



Spatio-temporal regulatory landscape of sex-determination

or a case for
Structure-Based Genome Editing (SBGE)

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Juan A. Rodríguez
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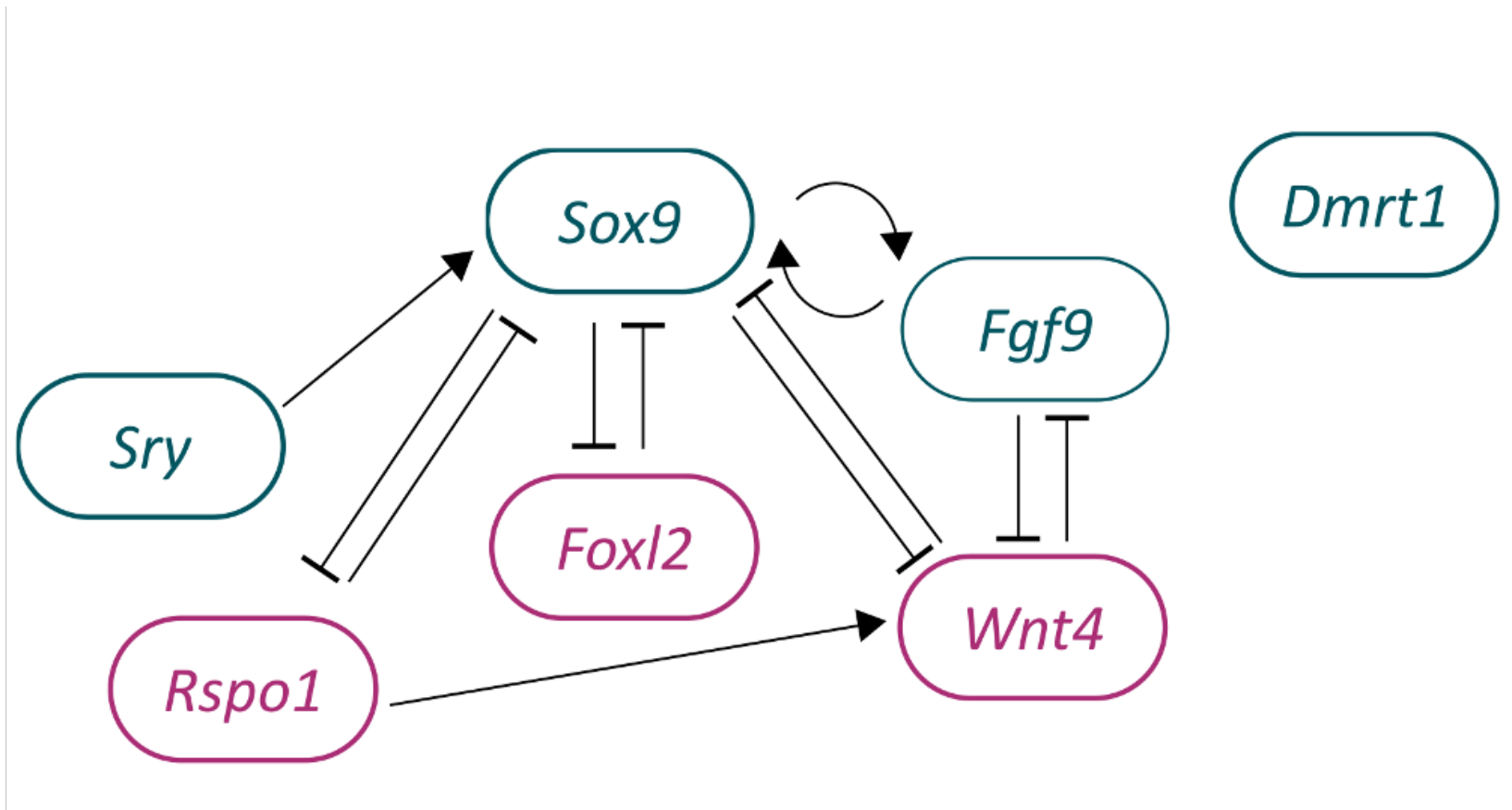


Irene Mota
MDC Berlin

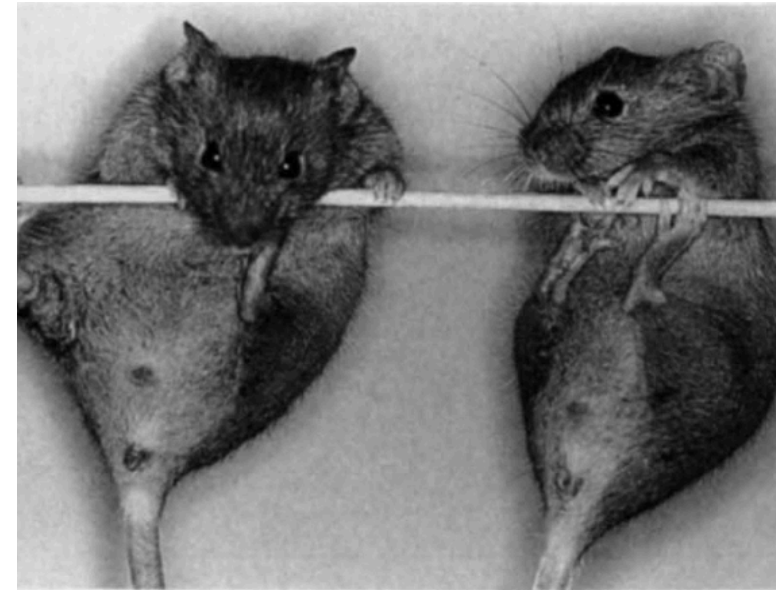


Dario Lupiañez
MDC Berlin
Now @CABD

Sex determination: a 3,000 year-old enigma

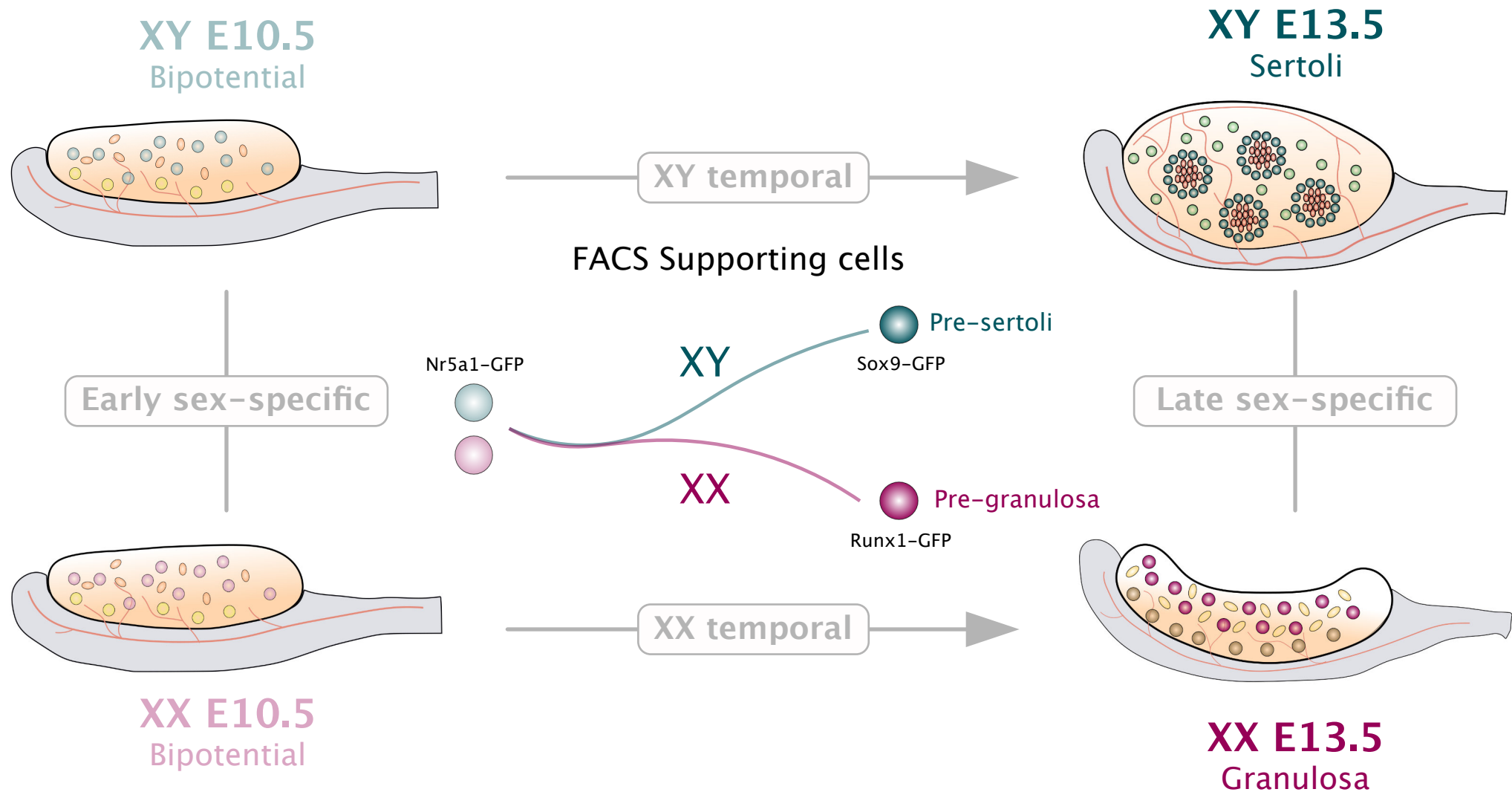


Genetics

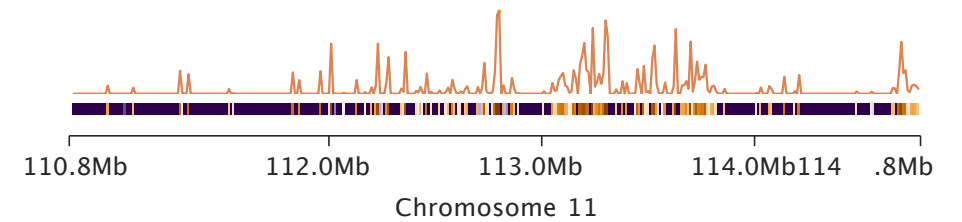
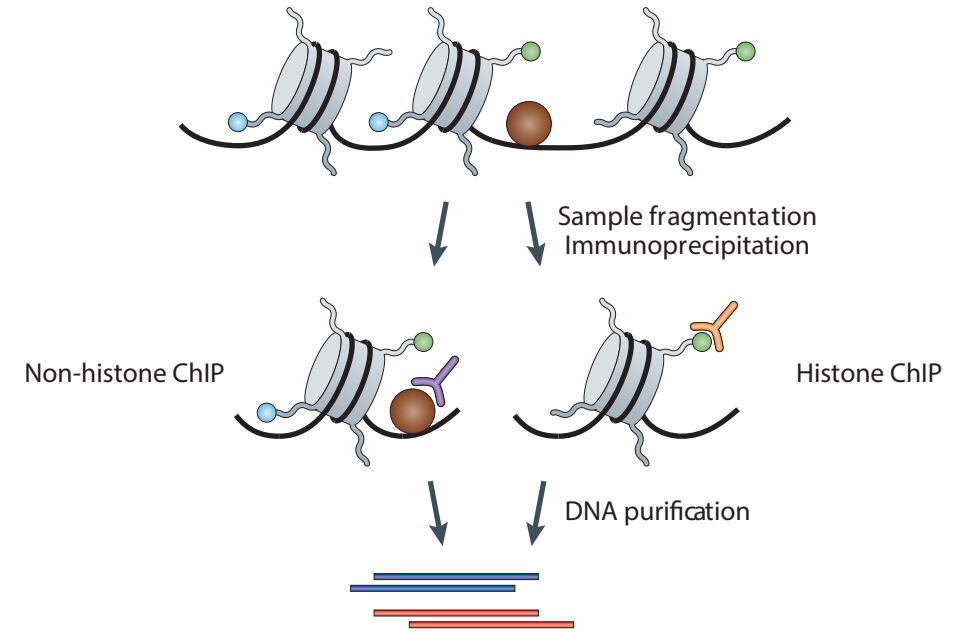
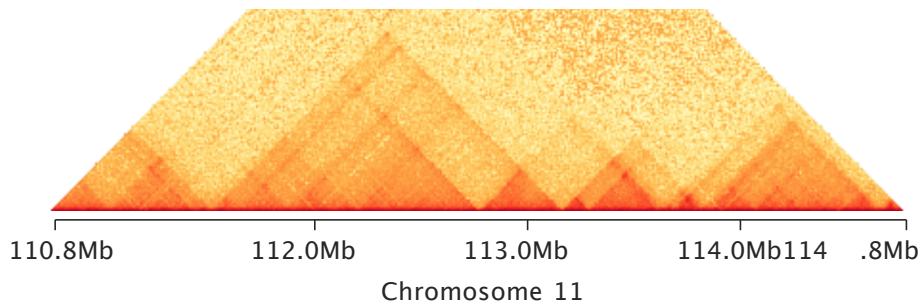
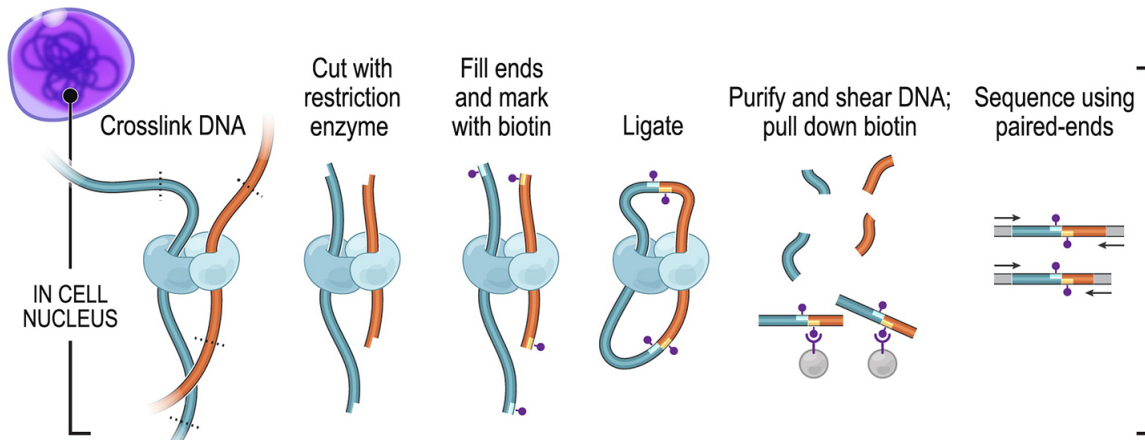


Discovery of *Sry* gene
Koopman et al., Nature, 1991
(*Goodfellow & Lovell-Badge labs*)

Sex-determination as a model for “bipotential” commitment



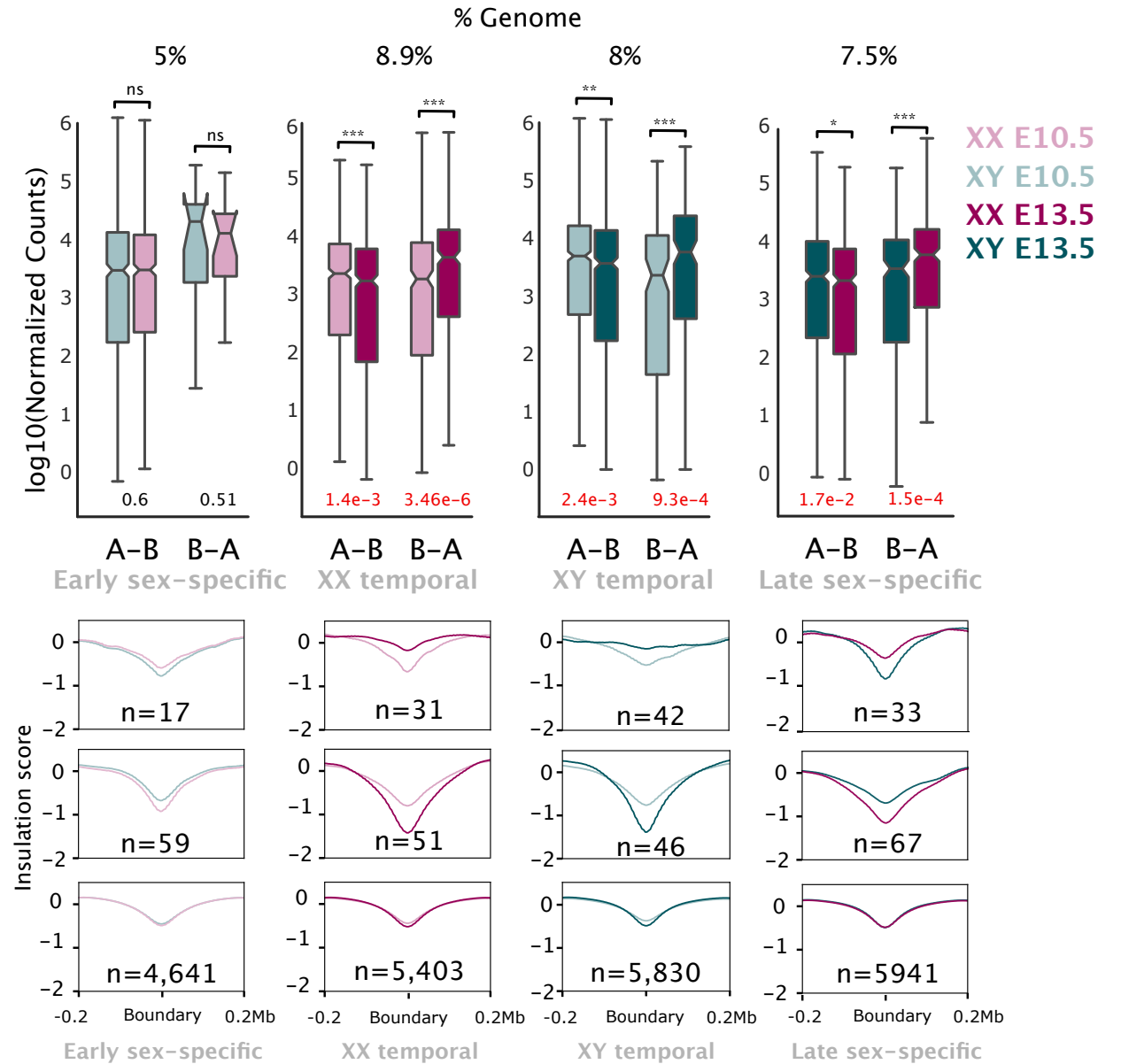
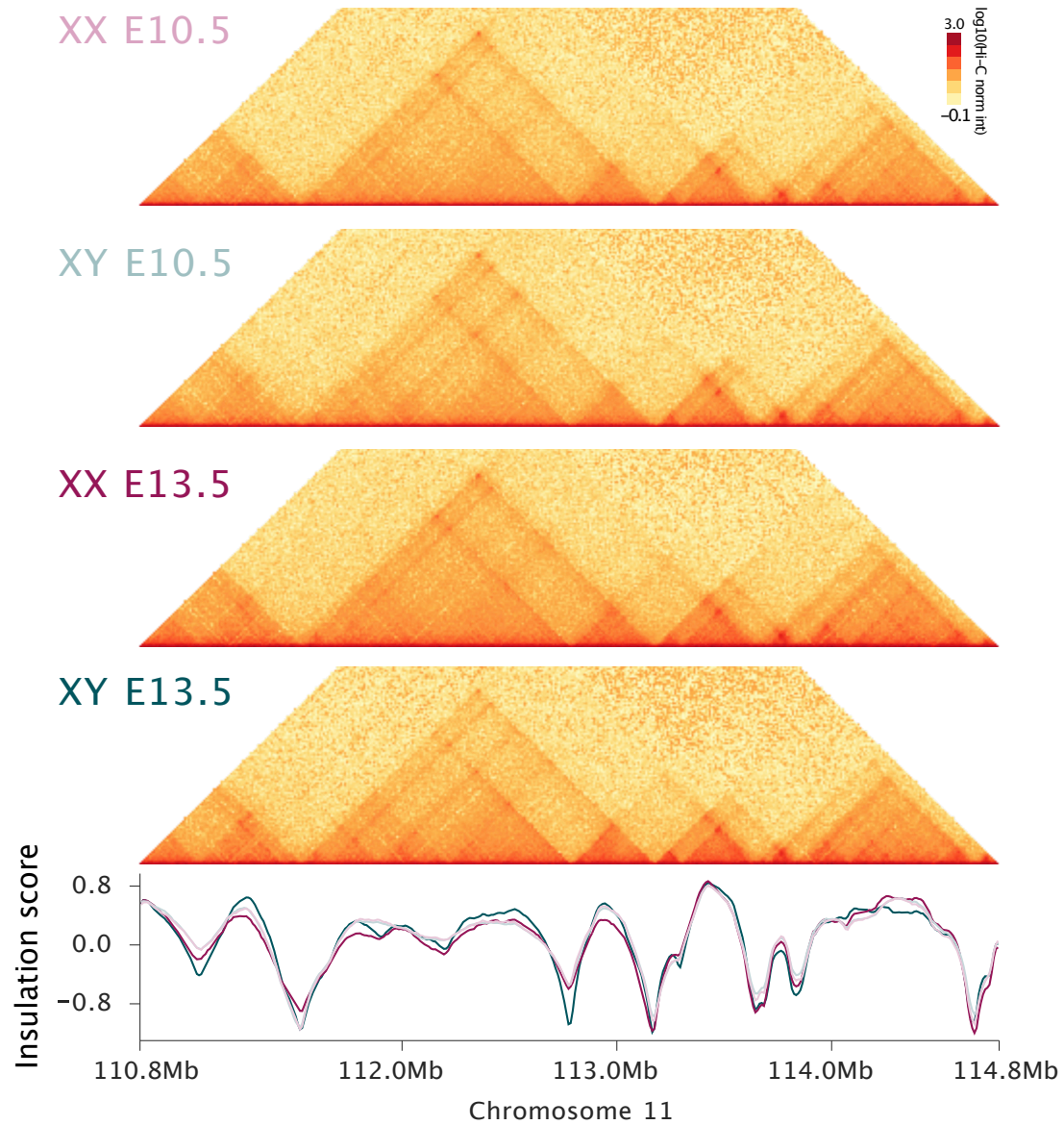
Hi-C & ChIP-seq

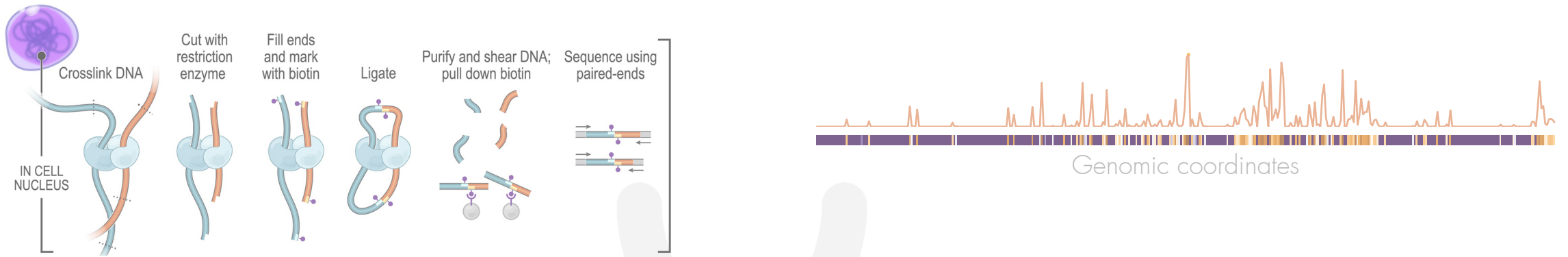


Dekker, J., Rippe, K., Dekker, M., & Kleckner, N. (2002). *Science*, 295(5558), 1306–1311.
Lieberman-Aiden, E., et al. (2009). *Science*, 326(5950), 289–293.

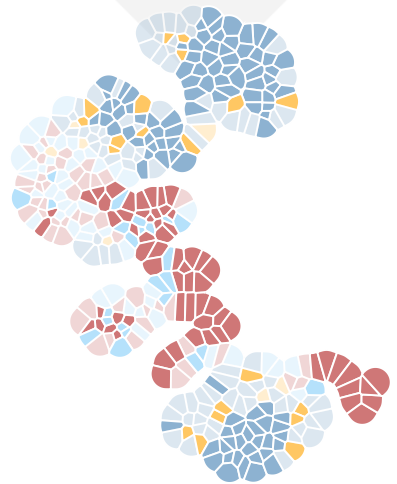
Solomon, M. J., Larsen, P. L. & Varshavsky, A. (1988) *Cell* 53, 937–947.
Park, P.J. (2009) *Nature Reviews Genetics* 10, 669–680.

No major structural (apparent) differences





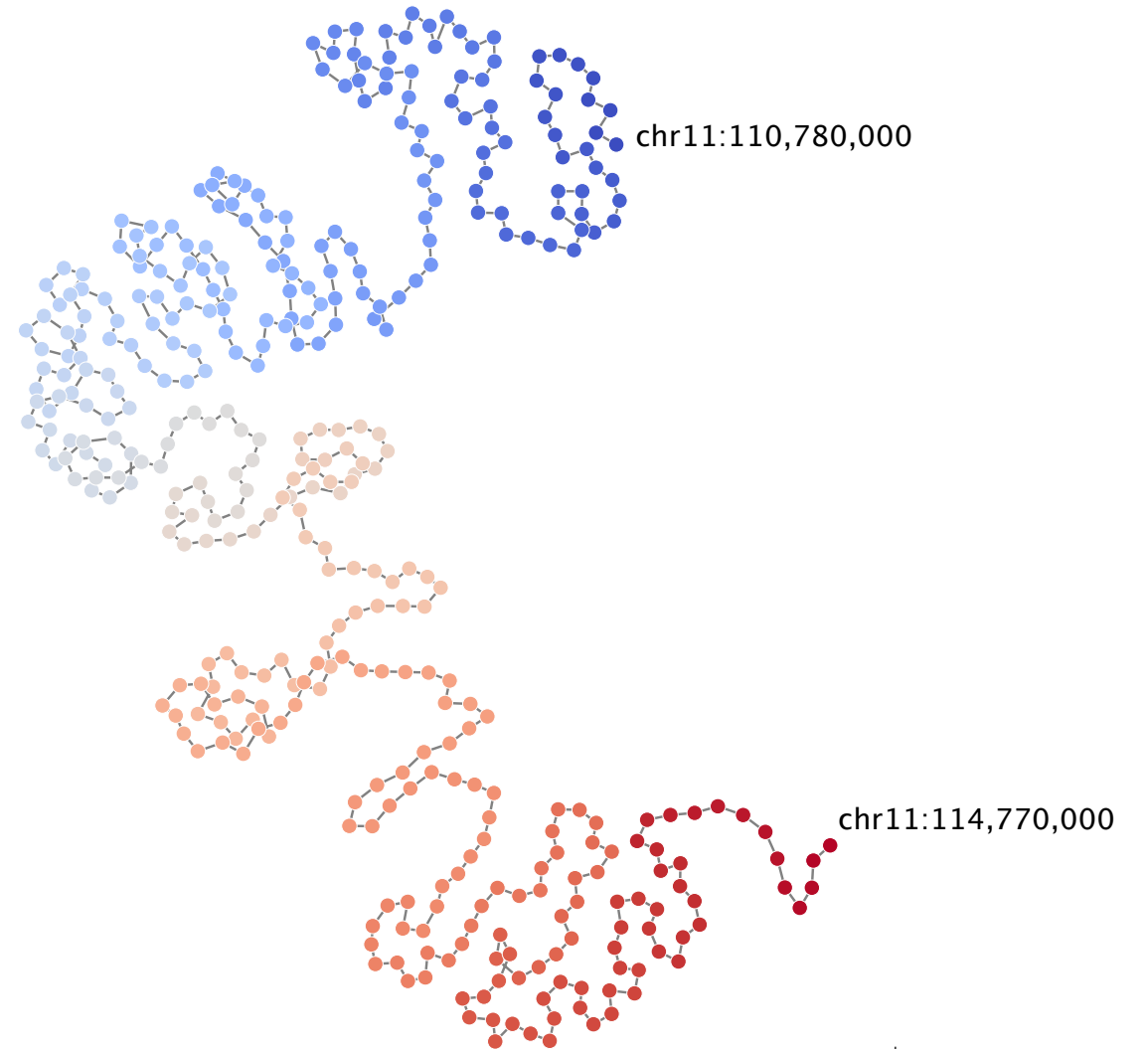
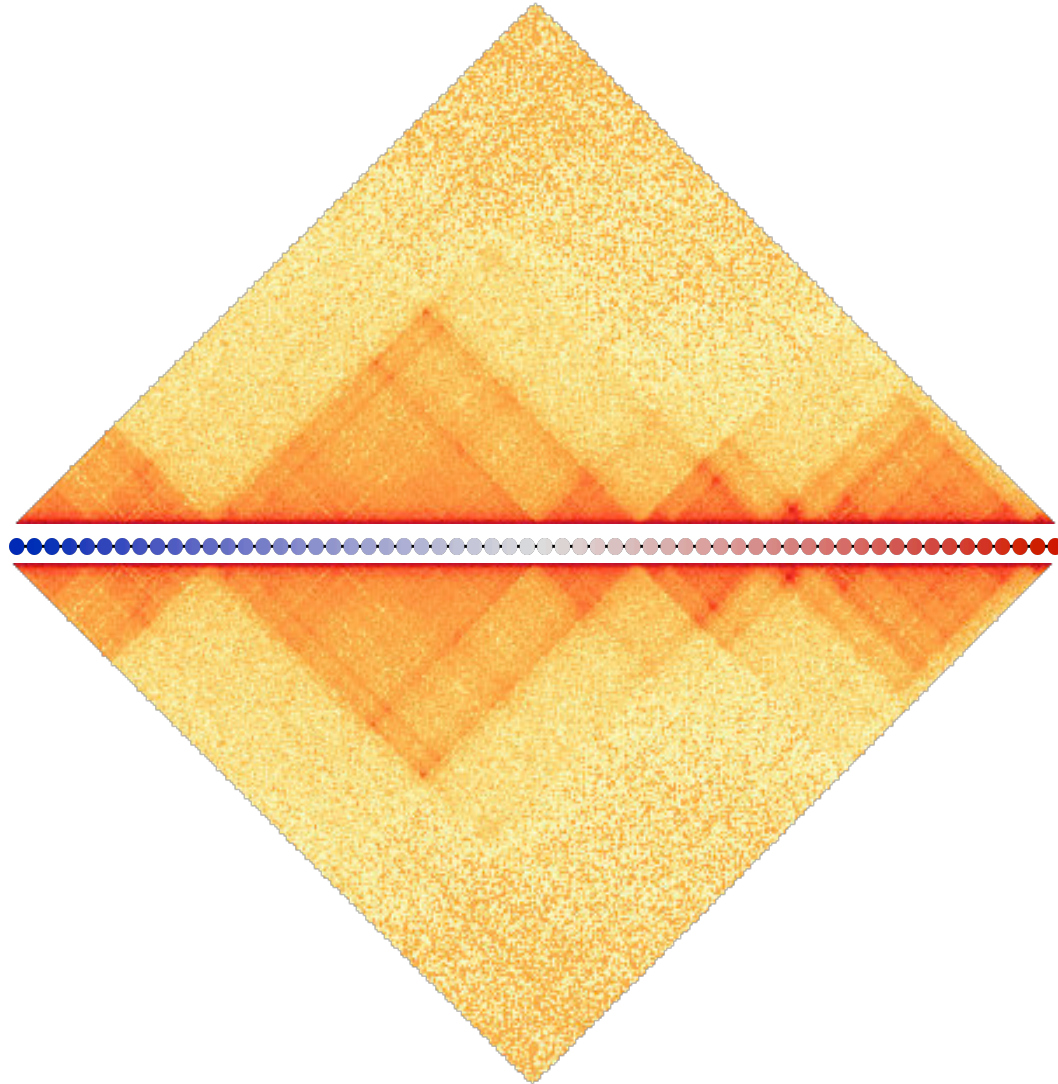
Hi-C



"Gaudi plot"

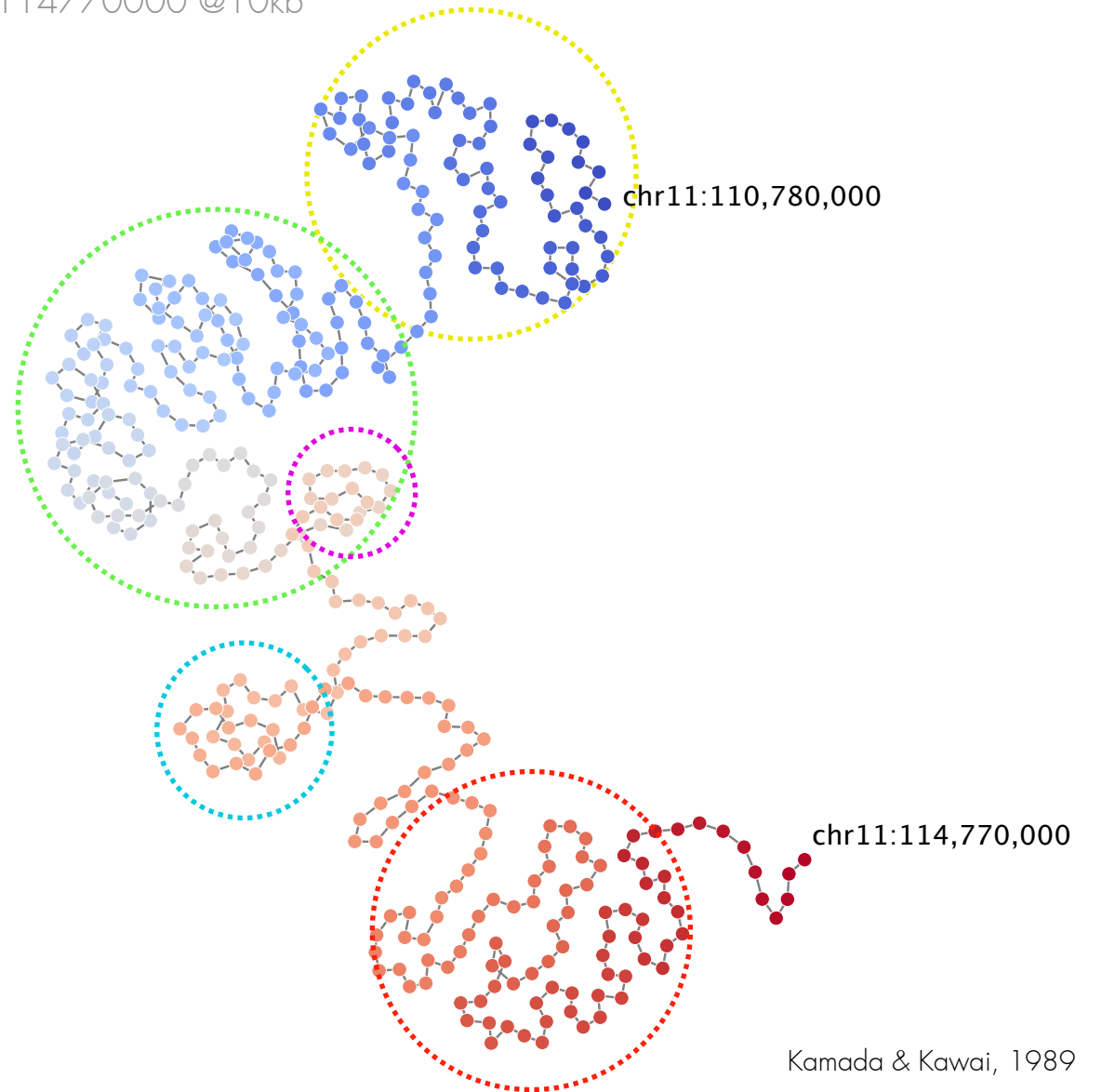
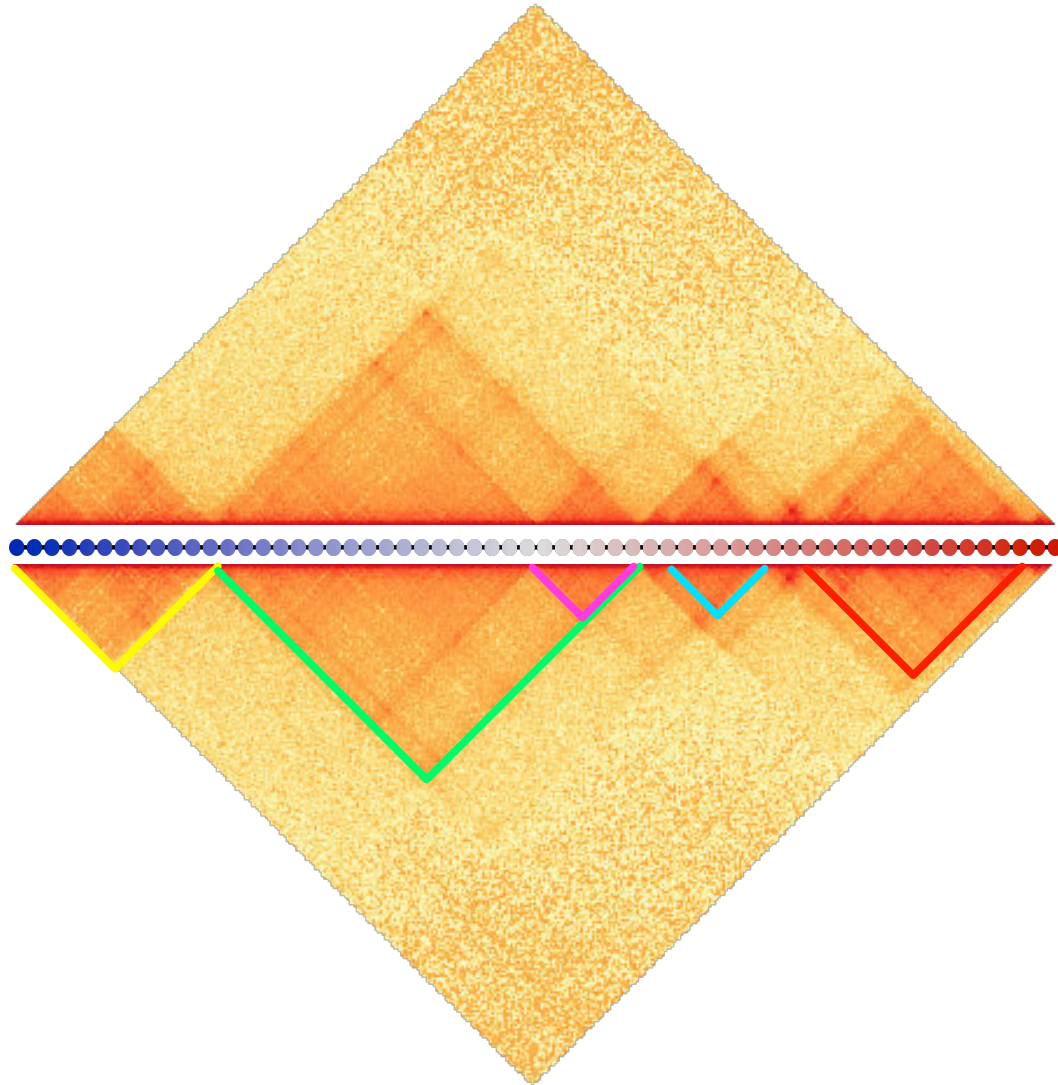
Spatial lay-out of significant interactions

chr11:110780000-114770000 @10kb



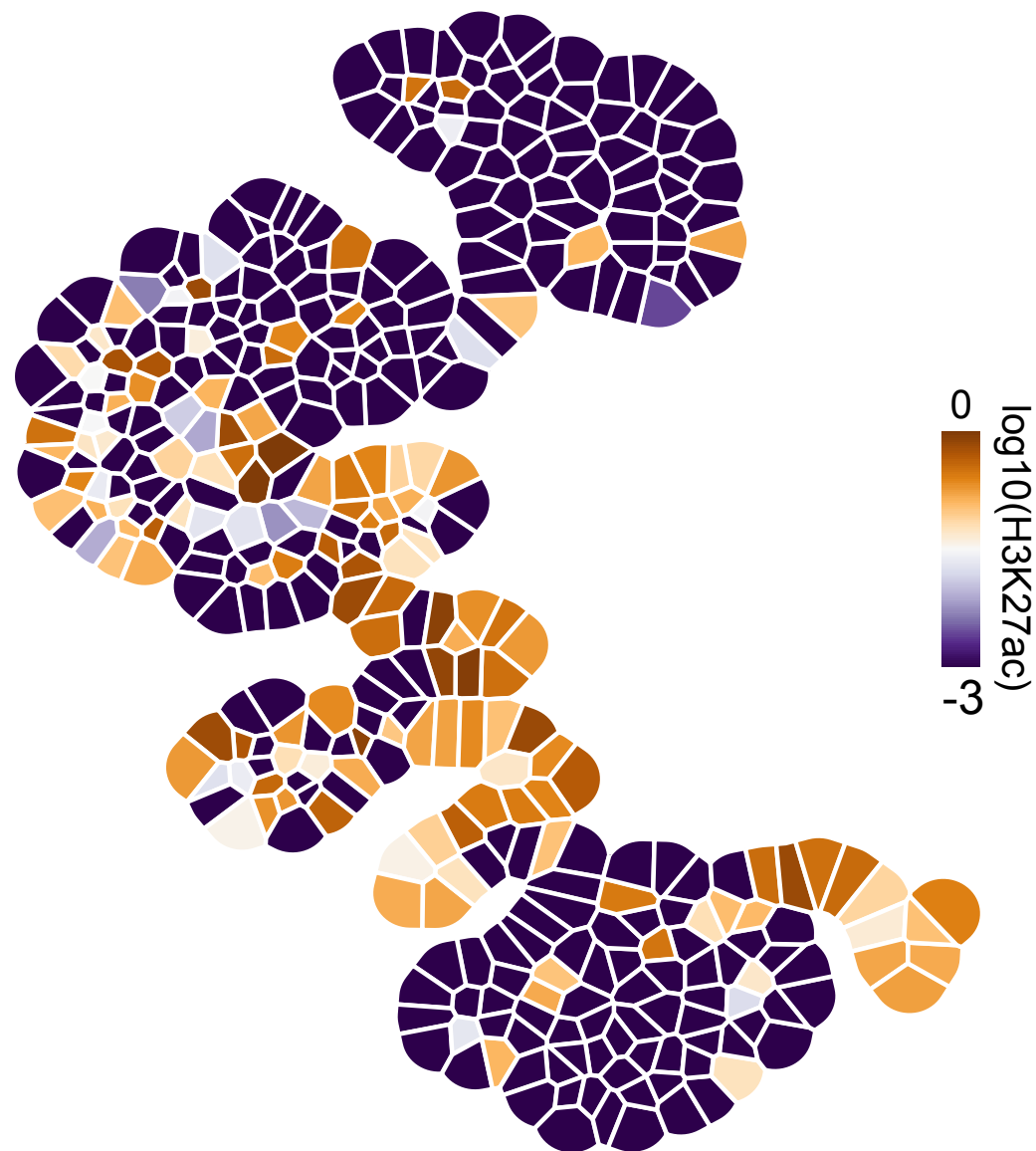
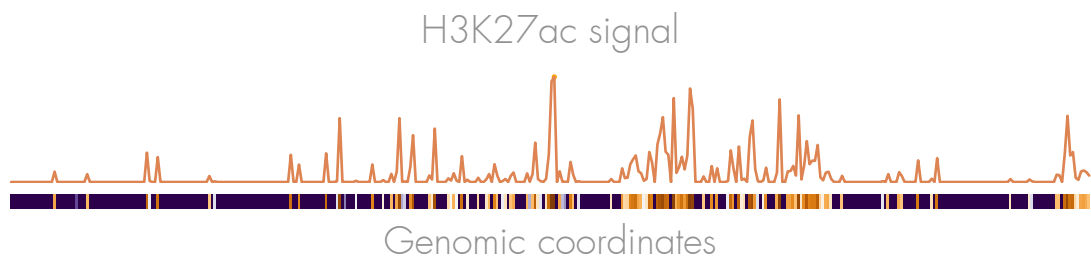
Spatial lay-out of significant interactions

chr11:110780000-114770000 @10kb



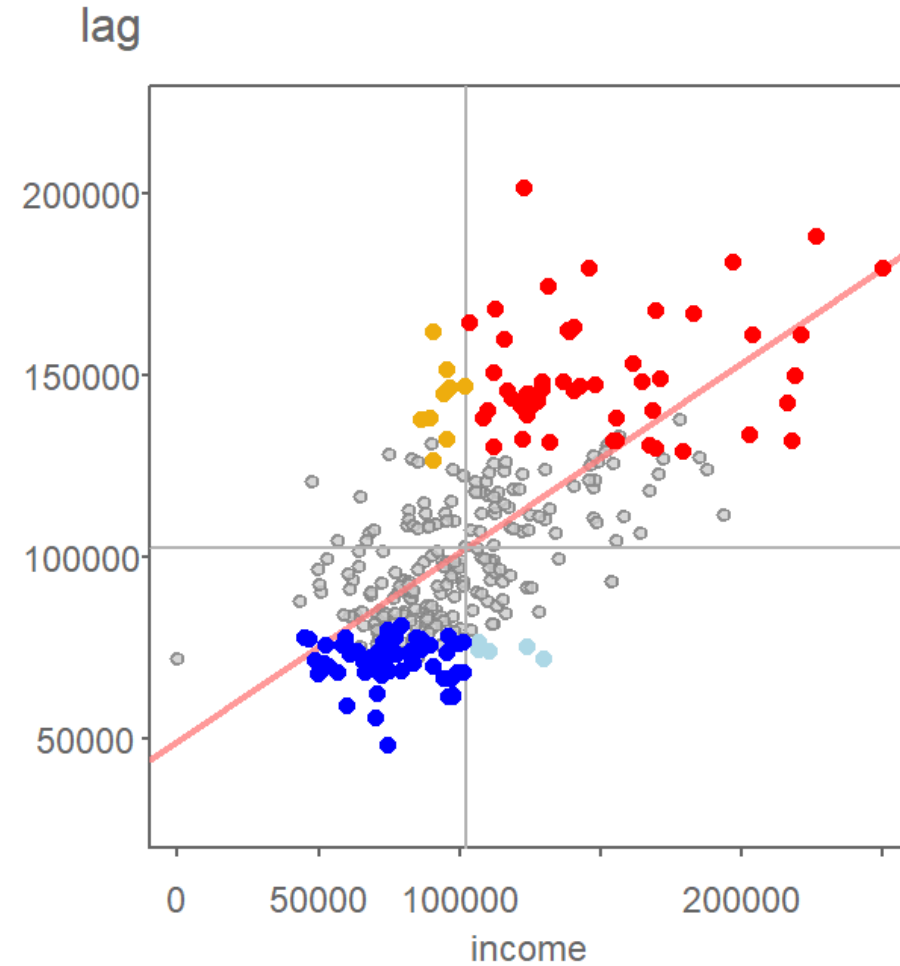
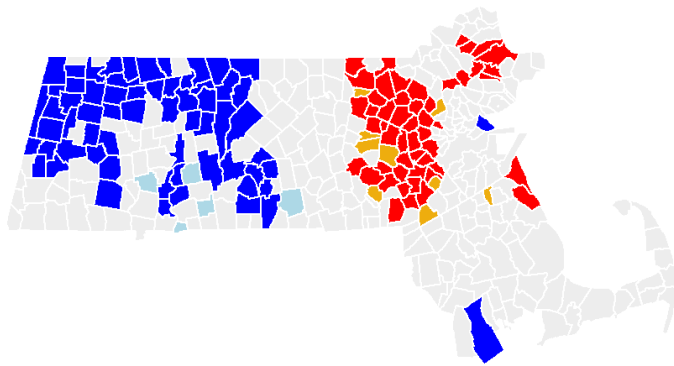
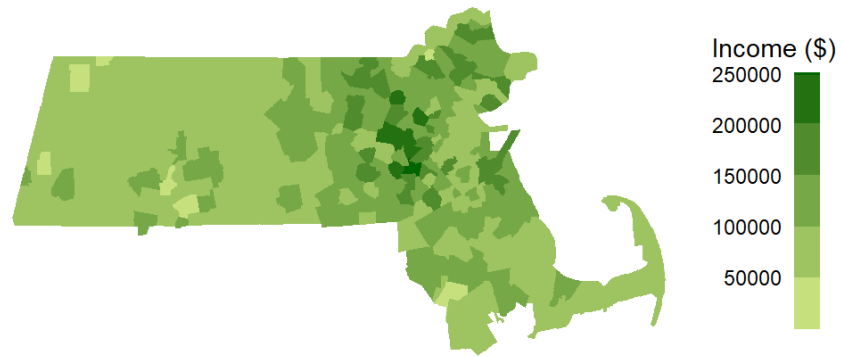
Marker (H3K27ac) into 2D mapping

chr11:110780000-114770000 @10kb

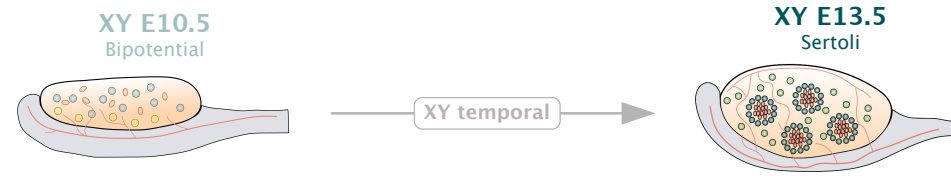


Local Moran Index

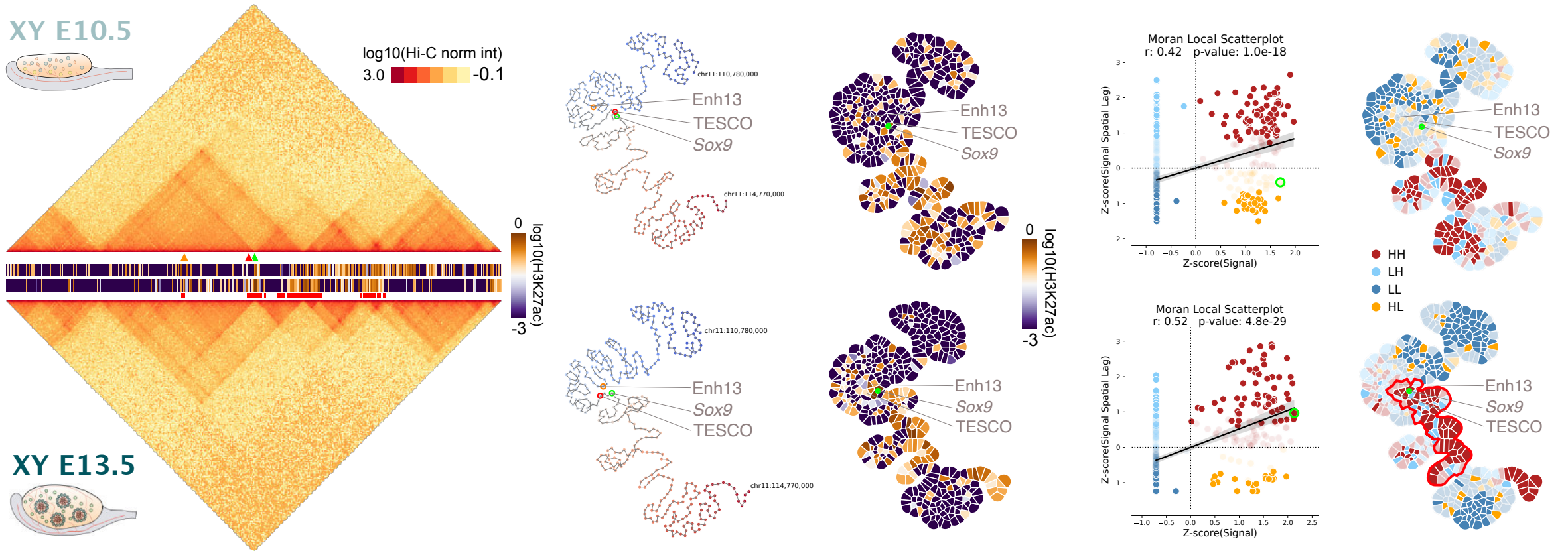
Massachusetts household income



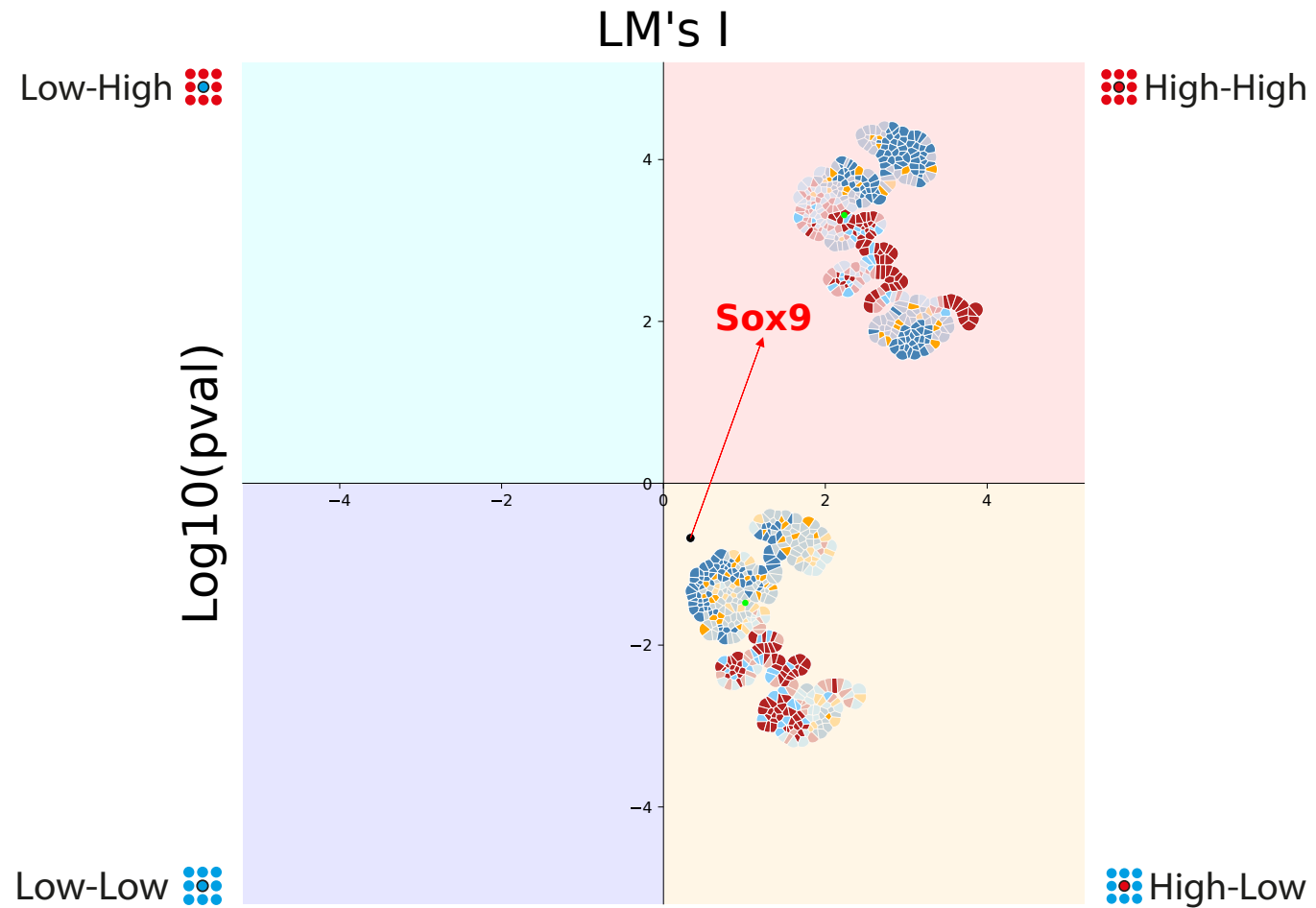
Quantifying regulatory environments bin by bin



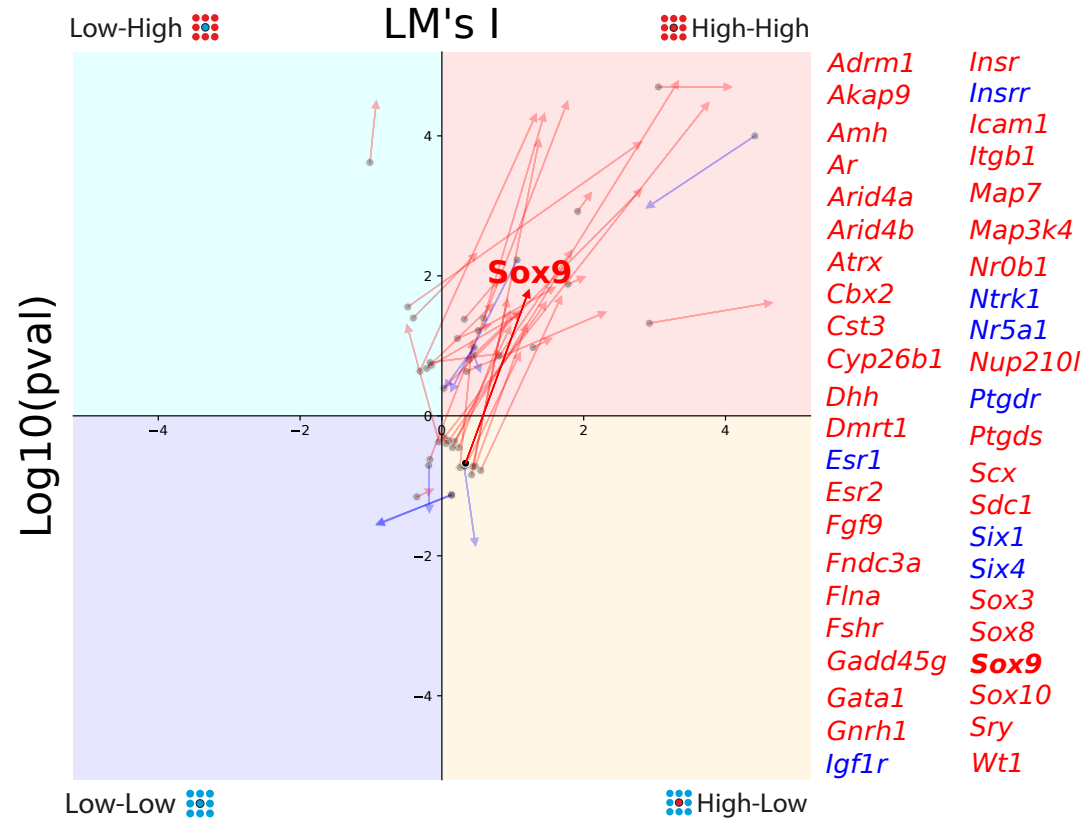
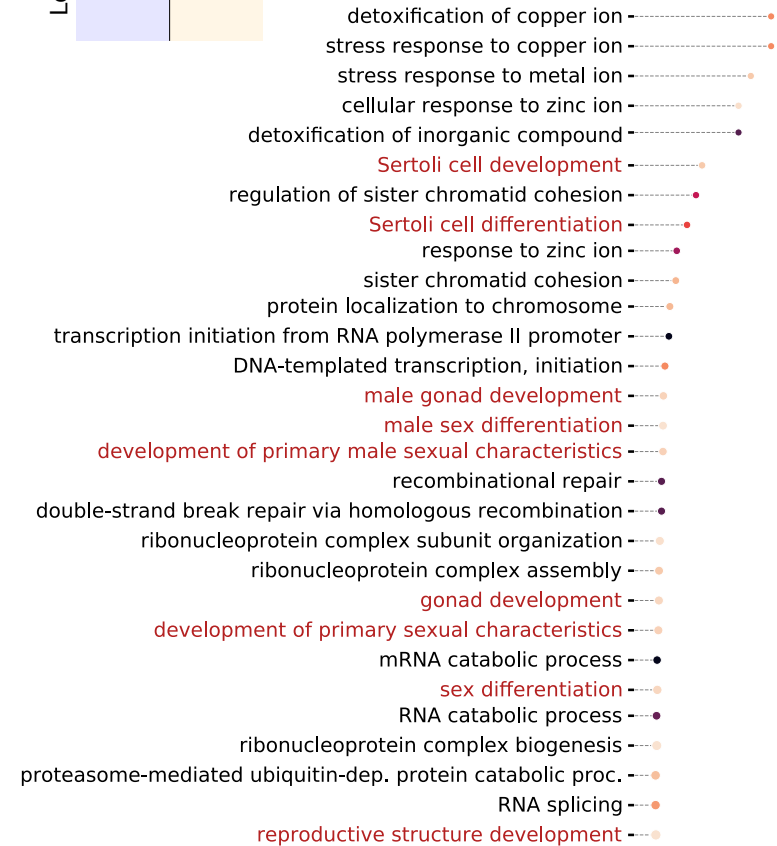
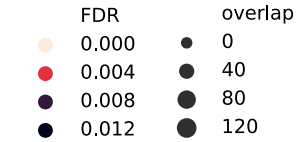
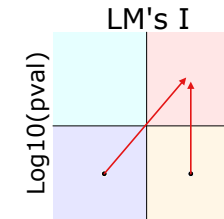
Sox9 locus chr11:110,780,000-114,770,000



LMI Trip for Sox9 gene



All genes LMI Trip

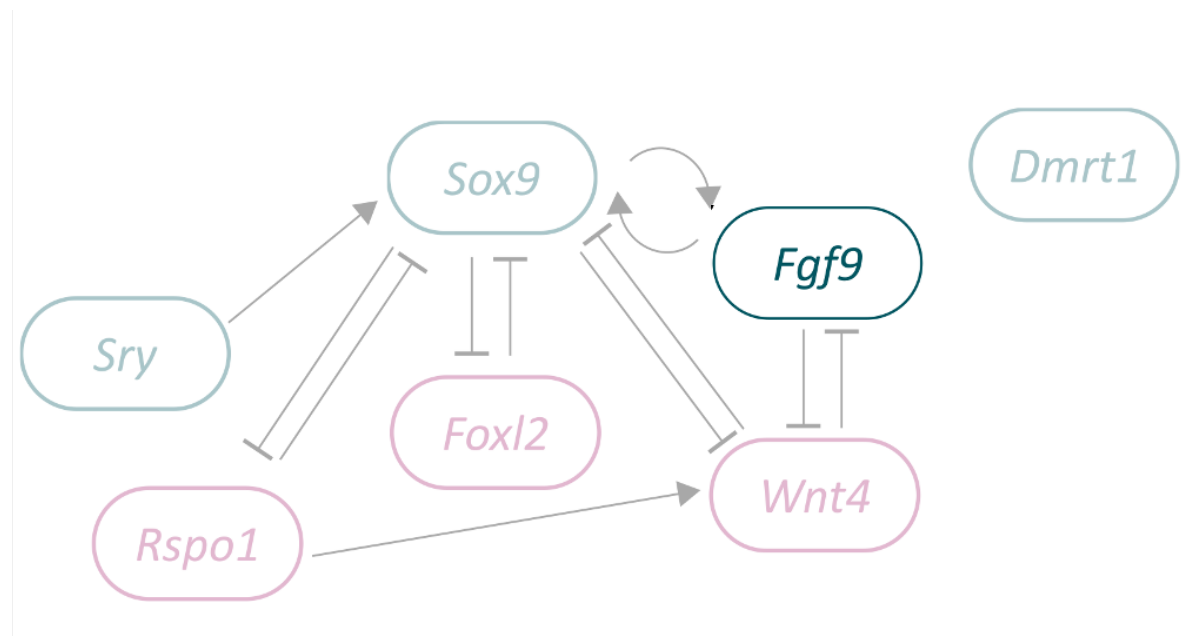


0 20
Enrichment Ratio



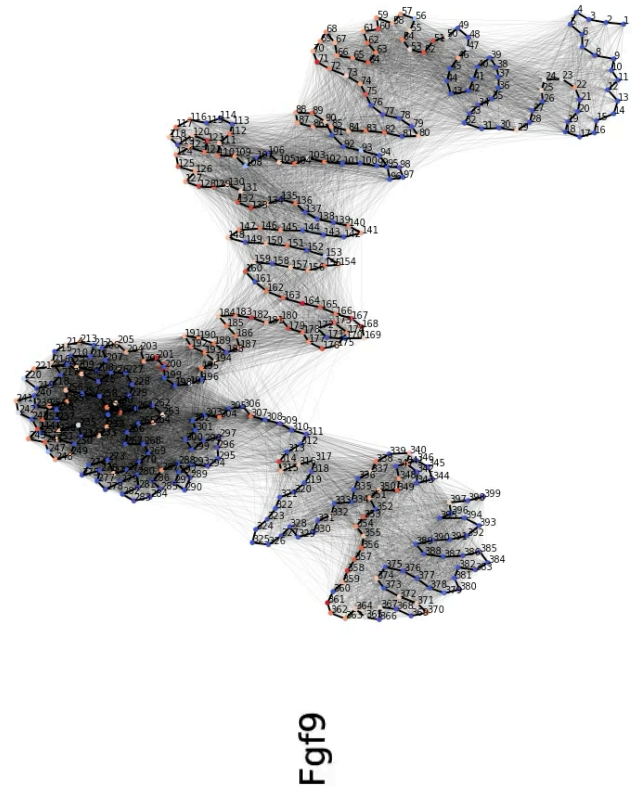
Now that we know the genes....

Can we identify regulatory elements using  METALoci

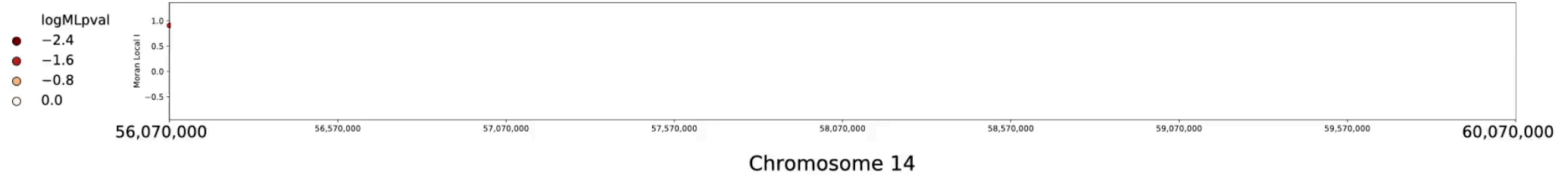


METALoci predictive mode

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



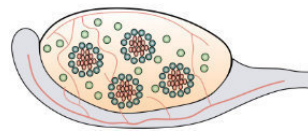
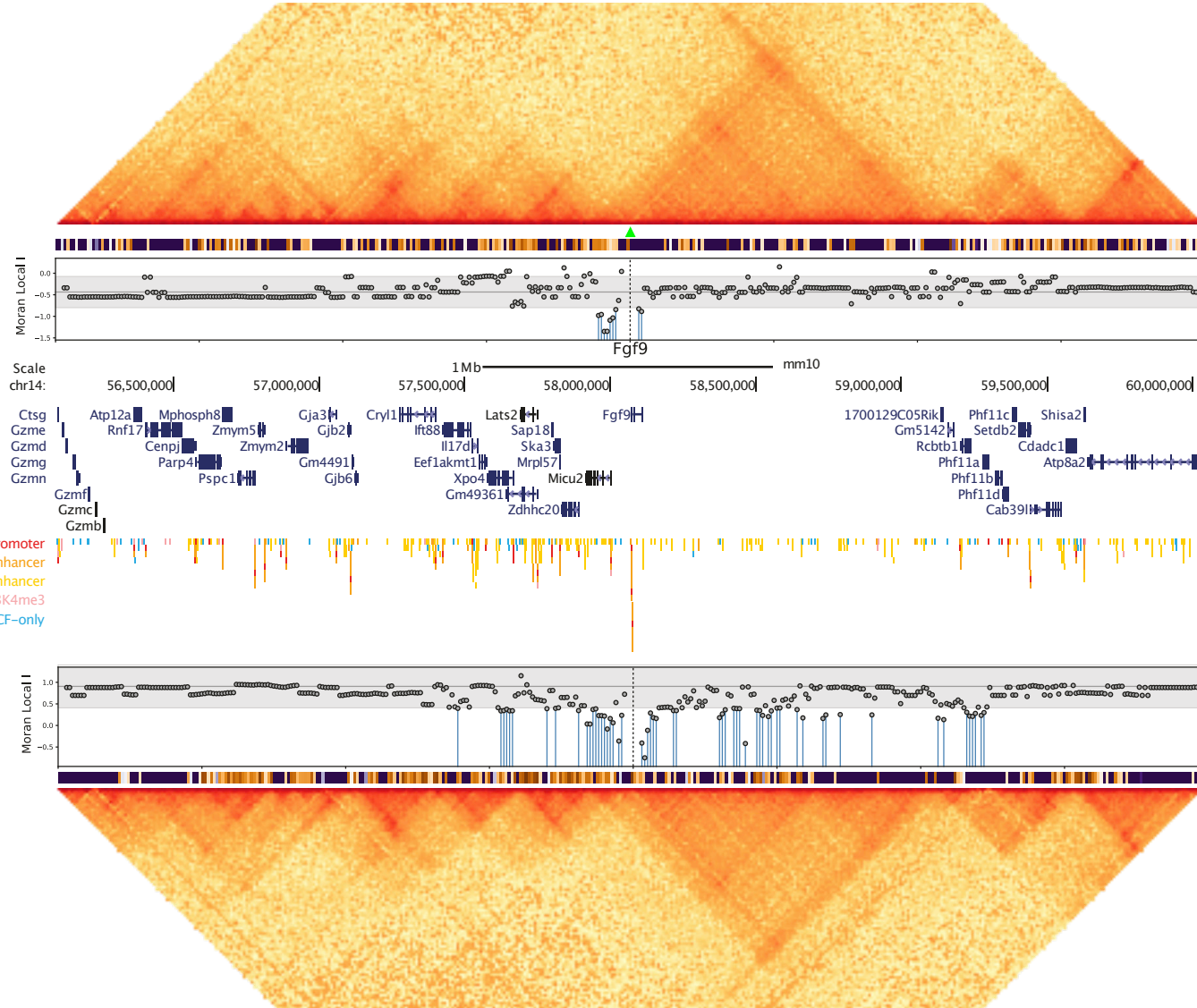
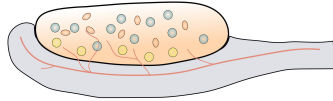
Fgf9



METALoci predictive mode

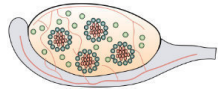
Fgf9 locus chr14:56,070,000-60,070,000

XY E10.5

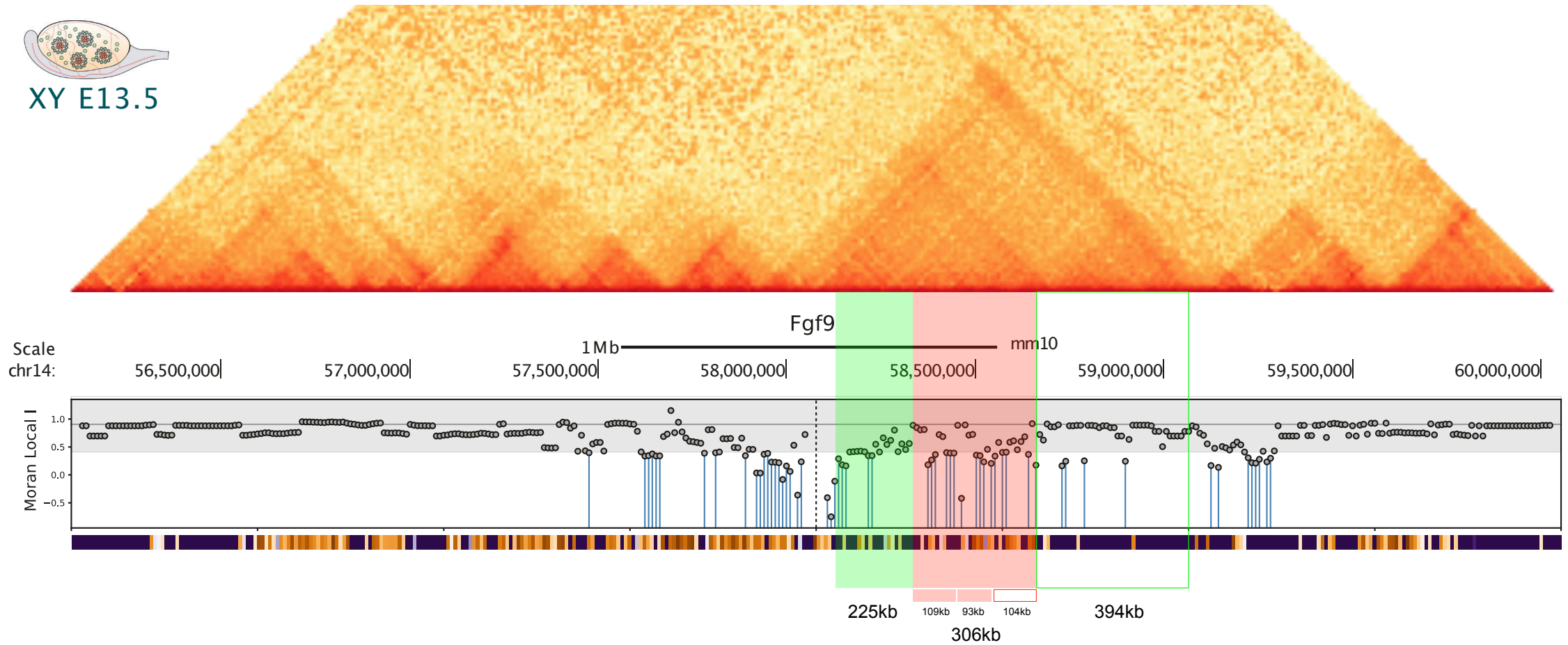


XY E13.5

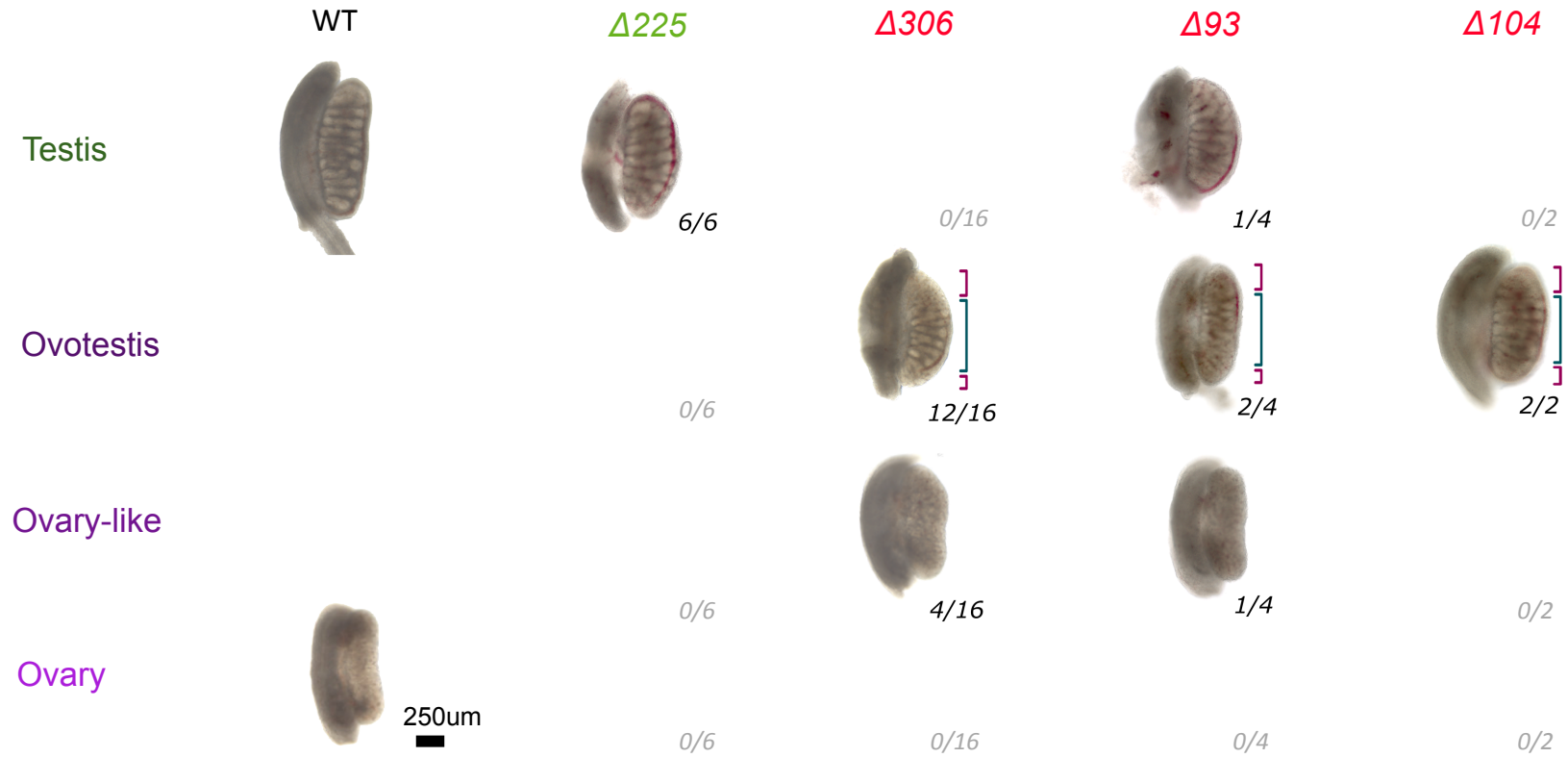
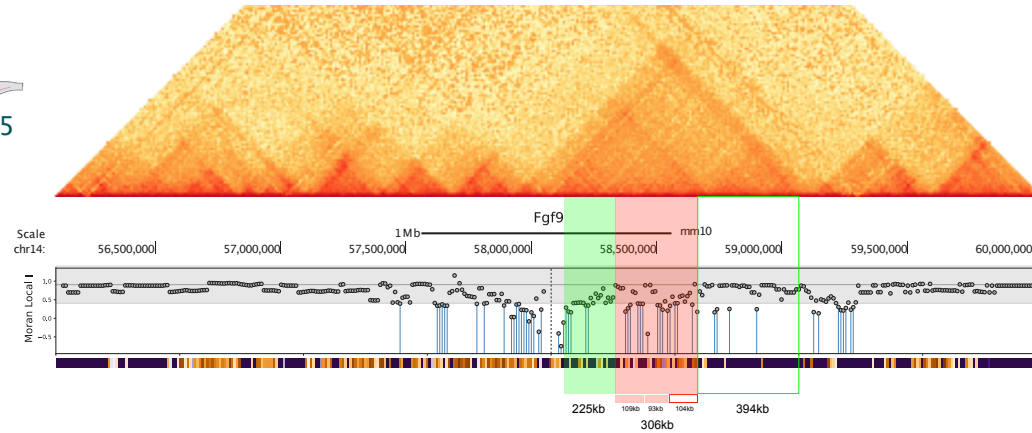
In silico prediction of regulatory regions at the Fgf9 locus



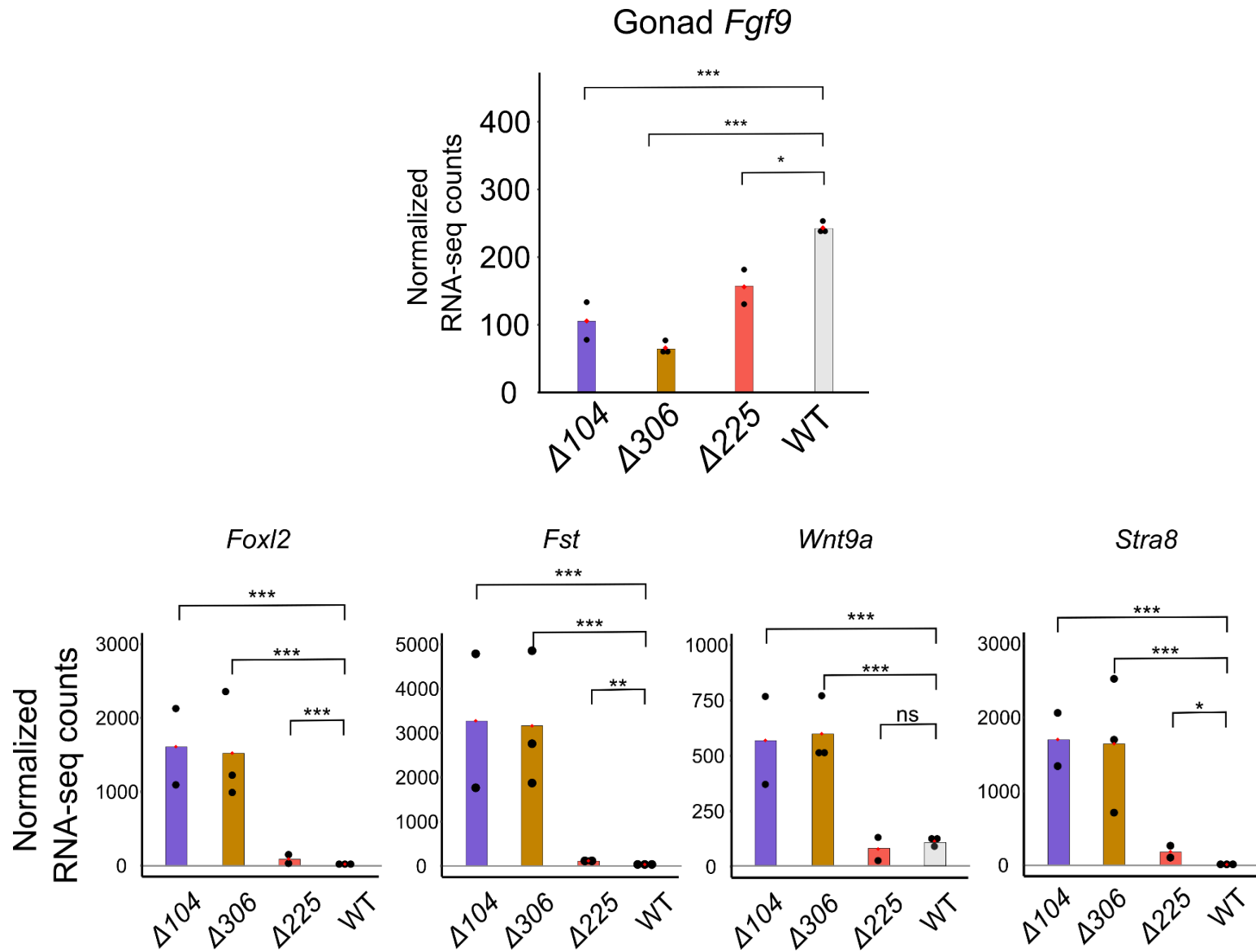
XY E13.5



Phenotype confirms METALoci predictions



RNA-seq confirms METALoci predictions



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

WE ARE HIRING!
Talk to me :)

@marciuslab
@mamartirenom

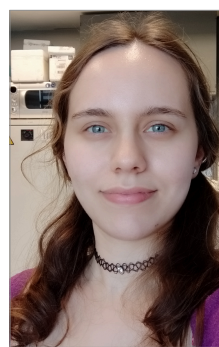
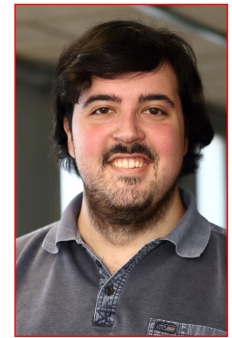
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Irene Mota

In collaboration with the
Capel Lab (Duke U.) and
Lupiañez Lab (CABD)



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Nikolai Bykov
Lana Kim
Peter Hoboth
Iago Maceda
John Markham
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Thanks to the 3D Genomics community!

Albert Jordan (IBMB)
Ana Losada (CNIO)
Ana Pombo (MDC)
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Dario Lupiáñez (MDC)
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