

BRCA1 and BRCA2 Genes



THEIR RELATIONSHIP TO BREAST AND
OVARIAN CANCER



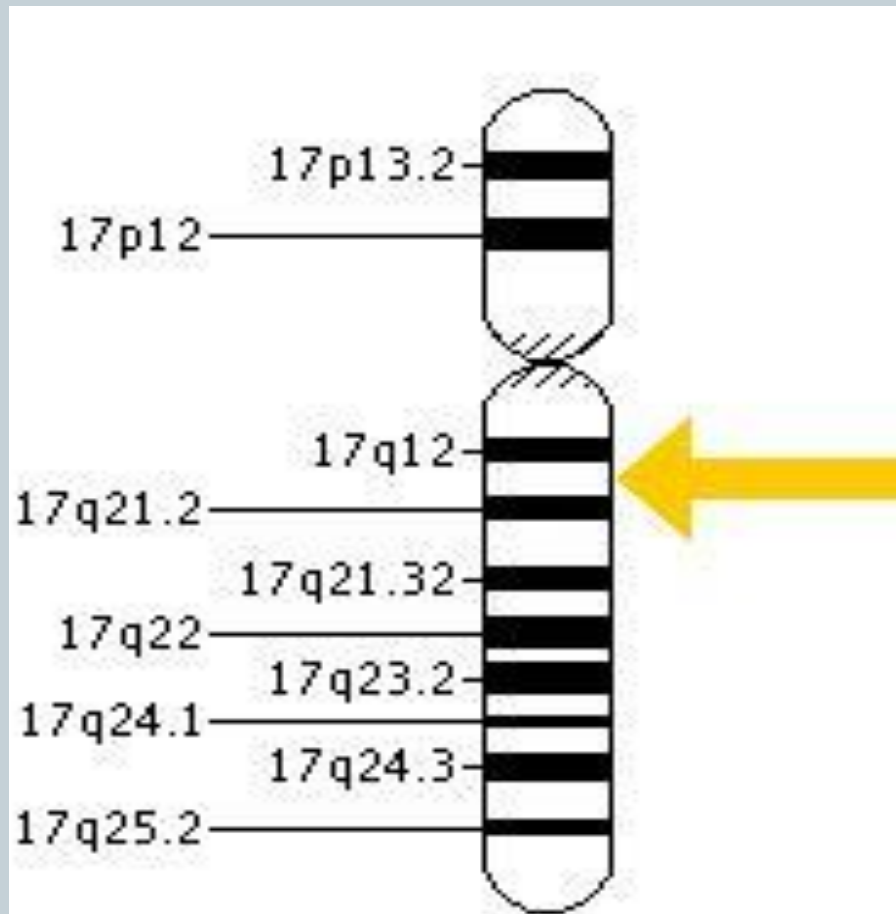
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BRCA1 and *BRCA2* Genes

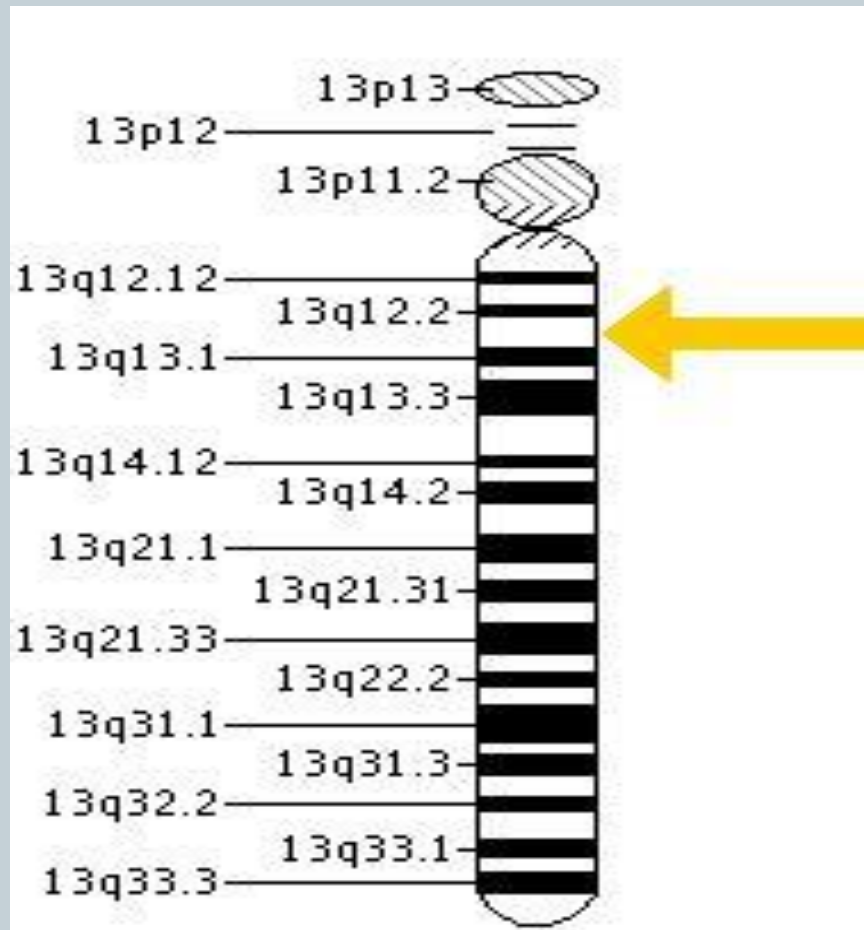


- In humans, the *BRCA1* and *BRCA2* genes code for proteins that work to suppress tumors.
- The gene names come from BReast CAncer genes 1 & 2. The official names of these genes is breast cancer1, early onset and breast cancer2, early onset.
- Everyone, male and female, has these genes which normally work to repair DNA and are involved in cell growth and cell division.

BRCA1 Gene Location at 17q21

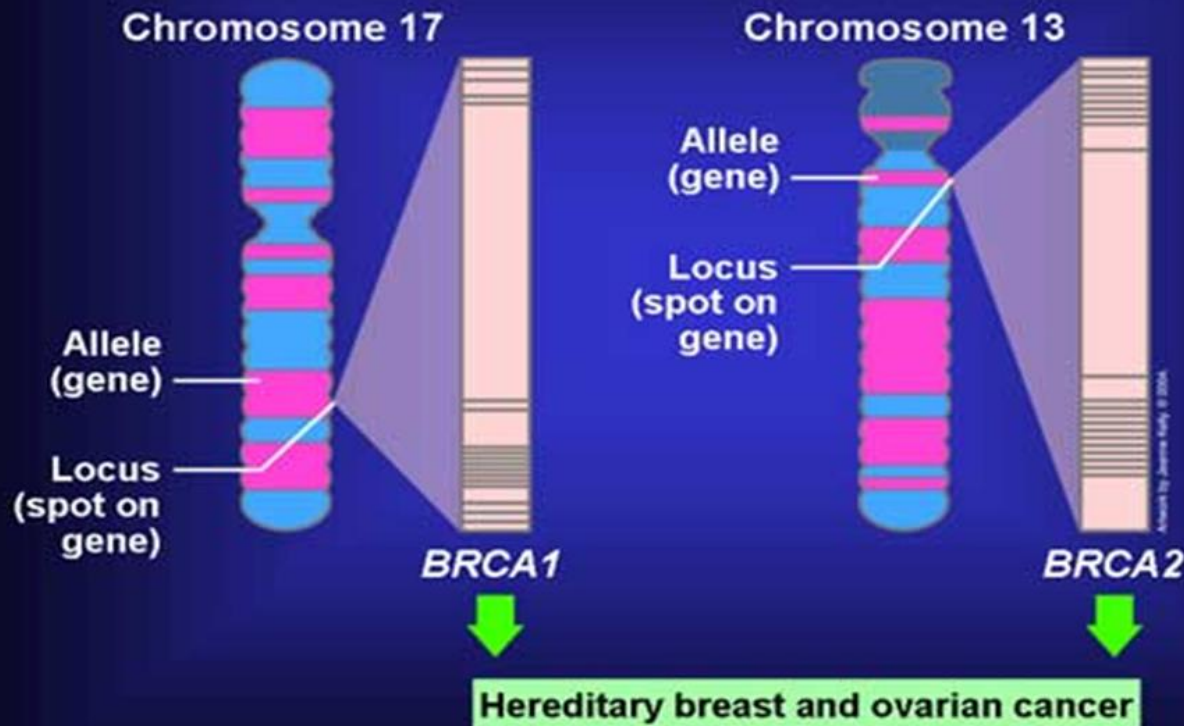


BRCA2 Gene Location at 13q12.3



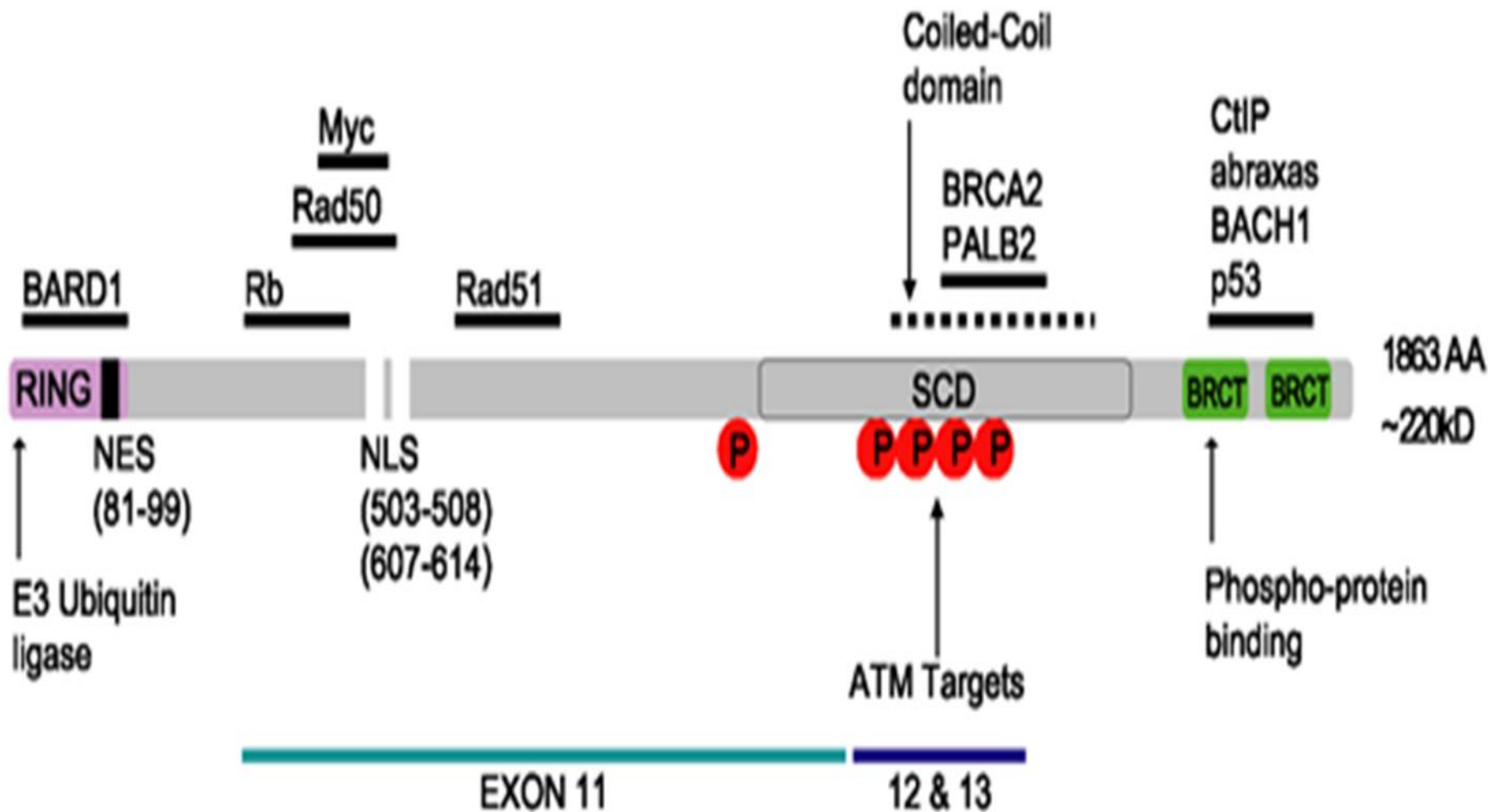
BRCA1 and *BRCA2* Genes

Different Locus, Different Allele, Same Phenotype



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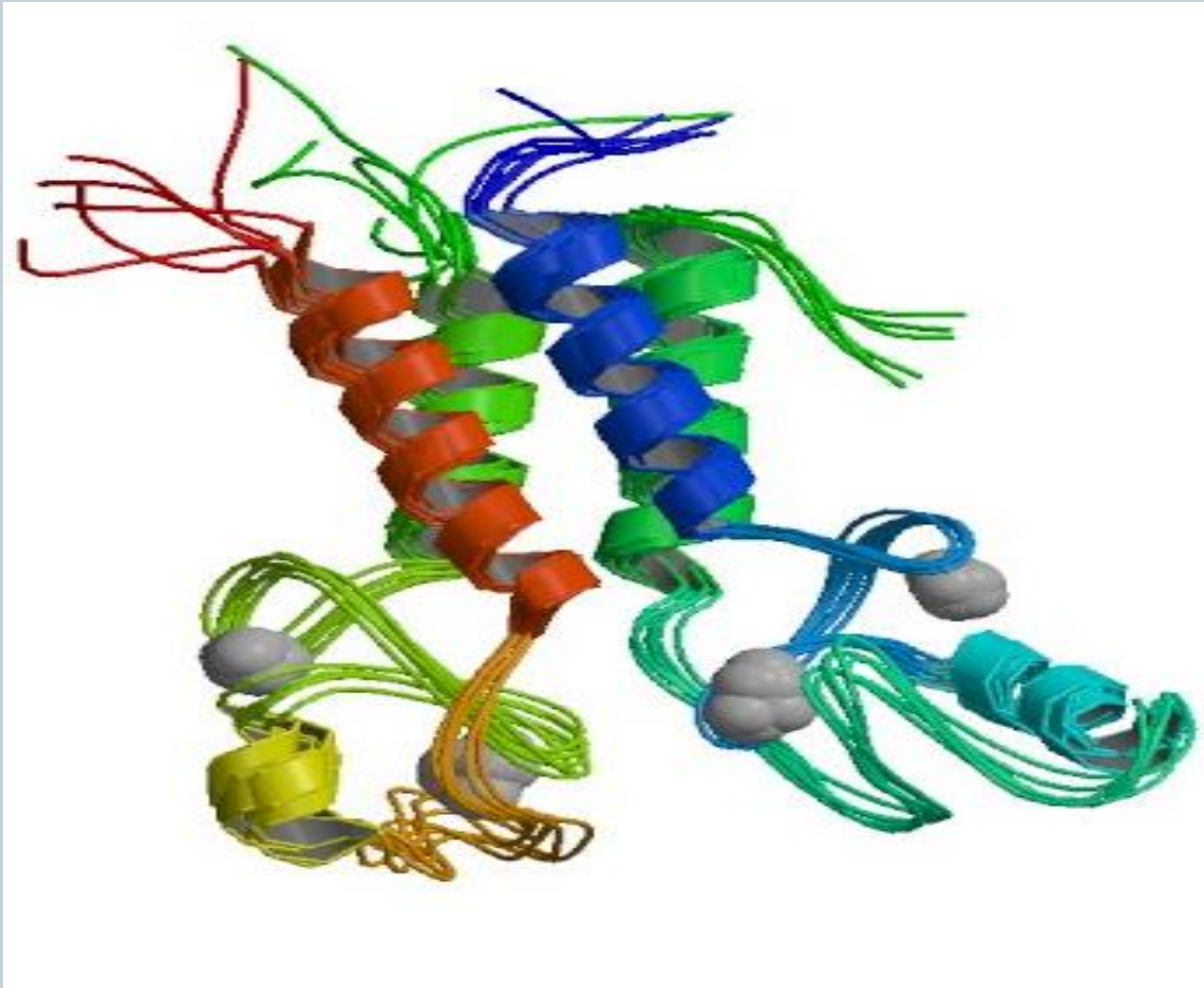
BRCA1 Protein Domain Map



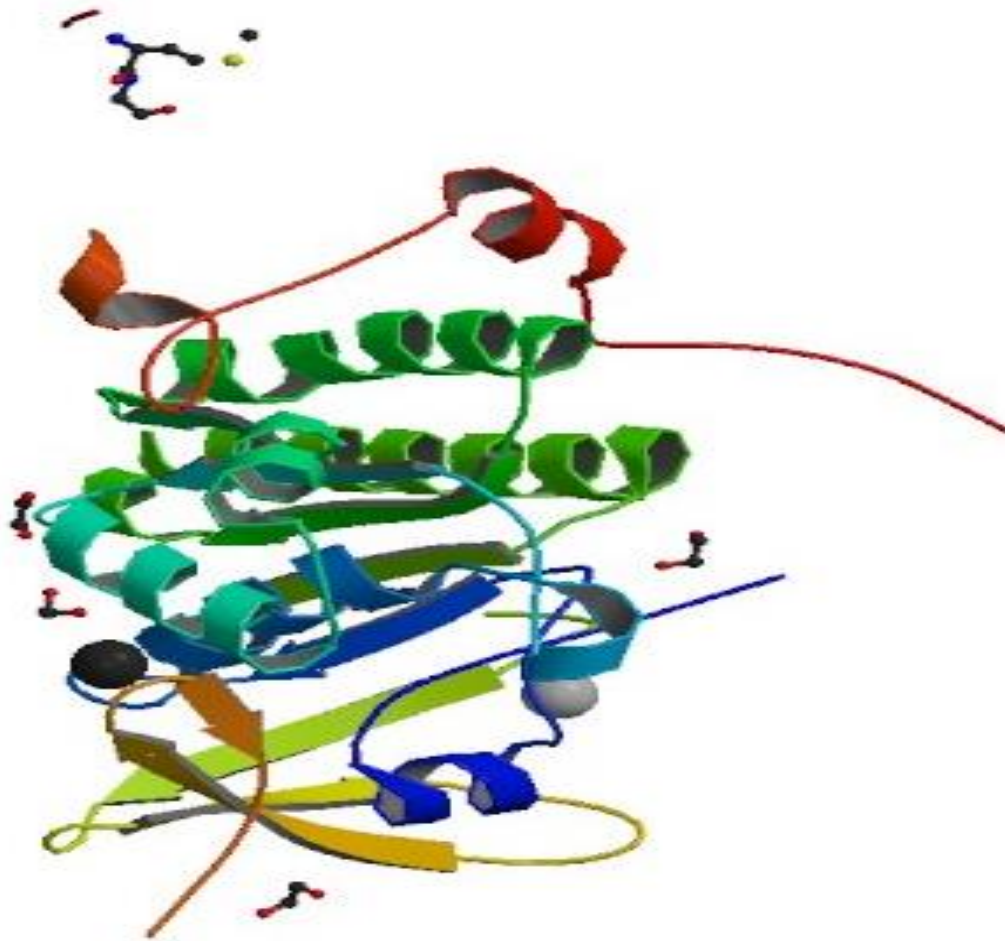
<http://en.wikipedia.org/wiki/File:BRCA1>

<http://creativecommons.org/licenses/by-sa/3.0/deed.en> No changes were made.

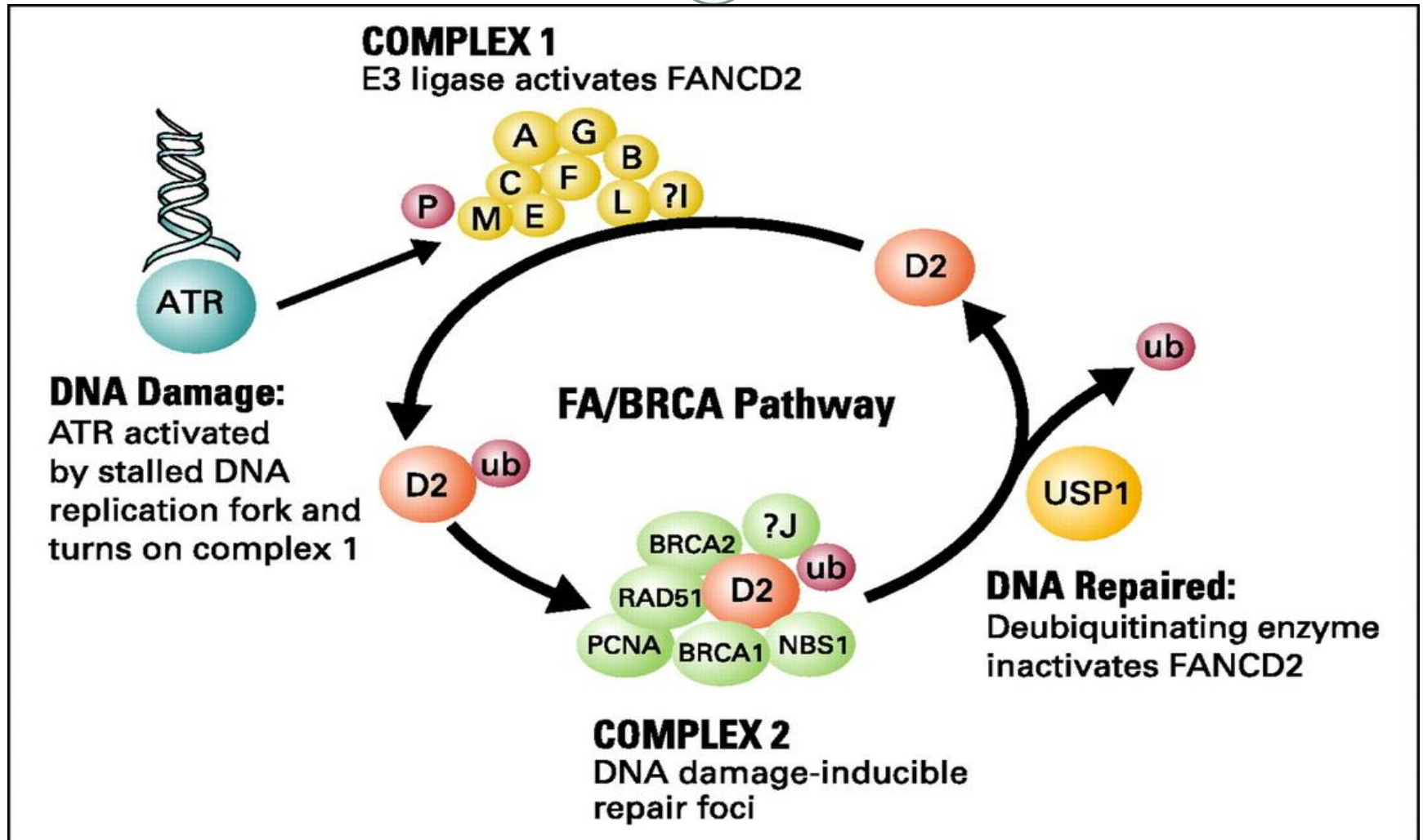
BRCA1-BARD1 Heterodimeric RING-RING Complex



BRCA2 and RAD51 Protein Complex



BRCA1 and *BRCA2* Work Together to Repair DNA



Mutations in Cancer Susceptibility Genes: *BRCA1*

■ On chromosome 17

■ Protein has role in
genomic stability

■ Autosomal dominant
transmission

■ ~500 different
mutations reported



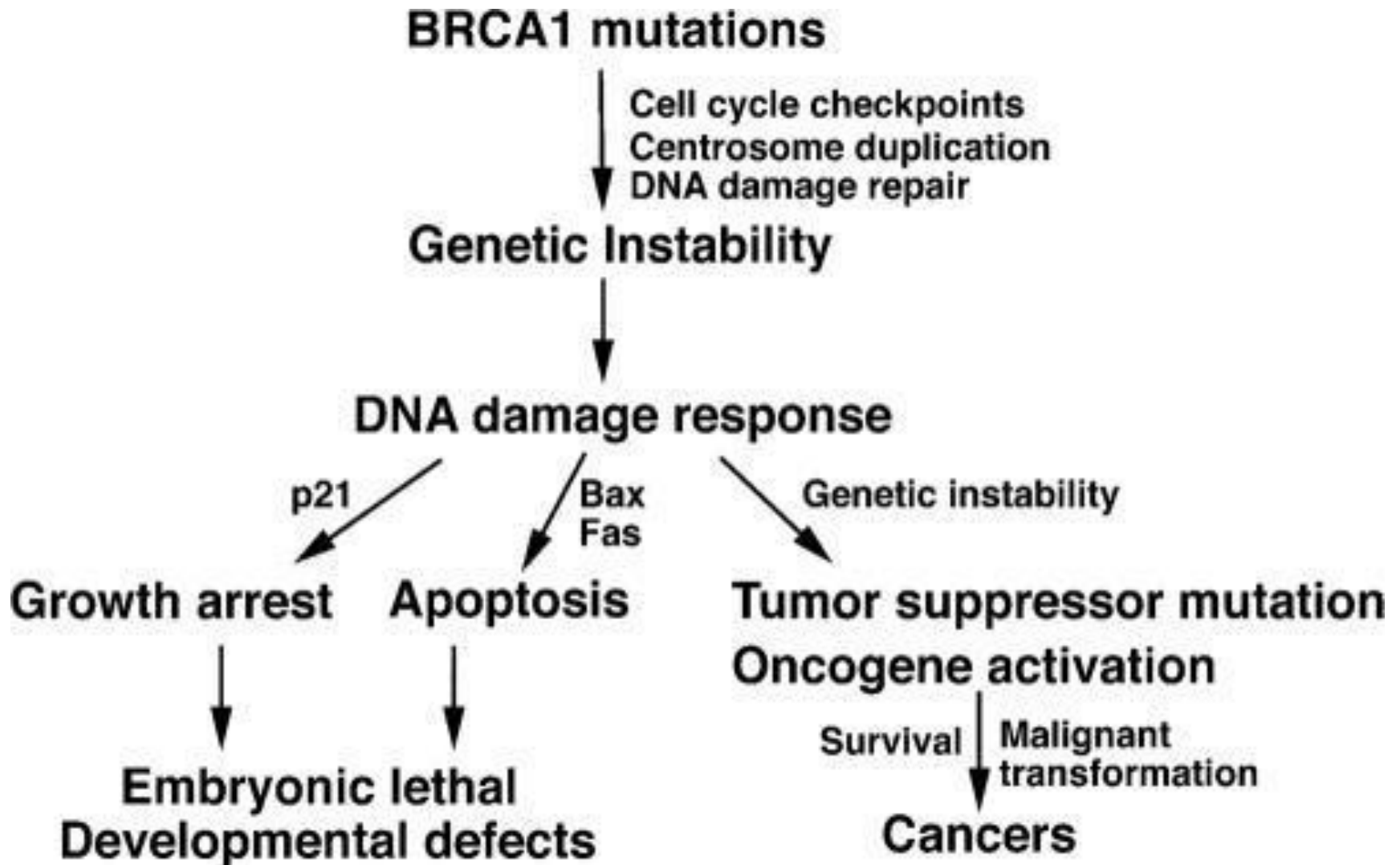
■ Nonsense/Frameshift

● Missense

◆ Splice-site

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Results of BRCA1 Mutations



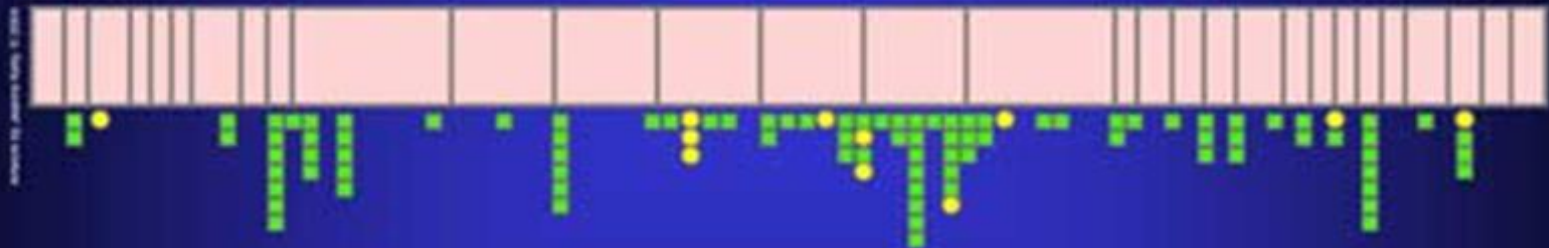
Mutations in Cancer Susceptibility Genes: *BRCA2*

■ On chromosome 13

■ Protein has role in
genomic stability

■ Autosomal dominant
transmission

■ ~300 different
mutations reported



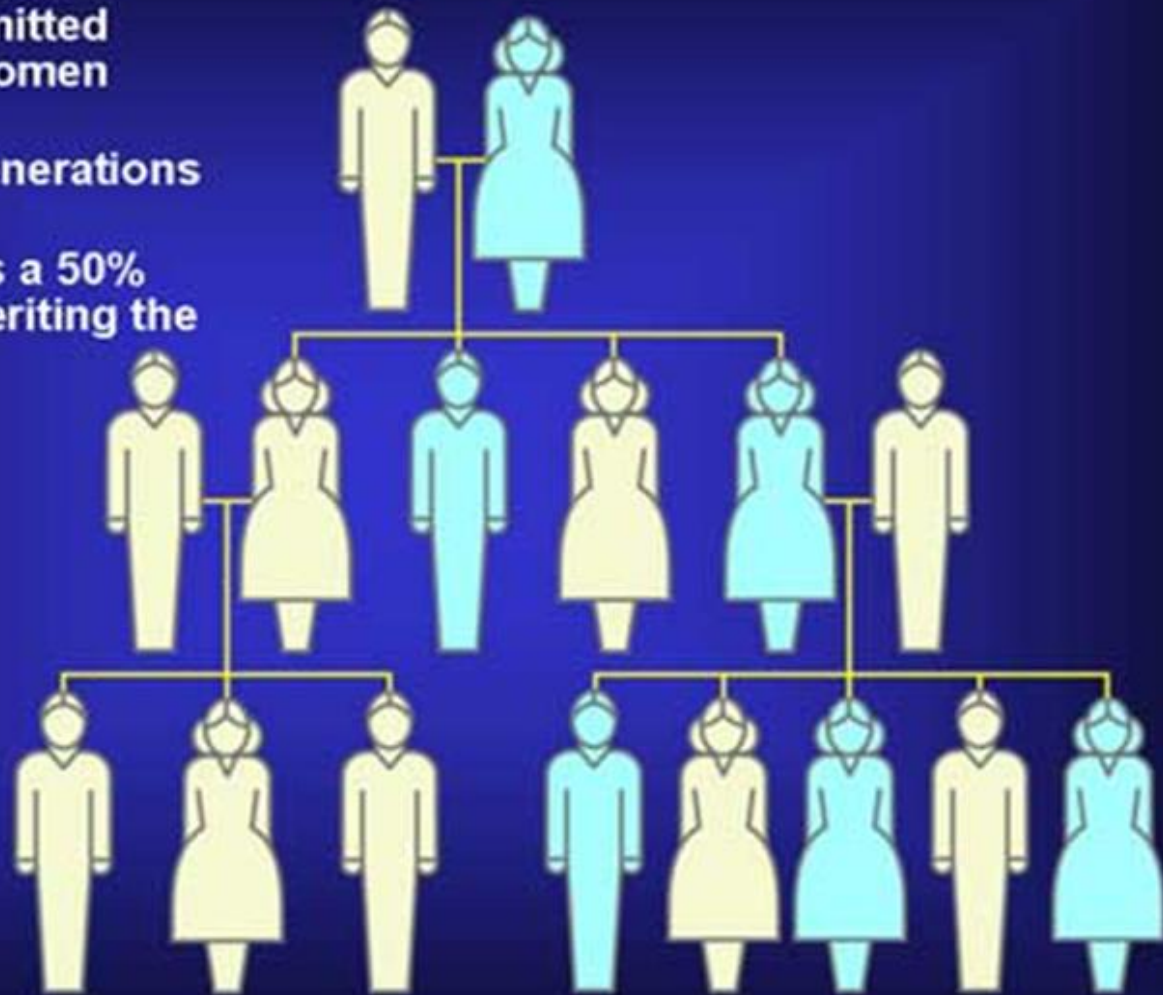
■ Nonsense/Frameshift

● Missense

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Autosomal Dominant Inheritance

- Equally transmitted by men and women
- No skipped generations
- Each child has a 50% chance of inheriting the mutation



Source: National Cancer Institute

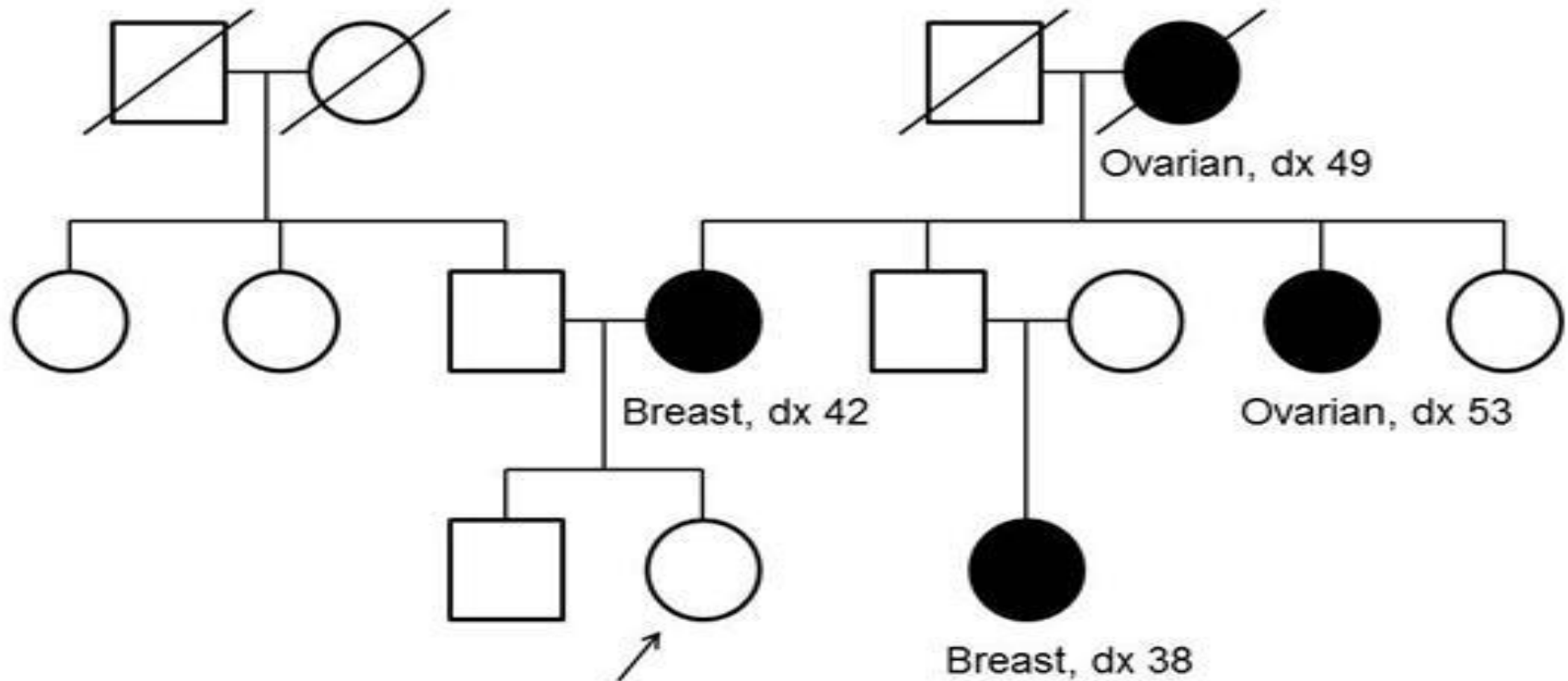
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Examples of Dominantly Inherited Cancer Syndromes

| Syndrome | Associated Gene |
|---|-------------------------------------|
| Familial retinoblastoma | <i>RB1</i> |
| Li-Fraumeni | <i>TP53</i> (p53 protein) |
| Familial adenomatous polyposis | <i>APC</i> |
| Hereditary nonpolyposis colorectal cancer | <i>MLH1, MSH2, MSH6, PMS1, PMS2</i> |
| Wilms' tumor | <i>WT1</i> |
| Breast and ovarian cancer | <i>BRCA1, BRCA2</i> |
| von Hippel-Lindau | <i>VHL</i> |
| Cowden | <i>PTEN</i> |

Adapted by Joanne Kelly, © 2004

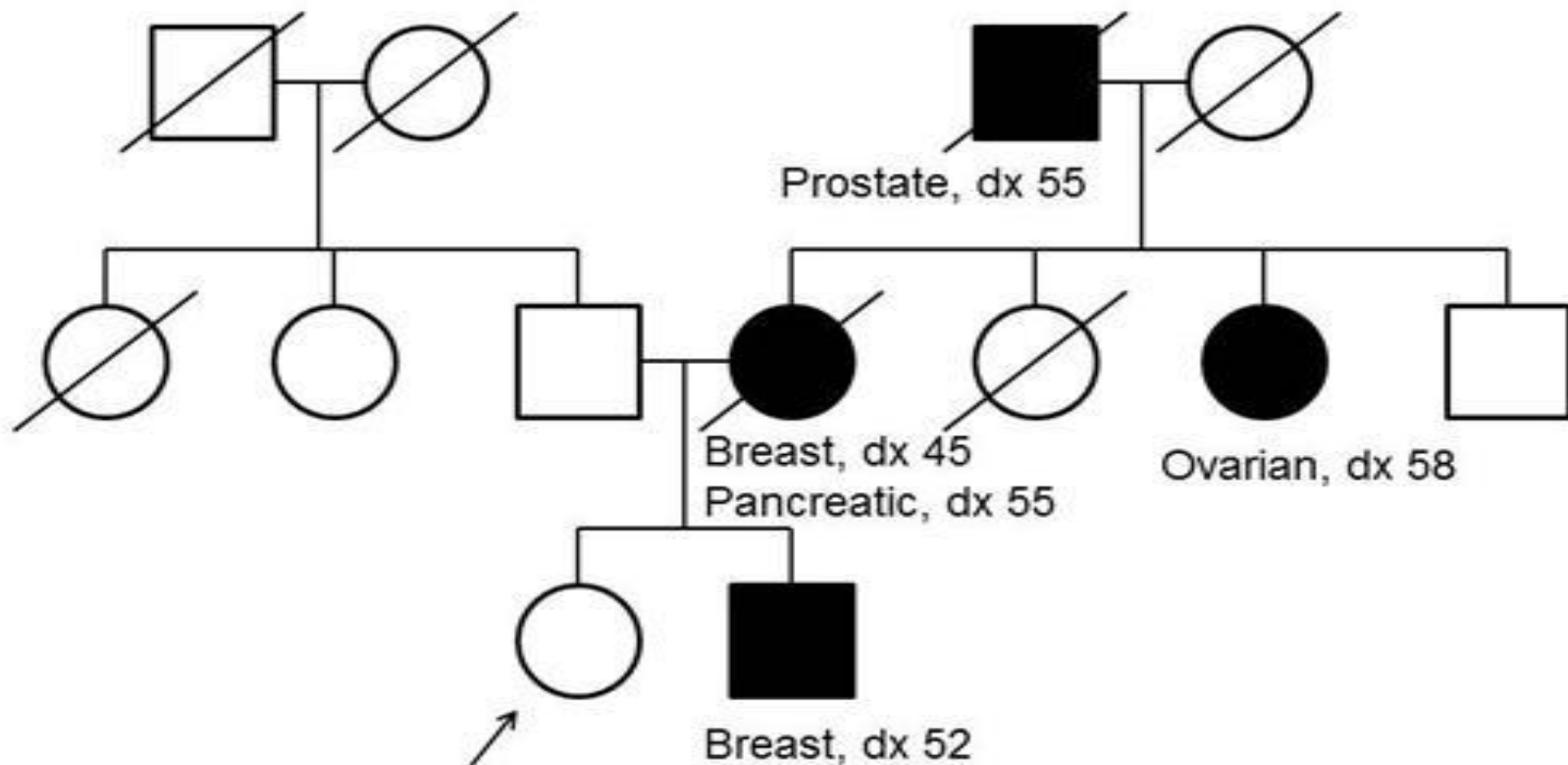
Classic *BRCA1* Pedigree



black=affected person; dx = diagnosed at a given age; diagonal line=deceased individual; arrow = patient in question

<http://www.cancer.gov/cancertopics/pdq/genetics/breast-and-ovarian/HealthProfessional/page1#Section15>

Classic *BRCA2* Pedigree



black=affected person; dx = diagnosed at a given age ; diagonal line=deceased individual; arrow = patient in question

BRCA1 and BRCA2 Inheritance and Cancer



| | | | | |
|--------------------|----------------|------|------|--------------------|
| Parents | $Bb \times Bb$ | | | B = mutated gene |
| Possible Offspring | BB | Bb | bb | b = normal gene |

- It is unclear in the literature whether or not it takes only one mutated (Bb) copy of *BRCA1* and *BRCA2* genes to cause cancer or if it takes two mutated (BB) copies.
- Even though a normal gene is inherited along with a mutated one in one who inherited Bb , 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 scientists think the normal gene in a person who inherited Bb must also become mutated before cancer will develop.

Chances of Developing Breast Cancer by Age 70



People now **have the option of knowing** if they are **more likely** to develop breast cancers.

Source:

See the references section of <http://www.cancer.gov/cancertopics/factsheet/Risk/BRCA>



Testing for *BRCA1* and *BRCA2* Mutations



The *BRCA1* gene was discovered and isolated in 1994.

The *BRCA2* gene was discovered and isolated in 1995.

At that point, the way was paved for testing individuals for mutation of these genes to determine further actions in regards to their health.

Who Should Be Tested?



- Family history would include incidence of breast cancer in:
 - a) in two 1st degree relatives (mother, daughter, sister)
 - b) in three or more 1st or 2nd degree relatives (grandmother or aunt)
 - c) in a 1st degree relative diagnosed at age 50 or younger
 - d) in a 1st degree relative diagnosed with cancer in both breasts
 - e) in a male relative
 - f) in 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:
 - 1) any 1st degree relative has been diagnosed with breast or ovarian cancer
 - 2) if two 2nd degree relatives on the same side of the family are diagnosed with breast or ovarian cancer.

BRCA1 and *BRCA2* Mutations Test Results



- If the test is negative for mutation, the individual may still have a predisposition for breast cancer and may or may not get cancer.
- If the test is positive for mutation, 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.

Test Kits for *BRCA1* and *BRCA2* Mutations



- In the United States, Myriad Genetics, Inc. owned exclusive right to test for the 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 the tests themselves or not to have them done at all.

BRCA1 and *BRCA2* Patents Controversy



- In 2009, 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 against the US Patent and Trademark Office and Myriad Genetics, Inc.
- In 2010, a US district court invalidated 7 of 23 of Myriad's patents on these genes and opened the door to possibly curtailing the rights of an individual or organization to patent a gene.

Supreme Court Results



- In June, 2013, the United States 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.