Genetic Material in Dissolution

By Ulrich Bahnsen | Source: DIE ZEIT, June 12, 2008, No. 25

The genome was considered the unchangeable blueprint of human beings, established at the beginning of our lives. Science must abandon this idea. In reality, our hereditary dispositions are in a state of constant change.

Two years ago, 25 geneticists sat together at the University of California in Berkeley to clarify the seemingly simple question: What is a gene? The attempt to define precisely the fundamental concept of their field, however, proved exceedingly difficult. The meeting of experts almost ended in disaster, recalls Karen Eilbeck, professor of human genetics at Berkeley and host of the gathering: “We had meetings lasting for hours. Everyone shouted at everyone else.”

The dispute in Berkeley had little to do with researchers’ vanity. It was an early symptom that the life sciences—still without the public noticing—were approaching a turning point. What researchers are uncovering in the strands of chromosomes in humans and animals is breaking apart established ways of thinking about genetics. Just as Einstein and his colleagues shaped a new physical worldview at the beginning of the twentieth century, an era of relativistic genetics may now be dawning.

Medical research in particular faces new challenges. The first outlines of a new picture are emerging: body and mind—their health, illness, development, and aging—are subject to genetic interactions of a complexity that exceeds all previous expectations. Geneticists must abandon their image of a stable genome in which changes are pathological exceptions. Everyone’s genetic material is constantly being remodeled. The consequence is that every organism, every person, indeed every cell of the body, is a genetic universe unto itself.

The first analysis of the human genome was still a lengthy and costly undertaking, the result—celebrated in 2000 by U.S. President Bill Clinton as the “book of life”—a sequence of three billion letters. Since then, new laboratory techniques, with whose help enormous amounts of data can be generated and analyzed, have produced a flood of new findings about the inner workings, above all, of the human genome. In the process, the book is dissolving before the eyes of its readers. The genome is not a stable text.

The state of knowledge also raises fundamental philosophical questions, such as that of the genetic and therefore biophysical identity of human beings—and possibly demands radically different answers. Geneticists have a new “Human Project” in their sights—motto: Everything about the Self.

“Our assumptions were so naive that it is almost embarrassing,” says Craig Venter

The latest findings show more clearly than ever that human beings are products of genetic processes. But they also show that these processes have many degrees of freedom. They constitute an open system in which by no means everything is predetermined. Few suspected this after the first decoding of the human genome. Experts believed they understood what a gene looked like, how it worked, and what functional principles governed the genetic material of humans and microbes. “Looking back, our assumptions at the time about how the genome works were so naive that it is almost embarrassing,” says Craig Venter, whose company Celera participated in the project.

Researchers had expected a collection of complicated but comprehensible recipes for the processes of life. Now it is becoming clear that the book of life is full of enigmatic prose.

It was only the first high point of the upheaval when, a few months ago, the conviction of the genetic uniformity and thus identity of humankind collapsed. Until then, the assumption had been that the genetic material of any two people differed in only about one per thousand of all DNA building blocks. But the differences in human genetic material are in truth so great that science now confirms what the Cologne vernacular had known for a long time: “Every Jeck is different.” Very different!

Craig Venter himself made a substantial contribution to this discovery. The charismatic genetics guru from Rockville, Maryland, had his own genome decoded. Almost simultaneously, experts at the company 454 Life Sciences sequenced the genome of Nobel laureate James Watson, co-discoverer of the DNA double helix and Venter’s bitter rival. Venter joked that he certainly hoped they would not discover too many similarities between himself and Watson.

Following the celebrity sequencing of these scientific stars, researchers in Shenzhen announced that they had completely sequenced the genome of an anonymous Han Chinese individual. A few days ago, geneticist Gert-Jan van Ommen of Leiden University reported the first decoding of a woman’s genome. The woman was clinical geneticist Marjolein Kriek, a member of his team.

Detailed analyses of genetic data now reveal that people’s genetic material is as varied as their physical and psychological characteristics. Venter’s genome made it possible for the first time to catalog those differences. The genetic material in human body cells consists of two sets of chromosomes, one inherited from the father and one from the mother. Researchers had expected differences between these parental contributions; it has long been known that individual letters in the genome are frequently exchanged (so-called SNPs, or single nucleotide polymorphisms). But they were surprised by the true scale of the differences: in almost every second gene in Venter’s genome, they found differences between the maternal and paternal copies.

In their comparison, the experts also detected so-called indels in abundance: millions of times, entire sections had been newly incorporated into the hereditary molecules (inversion) or had simply disappeared (deletion). Others had detached from their surroundings and been reinserted in reverse orientation.

The previous belief that each gene generally exists only twice in the genome—once in the paternal and once in the maternal chromosome set—is also incorrect. In reality, many pieces of genetic information undergo duplication and may exist in as many as 16 copies in the cell nucleus. Researchers have now found such copy number variations (CNVs) in at least 1,500 human genes; there are probably many more of these “Xerox genes,” and every person has an individual CNV profile.

The implications become even more striking with the discovery that CNV patterns in the genome are by no means stable. The number of copies of genes can rise or fall; even the body cells of a single person differ from one another. Under the weight of these findings, the idea that the genome is a natural constant, a fixed human source code, is crumbling. U.S. geneticist Matthew Hahn has already compared the genome to a revolving door: “Genes are constantly coming in, and others are going out.”

This discovery offers, for the first time, a plausible explanation for the diversity of human beings. Only dynamic processes of this kind, acting in concert, can have such powerful effects on psychological and physical traits. Those traits are controlled not by isolated genes but by networks often consisting of hundreds of genes. These genetic systems are frequently highly sensitive to subtle changes in individual genes.

If, for example, genes coding for signaling substances or their receptor molecules multiply, the organism’s communication systems change. The copying machinery of the genome may therefore be responsible for an individual’s physical peculiarities, but also for complex illnesses such as diabetes, autoimmune disorders, and heart disease.

Brain functions in particular seem to be affected: CNVs constitute the main cause of various forms of intellectual disability, autism, schizophrenia, and other organic brain-function disorders. Presumably, in interaction with other

genetic processes, they also regulate the development of healthy psychological characteristics.

“This is one of the most exciting and productive new areas of human genetics,” says U.S. geneticist David Haussler of the University of California, Santa Cruz. Genome-wide searches for such genetic variations have already yielded astonishing results. The medicine of the future, he predicts, will be shaped by ultrafast genome sequencing and immense computing power: “We need to look at hundreds, perhaps thousands, of genes simultaneously to understand diseases.”

Identical twins begin to diverge genetically even as embryos

To establish the true extent of the reconstruction taking place within the human genetic repertoire, the 1000 Genomes Project has now been launched. Over three years, a consortium of sequencing centers in the United States, Britain, and China intends to sequence the genomes of 1,000 people from around the world, documenting variations in genetic data across different populations.

The interplay within the human genome can explain not only each individual’s peculiarities; it also produces the genetic assortment from which evolution continues to shape humanity. This helps explain another unsettling finding: Homo sapiens apparently undergoes evolution at an accelerated pace. Hundreds of regions of the genome have changed far more rapidly than in other primates. New studies even conclude that civilization must have accelerated human evolution a hundredfold since the beginning of the Neolithic period.

The journal Science named the discovery of these genetic variations the breakthrough of the year 2007. Not even a year earlier, the specialist journal reflected, people had celebrated the prospect of soon isolating, by precise comparison of human and chimpanzee genomes, those factors marking the evolutionary path to Homo sapiens. Yet even before the question of what in our DNA makes us human had been answered, the next was already being posed: “What in my DNA makes me me?”

One of the first insights of the new genetics makes even that question almost obsolete. All signs point to an astonishing answer: I am many. At least physically, a human being no longer appears to be an individual but an alliance of self-interested cell colonies. For up to ten percent of all genes—and perhaps considerably more—only the maternal or the paternal variant is active. This pattern, known in technical language as “autosomal monoallelic expression,” is established in the embryo. And there each cell makes its own decision.

“We believe this happens when the embryo implants,” says geneticist Andrew Chess of Harvard University. As a result, the adult organism resembles a patchwork of groups of cells whose genetic networks are assembled differently. Contrary to previous assessments, whether individual pieces of genetic information in these cascades come from the father or mother has dramatic consequences. Their informational content may differ only slightly, yet those differences can have profound effects in the highly complex networks that govern human characteristics.

Andrew Chess’s Harvard laboratory has produced another fascinating finding: monoallelic expression particularly often affects genes that underwent accelerated evolution during human evolution, and genes that play important roles in the central nervous system. What this means for the functioning of the brain and the formation of the psyche cannot yet even begin to be assessed.

The belief that at least a healthy organism represents a harmonious system working in equilibrium with itself is now a thing of the past. Instead, the research findings portray a fragile puzzle composed of biologically disparate units. Health, in this view, would be an unstable state in which the competing interests of the mosaic pieces are held in check. In any case, even an individual’s biological identity appears to be open to question. What sounds frightening to many is an exhilarating thought to American geneticist Steven Henikoff: “I like the idea that we are mosaics.”

At its core, this also threatens the work of scientists trying to measure the influence of the environment on human development. For decades they have compared identical and fraternal twins in an effort to separate environmental influences from the dictates of genes. Differences between identical twins were taken as a measure of environmental influence on human traits—after all, the twins were thought to possess completely identical genes. Thus any differences would have to be cultural rather than biological.

But, as is now becoming clear, that is not the case: it is a fact that identical twins are not genetically identical, says Chess. “That is a really exciting result.” Clear differences can be found not only in the patterns of exclusively maternal or paternal gene activity but also in their CNV patterns. “We have always wondered why identical twins differ, for example in their susceptibility to complex diseases,” says Chess. “Our discovery provides an explanation.”

Social and material environmental factors can also shape a person indirectly through biology—by altering the way their genes function. Through so-called epigenetic processes, stress or torture, nutritional deficiencies, or deprivation of affection apparently can exert effects all the way into the cell nucleus.

Faced with this flood of still largely mysterious findings, genetic researchers find themselves in a situation similar to that of cosmologists who have spent recent years searching for the mysterious “dark matter” of the universe. Life scientists, too, are now puzzling over “the dark matter of the genome.”

Our genome does not determine what kind of person will develop from it

They may find this dark secret in the portion of the genome they previously dismissed as garbage—as “junk DNA.” To them, only the few percent of the genome that, according to the traditional definition of genes, contain the information necessary to build proteins in cells were relevant. The rest was regarded as evolutionary debris. At most, researchers imagined that this part of the genome might have a stabilizing role, acting like a binding glue between the genuinely important pieces of genetic information.

Now, however, it is becoming clear that many of the newly discovered processes take place precisely in this dark DNA matter within the chromosomes. The supposed “junk” is apparently full of unknown genes and populated by regulatory modules. In particular, so-called microRNAs—a class of genetic information almost unknown until recently—regulate a great many processes involved in development and disease.

The conclusion from all these new findings can only be this: although a person’s characteristics have their basis in the genome, the open system of the embryonic genetic material by no means determines what kind of person will eventually develop from it.

Even if it were possible to create an embryo duplicated exactly down to the last molecule and allow it to develop in the womb under identical conditions, “a different person would still emerge,” insists Berlin geneticist Nikolaus Rajewsky. And this would be true even without any influence from upbringing or culture.

In light of the complexity and indeterminacy of genetic processes, many visions of optimally designed human beings—and some warnings about the dangers of genetic research—are now revealed as grossly simplified, crude biological thinking. Tinkering with the genome turns out to be far more complicated than imagined. And the fantasy that cloning could bring gifted artists, brilliant researchers, or simply a loved one back to life in identical form will probably remain wishful thinking forever.