King for a Year

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Science+Technology

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CONVERSATION · Mary-Claire King discusses breast cancer research, complex traits, and human rights.

By Kevin Davies

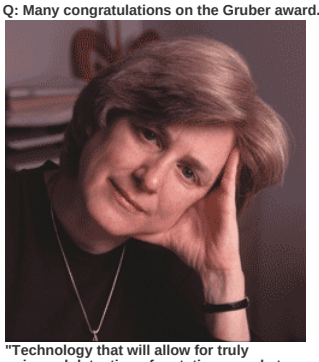
At last month's American Society of Human Genetics (ASHG) convention, the University of Washington's Mary-Claire King accepted the $200,000 Genetics Prize of the Peter Gruber Foundation.

A mathematician by training, King's career began in spectacular fashion by demonstrating that chimps and humans are 99-percent identical at the genetic level. She spent the next 15 years at University of California at Berkeley, determined to substantiate the hereditary component of breast cancer. At the 1990 ASHG conference in Cincinnati, she presented results mapping the BRCA1 breast cancer gene to chromosome 17. Myriad Genetics isolated the gene in 1994.

But King is also being lauded for applying genetic analysis to human rights - helping reunite children kidnapped during the military dictatorship in Argentina a quarter-century ago with their families. By helping develop DNA forensic technologies, King helped the "Abuelas" — the Grandmothers of the Plaza de Mayo in Buenos Aires — identify dozens of children of "the Disappeared."

King reflected on three decades of accomplishments with Kevin Davies. (Also see First Base.)

Q: Many congratulations on the Gruber award. What does this mean to you?



"Technology that will allow for truly universal detection of mutations needs to be developed."

A: It means that there is recognition for work in genetics that's outside the box. The Gruber committee mentioned two areas in particular: the work on breast cancer, which was certainly iconoclastic at the time I began it; and the human rights work, which is iconoclastic both in the sense of the nature of the hypothesis we were testing - namely, is this [kidnap victim] related to this family or not - and the technology that we had to develop to carry it out.

You began studying breast cancer in the early 1970s, while most experts were skeptical of a hereditary component.

Based on mathematics and carefully collected data that clinicians had been gathering for decades, it was clear to me that there was more clustering than would be expected by chance. Without knowing any molecular biology, the breast cancer appeared to include a subset of families in which the disease was likely to be inherited in a Mendelian way, and one could predict what that meant. That was certainly against the grain, and it was a lonely backwater for a long while, though it ultimately proved to be the case.

Does your breast cancer research offer strategies for studying other complex traits?

We underestimate the importance of this kind of biology for complex traits. In the mid-1970s, everyone said, 'Breast cancer is a complex disease - sure, there's an inherited susceptibility, but it's going to be the accumulation of a large number of common alleles.' Once we proved the existence of an inherited subset, BRCA1 was cloned, BRCA2 was cloned, and many folks said, 'Oh well, that part was easy.'

I think there is a tendency to attribute phenotypes one does not understand to the additive effect of many small changes. But the analysis of every trait thus far tells us that many traits occur as a combination of genetic predisposition and environmental exposures, and that those genetic predispositions are extremely heterogeneous. Many different genes and alleles can be involved, but in any one person one is likely to see only one or maybe two of these alleles. The only really good counter-example is APOE4 in Alzheimer's disease - that's a truly common allele that has a major impact. But how many other common alleles of major effect are there? In general, for complex traits, aside from the APOE4 story, I predict we will find multiple loci and multiple alleles at each locus.

My own bias is that that's the way to look for genetics of complex traits in general. Therefore, the way to try to find critical disease genes is to look at the tip of the iceberg - to look at the families that are most affected, and identify the genes responsible for their disease.

It's been argued that the [International] HapMap Project is useful for finding common alleles for complex traits - that would be true if there were common alleles for complex traits. But I would argue that the HapMap is also useful in a different way: for finding individually rare alleles that lead us to critical genes. In other words, the HapMap is indeed a map; it isn't just a collection of SNPs. Mapping

critical genes. In other words, the HapMap is indeed a map, it isn't just a collection of SNPs. Mapping and identifying genes for complex traits hasn't gone out of style - we simply aren't clever enough at it yet for truly complex traits.

Four years after mapping BRCA1 in 1990, Myriad Genetics got there first. Was that hard personally?
At the time, I think that it was honestly fine, and the reason is a subtle one: The scientific community and the scientific press recognized the value of our work. And that made an incredible difference ... It was an extraordinary cultural and personal experience for me to recognize that this was a community in which hard work and process was respected. So it honestly was fine. The public health and policy

consequences of having the gene cloned by a private firm that then exercised monopolistic rights to the patent have not been so good. That has been a problem.

Would it have been different if BRCA1 had been identified by academia?
We don't have to play 'What if?' because there are such examples: Cystic fibrosis, p53, and many other genes have either not been patented, or have been patented then licensed non-exclusively. This enables public and private sector groups to compete to develop ways of detecting mutations accurately and completely.

Myriad sequences coding and immediately flanking regions to identify mutations in BRCA1 and BRCA2. They do a nice job - I send samples to Myriad. But they miss at least one other class of mutations: all large deletions and rearrangements. They find these only if they look for them one at a time, but they check for only a few of the hundreds that must exist. Their approach, which is based on short-range PCR, will inevitably miss these rearrangements.

The kinds of technology that will allow for truly universal detection of mutations need to be developed. In my view, the existence of patents that are enforced in a monopolistic way slows down that development, and that is very unfortunate.