

BRCA1 and BRCA2 Genes and Their Relationship to Breast and Ovarian Cancer

Note: The Teacher Background Section is meant to provide information for the teacher about the topic and is tied very closely to the PowerPoint slide show. For greater understanding, the teacher may want to play the slide show as he/she reads the background section. For the students, the slide show can be used in its entirety or can be edited as necessary for a given class.

What Are BRCA1 and BRCA2 and Where Are the Genes Located?

BRCA1 and *BRCA2* genes in humans code for proteins that work to suppress tumors. The gene names come from BReast CAncer genes 1 and 2. The official names of these genes are breast cancer 1, early onset and breast cancer 2, early onset. Everyone, male and female, has these genes which normally work to repair DNA and are involved in cell growth and cell division. The *BRCA1* gene codes for the BRCA1 protein which regulates the activity of other genes and is involved in embryonic development during cell division. The *BRCA2* gene codes for the BRCA2 protein which is thought to help regulate cytokinesis during cell division and to regulate telomere homeostasis. By helping repair DNA, BRCA1 and BRCA2 proteins are thought to work in tandem to ensure the stability of the DNA in the cell. The BRCA1 protein combines with BRCA2 and other proteins to mend breaks in the DNA caused by natural and medical exposures to radiation and other environmental exposures and by recombination when the chromosomes exchange genetic material when replicating prior to cell division. (1, 2)

The *BRCA1* gene is located on the long (q) arm of chromosome 17 at position 21 (17q21). The gene begins at base pair 41,196,311 and ends at base pair 41,277,499, making the gene 81,188 base pairs long (another source said it ended at 41,322,290 making it 125, 979 base pairs long). (1,3) *BRCA1* gene was first identified and isolated in 1994 by Mark Skolnick and his colleagues at Myriad Genetics, Inc. in Salt Lake City working with groups, including Andrew Futreal and Roger Wiseman, at the University of Utah and the National Institutes of Health (NIH) . The Utah-NIH group published its results in Science (October 7, 1994), filed for a patent on the gene and several pathogenic mutations, and licensed the rights to Myriad. Another researcher, Mary-Claire King at the University of California, Berkeley also identified several BRCA1 markers which were licensed by UC, Berkeley to OncorMed. (4)

The *BRCA2* gene is located on the q arm of chromosome 13 at position 12.3 (13q12.3). It begins at base pair 32,889,616 and ends at 32, 973,808, making the gene 84, 192 base pairs long. (2, 5) *BRCA2* was discovered in 1995 by researchers Michael Stratton and Richard Wooster at the Institute of Cancer Research in the United Kingdom and isolated at the Wellcome Trust Sanger Institute, UK. (6)



This work is licensed under a [Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License](https://creativecommons.org/licenses/by-nc-sa/4.0/).

What Do the *BRCA1* and *BRCA2* Genes Look Like When Translated Into Protein?

The *BRCA1* gene codes for the BRCA1 protein which is 1863 amino acids in length. It belongs to a family of genes called *RNF* (RING-type zinc fingers) in which the amino acids cysteine and histidine fold around and hold a zinc ion. This configuration makes the protein very stable and enables it to bind to other molecules, like BARD1 and E2F1, near the N terminus which are necessary for DNA repair. There is a DNA binding domain in the middle of the BRCA1 protein. In addition, the protein has a C terminus (BRCT) domain which binds to BACH1, HDAC, CtIP, and p53 which are involved in G1/S arrest during interphase. (1, 3, 7, 8)

The BRCA2 protein is composed of 3418 amino acids and contains 39 amino acid repeats that are critical for binding to another protein called RAD51, a key protein used for DNA recombinant repair. The *BRCA2* gene belongs to the *FANC* family of genes which are involved in the Fanconi anemia pathway. (2, 5, 7, 8)

How Do the BRCA1 and BRCA2 Proteins Function?

The BRCA1 and BRCA2 proteins work together to repair DNA. DNA damage is thought to be one of the key triggers leading to activation of BRCA1 and other damage sensors, such as ataxia telangiectasia mutated (ATM), a protein that is located primarily in the nucleus of cells where it activates the DNA damage response in the event of DNA double strand breaks. BRCA1 and p53, a tumor suppressor protein, are phosphorylated which prevents cell division. Downstream targets of BRCA1 activation include binding to BRCA2, RAD51, and BARD1 to form a complex. This complex promotes G1 and G1/S-phase arrest during interphase and eventually relocates to an area of DNA replication where DNA can be repaired. (1, 2, 7, 8)

What Role Do Mutations in *BRCA1* and *BRCA2* Genes Play in Causing Cancer?

Mutations or changes in the DNA occur at times – some are beneficial, some are harmful, and some are neither. In *BRCA1* genes, 1000 mutations have been found and many are associated with an increased risk of cancer. In the Ashkenazi Jewish population of Eastern Europe, 1 in 40 carries one of the mutations and 25% of Jewish women who develop breast cancer by age 41 have one of these mutations compared to 5–12% of people in the general population. Three particular mutations have been found in this population that lead to a higher risk of breast cancer and include 185delAG (at base pair 185, deletion of adenine and guanine) and 5382insC (at base pair 5382, insertion of cytosine). Other carcinogenic mutations in this gene are also more common in people from Iceland, Scandinavia, Holland, and Poland. (7, 8, 9)

In *BRCA2* genes, 800 mutations have been found and lead to a high incidence in breast cancer. The Ashkenazi Jewish population has a *BRCA2* mutation 6174delT which is known to raise the risk of cancer.



Cancer Lab BRCA Teacher Background on DNA Bioinformatics Lab

The Dutch have a mutation at 5579insA, the Scots at 6503delTT, and the French Canadians at 8765delAG which raise the risk of cancer. With a deletion or insertion in the gene, it causes a frame shift in the codons resulting in a different sequence of the amino acids in the protein. This, in turn, causes the protein potentially to fold in a way that makes its active site(s) inoperable. When the active site is inoperable, the protein can no longer work to repair DNA damage. When mutations occur in either the *BRCA1* or *BRCA2* gene, the DNA remains unrepaired or is repaired in an error-prone fashion, such as non-homologous end-joining. These errors can lead to unstable chromosomal rearrangements which potentially can lead to cancer. (7, 8, 9)

How Are *BRCA1* and *BRCA2* Genes Inherited?

The inheritance of these mutated *BRCA1* and *BRCA2* genes is by autosomal dominance. (10) That means if the normal gene (b) is altered by mutation (B), then those who inherit one or two copies of the altered gene (Bb or BB) will be affected while those who inherit two normal genes (bb) will be normal. In this type of inheritance, there is a 50% chance that each offspring will inherit the faulty gene if one of the parents has the altered gene. In one family, the father had a normal gene (b) and a mutated gene (B) and had had colon cancer and the mother had two normal genes (bb) and no history in her family of cancer. The youngest daughter inherited the mutated gene and a normal gene (Bb) and at age 29 was being treated for breast cancer. Her sister inherited two normal genes (bb) and showed no signs of cancer development. Her oldest brother also inherited an abnormal gene and a normal one (Bb) and shows no sign of cancer to date. Her next oldest brother inherited two normal genes (bb) and shows no sign of cancer.

The inheritance of the mutated *BRCA1* genes increases the risk of early onset breast and/or ovarian cancer and of developing cervical, uterine, pancreatic, and colon cancer. Inheritance of a *BRCA2* mutation also increases the risk of pancreatic, stomach, gallbladder, and bile duct cancers and melanoma and prostate cancer in men. In addition, the children who inherited the mutated gene could pass the gene on to their children (as their father did to them). Note that not all men and women who inherit a harmful *BRCA1* or *BRCA2* mutation will develop breast cancer or ovarian cancer in women. Only about 60% of the women who inherited a harmful mutation in the *BRCA1* or *BRCA2* genes will develop breast cancer and 15 – 40% of the women will develop ovarian cancer. As a comparison, in the general population about 12% of women with normal *BRCA1* and *BRCA2* genes will develop breast cancer and 1.4% will develop ovarian cancer sometime in their life, largely due to life style choices such as smoking, eating a high fat and high sugar diet, and exercising very little. (10, 11, 12)

It is unclear in the literature whether or not it takes only one altered copy of the *BRCA1* and *BRCA2* genes to cause cancer or if it takes two altered copies. Even though a normal gene is inherited along with a mutated one, the amount of DNA that goes unrepaired mounts up and some scientists think this can lead to breast and/or ovarian cancer by the time one reaches menopause (by age 50). Other



Cancer Lab BRCA Teacher Background on DNA Bioinformatics Lab

scientists think the normal gene in a heterozygous inheritance (Bb) must also become mutated before cancer will develop. (8,10) Some people who inherit a known mutation in either *BRCA1* or *BRCA2* genes never develop cancer so perhaps their immune systems are recognizing and destroying the cells containing the damaged DNA. More research is needed to determine the inheritance and cancer issue.

Are There Tests to See If One Has a Mutated *BRCA1* or *BRCA2* Gene?

Once the *BRCA1* and *BRCA2* genes were discovered and isolated, the way was paved for testing individuals for mutations in these genes. Those who might choose to be tested are women who have a family history of breast and/or ovarian cancer. This family history would include incidence of breast cancer in two 1st degree relatives (mother, daughter, sister), in three or more 1st or 2nd degree relatives (grandmother or aunt), in a 1st degree relative diagnosed at age 50 or younger, in a 1st degree relative diagnosed with cancer in both breasts, in a male relative, or a 1st or 2nd degree relative diagnosed with both breast and ovarian cancer. Women who are of Ashkenazi Jewish descent might choose to be tested if any 1st degree relative has been diagnosed with breast or ovarian cancer and/or if two 2nd degree relatives on the same side of the family are diagnosed with breast or ovarian cancer. Often a genetics counselor can help individuals and families make the decision about testing. The risks of testing are small but test results may have an effect on the individual's emotions, medical choices, social relationships, and finances. (11)

If the test result is negative for mutation, the individual could still have a predisposition for breast cancer and may or may not get cancer. If the test is positive, the individual may or may not get cancer but the faulty gene could be passed on to the offspring. Frequent screenings with mammograms and clinical breast exams will help detect the cancer early if it does occur. The individual might choose to begin to take the drug tamoxifen, which has been found to reduce the risk of developing breast cancer by 50%. (12)

In the United States, Myriad Genetics, Inc. owned exclusive right to test for *BRCA1* and *BRCA2* genes and charged \$350 for a single mutation analysis and \$2975 for a full sequence analysis of both genes. The screen for several mutations found in the Ashkenazi Jewish population was \$415. Most of the time, insurance plans will cover the genetic testing, but some women fear their employer or insurance company will discriminate against them if the results are positive so choose to pay for it themselves or not have the testing done. (13)

The expense of the tests for *BRCA1* and *BRCA2* mutations and the monopoly that Myriad Genetics, Inc. had on the patents on *BRCA1* and *BRCA2* led The Association for Molecular Pathology, the American Civil Liberties Union (ACLU), and the Public Patent Foundation to file a lawsuit in 2009 against the US Patent and Trademark Office and Myriad Genetics, Inc. In 2010, a US district court invalidated 7 of 23 of



Cancer Lab BRCA Teacher Background on DNA Bioinformatics Lab

Myriad's patents on these genes and opened the door to possibly curtailing the rights of an individual or organization to patent a gene. In June, 2013, the Supreme Court ruled that genes which were naturally produced could not be patented. This means that Myriad Genetics, Inc. no longer holds the exclusive patent rights to *BRCA1* and *BRCA2* genes. (14)

How Does Bioinformatics Apply to Genetics Testing?

In the Bioinformatics exercise, since the *BRCA1* gene is 81,188 base pairs long, only a small portion of the gene is used to make the BLAST comparisons with patient DNA. Within this small portion, there is at least one mutation that is implemented in causing breast cancer. With this bioinformatics tool, patient DNA will be compared with normal DNA to determine if there are mutations.

Bibliography

1. <http://ghr.nlm.nih.gov/gene/BRCA1>
2. <http://ghr.nlm.nih.gov/gene/BRCA2>
3. <http://www.genecards.org/cgi-bin/carddisp.pl?gene=BRCA1&search=533622b82f51bc5431a771c088f3bdd9>
4. <http://www.sciencemag.org/content/278/5345/1874.full>
5. <http://www.genecards.org/cgi-bin/carddisp.pl?gene=BRCA2&search=6f3ef4a5ab86c1588ba1fc89f4c730bb>
6. <http://www.nature.com/nature/journal/v378/n6559/abs/378789a0.html>
7. <http://www.nature.com/onc/journal/v22/n37/full/1206678a.html>
8. <http://www.discoverymedicine.com/Steven-A-Narod/2009/07/16/brca1-and-brca2-in-2005/>
9. <http://www.discoverymedicine.com/Steven-A-Narod/2011/11/25/brca1-and-brca2-mutations-and-breast-cancer/>
10. <http://www.ncbi.nlm.nih.gov/books/NBK1247/>
11. <http://www.cancer.gov/cancertopics/genetics/brca-fact-sheet>
12. www.genome.gov/page.cfm?pageID=10000507
13. <http://www.myriad.com/patients-families/disease-info/breast-cancer/>
14. <http://www.nature.com/news/myriad-ruling-causes-confusion-1.13226>

