

Stories of Discovery: *Discovering a New Breast Cancer Risk Gene*

About 5 to 10 percent of all breast cancers are thought to be hereditary. This means they are caused by mutated or abnormal genes passed from parent to child. Two gene mutations commonly associated with hereditary breast cancer are BRCA1 (BREast CANcer gene one) and BRCA2 (BREast CANcer gene two) gene mutations; but BRCA mutations account for only 15 to 25 percent of all hereditary breast cancers.

Other inherited gene mutations have been identified, including recently identified PALB2. Yet combined, known mutations account for just half of all hereditary breast cancers. There are many genes yet to be discovered.

With Komen funding, Komen Scholar Dr. William Foulkes and collaborators at the University of Toronto, University of Laval in Quebec and Pomeranian University in Poland have discovered a new inherited gene mutation that may increase a woman's risk of developing breast cancer – RECQL.



Members of Dr. Foulkes' Laboratory, McGill University
Back row from left: Leanne De Kock, Nelly Sabbaghian, Barbara Rivera Polo, Jian Carrot-Zhang, Heidi Rothenmund, Talia Boshari. Front row from left: Mona Wu, Leora Witkowski, Nancy Hamel, Ester Castellsague Torrents, Nassim Taherian, William Foulkes

It's a Long Road to Breast Cancer Risk Genes

Breast cancer risk genes have been difficult to identify. Since the discovery of the BRCA1 gene in 1994, and shortly after that of BRCA2, only a handful of risk genes have been found to increase breast cancer risk in a way that can be meaningfully used in the clinic. The list includes TP53, CHEK2, ATM and PALB2. Although many other genes have been associated with breast cancer, the size and importance of the risk is not known for most of them.

In a new study, funded in part by Komen, Dr. Foulkes and several collaborators have found that RECQL may be a new breast cancer susceptibility gene. The project, led by Dr. Mohammad Akbari at the University of Toronto, studied more than 25,000 women in Canada and Poland.

Navigating the Genetic Map of Breast Cancer Risk

In the first phase of the project, the researchers studied 144 Polish women and 51 French Canadian women with breast cancer. The women had breast cancer at a young age (less than 50 years) and/or a strong family history of breast cancer, but did not have BRCA1/2, CHEK2 or PALB2 mutations. The goal was to identify inherited gene mutations that were common among these women.

Using a technique called whole exome sequencing, the research team was able to analyze over 20,000 genes. After sifting through millions of variations, they were able to narrow down their list to just a few genes. But they found only one – RECQL – that was similar in both populations of women and had a function known to be related to cancer.

The researchers identified five different RECQL mutations among the 195 women. Similar mutations were found in American populations when the team analyzed exome sequencing data from the National Heart, Lung and Blood Institute. This supported their suspicions that RECQL was an inherited breast cancer risk gene.

Whole exome sequencing is a technique where the DNA from nearly all coding genes is evaluated to determine whether it has mutations or variations that could be responsible for a disease.

DNA contains the code, or genetic instructions, which provide all the information necessary for a living organism to grow.



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Another Piece of the Puzzle

To confirm that RECQL was associated with inherited breast cancer, Foulkes and collaborators tested another 950 breast cancer patients for the five RECQL mutations they identified in the first phase. While they did not find any of the original RECQL mutations in these women, they identified another two mutations in the gene. One appeared to be unique to Polish patients and one unique to French Canadian patients with breast cancer.

The team then tested for these mutations in a larger population of more than 25,000 Polish and French Canadian women, consisting of over 13,000 breast cancer cases and nearly 12,000 cancer free women. In all, they found 32 Polish women and seven French Canadian women that had the unique mutation identified in the previous analysis. The RECQL mutation specific for the Polish group showed a five-fold increased risk for developing breast cancer compared to women without a mutation. The RECQL mutation identified in the French Canadian population occurred many times more frequently among familial breast cancer patients, compared to the expected number. Based on the findings in both populations taken together, the researchers concluded that RECQL is a breast cancer risk gene.

“Identifying novel breast cancer susceptibility genes has been difficult,” says Foulkes. “The identification of RECQL mutations adds another small but important piece to the breast cancer susceptibility puzzle that we have been working on for 20 or more years,” he adds.

What Does RECQL Do Anyway?

RECQL genes, like the BRCA genes, are considered ‘caretaker’ genes. They’re responsible for repairing any defects in our DNA and maintaining our genes, which can prevent tumors from forming. When they are functioning properly, they are considered to be tumor suppressors. When mutations or abnormalities occur in the RECQL genes, their function is disrupted. They cannot effectively repair DNA damage and defects accumulate, making cells more prone to cancer. There are five known RECQL genes, three of which have been associated with genetic disorders and an increased risk of various cancers.

Having an inherited gene mutation doesn't mean you will get breast cancer.



Researchers are learning that other abnormalities, in different parts of the gene, may determine which women are at highest risk for developing breast cancer and which will not likely develop breast cancer.

What's Next?

The results of this collaborative study suggest that mutations in *RECQL* are associated with a significantly increased risk for breast cancer. “But the exact magnitude of the risk is uncertain,” says Foulkes. Future studies are needed to determine whether testing for mutations in this gene will be useful. ***“One of the biggest clinical issues in inherited breast cancer susceptibility is to provide clinically useful risk estimates to women carrying mutations in breast cancer susceptibility genes. This will take collaborative efforts,” stresses Dr. Foulkes. Ultimately, better ways of preventing breast cancer will be the way forward,” he adds.***

Nevertheless, Dr. Foulkes’ and his collaborators work is yet another step towards untangling the breast cancer puzzle and could help develop new ways to identify women most at risk. Next, the team plans to search for the presence of RECQL mutations among women from other populations. Dr. Foulkes is also working to identify other new breast cancer risk genes, “more pieces in the puzzle,” he says.

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What it Means for Patients

There is still a lot to learn about RECQL and how it affects breast cancer risk. But, Dr. Foulkes' work lays the foundation for more discoveries that may one day help women assess their risk and take informed action for their health. We learned this from the identification of BRCA as a potential breast cancer risk gene. Researchers knew it was associated with breast cancer, but it took several years before it could be determined with certainty that BRCA1 mutation carriers have a 55 to 65 percent chance of developing breast cancer by age 70 (much higher than women at average risk). This knowledge led to tests for BRCA gene mutations that have helped women and men with the mutation make decisions about their own health, based on their individual risk. The same potential exists for the RECQL mutation if and when testing for the mutation is available.

“Although [RECQL] mutations are rare, breast cancer is a common disease, so there will be thousands of women who carry mutations in RECQL. It is possible, that like BRCA1/2, specific therapies will be possible for women with RECQL,” says Foulkes.

Identifying inherited gene mutations is critical to navigating the genetic map of breast cancer risk. The more details we know, the better we can help women and men understand their individual risk, and empower them to take preventive or protective measures for their future.

Behind the Science: Q&A with Dr. Foulkes

Q: What is the potential impact of your findings on RECQL?

A: Identifying novel breast cancer susceptibility genes has been difficult. Worldwide efforts to estimate the risks of breast cancer associated with mutations in RECQL can now follow. Although mutations are rare, breast cancer is a common disease, so there will be thousands of women who carry mutations in RECQL. It is possible, that like BRCA1/2, specific therapies will be possible for women with RECQL. The identification of RECQL mutations adds another small but important piece to the breast cancer susceptibility puzzle that we have been working on for 20 or more years.

Q: What made you decide to pursue scientific research? Who were your early influences, if any?

A: From my early days in school, I was always interested in biology. As a young medical student, I was interested in neurology, infectious diseases and oncology. Over time, I became more focused on cancer, but it was my experience doing a special project on cognitive mapping at University College London with future Nobel Prize winner John O’Keefe, when I was still a medical student, that was most influential in my future decision to undertake a PhD. Another influence was not a scientist, but a child psychiatrist, Dr. Terry Bruce, who I met while I was a medical student, doing a psychiatry rotation. His humane approach to his troubled patients is something I have never forgotten. Later, my PhD supervisor, John Trowsdale, was a great mentor who I learned a lot from in my four years in his laboratory.



William Foulkes, M.B., Ph.D., Professor, Departments of Medicine and Human Genetics and Oncology; Director, Cancer Genetics Service, McGill University

Q: How did you come to focus on breast cancer?

A: When I arrived in Montreal in late 1994, BRCA1 has just been identified, so there were many families who had taken part in the research effort to find the gene who now wished to be learn more about their risk. As an MD with a PhD in the molecular genetics of ovarian cancer, I was well-positioned to get involved in the clinical care of these patients. This inevitably led to research questions, which I immediately pursued.

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Q: What are the most exciting projects going on in your lab right now?

A: We have many projects focused on inherited cancer susceptibility. In breast cancer, we are still pursuing further genes that likely predispose to breast cancer. More pieces in the puzzle...

Q: What accomplishments have you and your team made that you are most proud of?

A: In terms of breast cancer, I think our early work on outcome in BRCA1 carriers, while initially controversial, was important, especially when we teamed up with Mark Robson and Ken Offit from MSKCC to show that the use of chemotherapy was critical in improving the outcome for BRCA1 carriers with breast cancer. We later showed that BRCA1-related breast cancer had a particular “basal-like” phenotype. This also has had some clinical relevance. Identifying a founder mutation in PALB2 was another finding that had immediate clinical relevance.

Q: What do you most enjoy about the scientific process?

A: Discovery. Finding something new that has the potential to change people’s thinking and, in the long run, improve people’s lives, is tremendously important to me. But it doesn’t have to be something major; it could be a refinement of something that is known, but if it has important clinical implications, then that’s great. I also enjoy seeing my students, postdocs and fellows make discoveries, start their careers and experience the thrill of their own work being published in the literature. These are all “Great Things”, to quote the English poet, Thomas Hardy.

Q: What do you see as the biggest challenges for breast cancer researchers – and for the field of breast cancer in general?

A: I cannot speak for the whole field, it is just too vast, but one of the biggest clinical issues in inherited breast cancer susceptibility is to provide clinically useful risk estimates to women carrying mutations in breast cancer susceptibility genes. This will take collaborative efforts. Ultimately, better ways of preventing breast cancer will be the way forward. Treatments will continue to make huge leaps and bounds, but there will always be treatment failures.

References: <http://ghr.nlm.nih.gov/condition/breast-cancer>



<http://sgk.mn/1hIEzkG>



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