

The shape of the DNA helix proves to be as important as its sequence

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The mechanism of DNA binding of the well-studied protein Polycomb, which is vital for cell division and embryogenesis, has finally been deciphered. A remarkable discovery, as it proves that the shape of DNA is at least as important for where the protein binds in the DNA as the DNA sequence. The role of the shape of DNA had not been demonstrated so clearly. Researchers at Radboud University will publish their findings on May 28th in the scientific journal *Nature Genetics*.

Besides the classical interpretation of the code (the 'sequence of letters') in DNA defining its function, it has been known for several years that the helix shape of DNA may also play a role. "We are currently able to read what is written in the human genome, but understanding the mechanisms is not an easy task," says Gert Jan Veenstra, Professor of Molecular Developmental Biology, one of the researchers involved in this study. "The concept that helix shape is also involved in how DNA functions, is an interesting new way of perceiving DNA. It could lead to understanding its functioning in general and of the way in which proteins can bind to DNA in certain places."

The Polycomb [protein](#) complex that was studied, consists of a group of proteins that are vital for cell division: by binding to DNA using the MTF2 protein, it switches off specific genes that determine the [cell division](#) rate. Besides being exceedingly important for the proper development of embryos, Polycomb mutations also play a significant role in the development of various types of cancer later in life.

Practising a new form of biology

The discovery of the mechanisms involved of DNA binding by Polycomb is one of the first concrete examples in which the shape of DNA plays a more important role for the protein's functioning than the code contained in the DNA. It turns out that the protein can only bind to the DNA helix if the latter is relatively unwound. Veenstra: "Because the DNA-binding protein does not bind to a specific sequence in the DNA, it was difficult to find the working mechanism of the protein using regular research methods." This mechanism had been actively sought by many people in the field for the past twenty years.

The researchers were able to distil the working model using an algorithm. "We would never have been able to find this [mechanism](#) without the use of the vast amount of data originating from humans, mice, zebrafish and frogs," says Simon van Heeringen, who was also involved in the research. This is a new way of practising biology, the researchers say. Van Heeringen: "Without this form of research, machine learning, this scientific field would not be able to get much further."

A boost in genetics and cancer research

According to Veenstra, their discovery will boost research into the shape of DNA: "There are many other proteins whose mechanisms we don't really understand: many of these also play a significant role in the development of cancer."

Follow-up studies in collaboration with Radboudumc and other medical researchers should provide additional insight into the exact role of Polycomb in cancer and the potential for new treatments.

More information: Matteo Perino et al. MTF2 recruits Polycomb

Repressive Complex 2 by helical-shape-selective DNA binding, *Nature Genetics* (2018). [DOI: 10.1038/s41588-018-0134-8](https://doi.org/10.1038/s41588-018-0134-8)

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