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Background on the award of the 2013 Paul Ehrlich and Ludwig Darmstaedter Prize to Professor Dr. Mary-Claire King

Breast cancer research and humanitarian commitment

The power of genetics

Genetics tells us about our inheritance, the traits and features of our genetic makeup. It helps us to better understand complex diseases and can benefit humanity. The €100,000 Paul Ehrlich and Ludwig Darmstaedter Prize goes this year to a scientist who has demonstrated this with her unique accomplishments: Mary-Claire King, American Cancer Society Professor in the Department of Genome Sciences and Medicine at the University of Washington in Seattle. Her name stands for four discoveries that at first glance may appear very different but whose common denominator is the science of genetics.

Humans and chimpanzees are 99% genetically identical

Mary-Claire King demonstrated in 1975 – decades before the mass sequencing of genomes – that the genetic makeup of humans and chimpanzees is 99% identical. Her finding was based on protein analyses and hydridization studies. The results of her investigations also showed that the lines of hominids and chimpanzees separated in the course of evolution at a much later date than had been previously assumed. King hypothesized that the obvious inequality between humans and chimpanzees was due to differences in gene regulation. The human genome was completely encoded twenty-five years in later (in 2000), that of the chimpanzee thirty years later (in 2005). The direct comparison of the DNA sequences showed that King was right. The genomes are indeed virtually identical. "In conceptual terms, we were right on track," says the human geneticist about her work. "As a rule, concepts are very conservative,

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only the methods develop very quickly." Genome research has identified three reasons for the obvious differences between humans and chimpanzees. These are regulatory RNAs, epigenetics and the realization that genes are only one aspect of a highly dynamic and highly complex network of external and internal factors.

Genes for hereditary breast cancer

Mary-Claire King has investigated the genetic predisposition for cancer intensively since 1974. She has shown that breast cancer and ovarian cancer are inherited as an autosomal dominant trait. Some of the mutations responsible are to be found in a gene that King called BRCA1, which stands for *breast cancer susceptibility gene 1*. She first demonstrated the connection by means of statistical analysis, later through linkage analysis, and finally by allocating the gene to a specific chromosome. In 1990 King published the approximate position of the BRCA1 gene in the human genome: position 17q21. Afterwards, there was a neck-and-neck race to clone the gene, a race that Myriad Genetics ultimately won in 1994. King later presented the complete sequence of the BRCA1 locus with 84 kilobases.

BRCA1 and the BRCA2 gene, which was identified later, are tumor suppressor genes. The corresponding proteins have the task of ensuring the stability of the DNA and preventing uncontrolled growth. Carriers of these mutations have a higher risk in life for breast and ovarian cancer. BRCA mutations account for some five to ten percent of all breast cancers and ten to fifteen percent of all ovarian cancers. King also calculated the exact disease risk. "In severe mutations, the risk is 80 percent for breast cancer and 40 percent for ovarian cancer," says the geneticist. "In other words, 800 out of 1000 women with severe BRCA mutations are likely to develop breast cancer during their lifetime, and 400 out of 1000 women with severe BRCA mutations can be expected to develop ovarian cancer during their lifetime. The figures for the general population are 120 out of 1000 women who will develop breast cancer and 10 out of 1000 women who will have ovarian cancer," King explains. Professor King also developed new methods for the genetic diagnosis of these and other breast cancer mutations, though their commercial use in the USA is blocked by the patent awarded to Myriad Genetics.

Mary-Claire King's research achievements have permanently changed thinking about genetics in complex common diseases. By identifying the BRCA1 gene, she showed that mutations also play a role in these diseases. Until then, genetics had only been concerned with monogenetic diseases. These are conditions in which damage to a single gene leads to a specific disease. In other words, the mutation is equivalent to the disease. A good example is Huntington's chorea. King showed that mutations are also involved in complex, multifactorial diseases, which may in addition be influenced by environmental and lifestyle factors. The discovery of BRCA1 and BRCA2 as well as of other breast cancer genes has led to the widespread establishment of programs specifically designed for women with hereditary breast

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cancer. In Germany, too, there is a Consortium for Family Breast and Ovarian Cancer with twelve centers all over the Federal Republic. At these centers, women can receive genetic counseling and take tests for possible mutations. Mary-Claire King's discoveries have revolutionized the way we approach hereditary breast cancer.

Other disease genes and the genetic basis of diversity

Mary-Claire King has identified a number of other disease genes in the past decades. The conditions in which these disease genes are involved include inherited deafness, schizophrenia, autism, and systemic lupus erythematosus. Together with colleagues from Costa Rica, King mapped and later cloned the first autosomal gene for inherited deafness. This gene was named DFNA1. Working with colleagues from Israel and Palestine, she identified four further genes for this disease. Inherited deafness is an especially frequent condition in the Middle East. Professor King is currently interested especially in the study of schizophrenia. "We have found evidence that many cases of schizophrenia can be traced back to mutations that occur during the development of the embryo," states King. "These diseases are genetic in origin, but they are acquired conditions and not hereditary." King believes that the new mutations impair brain development and in this way contribute to the pathogenesis of schizophrenia. She has also studied what genes can tell us about human evolution. When people move from one place to another, they take their genes with them and pass them on to their descendants in their new location. That explains why the genome of modern *Homo sapiens* is something like a logbook, recording the travels and encounters of our ancestors, but also a compendium reflecting the diversity of human life.

Reuniting families and giving victims names

Mary-Claire King is also held in high esteem for her humanitarian commitment because she uses genetic technologies to expose violations of human rights. Since 1984 she has been working with the grandmothers of Plaza de Mayo (*Abuelas de Plaza de Mayo*) in Argentina. These grandmothers are demanding the return of their grandchildren to their biological families. The children were kidnapped by the military junta between 1976 and 1983, orphaned and given up for adoption to sympathizers of the junta. Since the Argentine authorities demanded sound proof for the children's biological kinship, the Abuelas turned to the American Association for the Advancement of Science in 1983, requesting assistance. Mary-Claire King gave them her wholehearted support. "I agreed to help at the time," says the prizewinner, "because the grandmothers' concerns were very near to my heart. My own daughter was the age of the grandchildren for whom they were fighting and I myself was the age of the women who had given birth to these children and who had been murdered by the military junta." At the time of the military putsch, King was visiting professor in Santiago de Chile, so she knew what military governments are capable of doing. King first identified the children by means of tissue characteristics, so-called HLA markers, and later by means of

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genetic technologies. She gained a first significant victory at Christmas 1984 when Argentina's Supreme Court ruled that Paula Logares, one of the missing children who had been unambiguously identified by means of HLA typing, had to be returned to her biological family. To date, 87 of the children, who are now adults, have been reunited with their biological families.

King has also developed methods for the use of genetics in forensic science, for instance, by isolating mitochondrial DNA from a person's bones and teeth. The mitochondria are the cells' power plants. Mitochondrial DNA is interesting for a very particular reason, which is that it always derives from the mother. We know this because the part of the male sperm that fertilizes the ovum does not contain any mitochondria. Consequently, while both sons and daughters have the same mitochondrial DNA as their mothers, it is the daughters who hand this DNA on to their descendants. That means that all female descendants of a maternal line necessarily have the same DNA in their mitochondria. Armed with this knowledge, it is possible to determine the female line of descent beyond the shadow of a doubt. King succeeded in extracting this mtDNA from teeth. Many human skeletal remains have degraded so completely that it is no longer possible to examine hair or tissue, while the DNA in the bones is often too damaged to allow unambiguous identification. DNA is best preserved in the teeth, which is why nowadays it is often the teeth of a dead person that are investigated in order to rediscover the victim's name, identity, life story, and sufferings. King works together with the UN's War Crimes Tribunal. Her laboratory is classified as a secure DNA Identification Lab to which no belligerent party or terrorist regime can have access. King and her co-workers have in the past identified victims from Cambodia, Guatemala, El Salvador, Rwanda, Ethiopia and Bosnia. She was involved in the unambiguous identification of the Romanovs, the last Czarist family, whose members were shot the night of July 17, 1918 in Yekaterinburg and then buried in the forest. "Because forensic genetics enjoys a high standard worldwide, we are only consulted nowadays in special cases or if unimpeded analysis does not seem possible," says King about her commitment in this field today. Her work has defined benchmarks for decades.

Further information

You can obtain the full resume, selected publications, the list of publications and a photograph of the prize winner from the Press Office of the Paul Ehrlich Foundation (c/o Dr. Hildegard Kaulen, phone: +49 06122/52718, email: Paul-Ehrlich-Stiftung@pvw.uni-frankfurt.de) and at www.paul-ehrlich-stiftung.de.