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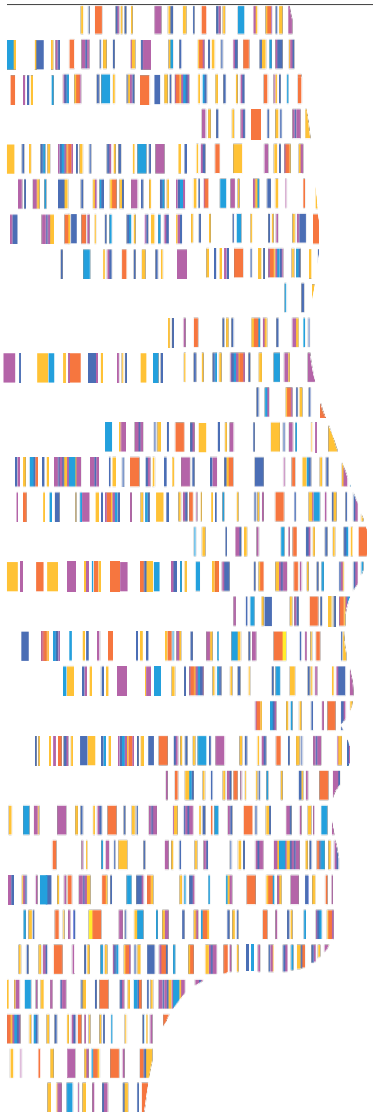
Her discovery has saved the lives of numerous women – now, she is helping to boost Israeli science.

Marie-Claire King is one of the world's most renowned geneticists, who demonstrated the considerable genetic similarity between humans and chimpanzees and discovered the BRCA1 gene, which is responsible for hereditary predisposition to breast and ovarian cancer ■ After decades of collaborating with Israeli scientists, she is participating in a research funding project, which she says has propelled Israel's medical and scientific research to a level on par with that of the U.S. ■ "In the past, scientists in the field were forced to leave Israel to be able to conduct research. That's over"



In the late 1970s, Mary-Claire King made a significant career decision: To move from the field of mathematics to life science at the University of Berkeley. When she was accepted to a position at the School of Public Health, the head of the Epidemiology Department told her, "I just want you to know that you are only here because of all these new (affirmative action) regulations, and we are really scraping the bottom of the barrel in hiring you."

King was unmoved, replying, "We'll see how long you feel that way." A few years later, she submitted her doctoral dissertation at Berkeley in the field of evolution, showing that humans and chimpanzees are 99% identical genetically. It was only the first of her groundbreaking studies.

Her next project, which is still ongoing, has changed the lives of millions of women the world over, and continues to save many of them. King studied genetic causes of cancer and showed that a single gene on chromosome 17 may carry mutations that increase the risk of breast and ovarian cancer. In 1991, she named it BRCA1. Today, the fact that some cancers have genetic causes is almost self-evident, but back then, it was far from the medical and scientific consensus. In subsequent research, she explored the genetics of schizophrenia, a groundbreaking field in which it still active.

King, 75, now a professor in the Department of Genome Sciences and Medical Genetics at the University of Washington's School of Medicine in Seattle, had said that one reason for her success, despite the fact that starting out, she was a young woman in a men's world "in the era even before the fax," is her decision to focus on a topic considered too trivial for anybody to care about. "When I suggested that cancer has genetic causes, people smiled." On the other hand, she says, many doctors, men older than her, chose to help her – and without them, she could not have succeeded. They trusted her because of their experience in the field. "They knew the families who had suffered from the disease over several generations, and referred me to study them," she said.

For a number of years, King has been involved in one of the major moves to promote applied scientific-medical research in Israel. Last month, the Israel Science Foundation announced the

distribution of NIS 32 million for research in the Israel Precision Medicine Partnership (IPMP).

Eleven research groups, including one led by Nobel Laureate Prof. Aaron Ciechanover, have won the grants in this cycle, out of 99 proposals. The program's goal is to develop new diagnostic and treatment methods for severe and chronic diseases, and to encourage collaborations between researchers from various fields and physicians. King is a member of a committee advising the Israel Science Foundation on matters related to the program's scientific management. Dr. Kornberg of Stanford University. The identity of the members of the judging committee is undisclosed except for its chairman – Nobel Laureate in Chemistry, Prof. Roger Kornberg of Stanford University.

Mary Claire King, Age 75, Family Status: Married + 1

"We had very successful projects together, which led to the discovery of genes and grants for further research studies. We developed a joint Israeli-Palestinian-American program to train Palestinian doctoral students. I am deeply involved in scientific research in Israel, and very much wish for its success. I already conducted reviews for the Israel Science Foundation, so they knew my reviews were very long and thorough," King says with a smile.

"For 25 years – until the outbreak of the coronavirus pandemic – I visited Israel several times a year, and realized two things," King says. "You train physicians just as well as any other country in the world. Medical education in Israel is excellent, though it begins at an older age than in the U.S., because of conscription. But once they finish their studies, the physicians are required to treat numerous patients at a feverish pace – leaving them no time to engage in research. Our program enabled the doctors to work in collaboration with researchers and contribute to the scientific process. This is one of the program's two successes, in addition to supporting the best scientists.

"The transformation in physicians' role can carry into the long term only if we'll be able to institutionalize it, so that young doctors will be able do what our grant recipients can. This program is just the tip of the iceberg, and I hope Israel will seize the opportunity, and enable this.

"The second thing I realized: Israel invests a lot in educating children: Excellent high schools, undergraduate studies among the best in the world in terms of equality, accessibility and quality. But then they are left to hang in the air. It's miserable! You need to invest in people who finish their undergraduate degrees and want to continues in science. The IPMP program has clearly proved that there is a huge pool of scientific talent in Israel."

What do you think is most important in future genetic research, and would you like to study in the future?

"I hope that the next big think in genetic research will be tool development for assessing epigenetic events – those that are not hereditary – in tissues that are not accessible, such as the brain, through examining small quantities of free DNA. Personally, I hope to contribute to the understanding of genetic causes for severe mental illnesses. My lab has contributed in the past decade to understanding the genetics of schizophrenia. The next step for me is to understand bi-polar disorder, whose genetic factors are probably quite different."

Knowledge to advance human rights

The story of King's life is astonishing. Her first discovery, of the genetic similarity between humans and chimpanzees, not only confirms the theory of evolution, published by Charles Darwin in the mid-19th century, but recognized that the large visible differences between humans and chimpanzees do not stem from the genes themselves but from the control regions that produce the proteins composing the genes. In both this field and in cancer research, King used mathematical tools she had initially learned as a mathematician. In an interview with Smadar Reisfeld in *Haaretz* in 2014, she said that the discovery of the BRCA1 gene stirred considerable opposition because it was based on mathematical modeling techniques, not the norm at the time.

King's research group studied families in which there were several women with breast or ovarian cancer. Based on a mathematical model she developed, she proposed the innovative hypothesis that severe hereditary mutations in a single gene may be responsible for breast cancer in some women. She then identified and mapped the gene, dubbed BRCA1. For the next four years, the race was on to clone the gene. Once it was cloned, King and her research colleagues developed genetic sequencing methods to identify mutations in this gene and in others, responsible for hereditary cancers.

Her scientific achievements, degrees, and awards are innumerable. Her name has topped Nobel Prize nominee lists, both this year and in previous years. She has applied her scientific knowledge in another area – human rights. In the 1970s, she participated in organizing demonstrations against the Vietnam War at the university, and helped social activist Ralph Neider in research on the impact of pesticides on farmers' health. In 1983, she participated in a project to locate Argentina's lost children. An Argentinian woman called her, asking that she would meet a group of grandmothers looking for their kidnapped grandchildren, who had disappeared in the dark days of the junta that ruled the country and eliminated dissidents. King took part in a joint work of finding bone remains in mass graves and identifying the family connection through genetic research. As part of the effort, 108 lost children were located and identified, and reunited with their families. This research method has become one of the important tools in the field of forensic genetics.

King was even featured in the film "Decoding Annie Parker," starring Helen Hunt, about the discovery of the mutated gene responsible for breast and ovarian cancer. King was concerned when she first heard of the film – she was not asked for permission or consulted when it was made – but said she was relieved when she watched it with her students.

You started studying mathematics at university, and moved on to life science, one of the most evolving fields of science in recent decades, certainly in terms of the applications based on classical science, which has actually stagnated a bit in recent years. Why did you choose the field?

"After a year of mathematics, I moved on to genetics. I took a course with geneticist Curt Stern at Berkeley. I remember telling him – making a living from such work is great fun. He replied that the money was fine, but no more than that. The truth is I left mathematics because I was not good enough to succeed in it professionally, and I knew what it took to be good enough. My younger brother was an excellent mathematician and I struggled with it. I switched fields and never looked back. Young people studying physics today, especially women, are very interested in combining physics with biology. Physics studies provide excellent training for developed thinking. Without researchers from the exact sciences – physicists, chemists and mathematicians – it would not have been possible to launch projects like human genome mapping. But genetics is a very quantitative science: We use mathematics all the time, and should be able to think in terms of hypotheses and proofs."

One common applications of genetics today are tests that anybody can do – to trace family heritage and map potential medical issues. I have heard of cases in which people got interesting results, but actual problems were completely overlooked. Even assuming there is always a range of error, is this worth doing? Isn't it too deterministic to know what may lie in store?

"There are issues with these commercial tests, and I would not use them for health purposes. They are fascinating for those who want to trace their roots, but in Israel most people know the origins of their family well. On the other hand, for African Americans, for example, it is fascinating to learn where in Africa they are from, and what are their non-African roots. In my opinion, the effectiveness of these tests is limited to this area. The example you gave, of someone with a medical condition which the test missed – that happens a lot."

Is it a fundamental problem in testing, or a matter of the depth and quality of the testing? "It's a fundamental issue," King explains. "Genetic susceptibility to severe illnesses is mainly due to the fact that a person has a mutation or a variant with a serious effect. The origin of most of these mutations, because of their severity, is relatively new. To find them, you need to conduct a full genetic sequencing, but that's not the technology these companies use. It is indeed a technical limitation: These companies could have identified the mutations if they would have conducted complete genome sequencing, testing variants and structural changes, but this would be very expensive. They usually work with a chip, which checks for the presence or absence of common mutations, most of which are not dangerous, and that is not the way to detect genetic predisposition to serious diseases – with a few exceptions, such as sickle cell anemia."

"Everyone has the right to the power that information provides"

Today, people can learn more about their genetic makeup, even without tests. They can see what parents and family members suffered from. Do we really need to know all these things? Doesn't it potentially lead to despair, or to people giving up on taking good care of themselves – I have a tendency for high cholesterol and obesity, so I won't bother with exercise because it doesn't help anyway – or is it better to know in advance, to get that warning?

"That is a profound question, which has guided me for 47 years of working on the genetic predisposition to breast and ovarian cancer. I am convinced that everyone has the right to the power the information provides, to use it to prevent the disease. And that is exactly what women with BRCA mutations need, because they lead to high risk. I firmly believe that every young woman in her thirties should take a genetic test – it should be a sequencing test, because there are many mutations. European Jews have three; Jews of North African and Iraqi descent, for example, have a wider spectrum of mutations. Every woman who reaches adulthood should be given a full sequencing of the BRCA1 and BRCA2 genes, to find out if she has a mutation. The reason is that she would then have an option to do something about it: At age 40, she could have surgery to remove her ovaries and breasts.

"There is a profound difference between knowing our genetic makeup and knowing about diseases for which there are prevention measures. The treatment may be drastic, but it can save lives. Thousands of people use this treatment. But knowing about genetic problems with no cure or treatment, such as Huntington's disease, is a strictly personal issue. I think you have to be agnostic about it: Give people who want to know what they want.

"Some diseases have treatments, but they are on a continuum, in terms of their severity. I fully support any woman taking the breast and ovarian cancer mutation test. In other situations, where there is no clear path to preventative treatment – it is a personal choice that we scientists and fellow doctors should respect.".

You once explained that breast and ovarian cancer is a disease of affluent societies: That women who are well nourished in youth, who do not start having children in their teens, run a higher cancer risk. It's a paradox of sorts, because we want a better life than to marry at 12 like our grandmothers. How can the paradox be reconciled?

"Breast and ovarian cancer are driven by the amount of estrogen available to tissues. Women who lived well and received good nutrition in their youth, whose menstrual cycle started early, who were educated and delayed childbearing, absorbed a lot of estrogen, and so their risk of disease increased, unrelated to genetics. The best way is preventative measures – through mammography and screening tests. Therefore it is also important to reduce estrogen intake after menopause, because it increases the risk, except in cases where it is essential. There is another

major risk factor for postmenopausal women – severe obesity. In Israel, you walk a lot, and generally do not have the same levels of obesity as American women. I wonder what happened during the pandemic. I hope they continued to train."

The implications and applications of genetic research and the information that emerges from it are extensive and enormous, such as screening embryos with unwanted traits, and even genetic engineering. Is the human race prepared, practically and ethically, to deal with these questions? Do we have enough defense against the misuse of science?

"This is an important question. I admire Jennifer Doudna, the biochemist who received the Nobel Prize for developing CRISPR – a gene-editing technology. She has changed the direction of her activity. She works with colleagues and the public to understand the benefits and positive uses of gene editing in research, as well as its risks. It is very important that we, as geneticists, are very involved in the positive and ethical application of our research in medicine. I tried to so in my work on breast cancer, in collaboration with Prof. Ephrat Levy-Lahad from Shaare Zedek, on identifying severe genetic defects prior to pregnancy and using early diagnosis to allow parents to avoid the mutations found in their families, thus enabling them to have healthy children from their eggs and sperm. This is a very common technology in Israel and the West Bank, and it is implemented in a very positive way."

Which genes are tested?

"There are several. Let's say a baby is born with a severe developmental impairment, and the gene responsible for this is unknown. The gene can be found through genetic research, then the information is shared with the parents. Ahead of the next pregnancy, the doctors can perform in vitro fertilization and subsequently, a pre-implantation diagnosis. The fetuses are tested, and only those without the familial mutation are returned to the uterus. The next child born to this family will be healthy. Ephrat has already enabled hundreds of babies to be born this way. She received one of the IPMP grants, to continue investigating interesting ways of detecting neurological problems for which there is no solution to date. Basically, thousands of different genes can lead to a neurological problem. This medical diagnosis has been around for several decades in Israel, which is at the forefront of the field. All of this is an example of genetic technology that can help families without abuse or endangerment. The BRCA1 test is in the health basket in Israel – that's great."

You talked about evolution taking place over several generations within a family and leading to genetic predisposition to cancer. It's an intriguing concept. Can it also be inferred that lifestyle changes in the digital age affect physical features over a short period, rather than over millions of years?

"I know this is an issue among people who work in technology fields. In my view, our progress has expanded the range of potentially successful genotypes (a person's gene composition). A simple example: People with a vision problem can wear glasses. People with hearing problems can get a cochlear implant. People who are prone to cancer can act in their youth to prevent the onset of the disease.

"Genetic research and modern medicine allow the population to be more diverse, and to thrive. At the same time, it has allowed families suffering from a tragic genetic event, such as a child with severe developmental impairment of genetic origin who died in childhood, to employ the technologies we talked about so that their next children will be healthy." In this respect, genetics and technology have changed the human race, but not because random mutations have been created, but because they have allowed people with a wider genetic diversity to live and succeed."

Last week, a scientist interviewed by Bloomberg said that during two years of the Covid-19 pandemic, we learned more about epidemics and viral research than we had over generations. Do you think it also contributed to genetics research?

"Certainly. On one level – the use of mRNA was a huge success in saving lives. This research began before the pandemic, but would not have progressed so quickly if the whole world was not the subject of the experiment. It has proven itself. The integration of epidemiological and genomic models has finally taken off. It was a

promising field in the hands of a few experts, but now it is very common, and even economists are involved in it.

"Genetic research has made it possible to sequence the virus. It has contributed a lot to the field. In general, when there are huge numbers of people in a crisis, good ideas emerge quickly, and governments are willing to invest resources. If we return to the IPMP, fortunately, it did not take an existential crisis to invest in Israeli science."

Were you surprised by governments' involvement and support – from science and health to incentives for households and workers?

"I thought that was the direction in which the world was going. In the U.S., of course, we had a problem of coping with the Trump administration, which was opposed for a long time. It took Biden's election to make that happen. World leaders really listened to their scientists. Scientists talk to each other all the time, and it is possible to reach a consensus, share and discuss information effectively. It is not surprising that world leaders have followed this path, they are supposed to be intelligent people who serve their public."

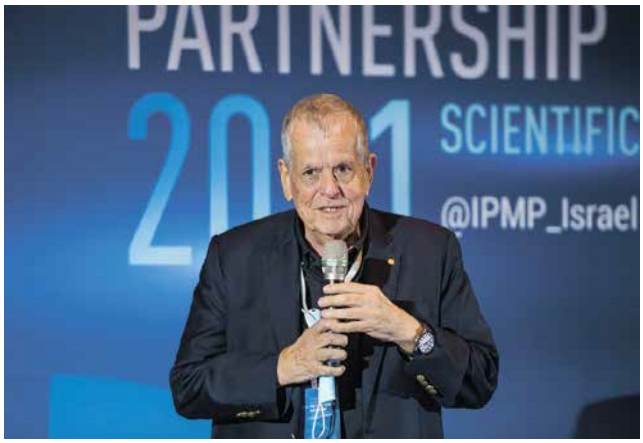
The IPMP Program: "Building Israeli Science"

The interview with Prof. Mary-Claire King was conducted via Zoom, on the day of the announcement of the IPMP program grant recipients. The program is founded on the pooling of resources involving the Council for Higher Education's Planning and Budgeting Committee, the Ministry of Health, the Ministry of Economy' Digital Israel, and two philanthropic foundations – Yad Hanadiv and the Klarman Family Foundation (Boston). The current round of funding is the third out of four in the program, whose total budget is NIS 210 million.

"I joined the program because for many years, I have worked with Israeli scientists and physicians, such as my friend, Prof. Karen Avraham of Tel Aviv University, the Vice Dean for Preclinical Affairs at the university's Faculty of Medicine and a genomics researcher whose primary focus is on deafness; and my friend Prof. Ephrat Levy-Lahad from Shaare Zedek, the director of unit at the Institute for Medical Genetics Research," says King.

"The IPMP program bridges a critical gap in the Israel Science Foundation, which I have complained about for decades. Up until recently, the money the Foundation could give to research was on a scale that could be called homeopathic – meager in comparison to the research work proposed by the scientists. It created the threat of brain drain, and in many cases actually caused it. This led to Israel's losing its best researchers to the U.S., where they prospered and received government funding, started companies. These researchers are simply wonderful, but that is not the goal of science in Israel.

The IPMP halted this. The program enables senior and young researchers to work together, and submit applications for significant grants, such as those accepted in the U.S., for joint projects with the potential for clinical applications. The three rounds of funding clearly demonstrate that Israel's fountain of this type of research is far from dry. It is just wonderful, like in the last round, to see who these researchers are. Prof. Aaron Ciechanover has finally received a grant. I don't know how many times he has applied for grants, but he is a Nobel Laureate, so presumably he knows how to write a research grant application.



Professor Aaron Ciechenover, 2021 IPMP recipient

"The program is a meaningful success. It did what was needed – creating collaborations between scientists and doctors, and as a result, leading to developments that can be applied clinically. Some have already done so, some are on the way – in diagnosis, in prevention consultation, in drug development, and in my opinion, also in establishing new businesses. Just today I heard

that Nir Friedman (Professor of Computer Science and Life Sciences at the Hebrew University) has founded a new company, Senseera, which develops advanced testing methods.

The point of the project was to build Israeli science, turn it into applicable for clinical use, keep Israeli scientists in Israel through sufficient support, and foster collaborations between young and veteran scientists. All these things have been achieved."

Prof. Yuval Dor of the Hebrew University, who heads the Israel Science Foundation's Life Sciences and Medicine Division, adds: "One by-product of the IPMP is that start-ups have been established, as a direct result of receiving the grant and collaborations between scientists and physicians. Nir Friedman is one example. Liran Shlush is another."

King is enthusiastic: "Liran Shlush, a doctor at Rambam Hospital and a scientist at the Weizmann Institute's Department of Immunology, is an excellent example. We were very close to losing him to the U.S., and he received a grant from the IPMP and decided to stay. I have never met an Israeli scientist who wanted to leave Israel in the first place, but knew many young scientists who were leaving so that they could conduct their research. I'm so glad Liran will not be leaving."

Dor: "Liran is a clinical hematologist and professor at the Weizmann Institute who has founded several companies. He is a real superstar. The IPMP project can fund scientists at the levels they would be able to secure in the U.S.. The grants are three to four times higher than the personal grants awarded by the Science Foundation."

King explains: "We are not talking about huge sums of money. As an American researcher, these are acceptable sums which can be obtained in the U.S. Israeli researchers can finally receive them."