Lasker Award Winner **Mary-Claire King**

Mary-Claire King, American Cancer Society Professor of Medicine and Genome Sciences at the University of Washington, Seattle, is recognized with the 2014 Lasker~Koshland Special Achievement Award for her wide range of contributions to biology and medicine as well as human rights. King's development of mathematical models of genetics and discovery of the role that a single gene locus, *BRCA1*, has in hereditary breast cancer have had wide influence, and she has worked tirelessly to apply genetics to reunite missing persons, such as the 'lost children' of Argentina, with their families.

How did you come to do your dissertation work at the University of California, Berkeley comparing human and chimpanzee protein-coding genes?

I fell in love with a field before I fell in love with that project. I had done math as an undergraduate and had gone to Berkeley to work in statistics and at that point had had essentially no biology ever, and certainly not a genetics course. And at the encouragement of my advisor from statistics, I took genetics from Dr. Curt Stern. And I just fell in love with that way of thinking. You had a sense that this was a matter of understanding nature at the most fundamental level and yet in a way that you could directly tie to the life of the organism, whether it was a fruit fly or a rabbit or a mouse or a person. I just found it enchanting.

So part of that enchantment was the prospect of understanding nature and the natural world?

Exactly. So I asked Dr. Stern at the end of his course if I could take another seminar from him and he said, "Of course, but I'm going to be here only one more semester, and then I'm retiring." In those days there was a required retirement age, which blessedly there is not anymore. And so I took his graduate seminar the next quarter—again with the blessing of my advisor over in statistics—and then I was completely hooked. And I asked Dr. Stern if I could transfer to genetics, and he said "Certainly, certainly—no issue at all." And so I transferred to genetics.

That was 1967, and the next year was 1968 in Berkeley. And of course Berkeley was completely pulled into the anti-Vietnam war activity, and civil rights activity was still continuing. There was an enormous amount of upheaval on campus.

Effectively, for a year I worked for Ralph Nader, who at the time was putting together the team to write the report on who owns the land in California and what are they doing with it. This was the Nader California Project. I worked on that project for a year and had a wonderful time, and Ralph asked me if I wanted to move to Washington, DC to found what has become PIRG [the Public Interest Research Group]. I spoke to Allan Wilson, who was a friend as well as, of course, a very fine geneticist and biochemist, and told him about this possibility. He said, "I'd really advise against it." Allan never said anything so strongly, so this was serious! He said "It's much better to finish your PhD, and then you'll have many more avenues open to you." At this point, I was working with Bruce Ames, who was incredibly patient with me. By this time, I'd taken all of my exams. It was just the experimental work that was holding me back: I couldn't get the experiments to work. I said, "But Allan, nothing works." He said if everyone for whom experiments did not work stopped doing science, no one would be doing science and said, "let's see if we can work out a project for you that exploits more of the ease with which you do mathematics and statistics." So he and Bruce and I worked out the project that became my dissertation in Allan's lab.

Over the decades, how has your thinking on the genetic closeness between humans and chimps evolved?

To me, the most meaningful part of that dissertation project is that Allan and I got it right. Our evidence was that humans and chimpanzees at the level of genes that code for proteins—which were the only ones you could look at at that time—were more than 99% identical. And that's correct! And then we went on to say that this is paradoxical because humans and chimpanzees are classified in different taxonomic families, and rightly so, because if you consider the relative length of bones and different body parts, differences in locomotion, differences in behavior—we belong in different families. We postulated that the differences might be due not to the protein sequences themselves but in differences in the timing of their expression during development. And it's true.

It took you 17 years to pinpoint the *BRCA1* locus. What, for you, was the toughest part of that somewhat lengthy scientific quest?

I think the limitations of technology.

You were doing a lot of the calculations and analysis by hand.

Of course. Everyone was. We were all working at the edge of what the technology would bear. But I wouldn't describe the process as one that was tough or discouraging. It was just one that one needed to stay with.

Once you uncovered the [*BRCA1*] locus, and once the evidence was out there, was it still difficult to convince people that breast cancer could be heritable?

Oh, I think that the people who most quickly accepted the idea were people outside of genetics—the people who actually encouraged me to do it in the first place, such as the surgeons and the families [affected by breast cancer] themselves. Once we published the work in 1990

and [others confirmed it], I think there was no doubt any more that breast cancer was clustered in families and that there was a gene on chromosome 17q that was responsible for a great deal of that clustering. Within the statistical branch of genetics there was not any respect for the work at all before it was published.

I have developed a sense about this that there are certain people in any field who will spend *years* saying, "I don't believe it, I don't believe it, I don't believe it," and then they will without pause move to, "I knew it all along, I knew it all along, I knew it all along." So you have to treasure that 15 minutes in the gap.

How do our attitudes toward a disease change when we learn it is heritable?

It's a wonderful question, and it's part of a bigger issue. In the 1960s I was very active as a geneticist in the movement against genetic determinism, and I still am active in that movement. I believe that people have enormous free will. Everyone has biological limits, but to an enormous extent we can influence our own destinies, and to the extent that we cannot, it is overwhelmingly for reasons other than genetics.

So why do I head out to look for genetic causes of diseases? I think it is because what struck me as soon as I began to meet women from these extremely severely affected families is that these were women who had done everything right. These were women who were extremely productive, they were fit, they had created for themselves and their families terrific environments. And yet, breast and ovarian cancer were afflicting them at completely abnormally high rates. There was nothing left to consider *but* genetics.

What does that bring to people then?

I think that it brings power. I think it brings actual evidence of something that is concrete, that is wrong, that is nobody's fault, with the awareness that there are things that can be done about it. Not simple, pretty things, but there is action that can be taken. And it saves lives.

Insurance companies vary with regards to the genetic testing they cover. What are your thoughts on that?

The current situation is that *BRCA1* and *BRCA2* sequencing are now virtually universally covered. The choke point now is covering the sister genes. That's a problem because *BRCA1* and *BRCA2* account for most inherited predisposition to cancer, but not all, and a woman with early onset breast cancer may have completely normal sequences of *BRCA1* and *BRCA2* but have an equally devastating mutation in any of at least a dozen other genes. It's a historical fluke that at the moment some insurance companies do not cover testing for all these genes, particularly given that it is now equally cheap to test them all compared to testing only *BRCA1* and *BRCA2*. So it doesn't make sense to not have them all tested, but it takes time for these things to percolate through the medical care system, and of course we just have to keep pushing on it.

You're now also looking into the genetic causes of schizophrenia. Why?

The great unsolved mystery of human genetics is serious mental illness. Genetics as a way of thinking is an enormously powerful tool, and it doesn't mean that one has the same genetic model for everything. One does not! But if you think in terms of the way that genetics can play out for any complex trait in any species, you can state a hypothesis, and you can test the hypothesis, and you may be right, or you may be wrong, but it's definable, and it's testable.

How can one test this?

[Schizophrenia occurs] at roughly the same frequency everywhere on the planet. People who are ill with schizophrenia have far fewer children than their siblings and neighbors who are well, and there's very good epidemiological evidence from Scandinavia that proves that. So if there were a genetic component to schizophrenia, there would be very strong selection against it because people who are schizophrenic have far fewer children. And it's not that they biologically can't have children, it's that they aren't selected as mates. It's a later-onset illness, so many people have children before they become schizophrenic, and they develop the illness later on. There's a very strong social selection against schizophrenia.

So why does it persist? It's highly familial in the sense that a person who is ill, if they have a child, that child is ten times as likely to develop schizophrenia as in the background population. And yet, people who treat schizophrenics will tell you that most of their patients come from families that are perfectly well. So all these things are paradoxical. How can all this happen?

And then on top of all that, there have been these two major historical events in the twentieth century: there have been two major historic events, the Dutch Hunger Winter and the Chinese famine after the Great Leap Forward, that involved periods of great starvation, and 20–30 years later [after these events you see] double the incidences of schizophrenia among persons who were *in utero* but survived the period of starvation of their mothers.

So how does one put all this together? The hypothesis we developed is that schizophrenia might for many people be the consequence of a new mutation that occurred in that person *in utero* that was compatible with life but that had an effect on the developing brain that manifested 20 years or so later as schizophrenia, and *that's* a testable hypothesis. And we tested it, and that's the paper that we put into *Cell* last year. Everybody has *de novo* mutations, that's not news, so there's only a modest increase in the number of such mutations among people who are schizophrenic compared with people who are well, but the nature of those mutations is radically different. Among persons who develop schizophrenia, they are profoundly more likely to have *de novo* mutation in genes that control neurodevelopment.

For many years you have worked on issues of social justice, for example, working with the Grandmothers of the Plaza de Mayo of Argentina and using genetics to help identify grandchildren who were kidnapped as infants after their parents were murdered during the Argentinean military dictatorship of 1975–1983. What do you think is the toughest aspect of applying genetics to matters of social justice?

The most important thing I learned from that project is that the genetics is the easy part. That is by far the easiest part. The context in which this work takes place is enormously challenging. [There's a] long-term time commitment required to make sure that the genetic evidence is actually used. The process takes a very long time.

So what would you advise to scientists who want to get involved in such projects?

It takes sustained commitment over a very long period of time. You can't consult and walk away; you must stay engaged. What I did in Argentina more than anything else was listen to the grandmothers. Yes, I did molecular genetics. That was far more straightforward, and it was 2% of the work. Engagement is just listening, and my view has always been that the most important questions are asked by people on the front lines. You need to listen long-term so that the trust is built. You just don't give up.