How genes interact to build tissues and organisms

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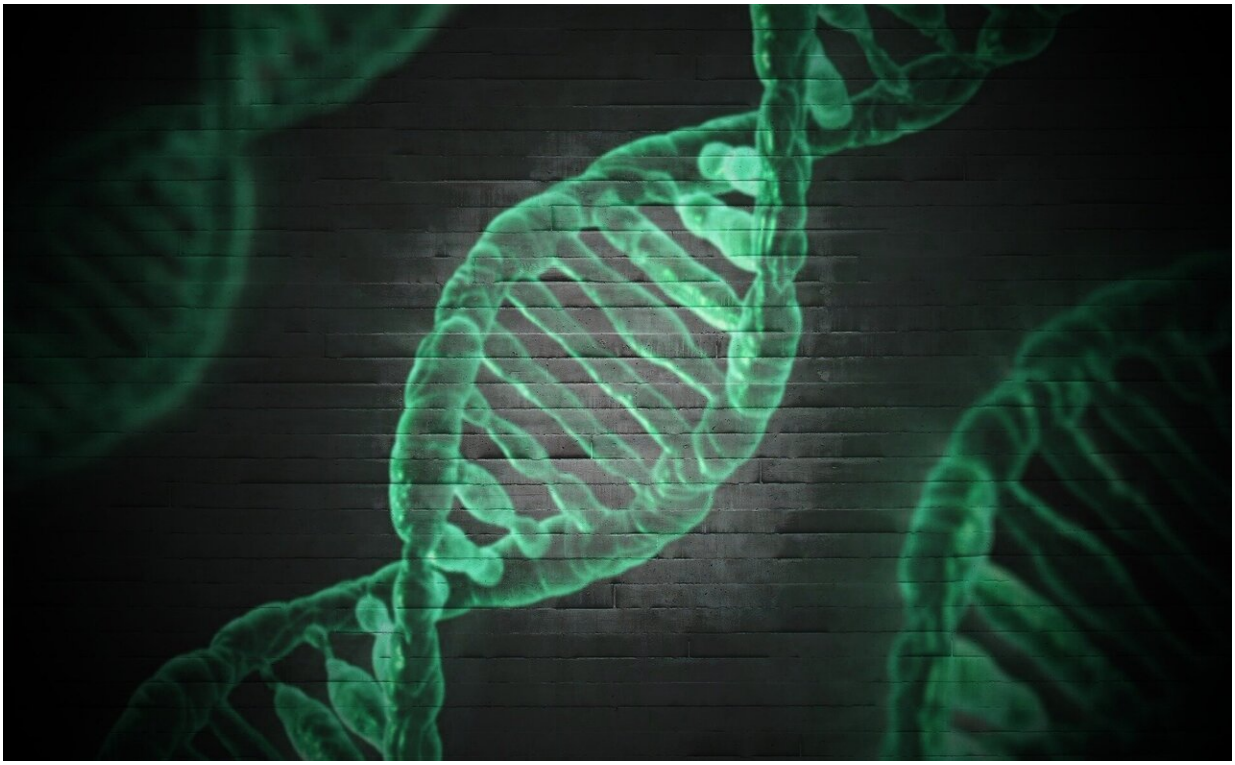

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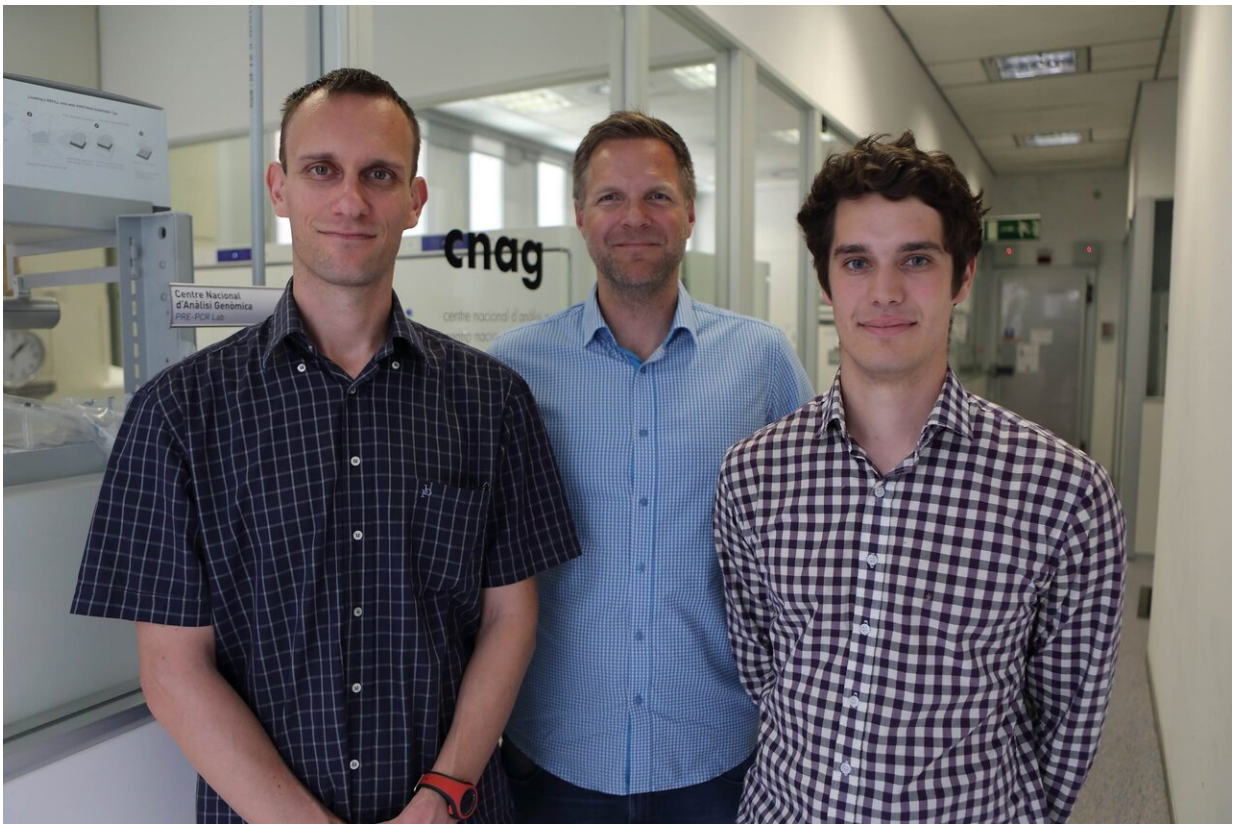
Although the knowledge we have about human cells and tissues has steadily increased over recent decades, many things remain unknown. For instance, cells exist in transient, dynamic states and understanding them is fundamental to decipher diseases and find cures. Classic

techniques used in the lab to study cell types faced limitations and did not enable a finely detailed profile of cell function.

To overcome this obstacle, a group of scientists at the National Centre for Genomic Analysis (CNAG-CRG) from the Centre for Genomic Regulation (CRG), in Barcelona, Spain, led by Holger Heyn, developed a new computational tool, based on the mathematical Graph theory, to infer global, large-scale regulatory networks, from healthy and pathological organs, such as those affected by diabetes or Alzheimer's disease. The researchers were able to pinpoint genes relevant to organ function and potential drivers of diseases. They are publishing their results in the current issue of the *Genome Biology* journal.

"Our previously developed single-cell transcriptomic tools were very useful to discover unknown cell types," says Giovanni Iacono, senior postdoc researcher at the CNAG-CRG and first author of the study. "Those tools allowed us to describe new types and subtypes of cells, with their unique biological roles and hierarchical relationships," he adds.



From left to right: Giovanni Iacono, Holger Heyn and Ramon Massoni-Badosa. Credit: CRG

Up to now, single-cell analysis had been used to understand cell types and their function within tissue. "Large-scale consortia like the Human Cell Atlas Project generate single-cell maps of entire organisms and sophisticated analysis strategies are required to transform big data into disruptive biological and clinical insights," says Holger Heyn, team leader of the Single Cell Genomics Group at the CNAG-CRG and senior author of the article.

The tool that this scientific team has now developed will enable them to go one step further, to see how genes interact to form tissues. "Our tool tries to address precisely the regulatory process that controls the

morphology and functions of a cell," highlights Iacono.

The tool is based on the Graph theory, an abstract mathematical model in which there are nodes connected by edges. Once you have a graph, a structure, you can measure the importance of each node for the network. In this case, each node was a gene and importance was defined as the function of that gene being key for the biological system under study.

CNAG-CRG researchers processed datasets from ten-thousands of cells to infer the regulatory networks that drive cell phenotype formation and their respective functions. They applied their tool to study type 2 diabetes and Alzheimer's disease and were able to find the functional changes relevant to those diseases. Importantly, this opens the door to finding new drug targets.

"The network analysis we have developed goes beyond currently applied approaches to provide deep insights into how gene activities shape tissues and organs. This is critical to understand diseases in which these networks are disrupted and find their "Achilles heels' for effective treatments." says Heyn.

Potentially, the tool can be applied to any disease, from Alzheimer's to chronic lymphocytic leukaemia. "We will apply our tool to propose new target genes for many diseases that can then be validated in further studies." Iacono states.

More information: Giovanni Iacono et al. Single-cell transcriptomics unveils gene regulatory network plasticity, *Genome Biology* (2019). DOI: 10.1186/s13059-019-1713-4

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