Murine osteosarcoma model reproduces the complex genomic rearrangements and heterogeneity of human disease

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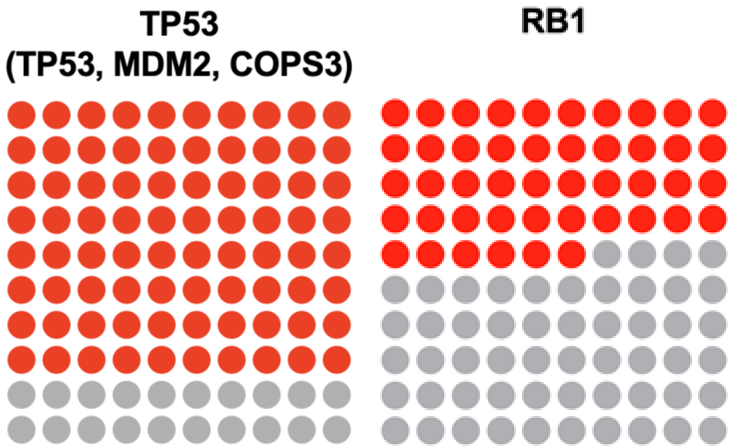
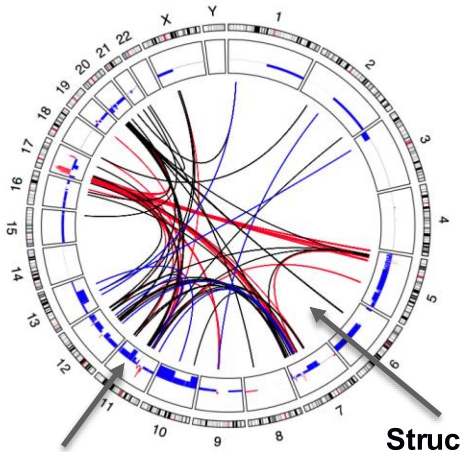
for Integrative Cancer Research at MIT

Genomic Hallmarks of Osteosarcoma

Tumor suppressor loss



Highly rearranged genomes

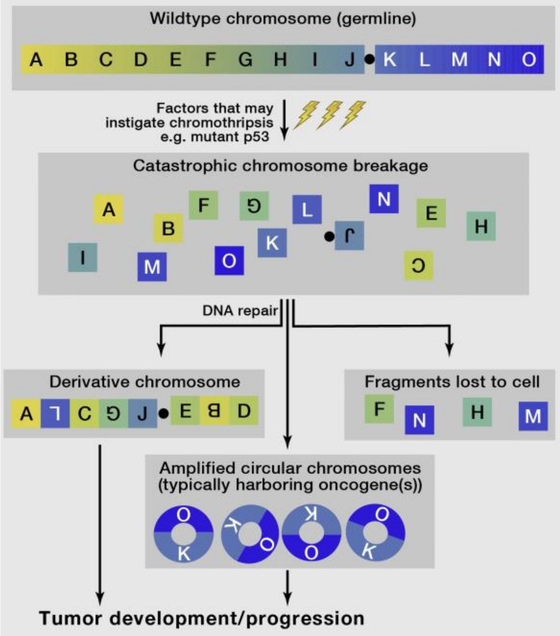


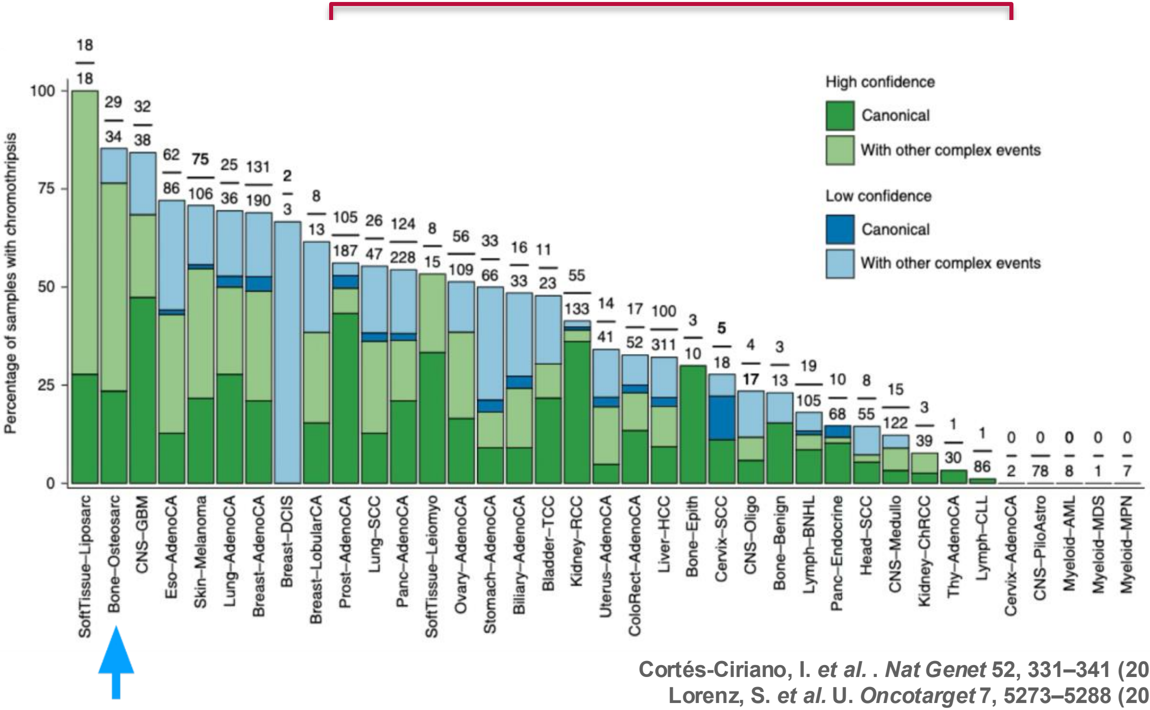
Structural Variants

Copy Number changes
gain / loss

Lorenz, S. *et al.* U. *Oncotarget* 7, 5273–5288 (2015).

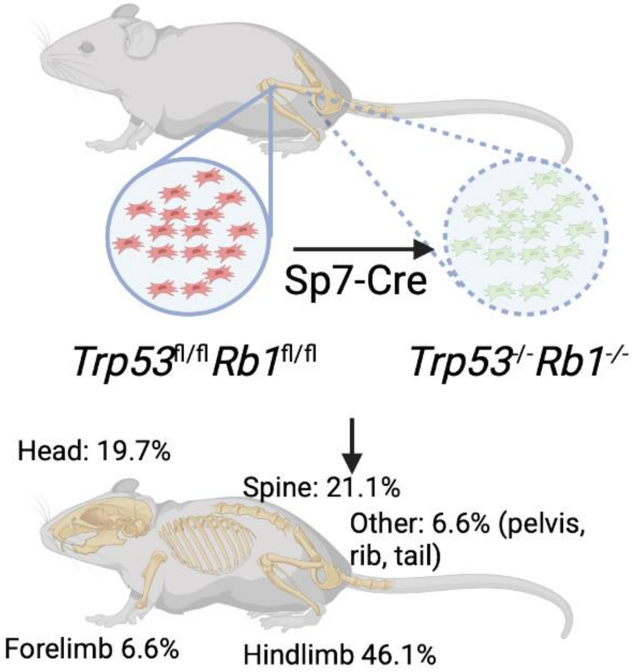
Chromothripsis generates complex genomic rearrangements





Cortés-Ciriano, I. *et al.* . *Nat Genet* 52, 331–341 (2020).
Lorenz, S. *et al.* U. *Oncotarget* 7, 5273–5288 (2015).
Korbel, J. O. & Campbell, P. J. Cell 152, 1226–1236 (2013)

Murine Osteosarcoma reproduces key features of human disease



Sp7-Cre

Trp53$^{fl/fl}$ *Rb1*$^{fl/fl}$

Trp53$^{-/-}$ *Rb1*$^{-/-}$

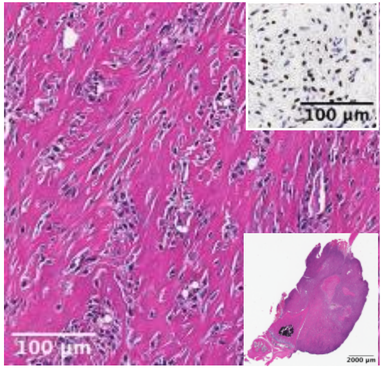
Head: 19.7%

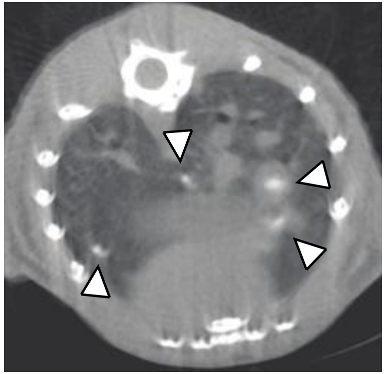
Spine: 21.1%

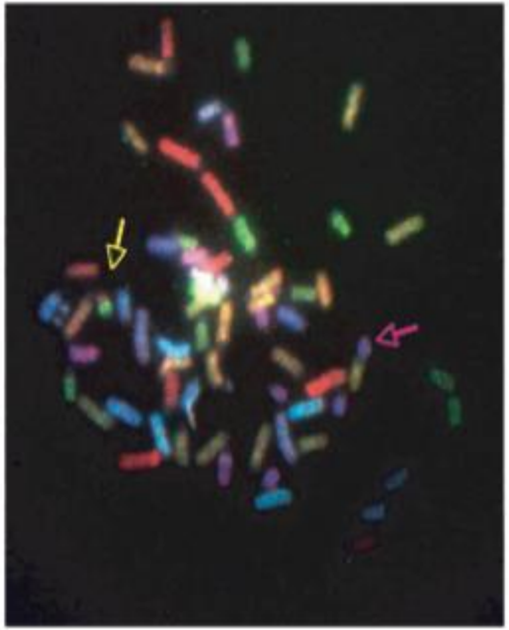
Other: 6.6% (pelvis, rib, tail)

Forelimb 6.6%

Hindlimb 46.1%

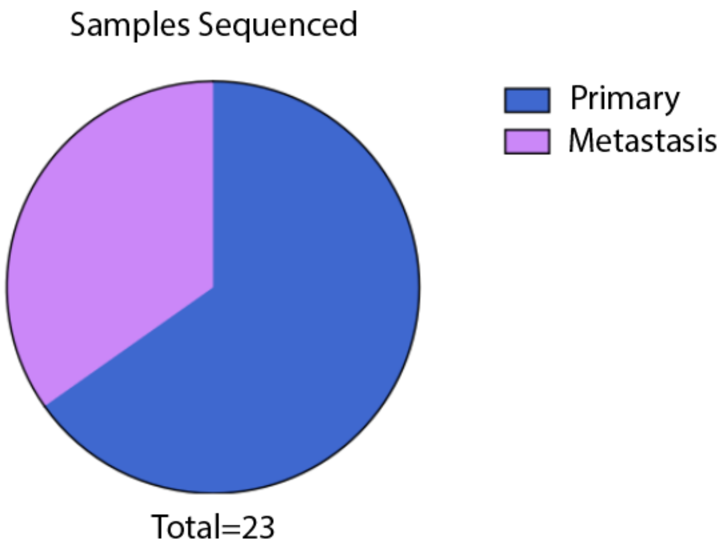


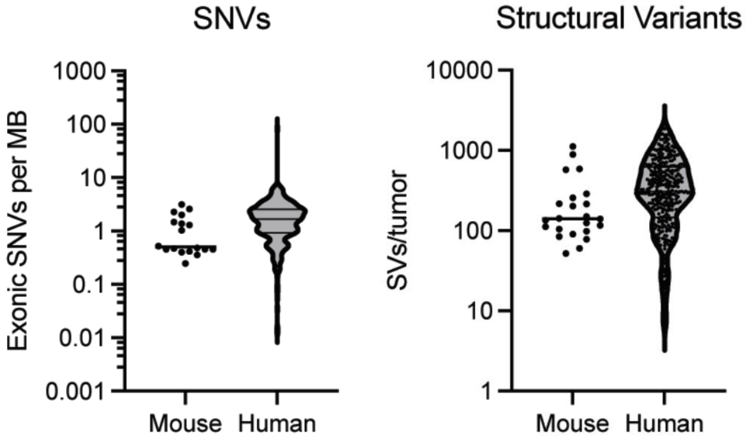




Walkley, C. R. …Orkin, S *Gene Dev* 22, 1662–1676 (2008).

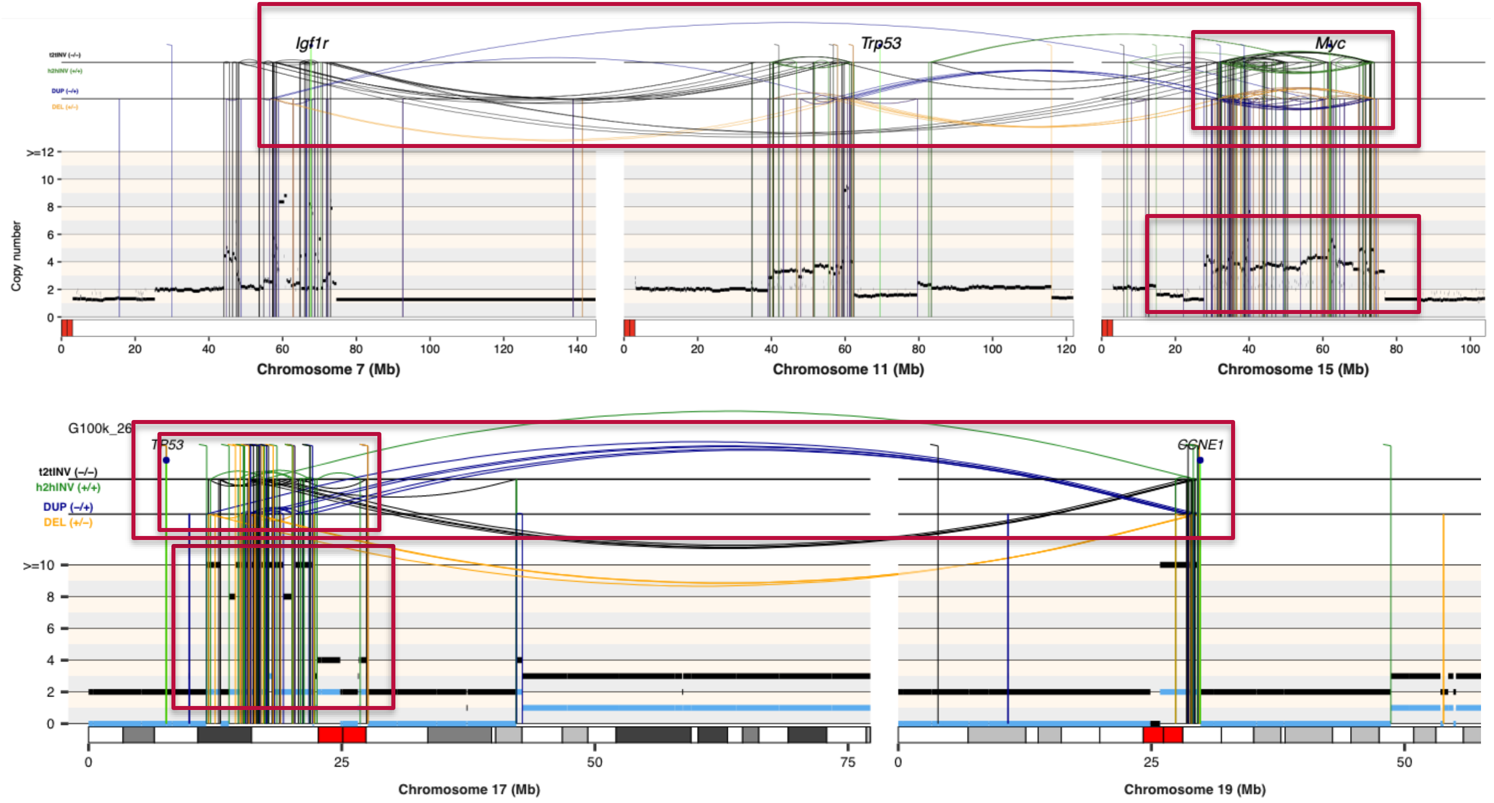
mOS bears a comparable single nucleotide variant and structural variant burden to human disease





	mOS	Human (Valle-Inclan)
TMB (SNV/mb)	0.50 (0.25 - 1.61)	1.67 (0.93 - 2.54)
SVs (/tumor)	140 (98 - 256)	309 (146 - 621)

mOS recapitulates complexity of rearrangements found in human osteosarcoma

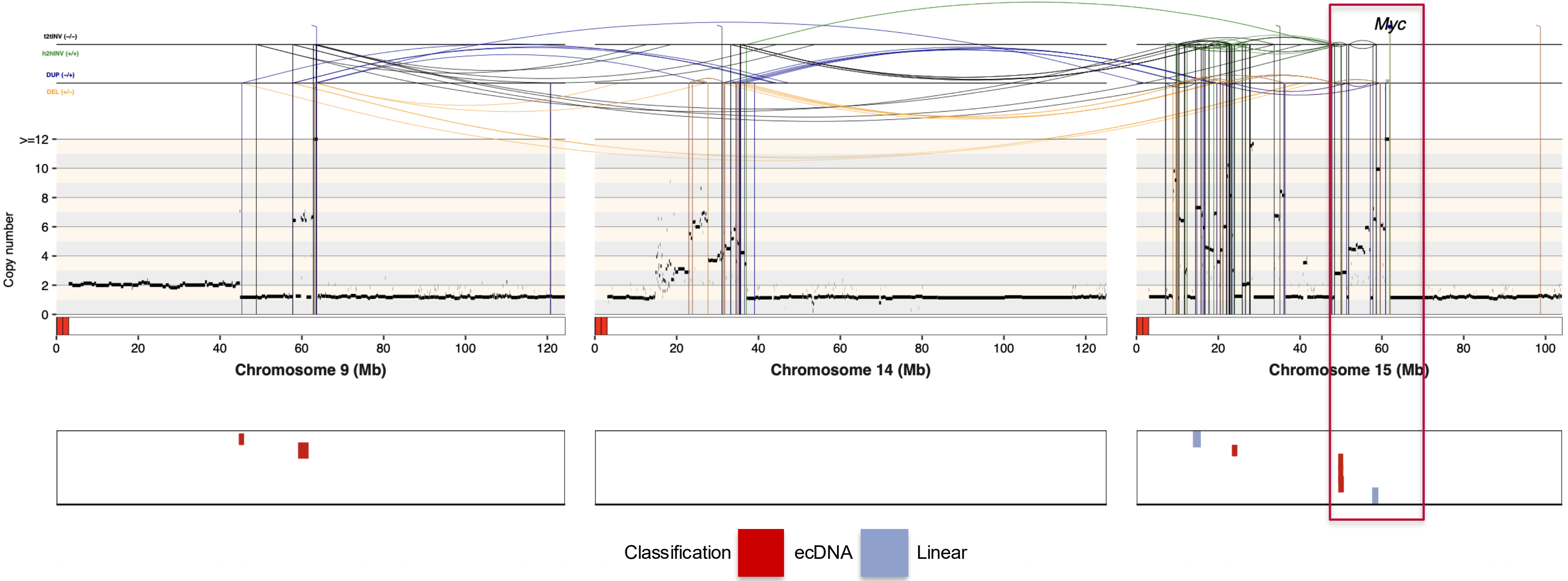


Mouse OS

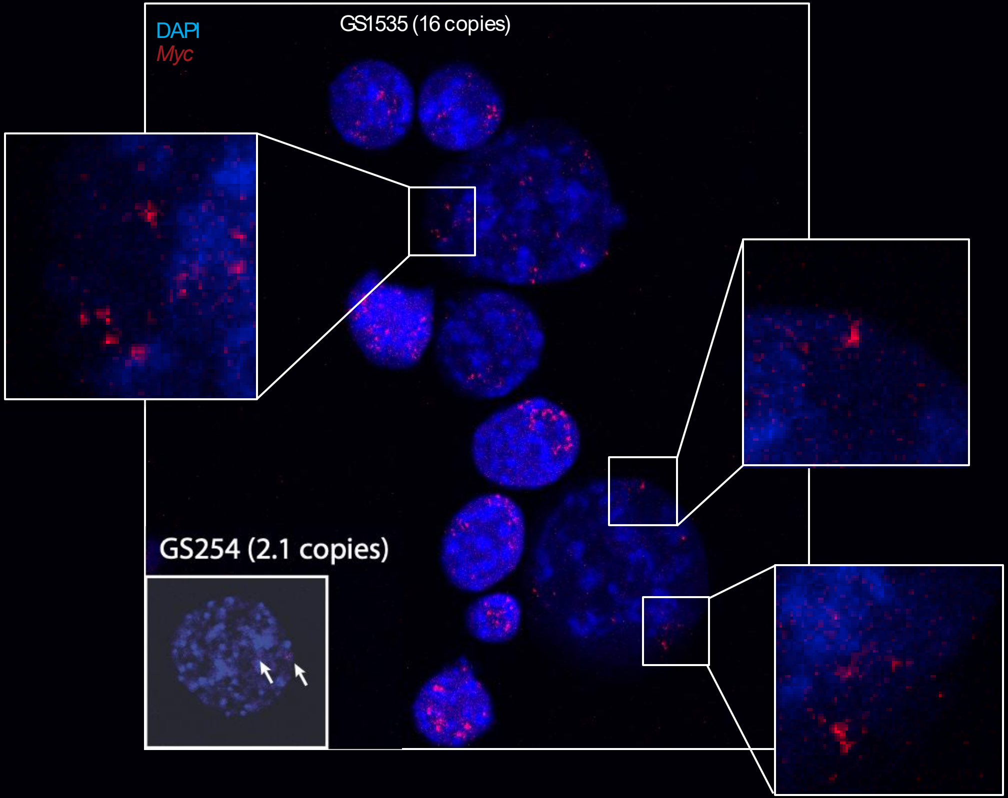
Human OS

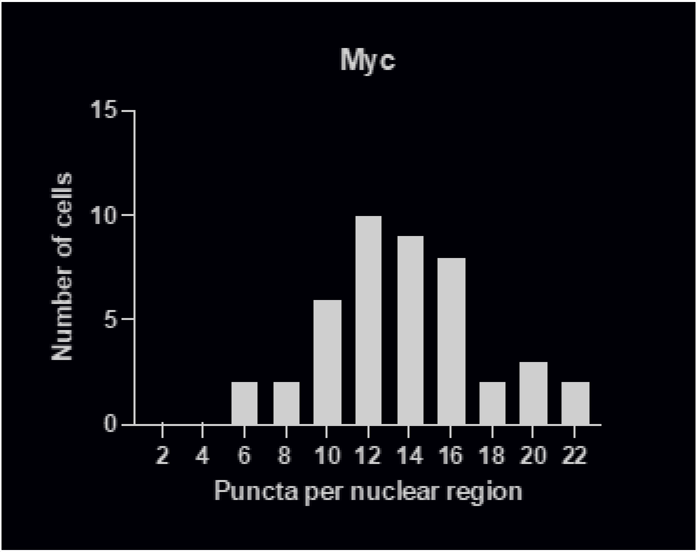
Ianthe Van Belzen

Complex genomic rearrangements can amplify oncogenes



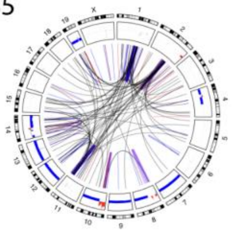
MYC is amplified in ecDNA





mOS generates a range of genomic complexity, including complex genomic rearrangements

1285



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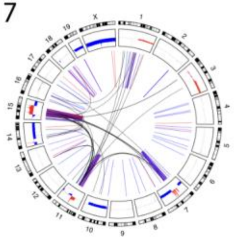

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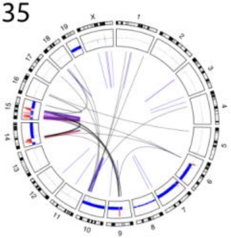

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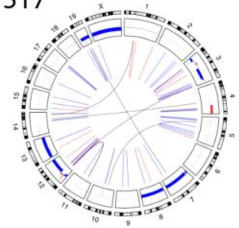
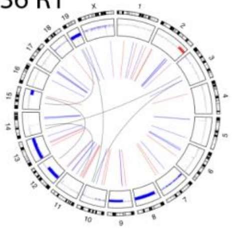


2436 R1



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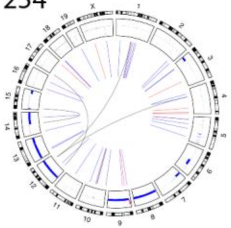

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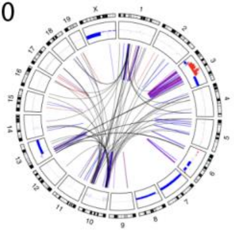

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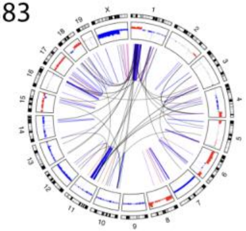

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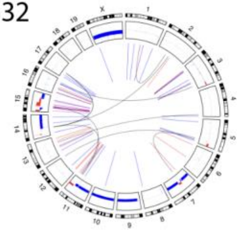

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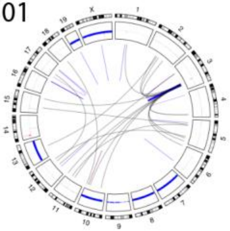

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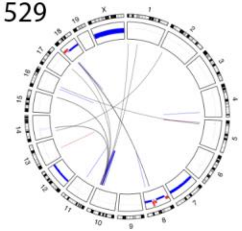
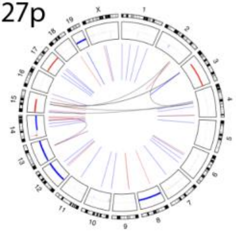


727p

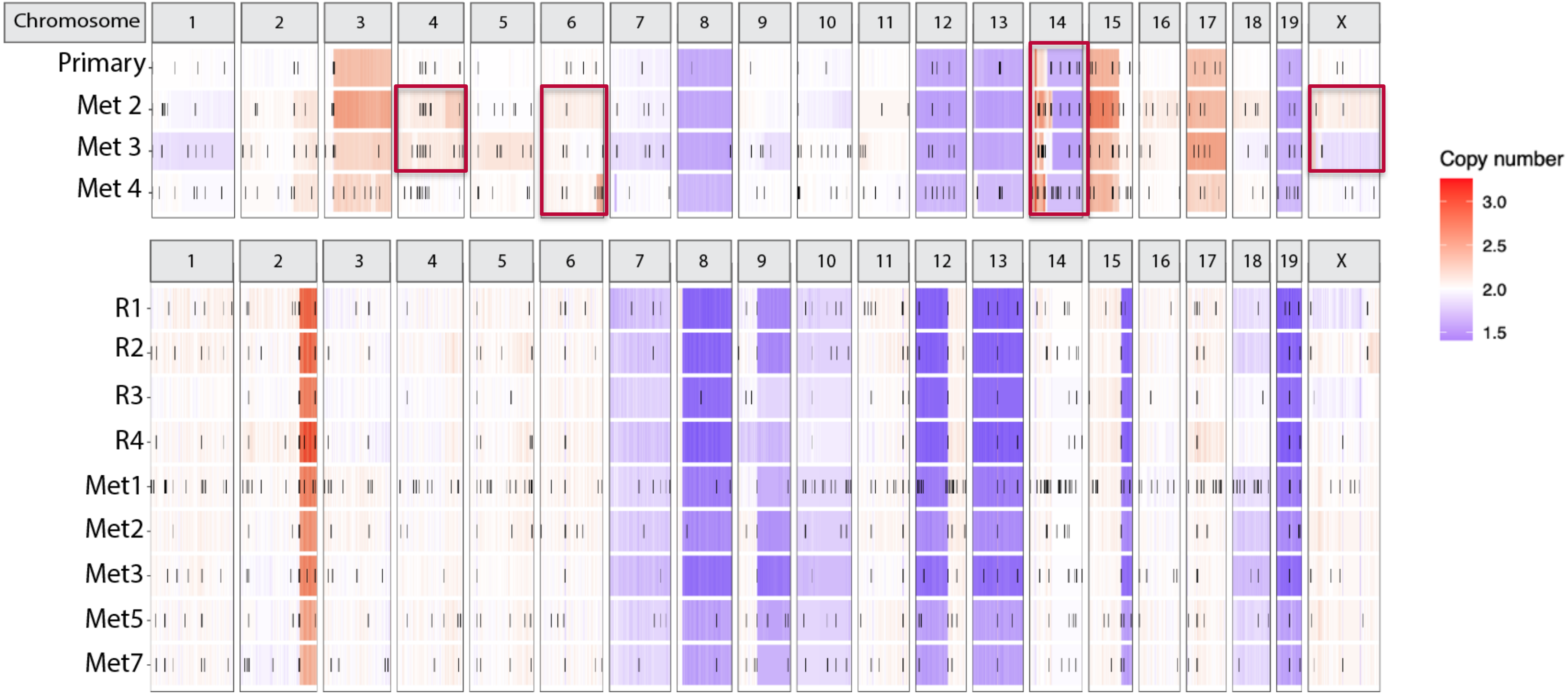


High genomic complexity

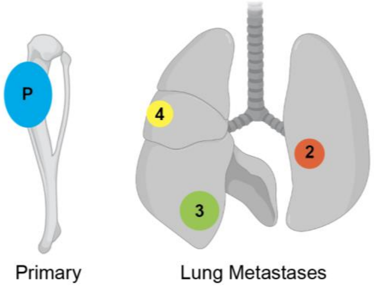
Low genomic complexity

Multi-region sequencing reveals tumor evolution and heterogeneity

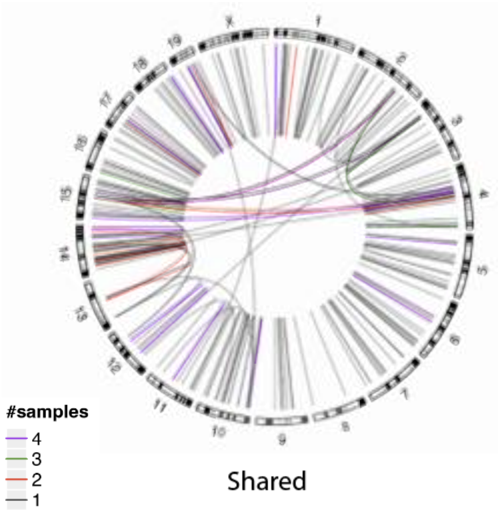
mOS maintains initial karyotype and displays ongoing evolution

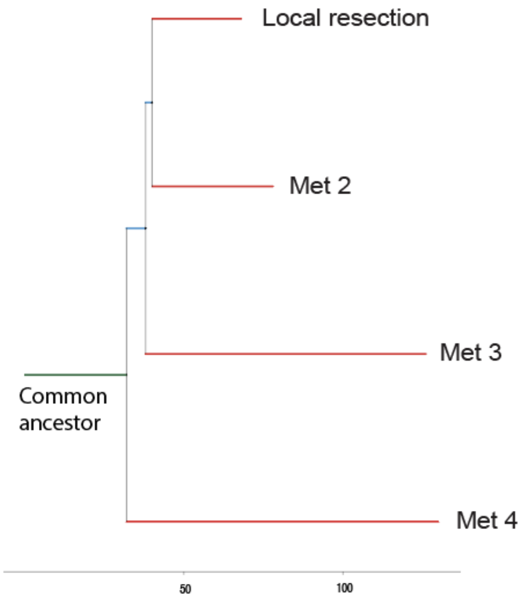


Metastatic murine osteosarcoma can undergo continuous structural rearrangement



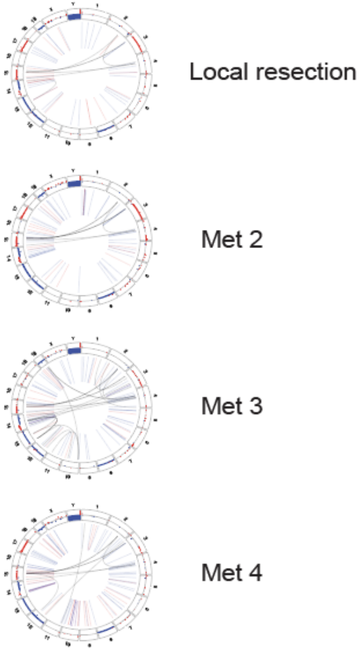
GS727





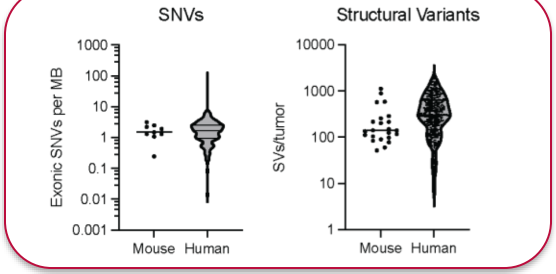
Number of Structural Variants

Clonal: 32, private: 252, subclonal: 40 total: 324

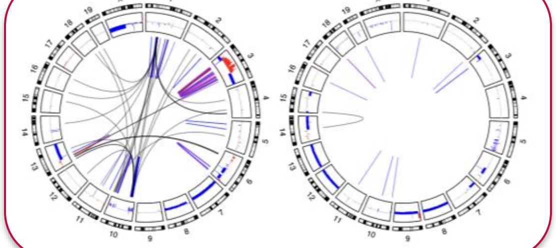


Conclusions from the model

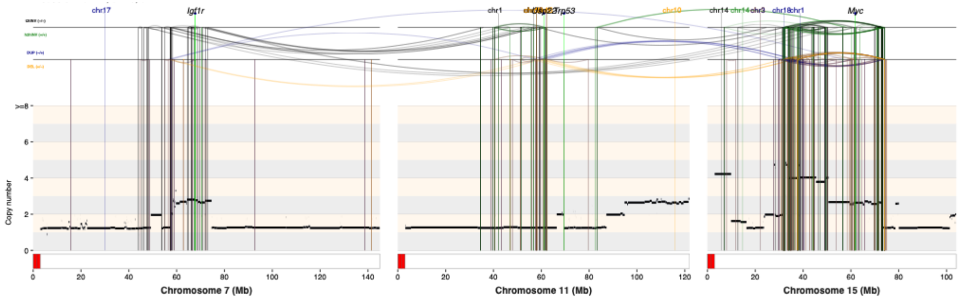
Similar TMB and SV burden to human OS



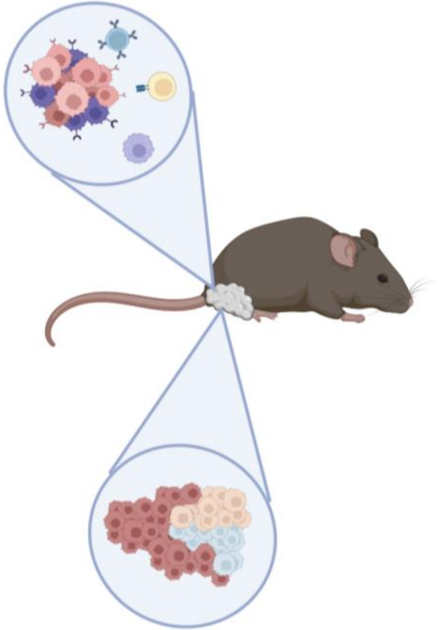
Generates a range of genomic complexity



Mechanisms of genomic instability mirror the human disease



Tool to study chromothripsis and immunogenomics



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