# Hitting BRCA1/2 Mutant Cells in their Achilles Heel

1. The BRCA2 gene is located on chromosome 13 and contains approximately 27 exons, 1000 bases and 3418 amino acids.
2. In Dec 1995, a group of scientists found that **one missing coding "base"** in the gene sequence increases the risk of cancer (both ovarian and breast).
   - This deletion causes a frameshift, which leads to a stop codon in its place and thus the **truncation** of the protein.

3. Most people have two normal BRCA2 genes, but carriers of mutations have **one normal and one fault gene.**
   - This means that these individuals have an 85% lifetime risk of breast and 30% risk of ovarian cancer.
   - Therefore, cancers develop from cell that **lost the final normal BRCA2 copy.**
   - The mere presence of the mutant allele increases the risk of further mutations of the normal copy.

## What do the normal BRCA1 and 2 proteins do in the cell?




1. THE BRCA2 gene contains 30-40 residue motifs – the so-called BRC repeats – which are encoded in exon 11 and are *conserved* between several mammalian species, thus suggesting that they have an essential function.
2. In fact, the BRC repeats have been shown to **mediate the binding of BRCA2 to RAD51,** which is a mammalian protein that is essential for DNA repair and genetic recombination.
3. Evidence supporting importance of this protein in gene repair:
   - Knockout experiments have shown that a lack of this gene causes chromosomal breaks or chromosomal aberrations, for example, the formation of a tri-radial chromosome.
   - Differential mutational processes often generate different combinations of mutation types, and are termed '**signatures'**.
     - Analysis of 21 breast cancer whole-genome sequences found that breast cancer contains **highly variable chromosomal structural instability.**
     - This means that the BRCA2 genome is unstable, and is possibly due to faulty DNA repair mechanisms.

   - Breast cancers develop through the **acquisition of mutations** over time.
     - An inherited mutant copy increases the risk of developing serial mutations that are needed to develop cancer.