

6. **Genome Instability and Chromosomal Chaos**

1 unit, John Maciejowski, November 23, 2026

Reading catastrophe out of a cancer genome

- Oscillating copy number and clustered rearrangement
- Criteria for calling chromothripsis
- Prevalence across tumor types

Extrachromosomal DNA

- Circular oncogene amplification without a centromere
- Random segregation and non-Mendelian inheritance
- Copy number heterogeneity within a single tumor
- Chromatin accessibility and oncogene output

Routes to oncogene amplification

- Breakage-fusion-bridge amplification
- Chromothripsis followed by circularization
- Interconversion of extrachromosomal DNA and homogeneously staining regions

Selection, therapy, and resistance

- Reversible copy number gain as a resistance mechanism
- Amplification as a therapeutic vulnerability

Chromosomal instability and innate immunity

- Cytosolic DNA sensing by cGAS-STING
- TREX1 and degradation of cytosolic DNA
- Chronic inflammatory signaling compared with acute immune activation
- Consequences for metastasis and immunotherapy response

Open questions in the field

Discussion Paper:

Nathanson DA, Gini B, Mottahedeh J, Visnyei K, Koga T, Gomez G, Eskin A, Hwang K, Wang J, Masui K, Paucar A, Yang H, Ohashi M, Zhu S, Wykosky J, Reed R, Nelson SF, Cloughesy TF, James CD, Rao PN, Kornblum HI, Heath JR, Cavenee WK, Furnari FB, Mischel PS. Targeted therapy resistance mediated by dynamic regulation of extrachromosomal mutant EGFR DNA. *Science*. 2014 Jan 3;343(6166):72-76. doi: 10.1126/science.1241328. Epub 2013 Dec 5. PMID: 24310612.

Background Paper:

Wu S, Turner KM, Nguyen N, Raviram R, Erb M, Santini J, Luebeck J, Rajkumar U, Diao Y, Li B, Zhang W, Jameson N, Corces MR, Granja JM, Chen X, Coruh C, Abnoui A, Houston J, Ye Z, Hu R, Yu M, Kim H, Law JA, Verhaak RGW, Hu M, Furnari FB, Chang HY, Ren B, Bafna V, Mischel PS. Circular ecDNA promotes accessible chromatin and high oncogene expression. *Nature*. 2019 Nov;575(7784):699-703. doi: 10.1038/s41586-019-1763-5. Epub 2019 Nov 20. PMID: 31748743.

Review Paper:

Yi E, Chamorro Gonzalez R, Henssen AG, Verhaak RGW. Extrachromosomal DNA amplifications in cancer. *Nat Rev Genet*. 2022 Dec;23(12):760-771. doi: 10.1038/s41576-022-00521-5. Epub 2022 Aug 11. PMID: 35953594; PMCID: PMC9671848.