

Spatio-temporal regulatory landscape of sex-determination

#### or a case for:

Structure-Based Genome Editing (SBGE) guided by genome spatial autocorrelation analysis

#### Marc A. Marti-Renom

CNAG · CRG · ICREA BioRxiv

http://marciuslab.org
http://3DGenomes.org





Juan A. Rodríguez CNAG-CRG now @Globe I. Denmark



Irene Mota MDC Berlin



Dario Lupiañez MDC Berlin Now @CABD

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







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.





#### No major structural (apparent) differences







#### Spatial lay-out of significant interactions chr11:110780000-114770000 @10kb







#### Local Moran Index











## All genes LMI Trip

36

Log10(pval)

--6

136

28

266

Log10(pval)



20





Now that we know the genes.... Can we identify regulatory elements using

## METALoci predictive mode

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







Chromosome 14

## METALoci predictive mode

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



### In silico prediction of regulatory regions at the Fgf9 locus



-0.5



394kb

225kb

### Phenotype confirms METALoci predictions



#### RNA-seq confirms METALoci predictions



## But... is there more NEW regulatory TFs associated to sex-determniation?













## Granulosa cells regulatory landscape by SCENIC+ & METALoci

Meis 1 and 2 negatively control granulosa cells development



Mutant embryos by Miguel Torres, CNIC

# 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
- Set of "regulons" identified related to sex determination
- Previously unknown, Meis1 and Meis2 control female gonad development



#### http://marciuslab.org





Juan A. Rodríguez

Irene Mota



Alexander Barclay Nikolai Bykov Iana Kim Peter Hoboth Anne Lee Iago Maceda John Markham Maria Marti-Marimon Ana Nikolovska Mireia Novell Meritxell Novillo Aleksandra Sparavier Leo Zuber

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

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