New research demonstrates the role of "junk DNA" in the activation and regulation of genes

Around 8,000 different genetic conditions and diseases are known today and the discovery of a new disease, while important for the individuals concerned and their families, is no longer exceptional. However, new research has shown for the first time that genetic malformations and diseases can be produced not only by changes in one of the 20,000 known protein-coding genes, but also in material distant from a gene which is nevertheless important for its activation and regulation.

The research was carried out by three groups working closely together, led by Professor Andrea Superti-Furga (University of Lausanne and CHUV), Professor Carlo Rivolta (University of Lausanne, University of Basel, and Institute of Molecular and Clinical Ophthalmology, Basel), and Professor Stefan Mundlos (Max Planck Institute and Charité University Teaching Hospital, Berlin), with clinical contributions from physicians in Brasilia, Ribeirao Preto and Sao José do Rio Preto in Brazil as well as from Chennai and Cochin in India.

The article published today in Nature, the prestigious international scientific journal, describes a study of the cause of congenital limb malformations in four unrelated individuals. The doctors were surprised to find no variant in any of the 20,000 known human genes that could explain the malformations. Further research revealed that the cause of the malformations appeared to be the deletion of a small segment of DNA ("missing" DNA), at a distance of some 300,000 nucleotides from the closest known gene in a region commonly known as a "gene desert" or "junk DNA". Bioinformatic analysis of the gene desert suggested that the missing DNA segment coded for a type of RNA (long non-coding RNA - LncRNA) and in further experiments the researchers were able to show that this previously undiscovered LncRNA was indeed necessary for remote activation of the gene EN1. Although the EN1 gene was itself intact, the failure to activate it was responsible for the malformations.

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Like the identified LncRNA, which was found in a segment of what had been considered to be “junk DNA”, most such material remains to be discovered. Consequently, while the known protein-coding genes, which represent only 2% of the human genome, are the basic functional units of life in cells and organisms, the remaining 98% of the genome may be responsible for the activation and regulation of the genes themselves.

The results of this research do not simply identify a new mechanism in genetic diseases. They have very significant implications for the entire field of human and medical genetics. Currently, even the most sophisticated genetic tests, such as whole genome sequencing (WGS), allow precise diagnosis in no more than 50% of cases of presumed genetic disease. These new results suggest that some of the “undiagnosed” cases may be associated with changes in regions of the genome whose functions have yet to be identified. From now on, every piece of DNA in the human genome, even if previously considered to be “junk DNA”, is a candidate for new functions or to explain genetic diseases. A whole new field of research is opening up.

Article
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