3D Genomic Hubs

Spatio-temporal regulatory landscape of sex-determination

Marc A. Marti-Renom CNAG-CRG · ICREA

3D hubs

Miguel-Escalada, Bonàs-Guash, Cebola, et al. 2019 Nature Genetis



Human pancreatic islets







Spatio-temporal regulatory landscape of sex-determination

Marc A. Marti-Renom CNAG-CRG · ICREA BioRxiv 2022

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





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

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)

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.

Sex-determination as a model for "bipotential" commitment



No major structural (apparent) differences







Hi-C normalization and interaction selection

chr11:110780000-114770000















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

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







Chromosome 14

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



Fgf9 XY Δ 306 mutant



Fgf9 XY Δ 306 mutant

XY Wildtype

XY Δ306

XX Wildtype



0/16



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

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





Interested? 2024 PhD position open, contact me.







David Castillo Marco Di Stefano Irene Farabella Alicia Hernández Francesca Mugianesi Juan A. Rodriguez

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

.: Our current sponsors :.













.: Conflict of Interest Statement :.

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