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Abstract

During the talk, I will introduce Structure-Based Genome Editing and its application to the identification of sex-determining 3D regulatory hubs. Mammalian sex is determined by opposing networks of ovarian and testicular genes that are well characterized. However, its epigenetic regulation is still largely unknown, thus limiting our understanding of a fundamental process for species propagation. Here we explore the 3D chromatin landscape of sex determination *in vivo*, by profiling FACS-sorted embryonic mouse gonadal populations, prior and after sex determination, in both sexes. We integrate Hi-C with ChIP-seq experiments using METALoci, a novel genome spatial auto-correlation analysis that identifies 3D enhancer hubs across the genome. We uncover a prominent rewiring of chromatin interactions during sex determination, affecting the enhancer hubs of hundreds of genes that display temporal- and sex-specific expression. Moreover, the identification of the 3D enhancer hubs allows the reconstruction of regulatory networks, revealing key transcription factors involved in sex determination. By combining predictive approaches and validations in transgenic mice we identify a novel *Fgf9* regulatory hub, deletion of which results in male-to-female sex reversal with the upregulation of ovarian-specific markers and the initiation of meiosis. Thus, spatial auto-correlation analysis is an effective strategy to identify regulatory networks associated to biological processes and to further characterize the functional role of the 3D genome.



Short Bio

My Ph.D. work involved using Molecular Dynamics simulations to study protein folding and unfolding under the supervision of Profs. Karplus, Oliva and Avilés. This led to a postdoctoral fellowship at The Rockefeller University, where I later became a Research Assistant at the Sali Lab. Next, I moved to San Francisco where I was Assistant Adjunct Professor at the UCSF. There, my research focused on using statistics and evolution to study proteins and their complexes, and I contributed to the development of the MODELLER program and the Integrative Modeling Platform (IMP). My time at UCSF also included being a key member of three NIH research grants for the Structural Genomics Initiative and co-initiating the Tropical Disease Initiative, an open-source drug discovery project for tropical diseases. My experiences at the UCSF helped me develop leadership skills and a broader understanding of structural computational biology. Since 2006, I have led my own research group starting at the CIPF in Valencia (Spain) and currently at the National Center for Genomic Analysis (CNAG) and the Centre for Genomic Regulation (CRG) in Barcelona. My group uses experimental and computational approaches to study the molecular regulation of cells, specifically focusing on the genome. Our research has resulted in over 135 peer-reviewed articles and 165 oral presentations. I have also been involved in several EU funded projects and currently serve as co-PI on the ChromDesign, PerMed, and 3D'Omic projects funded by the European Commission. In 2021, I became co-PI of the Center for Genome Imaging at the National Human Genome Research Institute of the NIH. Additionally, I have been involved in promoting 4DNucleomics research in Europe as Chair and Vice-Chair of the INC COST Action, coordinator of the INC Spain, and co-coordinator of the EpiGene3Sys networks.

Speakers

Speaker: Marc Martí Renom, ICREA Research Professor at CNAG-CRG

Host: David Torrents, Computational Genomics Leading Researcher
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