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Copy number signatures elucidate mechanisms underlying sarcoma heterogeneity

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Background: Genomic instability is a recognised hallmark of cancer which can lead to numerous copy number driver alterations in a tumour. Sarcomas are a histologically and genetically heterogeneous group of cancers ranging from fusion-driven to karyotypically complex tumour subtypes. The genomic complexity of some of these tumour types has hindered the inference of their evolutionary histories.

Methods: Inspired by recent work on mutational signatures, we utilised a non-negative matrix factorization framework to generate copy number signatures from allele specific copy number profiles in a cohort of 320 sarcomas; 43 chondrosarcoma, 51 dedifferentiated liposarcoma, 17 myxofibrosarcoma, 6 malignant peripheral nerve sheath tumour, 112 osteosarcoma, 10 synovial sarcoma, 52 soft tissue leiomyosarcoma, 27 uterine leiomyosarcoma and 43 undifferentiated pleomorphic sarcoma SNP arrays, as well as 12 low-grade sarcoma whole-genomes. We extended the copy number signatures to a cohort of 53 undifferentiated sarcoma whole genomes to further elucidate some of the mechanisms underlying copy number signatures.

Results: Copy number signatures were identified that indicate chromothriptic events, early near-haploidisation, sequential genome doubling and hypodiploidy. The hypodiploid signature was found to associate with sarcoma subtypes such as synovial sarcoma (90% of samples clustered by largest exposure to this signature) or low-grade sarcomas (67%), whereas signatures of one or two genome doubling events associated with karyotypically complex sarcoma subtypes such as undifferentiated pleomorphic sarcoma (72% and 19% respectively).

Conclusion: Copy number signatures are a powerful tool to deconvolute complex copy number profiles, allowing inference about the life history of a tumour, and evolutionary processes that contribute to karyotypic complexity.