Mechanisms and evolutionary trajectories of complex genome rearrangements in osteosarcoma

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UNPUBLISHED RESULTS – DO NOT POST
Genomic landscape of osteosarcoma

Paediatric and adult osteosarcoma WGS cohorts with clinical annotations

- 128 published WGS data sets from 112 donors
- New data: WGS for 228 tumour regions from 85 donors
- Uniform processing:
  - 356 WGS data sets from 197 cases

Oncogene amplification

- HGOS (141 donors)
- Parosteal (18 donors)
- Other (38 donors)

Bi-allelic inactivation

- Chromothripsis
- WGD

n=41

n=69
Chromothripsis is pervasive across cancer types


- Up to 40% of all tumours
- Nearly ubiquitous in soft tissue and bone sarcomas
- Detected in most osteosarcomas

Cortés-Ciriano et al. Nature Genetics 2020
Cortés-Ciriano et al. Nature Reviews Genetics 2021
Chromothripsis events in human cancers are diverse
Most SVs in osteosarcoma occur as part of chromothripsis events that cannot be explained by known mechanisms.
What mechanisms underpin osteosarcoma genome complexity and karyotypic heterogeneity?
Multi-region WGS of osteosarcomas
Multi-regional WGS of osteosarcomas reveals that subclonal chromothripsis occurs frequently.
Remarkable karyotypic diversity across regions from the same tumour
Which regions of the genome are recurrently affected by rearrangements?

Analysis of SV recurrence in high-grade osteosarcomas

**TP53**
How are TP53 and chr17 rearranged in osteosarcoma?

Canonical chromothripsis only detected in 1 tumour in the entire cohort
How are TP53 and chr17 rearranged?

TP53

High-grade osteosarcomas

Paediatric cases (n=53)

Adult cases (n=88)
Loss-Translocation-Amplification (LTA) chromothripsis drives osteosarcoma evolution
Loss-Translocation-Amplification (LTA) chromothripsis leads to concomitant TP53 loss, oncogene amplification and WGD.
Loss-Translocation-Amplification (LTA) chromothripsis explains the most complex events observed in osteosarcomas.
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Summary

• Osteosarcoma genome complexity and intra-tumour heterogeneity are driven by complex chromothripsis events

• **Loss-Translocation-Amplification (LTA)** chromothripsis is a new rearrangement mechanism underpinning the most complex osteosarcoma genome configurations and causes the expansion of the MRCA in a few cell divisions and intra-tumour heterogeneity

• LTA is recurrent in osteosarcoma but not observed in PCAWG tumours (31 cancer types)
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