A201 · Somatic copy number changes of the active and inactive X chromosome are new genomic hallmarks of cancer

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Somatic copy number alterations (SCNAs) are prevalent in cancer and can drive neoplastic transformation and therapeutic resistance by amplifying oncogenes or inactivating tumor suppressors. SCNAs affecting the X chromosome, especially those in female cancers where SCNAs can occur to either the transcriptionally active X (Xa) or the epigenetically silenced X (Xi), have been largely left out of cancer genomic studies. We developed a computational method that robustly identifies SCNAs to Xa or Xi from a joint analysis of whole genome sequencing and RNA-sequencing data. We applied our method to high-coverage whole-genome sequencing data in >8000 tumors and found that loss of Xi or gain of Xa were recurrent events in cancer. We found that Xi loss is a recurrent feature in all female cancers that is associated with worse progression-free survival in ovarian cancer. We observed that X chromosome dosage is dysregulated through SCNAs on Xa or reactivation of Xi after somatic rearrangements. Somatic mutation analysis found that Xa and Xi are hypermutated relative to autosomes. This result implies that Xa amplification could increase the dosage of somatic mutations on the X chromosome. We found that colorectal cancer cell lines with recurrent, focal amplification of Xa were selectively dependent on OGDH CRISPR knockout and RNAi knockdown. This study shows that X chromosome dosage is dysregulated in cancer. Our results show that this change in gene dosage can be therapeutically targeted in colorectal cancer. Future work will determine how Xi loss leads to worse progression-free survival in ovarian cancer.