Universitat Pompeu Fabra Barcelona | Master in Bioinformatics for Health Sciences

Master project 2020-2021

Personal Information

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Project

Computational genomics

Project Title:

Dissecting The Role Of Spatial-Temporal Genome Architecture In Pediatric Acute Lymphoblastic Leukemia

Keywords:

leukemia, ¨omics¨ data, 3D genome architecture

Summary:

Most of mutations and epimutations associated with complex diseases lie in non-coding regions, frequently at regulatory regions, and potentially exert their functions by altering the regulation of the target genes. The vast majority of regulatory elements that regulate each gene in each cell type are uncharted, constituting a major missing link in understanding genome control. We previously developed a new method called Promoter Capture Hi-C (PCHi-C), which allows the pioneer genome-wide systematic identification of the long-range regulatory elements that control more than 20000 genes. Using this method, we connected for the first-time non-coding autoimmune disease variants to putative target promoters prioritizing thousands of disease-candidate genes and implicating disease pathways, quarters of which not previously implicated (Cell 2016). Based on preliminary data recently generated, we hypothese that the novel description of the regulatory elements that control each gene along human B lymphpoiesis could allow to understand the contributions of mutations and epimutations in B cell cancer development and to discover new genes potentially implicated in malignant transformation. First, we are developing a novel experimental and computational methodology to genome-wide detect distal interacting regions of the genome for all genes in rare cell types with an improved resolution. Second, using this new methodology and other omics such as CHiP-seq, RAN-seq and ATAC-seq, we will unravel the dynamic rewiring of promoter interactomes along B cell differentiation. Third, we will link non-coding mutations and epimutations to their putative target genes, describing potential novel genes and gene pathways associated with B cell pediatric acute lymphoblastic leukemia. In summary, this interdisciplinary project will provide unprecedented insights into our understanding of how cells decide their identity with an impact on regenerative medicine, autoimmunity, immunodeficiency and B cell malignancies. SPECIFIC AIMS. - Mapping, filtering, interaction peak calling and analysis of the new method inspired on PCHiC data (HICUP and CHiCAGO pipelines). - Mapping, filtering, calling and analysis of CHIP-seq, ATAC-seq and RNA-seq - Analysis of GWAS data, WGS and WBGS data. - Integration of non-coding mutations and epimutations (Differentially Methylated Regions) with the previously omics data to define new genes and gene pathways associated with pediatric acute lymphoblastic leukemia.

References:

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promoters. Cell 167, 1369-1384.e19 (2016). This study focused on 17 human primary hematopoietic cell types, demonstrates that promoter interactions are highly cell-type- and lineage-specific and that they allow the association of non-coding mutations with potential target genes. - Cairns, J. Freire-Pritchett, P., Wingett, S.W., Várnai, C., Dimond, A., Plagnol, V., Zerbino, D., Schoenfelder, S., Javierre, B.M. et al. CHiCAGO: robust detection of DNA looping interactions in Capture Hi-C data. Genome Biol. 17, 127 (2016). This paper describes the algorithms for detecting significant interactions from capture Hi-C. - Pancaldi, V., Carrillo-de-Santa-Pau, E., Javierre, B.M. et al. Integrating epigenomic data and 3D genomic structure with a new measure of chromatin assortativity. Genome Biol. 17, 152 (2016) This manuscript summarizes the computational method used to calculate the enrichment of specific epigenomic features in the chromatin fragments constituting the nodes of the network. - Azagra A, Marina-Zarate E, Ramiro AR, Javierre BM #, Parra M # (#Corresponding author). From Loops to Looks: Transcription Factors and Chromatin Organization Shaping Terminal B Cell Differentiation. Trends Immunol (2020) This review summarizes the role of genome architecture in B cell differentiation and biology - Watt S, Vasquez L, Walter K, Mann AL, Kundu K, Chen L, Yan Y, Ecker S, Burden F, Farrow S, Farr B, Iotchkova V, Elding H, Mead D, Tardaguila M, Ponstingl H, Richardson D, Datta A, Flicek P, Clarke L, Downes K, Pastinen T, Fraser, P, Frontini M, Javierre BM #, Spivakov M#, Soranzo N# (#Corresponding author). Variation in PU.1 binding and chromatin looping at neutrophil enhancers influences autoimmune disease susceptibility. Nat Commun. (Under review) bioRxiv 620260; doi: https://doi.org/10.1101/620260 This manuscript describes the interplay between SNPs, transcription factor binding, gene expression, histone modifications, 3D chromatin organization and disease.

Expected skills::

High level of motivation and interest, Proficiency in at least one scripting or programming language, Proficiency in scripting environments for statistics and data analysis, Competitive CV, High level of collaborative and communicative skills, Good level of English speaking and writing skills.

Possibility of funding::

No

Possible continuity with PhD: :

Yes