



## 3DGenomics... because the genome is not linear

#### Marc A. Marti-Renom CNAG-CRG · ICREA

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







# Chromosome Conformation Capture



Hakim, O., & Misteli, T. (2012). SnapShot: Chromosome Confirmation Capture. Cell, 148(5), 1068–1068.e2.

#### ARTICLE

doi:10.1038/nature12593

#### Single-cell Hi-C reveals cell-to-cell variability in chromosome structure

Takashi Nagano<sup>1</sup>\*, Yaniv Lubling<sup>2</sup>\*, Tim J. Stevens<sup>3</sup>\*, Stefan Schoenfelder<sup>1</sup>, Eitan Yaffe<sup>2</sup>, Wendy Dean<sup>4</sup>, Ernest D. Laue<sup>3</sup>, Amos Tanay<sup>2</sup> & Peter Fraser<sup>1</sup>

#### LETTER

doi:10.1038/nature20158

#### Capturing pairwise and multi-way chromosomal conformations using chromosomal walks

Pedro Olivares-Chauvet<sup>1</sup>, Zohar Mukamel<sup>1</sup>, Aviezer Lifshitz<sup>1</sup>, Omer Schwartzman<sup>1</sup>, Noa Oded Elkayam<sup>1</sup>, Yaniv Lubling<sup>1</sup>, Gintaras Deikus<sup>2</sup>, Robert P. Sebra<sup>2</sup> & Amos Tanay<sup>1</sup>

| nature . |   |
|----------|---|
| geneti   | C |

ARTICLES https://doi.org/10.1038/s41588-018-0161-5

#### Enhancer hubs and loop collisions identified from single-allele topologies

Amin Allahyar<sup>1,2,7</sup>, Carlo Vermeulen<sup>3,7</sup>, Britta A. M. Bouwman<sup>3</sup>, Peter H. L. Krijger<sup>3</sup>, Marjon J. A. M. Verstegen<sup>3</sup>, Geert Geeven<sup>3</sup>, Melissa van Kranenburg<sup>3</sup>, Mark Pieterse<sup>3</sup>, Roy Straver<sup>1</sup>, Judith H. I. Haarhuis<sup>4</sup>, Kees Jalink<sup>5</sup>, Hans Teunissen<sup>6</sup>, Ivo J. Renkens<sup>1</sup>, Wigard P. Kloosterman<sup>1</sup>, Benjamin D. Rowland<sup>4</sup>, Elzo de Wit<sup>6</sup>, Jeroen de Ridder<sup>1</sup><sup>1</sup> and Wouter de Laat<sup>3\*</sup>

Resource

#### Higher-Order Inter-chromosomal Hubs Shape 3D Genome Organization in the Nucleus

#### Graphical Abstract

Cell



Sofia A. Quinodoz, Noah Ollikainen, Barbara Tabak, ..., Patrick McDonel Manuel Garber, Mitchell Guttman

Correspondence mguttman@caltech.edu

Authors

#### ARTICLE

DOI: 10.1038/s41467-018-06961-0 OPEN

#### Chromatin conformation analysis of primary patient tissue using a low input Hi-C method

Noelia Díaz 💿 <sup>1</sup>, Kai Kruse 💿 <sup>1</sup>, Tabea Erdmann<sup>2</sup>, Annette M. Staiger<sup>3,4,5</sup>, German Ott<sup>3</sup>, Georg Lenz<sup>2</sup> & Juan M. Vaquerizas 💿 <sup>1</sup>

Article Published: 11 February 2021

#### Liquid chromatin Hi-C characterizes compartmentdependent chromatin interaction dynamics

Houda Belaghzal, Tyler Borrman, Andrew D. Stephens, Denis L. Lafontaine, Sergey V. Venev, Zhiping Weng, John F. Marko & Job Dekker 🖂

Nature Genetics53, 367–378 (2021)Cite this article7436Accesses8Citations20AltmetricMetrics

# Chromosome Conformation Capture

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.





# Hierarchical genome organisation

Lieberman-Aiden, E., et al. (2009). Science, 326(5950), 289–293. Rao, S. S. P., et al. (2014). Cell, 1–29.







# Spatio-temporal regulatory landscape of sex-determination







Juan A. Rodríguez Irene Mota Dario Lupiañez

#### Marc A. Marti-Renom CNAG-CRG · ICREA

BioRxiv 2022

http://marciuslab.org 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

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

## Theories

## Genetics



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

# Sex-determination as a model for "bipotential" commitment



**Bipotential** 



Granulosa

# No major structural (apparent) differences











# Hi-C normalization and interaction selection



#### Normalized Hi-C

Top interactions



























### Marker (H3K27ac) into 2D mapping chr11:110780000-114770000



# Local Moran Index





# Quantifying regulatory environments bin by bin

#### XY E10.5 Bipotential



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



#### XY E13.5

**XY temporal** 







-2





High-Low



-4





#### LM's I



#### High-High



# All genes LMI Trip



Low-Low (LL)







- detoxification of copper ion -
- stress response to copper ion -
- stress response to metal ion -
- cellular response to zinc ion -
- detoxification of inorganic compound -
  - Sertoli cell development -----
- regulation of sister chromatid cohesion -------
  - Sertoli cell differentiation -----
    - response to zinc ion ------
  - sister chromatid cohesion ------
  - protein localization to chromosome ------
- transcription initiation from RNA polymerase II promoter -----•
  - DNA-templated transcription, initiation -----•
    - male gonad development -----•
    - male sex differentiation -----
  - development of primary male sexual characteristics -----•
    - recombinational repair -----•
- double-strand break repair via homologous recombination -----•
  - ribonucleoprotein complex subunit organization ----
    - ribonucleoprotein complex assembly ----
      - gonad development -----
  - development of primary sexual characteristics ----
    - mRNA catabolic process ----•
      - sex differentiation -----
    - RNA catabolic process ----•
    - ribonucleoprotein complex biogenesis ----
- proteasome-mediated ubiquitin-dep. protein catabolic proc. ----•
  - RNA splicing ----•
  - reproductive structure development ----•

**1 1 1** 20

**Enrichment Ratio** 





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

## METALoci predictive mode Fgf9 locus chr14:56,070,000-60,070,000





Fgf9

58,070,000 58,570,000 59,070,000 59,570,000 60,070,000

Chromosome 14





# METALoci predictive mode

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



# METALoci predictive mode

## XY Wildtype





#### Testis

# METALoci predictive mode

Fgf9 XY ⊿306 mutant

## **XY** Δ306

## XX Wildtype

# **Ovary-like**

250um



## METALoci predictive mode Fgf9 XY 🗚 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

# Take home messages:





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



Alexander Barclay Nikolai Bykov Ronan Duchesne lana Kim François Le Dily lago Maceda Maria Marti-Marimon Meritxell Novillo Aleksandra Sparavier Leo Zuber



















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





#### We are HIRING at all levels!!!









PURO SIQUE

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

.: Our current sponsors :.





**National Human Genome Research Institute** 





