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Spatio-temporal regulatory landscape of sex-determination



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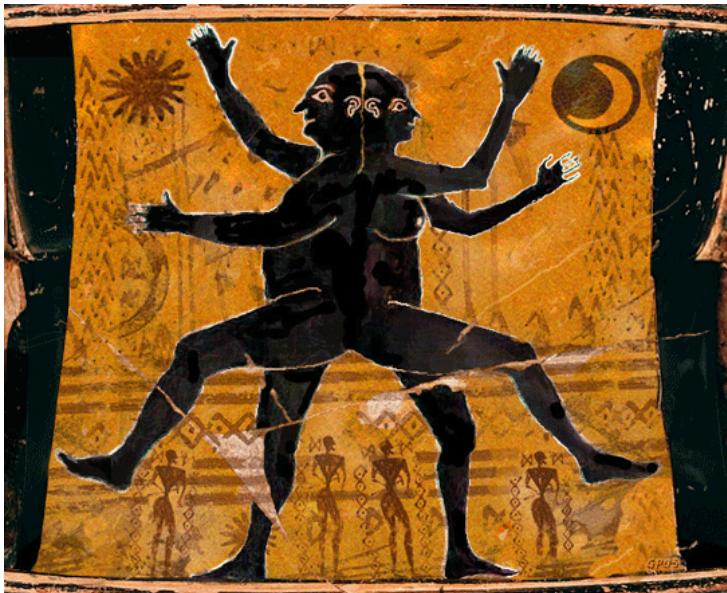
CNAG-CRG · ICREA

BioRxiv 2022

<http://marciuslab.org>
<http://3DGenomes.org>
<http://cnag.crg.eu>

Sex determination: a 3,000 year-old enigma

Mythology



Hermaphrodite primeval men

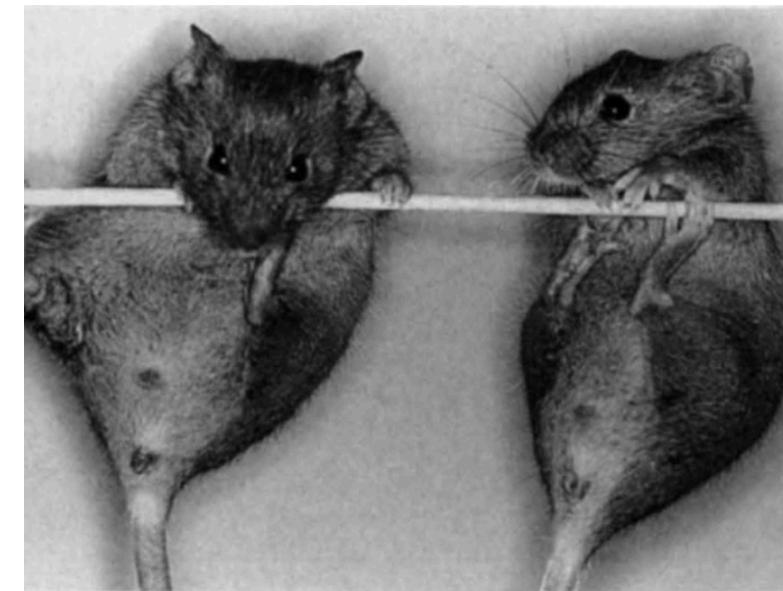
Plato's symposium, 385-370 BC

Theories



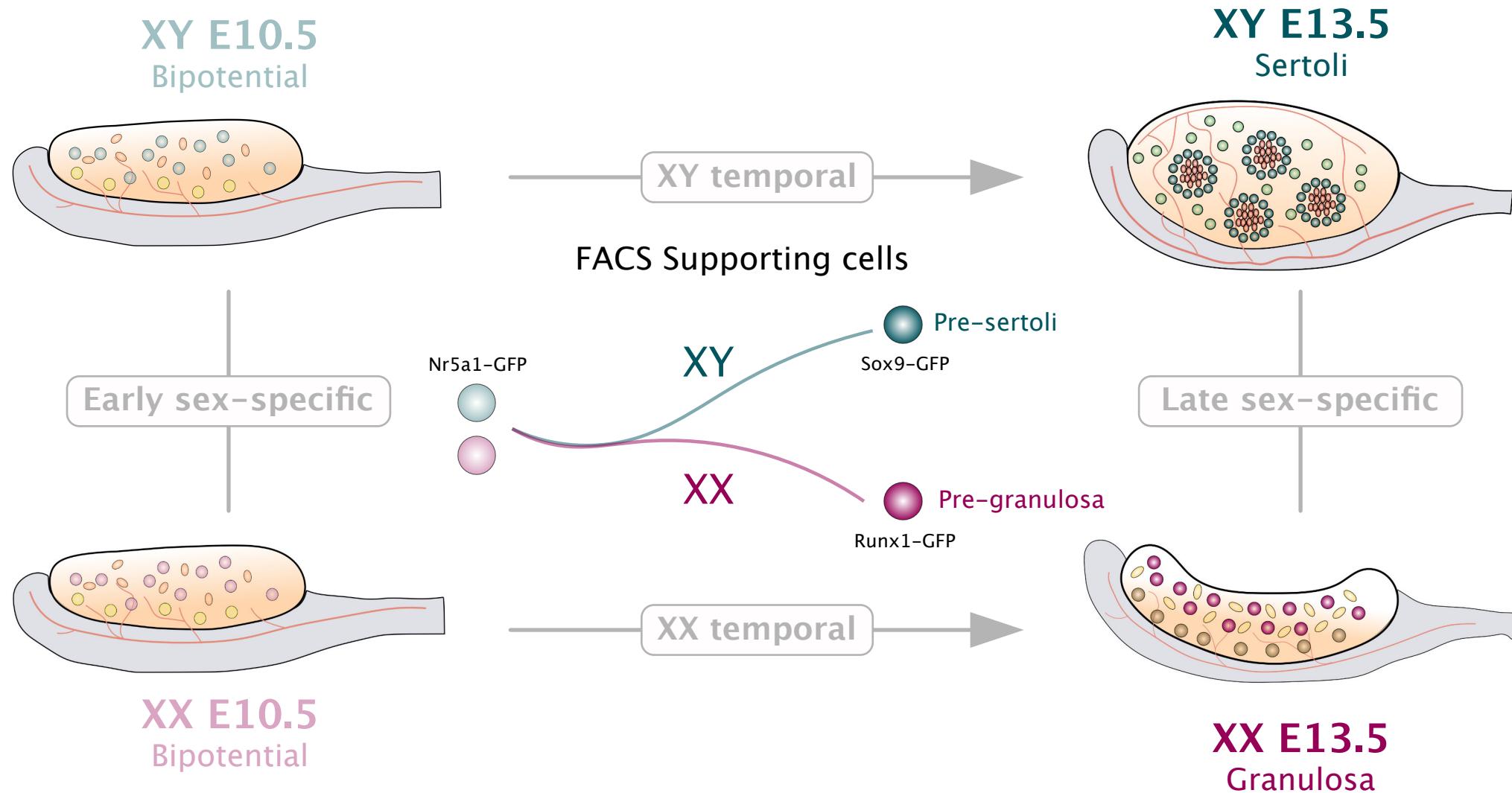
Left-right theory
Alexandrian manuscripts, 1st cent. BC

Genetics

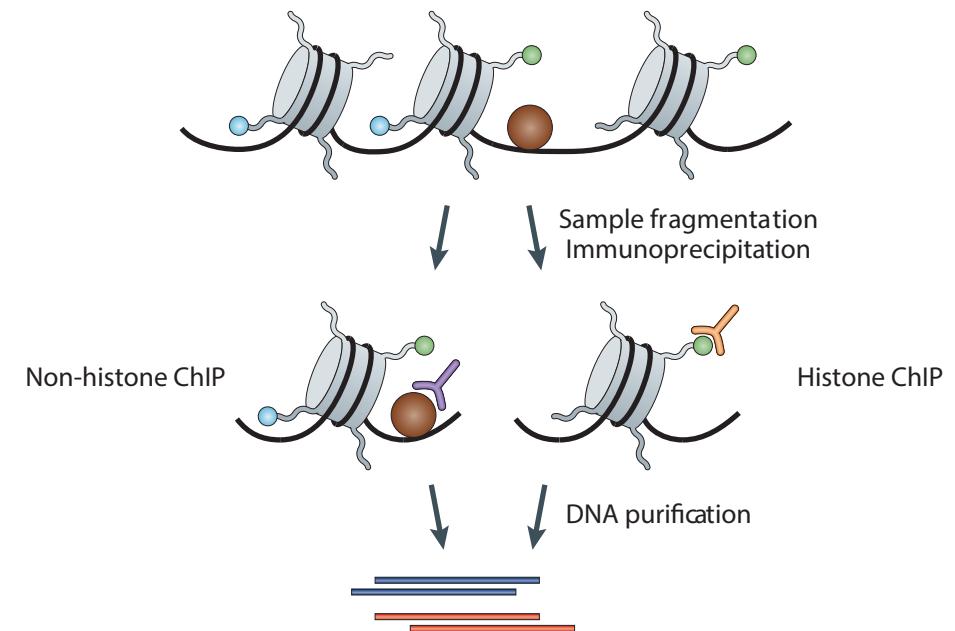
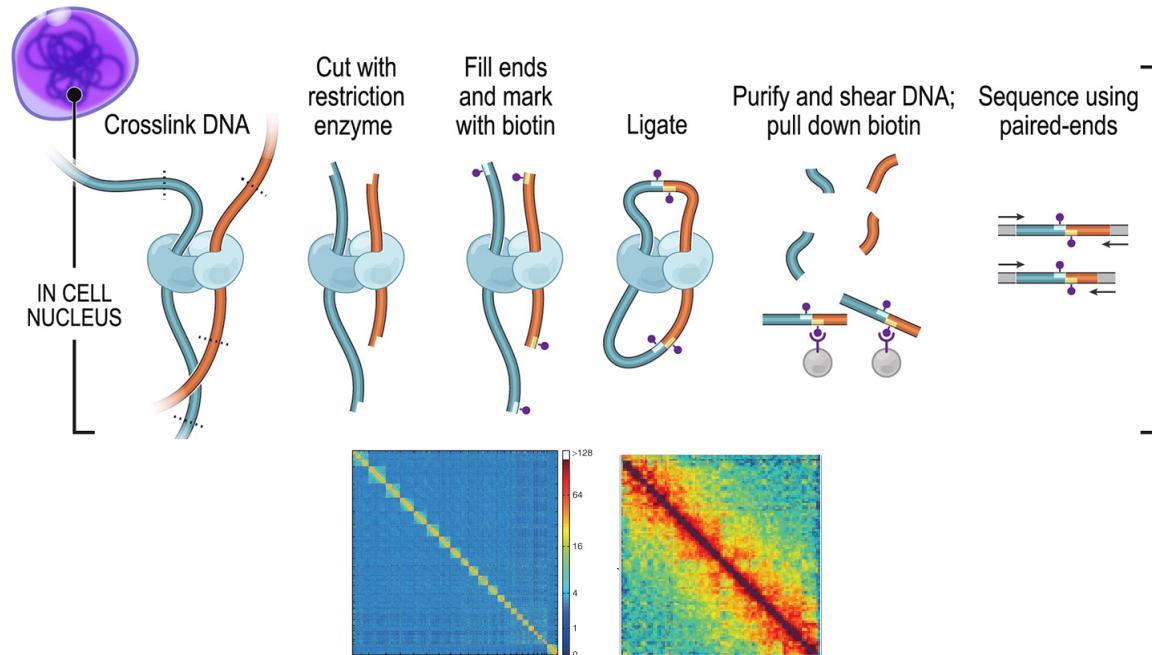


Discovery of *Sry* gene
Koopman et al., Nature, 1991
(Goodfellow & LovellBadge labs)

Sex-determination as a model for “bipotential” commitment



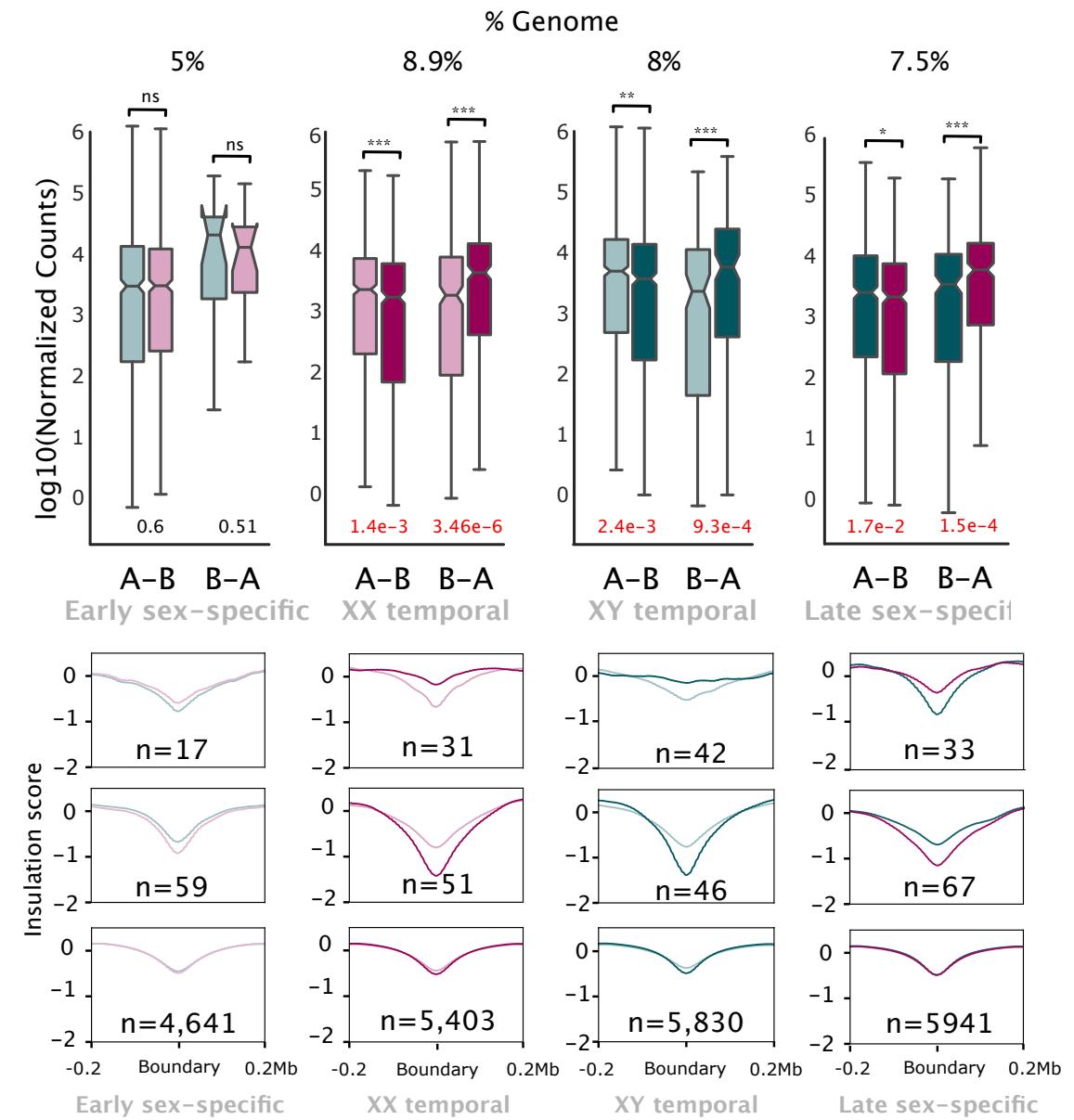
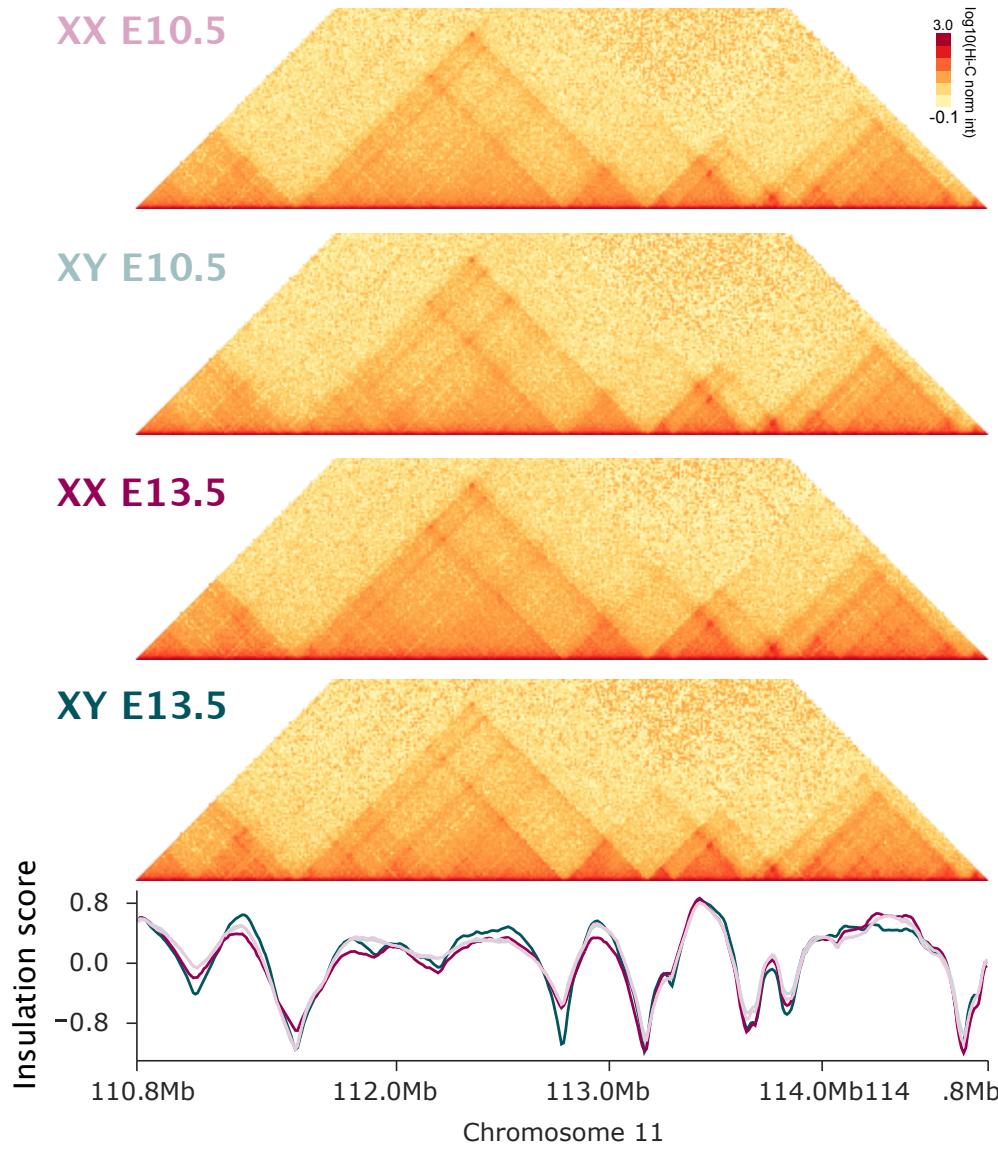
Hi-C & ChIP-seq

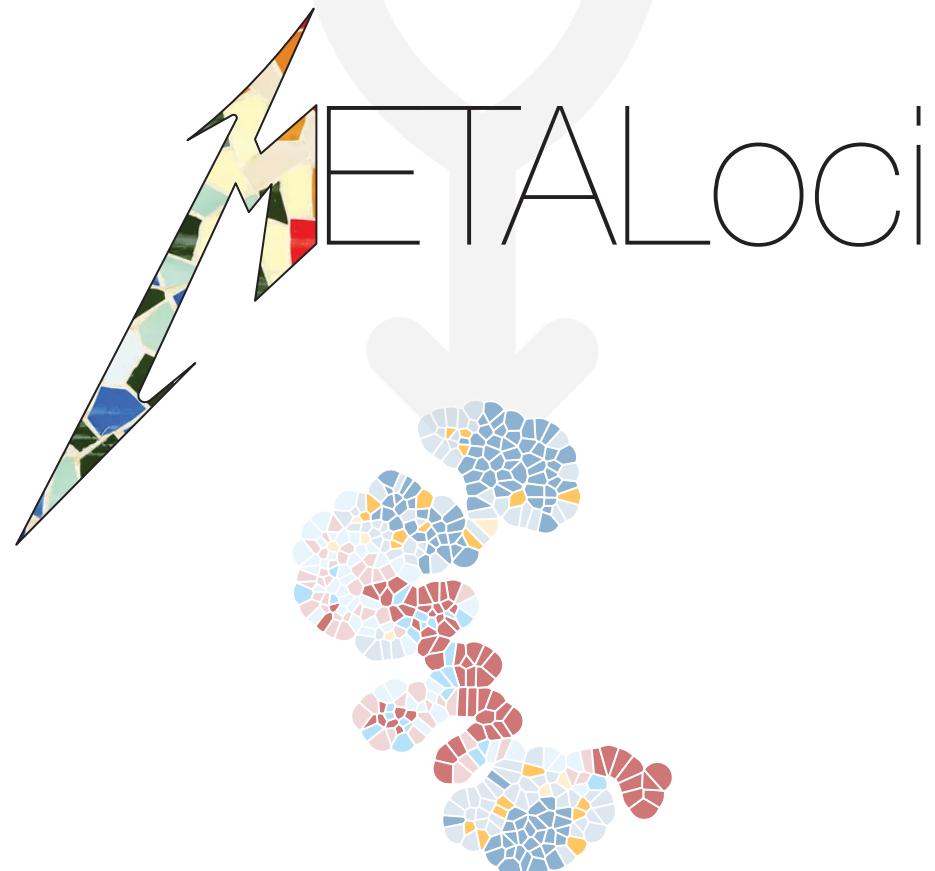
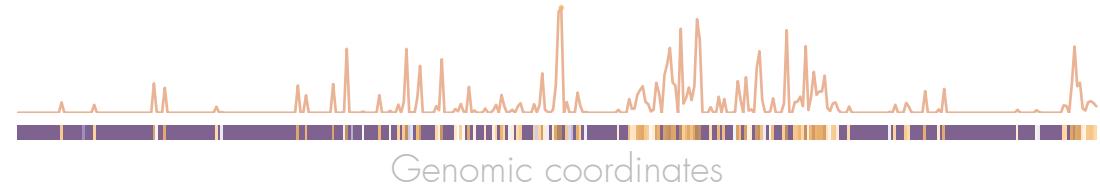
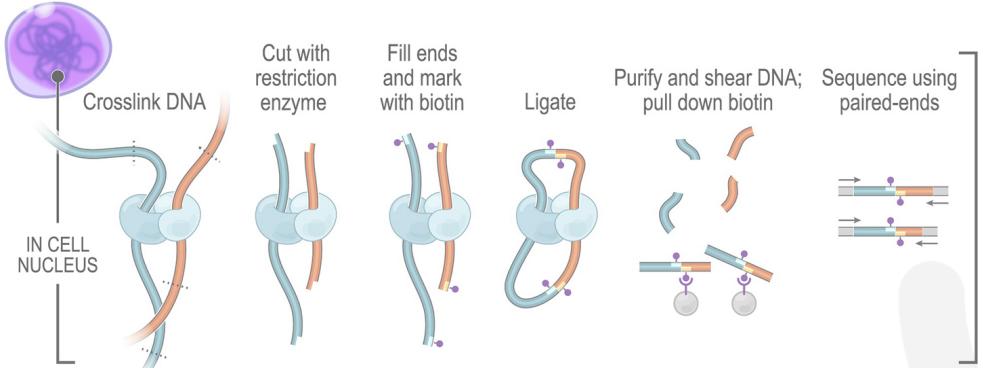


Dekker, J., Rippe, K., Dekker, M., & Kleckner, N. (2002). *Science*, 295(5558), 1306–1311.
 Lieberman-Aiden, E., et al. (2009). *Science*, 326(5950), 289–293.

Solomon, M. J., Larsen, P. L. & Varshavsky, A. (1988) *Cell* 53, 937–947.
 Park, P.J. (2009) *Nature Reviews Genetics* 10, 669–680.

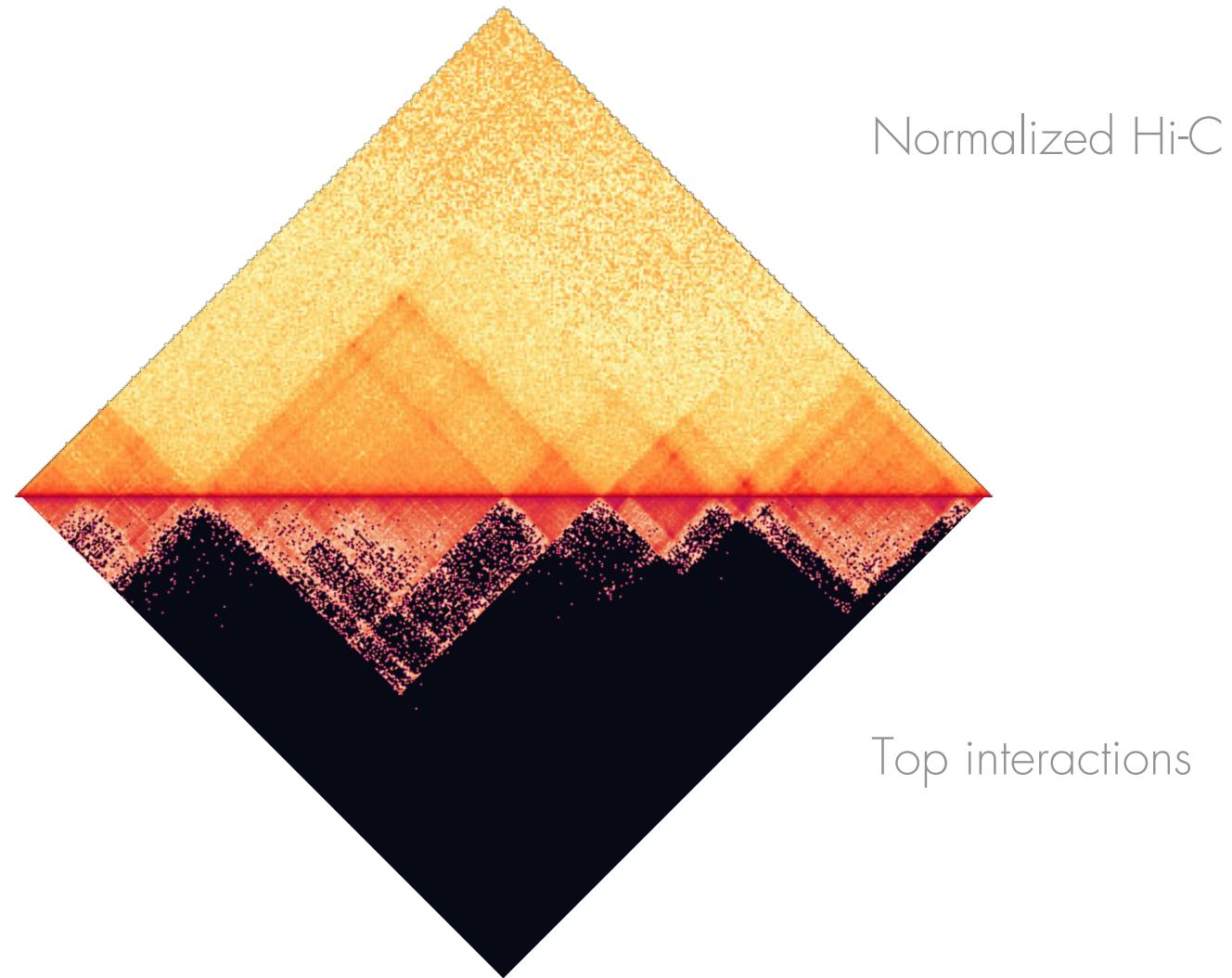
No major structural (apparent) differences





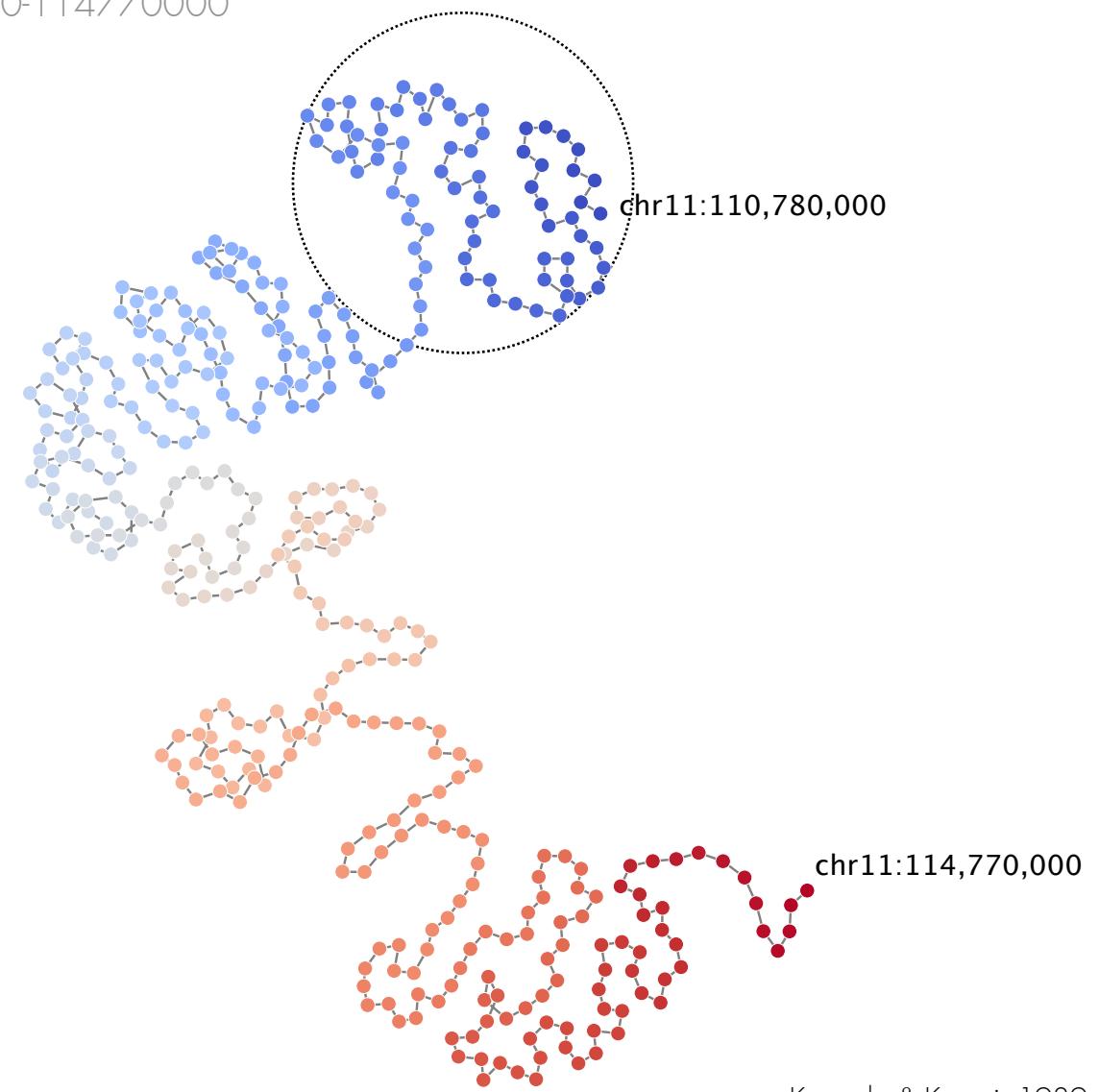
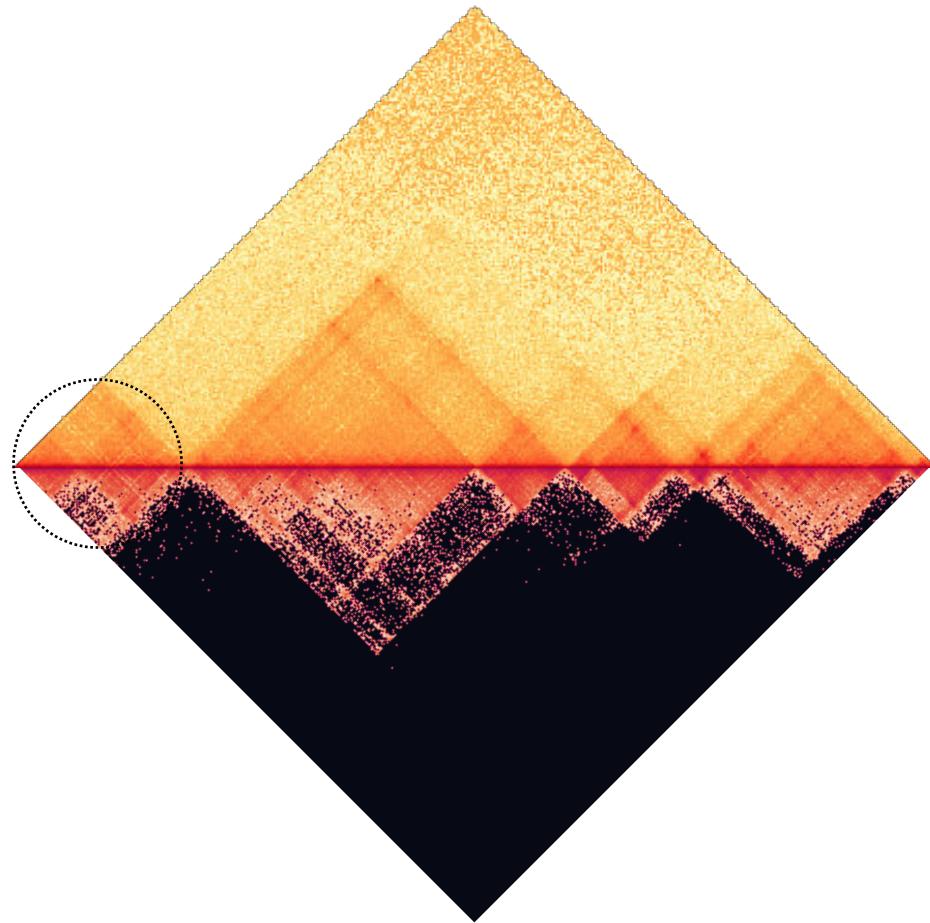
Hi-C normalization and interaction selection

chr11:110780000-114770000



Spatial lay-out of significant interactions

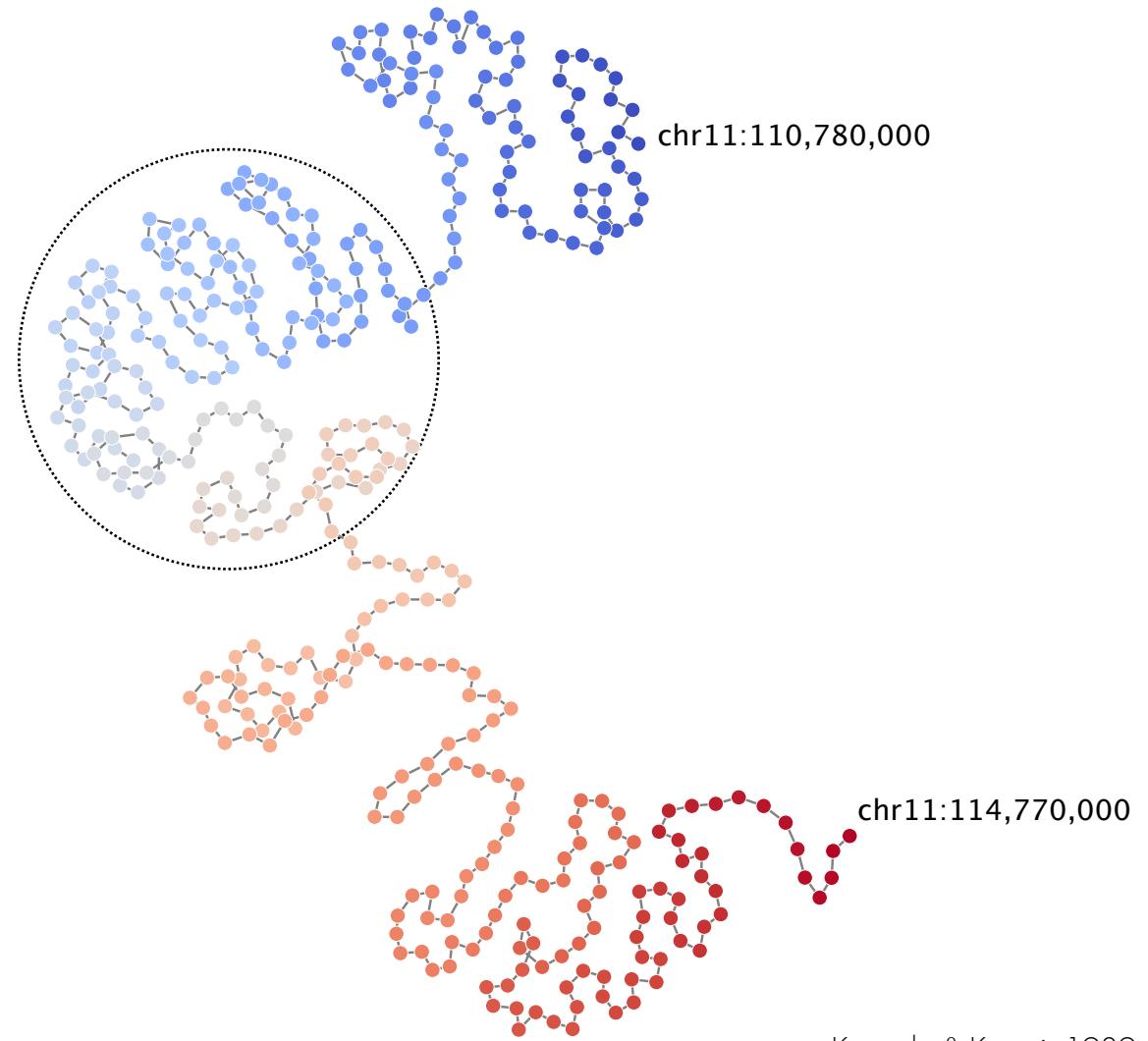
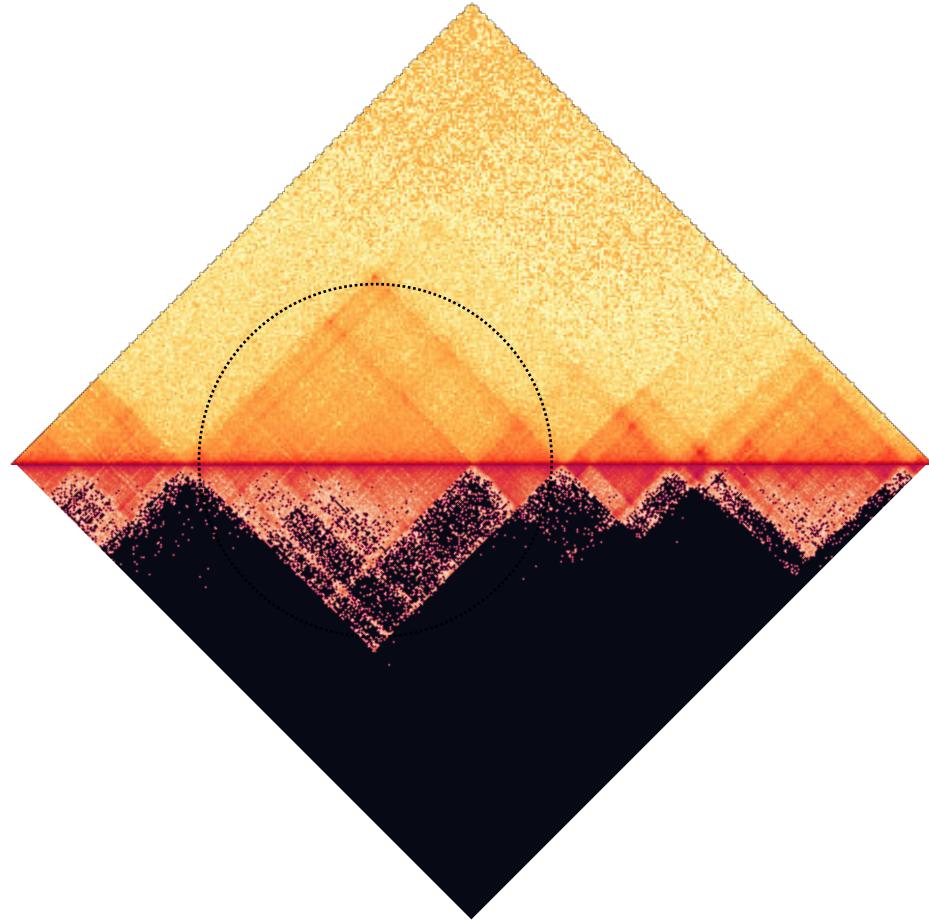
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Kamada & Kawai, 1989

Spatial lay-out of significant interactions

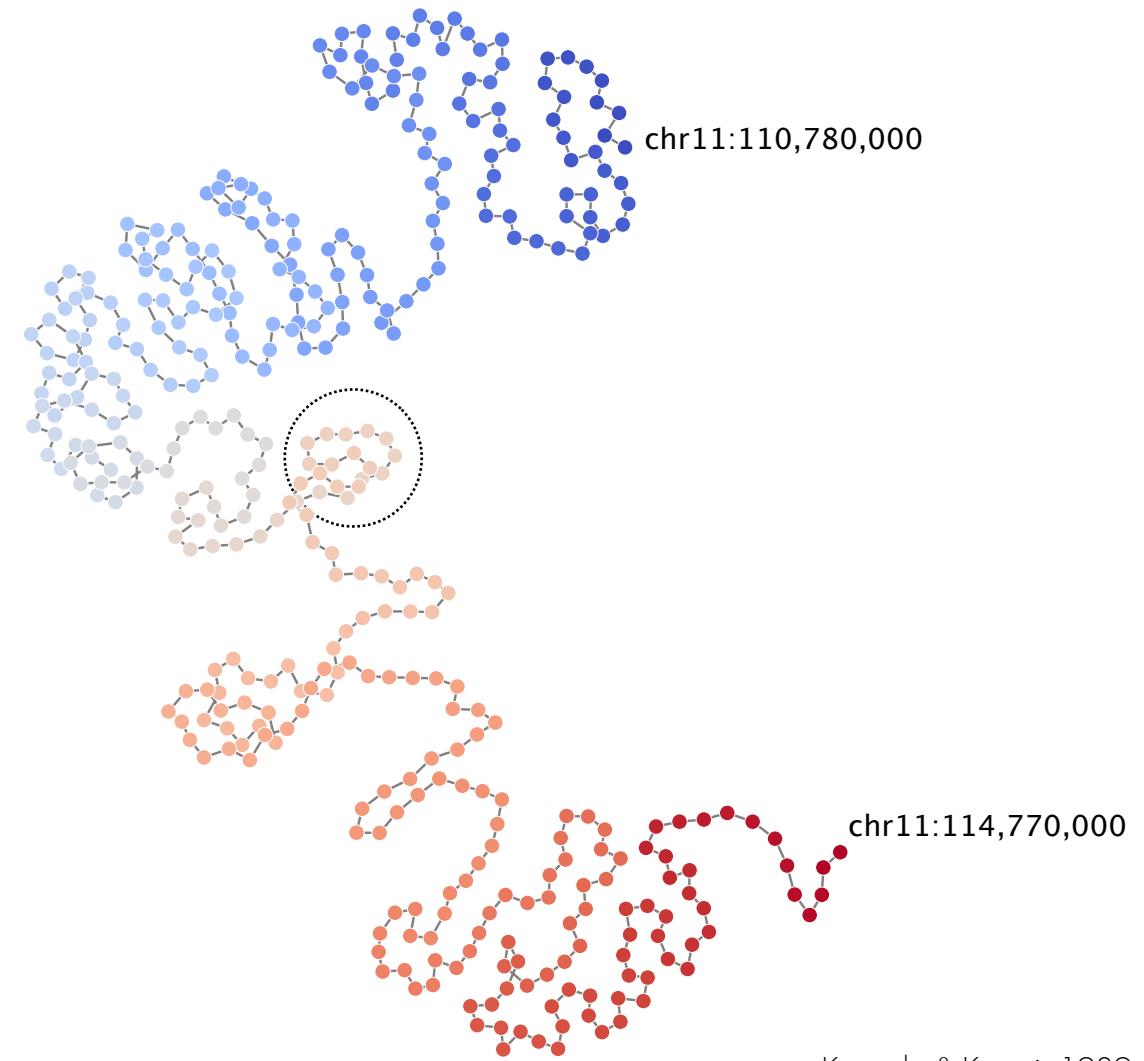
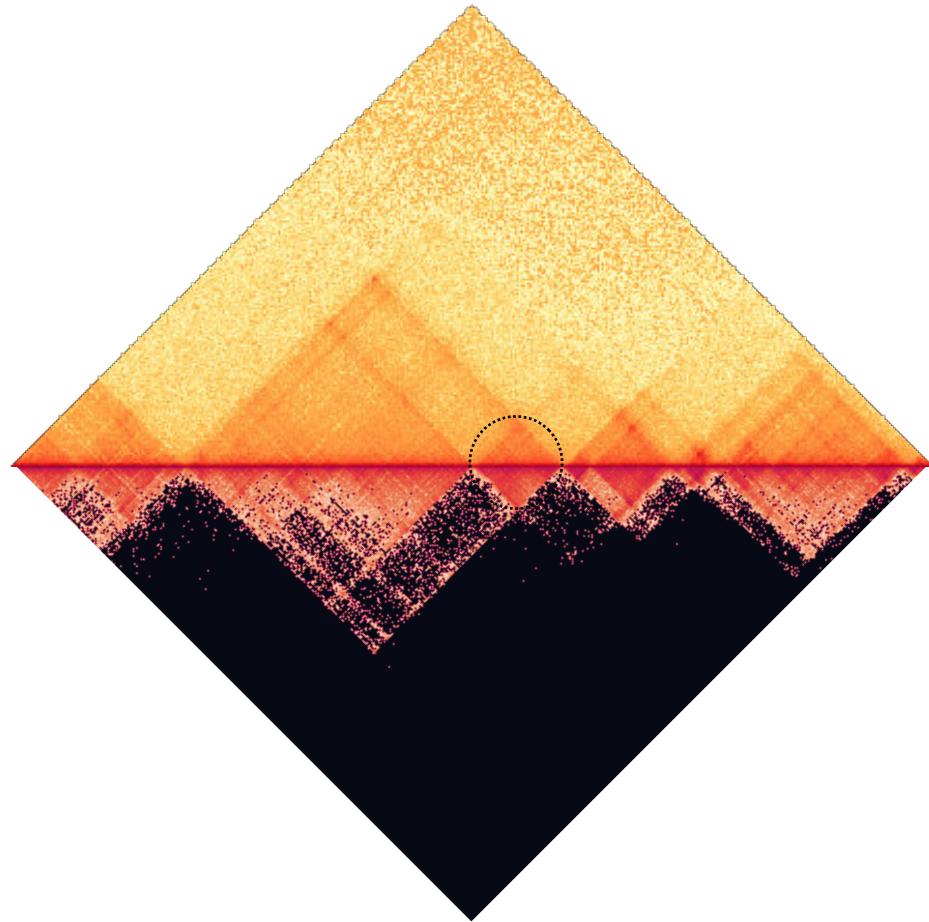
chr11:110780000-114770000



Kamada & Kawai, 1989

Spatial lay-out of significant interactions

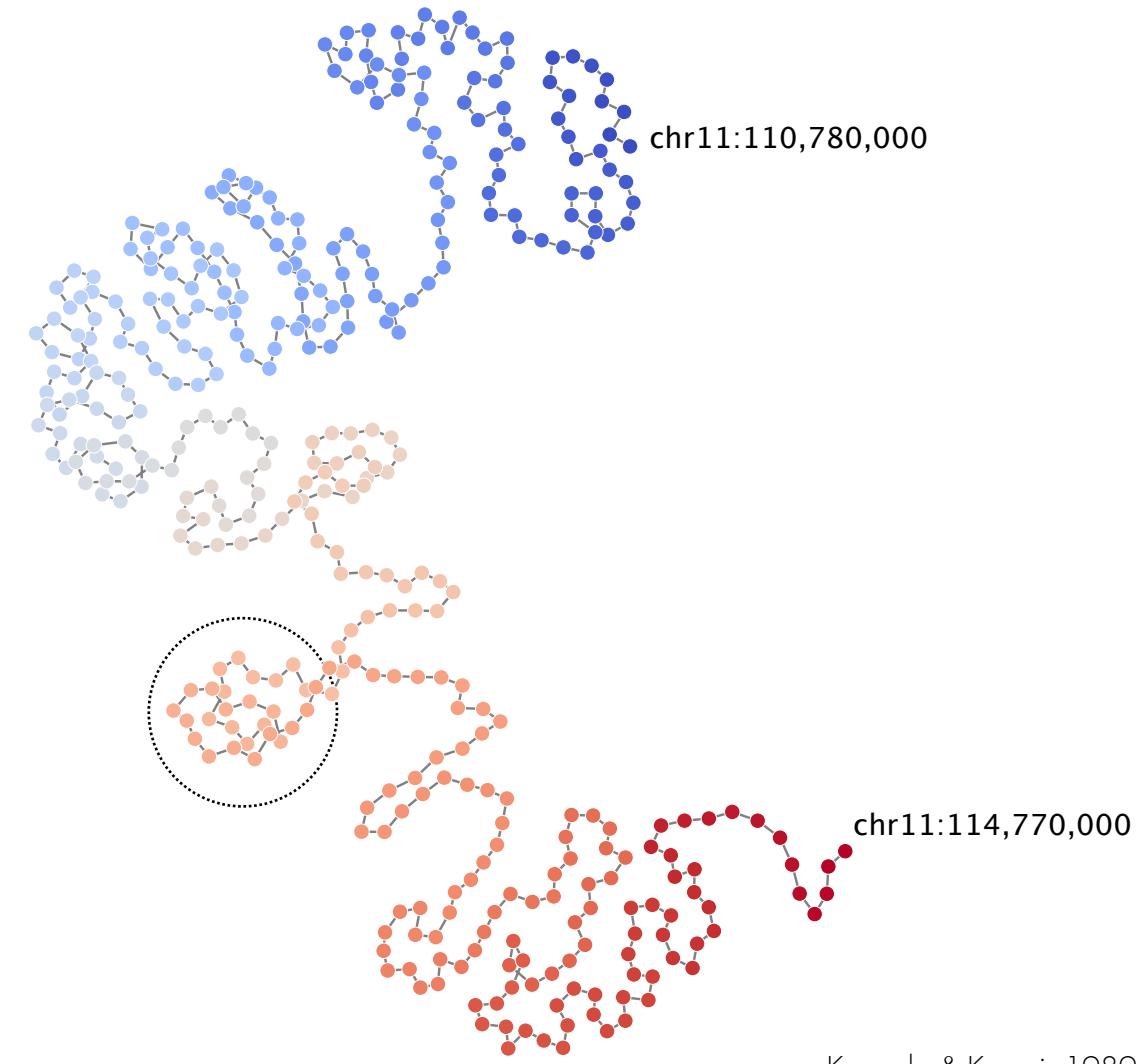
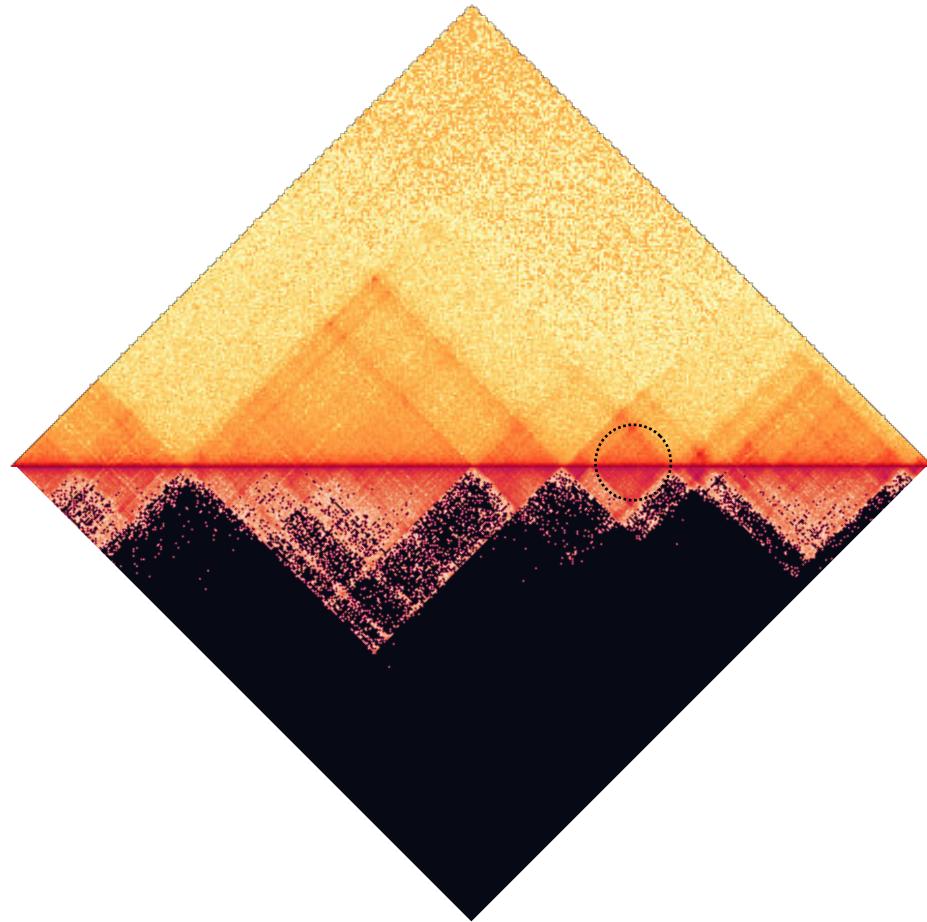
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Kamada & Kawai, 1989

Spatial lay-out of significant interactions

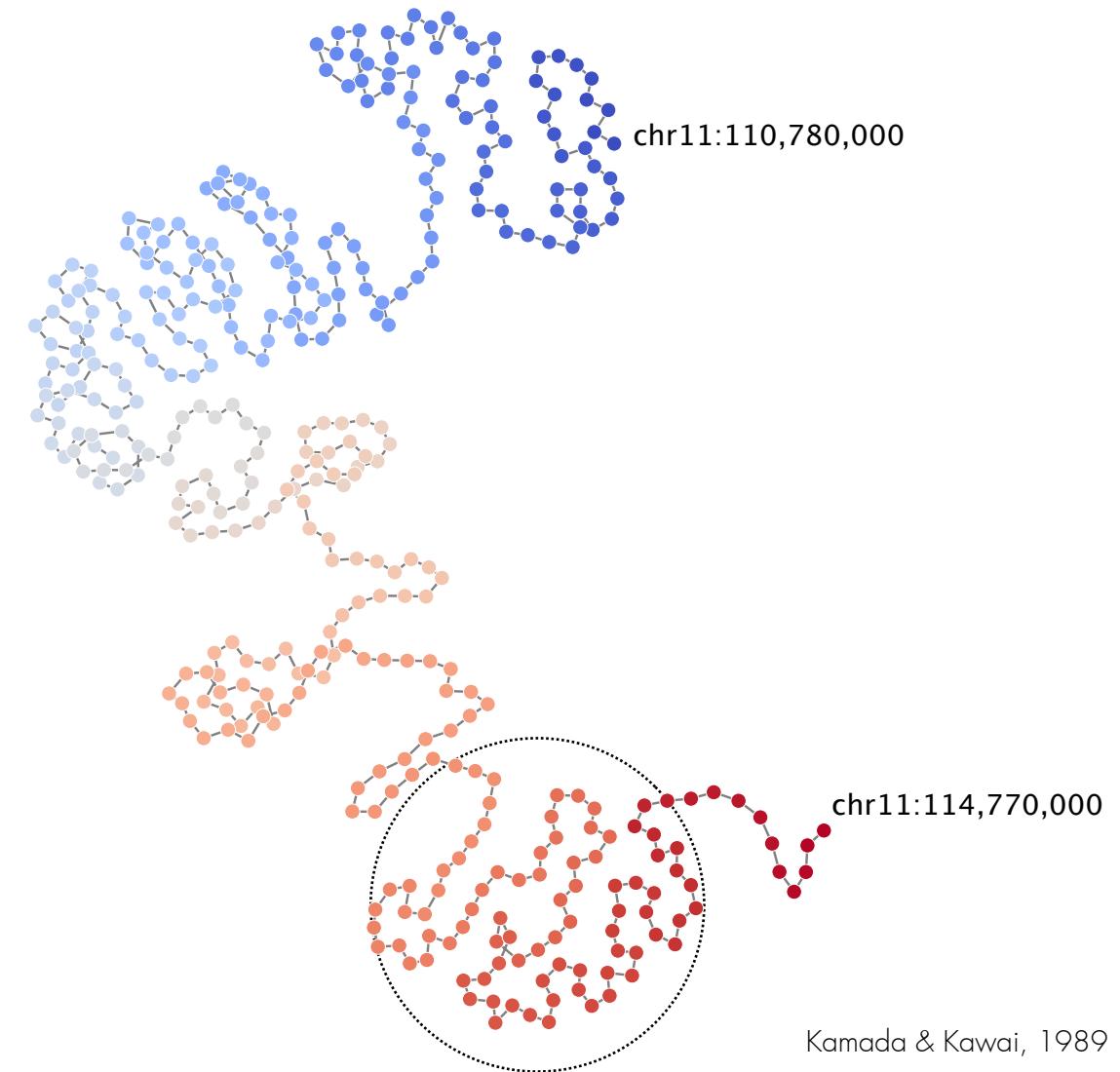
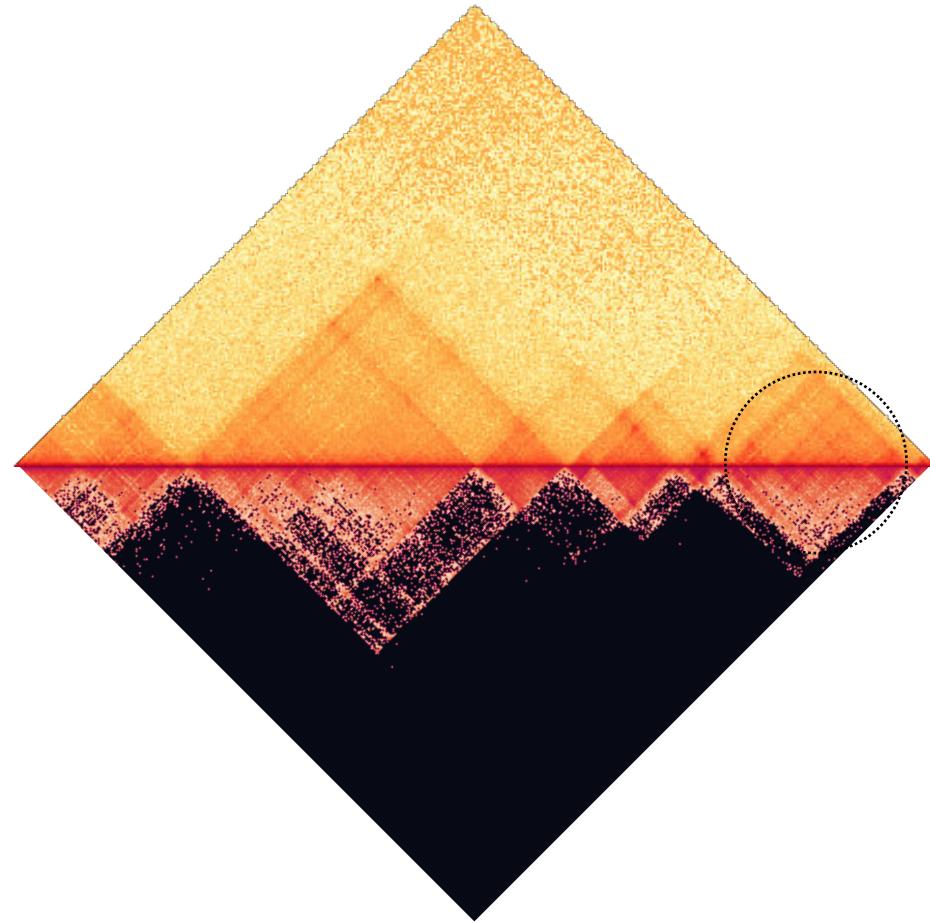
chr11:110780000-114770000



Kamada & Kawai, 1989

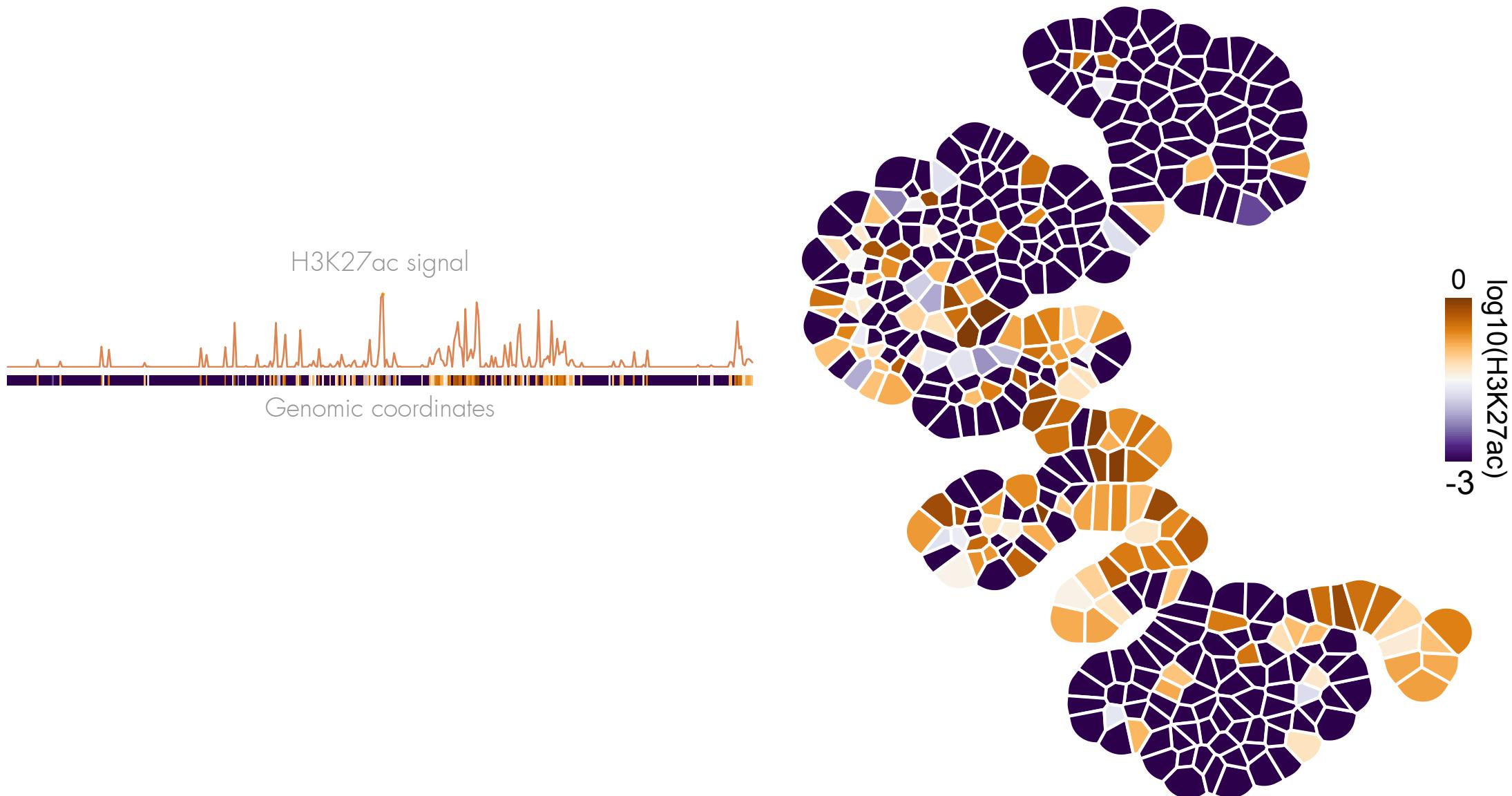
Spatial lay-out of significant interactions

chr11:110780000-114770000

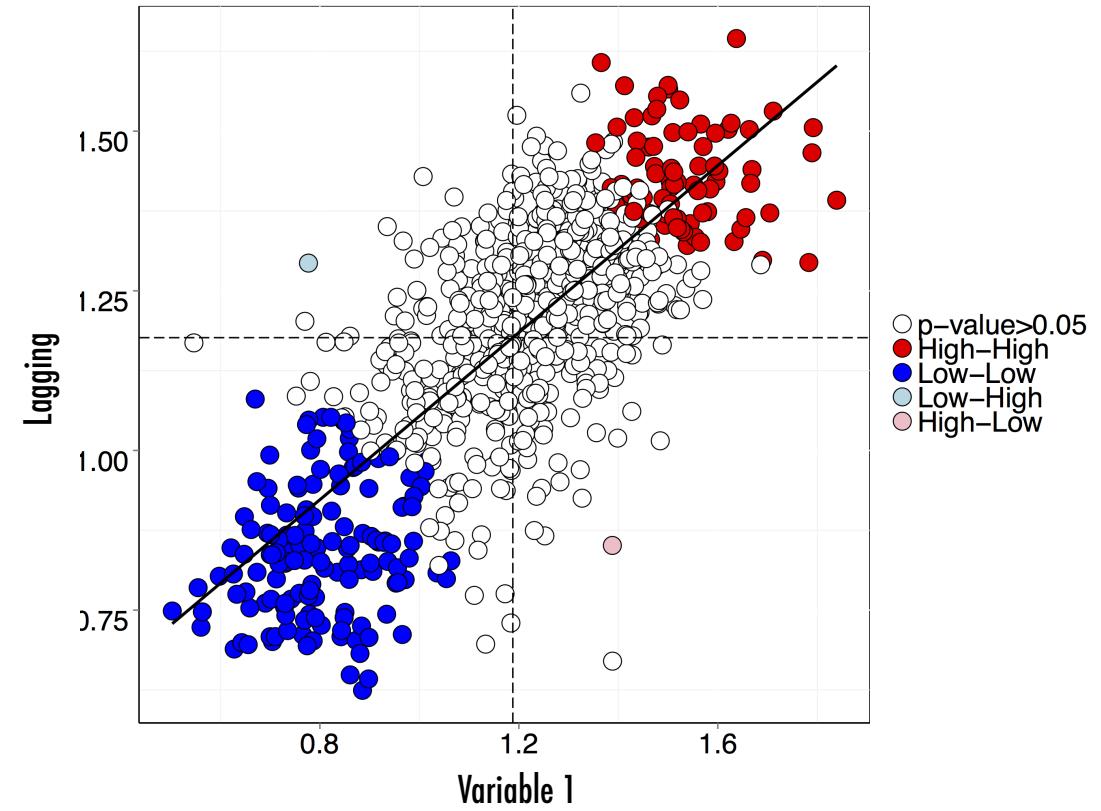
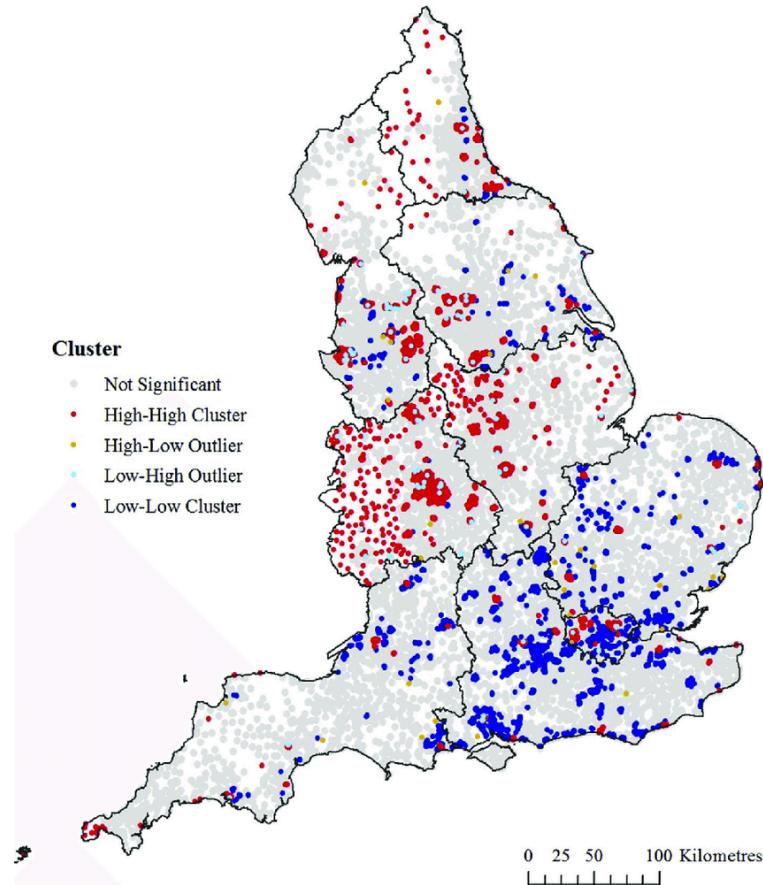


Marker (H3K27ac) into 2D mapping

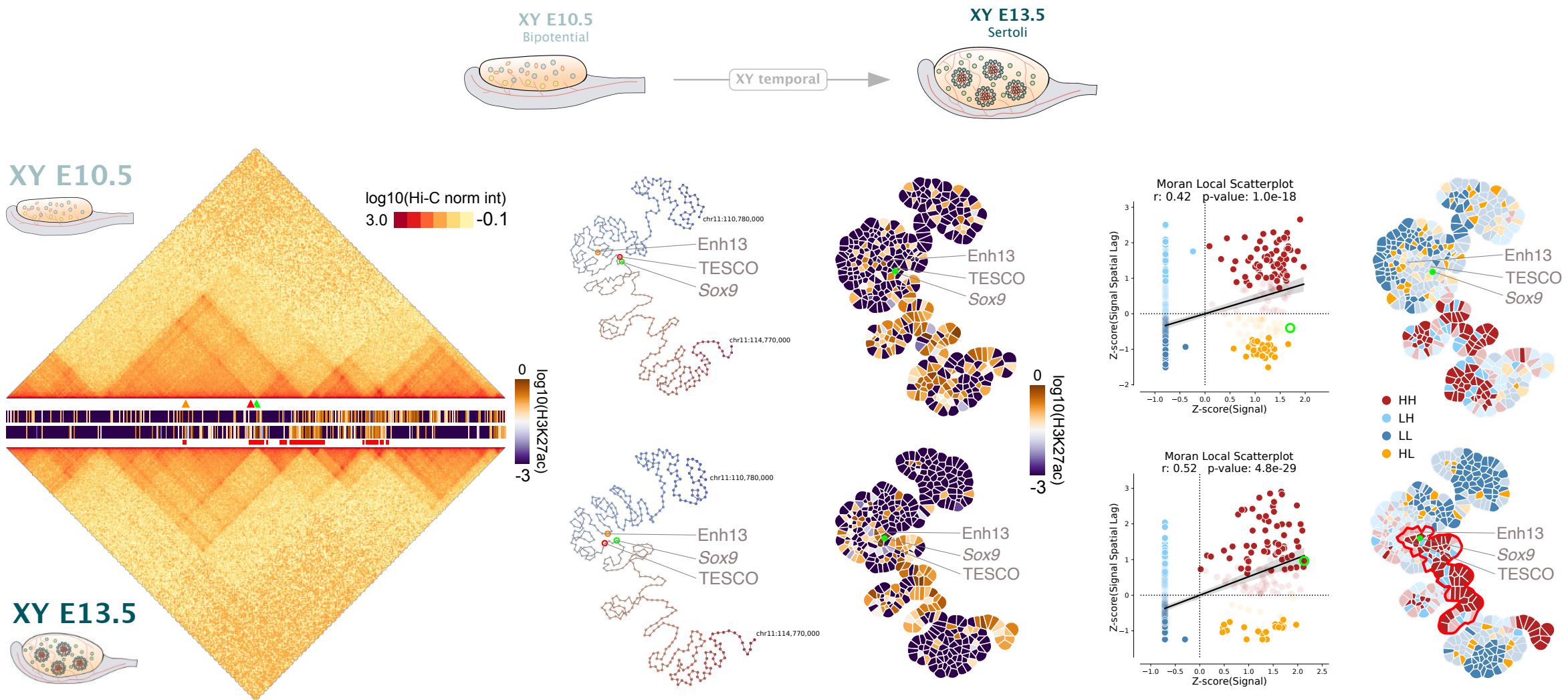
chr11:110780000-114770000



Local Moran Index

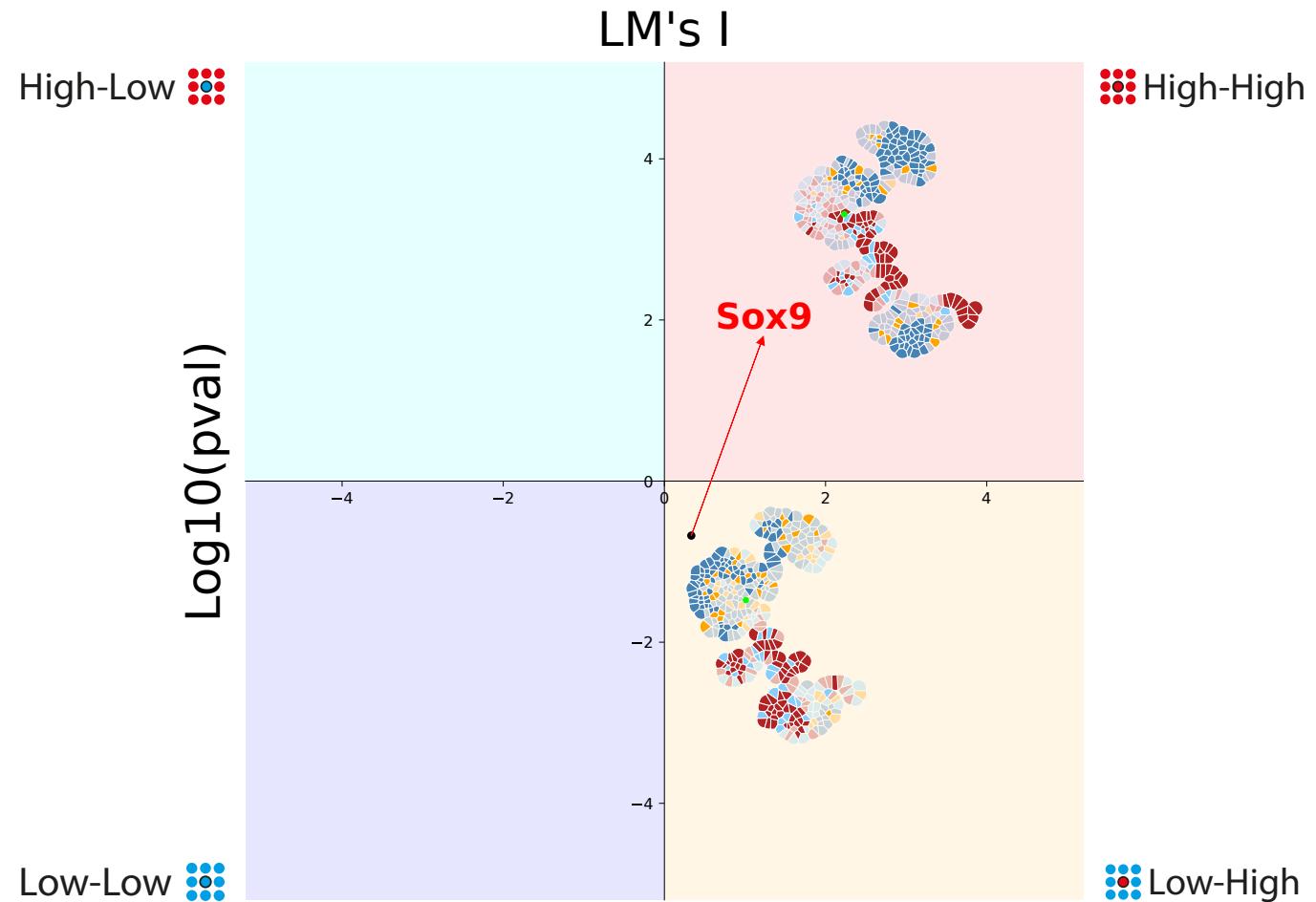


Quantifying regulatory environments bin by bin

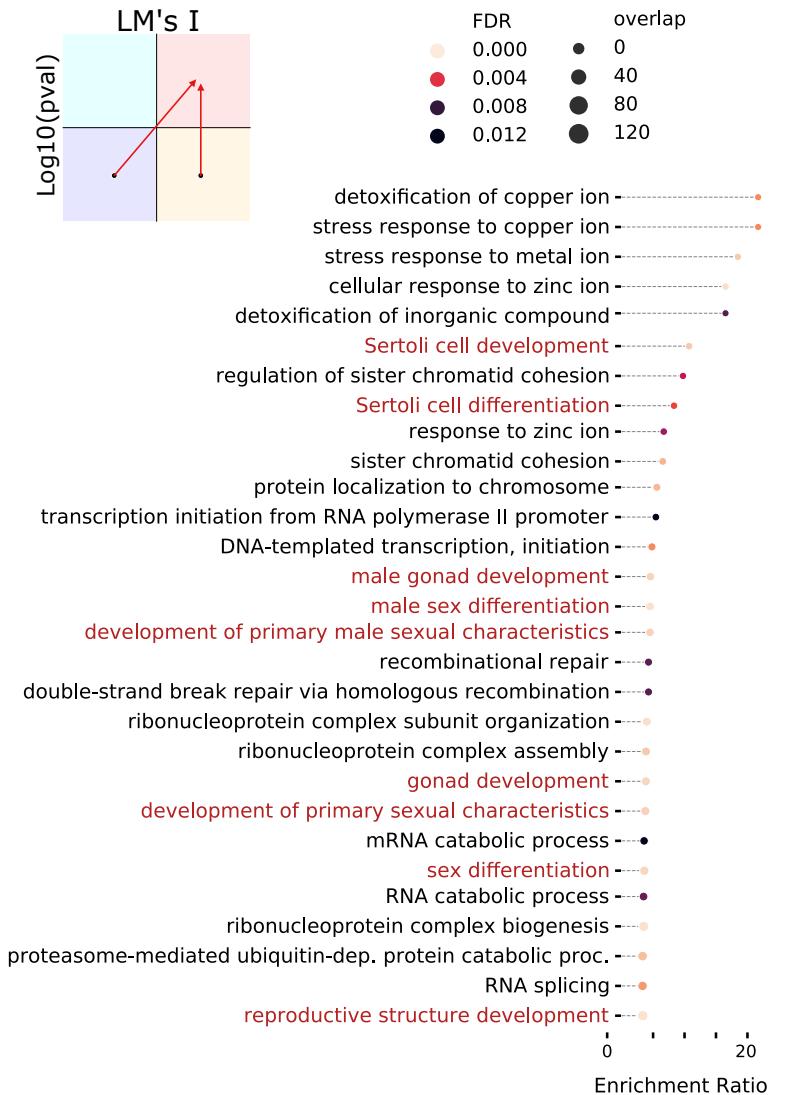
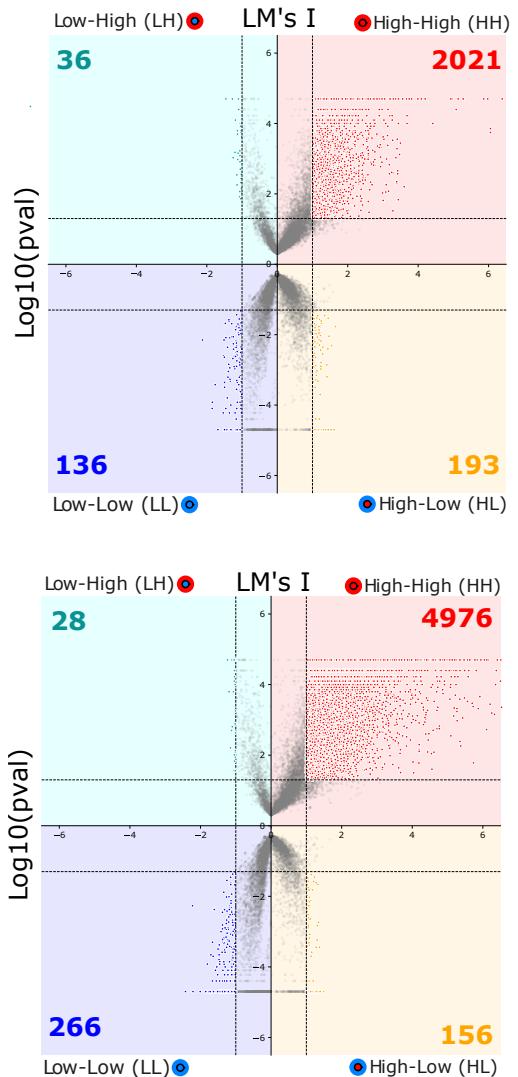
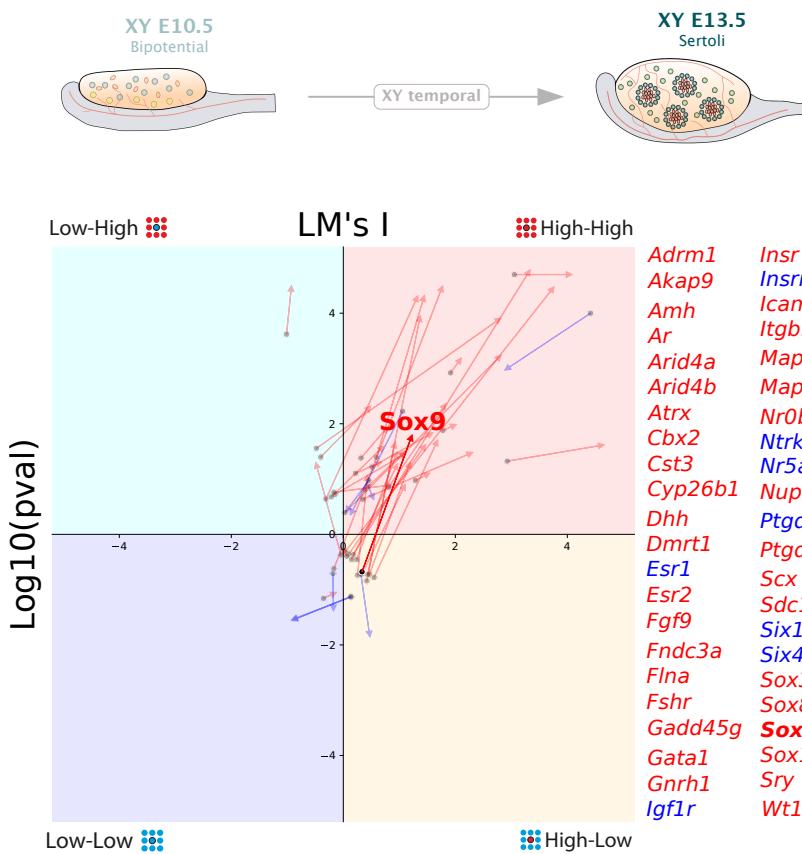


Sox9 locus chr11:110,780,000-114,770,000

LMI Trip for Sox9 gene



All genes LM's Trip



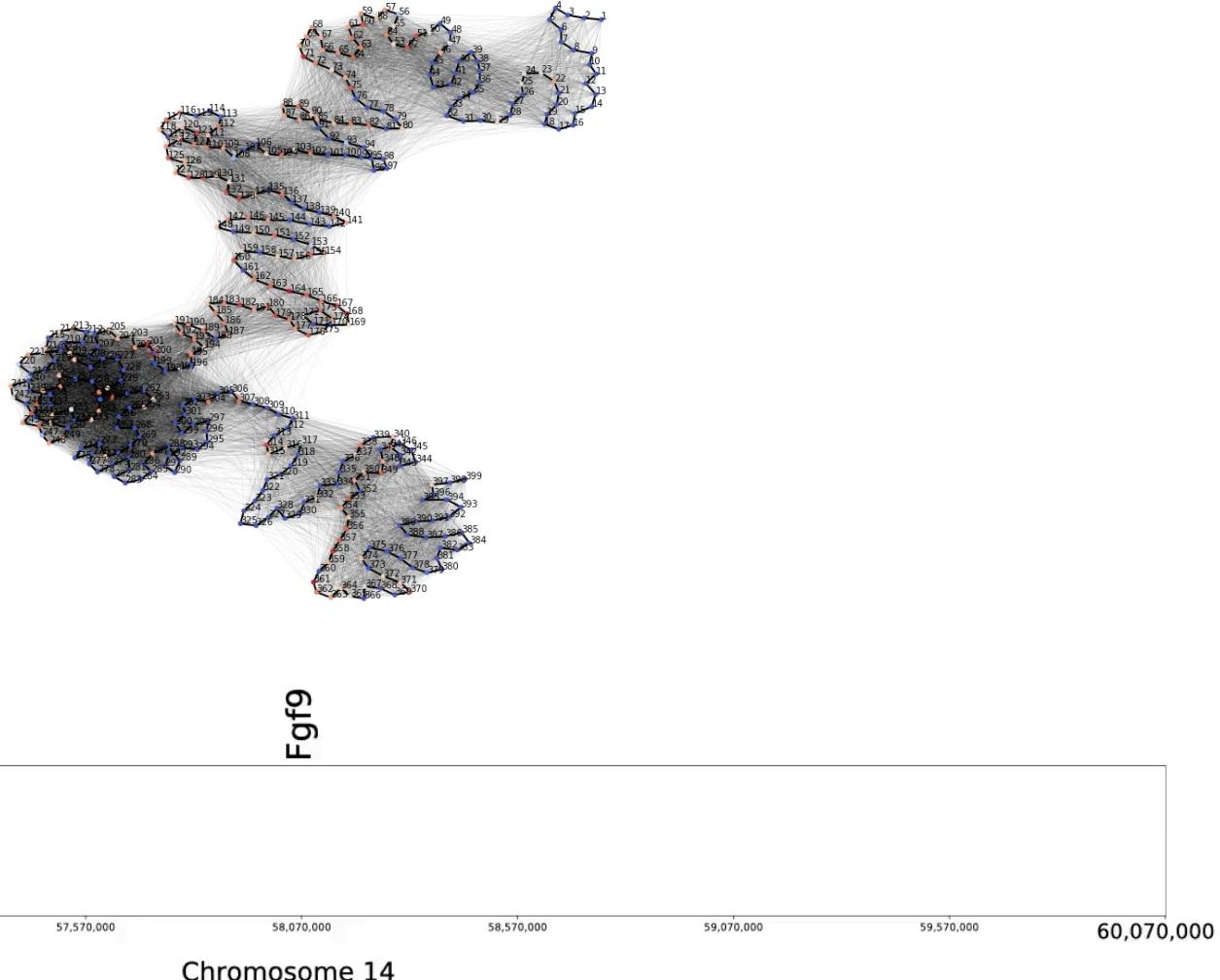
Now that we know the genes....

Can we identify regulatory elements using



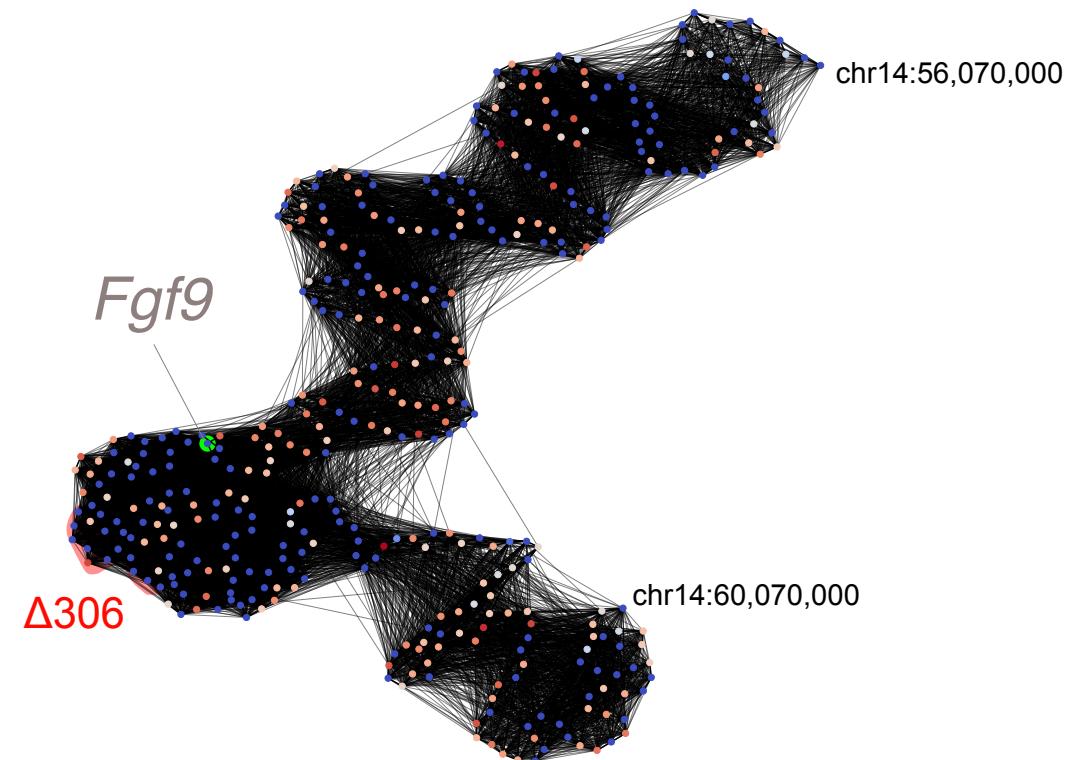
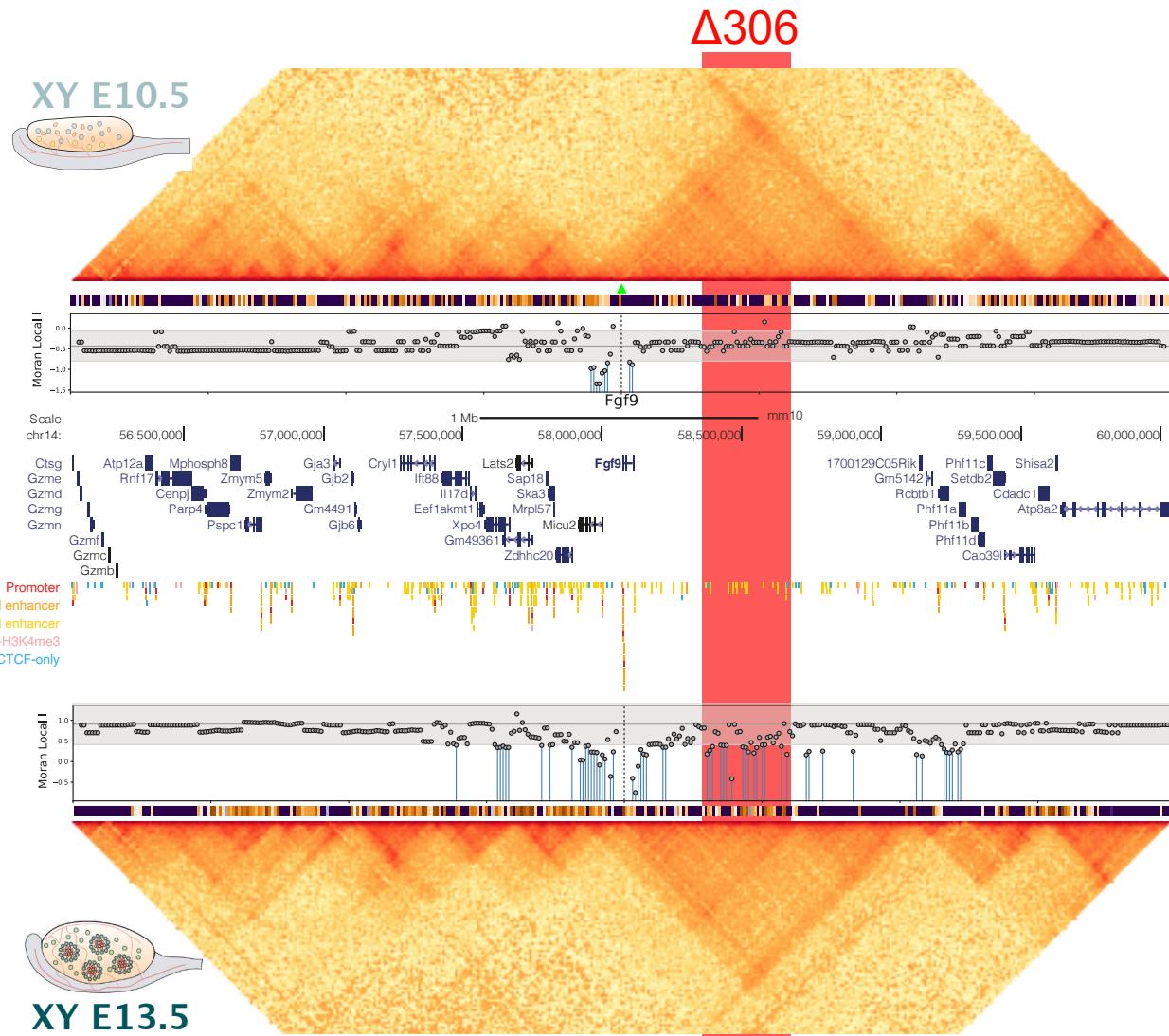
METALoci predictive mode

Fgf9 locus chr14:56,070,000-60,070,000



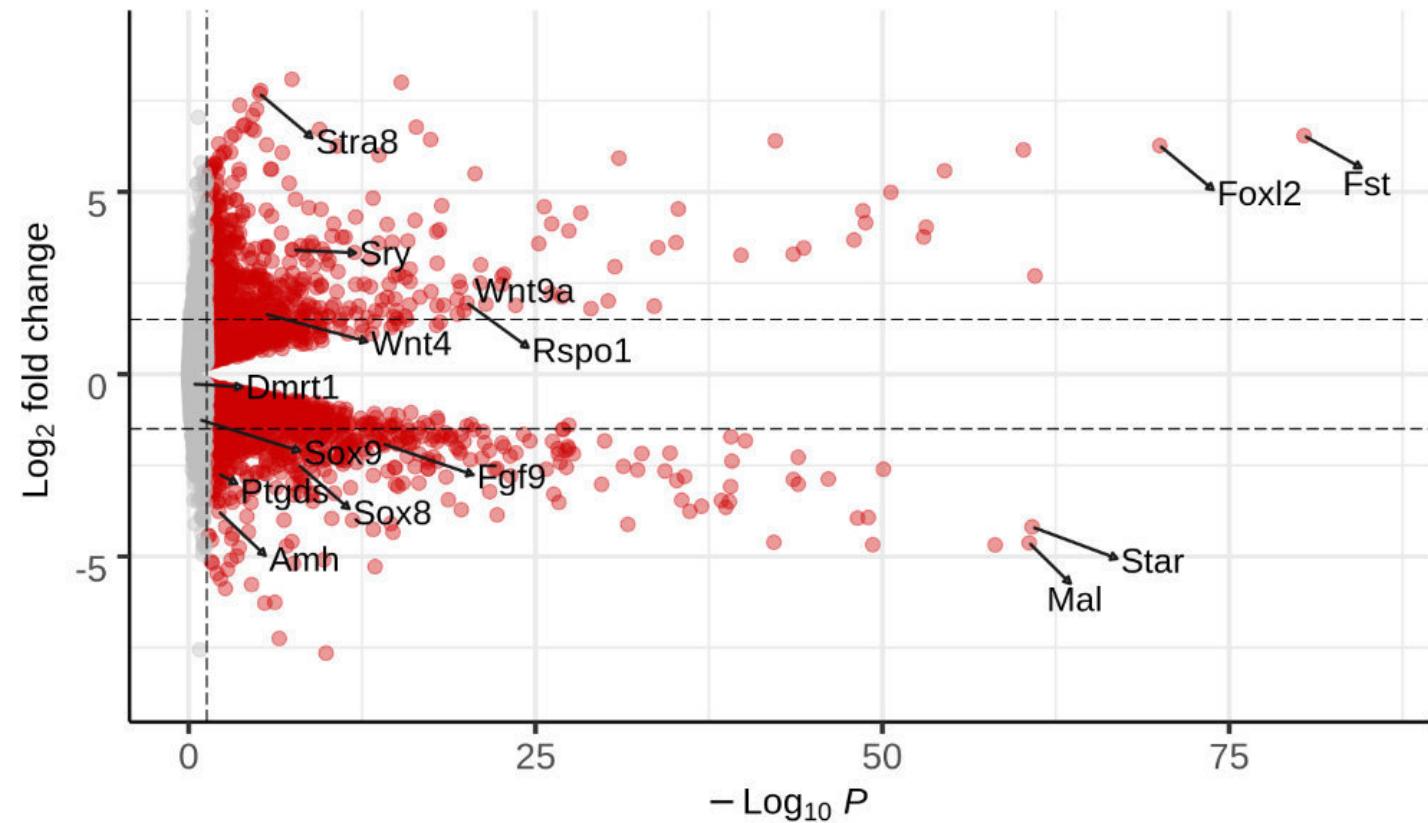
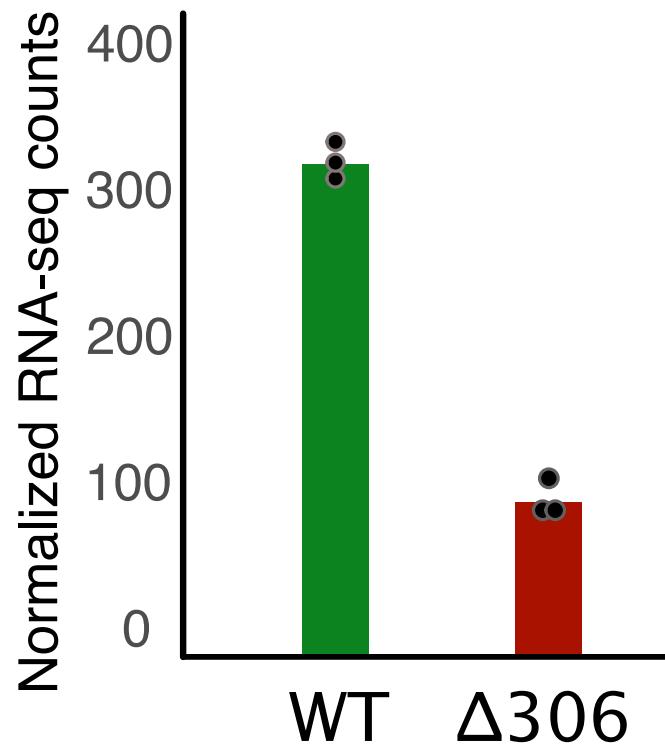
METALoci predictive mode

Fgf9 locus chr14:56,070,000-60,070,000



METALoci predictive mode

Fgf9 XY $\Delta 306$ mutant



METALoci predictive mode

Fgf9 XY Δ306 mutant

XY Wildtype



Testis

XY Δ306



Ovotestis

XX Wildtype



Ovary-like



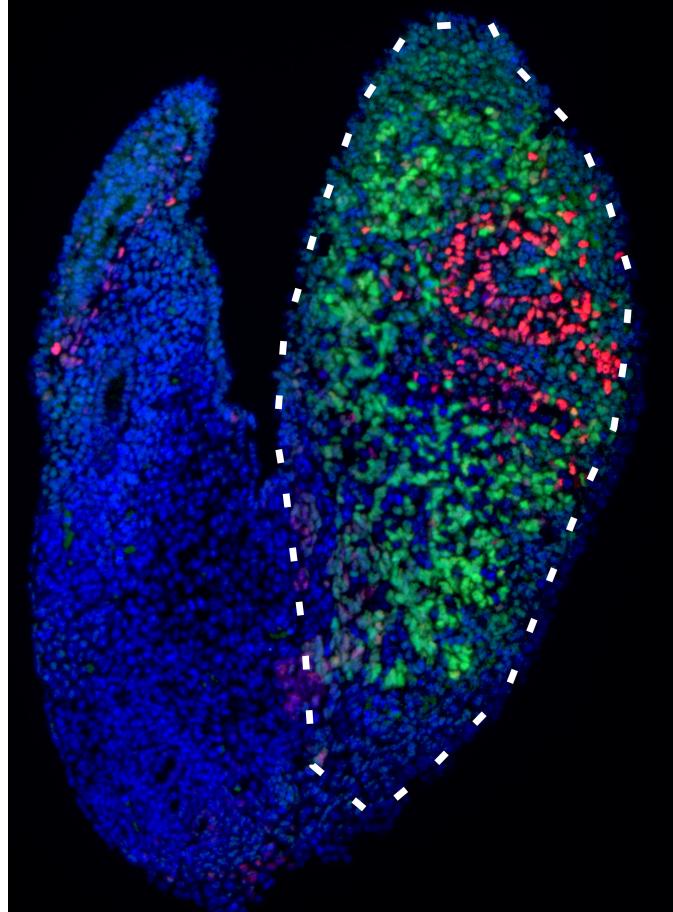
Ovary

250um

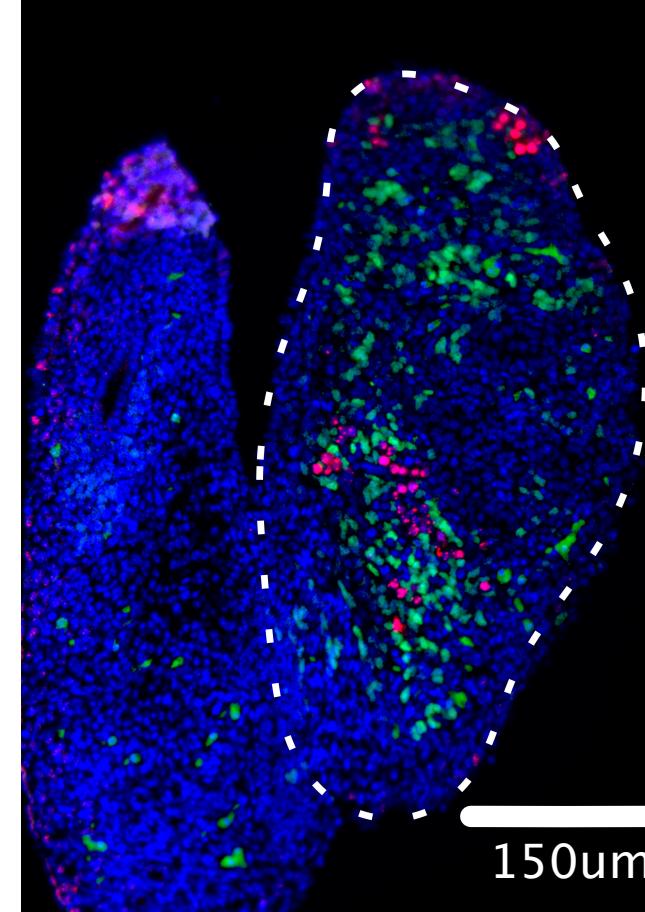
METALoci predictive mode

Fgf9 XY Δ306 mutant

FOXL2SOX9



FOXL2SYCP3



Take home messages:

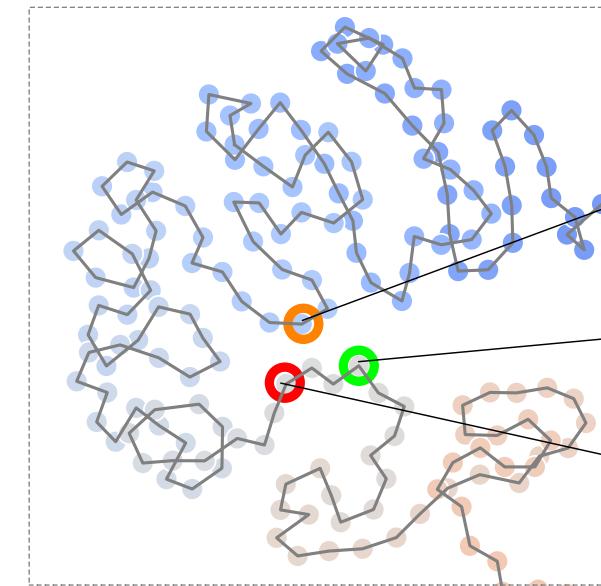
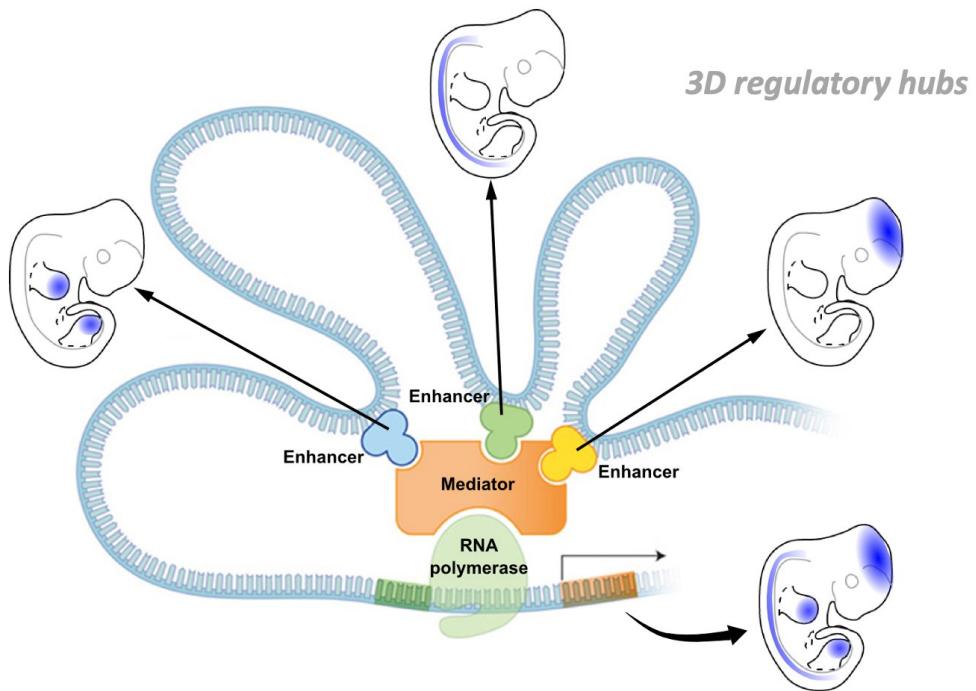
First characterization of the 3D regulatory landscape of sex determination

METALoci is an unbiased approach to quantify gene regulatory activity

METALoci is a predictive tool to identify critical regulatory loci

Discovery of a novel non-coding region controlling sex determination

Take home messages:



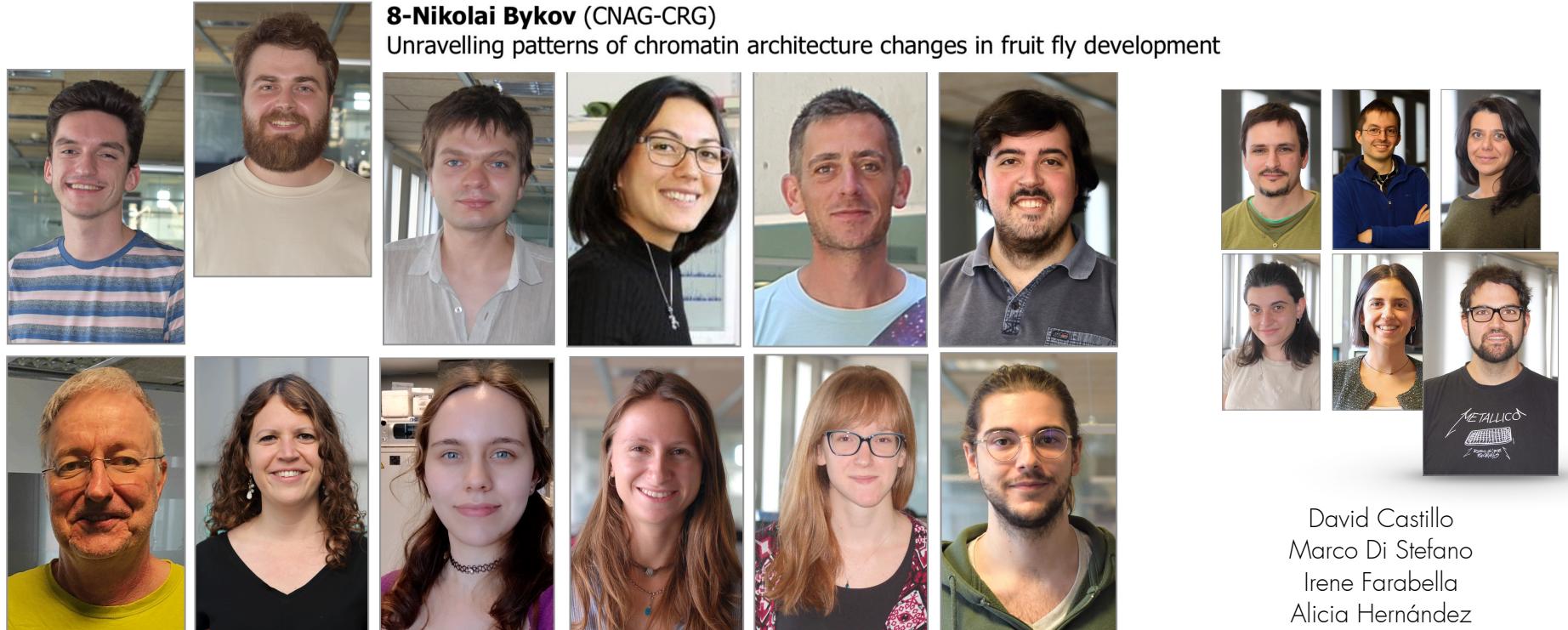
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Sox9
TESCO

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.: Our current sponsors :.



.: Conflict of Interest Statement :.

Marc A. Martí-Renom serves as a consultant to Acuity Spatial Genomics, Inc., and receives compensation for these services.