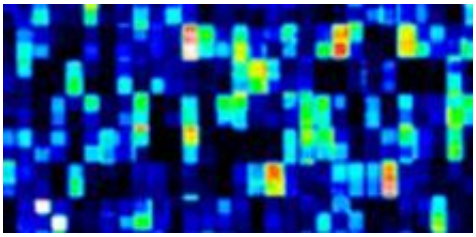
Medical Xpress

The human genome: A complex orchestra

August 20 2015



A team of Swiss geneticists from the University of Geneva (UNIGE), the École Polytechnique Fédérale de Lausanne (EPFL), and the University of Lausanne (UNIL) discovered that genetic variation has the potential to affect the state of the genome at many, seemingly separated, positions and thus modulate gene activity, much like a conductor directing the performers of a musical ensemble to play in harmony. These unexpected results, published in *Cell*, reveal the versatility of genome regulation and offer insights into the way it is orchestrated.

Chromatin, a complex of protein and DNA, packages the genome in a cell. It also arranges DNA in a way that it can be "read" by a group of proteins called transcription factors, which activate or repress gene expression. However, DNA sequence varies between individuals and thus it leads to molecular variation between people's chromatin states. This ultimately causes variation in the way humans respond to the environment. Understanding the genetic and molecular processes that govern chromatin variability is one of the great outstanding challenges in

life sciences, and would open the door to fully uncover how genetic variation predisposes individuals to a wide range of complex diseases, including cancer, diabetes, and autoimmune diseases.

The scientists' study in *Cell* reports how genetic variation affected three molecular layers in immune cell lines that were derived from 47 individuals whose genomes had been fully sequenced: transcription factor-DNA interactions, chromatin states, and gene expression levels. "We observed that genetic variation at a single genomic position impacted multiple, separated gene regulatory elements at the same time. This extensive coordination was quite surprising, much like a music conductor (i.e. genetic variant) directing all the performers (i.e. transcription factors, chromatin modifications) of a musical ensemble to change the volume (i.e. gene expression) of the music," explains Professor Bart Deplancke from EPFL. Contrary to the traditional model, which holds that gene regulatory elements impact gene expression in a quasi-independent fashion, researchers identified a much more harmonized and synergistic behavior: far from being linear, gene regulatory elements are actually coordinated in their actions.

The new evidence shows that the genome is not just a linear assembly of elements that interact in a pairwise fashion, but rather that it takes place under a more complex organization where different elements form intricate networks. If one element does not act properly, the whole system in which this element is embedded will be disturbed. "We have discovered basic biology rules of how the genome functions and how regulatory sequences act together to impact the expression of a gene," says Professor Alexandre Reymond from UNIL.

Although the Swiss scientists are still far from medical applications, the mechanistic principles they uncovered shed light on very fundamental aspects of genome biology. "It is still too early to determine if one day we would be able to modulate gene expression in a targeted way, but this

study reveals a level of complexity of genome function that was previously unanticipated", concludes Professor Emmanouil Dermitzakis from UNIGE. "Applying our discovery to medicine would mean identifying a single conductor and defining its role among all the other conductors for each musical ensemble - rather than merely listing all the performers playing in our genome orchestra."

Provided by University of Geneva