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**Marc A. Martí-Renom**

CNAG-CRG · ICREA

Unpublished

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

**cnag CRG**  ICREA



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# Spatio-temporal regulatory landscape of sex-determination



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Irene Mota  
Dario Lupiañez

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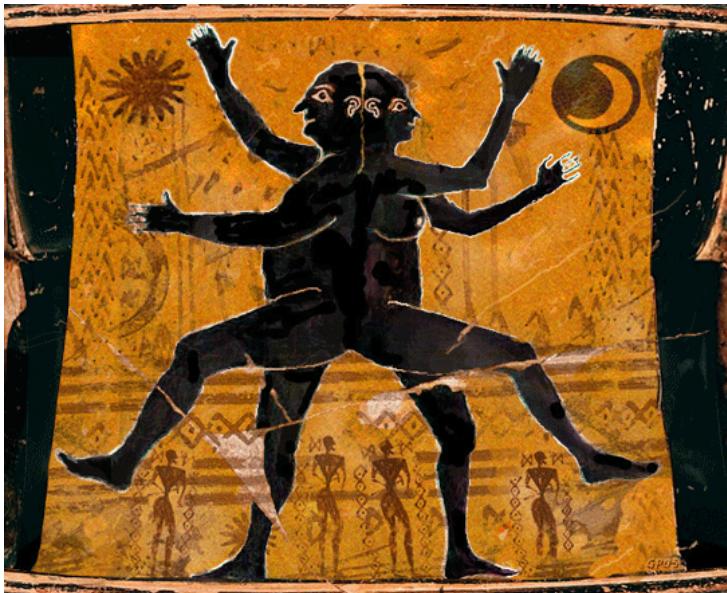
CNAG-CRG · ICREA

Unpublished

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

# Sex determination: a 3,000 year-old enigma

## Mythology



Hermaphrodite primeval men

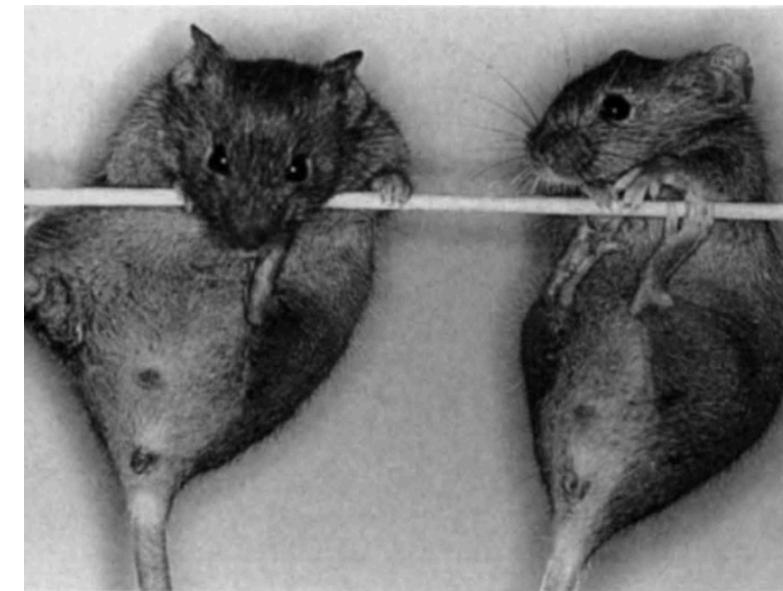
*Plato's symposium, 385-370 BC*

## Theories



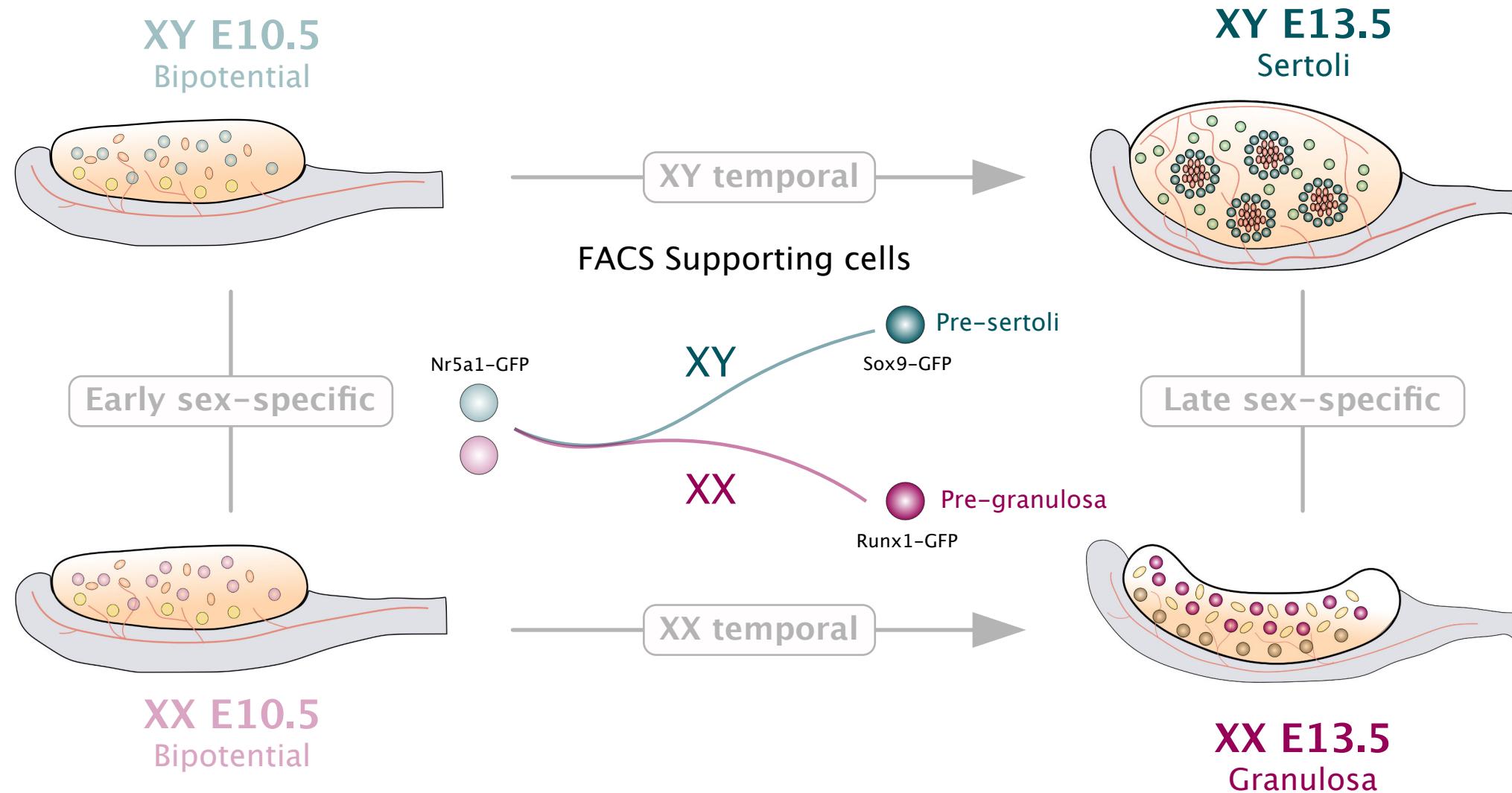
Left-right theory  
*Alexandrian manuscripts, 1st cent. BC*

## Genetics

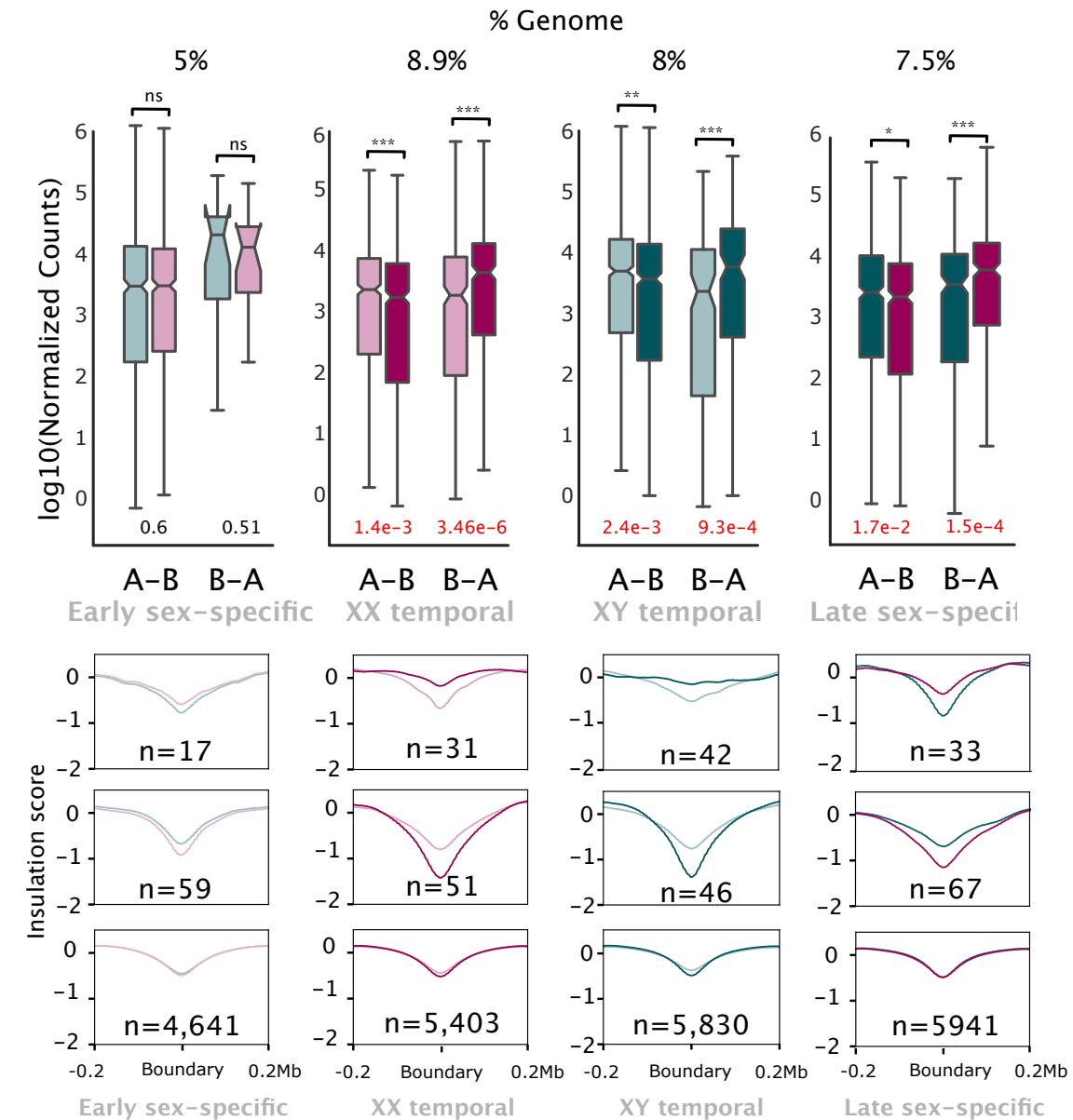
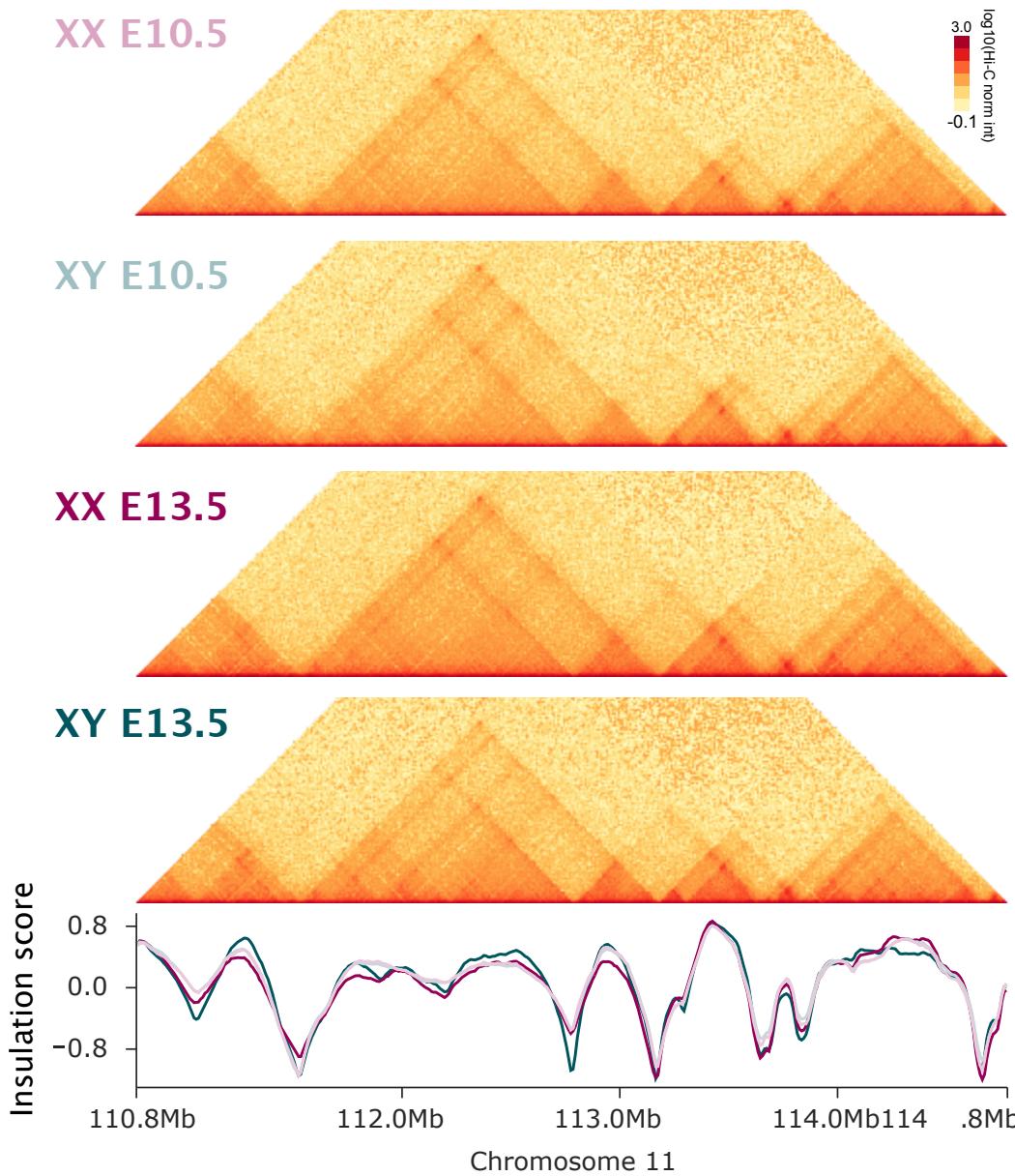


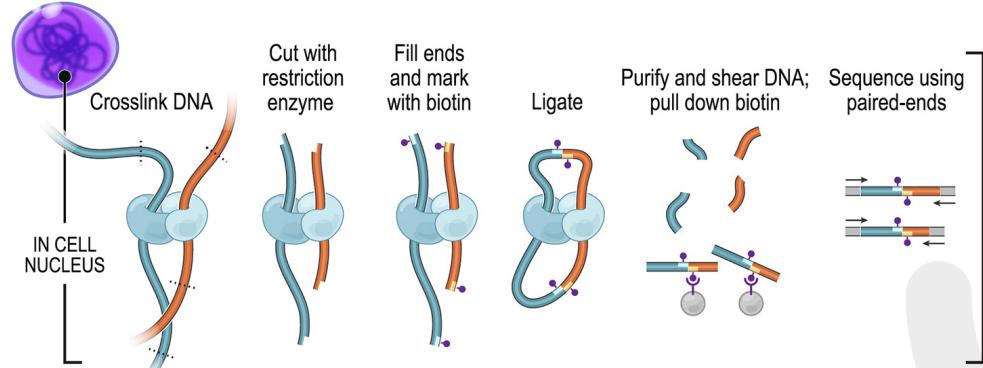
Discovery of *Sry* gene  
*Koopman et al., Nature, 1991*  
*(Goodfellow & LovellBadge labs)*

# Sex-determination as a model for “bipotential” commitment



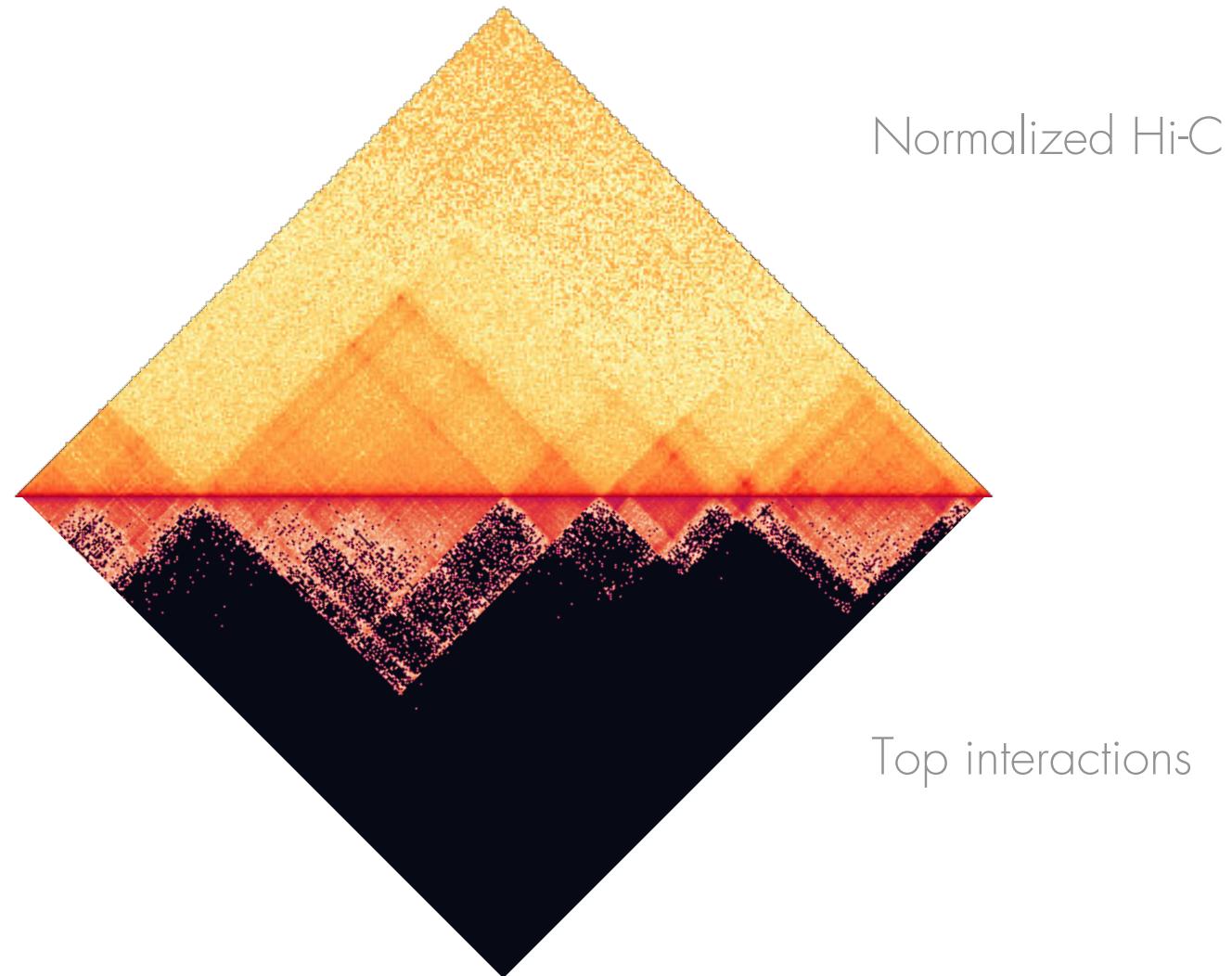
# No major structural (apparent) differences





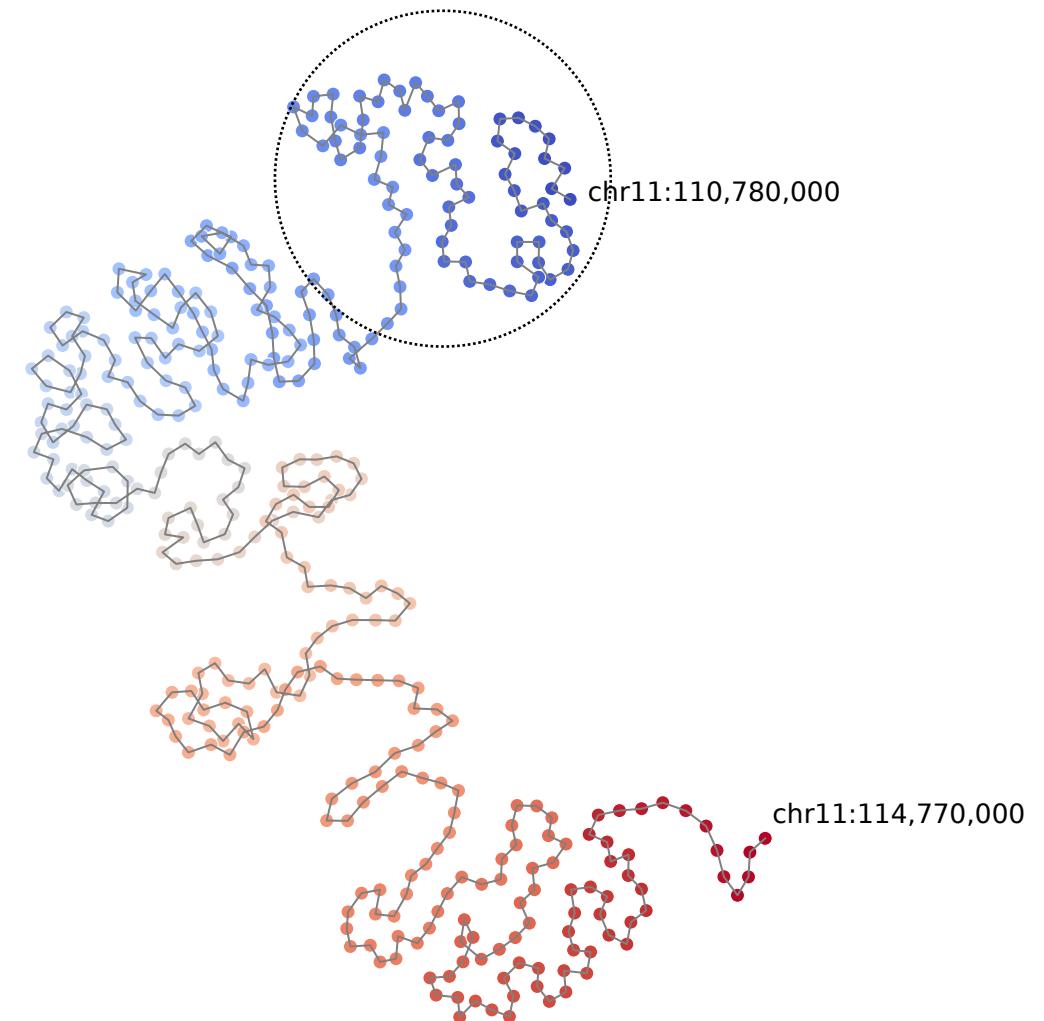
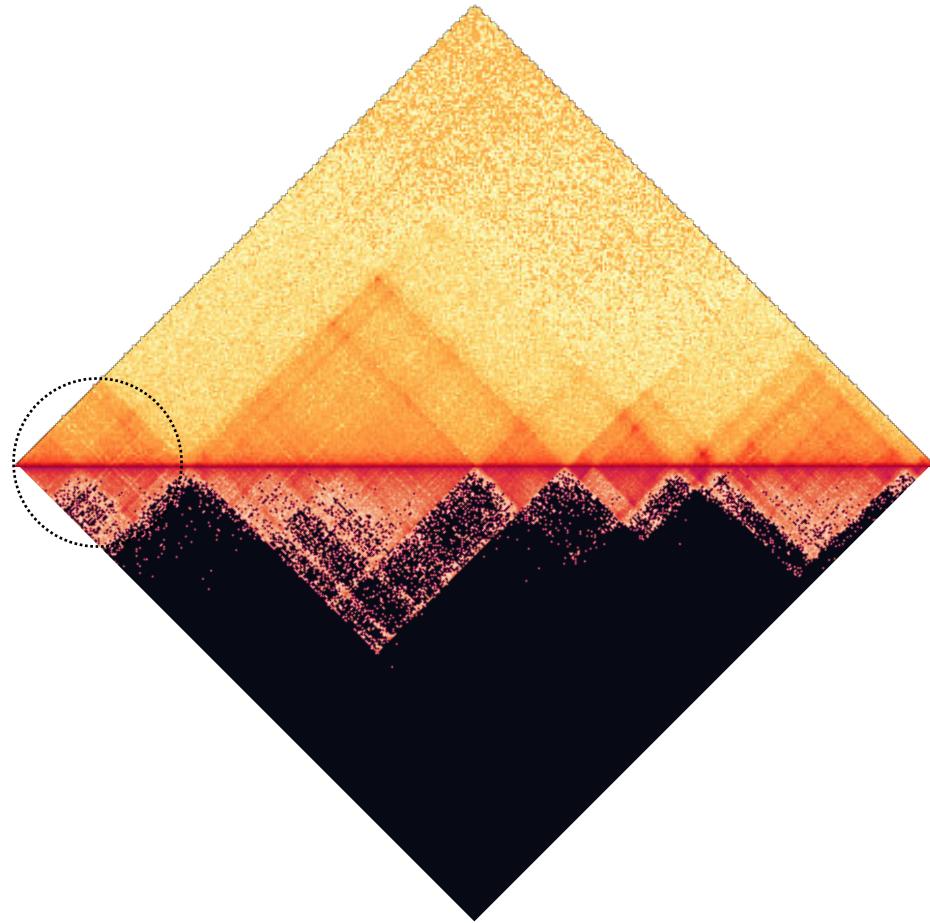
# Hi-C normalization and interaction selection

chr11:110780000-114770000



# Spatial lay-out of significant interactions

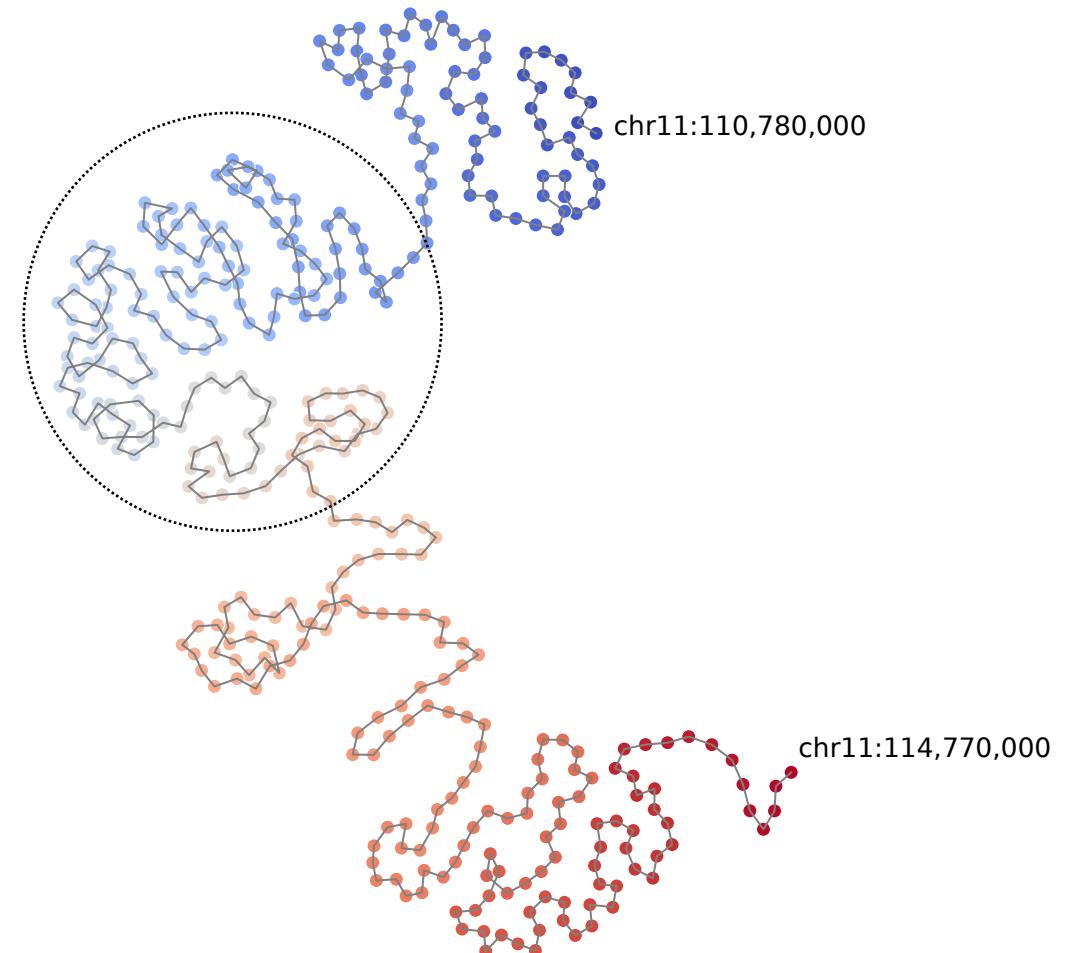
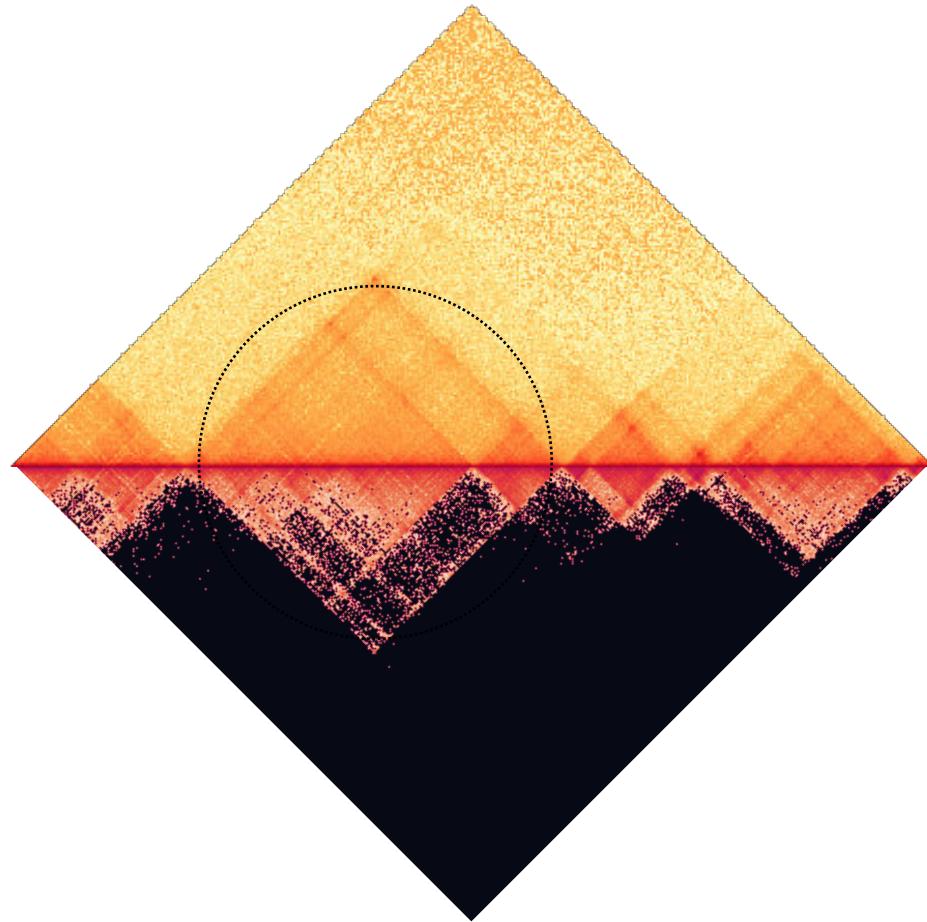
chr11:110780000-114770000



Kamada & Kawai, 1989

# Spatial lay-out of significant interactions

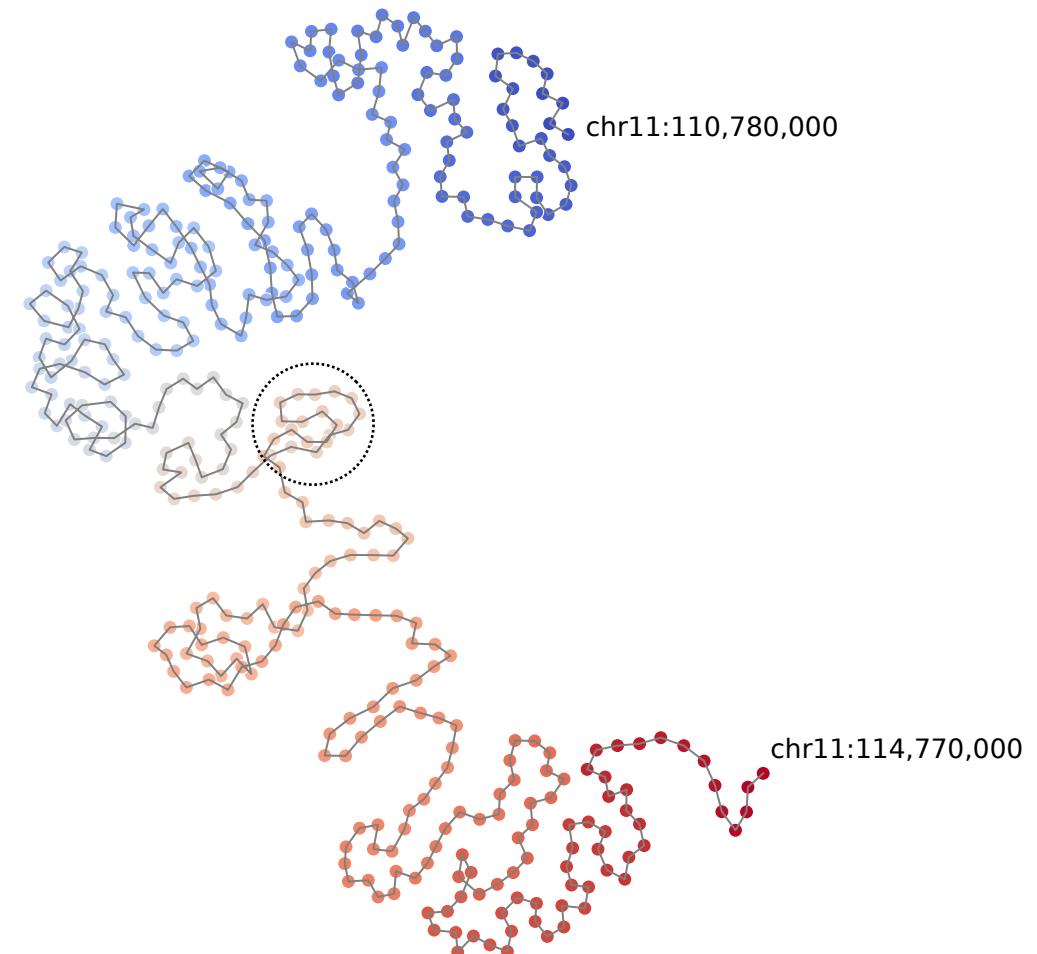
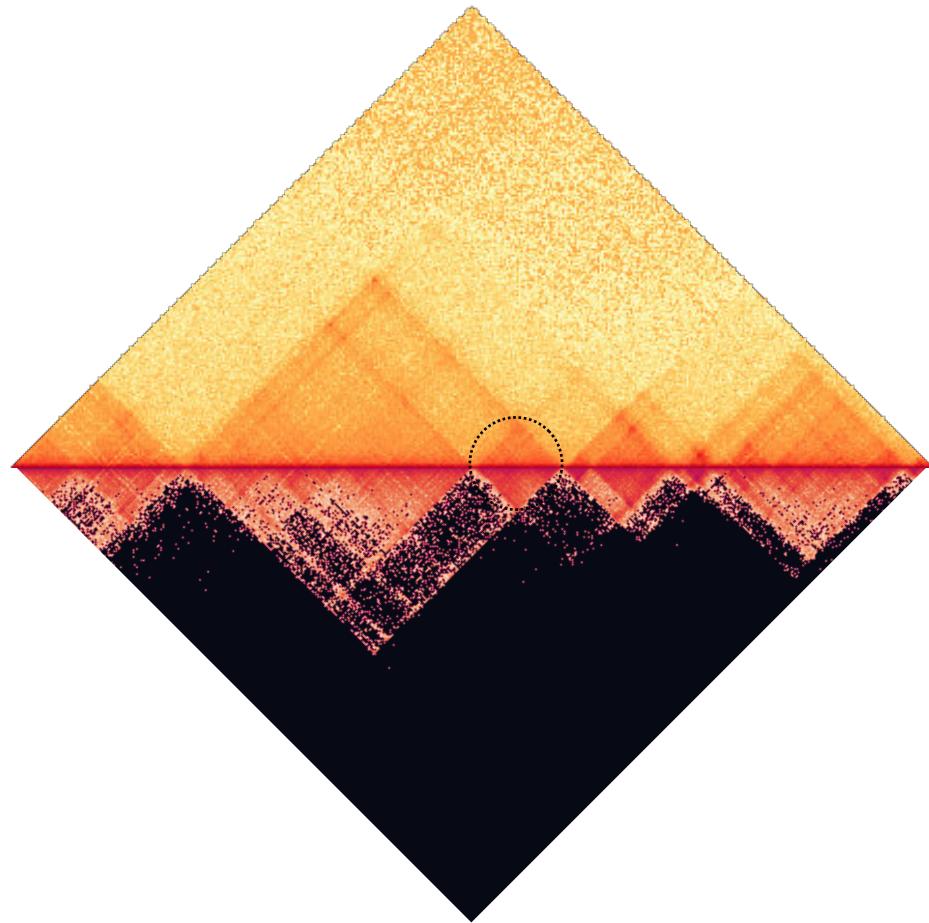
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Kamada & Kawai, 1989

# Spatial lay-out of significant interactions

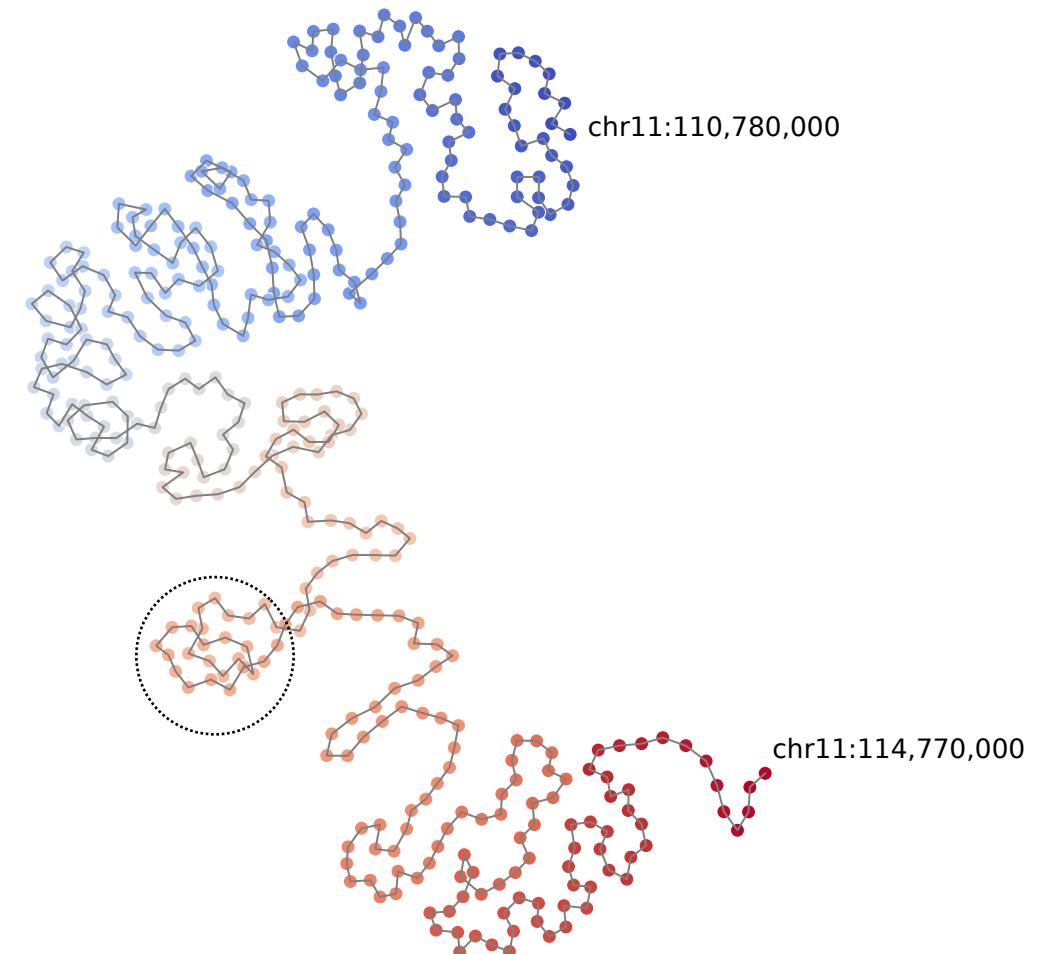
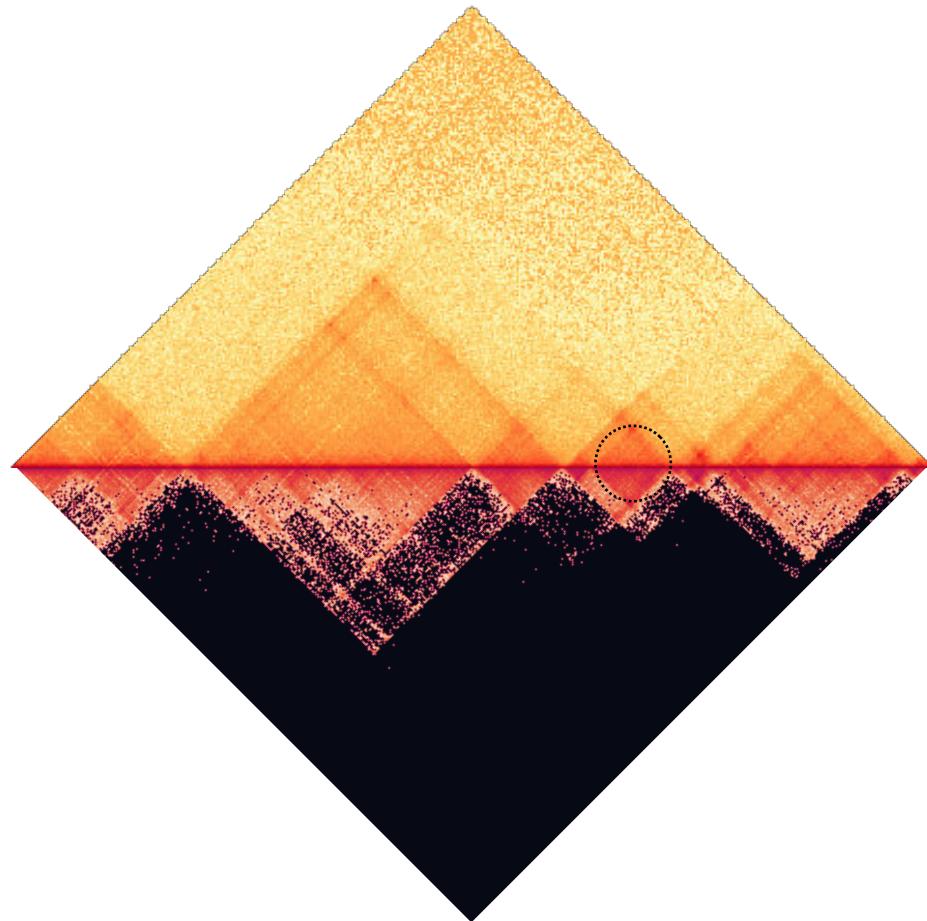
chr11:110780000-114770000



Kamada & Kawai, 1989

# Spatial lay-out of significant interactions

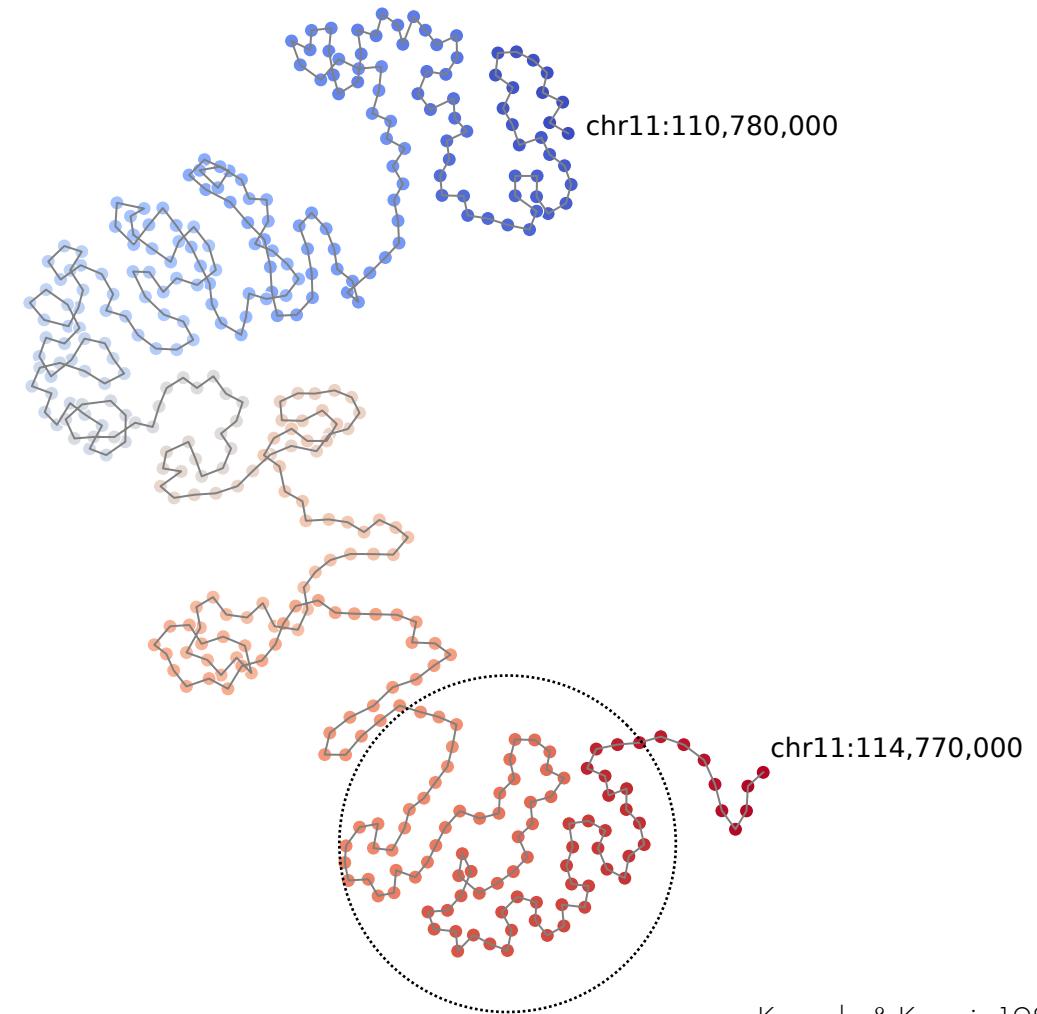
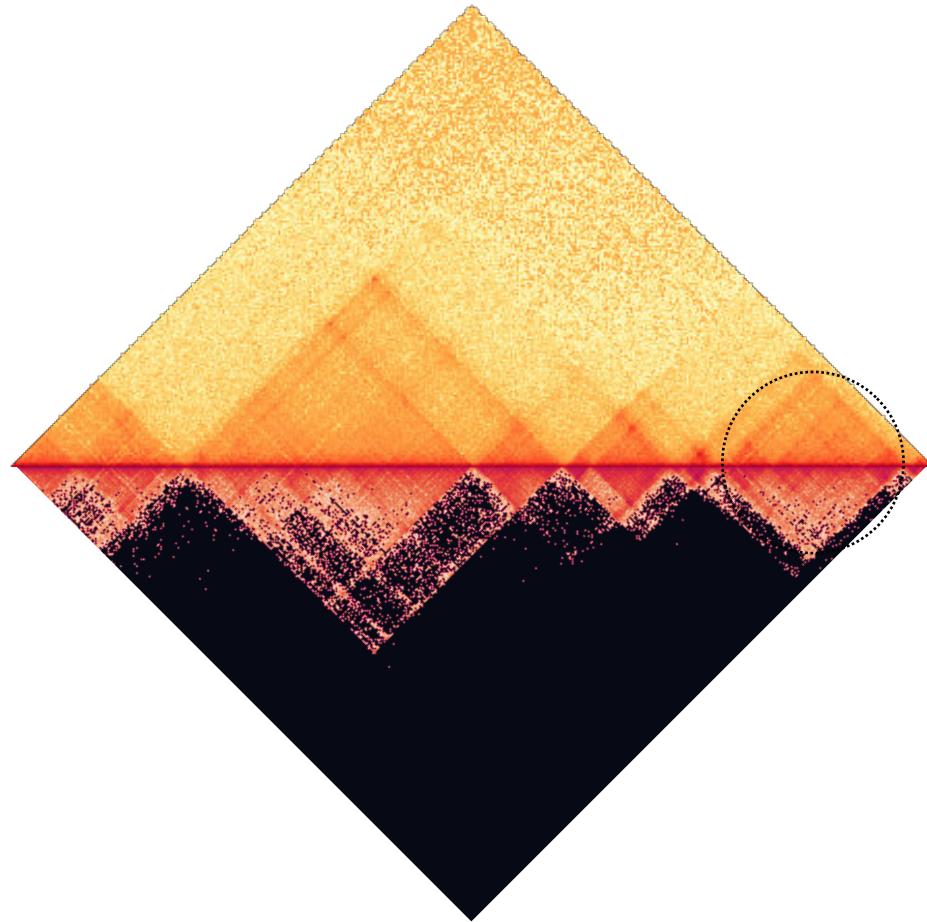
chr11:110780000-114770000



Kamada & Kawai, 1989

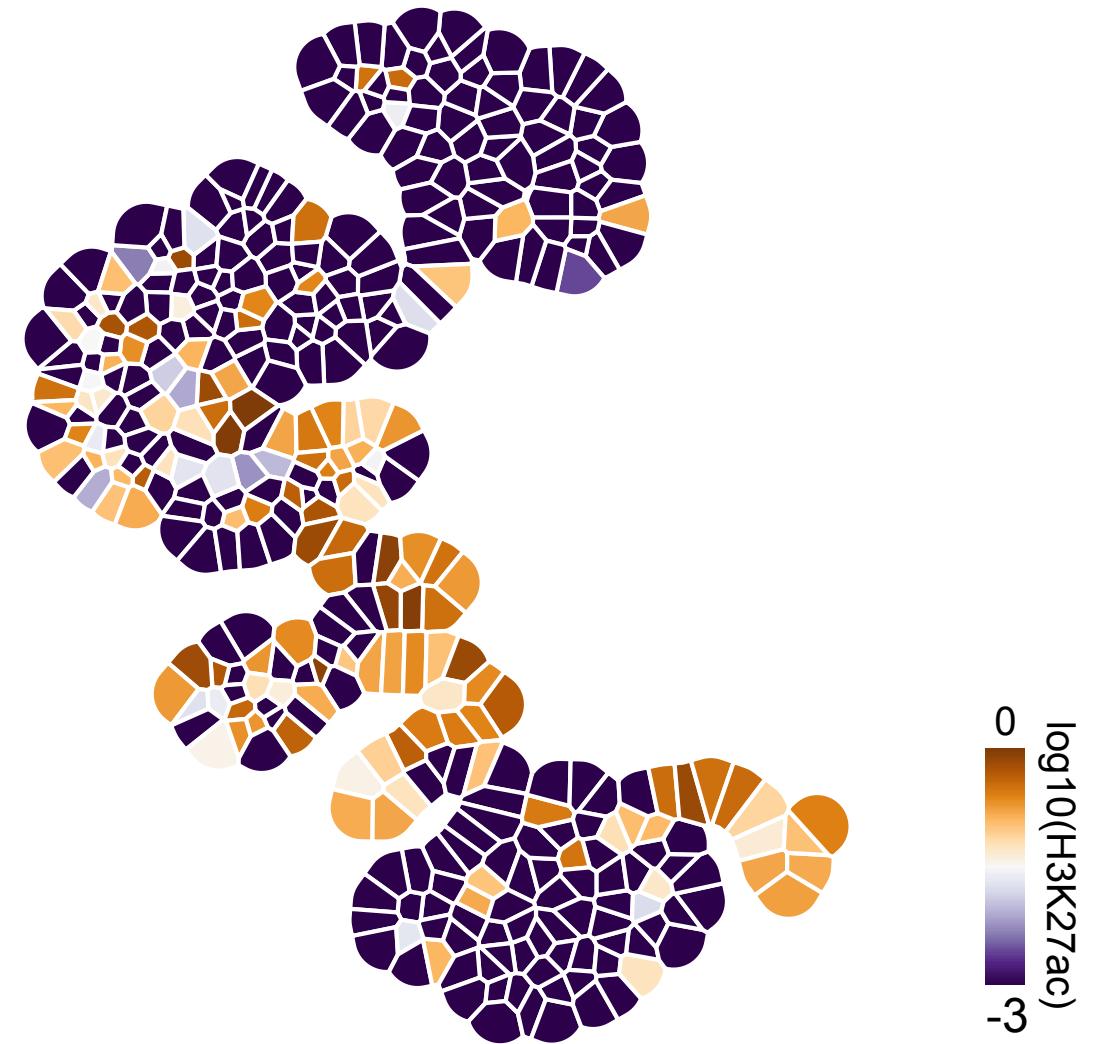
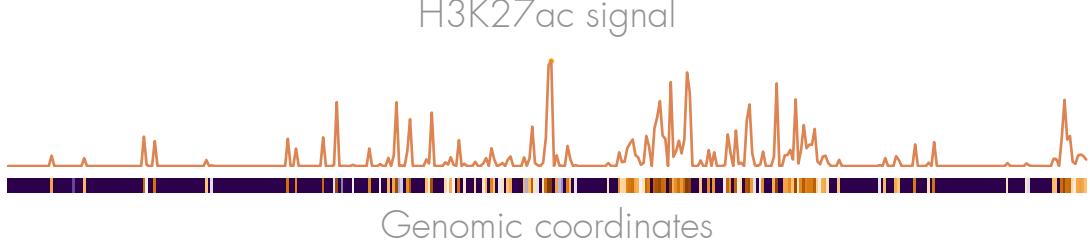
# Spatial lay-out of significant interactions

chr11:110780000-114770000

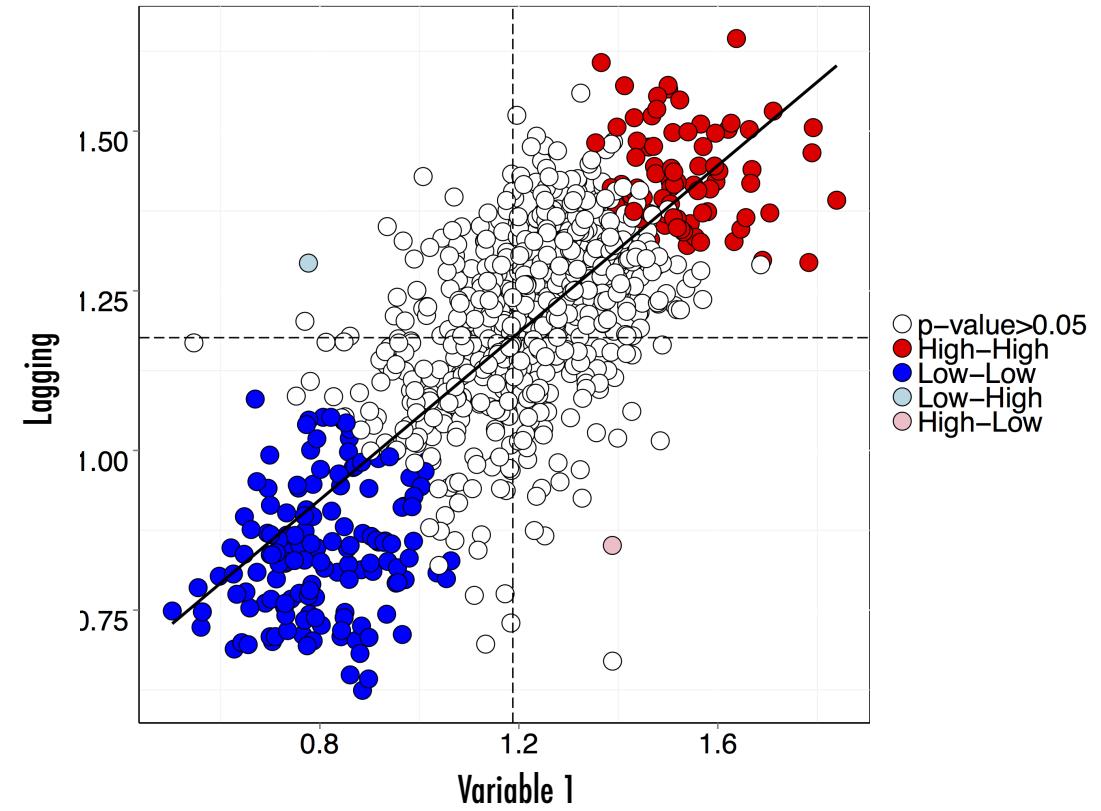
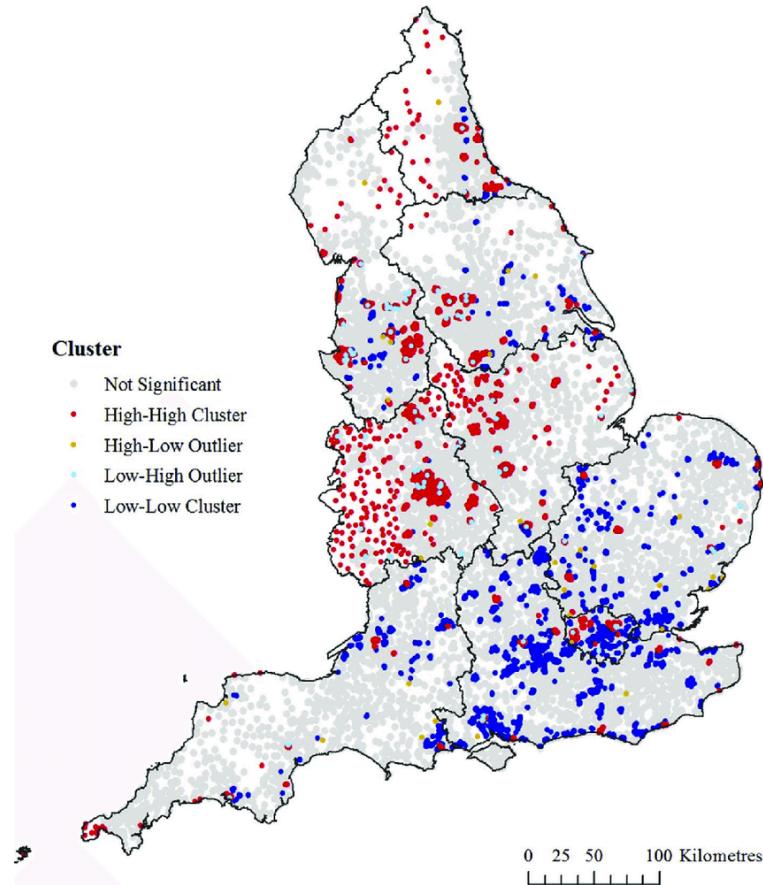


# Marker (H3K27ac) into 2D mapping

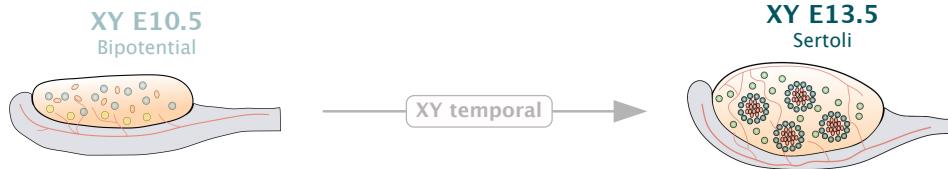
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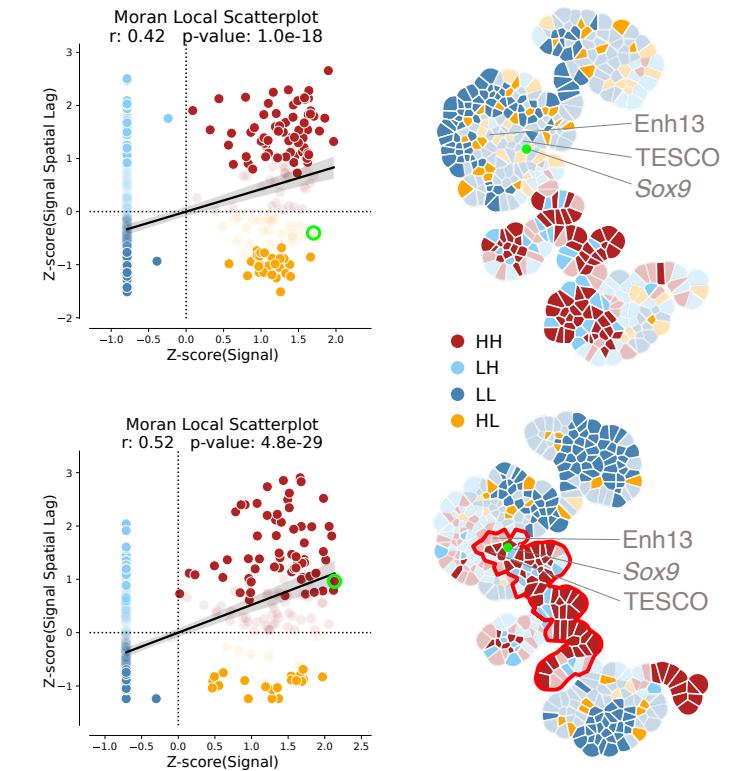
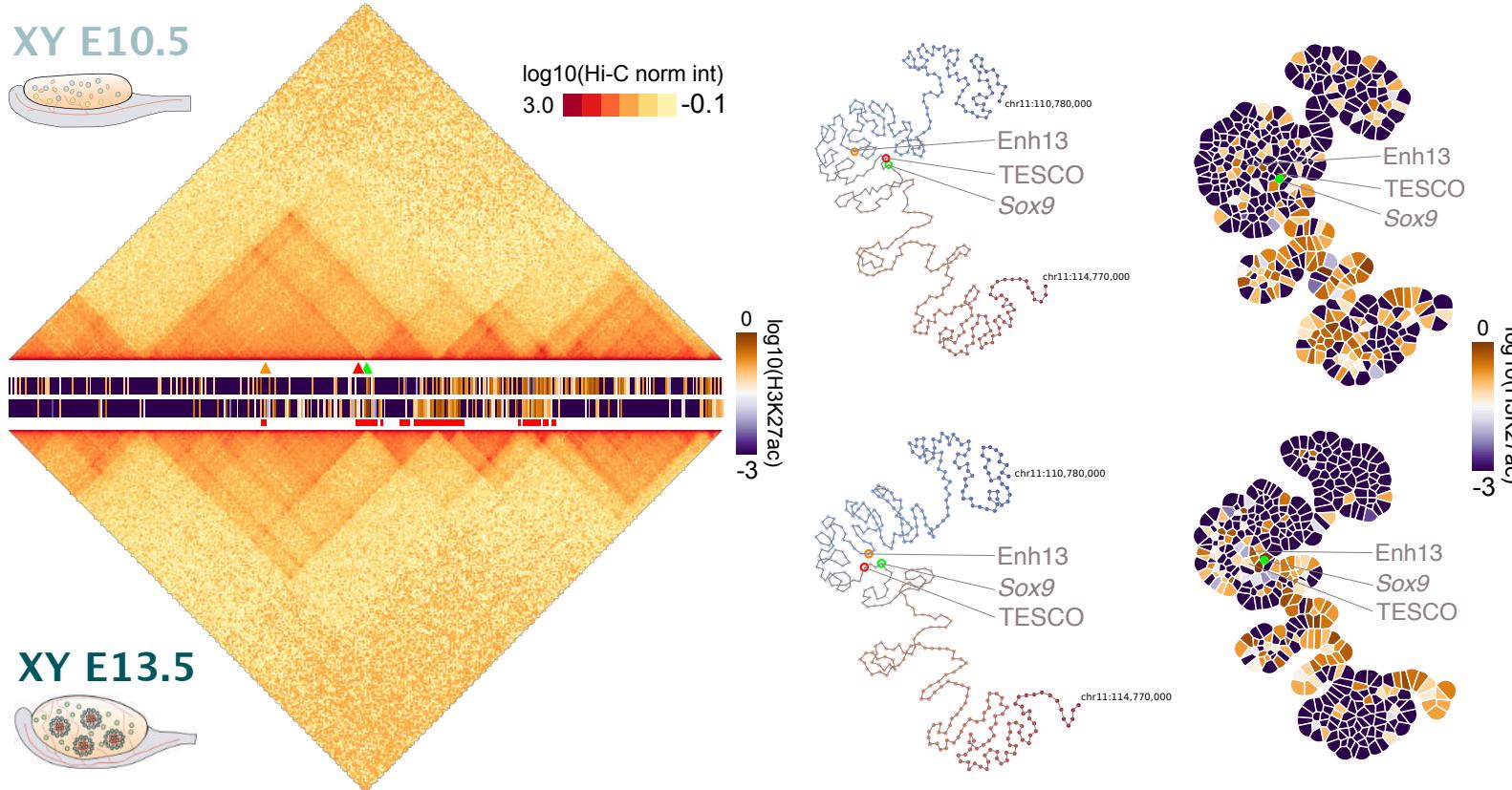
# Local Moran Index



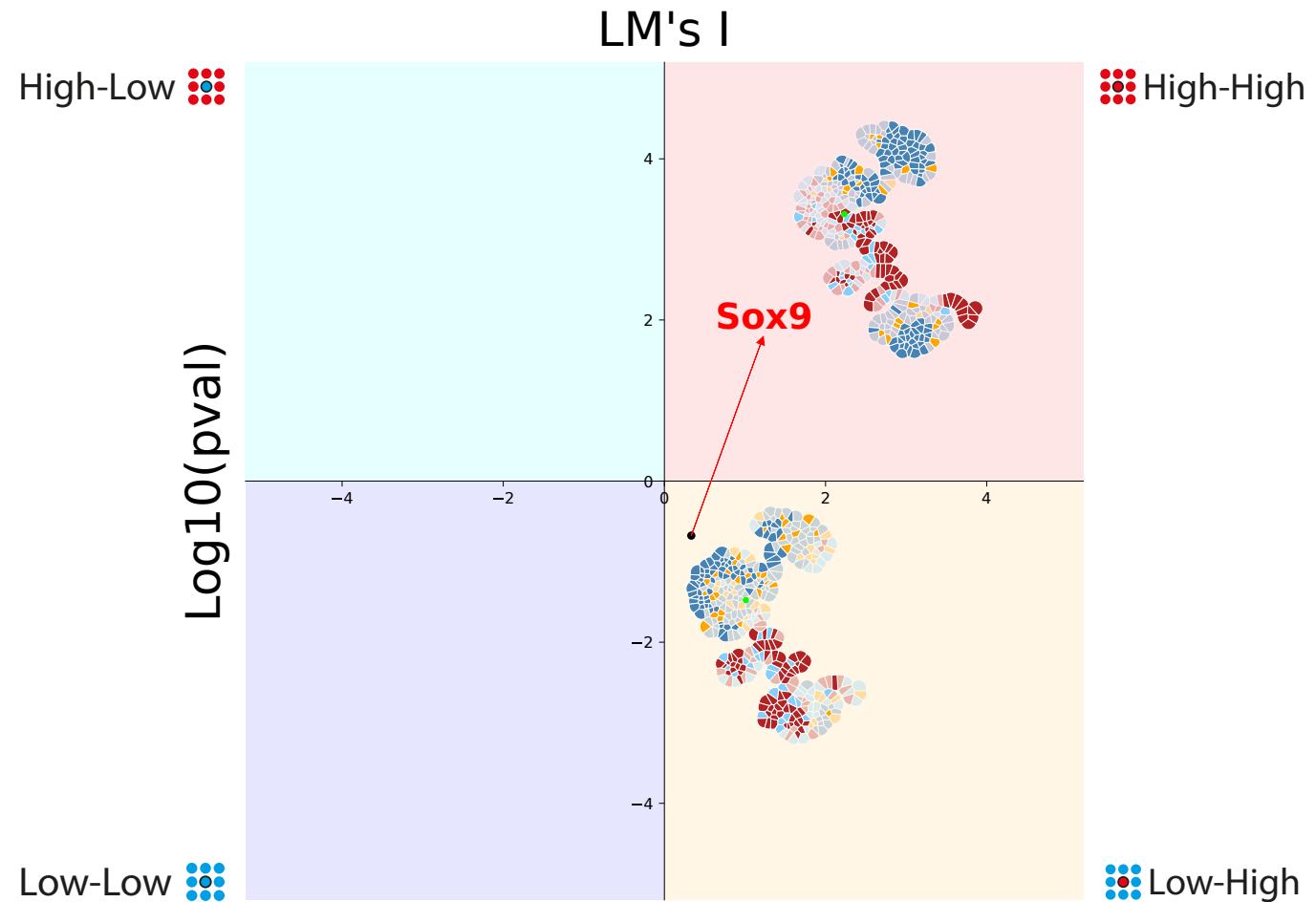
# Quantifying regulatory environments bin by bin



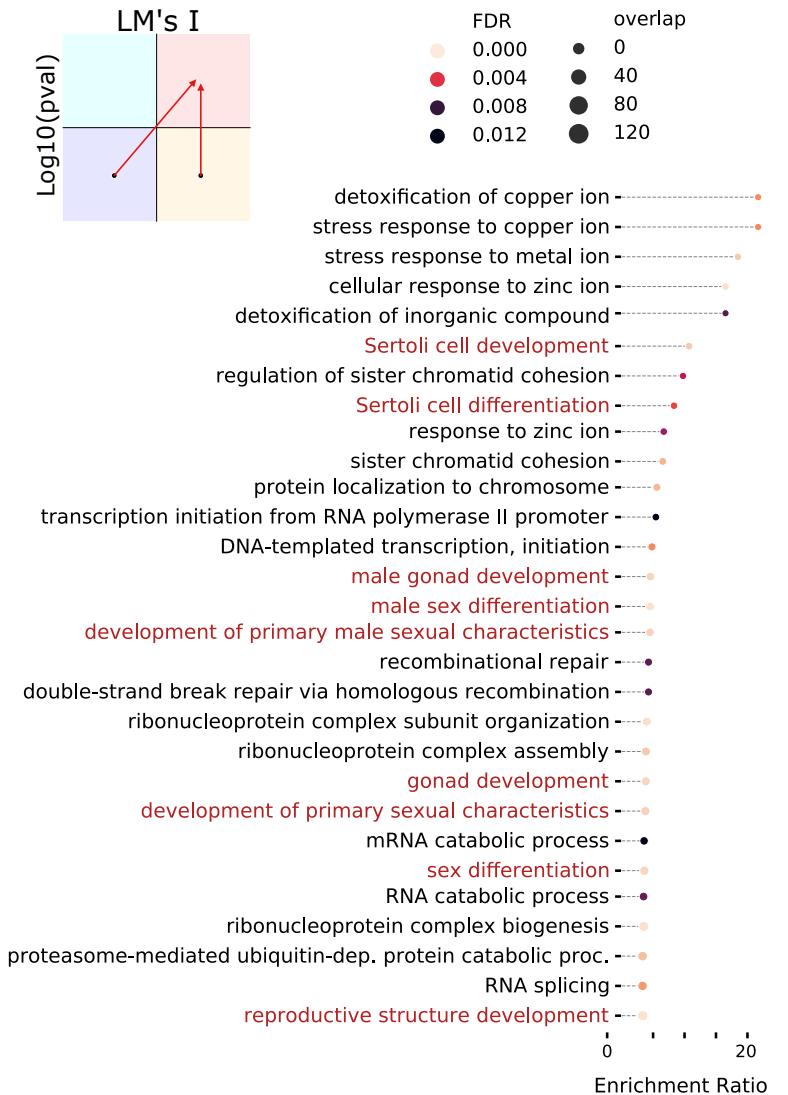
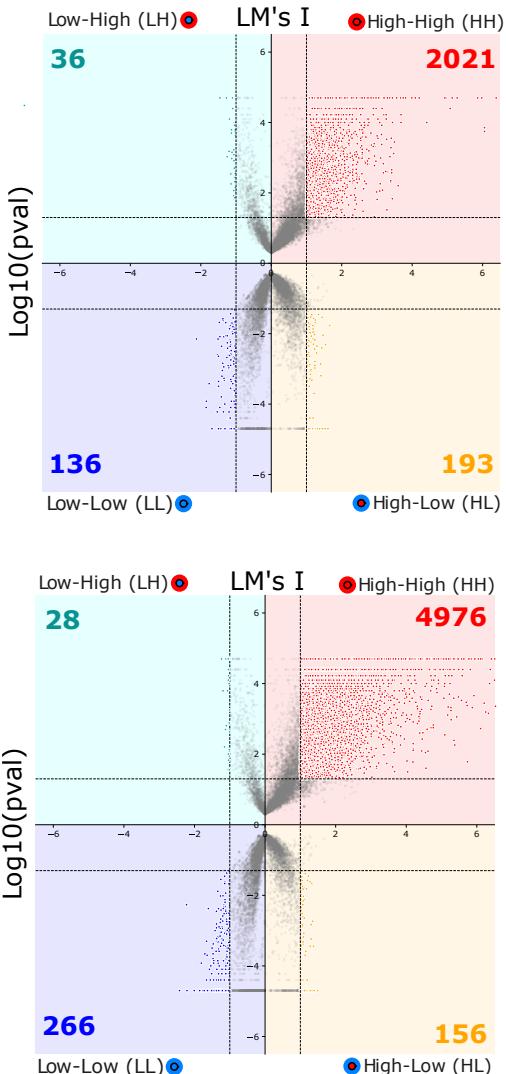
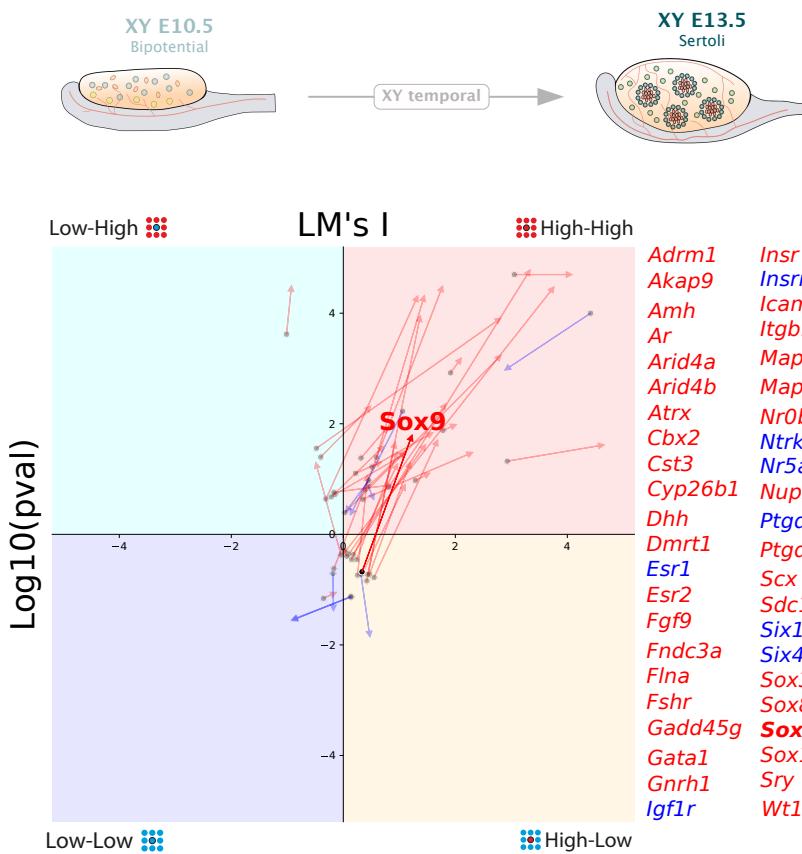
Sox9 locus chr11:110,780,000-114,770,000



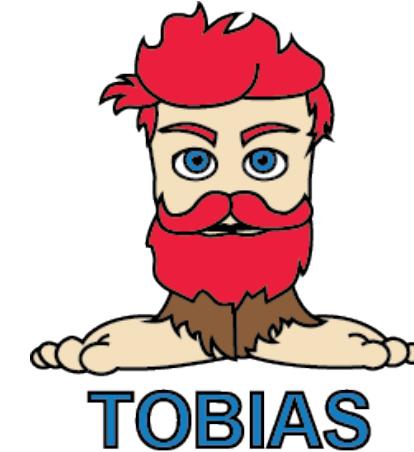
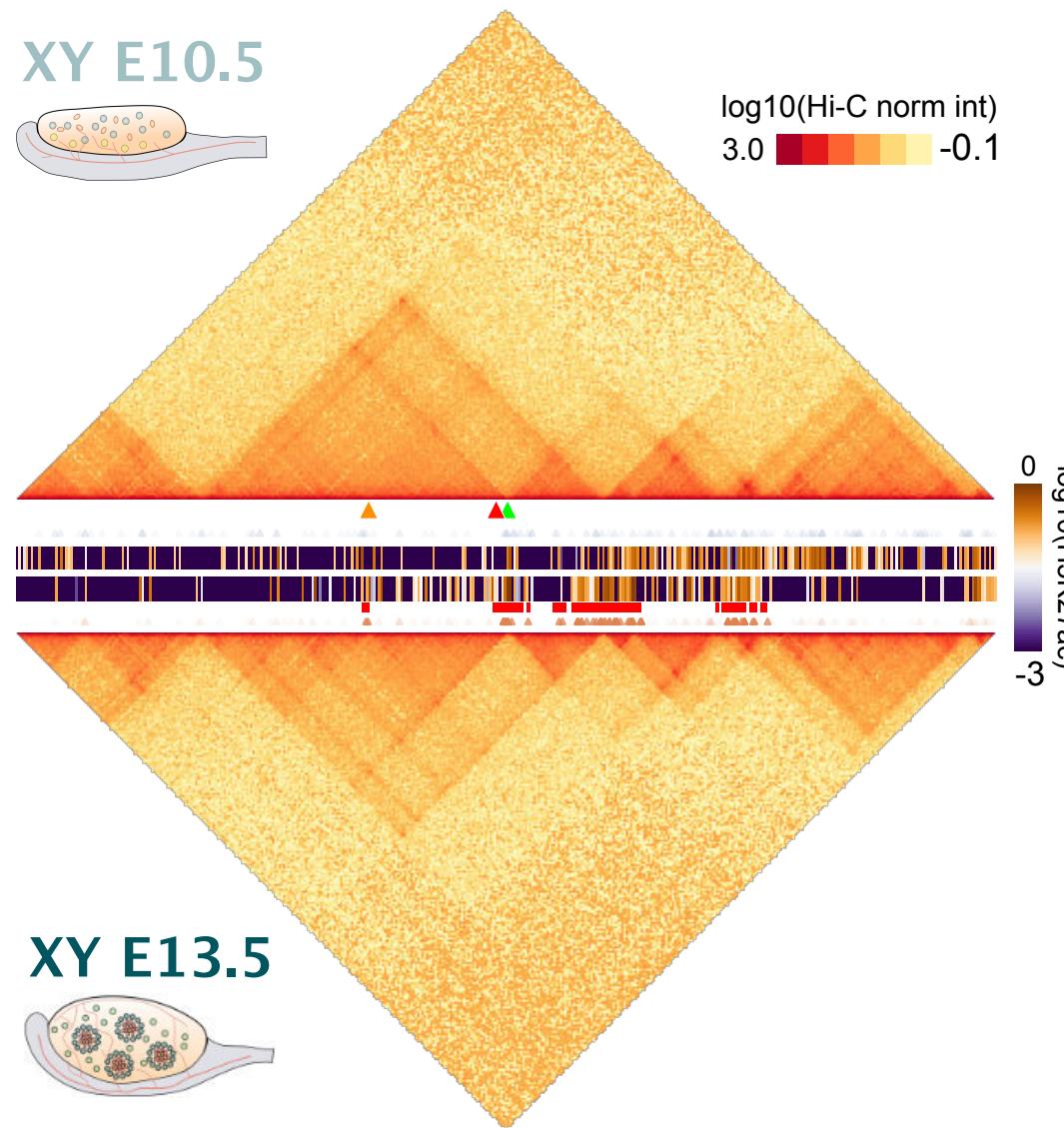
# LMI Trip for Sox9 gene



# All genes LM's Trip

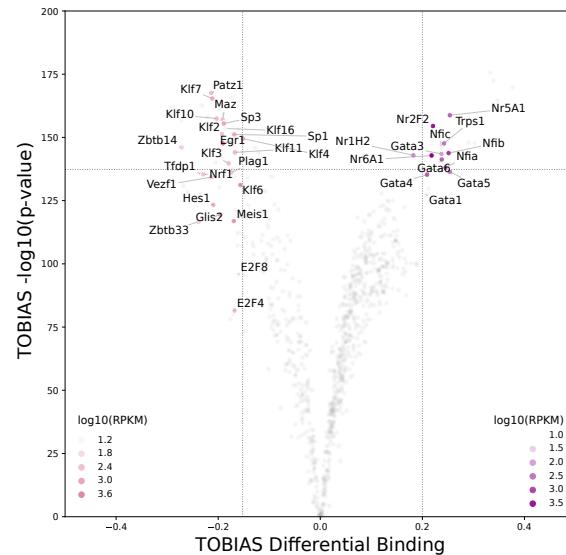
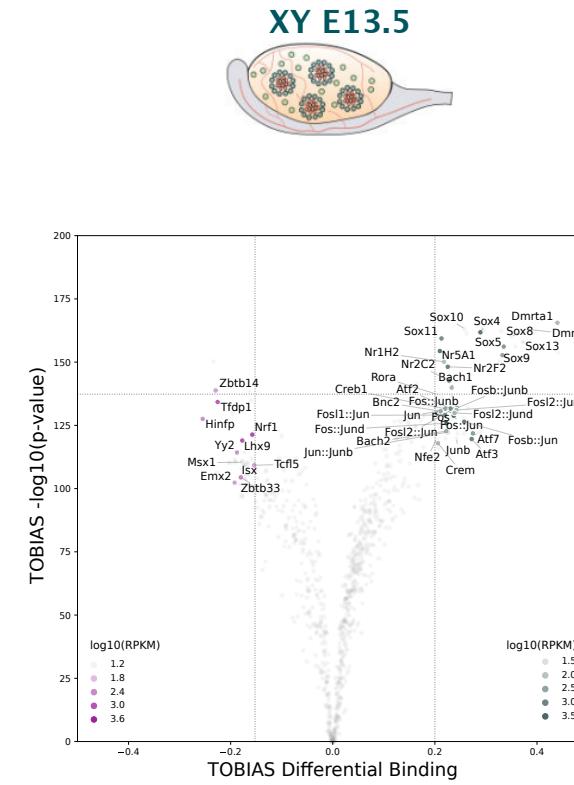
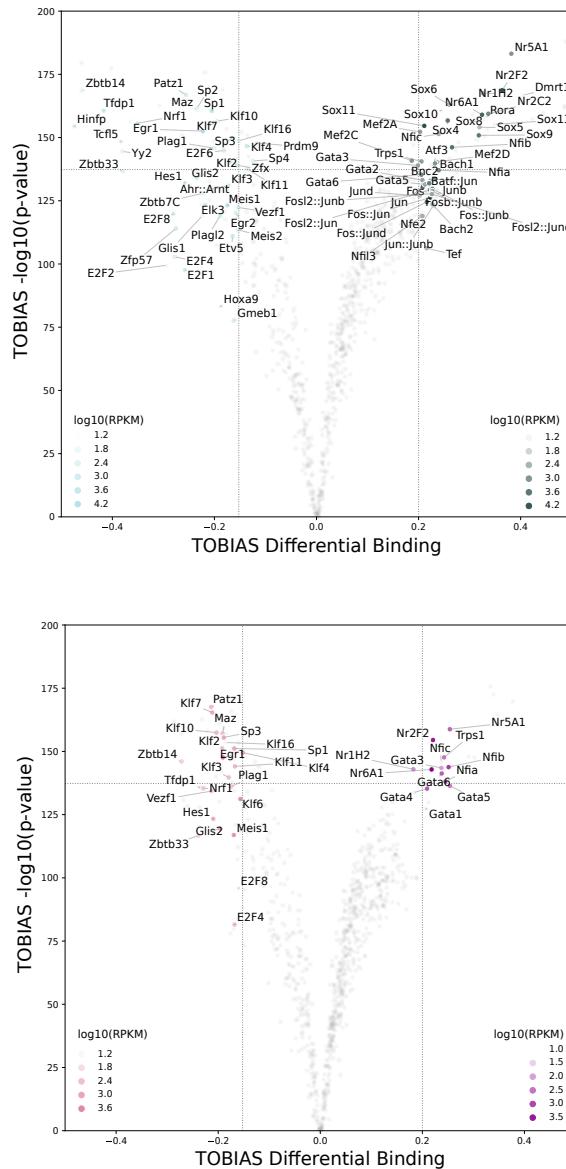
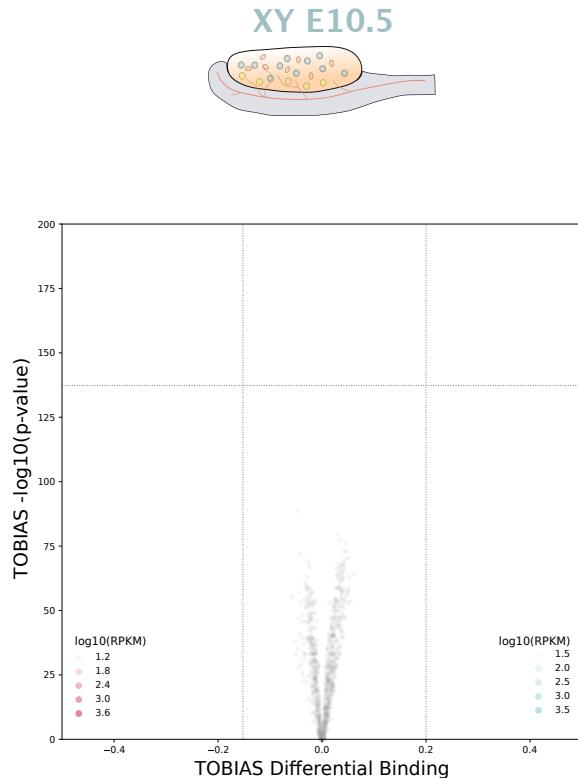


Are there specific Transcription Factors within the metaloci of Sox9?



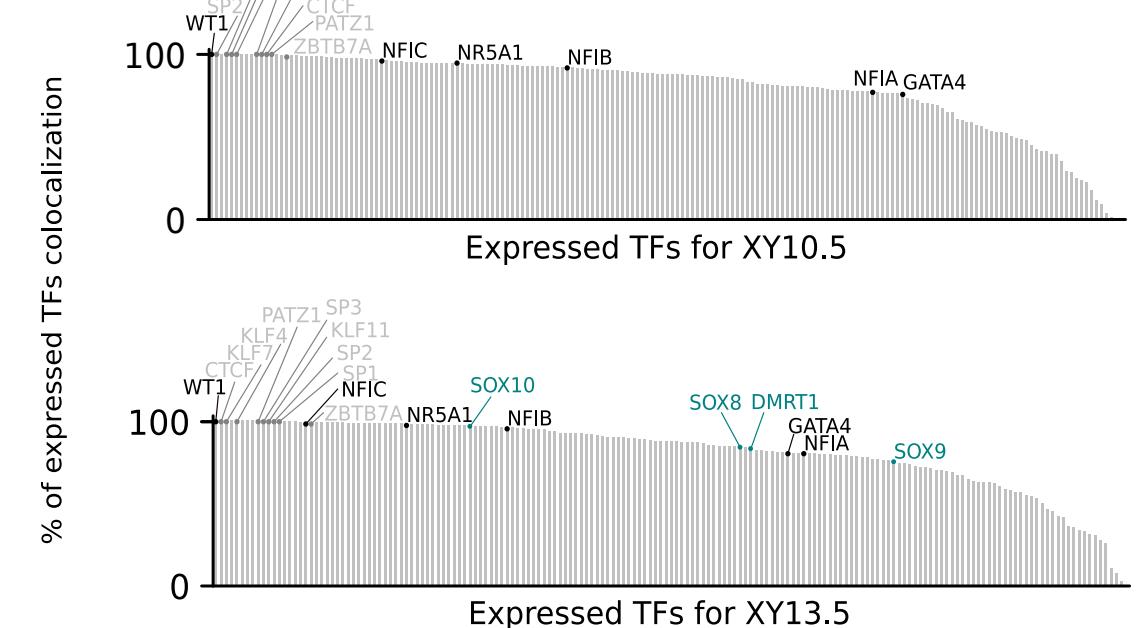
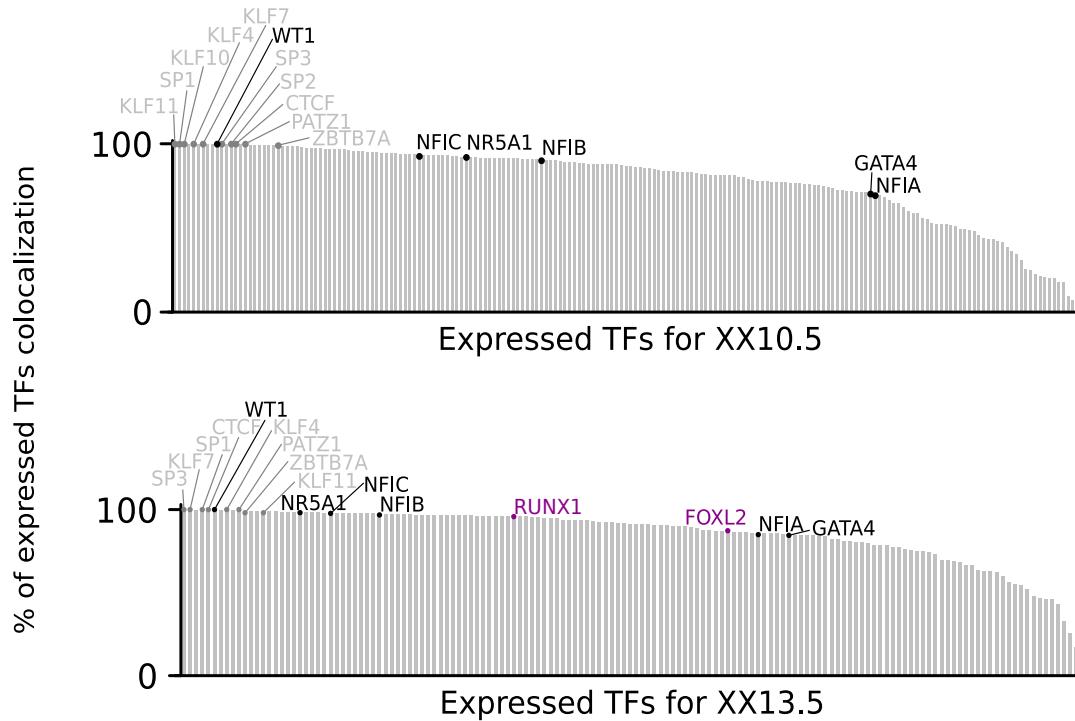


# TF footprints





# TF footprints



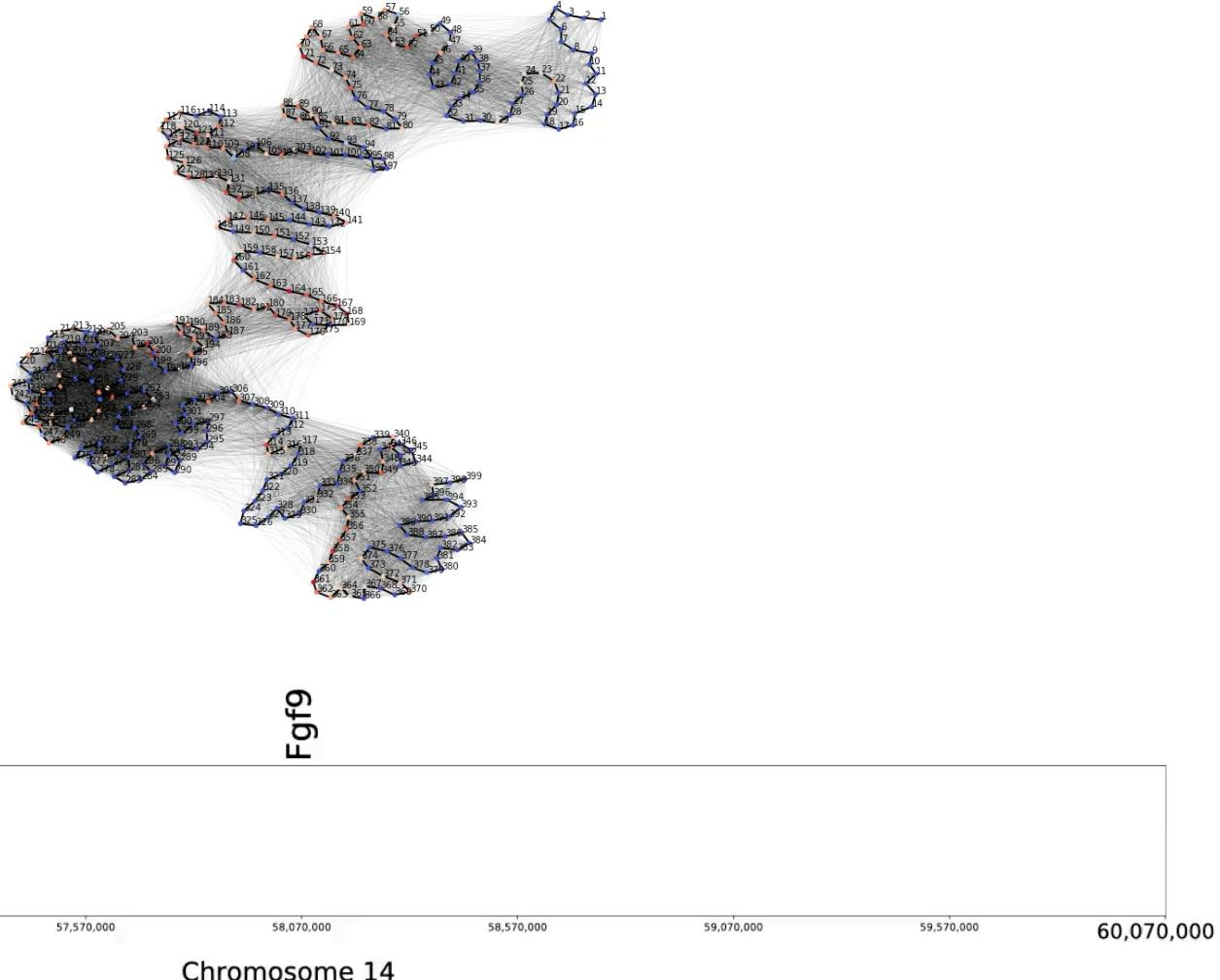
Now that we know the genes....

Can we identify regulatory elements using



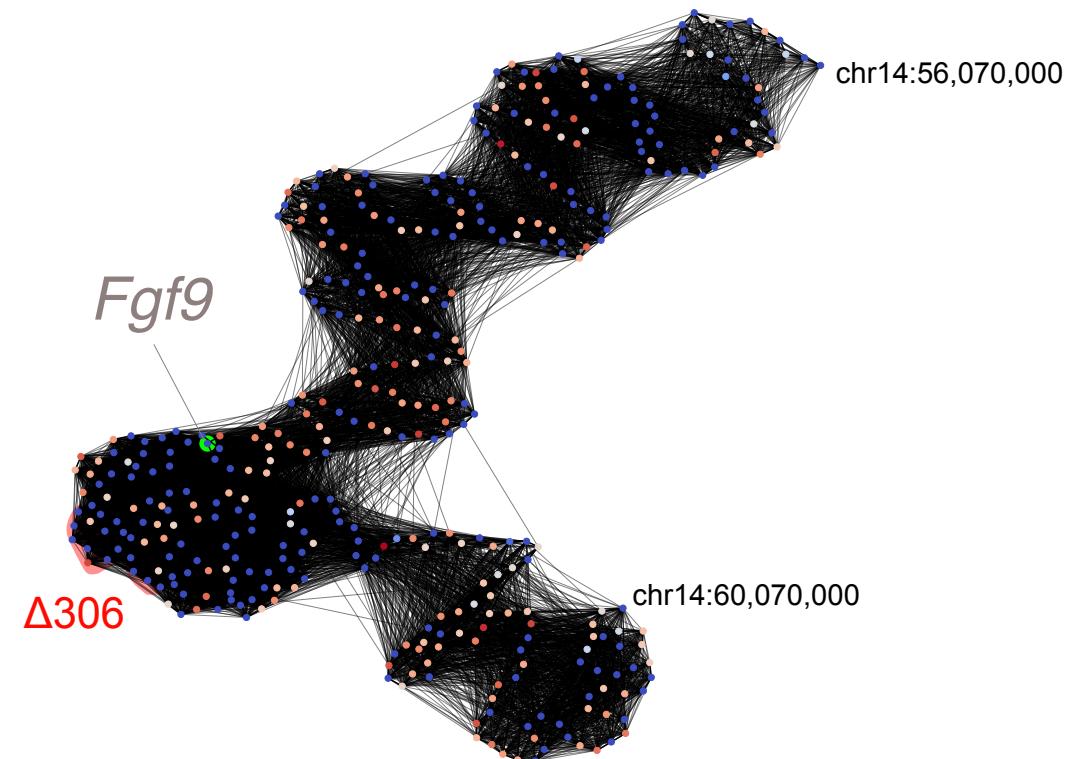
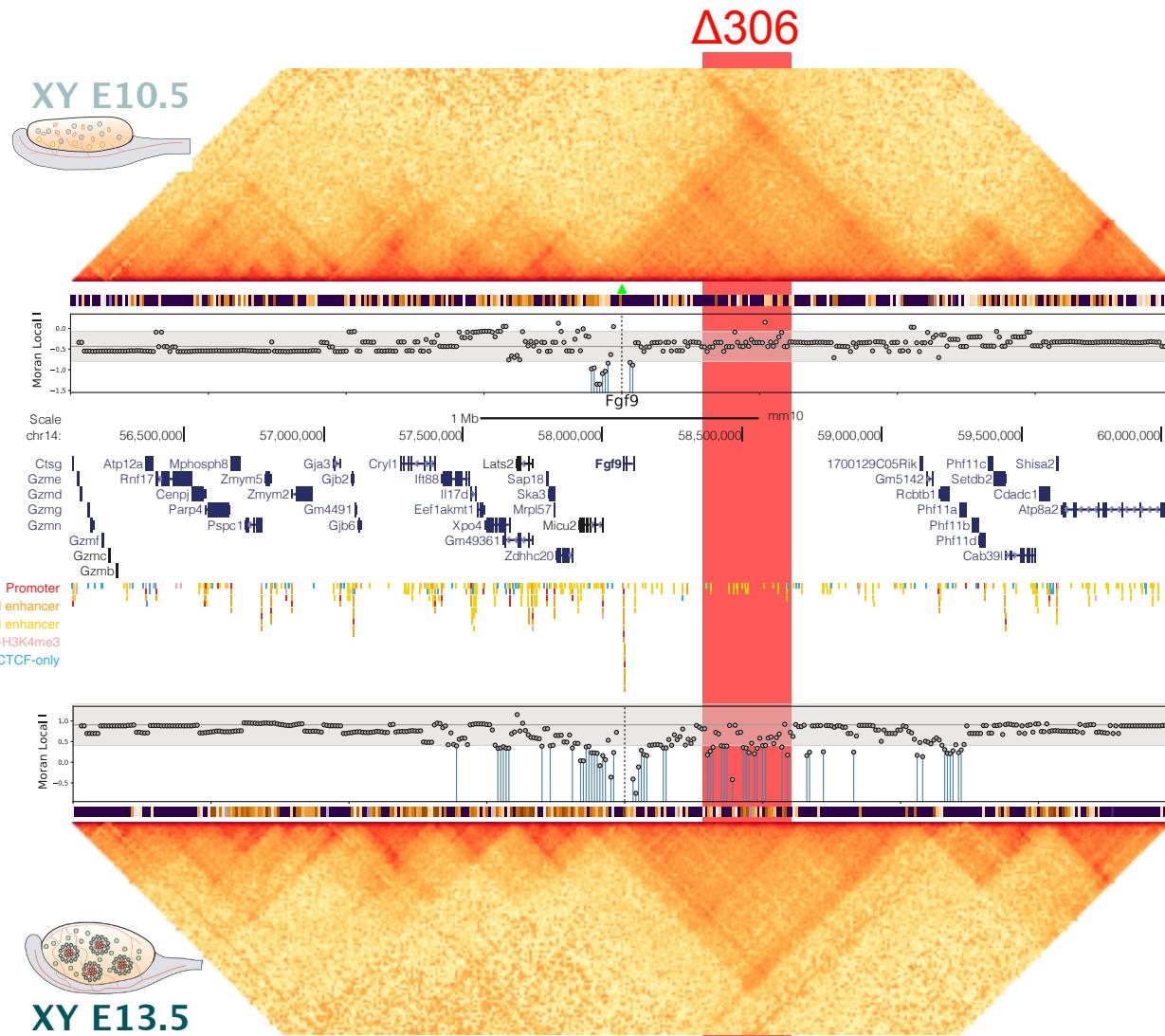
# METALoci predictive mode

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



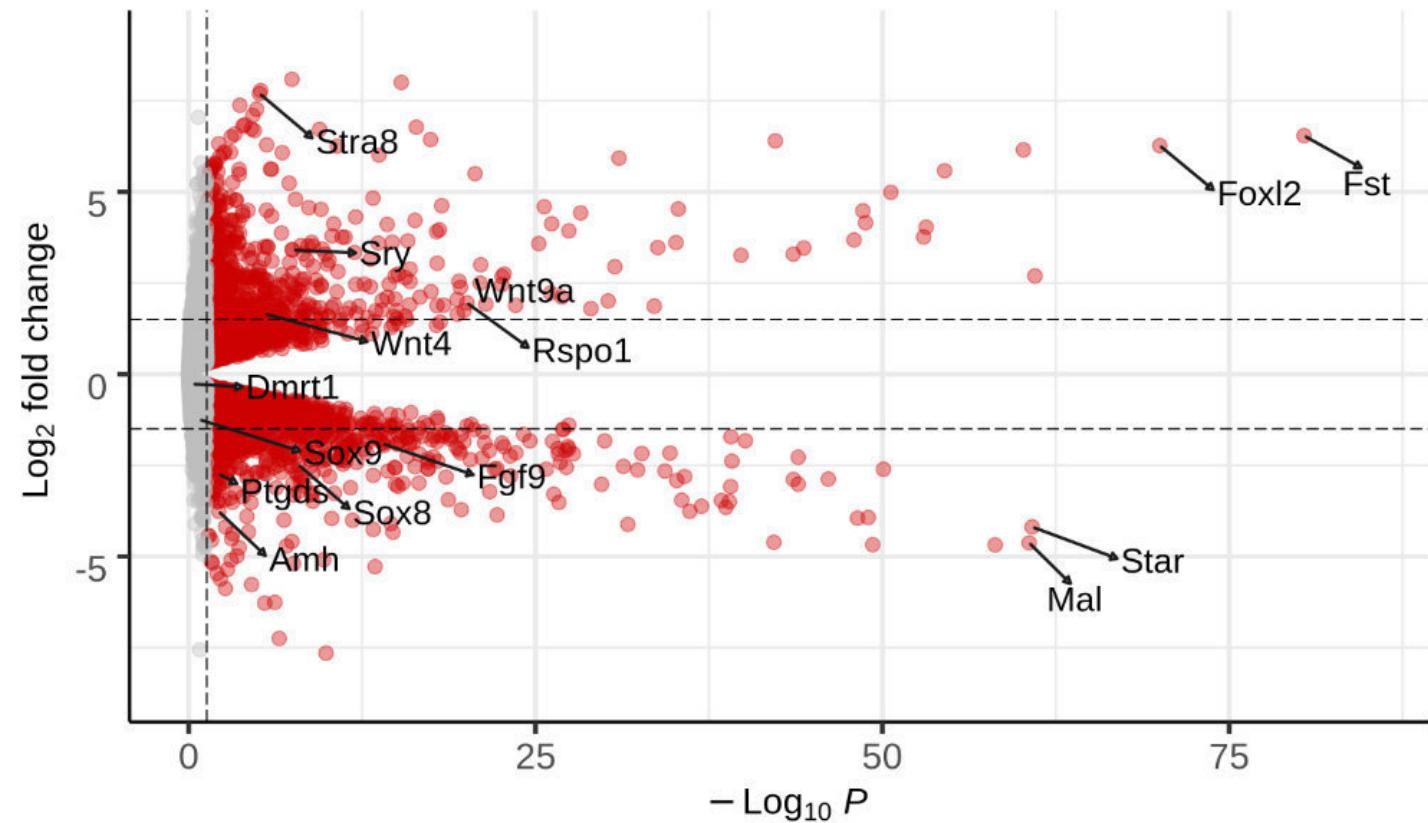
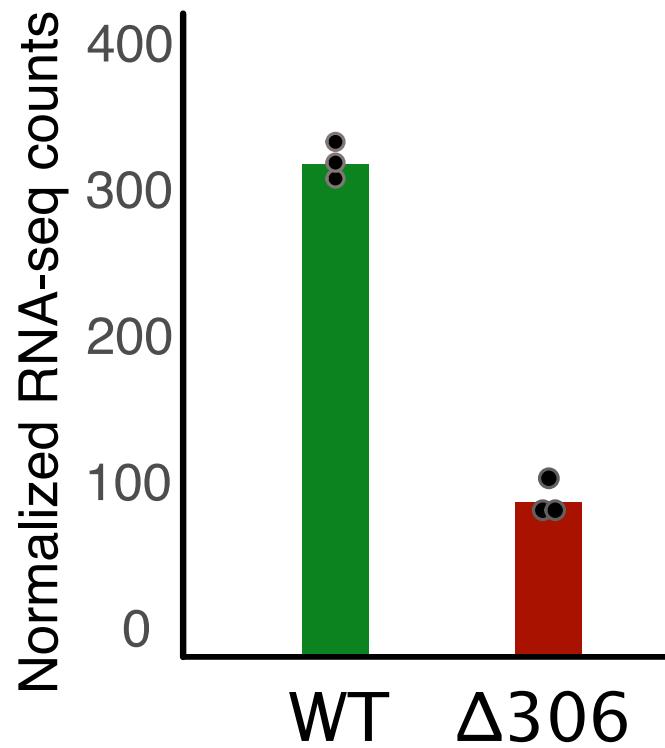
# METALoci predictive mode

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**



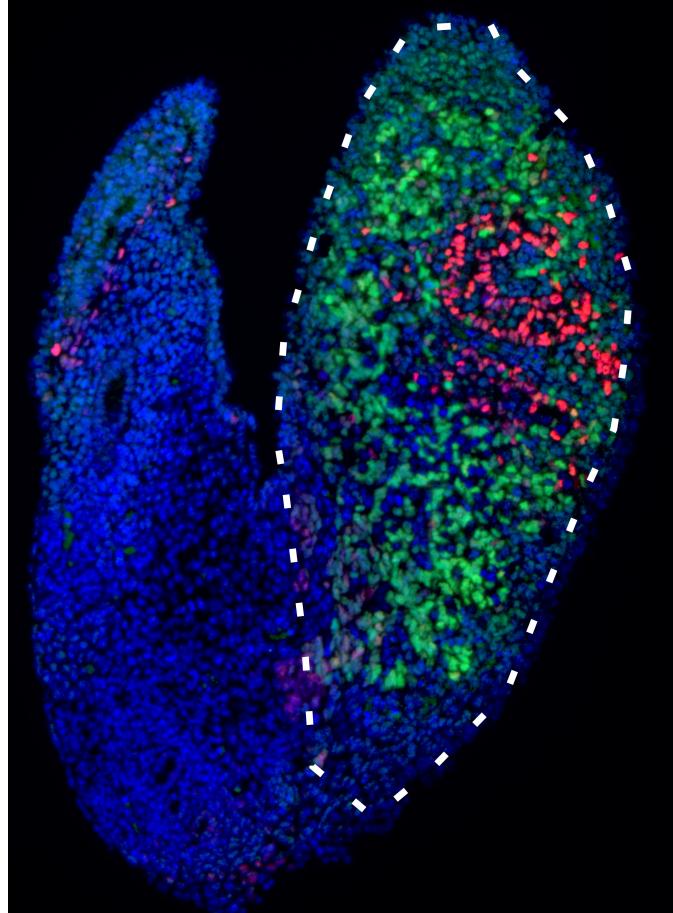
**Ovary**

250um

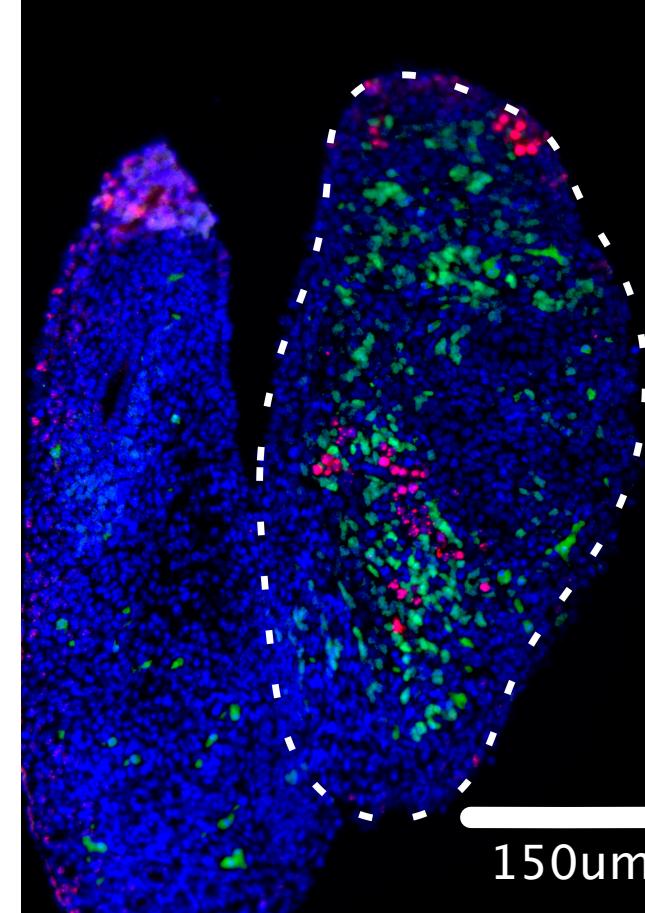
# METALoci predictive mode

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