The Second Heredity

By Sascha Karberg

It is a custody case like many before and many to come. And yet, it may write legal history: The single mother of a teenager called Tom has died, and the biological father Toni is to be given custody, even though he does not even know Tom. Bob, Tom's mother's partner, who has cared for the boy like a father since he was born, is contesting this - with an unusual argument: That he is at least as much Tom's biological father as Tom's progenitor. Because what he gave the boy to eat over all the years, what he taught him and experienced with him, has defined Tom at least as much as the genes he inherited from his progenitor, Toni, during conception. The judge is confused, but Bob has already begun to explain what he means.

First, Bob holds up an image of three fruit flies, *Drosophila melanogaster*, one of the classic model organisms that have helped biologists to research the laws of heredity for over one hundred years. One of the three flies has normal, bright-red eyes. The compound eyes of the second, on the other hand, are a colourless white - the result of a mutation in a gene that determines eye colour. The third fly, in contrast, has red and white mottled eyes; some facets of the compound eyes are white, others are red. For decades, researchers could not explain this phenomenon, as the gene determining eye colour in the flies with mottled eyes is as intact as in the red-eyed fly. The only difference is that it is in a different position in the genome, which is why geneticists called the phenomenon "Position Effect Variegation" (PEV). Since then, it has been discovered that the gene is transposed to a region of the genome where genes are "packed". In other words, the DNA strands are tied up like a ball of wool. This means that the proteins that read the genetic information of a gene can no longer access the DNA; the gene remains "silent" and, as a result, the facets of the fly's compound eye remain white. In other facet cells, the eye colour gene is - by chance - a little less tightly tied up, so that is can still be read, making the facets red. This is how the red and white mottled compound eyes come to be.

Genes do not work like computers

"Yes, but what does that have to do with our case?" the judge interjects. "Depending on what the researchers feed the larvae of the PEV fly, the proportion of red and white facets in the eyes of the hatched flies varies," explains Bob. This means that genetic information is not just stoically read like a computer programme as an organism develops, but that the cells react to environmental influences - for example, the composition of the feed. The genes are packed to a greater or lesser extent and are therefore read to a greater or lesser extent. This essentially applies to all genes. But in the case of the eye colour of the PEV fly, this can easily be identified - from the eyes. "In this case, it means that not only the direct genetic ancestors determine the appearance of fly, but also environmental influences for which unrelated persons, in this case the researchers, are responsible," says Bob, who is now holding up

a picture of two bees - a queen and a worker. "This example here shows that: It is not just genetic make-up that makes us what we are."

Queen thanks to an enzyme

The difference between queen bees, who are particularly large and can lay eggs, and workers, who are barren, is a prime example of the huge influence diet can have on genes. Because as different as the queen and the workers are, their genotype is identical! A queen only hatches if a bee larva is fed "royal jelly", a secretion from special glands of the workers. In addition to water, sugar and amino acids, royal jelly contains a substance which inhibits a particular enzyme in the cells of the bee larvae. When the biologist Ryszard Maleshka of the Australian National University in Canberra blocked the production of this Dnmt3 enzyme in bee larvae, they developed into queens - without any royal jelly at all.

Genes in slumber like Sleeping Beauty

"That might be the case for flies and bees, but humans?" the judge interjects. "Even mammals such as humans have this Dnmt3 enzyme," Bob responds. It regulates the activation or deactivation of genes by sticking chemical attachments like thorns, called methyl groups, to the DNA. To a certain extent, it distributes thorns in the genome, so genes that have these "methyl thorns" fall into a kind of slumber like Sleeping Beauty and are switched off. The amount and pattern of these methyl thorns changes depending on lifestyle. Dozens of enzymes and proteins have now been identified that all ultimately influence the packing and thus the level of activity of genes. Epigenetics (Greek epi = on, at) is the branch of research within genetics that tries to explain what happens "on" or to the genes without altering the DNA blocks themselves.

Nutrition and epimutations

The effects of such epigenetic differences in humans is difficult to explore. In experiments with mice, the relationship between nutrition and gene marking can be proven by the coat colour. However, the researchers have also discovered others consequences: with a modified diet, the animals also developed certain types of cancer, diabetes and obesity far more frequently than normally. Because if methyl thorns are falsely attached to genes that counteract cancer or diabetes, then these genes are switched off - and the likelihood of these diseases increases. Therefore, some researchers no longer speak only of differences in the methylation patterns but even of "epimutations".

And these can also be researched in humans: Simone Wahl of the Department of Molecular Epidemiology at the Helmholtz Centre in Munich found epigenetic changes in blood samples from 10,000 men and women where the test person had a particularly high body mass index (BMI), i.e. if they were obese. In particular, genes that regulate fat metabolism and inflammation developed epimutations due to poor nutrition - which increased the probability of diseases such as diabetes.

"In other words, If I had allowed Tom to eat French fries and curried sausage all of the time, he would probably have developed disease-inducing epimutations," says Bob.

The same genetic material, different epigenetic patterns

However, such studies cannot completely rule out the possibility that the epigenetic differences are a result of the different gene variants of the non-related subjects. Because of this, Manel Esteller from the Spanish National Cancer Research Centre in Madrid is examining identical twins. Their genetic heritage is, by its very nature, virtually identical.

The younger the twins are and the longer they live together, the more similar their epigenetics, i.e. the epigenetic marking pattern and thus the activity level of their genes. However, if they had been separated at an early age or developed different eating habits, Esteller found significant differences in the epigenetic patterns.

Hereditary; Altered methylation signals

"This is all well and good, but it does not make Tom your biological son," the judge interjects. "After all, he got his genes from his mother and his biological father and he will only pass those on to his children, not the so-called epimutations caused by his upbringing and nutrition." "No, in addition to the genes from his biological parents, Tom will probably pass on epimutations he develops during the course of his life," says Bob, handing the judge the results of research by Michael Skinner. The biologist from Washington State University treated rats with insecticides and fungicides, so that their fertility was significantly reduced. This "environmental" damage was hereditary, because the untreated descendents of the rats were less fertile - at least into the fourth generation of offspring. When Skinner looked for the cause, he found abnormal methylation signals in two fertility-relevant genes.

Influences across generations

Of course, such experiments are not done on humans. However, there are also indications of the hereditability of environmental influences in humans: A Dutch study examined pregnant women and their children, who were starving for a long period of time in Amsterdam in 1944 because of the German occupation during World War II. Not only did they give birth to children with significantly lower birth weights, their children and grandchildren also seemed to be particularly susceptible to diabetes, obesity, cancer and cardiovascular disease in later life.

Biological and epigenetic paternity

"Allow me to summarise," says Bob to the judge. "I spent fifteen years eating with Tom, teaching him to speak and to run, rules, ideas and behaviours, trying to encourage his self-confidence and take away his fears. All of this has, if you like, left epimutations in his genome, which define his personality and will perhaps even be passed on to his children and grandchildren. In the same way as the gene variants - the specific composition of the genetic building blocks Tom inherited from his biological father Toni - will be passed on to Tom's children and grandchildren. I am therefore as much Tom's biological father as Toni and want to remain so in the future."

Difficult decision

What the judge will decide remains open. There has never been such a custody case, and not all of the experts have been heard yet, because epigenetic research is still in its infancy and many questions have yet to be answered. For example, how are environmental epimutations represented in nerve cells or fat tissue in the sperm and ova, so that the genes are similarly active or inactive in the nerve and fat cells of the next generation? However, it is likely that, in the future, judges and society will no longer only consider genetics but also epigenetics when it comes to questions of heredity.