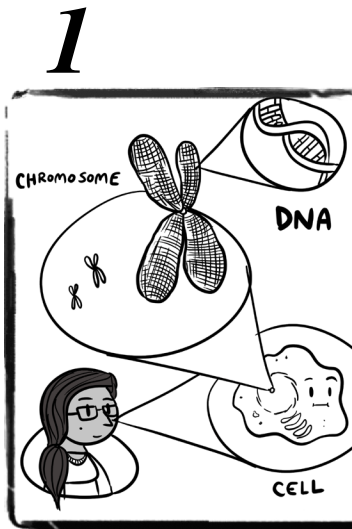
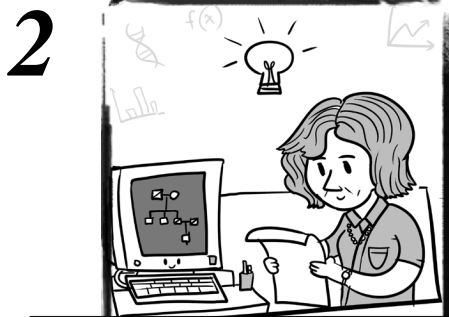


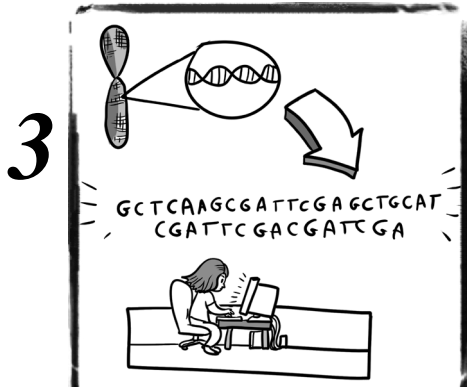
Discovering the Breast Cancer Gene



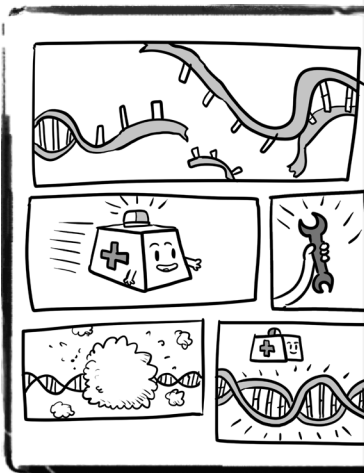
Our DNA codes for a blueprint that makes you, you! This information is organized into working units called genes, which in turn are found on 23 pairs of chromosomes. All of this DNA is packed into each and every cell in your body. Today, we know that deciphering the code in your genes can give us clues on your risk of developing certain types of cancers, such as breast cancer.



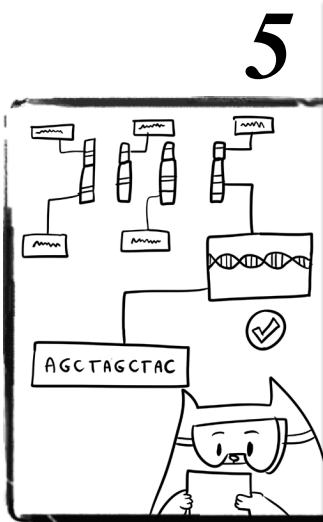
Scientist Dr. Mary-Claire King was one of the first to investigate this, and she did this by first using math to monitor families with breast cancer. Here, she found that tracking these breast cancer cases led to calculations that strongly suggested genetic inheritance of the disease.



However, she still had to find a gene responsible. In 1990, she was able to use new technology to pinpoint the gene to a region on chromosome 17. From there, the race was on to sequence and characterize this gene.



This gene became known as the Breast Cancer 1 (BRCA1) gene. BRCA1, and its sister gene, BRCA2, both encode proteins that function as tumour suppressors. This means that they actively try to stop cancer from starting. BRCA proteins are important in repairing DNA breaks, which helps protect cells from cancer causing mutations.



Now, people can have their genes sequenced to determine if they have any mutations in their BRCA1 or BRCA2 genes. Finding a mutation could mean that the BRCA is not working properly and therefore makes the person more susceptible to harmful DNA mutations. This allows patients to take preventative action to help lower their risk of developing cancer.



Dr. Mary-Claire King's lasting legacy in the cancer field is the revolutionary idea that cancer could be genetically inherited. This is a crucial part of cancer research as scientists now recognize that there are many genes involved in the development of human cancers.

Discovering the Breast Cancer Gene



Using math to find the link between cancer and genetic inheritance.

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October 2021

You probably know at least one person who has been affected by cancer. In fact, statistics show that almost half of all Canadians will develop cancer at some point in their life. Cancer occurs when cells malfunction and multiply uncontrollably. This is similar to weeds in your garden that can overpopulate and take over. This loss of control develops into large growth of cells, known as tumours, which can impede the functioning of surrounding tissues.

There are over 200 different types of cancer from all different parts of our body, and most are named after the location where they occur. One example of this is breast cancer. Here, you may have participated in some of the popular fundraising activities, like walks or races, where money is raised for breast cancer research. In addition, you may have seen the pink ribbons that are used to represent the cause. Breast cancer is currently one of the most common types of cancer, affecting 1 in 8 women in Canada.

Scientists still haven't completely worked out all the causes of breast cancer, but originally, it was thought that the development of this disease was primarily due to environmental factors such as toxins or viral infections. This all changed in 1970, when Dr. Mary-Claire King, one of the 2021 Gairdner International Award winners, hypothesized that there may be **genetic markers** in our DNA that could influence one's likelihood to de-

velop breast cancer. In the same way that DNA can encode for things like hair colour, she wondered if DNA could also encode for susceptibility to the disease.



What is a gene and how do we inherit them from our parents?

Dr. King noticed that many women who had breast cancer, also had mothers who had breast cancer. This suggested to her that breast cancer could be the result of DNA mutations that are inherited.

In order to understand how breast cancer can be passed through generations, it is important to understand the concept of genes. A **gene** is usually

thought of as a discrete sequence of DNA code that results in or influences a characteristic. Because there can be variations in the sequences of the gene, the characteristic may exhibit itself in different ways. For example, hair colour can come in many forms, and it is the variation in the sequence of genes involved in hair colour that causes the actual different colours.

In terms of terminology, differing variations in a gene are referred to as differing **alleles**. Importantly, for any given gene, our DNA blueprint is such that we inherit one allele from our mother, and one allele from our father, creating an allelic pair that ultimately results in how the characteristic turns out. Geneticists call this output your **phenotype**. For example, if you have brown coloured hair - brown would be your hair colour phenotype.

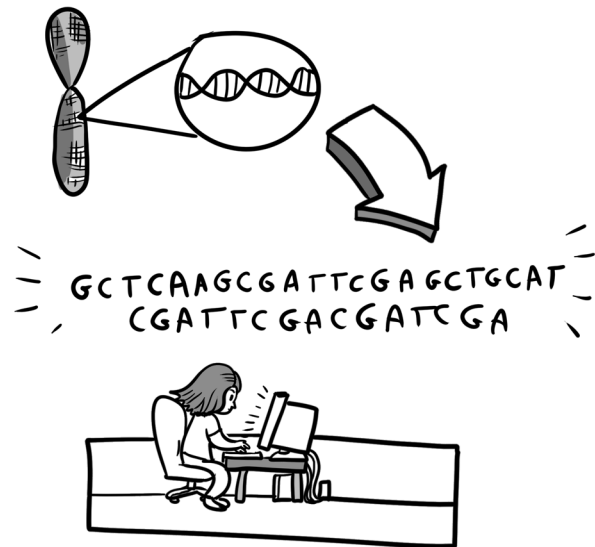
Because your phenotype can be influenced by the alleles you inherit from your parents, characteristics tend to be hereditary in nature. Put another way, phenotypes can be passed down from generation to generation. Note that there are many inheritance patterns that your genes can follow that affect your phenotype. In particular, one common way is to think of alleles as being **dominant** or **recessive**. In this case, if a dominant allele is inherited from one parent, its resulting phenotype dictates the final outcome, effectively overpowering the recessive allele of the other parent. This can be dangerous if the dominant allele carries a mutation that results in a harmful phenotype.

The Discovery of the “Breast Cancer Gene”

Coming from a background in mathematics and evolution, Dr. King was able to examine the incidence of breast cancer, using large sets of data from over 1500 families. And since the world of genetics was still in its infancy in 1970, Dr. King relied heavily on using mathematical methods to calculate if there might be inheritance patterns that were suggestive of the disease being caused by a single gene.

Her results conclusively showed that in about 4% of families, there appeared to be a clear dominant

method of inheritance. Although this seems like a low percentage of the total dataset, for those in the 4%, there was a substantial impact in that the math predicted up to an 82% likelihood of developing breast cancer before the age of 70.



However, due to limitations of technology at the time, she was not able to identify the specific gene and allele responsible for this observation. Indeed, it wasn't until 1990 that Dr. King and her team were able to employ new technologies allowing

In addition to her revolutionary work on the BRCA genes, Dr. King has numerous other achievements in the field of genetics. Her PhD work investigated similarities between humans and chimpanzees, with the shocking discovery that our genetic codes are 99% similar.

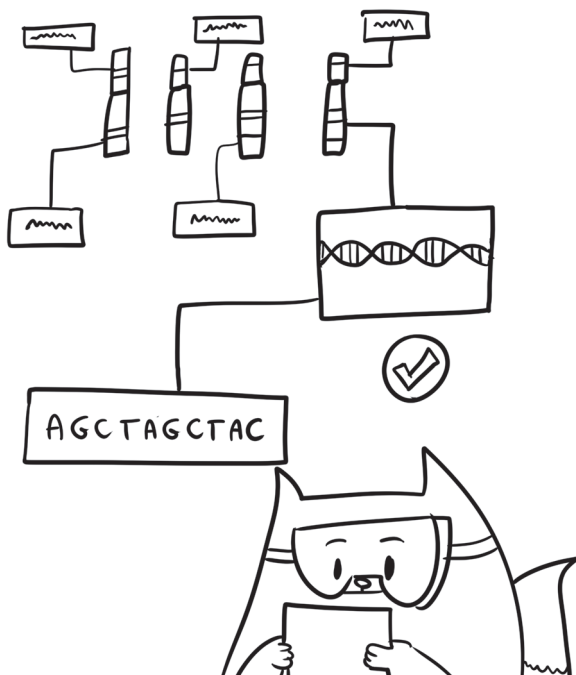
As well, during the 1980's, she began a collaboration with the human rights group Abuelas de Plaza de Mayo (Grandmothers of Plaza de Mayo), that reunited grandparents with children kidnapped during the war in Argentina. Here, she developed a specialized DNA sequencing test that could be used to prove the relationship between grandparents and children who were left without parents or born into captivity. Even later, this test was used to identify the remains of soldiers in Vietnam, Korean, and WWII.

“Those of us who work in science have a responsibility to present facts and speak truth about issues that we know well,” Dr. King declared. She has continued to do just this by advocating for human rights issues, and has been a continued voice for equality and women's rights.

them to identify a small region of the genome that was associated with increased inheritance and likelihood of developing early-onset breast cancer.

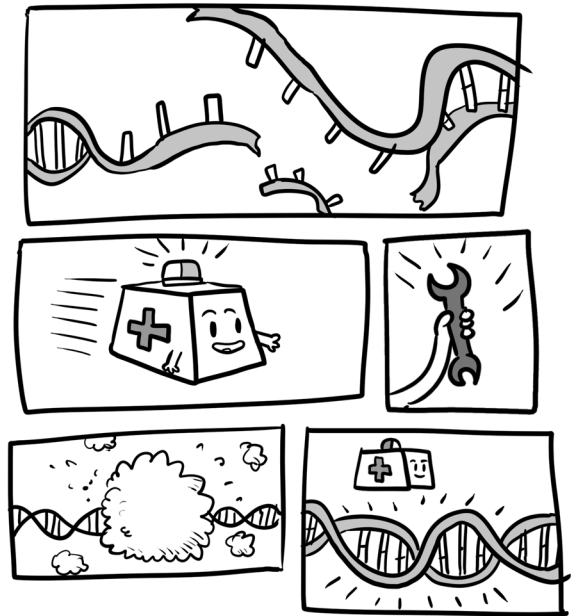
She reflects: “Once this hypothetical breast cancer susceptibility gene was mapped to a patch of chromosome 17, it was clear to many people in the public and private sectors that the gene was real” As a result, the race was on to find and characterize the **Breast Cancer 1** gene, or **BRCA1** gene as it is known today.

It wasn't until 1994, that the BRCA1 gene was finally cloned and sequenced. In this case, the winner of the race was a group at the biotechnology company, Myriad Genetics. By examining the gene in breast cancer patients, the company was able to identify several mutations in the BRCA1 gene that could result in increased breast cancer risk. Later that year, Myriad Genetics also sequenced and characterized another breast cancer gene, **BRCA2**, and the company was subsequently awarded a patent on the two genes. This allowed them to provide commercial genetic testing for hereditary breast and ovarian cancer.



What is BRCA1 and BRCA2's function in cancer?

With advances in technology and our understanding of genetics, we now know much more about



the function of the BRCA1 and BRCA2 genes. In particular, we can understand how mutations in these genes can lead to phenotypes of increased risk of breast and ovarian cancer. Here, the BRCA1 and BRCA2 genes encode proteins known as tumour suppressors. These can act to directly protect cells from DNA mutations, and in doing so, suppress the formation of cancerous cells. More specifically, when damage or breakage of DNA is caused by radiation or other environmental factors, these proteins function to repair those errors. You can imagine that if a person has alleles of BRCA1 or BRCA2 that work less efficiently, they will be more prone to accumulating harmful mutations which leads to the increased likelihood of disease.

Impact on the Cancer Field

Dr. Mary-Claire King's lasting legacy in the cancer field is the revolutionary idea that cancer could be genetically inherited. Her expertise and diverse background had allowed her to view things from a different angle. With a bit of mathematics and molecular biology, her findings shifted the cancer field to investigate genetic inheritance of mutations underlying different types of cancer.

Nearly 40 years later, Dr. King continues to lead ground breaking research on the BRCA1 and

BRCA2 genes, now using the most advanced sequencing technologies and genetic tools.

Thanks to Dr. King's discovery, people with a family history of breast and ovarian cancer are able to get genetic testing to examine their BRCA1 or BRCA2 genes. This information informs them of their risks of getting the disease in their lifetime. Knowing that they have these mutations is powerful because it allows for patients to seek preventative measures against these forms of cancer.