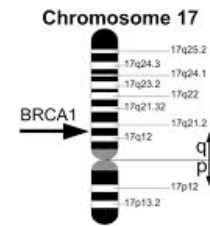


Hands-On Ten The BRCA1 Gene (Part Two)



C) We are going to look for more information about the human breast cancer susceptibility gene, BRCA1.

- Go to the main page of NCBI: <http://www.ncbi.nlm.nih.gov> and click on “Genomes & Maps” at the left-hand side of the page.
- From the new page, click on “Map Viewer” under “Quick Links” at the right-hand side.
- From the “Map Viewer Home” page, choose the “*Homo sapiens*” row and click on “Annotation Release 106” to get to the “NCBI Map Viewer” page. The Map Viewer provides a wide variety of genome mapping and sequencing data.
- In the new page, type in “BRCA1” in the “Search for” window.
- Click on “Find” and carefully examine the new page we obtain: “*Homo sapiens (human)* genome view” and answer the following questions.

13. a) How many hits are reported by “Search results for query BRCA1”? ____
- b) On which chromosome do we find the majority of the hits? ____ .
- c) What chromosome contains the actual BRCA1 locus? ____ .

14. To see the names of some of the genes whose encoded proteins interact with the BRCA1 protein:

- Click on “Advanced Search” button on the top right of the page
- Under “Type of mapped object:”, click clear to uncheck all the options. And check only “Gene”
- Click on “Find” button

How many hits are reported by “Search results for query "BRCA1 AND

gene[obj_type]"? ____ .

We have: “reference” “CHM1” and “HuRef” under “Assembly”. Consider the information reported by “reference” only.

15. Fill in the following table for the 6 genes whose products interact with BRCA1.

Chromosome	Match	Map element	Type

Consider the information under “17 reference”.

- Go to the row that starts with “BRCA1 : protein phosphatase 1, regulatory subunit 53”.
- Click on "[Genes seq](#)" under “Maps”.

Examine the map view. It illustrates a portion of the chromosome with some of its genes. Study the information at the top and bottom of the page and answer the following questions:

16. What is the total number of genes on this chromosome? _____
.

17. What is the locus (chromosome location) of the BRCA1 gene? (e.g., 18p14.25) _____ .

18. What region of the chromosome is illustrated (from nucleotide to nucleotide)? _____ .

19. Write down the names of the other genes that are identified in the illustrated region of the chromosome.

20. Are these genes encoded on the same or on different strands of the chromosome? _____. On what strand is BRCA1? _____.
Hint: See the orientation column (with header “Q”).

21. What is the total length in bp of the entire chromosome?

Hint: You can zoom out completely (left side of the page) or enter “1” in the upper box of “Region Shown” and clear the lower box and leave it empty and then hit “Go”.

Go to the line that has: “[BRCA1](#) [□](#) [OMIM](#) [HGNC](#) [sv](#) [pr](#) [dl](#) [ev](#) [hm](#) [sts](#) [CCDS](#) [SNP](#)” and click on “[BRCA1](#)”. You will now find yourself in “Entrez Gene” which provides a variety of information on BRCA1. Check out the “Updated Date” at the top left-hand corner. What is it? _____ .

By carefully reading “Summary”, we learn that BRCA1 encodes a nuclear phosphoprotein that plays a role in maintaining genomic stability. The following is a list of the normal functional roles of BRCA1:

- It is a tumor suppressor in human breast cancer cells
- BRCA1 may function as a transcriptional regulator
- It plays a role in DNA repair of double-stranded breaks
- It also plays some role in recombination.

22. What alterations may lead to breast cancer?

In higher eukaryotes there are often variations in gene transcripts due to alternative splicing of mRNAs. BRCA1 has a number of such splice variants.

Scroll down to: “NCBI Reference Sequences (RefSeq)”. This section describes the gene-specific NCBI reference sequences (RefSeqs) that have been established for this gene. In addition to enumerating the accessions and providing links to the appropriate Entrez sequence database, this section includes descriptions of each transcript variant, accessions of the public sequences used to support any transcript, and a listing of computed domains in an encoded protein.

23. What is the phenotypic effect on the BRCA1 protein of the following transcript variants? In other words, what is the resulting BRCA1 protein obtained from the following transcript variants?

- i) mRNA Sequence NM_007294.3
- ii) mRNA Sequence NM_007297.3
- iii) mRNA Sequence NM_007298.3

- Scroll up of the “Entrez Gene” page and stop at “Genomic context”.

24. What nucleotide sequence region of the chromosome is shown (from which nucleotide to which nucleotide)?

_____.

25. What does the orientation of the arrow tell us about the strand of DNA the mRNA is derived from?

_____ .

- Scroll down to “Genomic regions, transcripts, and products”.

26. How many transcript variants are illustrated? _____ .

27. Have you already encountered some of these variants?

_____ .

D) We are going to explore the Cancer Genome Anatomy Project (CGAP) which is maintained by the National Cancer Institute.

- Go to the CGAP web site: <http://cgap.nci.nih.gov>

CGAP pulls together a large amount of public data on genes altered in cancer cells. This ranges from gene sequence, mutational analysis, cytogenetic localization, chromosomal aberration, biochemistry, and clinical manifestation for cancers. By making all of this information easily accessible, CGAP helps the researcher analyze new information and relate it to what is already known. Since cancer ultimately is a problem of expression of a mutated gene product(s) and consequent inappropriate expression of other genes to give the cancer phenotype, analysis of gene expression has been one of the major efforts of CGAP.

- Click on the “Cancer Genome Anatomy Project” link in blue, to go to CGAP’s homepage (<http://cgap.nci.nih.gov/cgap.html>).

As we unravel the biochemical function of various genes and gene products, we can place them in functional pathways using all of the information available to us. As mentioned in the CGAP homepage, under “Pathways”, the latter are diagrams of biological pathways and proteins, with links to genetic resources to known proteins.

- Click on “Pathways” to obtain a new page.
- Click on the “BioCarta Pathways on CGAP” to obtain a new page.

BioCarta has an extensive list of biochemical pathway charts.

- Under A, click on “ATM Signaling Pathway” to go to a new page.

Notice the very first line at the top of the map.

28. What are the phases G1, S, G2, and M part of?
_____ .

The ATM pathway is important for delaying cell cycle progression to allow time for repair if there has been damage to DNA. This helps to prevent permanent damage or chromosome breakage and the consequent genomic instability. Maps of this type help the researcher place a particular gene product into a broader context. The BRCA1 gene product is shown just to the left of the center. Its precise role, since mutations in BRCA1 lead to a high risk of breast cancer, is the focus of much research around the world. Clicking on any of the icons in the map takes us to the Gene Info page for that gene.

29. The diagram contains many products that interact with one another. Do you recognize some of the proteins that interact with BRCA1? _____ .
If yes, which ones? _____ .

Notice that the gene products have different shapes.

- Click on “legend” right above the display panel to get an explanation of the various shapes.

30. What is BRCA1 according to the “legend”? _____ .

- Go back to the ATM Signaling Pathway.

31. Explain how one can go to the “ATM Signaling Pathway” of the mouse.

32. Go to the “ATM Signaling Pathway” of the mouse. Is it very different than the human “ATM Signaling Pathway”? _____ .

The Information provided in this hands-on exercise is for instructional purposes only.

More about the BRCA1 Gene

A) Some basic information about the BRCA1 gene

- 1) What is the official name of the BRCA1 gene?
- 2) What is the normal function of the BRCA1 gene?
- 3) What conditions are related to the BRCA1 gene?
- 4) Where is the BRCA1 gene located?
- 5) Where can I find additional information about BRCA1?

6) What other names do people use for the BRCA1 gene or gene products?

7) What glossary definitions help with understanding BRCA1?

Answers to the above questions can be found at the Genetics Home Reference at: <http://ghr.nlm.nih.gov/gene=brca1>

B) What is the role of heredity in susceptibility to cancer?

1) Given that individuals normally inherit a predisposition to cancer, not the cancer itself, how is the predisposition transmitted?

2) If women with BRCA1 and BRCA2 mutants have an increased risk of breast cancer, is the risk associated with a specific protein product of these genes or the lack of a functional product?

3) Are women with BRCA1 and BRCA2 mutations at higher-than-average risk for cancers other than breast cancer?

The article found at <http://www.breastdiseases.com/genebr3.htm> on the characteristics of inherited forms of breast cancer will help in answering the above questions.

C) What is the role of heredity in susceptibility to cancer?

A wealth of information can be found at:

<http://www.cancerindex.org/geneweb/BRCA1.htm>

1) Gene Database Entries for BRCA1

2) Other BRCA1 Related Resources

3) Hereditary Breast and Ovarian Cancer Syndromes

i) BRCA1 Screening

ii) BRCA1 and Genetic Counseling

4) BRCA1 Functions and Carcinogenesis

5) BRCA1 and Breast Cancer

- Prophylactic Treatments for Women with BRAC1 mutations

6) BRCA1 and Ovarian Cancer

- TP53 Mutations in BRCA1/BRCA2 Ovarian Cancers

7) BRCA1 - Somatic mutations

8) BRCA1 Mutations

i) 185delAG Mutations

ii) 5382InsC Mutations

9) BRCA1 and Colon Cancer Risk

10) BRCA1 and Fallopian Tub