Genetics: Genome in Dissolution

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By Ulrich Bahnsen - November 6, 2008

The genome was considered to be the unchangeable blueprint of the human being, which is determined at the beginning of our life. Science must bid farewell to this idea. In reality, our genetic make-up is in a state of constant change

Two years ago, 25 geneticists sat down at the University of California at Berkeley to answer this seemingly simple question: What is a gene? However, the attempt to define the basic concept of their field precisely proved to be extremely difficult. The expert meeting almost ended in disaster, recalls Karen Eilbeck, Professor of Human Genetics at Berkeley and host of the round table: "We had meetings for hours. Everyone was screaming at everyone else."

The argument at Berkeley has little to do with research readiness. It was a first symptom that the life sciences - as yet unnoticed by the public - are on the verge of a turning point. What researchers are bringing to light in the chromosomal strands of humans or animals goes beyond the previous thought patterns of genetics. Similar to the beginning of the 20th century, when Einstein and his comrades-in-arms formed a new physical world view, the age of relativistic genetics may be dawning.

Medical research in particular is facing new challenges. The first outlines show that body and soul, their health, disease, development and aging are subject to a genetic interplay whose complexity exceeds all previous conceptions. Geneticists must abandon their image of a stable genome, in which changes are pathological exceptions. The genome of each individual is in a state of constant transformation. As a result, every organism, every human being, even every cell of the body is a genetic universe in itself.

The first analysis of the human genome was still a lengthy and costly affair, the result - celebrated in 2000 by US President Bill Clinton as the "Book of Life" - a sequence of three billion letters. Since then, new laboratory techniques, with the help of which enormous amounts of data can be generated and analyzed, have generated a flood of new findings on the inner life of the human genome in particular. In the process, the book dissolves before the eyes of the readers. The genome is not a stable text. The state of knowledge also raises basic philosophical questions such as the genetic and thus biophysical identity of the human being - and possibly demands radically different answers. The geneticists have their sights set on a new "human project" - motto: All about the ego.

"Our assumptions were so naive that it's almost embarrassing," says Craig Venter

The latest results show more than ever that humans are a product of genetic processes. But also that these processes are equipped with many degrees of freedom. They form an open system in which by no means everything is predetermined.

After the first genome coding, only a few people suspected this. The experts believed they had understood how a gene looks and functions, which functional principles the human or microbial genome follows. "In retrospect, our assumptions about how the genome works back then were so naive that it is almost embarrassing," says Craig Venter, who was involved in the project with his company Celera. What was expected was a collection of complicated but understandable recipes for the life processes. Now it becomes clear: The book of life is full of enigmatic prose.

It was only the first climax of the upheaval, when a few months ago the conviction of the genetic uniformity and thus identity of mankind broke down. Until then, the assumption had been that the genetic material of any two people differed only by about one per mille of all DNA building blocks. But the differences in the genetic makeup of humans are in reality so great that science now confirms what the vernacular has long known: "Every man is different. Completely different!

Craig Venter himself has contributed greatly to this insight. The charismatic genetic guru from Rockville in the US state of Maryland has had his own genetic makeup deciphered. Almost simultaneously, experts from the 454 Life Sciences Company decoded the genome of Nobel Prize winner James Watson, discoverer of the DNA double helix and Venter's intimate enemy. He did not want to hope, Venter teased, that too many similarities would be discovered between him and Watson.

After the celebrity sequencing of the research divas, scientists in Shenzhen announced that they had completely decoded an anonymous Han Chinese. A few days ago, the geneticist Gert-Jan van Ommen from the University of Leiden reported the first decoding of a woman. This was the clinical geneticist Marjolein Kriek, a member of van Ommen's team. The detailed analyses of the genetic data now reveal The human genome is just as diverse as the body and psyche.

Using Venter's genome, it was possible for the first time to catalog the differences. The genome of human somatic cells consists of half of a chromosome set inherited from the father and half from the mother. The researchers had expected that the parental dowry would show differences; it has long been known that there are numerous exchanges of individual letters in the genome (so-called SNPs - single nucleotide polymorphisms). However, they were surprised by the true extent of the differences: in almost every second gene of the researcher they found differences between the maternal and paternal gene copies. During the comparison, the experts also detected a large number of so-called indels: millions of times, entire sections had been newly incorporated into the genetic molecules (inversion) or had simply disappeared (deletion). Others had been detached from their environment and reinserted upside down.

The previous conviction that each gene usually exists only twice in the genome (once in the paternal, once in the maternally inherited set of chromosomes) is also incorrect. In reality, a great deal of genetic information is subject to a process of duplication and exists in up to 16 copies in the cell nucleus. Various research teams have now discovered such copy number variants (CNVs) in at least 1500 human genes; there are probably many more of these Xerox genes, with each person having a different CNV profile. The explosiveness of the findings is exacerbated by the discovery that the CNV patterns in the genome are by no means stable, the copy number of the genes may decrease or increase, and even the somatic cells of an individual human differ from each other.

The idea that the genome represents a natural constant, a fixed source code of the human being, is now crumbling under the weight of the findings. The US geneticist Matthew Hahn already compared the genome with a revolving door: "Genes constantly come, others go.

Especially the brain functions seem to be affected: CNVs are the main cause of various forms of mental retardation, autism, schizophrenia and other organic brain disorders. However, in interaction with other genetic processes, they probably also regulate the expression of healthy mental characteristics. "This is one of the most exciting and fruitful new areas of human genetics," says U.S. geneticist David Haussler of the University of California at Santa Cruz. The genome-wide search for such gene variations has already yielded astonishing results. The medicine of the future, the researcher predicts, will be characterized by the results of ultra-fast genome sequencing and massive computing power: "We have to keep an eye on hundreds, maybe thousands of genes simultaneously to understand diseases.

Identical twins develop genetically apart even as embryos

The 1000 Genomes Project has now been launched to determine the true extent of the construction work in the gene pool. Over a period of three years, the consortium of sequencing centers in the United States, the United Kingdom and China will sequence the genomes of 1000 people from around the world, recording the variance of genetic data from various populations around the world.

The interplay in the human genome is not only able to explain the individual peculiarities of the individual, it also produces the genetic assortment from which evolution continues to shape humans. This makes another disturbing finding understandable: The species Homo sapiens is apparently undergoing a turboevolution. Hundreds of areas of the genome have changed much faster than in other primates. New research even concludes that civilization must have accelerated human evolution 100-fold since the beginning of the Neolithic Age.

Science magazine named the discovery of these genetic variations as the breakthrough of 2007. Not even a year earlier, the journal mused, the prospect of soon distilling the factors that mark the evolutionary path to Homo sapiens through the precise comparison of the genomes of humans and chimpanzees had been celebrated. But even before the question of what in our DNA makes us human is answered, the next question is already in the room: "What in my DNA makes me myself?

One of the first insights of the new genetics also makes this question almost obsolete. Everything points to a startling answer: I am many.

At least physically, man no longer appears as an individual, but as an association of selfish cell colonies. In up to ten percent of all genetic material - and perhaps far more - either the maternal or the paternal variant is active. This pattern, called "autosomal monoallelic expression" in technical jargon, is already established in the embryo. And there each cell makes its own decision. "We believe that this happens when the embryo implants itself," says geneticist Andrew Chess of Harvard University. As a result, the adult organism resembles a patchwork of cell groups whose genetic networks are knitted differently.

Whether individual genetic information in these gene cascades originates from father or mother has drastic consequences, contrary to previous assessments. Their information content may show subtle differences, but these have profound consequences in the highly complex networks that control human traits. Another fascinating finding comes from Andrew Chess' Harvard laboratory: monoallelic expression is particularly common in genes that underwent accelerated evolution during the course of human development and those with important functions in the central nervous system. What this means for the functioning of the brain and the construction of the psyche cannot even be estimated at present.

Since then, the belief has been held that at least the healthy organism represents a harmonious system that works in harmony with itself. Instead, the research findings paint the picture of a fragile puzzle of biologically disparate units. Health would thus be an unstable state in which the egoisms of the mosaic pieces are kept in check. In any case, even the biological identity of the individual is at stake. What sounds frightening to many is an inspiring idea for the American geneticist Steven Henikoff: "I like the idea that we are mosaics.

At its core, this also threatens the work of those scientists who want to measure the influence of the environment on human development. For decades they have been trying to distinguish the influence of the environment from the dictates of genes when comparing monozygotic and dizygotic twins. They have used the differences between pairs of identical twins as a measure of the influence of the environment on the characteristics of humans - after all, these twins have completely identical genes. Therefore, all differences must be culturally and not biologically determined.

However, as it now turns out, there is no question of this: it is a fact that identical twins are genetically not identical, says Chess, "this is a really exciting result". Not only in the exclusively maternal or paternal activity pattern of their genes, but also in their CNV pattern there are clear differences. "We have always wondered why there are differences between identical twins, for example in their susceptibility to complex diseases," says Chess, "our discovery is one explanation." Social and material external factors can also shape a person in a detour via biology - by changing his or her gene

functions. Through so-called epigenetic processes, stress or torture, lack of nutrition or withdrawal of love can apparently have an effect right into the cell nucleus.

In view of the flood of these still largely mysterious findings, genetic researchers are facing a similar fate to cosmologists who have been researching the mysterious "dark matter" in the universe for several years. Bioscientists are now also puzzling over the dark matter of the genome.

Our genome does not determine what kind of person develops from it

They might find the dark secret in that part of the genetic material that they have so far dismissed as garbage, as "junk DNA". Relevant for them were only those few percent of the genome which, as genes of conventional definition, contain the necessary information for the construction of proteins in the cells. The rest was considered evolutionary junk. At best, this part of the genome could be imagined as a stabilizing element, as a kind of connecting cement between the actually important genetic information.

Now, however, it has become clear that it is above all the dark DNA matter in the chromosomes in which many of the newly discovered processes take place. Apparently the "junk" is full of unknown genes, populated by control modules. Especially the so-called microRNAs, a class of genetic information unknown until recently, regulate a multitude of developmental and disease processes.

The conclusion from all these new findings can only be Although the characteristics of a human being are rooted in its genome, in the open system of the embryonic genome it is by no means determined which human being will one day grow out of it. Even if an embryo that has been exactly duplicated down to the last molecule could be allowed to grow in the womb under identical circumstances - "another human being would still emerge," assures the Berlin geneticist Nikolaus Rajewsky. And that even without the influence of education and culture.

In view of the complexity and indeterminacy of genetic processes, many visions of the optimized design human, but also many warnings of the dangers of genetic research are now being exposed as a greatly simplified vulgar biologism. Tinkering with the genome is proving to be much more complicated than expected. And the fantasy that cloning could be used to resurrect gifted artists, brilliant researchers or simply a loved one in identical form will probably remain wishful thinking forever.

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