The logo for METALOCI features a stylized, multi-colored arrow pointing upwards and to the right, composed of various geometric shapes in shades of yellow, green, blue, and red.

METALOCI

Identification of
spatial hubs.

Marc A. Marti-Renom

CNAG-CRG · ICREA

Unpublished

Photo by David Oliete - www.davidoliete.com

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

cnag CRG  ICREA



Photo by David Oliete - www.davidoliete.com

Spatio-temporal regulatory landscape of sex-determination



Juan A. Rodríguez
Irene Mota
Dario Lupiañez

Marc A. Marti-Renom

CNAG-CRG · ICREA

Unpublished

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

cnag CRG  ICREA

Sex determination: a 3,000 year-old enigma

Mythology



Hermaphrodite primeval men

Plato's symposium, 385-370 BC

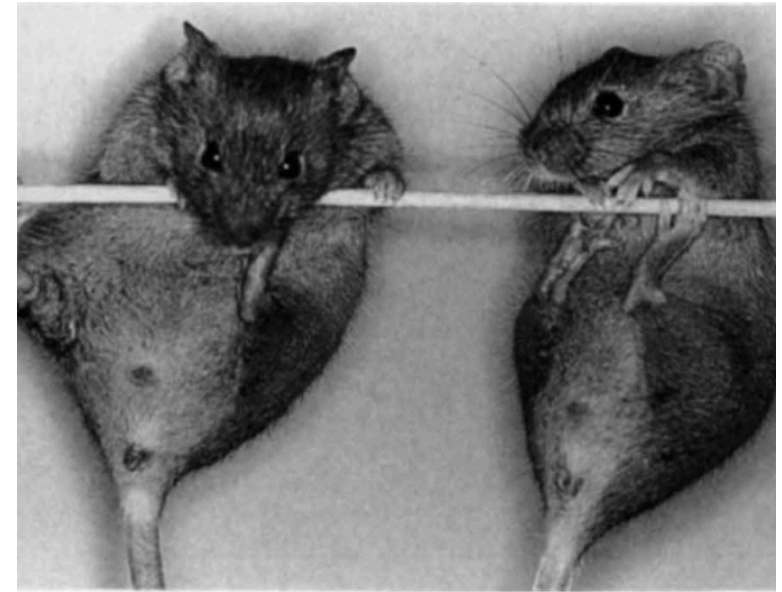
Theories



Left-right theory

Alexandrian manuscripts, 1st cent. BC

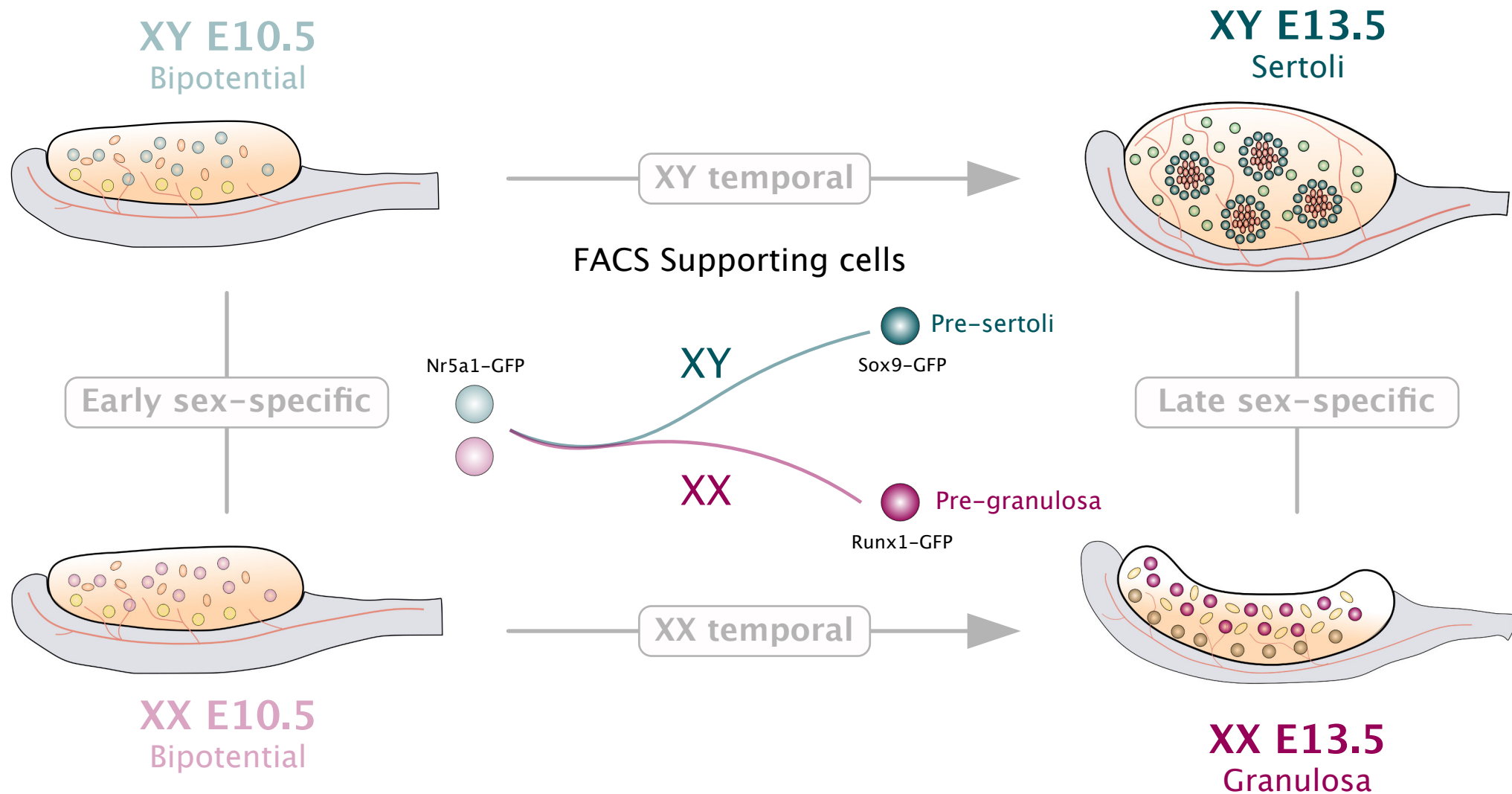
Genetics



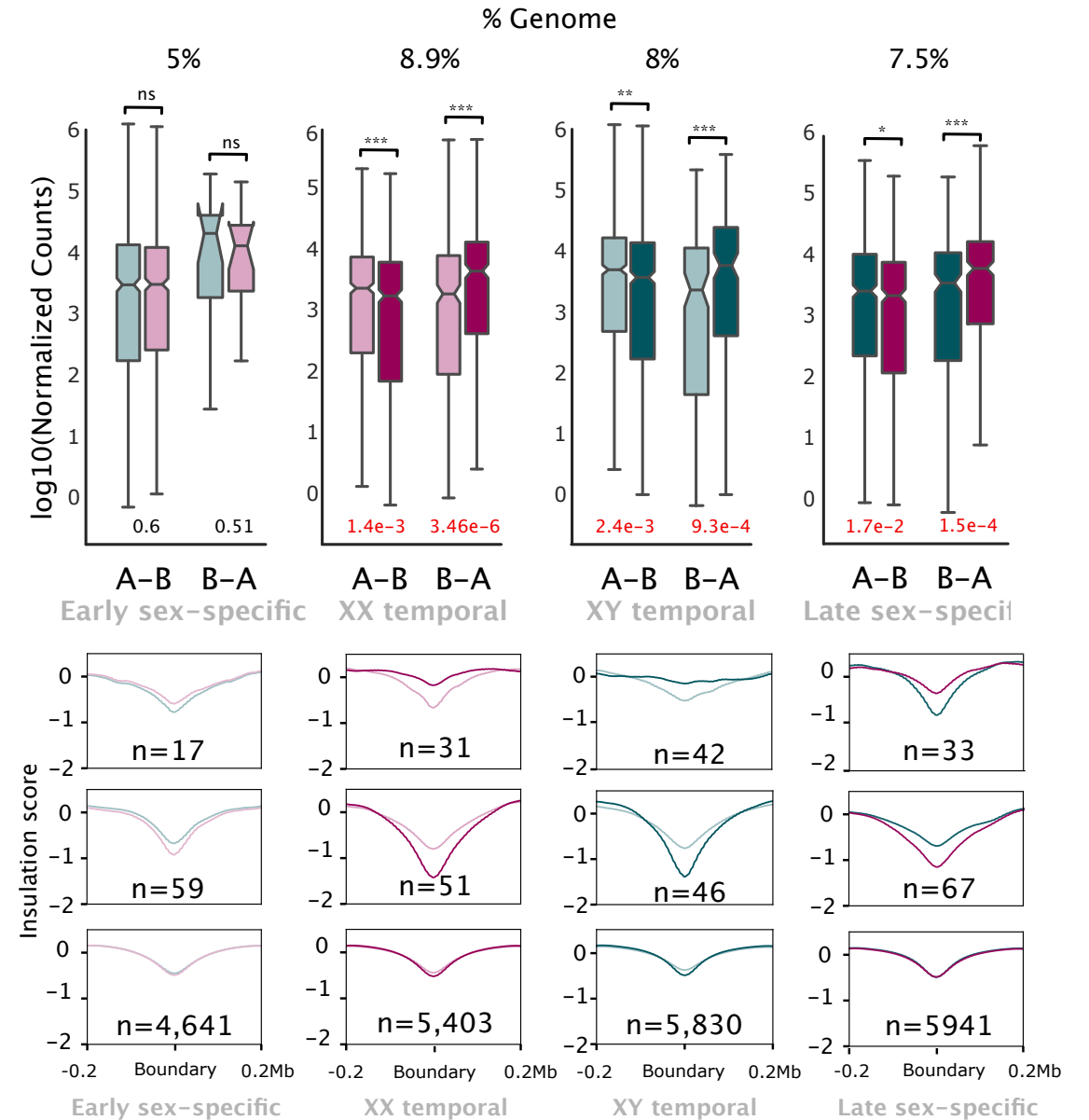
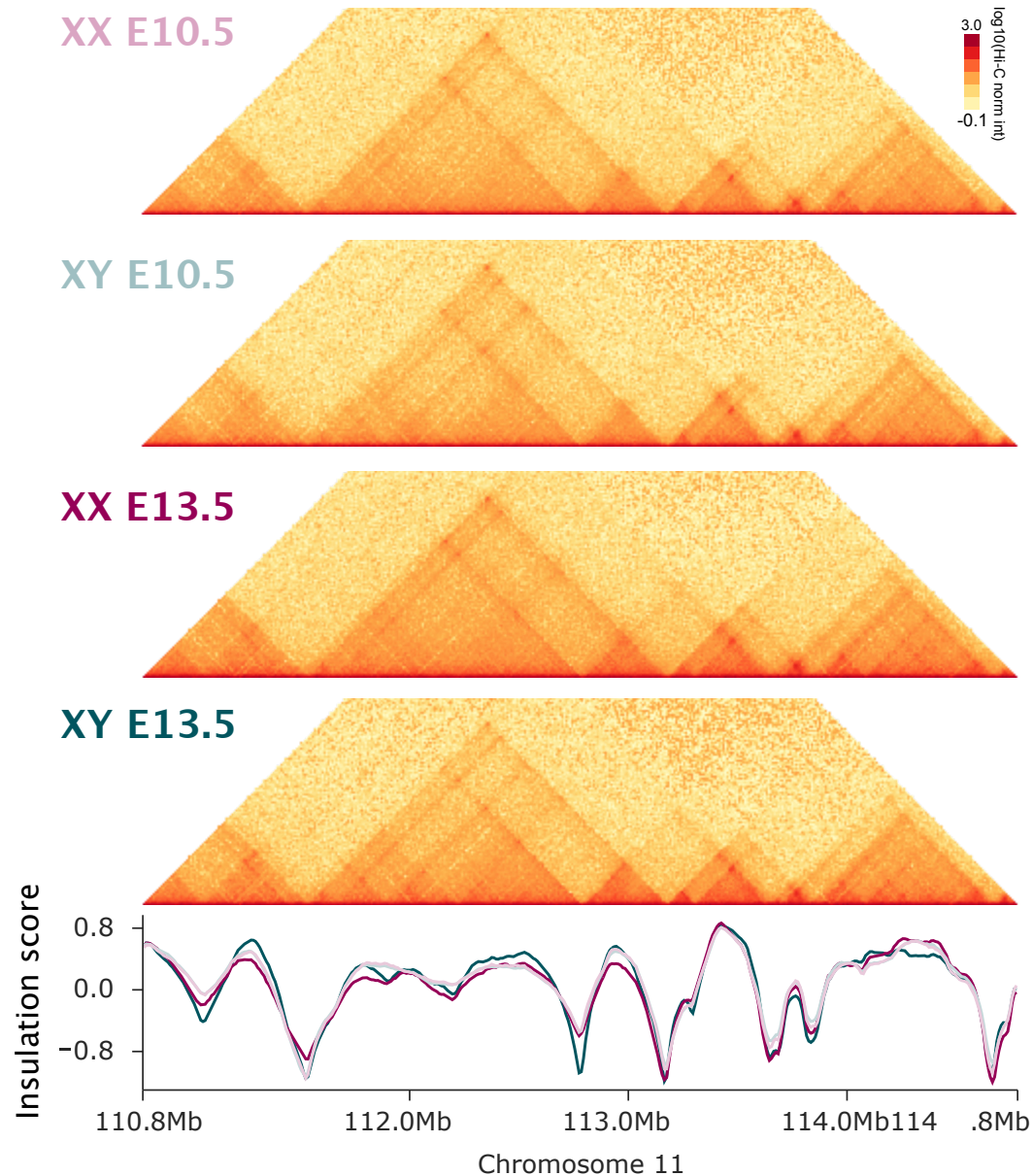
Discovery of Sry gene

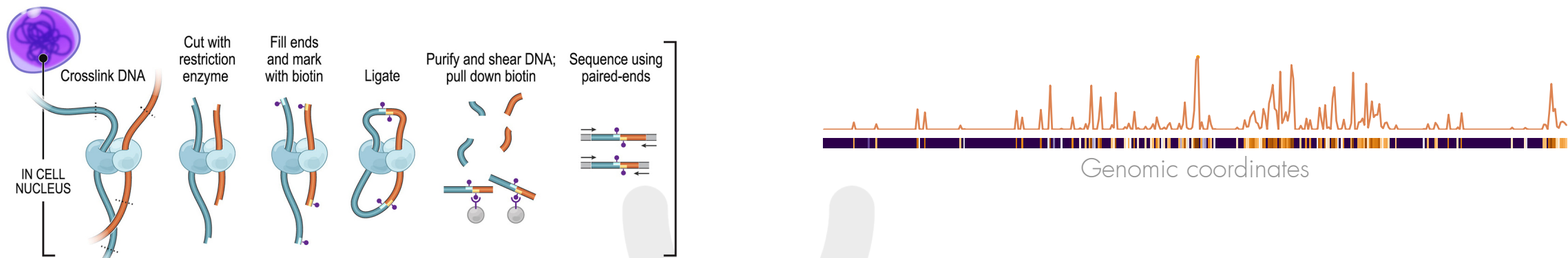
*Koopman et al., Nature, 1991
(Goodfellow & Lovell Badge labs)*

Sex-determination as a model for “bipotential” commitment



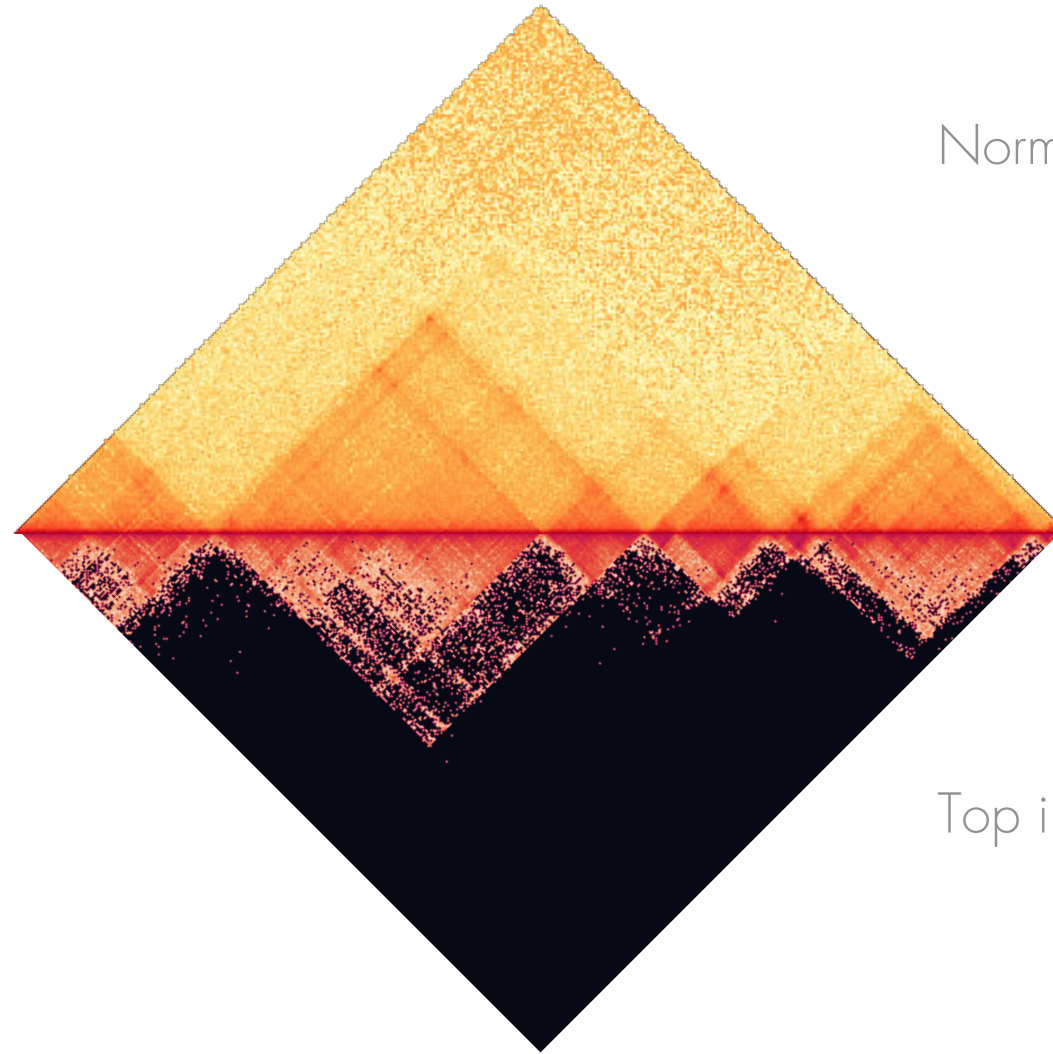
No major structural (apparent) differences





Hi-C normalization and interaction selection

chr11:110780000-114770000

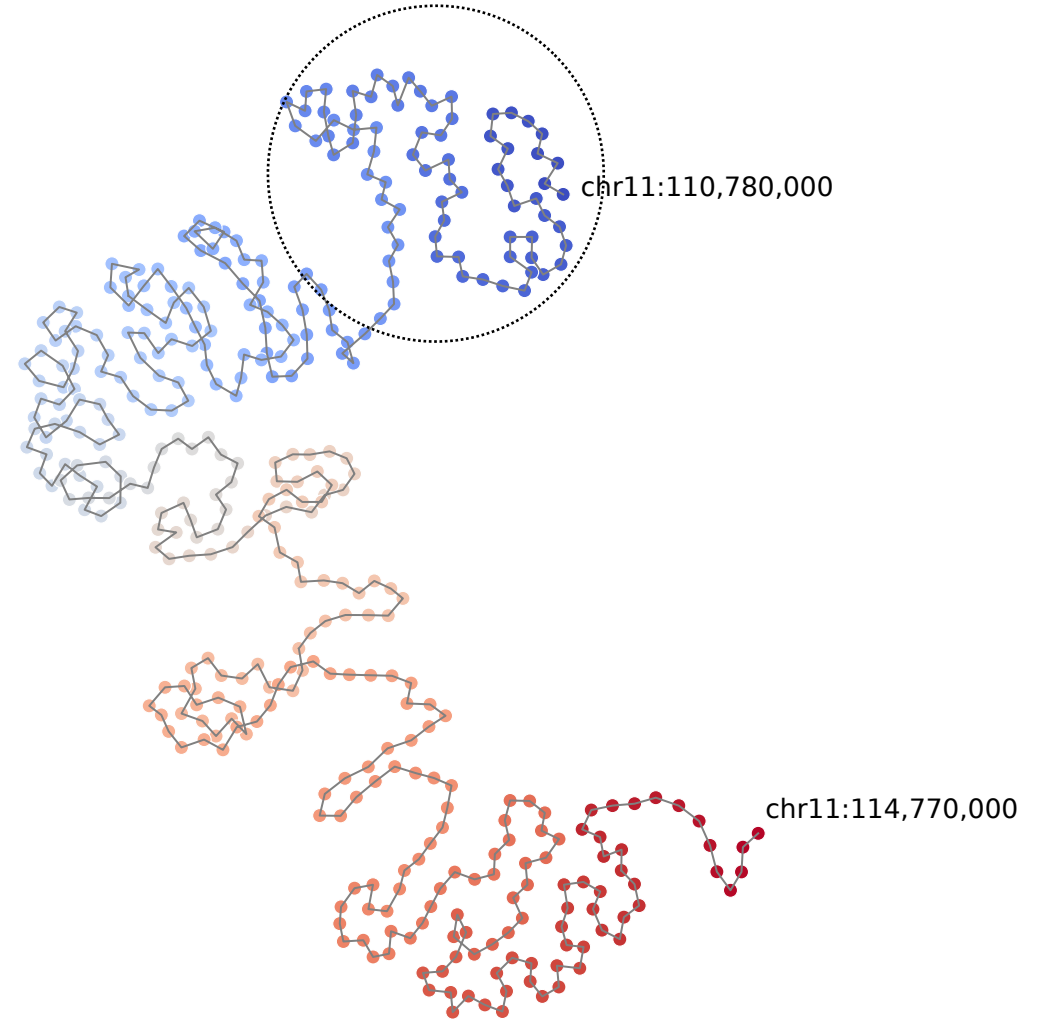
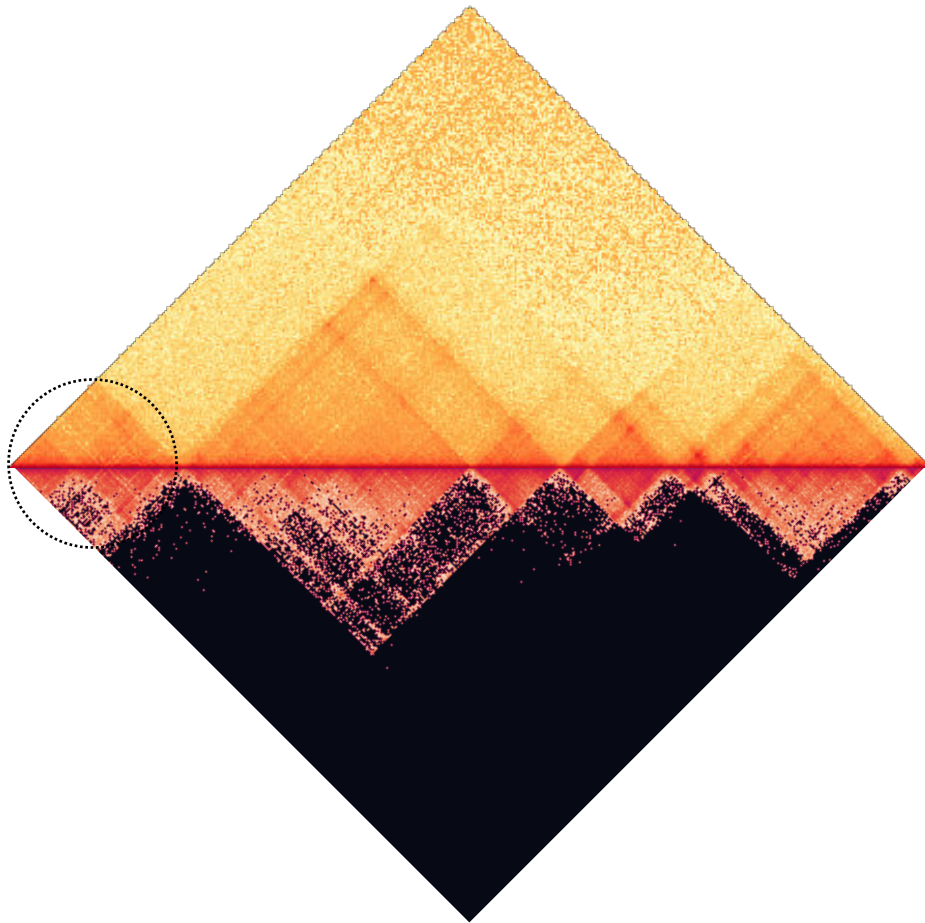


Normalized Hi-C

Top interactions

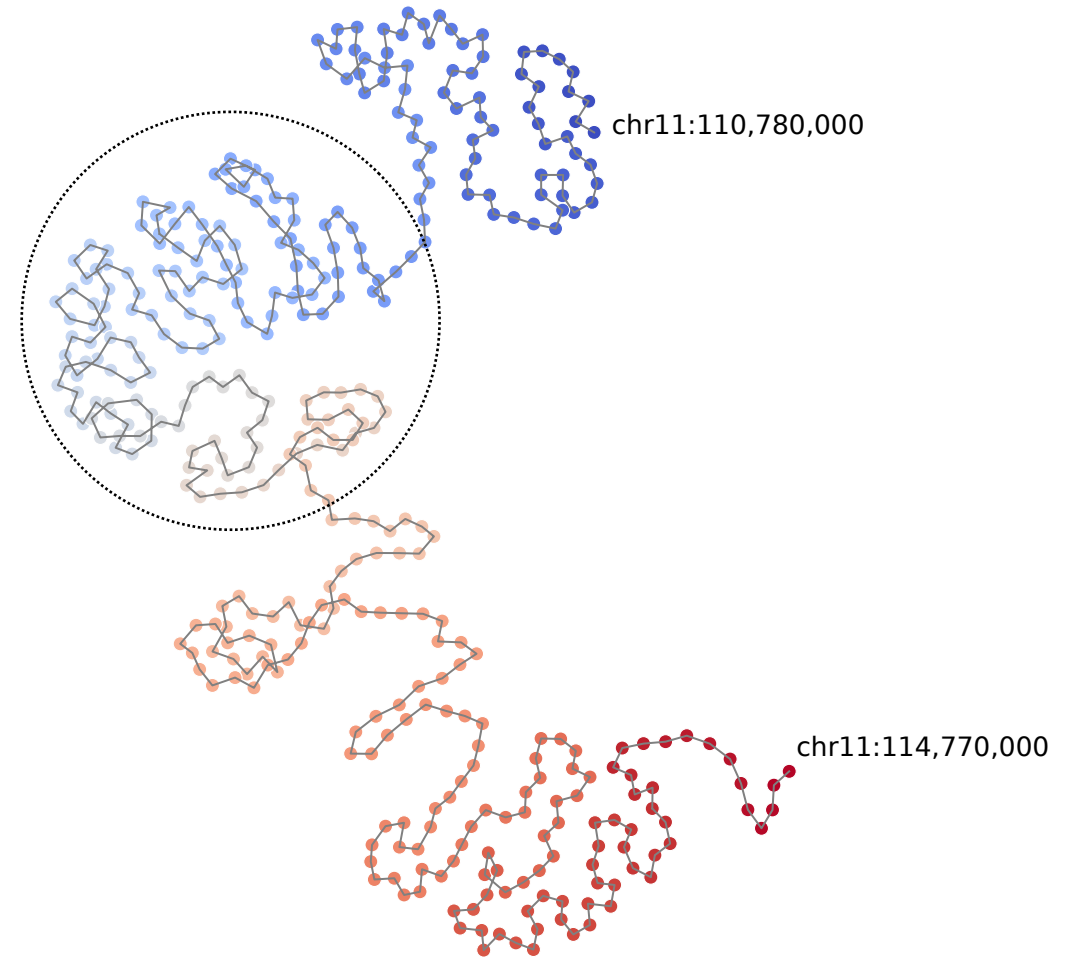
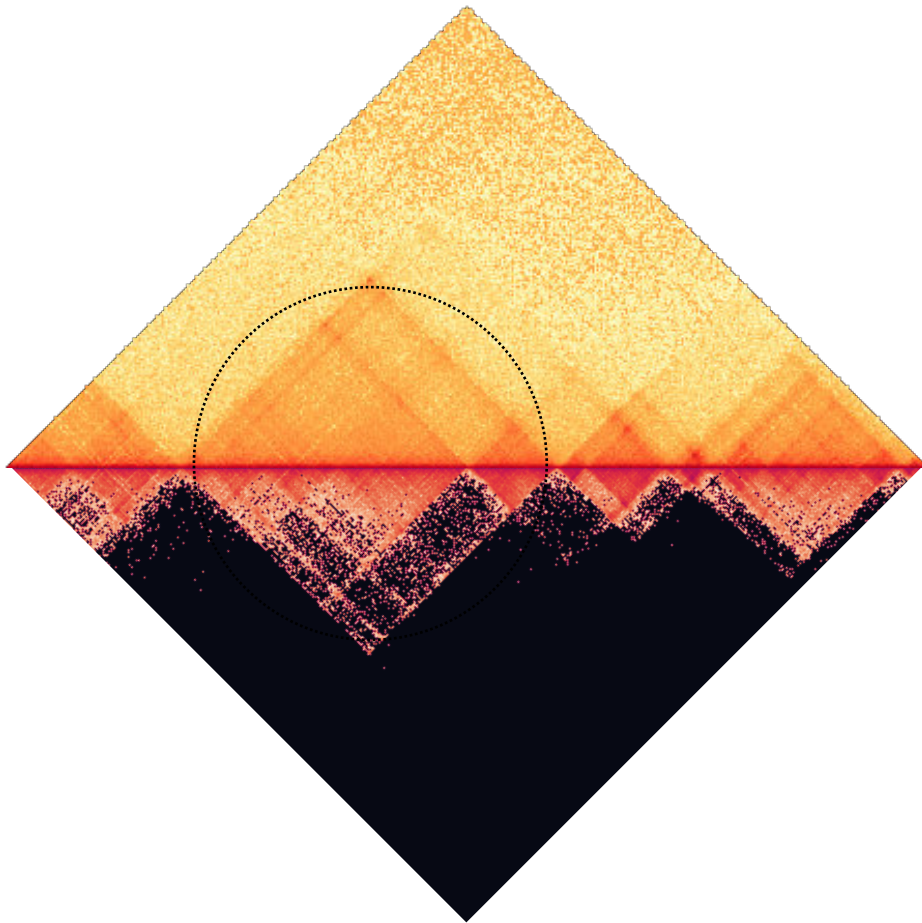
Spatial lay-out of significant interactions

chr11:110780000-114770000



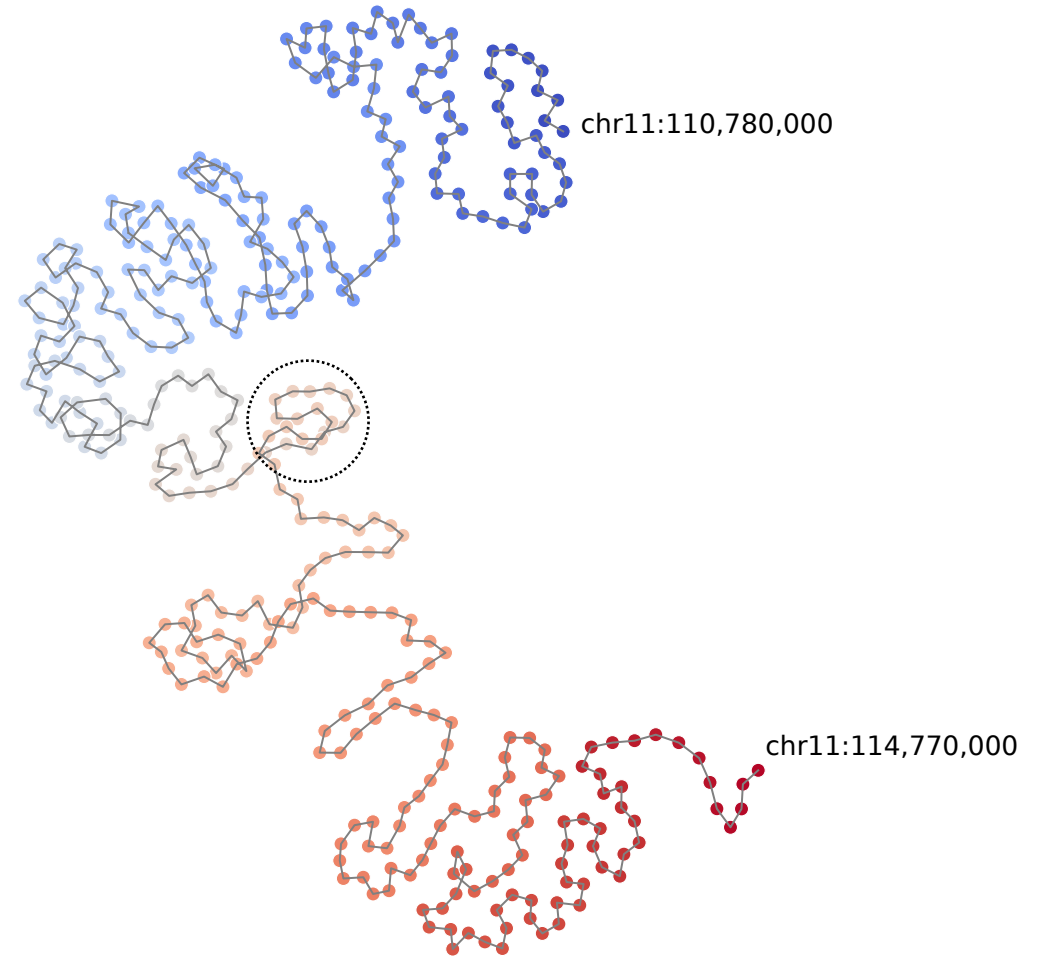
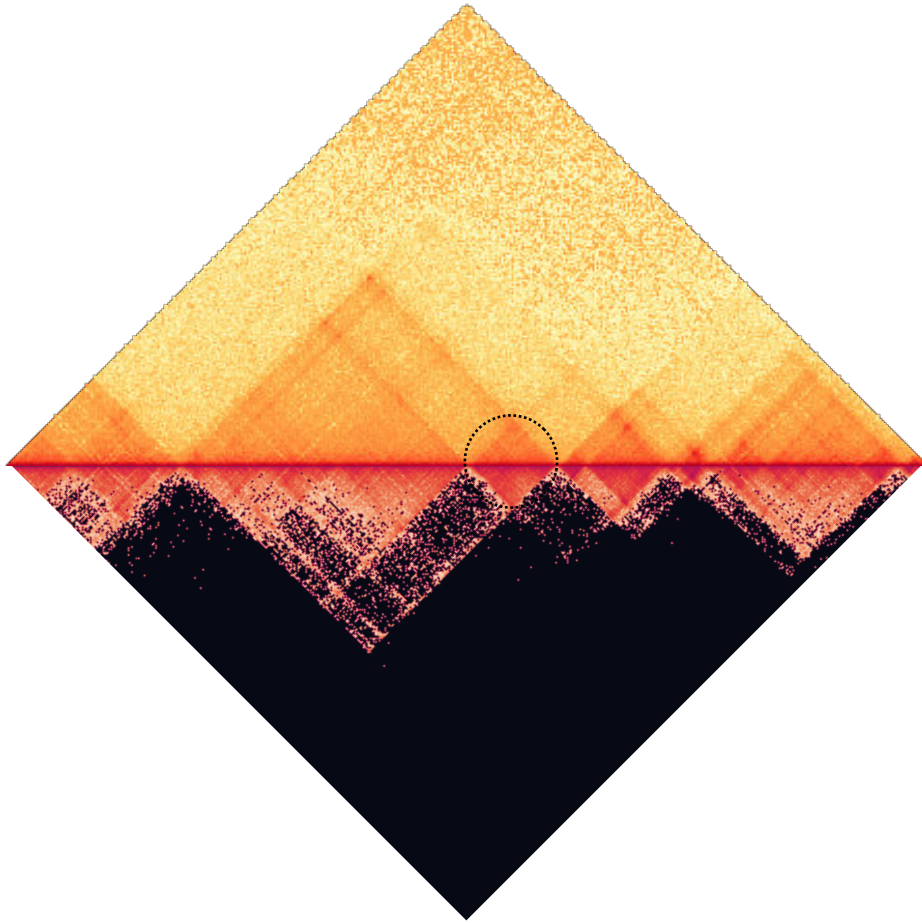
Spatial lay-out of significant interactions

chr11:110780000-114770000



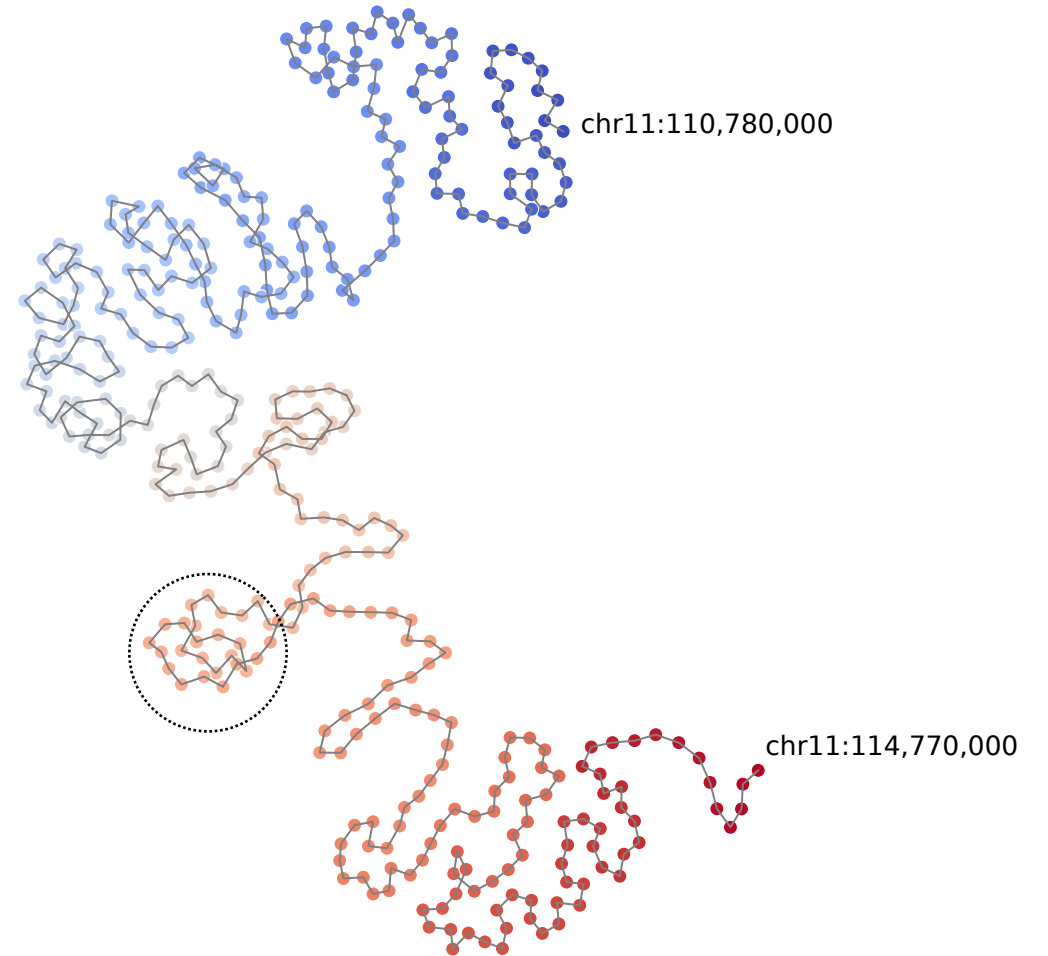
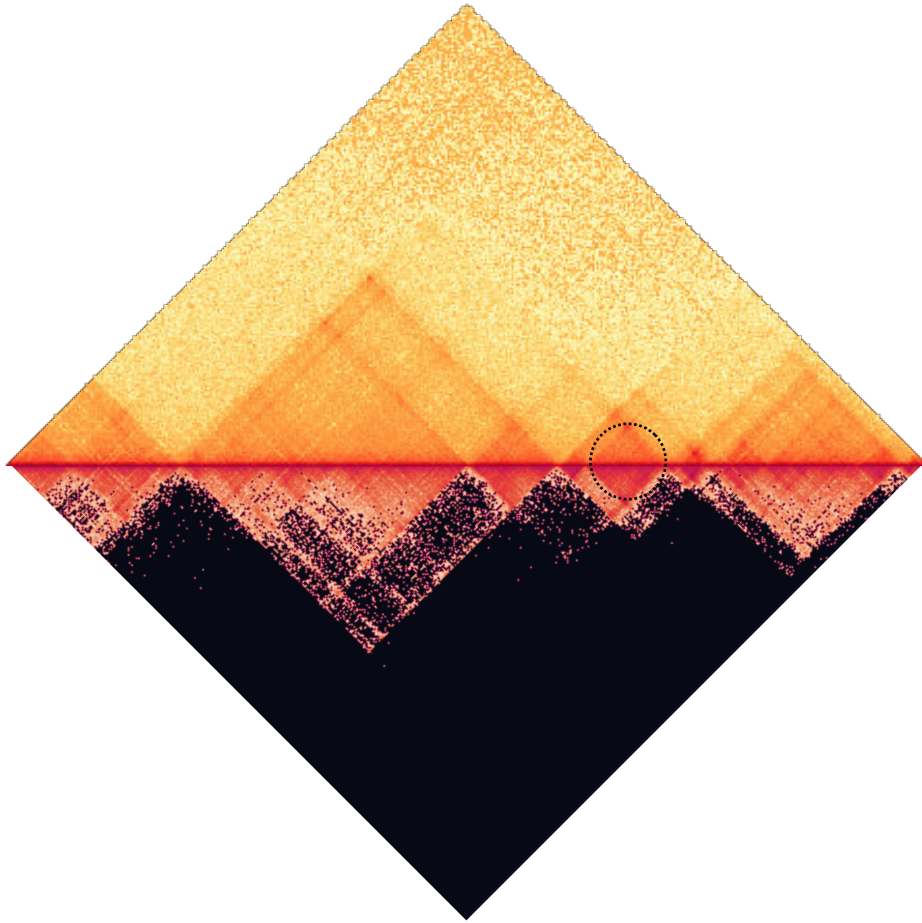
Spatial lay-out of significant interactions

chr11:110780000-114770000



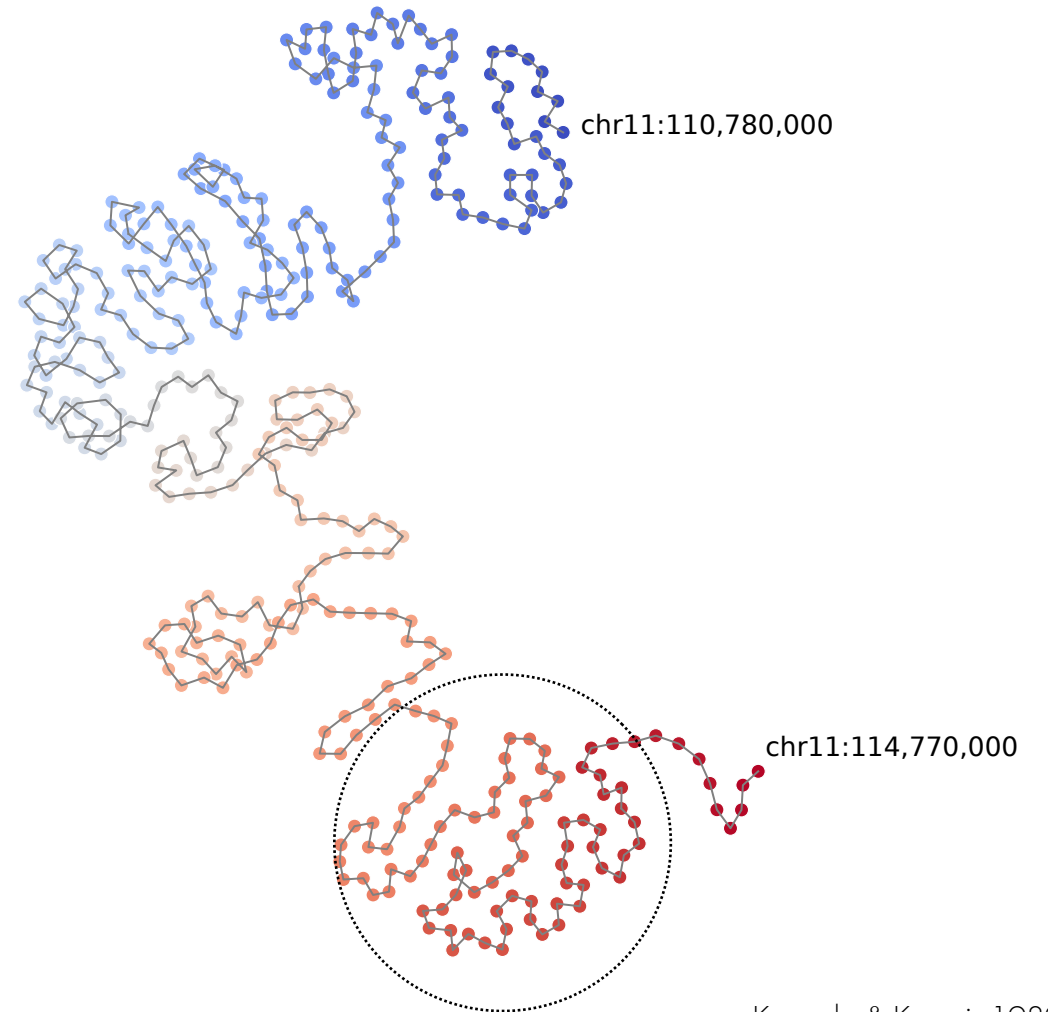
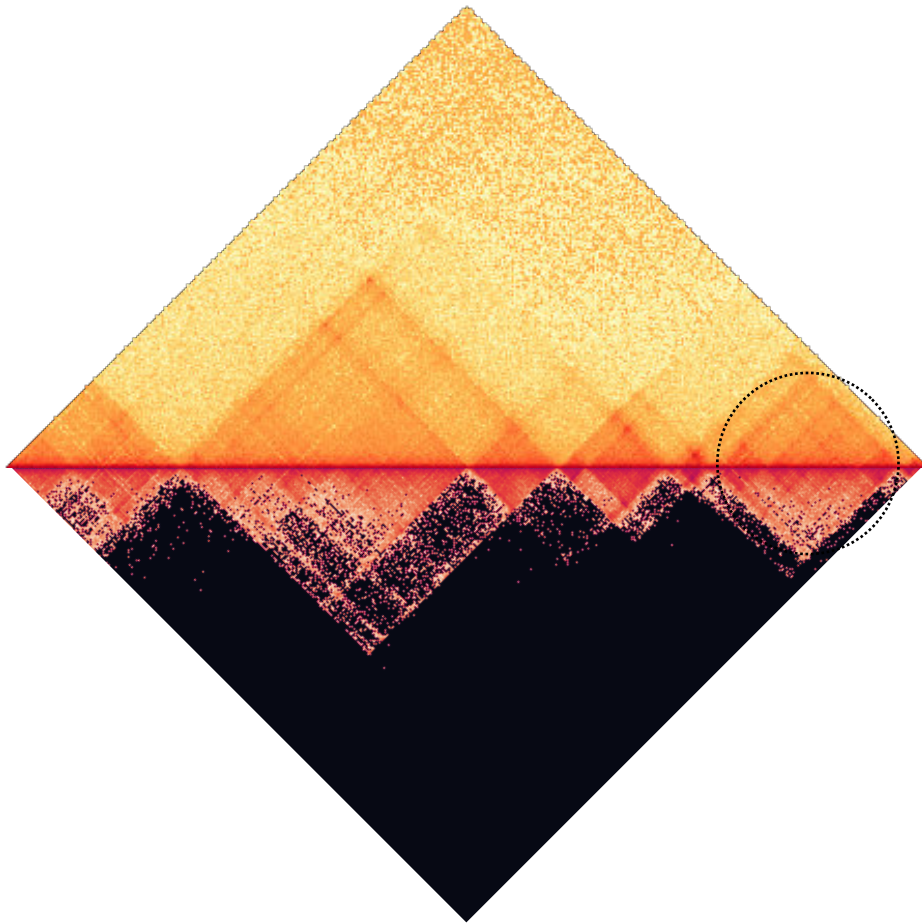
Spatial lay-out of significant interactions

chr11:110780000-114770000



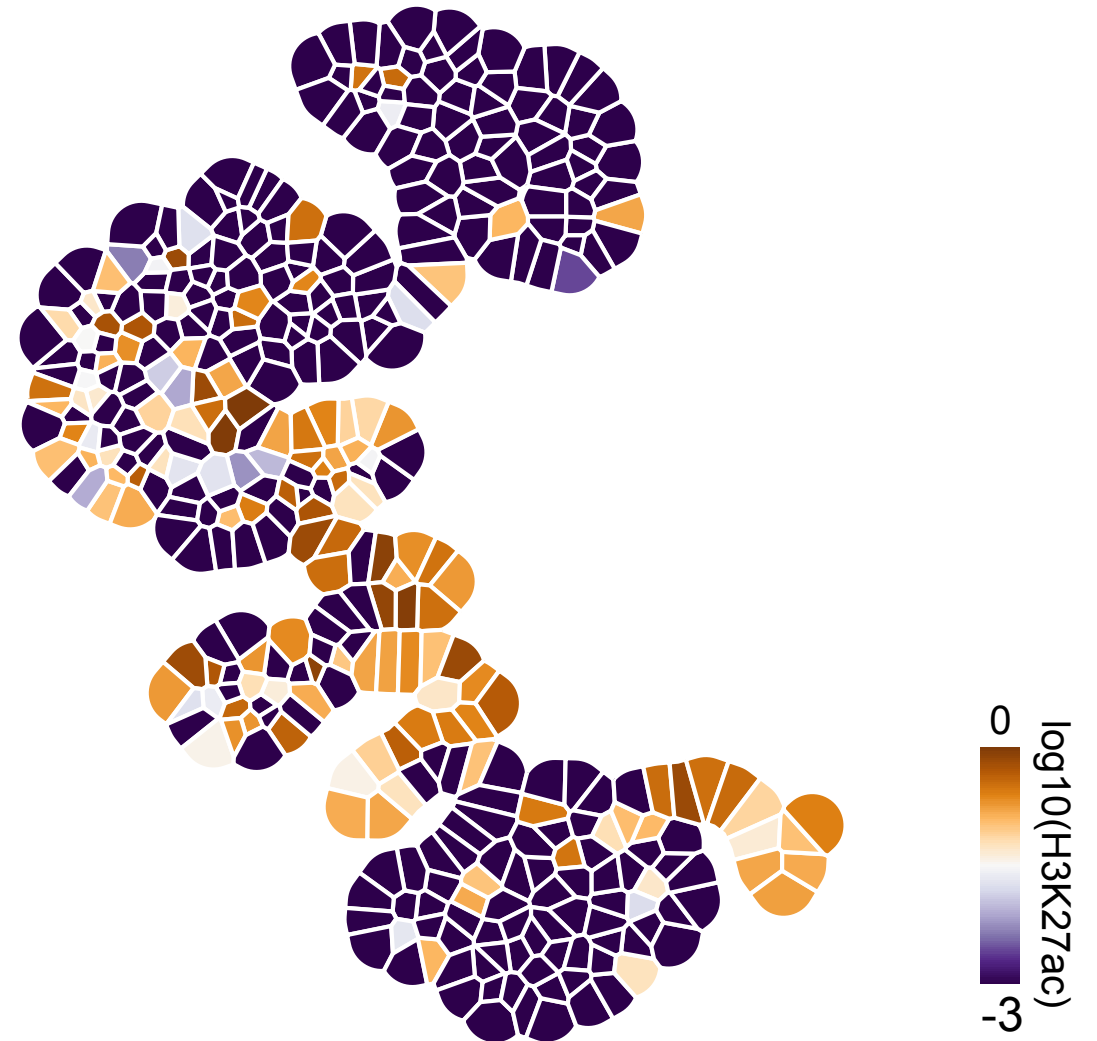
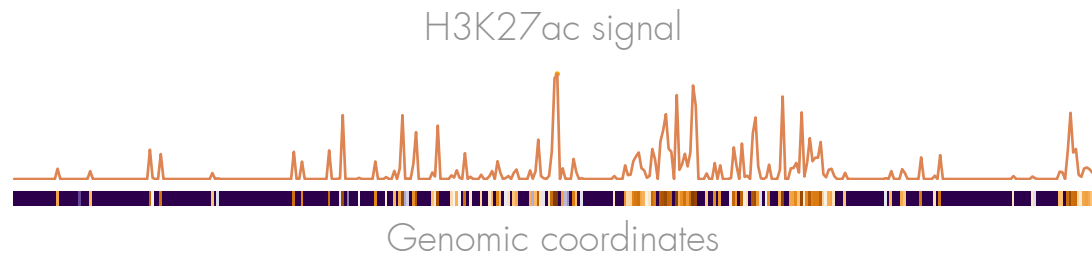
Spatial lay-out of significant interactions

chr11:110780000-114770000

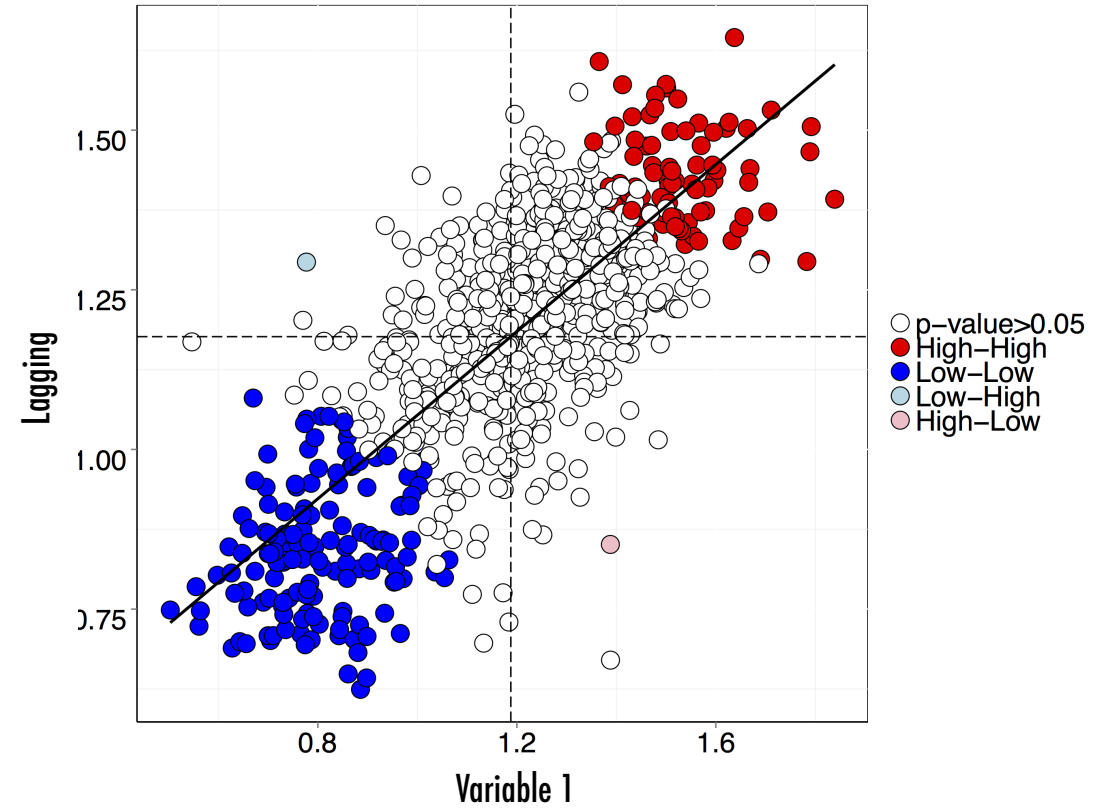
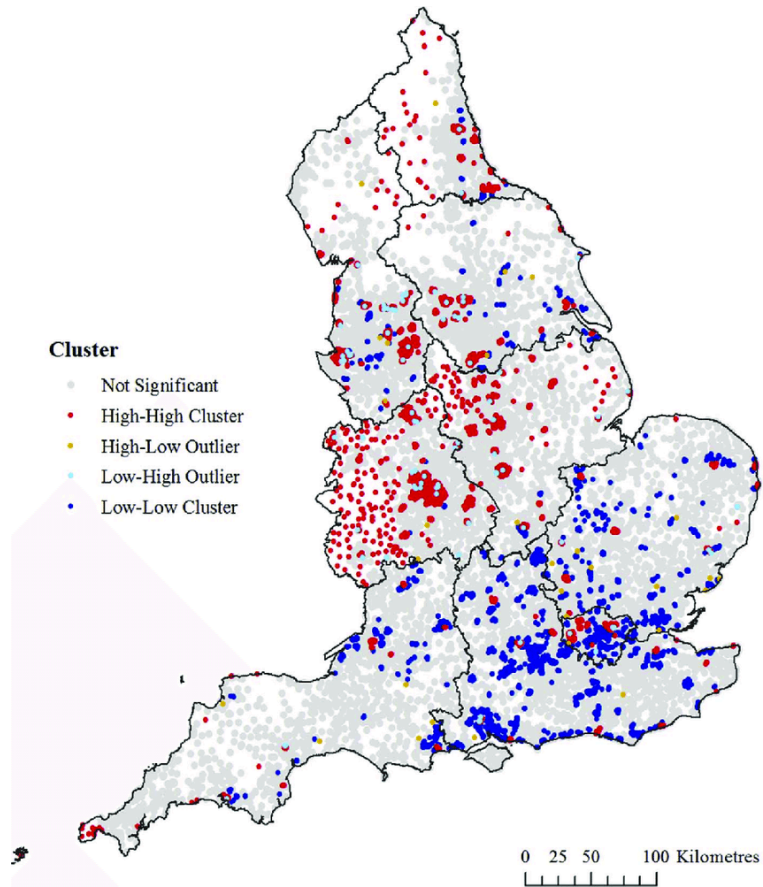


Marker (H3K27ac) into 2D mapping

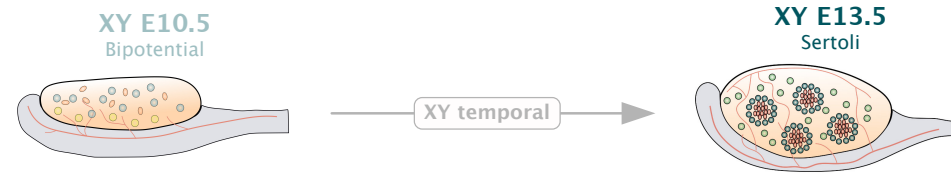
chr11:110780000-114770000



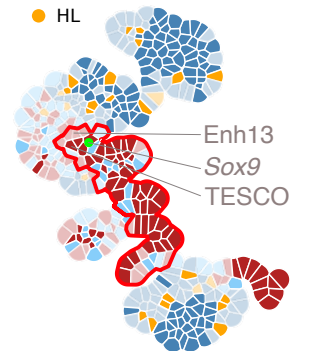
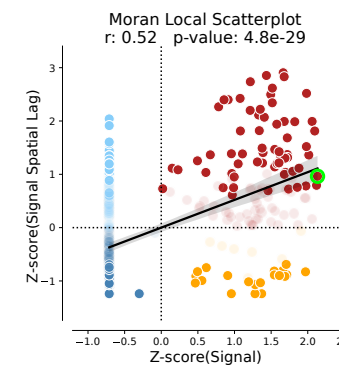
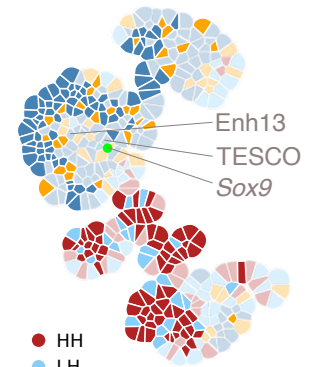
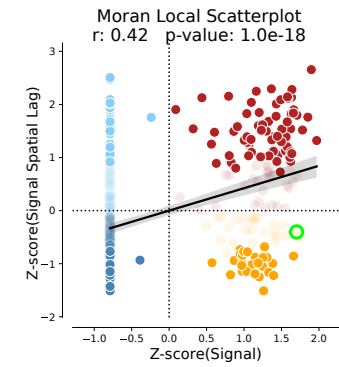
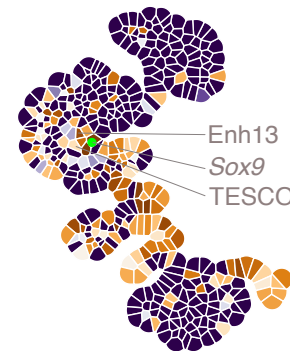
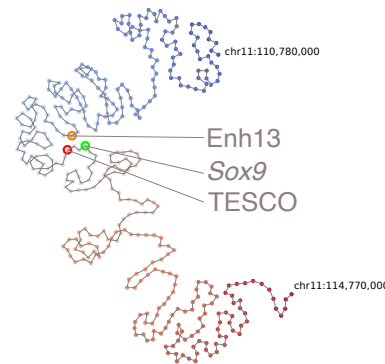
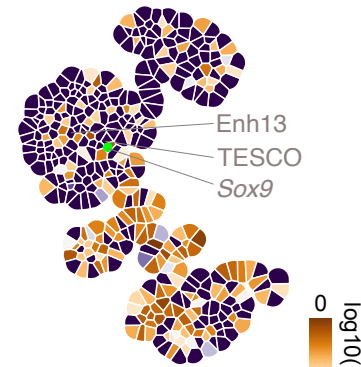
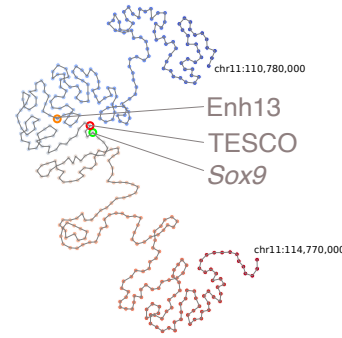
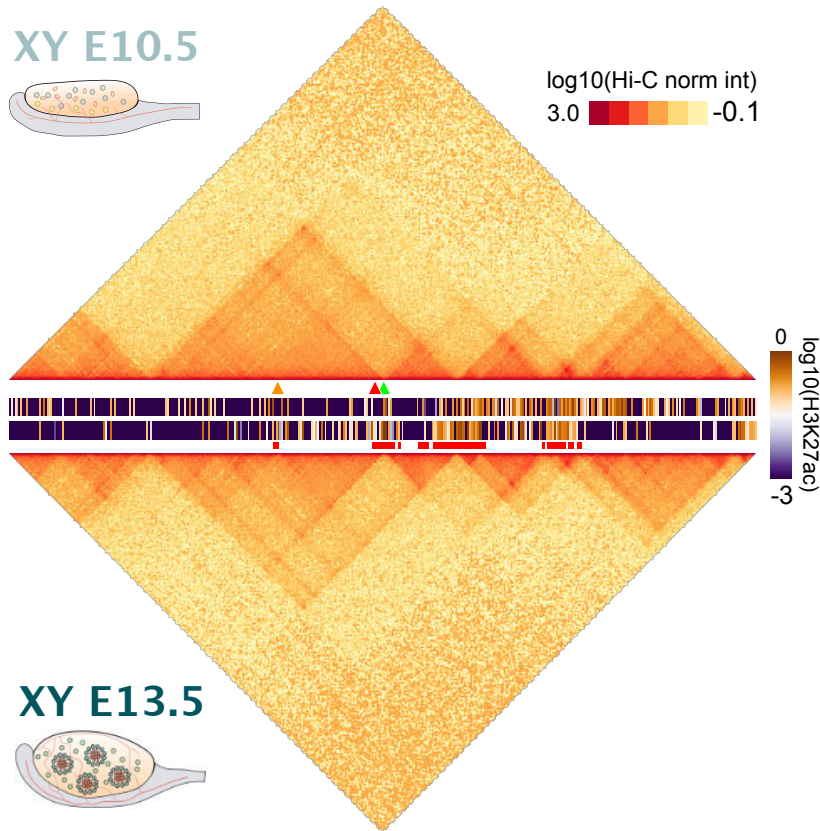
Local Moran Index



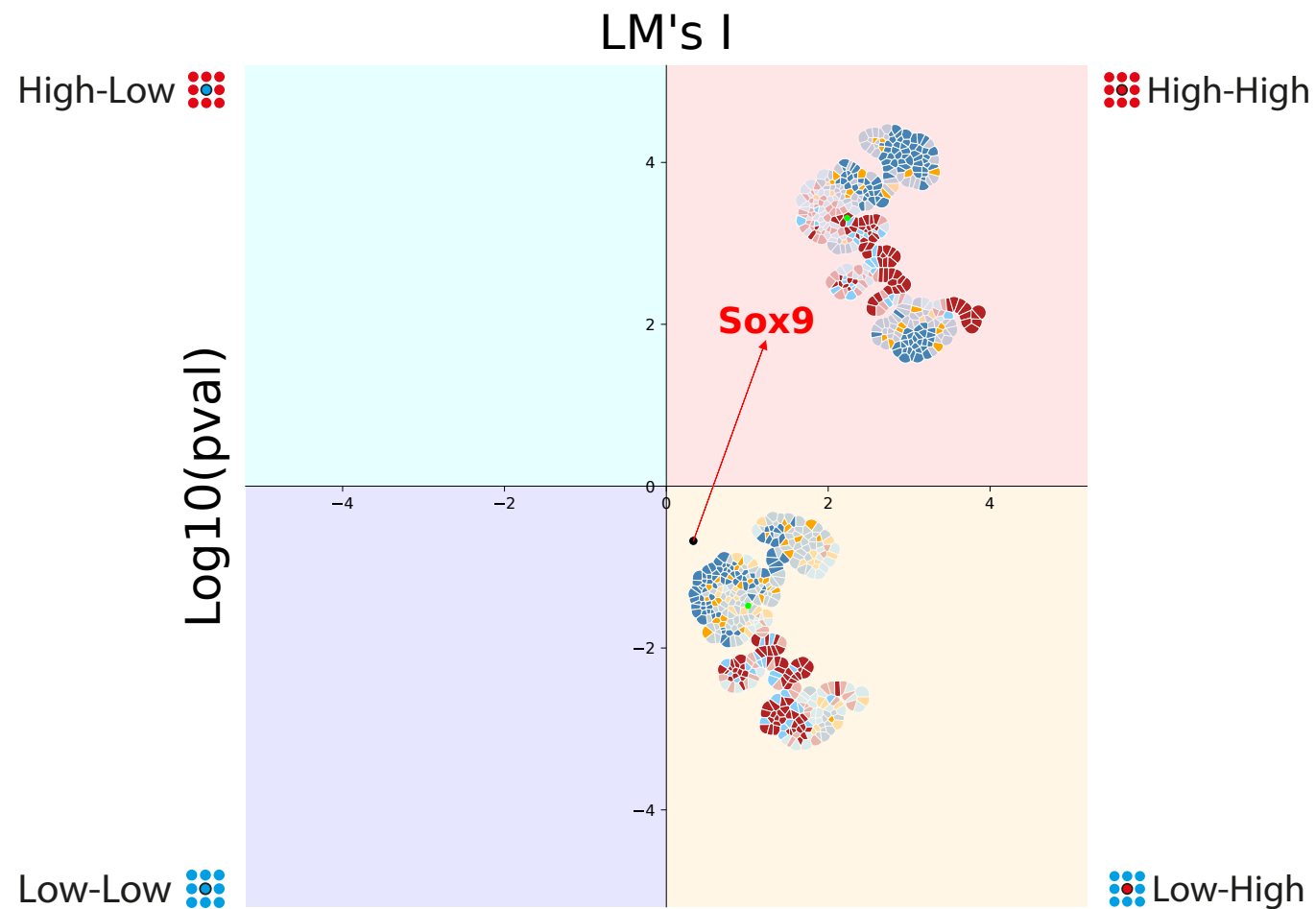
Quantifying regulatory environments bin by bin



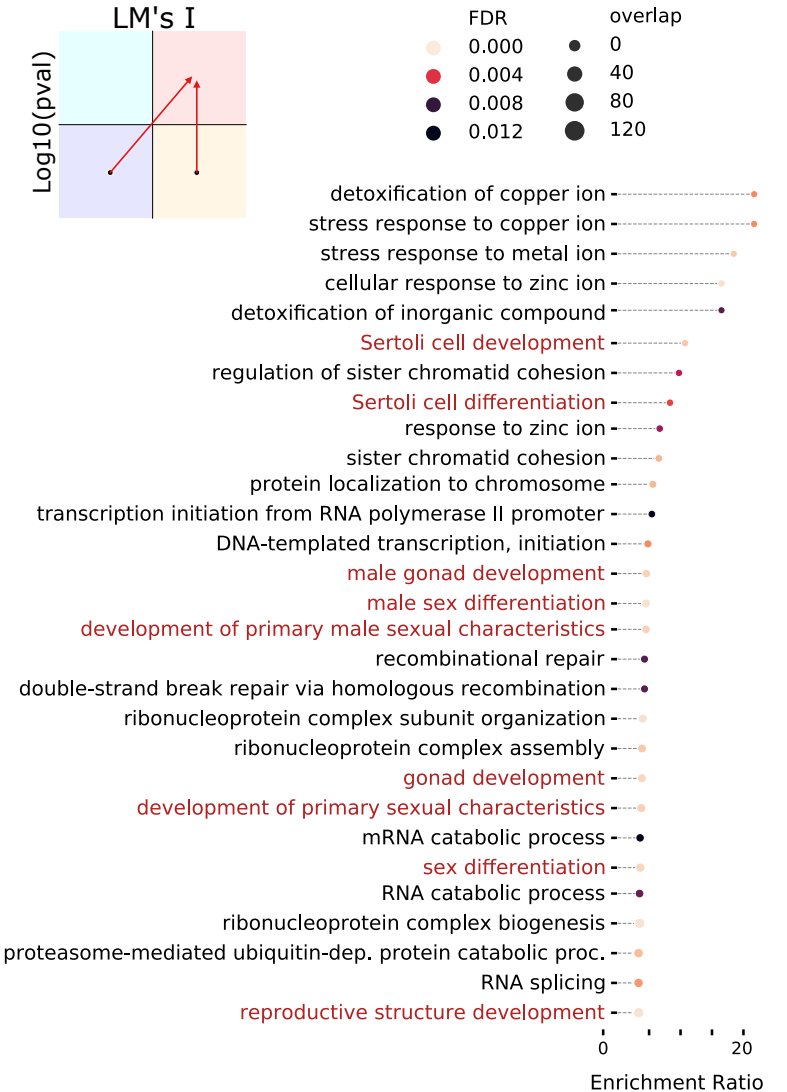
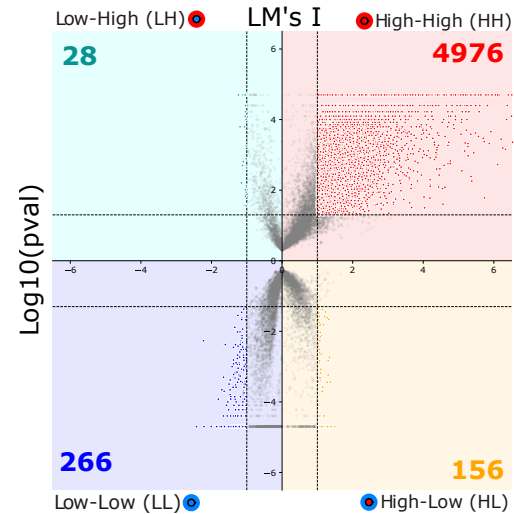
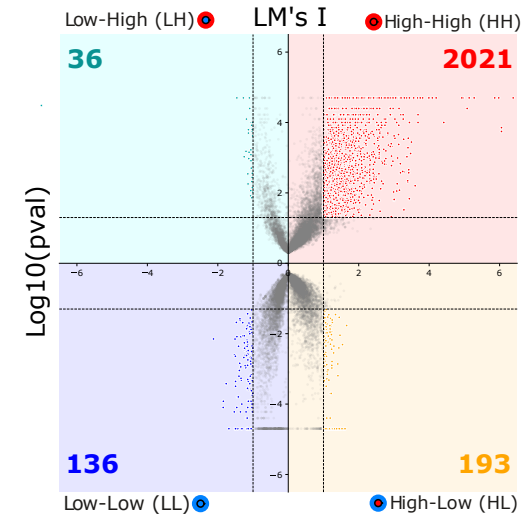
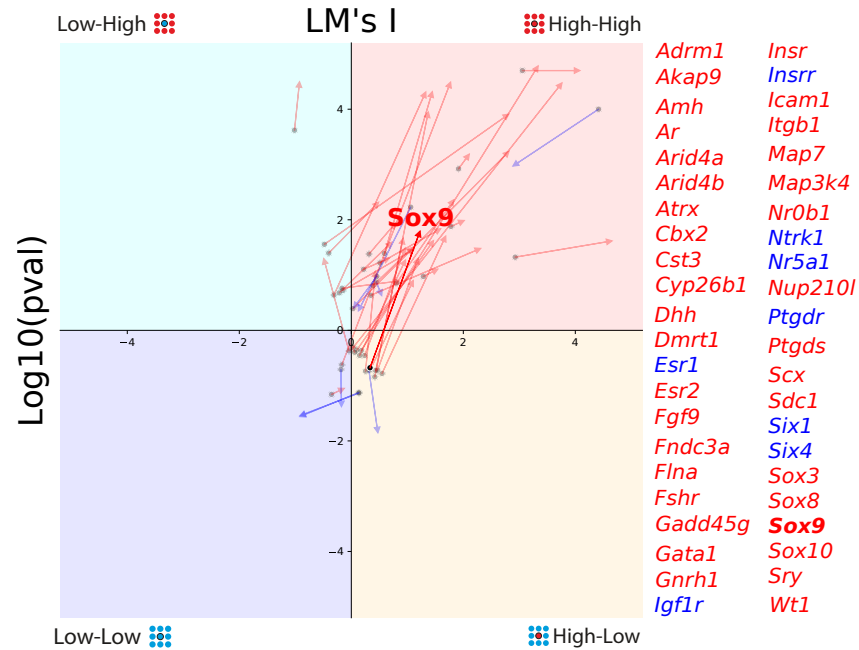
Sox9 locus chr11:110,780,000-114,770,000



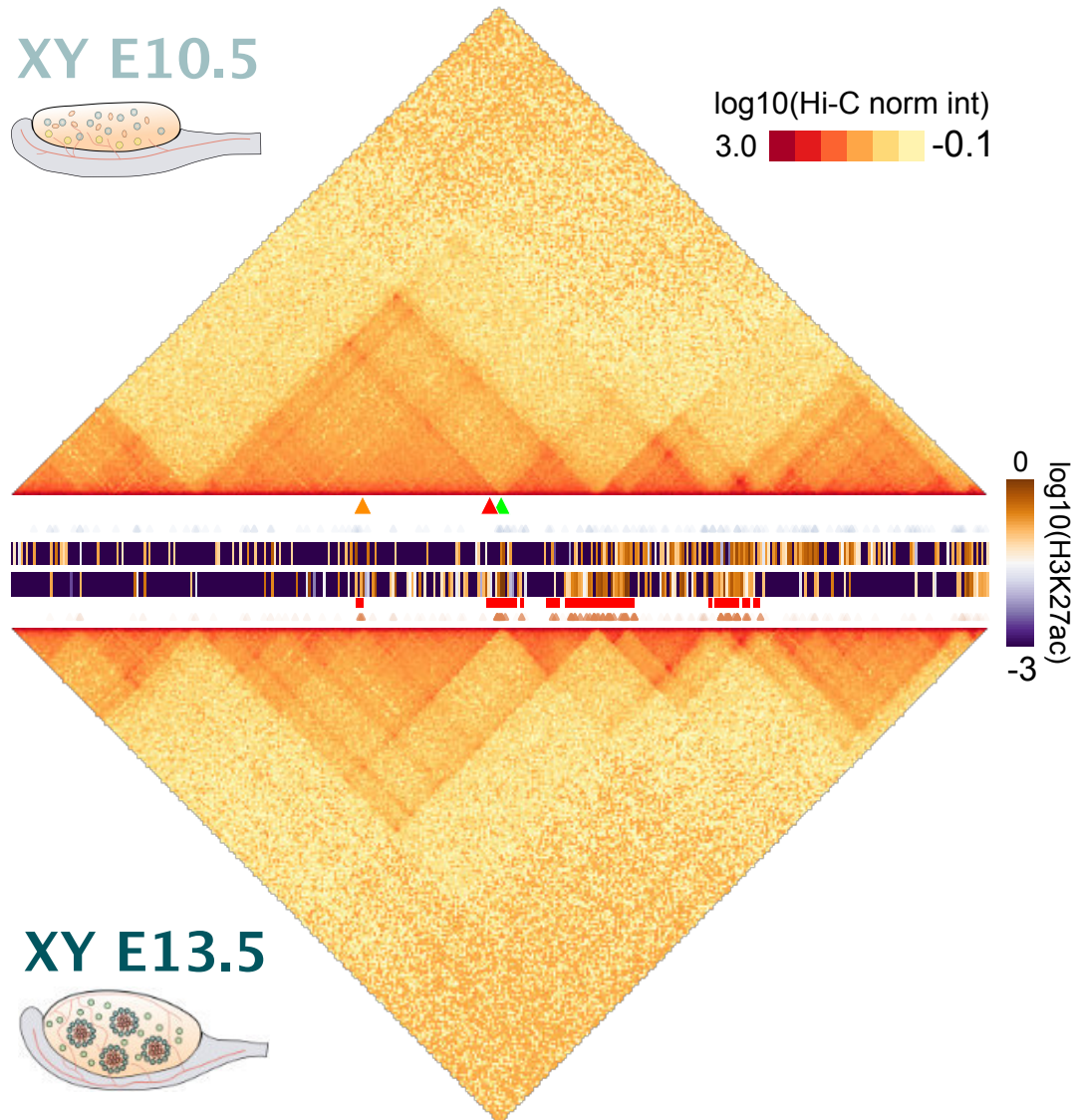
LMI Trip for Sox9 gene



All genes LMI Trip

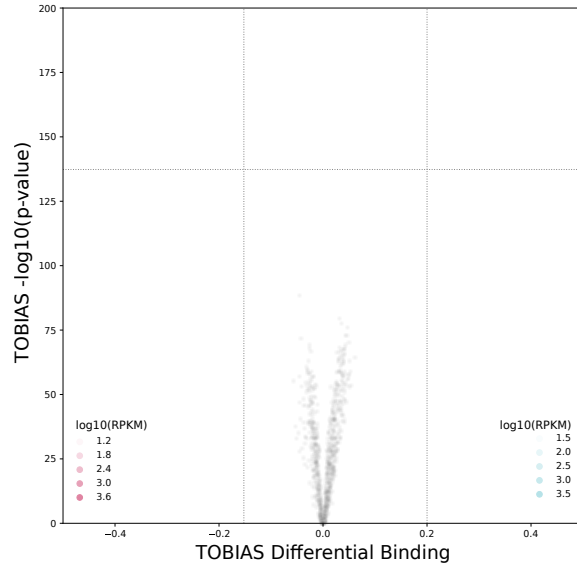
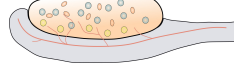


Are there specific Transcription Factors within the metaloci of Sox9?

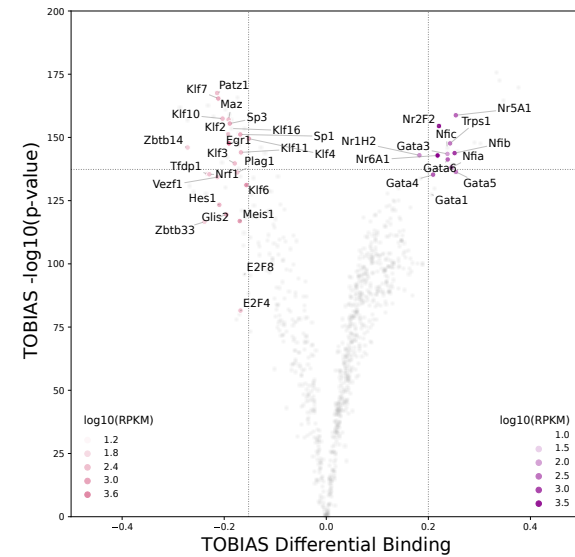
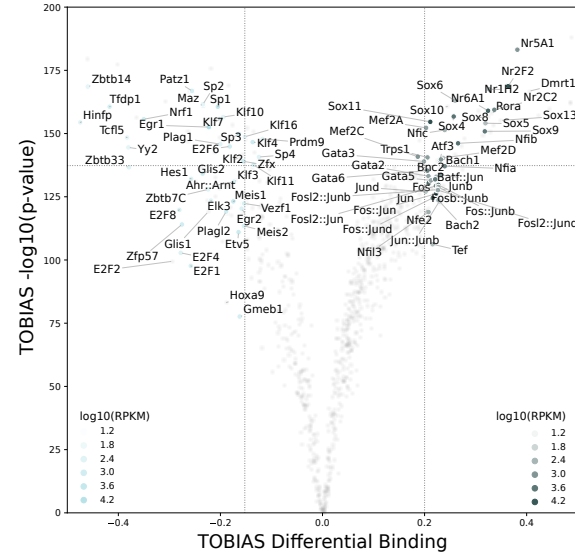
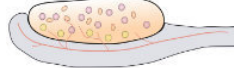


TF footprints

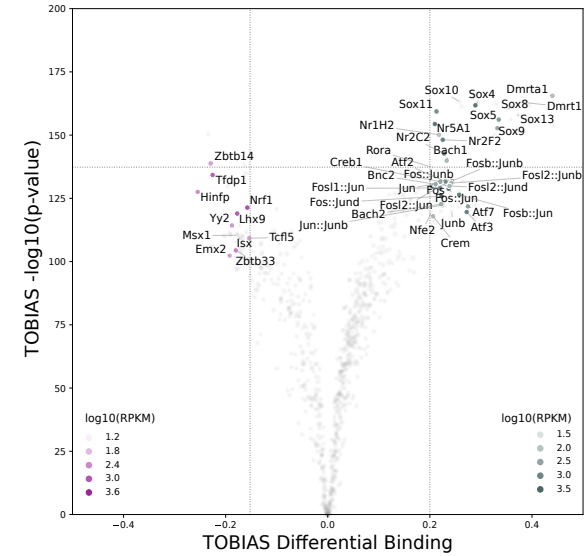
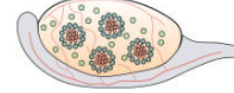
XY E10.5



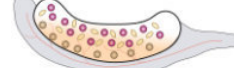
XX E10.5



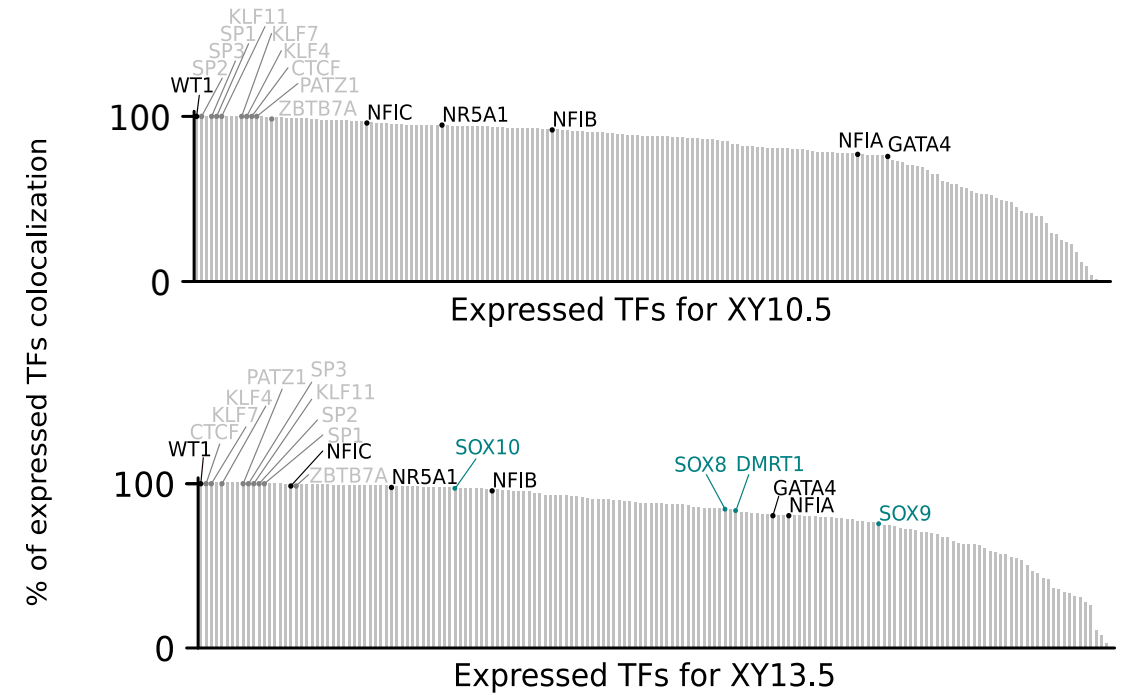
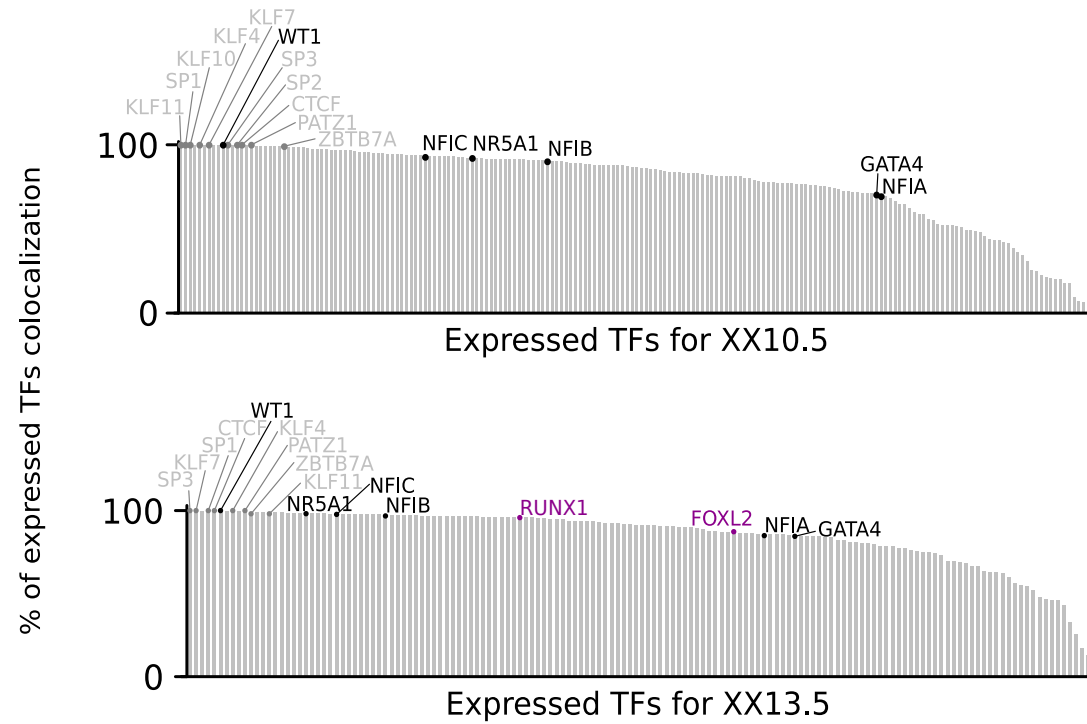
XY E13.5



XX E13.5



TF footprints

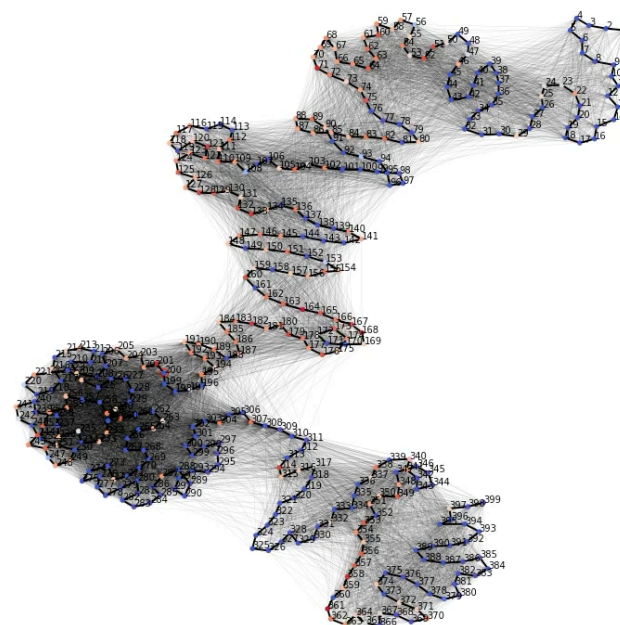


Now that we know the genes....

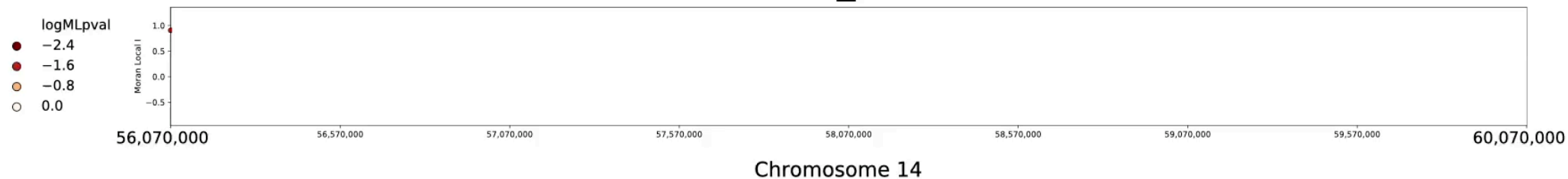
Can we identify regulatory elements using  METALoci

METALoci predictive mode

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



Fgf9

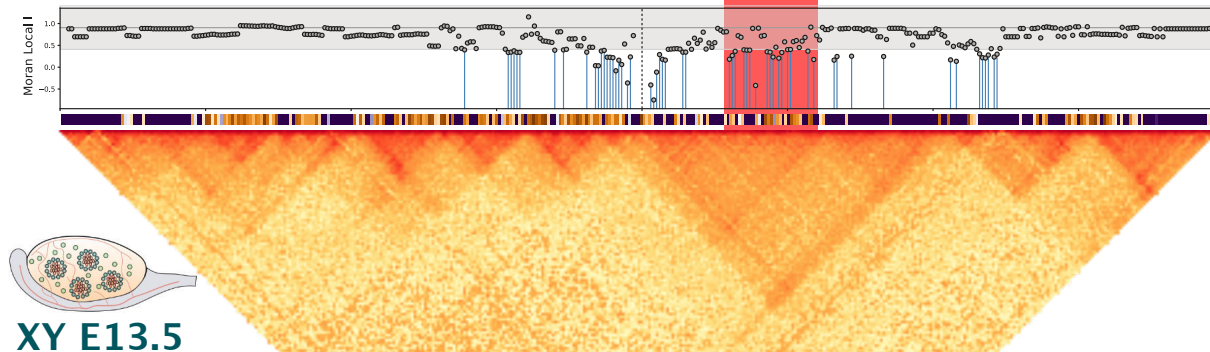
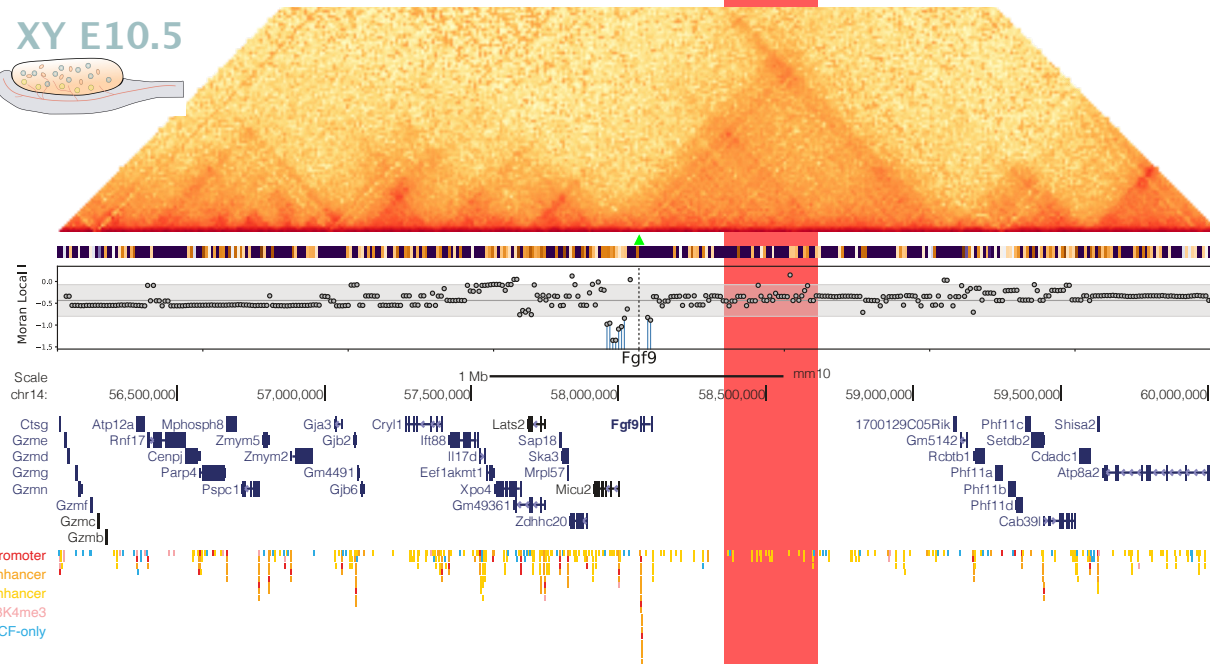
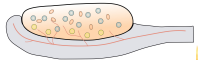


METALoci predictive mode

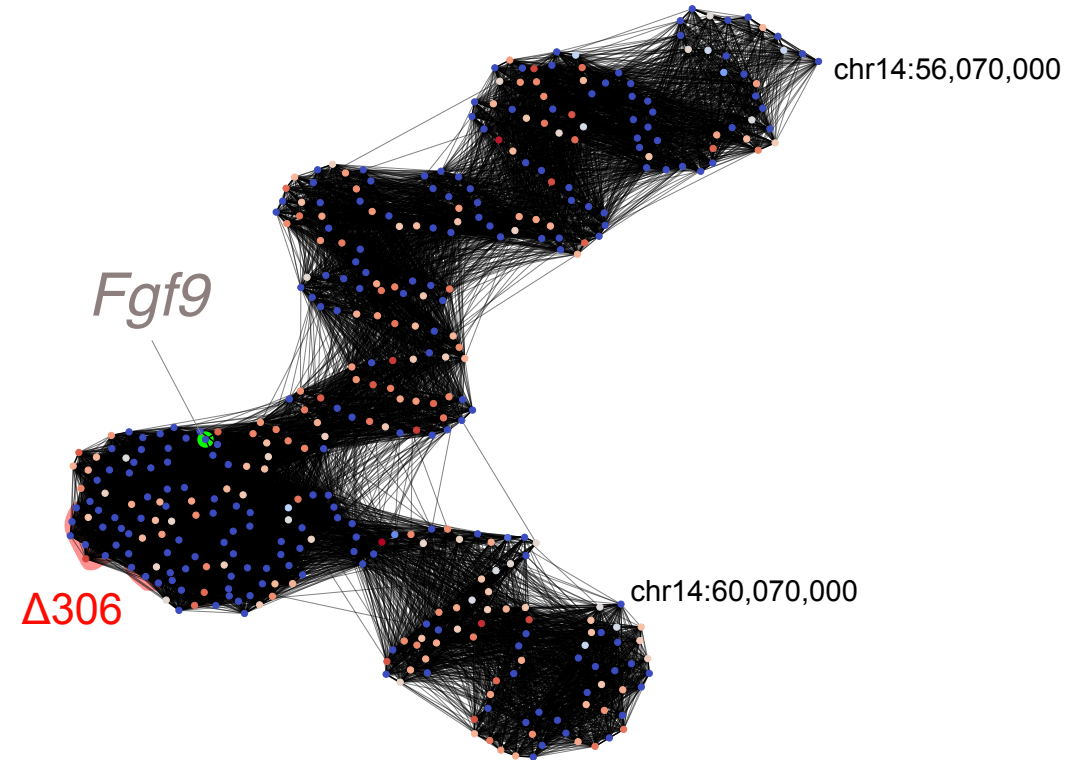
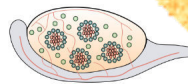
Fgf9 locus chr14:56,070,000-60,070,000

$\Delta 306$

XY E10.5

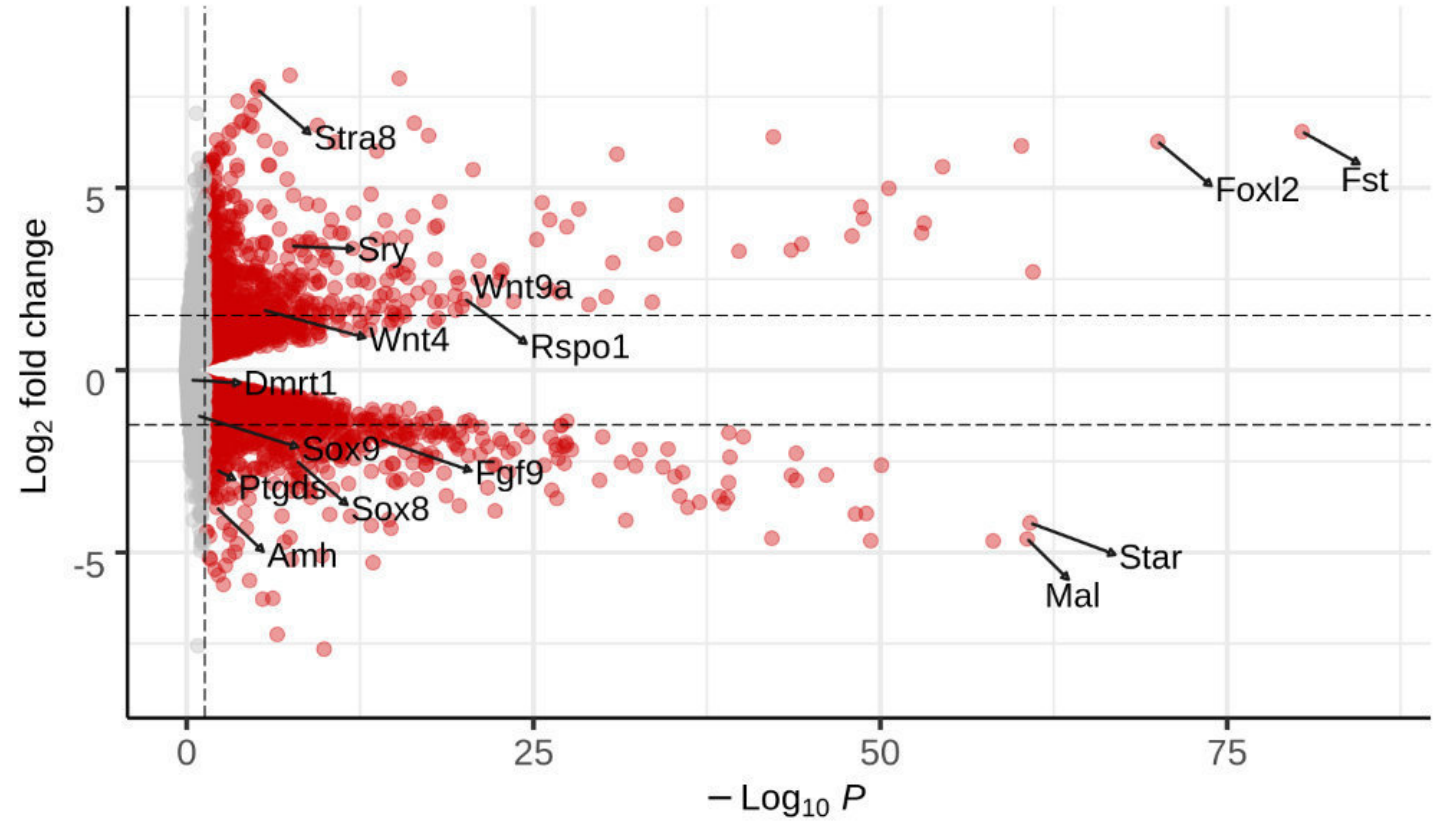
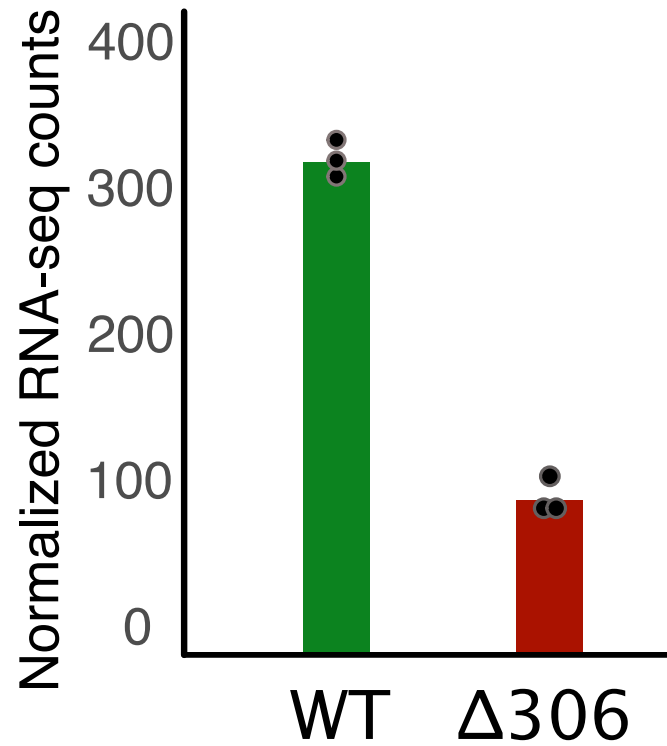


XY E13.5



METALoci predictive mode

Fgf9 XY $\Delta 306$ mutant



METALoci predictive mode

Fgf9 XY $\Delta 306$ mutant

XY Wildtype



Testis

XY $\Delta 306$



Ovotestis



Ovary-like

XX Wildtype

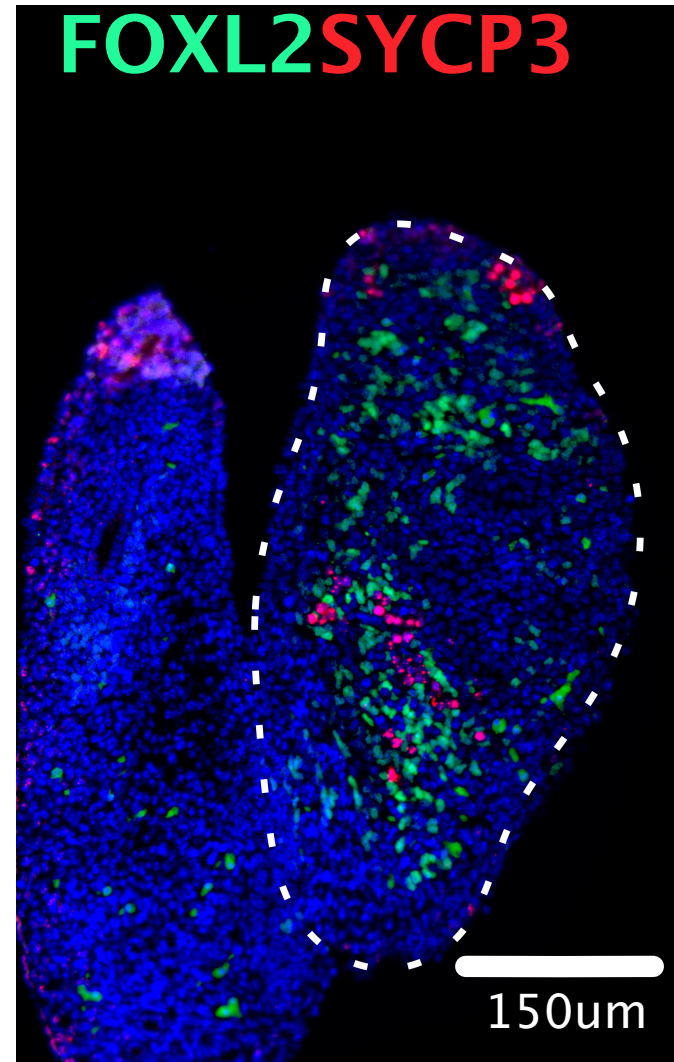
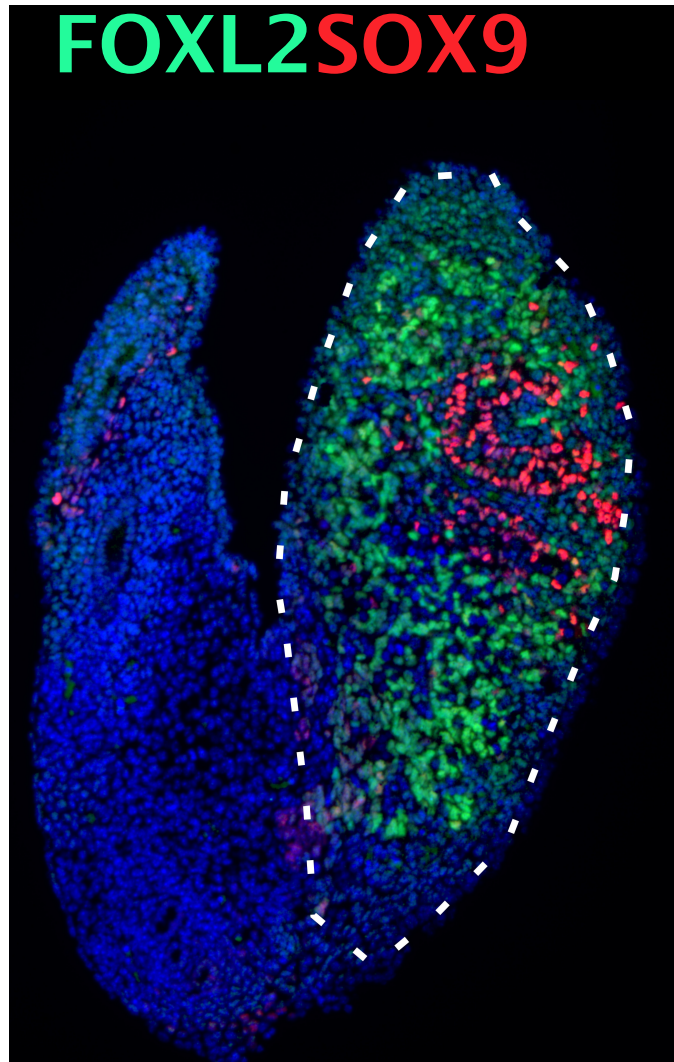


Ovary

250um

METALoci predictive mode

Fgf9 XY $\Delta 306$ mutant



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