**Microchromosomes – a new recurrent genetic element associated with cancer**

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**ABSTRACT**

Genome instability is one of the core hallmarks of cancer. Fragile sites sparsely located across the genome have been identified as a contributing factor facilitating genomic rearrangements. However, many recurrent genomic rearrangements are seldom adjoined by a fragile site, indicating the possibility of yet uncharacterized genetic elements. A recent evolutionary study by Waters et al. highlighted a new genetic element called microchromosome as a building block of many vertebrate genomes. The microchromosomes are now extinct from most modern mammals including the humans. Interestingly, we observe 1-4 microchromosome-like structures in 75% of metaphase cells (n=25) of four in-house head & neck cancer cell lines. Reanalysis of published data confirms recurrent observation of microchromosomes in 58 other commonly used cancer cell lines. Further analysis of published literature using artificial intelligence methods identifies recurrent observation of microchromosomes in the cancer patients (~ 47%) out of nearly 3,000 clinical conditions analysed. Comparative genomic analysis of vertebrate microchromosomes with human genome reveals synteny blocks as a stronger and independent predictor of gene-fusion events compared to the known fragile sites in the human genome. Thus, we propose that developing microchromosomes from the human genome can contribute to the evolutionary adaptation of cancer cells in synergism with conventional chromosome-based aneuploidy. Overall, this study provides the first evidence of yet uncharacterized but critical role of microchromosomes in the genomic instability of cancer and several other diseases.