is going to be prevailing. Chromothripsis is a form of complex catastrophic chromosome rearrangement, discovered from whole-genome sequencing and defined from four hallmarks – alternating copy number profiles, loss and preservation of heterozygosity, pairing of the breakpoint ends, and clustering of rearrangements [1]. The authors at first documented the prevalence of chromothripsis in breast cancer. Chromothripsis affected various chromosomes in 41% of high-risk tumors. Clinical implication of this phenomenon remains undetermined.

Zhang C-Z, Leibowitz ML, L, Pellman D. Chromothripsis and beyond: rapid genome evolution from complex chromosomal rearrangements. *Genes Dev.* 27(23), 2512–2530 (2013).

Recent technologies of comprehensive genome analyses have discovered a new classes of complex catastrophic chromosomal rearrangement: chromothripsis [2], chromoanasythesis [3], and chromoplexy [4]. They appear to originate from single events that involve hundreds of rearrangements and DNA copy number changes, which is against conventional multistage carcinogenesis models if these classes are key mechanisms for cancer evolution. Chromothripsis sometimes is certainly a mechanism to form high-level gene amplifications and, rarely, oncogenic translocations. However, disruption of chromosomal integrity in chromothripsis and chromoanasythesis should be generally deleterious to the cell, and their breakpoints are clustered in a highly localized manner. Furthermore, the event similar to chromothripsis is reported to occur constitutionally in some patients with congenital developmental disorders. Chromoplexy is characterized by chain translocations involving multiple chromosomes, and unstable chromosomes whereby generated may result in additional chromothripsis. The true incidence of these complex chromosomal rearrangements and their association with molecular carcinogenesis are under investigation.

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- 3 Liu P, Erez A, Nagamani SC *et al.* Chromosome catastrophes involve replication mechanisms generating complex genomic rearrangements. *Cell* 146(6), 889–903 (2011).
- 4 Baca SC, Prandi D, Lawrence S *et al.* Punctuated evolution of prostate cancer genomes. *Cell* 153(3), 666–677 (2013).