GENDER GAP – EVEN IN THE GENOME

Men and women possess different sex chromosomes. Nature, however, manages to reconcile this genetic gender gap. Asifa Akhtar, the Director of the Max Planck Institute of Immunobiology and Epigenetics in Freiburg, and her team are researching the sophisticated epigenetic mechanisms responsible for this process. As the Vice-President of the Biological and Medical Section in the Max Planck Society, she is also committed to reducing the gender gap in science.

TEXT: STEFANIE REINBERGER

Asifa Akhtar is running a little late. Even though our appointment is scheduled for early morning, she has already attended a meeting beforehand. And it's gone on a little longer than planned. She appears, holding a cup of coffee. "My first cup of coffee today. My schedule is pretty crazy these days," she says. The pandemic is making work trips almost impossible, and meetings are mainly being conducted on-line. "That means there's usually no respite – from one meeting to the next with only brief breaks in between," she says. "It's exhausting, but very efficient." And Akhtar has to rush right off to her next appointment after our conversation as well. Akhtar, 50, is the Director of the Max Planck Institute of Immunobiology and Epigenetics in Freiburg. Her research at the Institute examines the mechanisms involved in packaging genetic material in the chromosomes so that it can be meaningfully read. Such mechanisms are the prerequisite enabling individual cells to take on their proper characteristics and fulfill their intended functions in the body. Akhtar's main focus is the X chromosome.

Her research has already earned her several awards. Most recently, she received the Leibniz Prize, Germany's most important research funding award: "It's hugely satisfying to know that your work is not only being noticed but also being recognized at such a high level. My team in particular were completely over the moon; I'm extremely proud of what they've achieved," emphasizes Akhtar.

In 2020, she became the Vice President of the Biological and Medical Section of the Max Planck Society, the first woman from abroad in the role, and also the youngest. It's something that has also aroused a great deal of interest in her home country of Pakistan, and elicited a number of questions from the press. Moreover, Akhtar is also a wife and mother of two children, a son and a daughter. So life's really busy for her right now – but it doesn't seem to show.

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VISIT TO

ASIFA AKHTAR

PHOTO: MARCUS ROCKOFF

Asifa Akhtar joined the Max Planck Institute of Immunobiology and Epigenetics in Freiburg in 2009 as a Max Planck Investigator. In 2013, she was appointed Director of the Institute leading the Department of Chromatin Regulation.

PHOTO: MARCUS ROCKOFF

As Vice President, Asifa Akhtar is committed to supporting young researchers in their careers, especially young women: "It's up to us to create the conditions that make a career in science possible for women, including when they have children," she says.

Quite the opposite, she comes across as energized at our interview, coffee cup in hand, and her smile is genuine – relaxed and approachable. Bouncing from one appointment one task to the next seems to come easily to her, even while she's talking to me. She has an almost playful ability to switch the conversation between science, her personal interests, and gender issues – a topic that is close to her heart.

"The different countries and cultures I've had the opportunity to experience have taught me, above all else, to be open-minded and tolerant of others."

This incredible versatility may have something to do with her personal history. Asifa Akhtar was born in 1971 in Karachi, Pakistan. Her upbringing, however, was international. When she was a child, her family moved from Karachi to Abu Dhabi for a few years, before returning to Pakistan. Then her family moved to Paris when Asifa was 15. "My school was on a street just off the Champs-Élysées," recounts the scientist. "Try and imagine that – from Karachi to the Champs-Élysées; it was overwhelming." After graduating from school in the early 1990s, she moved countries once again – this time without her family. She went to London to study biology at University College London.

"The different countries and cultures I've had the opportunity to experience have taught me, above all else, to be open-minded and tolerant of others," Akhtar says. "And to stay flexible and be able to adapt to my new environment." What surprised her most about Germany was how people stick to timetables, arriving at a bus stop shortly before the bus is scheduled to depart. Buses that are reasonably punctual was a novel experience for her at the time. "My general impression of Germany was that it's very clean and tidy. It made it easy for me to settle here." Nevertheless, when Akhtar arrived in Germany in 1997 as a postdoc (more specifically, to work at the European Molecular Biology Laboratory (EMBL) in Heidelberg), she couldn't speak the language, which, she recalls, was "quite discouraging in the early days." After her term as a postdoc, she actually planned to leave the country again. "But, at every juncture of my career, Germany has been very good at convincing me to stay. And what could be better than moving to a Max Planck Institute?" Initially, Akhtar was a Max Planck Investigator, and in 2013 she became the Institute's Director. Her research is also focused on adaptation and interaction. All organisms react to their environment, and that includes individual cells. And despite the fact that all cells in the body possess exactly the same genetic information, they develop profoundly different properties and functions, "depending on where they end up, in which tissues and in which organs," Akhtar explains. The key to this phenomenon is epigenetics, the regulatory level beyond that of genes.

Epigenetics incorporates various mechanisms that determine which genes are switched off and which are switched on, and to what extent. "DNA is like an official operating manual for a complicated machine. Not every page of the manual is needed to get the device running. Epigenetics works a bit like a text highlighter pen; it tags important passages," explains Akhtar. Such tagging activates the highlighted information, causing it to be read and translated into proteins. This, in turn, makes other passages essentially unreadable, or "silent" in the language of molecular biology. The whole process is impacted by molecular factors, such as developmental signals and growth factors. However, stress and a person's lifestyle – sport, nutrition, smoking – also leave marks in the genome, which in some cases are even passed on to the person's descendants.

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The Max Planck Director from Freiburg is particularly interested in how this occurs at the level of complete chromosomes. What are the molecular biological mechanisms that govern why large areas on chromosomes are muted while others are activated? The central focus of Akhtar's work is the X chromosome, one of the two sex chromosomes in humans. Men possess one X chromosome and one Y chromosome; women, two X chromosomes. To prevent women from having a double dose of all the proteins encoded on the X chromosome, however, this imbalance between the sexes needs to be compensated for.

There are a host of factors that render the chromatin of the single X chromosome in Drosophila males as active as the two X chromosomes in the females. "We've demonstrated that the decisive factor in the process is an enzyme called MOF," says Akhtar. It chemically modifies the histones (the protein spools upon which the DNA thread is wound), tagging them with so-called acetyl groups, making the associated regions easier to read. A typical feature of dosage compensation in Drosophila is that one particular histone, termed the H4 histone, undergoes "hyperacetylation", meaning it is tagged with a large number of acetyl groups.

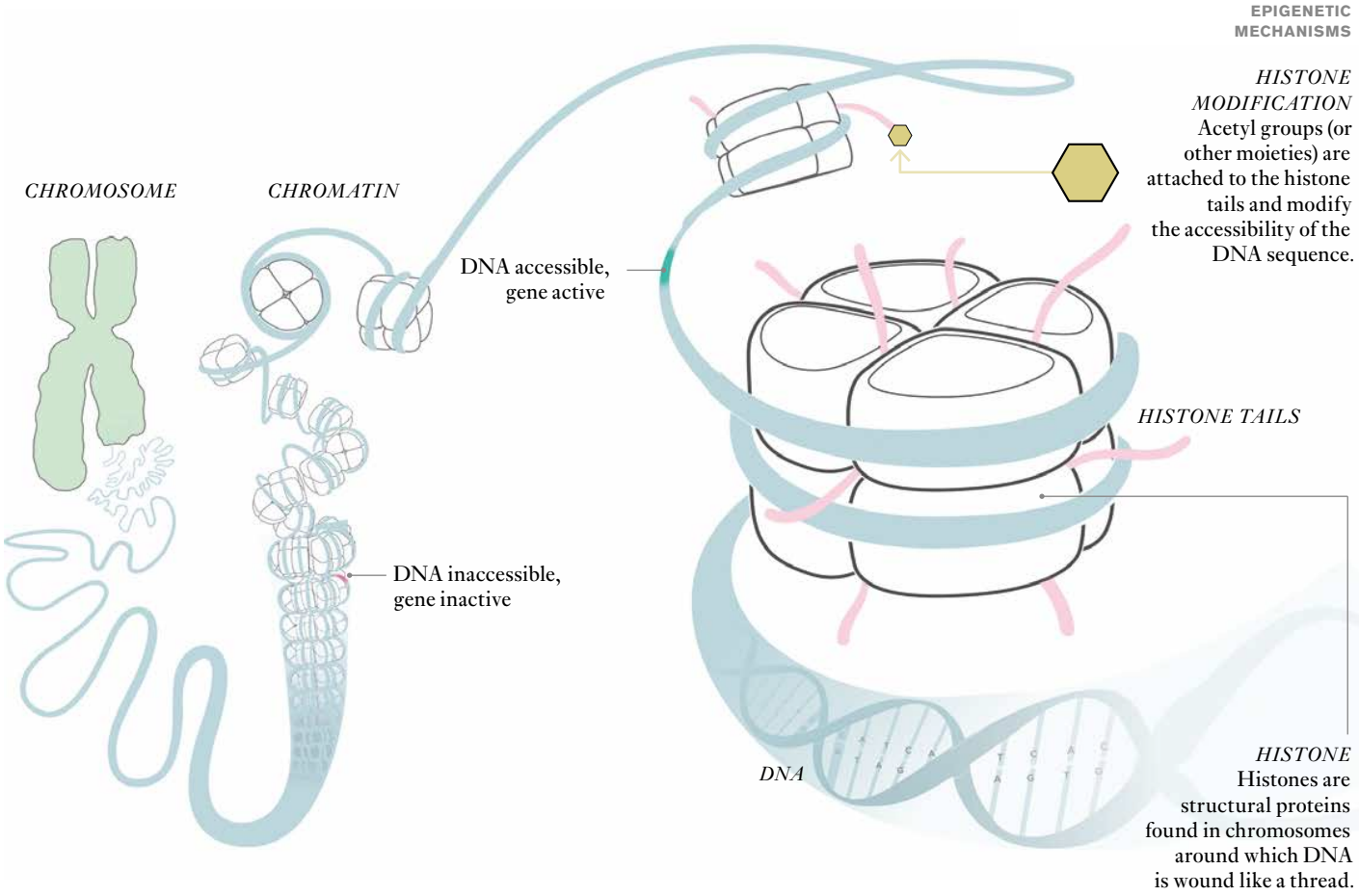
"I don't think I'll ever lose my fascination for this field of research."

"An overdose of active genes has serious consequences for cells and the organism," Akhtar says. This can occur, for instance, in the case of trisomies (three copies of one chromosome), and in conditions in which certain sections of the genome are duplicated, as well as in cancers involving unevenly distributed chromosomes. "In other words, a dosage compensation needs to occur," she explains. In humans and other mammals, this is done by inactivating one of the X chromosomes in females. In contrast, in the fruit fly Drosophila – Akhtar's favored animal model – the single X chromosome in males doubles its activity.

Akhtar has been working on the X chromosome and the phenomenon of dosage compensation since her post-doctorate phase. "I don't think I'll ever lose my fascination for this field of research." What drives her is curiosity, coupled with the excitement of knowing that experiments that are currently underway may reveal new, unimagined insights: "You never know in advance what the outcome of an experiment will be. Back when my duties were still lab-based, I often couldn't sleep at night, because I was so excited about seeing the results," says Akhtar. That's actually still the case, she adds, even though these days her team members perform the hands-on work in the lab. "If that were ever to change, I'd stop doing scientific research."

"We then explored the question as to what role MOF plays in mammals, in which dosage compensation follows the inverse principle," recounts Akhtar. The answer took the researchers by complete surprise. They detected MOF in mice not only in the cell nucleus, but also in the mitochondria, the power generators of the cell. Mitochondria, crucially, are the only cell organelles apart from the cell nucleus that possess their own genetic material. "And as we discovered, MOF is also involved in regulating gene activity in mitochondria, just as it is in the nucleus," Akhtar explains. Based on this finding, a direct link exists between metabolism and gene regulation. "This may explain how nutrition, for example, can influence epigenetics and thus gene activity. Or what effect stress has."

The research conducted by Asifa Akhtar and her team represents pure basic research, in keeping with the remit of the Max Planck Society. Anyone conducting research on fundamental biological mechanisms mechanisms, especially on fruit flies, needs to be prepared to explain how their work can benefit society as a whole. "Basic research is absolutely essential to understanding disease. If we don't know how our body works when it's healthy, we won't know what's wrong with it when we get sick," Akhtar stresses. Or to quote Max Planck, the physicist after whom the society is named: "Application must be



GRAPHIC: GCO BASED ON A DESIGN BY THE MPI OF IMMUNOBIOLOGY AND EPIGENETICS

preceded by knowledge." Asifa Akhtar has long since proven this maxim in her research into epigenetics. In 2018, together with her team and French colleagues from the University of Dijon, she succeeded in deciphering the molecular basis of a rare disease. Mental development is severely delayed in children who suffer from it. Among other problems, they have difficulty eating and with body tension (hypotonia), their gait is often unstable, and their language skills are limited or non-existent. Until recently, no one could say why this is so. Using modern high-throughput sequencing techniques, the French team searched specifically for genetic abnormalities in sufferers – and discovered a mutation in the "MSL3" gene. "MSL3, as we already knew at the time, acts as a type of volume control. It has the ability to activate a gene precisely to the required level," Akhtar explains. The researchers discovered that the defective MSL3 gene also interferes with the functioning of the MOF enzyme. As a result, certain genes become insufficiently acetylated and are thus inadequately transcribed. Development as a whole is thrown out of equilibrium. It's like a botched performance of a symphony in which the flautist misses the conductor's cue, causing all the other instruments to also come in late.

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The good news is that, at least in theory, epigenetic dysregulation can be reversed. "There's a particular drug that is currently being used to treat cancer. It targets precisely this mechanism," says Akhtar. In vitro, the drug successfully compensates the adverse effect of the mutant MSL3. Needless to say that the road from the Petri dish to a medicinal product is long, but there's hope that one day we'll be able to treat the children affected by the disease in a targeted way.

The syndrome has now been named "Basilicata-Akhtar syndrome" after the two scientists from Freiburg who were primarily responsible for elucidating its mechanism. Asifa Akhtar probably never imagined as a child that a disease would one day be named after her. "I never dreamed of becoming a scientist when I was a young girl," she says. "In Pakistan, I had no scientific role models." Only after completing her Bachelor of Science degree did she decide to embark on a PhD: "I wanted to find out how science works." That got the ball rolling.

However, she doesn't just have her talent and curiosity to thank for her storybook scientific career. A large portion of perseverance and great dedication have also been required. "I've had to work hard at every stage of my career – it's not something that just lands in your lap," she stresses. She has only been able to balance family and science thanks, in part, to the good childcare affiliated with the research institutions where she has worked. However, her husband, who is a firm believer in equal rights, is also a big part of the story. "A well-organized daily routine and an understanding partner are enormously important," emphasizes Akhtar.

As Vice President, Asifa Akhtar is committed to supporting young researchers in their careers, especially young women. One of her goals is to play a role in closing the gender gap in science. "Nature intended that women are the sex that bears children and, initially, provides them with nourishment," Akhtar says. "But it's up to us to create the conditions that make a career in science possible in spite of that." She is not simply referring to ensuring a good infrastructure and flexible working hours. "Equality needs to start in the home," she says. "If both parents want to pursue a career, then it should go without saying that they also share the work at home." And, of course, society has a role to play. As long as women continue to be labeled bad mothers if they put their children in childcare at an early age, it should come as no surprise that many of them won't have the courage to pursue their careers. "A lot more action needs to be taken," urges the scientist.

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Asifa Akhtar's research shows that with the help of sophisticated mechanisms, nature has managed to compensate for inequalities between the sexes. Achieving gender equality in society, however, is something we humans still need to work on.

Sunrise reloaded

In the summer of 2022, Sami Solanki's balloon carried SUNRISE observatory will again take a closer look at the sun's magnetic fields.

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