Reply to Heng: Inborn aneuploidy and chromosomal instability

It is with great interest that we read the letter by Heng (1), who kindly brought up the interesting topic of nonclonal-chromosome aberrations (NCCAs) in the context of our recent report on the relationship between inborn aneuploidy and chromosome instability (CIN). We fully agree with Heng that NCCAs are better proxies for CIN than clonal-chromosome aberrations (CCAs). In fact, we used the frequency of NCCA as proxy to CIN in our study (2). We also agree that it might well be that aneuploidy causes other forms of genomic instability, but our focus lay on whether aneuploidy per se is a cause of CIN. Measuring instability at the level of single nuclear variants or small segmental changes in single cells is still very much a technical challenge. As pointed out in our report, as well as by Heng in his letter (1), our study does not exclude that certain combinations of CCA may trigger further NCCAs/CIN in specific biological contexts. It is still possible that some trisomies or aneuploidies have a more profound effect on the CIN-phenotype than others. However, this would not be in line with recent work showing that there seems to be a rather uniform cellular response to whole chromosome gains (3). Furthermore, our report included cells from patients with constitutional trisomy 8, a type of aneuploidy common in hematological as well as solid neoplasms. We also included cells with multiple trisomies. Neither trisomy 8 nor such double trisomies are compatible with live birth.

In summary, we showed that none of a fairly large spectrum of whole chromosome gains could automatically destabilize the chromosome number when present in benign human cells. Our findings thereby infer that some change other than initial aneuploidization is necessary to cause CIN. This change may not always be a single gene mutation linked to abnormal chromosome segregation (4), but could also depend on more complex factors, such as alterations in a cell's tolerance level toward changes in chromosome number (5, 6). We believe that the burden of proof in showing that aneuploidy in the form of NCCAs or CCAs causes CIN in an autocatalytic fashion now rests on scientists claiming that this is the case, preferably using a model based on benign human untransformed cells to avoid the many confounding factors of cancer cell lines. We thank Heng for bringing up the interesting topic of NCCAs in cancer, but we still feel that the title of our report is justified by its results.

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5 Torres EM, et al. (2010) Identification of aneuploidy-tolerating mutations. *Cell* 143(1):71–83.
6 Valind A, Jin Y, Gisselsson D (2013) Elevated tolerance to aneuploidy in cancer cells: estimating the fitness effects of chromosome number alterations by in silico modelling of somatic genome evolution. *PLoS ONE* 8(7):e70445.

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The authors declare no conflict of interest.

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