LETTER

# Distinguishing constitutional and acquired nonclonal aneuploidy

Valind et al. report a significant finding, that constitutional aneuploidy itself does not lead to cancer-like chromosomal instability (CIN) (1). This observation, however, may not fully support the conclusion that aneuploidy does not directly lead to chromosomal instability. There is a significant difference between constitutional aneuploidy and the acquired aneuploidy in cancer, especially when that aneuploidy is nonclonal.

Constitutional aneuploidy is a clonal-chromosome aberration (CCA), whereas many acquired somatic aneuploidies are nonclonal-chromosome aberrations (NCCAs). CCAs significantly differ from NCCAs (2). CIN means decreased stability and increased cell-to-cell variability of karyotypes (both numerical and structural changes) within a given cell population. CIN should be measured by the frequencies of NCCAs. However, in cancer cytogenetics, only the recurrent CCAs (clonal aneuploidy, and clonal structural-aberrations) are systematically studied, whereas NCCAs are considered insignificant background or noise. Accordingly, many researchers have mistakenly used CCAs to measure CIN, while the NCCAs—the key indicators of CIN—are ignored. Recently, studies have demonstrated that the elevated NCCAs can be detected in many disease conditions. NCCAs are clearly linked to transcriptome dynamics, tumorigenicity and drug resistance, and the phase transition (stepwise and punctuated) during cancer evolution (3, 4). Thus, constitutional aneuploidy represents stable CCAs and should not be confused with acquired NCCAs that are frequently detected in cancer cells (4). In the trisomy 21 cellular environment, trisomy 21 is the dominating "normal" genome and any other genomes (including the "normal" 46 XY or XX karyotype) are "abnormal"; the homeostasis of trisomy 21 could actually generate less cellular variation, which explains the resulted low levels of cell-to-cell variations. In addition, only numerical CIN was measured in Valind et al.'s study (1). In contrast, in somatic cells nonrecurrent or stochastic aneuploidy is often associated with different types of CIN, and the resultant cellular variation then provides the necessary condition for cancer evolution. This relationship has been illustrated using in vivo animal models of aneuploidy. The finding that CIN in a stable cancer cell line is higher than in cells with constitutional aneuploidy is explained by the fact that many previous efforts, which characterized cancer cell line stability, were based on CCAs and did not account for NCCAs (2).

Only limited human constitutional aneuploidies are survivable. It is likely that the studied trisomies are less harmful than other trisomies, and it is possible that some aneuploidies and combinations thereof will have more profound effects on CIN than these survivable trisomies when acquired.

Cancer evolution is initiated and promoted by various stresses, genetic and environmental alike, illustrated by the evolutionary mechanism of cancer (4). It is possible that CIN could occur differently in individuals with and without constitutional aneuploidy in response to stress. In addition, individuals with different degrees of chimerism of constitutional aneuploidy should be compared in future studies.

In conclusion, although the specific constitutional aneuploidy alone is not sufficient for generating numerical CIN, it is necessary to examine the impact of nonrecurrent, stochastic aneuploidy for generating all types of CIN (4, 5). At this stage Valind et al.'s article would be more appropriately titled "Constitutional single whole chromosome gain does not in itself confer cancer-like numerical chromosomal instability."

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