Discovery reveals chromosomes organize into 'yarns'

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Chromosomes, the molecular basis of genetic heredity, remain enigmatic 130 years after their discovery in 1882 by Walther Flemming. New research published online in *Nature* by the team of Edith Heard, PhD, from the Curie Institute and Job Dekker, PhD, from the University of Massachusetts Medical School (UMMS), reveals a new layer in the complex organization of chromosomes. The scientists have shown that chromosomes fold in a series of contiguous "yarns" that harbor groups of genes and regulatory elements, bringing them in contact with each other and allowing them to work in a coordinated manner during development.

Chromosomes are relatively large molecules that, when spread out, can measure up to the length of an entire human arm. Despite their size, however, they are actually confined within the small space of the cell nucleus which is just a few micrometers in size. Furthermore, within each cell nucleus are multiple chromosomes. In humans, for example, there are 23 pairs of chromosomes. In order to fit all this material into this small area, chromosomes are folded, compacted and mingled in the three-dimensional space of the nucleus.

So do chromosomes fill the nucleus just like spaghetti fills a plate? "Not quite," said Elphege Nora, PhD, a post-doctoral fellow on the team of Dr. Heard, head of the Genetics and Developmental Biology Lab at the Curie Institute. "Chromosome folding follows a pattern, and this actually turns out to be important for ensuring their proper function."

A chromosome looks like a series of tiny yarns

"We have known for decades that the DNA of individual genes is wrapped around nucleosomes to form the classical 'beads-on-a-string' structure," said Dekker, co-director of the Program in Systems Biology at UMMS. "Our new study now shows that these beads-on-a-string subsequently fold up to form 'yarns-on-a-string,' where each yarn is a group of genes. This domainal organization of chromosomes represents a previously unknown higher order level of folding that we believe is a fundamental organizing principle of genomes."

These globule-like yarns span anything from a few hundred thousand to a million base pairs, explained Heard. Base pairs (abbreviated as A, C, G and Ts) are the genome's unit of measurement, and a person's DNA consists of over 3 billion pairs. "The real surprise, however, lies in how this spatial folding of chromosomes links up to their functional organization," said Heard. "This chromosome folding pattern brings together, into the same 'yarn,' several genes, up to 10 of them, or even more."

However, there are not just genes in these yarns. So called "regulatory genomic elements," that can control the activity of neighboring genes like switches are also found clustered together with the genes in these chromosomal yarns. A group of genes belonging to the same yarn will therefore be likely to contact a similar set of regulatory elements, and this can result in the coordinated activity of these genes during development.

These new observations shed some light on several long-standing mysteries of genetics, such as the reason why some DNA mutations can end up affecting genes that are located thousands or even a million base pairs away.

"The cell nucleus is packed with genes, and the cell is faced with the challenge to turn on or off each one of them correctly," said Dekker. "By organizing groups of genes in isolated domains, or yarns that do not mingle or mix with other genes, the cell has solved the problem of how to regulate groups of genes coordinately and without interference from other genes."

However, damaging one of these "chromosome yarns" can lead to the misbehavior of all the genes it contains. "The three-dimensional organization of chromosomes allows distal genomic elements to be brought together and to functionally interact with each other. At certain points during development it is thus possible to precisely orchestrate the activity of genes that are far away from each other on the linear chromosome thread, but that are actually in contact physically, within a chromosome yarn," said Nora. "The down side of this type of organization is that a single mutation altering the organization of such a 'chromosome yarn' can affect a whole group of genes."

Three-dimensional folding provides shortcuts through the chromosome

"Together with Job Dekker, who has pioneered chromosome conformation capture technologies, we have discovered these principles by studying a critical region of the X chromosome, the X-inactivation center," said Heard. "Thanks to a parallel study conducted by the team of Bing Ren, PhD, at the University of San Diego (and published in *Nature* alongside the Heard and Dekker study), we now know that the principles of chromosome folding we have seen on the X chromosome actually apply to the whole mouse and human genomes."

Beyond advancing our fundamental understanding of chromosome biology, these studies also open up new avenues for studying certain

diseases, such as genetic disorders that are due to mutations in the DNA sequence which disrupt the proper activity of certain genes. Sometimes the mutation causing these defects is not directly in the gene, but affects one of its regulatory elements somewhere in its extended chromosomal neighborhood. Finding such mutations along the chromosome has been a bit like looking for a needle in a haystack because scientists did not know which genes were partnered with which regulatory elements. The hunt for such mutations can now be directed first to the chromosomal region most likely to harbor the regulatory elements of the misbehaving gene – inside the chromosome "yarn" to which that gene belongs.

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