BRACA2 Disease Mutation Analysis

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Literature Review

Gemline and Somatic mutations

BRCA2 is a breast cancer gene that helps prevent the development of cancers such as breast and ovarian cancers. It helps maintain the stability and functions of our cells by providing information for making the proteins that repair damaged DNA. This process can get disrupted when there are mutations in the BRCA2 genes which leads to a disruption in the cell repair process. This leads to increased chances of developing breast and ovarian cancers, this mutation can also be inherited. Future research into this topic is crucial for understanding preventative strategies, risk factors, and cures. By analyzing specific populations, we can share insight into risk factors and preventative measures leading to potential treatments and cures for cancer mutations. For effective research, it is crusial to understand the to loss functions invodled in higher cancer risks. In BRACA2 mutations are categoried as deletetion, bustitution and insertion. These can disrupt the functionality of each DNA protein and impact its ability to repear and mitigate cancer risks.
Deletion is the removal of one or more of the building blocks for DNA structure leading to a malfunctioning protein.
Substitution replaces nucleotides with each other causing inconsistencies in the DNA sequence.
Insertion adds additional nucleotides into the sequence, also disrupting the sequence in protein productions.
The impacts of these mutations can have adverse or negative consequences on the BRACA2 genes ability to repair DNA.

Breast and Cancer

Breast cancer originates in the cells containe in the breast that forms lumps also known as tumors. Although it can affect both male and female, it is most common amongst women. Ovarian cancer is a cancer of the ovaries and can spread througouhg the femal reproductive system. Thesse cancers are associated the The BRCA1 and BRCA2 genes. According to the World Health Organization (WHO), there are more than 2.3 million cases of breast cancer and 313,00 new cases of ovarian cancer globally in 2020. Breast is the leading cause og cancer deaths in women world wide, and ovarian cancel has the highest mortality rate considering the limited research and knowledge of this disorder. This study will evaluate the affects of the BRACA1 and BRACA2 genes for both cancers with a primary focus on ovarian cancer.

Define Research Objectives

By investigating the effects of the BRCA2 gene mutation and cell repair process, we can discover patterns and correlations that increase the chances of cancers. Our goal is to understand how BRACA2 helps

develop proteins that are designed to repair DNA damage and stabilize the functions of cells. In addition, we will explore the hereditary components of BRCA2 mutations and the links to cancer development in patients. Our goal is to contribute to understanding the genetic factors that increase breast and ovarian cancer as a result of BRCA2 and create a path for developing preventative, treatable, and curable solutions. Overall, We aim to provide a broader insight into solutions designed for the prevention, diagnosis, and cure of the BRCA 1 and 2 factors.

Common Challenges and gaps in BRCA2 research:

Health disparities and access:
The limited access to testing and informational sites specifically for underserved populations creates a gap in healthcare equity and ensures proper research is conducted to better understand BRCA2. This also creates a gap in preventative measures and access to screening, minimizing the impact of preventative measures and strategies. This has led to an underdevelopment of the consequences of BRCA2 mutations and the different varieties of the mutations. We aim to research to discover the specific impacts of the various mutations based on DNA code trends to understand how the complexities lead to cancer. We are also aiming to explore population studies and how the BRCA mutation contributes to specific geographic groups. why understanding external environmental factors is crucial to the development of comprehensive developmental solutions.

Design

After conducting an extensive review of existing literature, I will identify GAPS in knowledge to establish our research focus;focusing on population-related studies will ched better insight into the diverse fomations of BRCsmutations

Utilize the following tools:

Data collection in Ensemble:

Retrieve genomic information on BRACA2 mutations to analyze the data on genetic variations, and changes that affect its functions

Cancer patient data collections in the GCD Portal:
Access the Genomic Data Commons portal to collect data sets for BRCA2 cancer patients to find the correlations between mutations and cancer using genomic data.
cBioportal

Analysis using cBioPortal:
Explore the effects of BRCA2 mutations on cell functions regarding DNA repair.

Hereditary Explorations:
Conduction inquiry on familiar cancer cases to observe patterns associated with the mutation. Create a guideline based on patterns and associations that could benefit healthcare professionals.

Expected outcomes:
The goal of this research is to contribute to the understanding of preventable and treatable measures for BRCA2-related cancers. Our focus is to provide insight into the factors influencing BRCA-related concerts and help pave the way for more advanced solutions for treatments and cures.

Ethical Considerations

We aim to follow ethical principles and socially responsible methods to analyze and understand our data. We also intend to be cautious in preventing biased observations based on stigmatizations related to cancer patients by using language that is respectful and represents principles relating to all communities. We will prioritize practicing integrity in our research, transparency, and accountability by consistently providing updates and insights to our mentor Dr. Chakrabarty. Incorporating these ethical practices we will hold strong principles ensuring valuable insight and information is delivered..

Genomic Analysis

In a 2009 study done by Stacey A South and her team for the American cancer society; they site 10% of ovarian cancers are inherited. BRCA1 and BRCA2 are 85% responsible for this outcome in both breast and ovarian cancer.

Protein Analysis

In the article written by Sarkisan C.J., "Analysis of murine Brca2 reveals conservation of protein-protein interactions but differences in nuclear localization signals." The others found that the BRACA2 protein in macie were quite similar to the structure of the protein in humans. The Braca2 protein controlled how cells grow and divide by moving through a part of the cell calle nuclear foci, interacting with other proteins like BRACA1 and RAD51. This also discusses the possibility for BRACA2 in mice to connect to BRACA1 in humans; opening up the possibility for additional research for the development of medicines in labs. The BRACA2 gene has quite a complex structure with various components playing crucial roles in the development and growth of cells. The beginning of the protein contains N-terminal; This helps BRCA2 connect with other proteins that help fix damaged DNA. The middle, also known as the central regian, consists of multiple and repeated of the BRC portion of the gene. BRC motives are repeat sequence patterns that are crucial for interacting with other proteins such as RAD51 wich plays a roll in in cell repair damaged DNA. Essentially BRC helps RAD51 operate more efficiently by acting that connectivity stations to enable stability in the repair process.

At the end of the BRACA protein we find the C-terminal, this helps the BRACA2 protein bind to the DNA strands, latching them in place during the repair process.

Before we can move on with our analysys we must discuss the nucleotide bases of DNA building blockers that influence BRACA2

Adenine (A) is a purine base, it has a double rind structure hydrogene bonds that pair with Thymine wich is a pyridimedine base. Adenine helps with DNA repair, energy transfer, and regulating gene expressions. Pyrimidine means it has a singel ring. It plays a critical role in DNA replications, repair and replacement. Thymine bases can also be modified chemically to regulator or transform genetic processes.
Cytonince is also foud in RNA it also has a Pyrimidine base and pairs with Guanine with is also purine. Cytonine stores genetic structure and codes. It can also me modified chemically and helios with gene regulation, imprinting repairing and prevention of mutations.It pairs well with Guanine wich is a stability and fidelity base. It helps stabalise the over all process of cell generation by regulating the expressions, signals and repair. These bases play a critical role in coding DNA by storing genetic information to insure the expressions are regulated and stable.

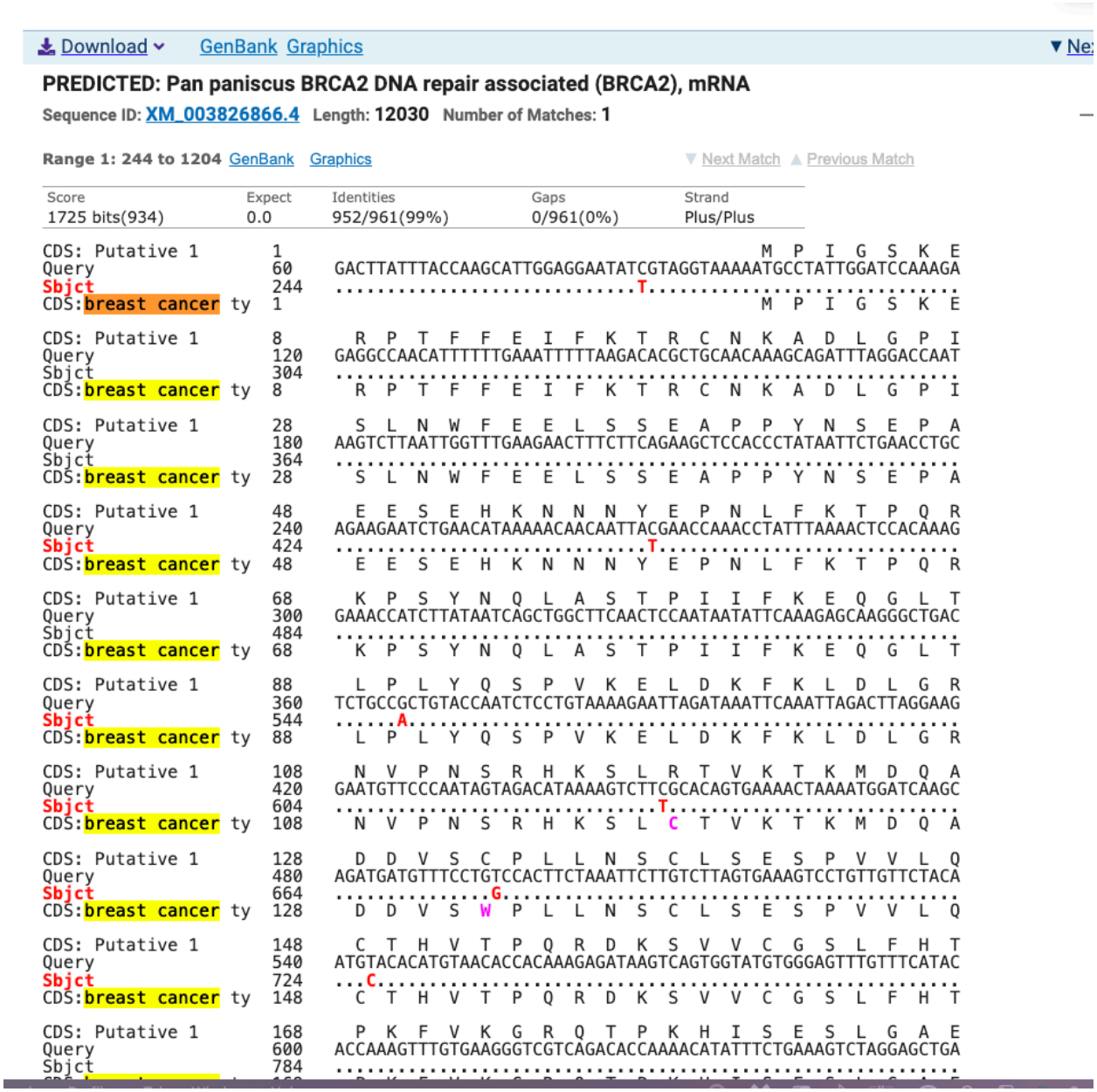
Disease Association Studies: Breat and Ovarian Cancer

Data Interpretation

"CDS: Putative" and "CDS:breast cancer ty"

We did two analyses on nucleotide sequential data to perform basic analysis and a blast to find alignments in our data:

The first sequence from humans pieces with breast cancer 2 had a length of 2,005,787 with a 31.68 percent guanine and cytosine count and 57.69 Adenine and thymine count. Suggesting thatThis can have an impact on the process and stability of BRACA2, which can affect things like replication and repair. It also has a higher impact on gene regulation and mutation risks. proteins high in AT are mor eprone to transitions and framshift tyoe of muttations which can help researchers find hotspots in the developement of breast and ovarian cancers.


Download GenBank Graphics

PREDICTED: Pan paniscus BRCA2 DNA repair associated (BRCA2), mRNA

Sequence ID: XM_003826866.4 Length: 12030 Number of Matches: 1

Range 1: 244 to 1204 GenBank Graphics Next Match Previous Match

Score	Expect	Identities	Gaps	Strand
1725 bits(934)	0.0	952/961(99%)	0/961(0%)	Plus/Plus

```
CDS: Putative 1       1                                                 M  P  I  G  S  K  E
Query                 60    GACTTATTTACCAAGCATTGGAGGAATATCGTAGGTAAAAATGCCTATTGGATCCAAAGA
Sbjct                 244   ............................T................................
CDS:breast cancer ty  1                                                 M  P  I  G  S  K  E

CDS: Putative 1       8       R  P  T  F  F  E  I  F  K  T  R  C  N  K  A  D  L  G  P  I
Query                 120   GAGGCCAACATTTTTTGAAATTTTTAAGACACGCTGCAACAAAGCAGATTTAGGACCAAT
Sbjct                 304   ............................................................
CDS:breast cancer ty  8       R  P  T  F  F  E  I  F  K  T  R  C  N  K  A  D  L  G  P  I

CDS: Putative 1       28      S  L  N  W  F  E  E  L  S  S  E  A  P  P  Y  N  S  E  P  A
Query                 180   AAGTCTTAATTGGTTTGAAGAACTTTCTTCAGAAGCTCCACCCTATAATTCTGAACCTGC
Sbjct                 364   ............................................................
CDS:breast cancer ty  28      S  L  N  W  F  E  E  L  S  S  E  A  P  P  Y  N  S  E  P  A

CDS: Putative 1       48      E  E  S  E  H  K  N  N  N  Y  E  P  N  L  F  K  T  P  Q  R
Query                 240   AGAAGAATCTGAACATAAAAACAACAATTACGAACCAAACCTATTTAAAACTCCACAAAG
Sbjct                 424   ............................T................................
CDS:breast cancer ty  48      E  E  S  E  H  K  N  N  N  Y  E  P  N  L  F  K  T  P  Q  R

CDS: Putative 1       68      K  P  S  Y  N  Q  L  A  S  T  P  I  I  F  K  E  Q  G  L  T
Query                 300   GAAACCATCTTATAATCAGCTGGCTTCAACTCCAATAATATTCAAAGAGCAAGGGCTGAC
Sbjct                 484   ............................................................
CDS:breast cancer ty  68      K  P  S  Y  N  Q  L  A  S  T  P  I  I  F  K  E  Q  G  L  T

CDS: Putative 1       88      L  P  L  Y  Q  S  P  V  K  E  L  D  K  F  K  L  D  L  G  R
Query                 360   TCTGCCGCTGTACCAATCTCCTGTAAAAGAATTAGATAAATTCAAATTAGACTTAGGAAG
Sbjct                 544   ......A.....................................................
CDS:breast cancer ty  88      L  P  L  Y  Q  S  P  V  K  E  L  D  K  F  K  L  D  L  G  R

CDS: Putative 1       108     N  V  P  N  S  R  H  K  S  L  R  T  V  K  T  K  M  D  Q  A
Query                 420   GAATGTTCCCAATAGTAGACATAAAAGTCTTCGCACAGTGAAAACTAAAATGGATCAAGC
Sbjct                 604   ............................T................................
CDS:breast cancer ty  108     N  V  P  N  S  R  H  K  S  L  C  T  V  K  T  K  M  D  Q  A

CDS: Putative 1       128     D  D  V  S  C  P  L  L  N  S  C  L  S  E  S  P  V  V  L  Q
Query                 480   AGATGATGTTTCCTGTCCACTTCTAAATTCTTGTCTTAGTGAAAGTCCTGTTGTTCTACA
Sbjct                 664   ..............G.............................................
CDS:breast cancer ty  128     D  D  V  S  W  P  L  L  N  S  C  L  S  E  S  P  V  V  L  Q

CDS: Putative 1       148     C  T  H  V  T  P  Q  R  D  K  S  V  V  C  G  S  L  F  H  T
Query                 540   ATGTACACATGTAACACCACAAAGAGATAAGTCAGTGGTATGTGGGAGTTTGTTTCATAC
Sbjct                 724   ...C........................................................
CDS:breast cancer ty  148     C  T  H  V  T  P  Q  R  D  K  S  V  V  C  G  S  L  F  H  T

CDS: Putative 1       168     P  K  F  V  K  G  R  Q  T  P  K  H  I  S  E  S  L  G  A  E
Query                 600   ACCAAAGTTTGTGAAGGGTCGTCAGACACCAAAACATATTTCTGAAAGTCTAGGAGCTGA
Sbjct                 784   ............................................................
```

This particular alignment shows similarieis in the sequences after conducting a blast. Wich is indicated by the dots showing the conserved regions. The letters will represent the substitutions or mutations. There are nto many gaps in the alignment however mutations are present in position 228 where we see a substitution for asparagine in the putative sequence which has been swapped with cysteine in the breast cancer sequence. This is essentially swapping a polar amino acid with a sulfur amino acid from a different group; affecting the protein structure and how it functions as a result of the different chemicals.

The following additional mutations were observed:

Positions 248: This swaps Alanine with serine. Serine contains hydroxyl which also makes it polar; this swap will impact the stability and responsiveness of the protein since Alanine is best functioning as a nonpolar base.

Position 268:
Substitution of Lysine for Threonine. Lysine is a positively charged protein while threonine is uncharged; altering the makeup of the amino acid. This could affect the protein in how it interacts with other proteins and its overall stability.

Position 488:
Valine is substituted for Glycine. This substitution affects the flexibility of the protein because Glycine traditionally has a bulky chain attached to its side. This will affect the protein's formation and overall stability.

Position 628:
Substitution of Glutamic Acid with Aspartic Acid. These are both acidic and negatively charged acids but this change can affect the distribution of the proteins in terms of length and structure formation.

Conclusion

The variances [resent in CDS: Putative" and "CDS:breast cancer ty" sequences show how mutations have a significant impact on the function and structure of the protein, By experimenting in this area we can find how the effects of these mutations dictate specific behaviors that lead to breast and ovarian cancer. Further research can identify if there are patterns in substitution and shed light on the randomized differences or probable causes leading to such instabilities in the protein.

Narrowing down To two proteins at position 248 and 268

This sectionsr focuses on elucidating the effects of mutations at positions 248 and 268 within the BRCA2 gene on protein structure and function, particularly in the context of breast and ovarian cancer development. By scrutinizing these specific loci, we aim to deepen our understanding of the molecular

mechanisms underlying BRCA2-related cancers, paving the way for targeted therapeutic interventions and personalized treatment strategies.

The BRCA2 gene is renowned for its crucial role in DNA repair mechanisms and cellular stability. Mutations within this gene significantly elevate the risk of breast and ovarian cancers. Our focus lies specifically on mutations occurring at positions 248 and 268 within the BRCA2 gene. These mutations entail amino acid substitutions, potentially leading to alterations in protein structure and function. Understanding the implications of mutations at these specific loci is paramount for elucidating the molecular underpinnings of BRCA2-related cancers.

Our research objectives center on investigating the specific impact of mutations at positions 248 and 268 on BRCA2 protein functionality and their correlation with breast and ovarian cancer development. By elucidating the molecular consequences of these mutations, we aim to identify targeted therapeutic interventions and advance personalized medicine approaches for BRCA2-related cancers. Furthermore, we seek to uncover potential biomarkers associated with these mutations to facilitate early detection and intervention strategies.

To achieve our research objectives, we will employ a multi-faceted approach. Utilizing advanced tools such as Ensemble for data collection, we will gather genomic information on mutations at positions 248 and 268 within the BRCA2 gene. Subsequently, utilizing cBioPortal for analysis, we will scrutinize the genetic variations at these loci and assess their functional implications. Additionally, we will conduct a comprehensive protein analysis to evaluate the structural and functional ramifications of amino acid substitutions at positions 248 and 268.

Results:

Preliminary analysis reveals intriguing insights into the molecular consequences of mutations at positions 248 and 268 within the BRCA2 gene. These mutations significantly alter the polarity and charge distribution of the BRCA2 protein, potentially affecting its interactions with other cellular components and overall stability. Moreover, we observe differential effects on protein functionality, suggesting diverse impacts on cancer predisposition.

The elucidation of the molecular mechanisms underlying mutations at positions 248 and 268 within the BRCA2 gene sheds light on the intricate interplay between protein structure and function in cancer predisposition. By unraveling these mechanisms, we can identify targeted therapeutic interventions tailored to individuals harboring these specific mutations. Furthermore, the identification of potential biomarkers associated with these mutations holds promise for facilitating early detection and intervention strategies, thereby improving clinical outcomes for individuals at risk of BRCA2-related cancers.

In conclusion, mutations at positions 248 and 268 within the BRCA2 gene represent critical determinants of breast and ovarian cancer predisposition. By elucidating the molecular consequences of these mutations, we can pave the way for targeted therapeutic interventions and personalized treatment strategies, ultimately improving outcomes for individuals at risk of BRCA2-related cancers. This comprehensive understanding of the molecular underpinnings of BRCA2-related cancers opens avenues for precision medicine approaches, bringing us closer to effective prevention, diagnosis, and treatment strategies tailored to individual patients.

Resources

South, Stacey A et al. “Consideration of hereditary nonpolyposis colorectal cancer in BRCA mutation-negative familial ovarian cancers.” *Cancer* vol. 115,2 (2009): 324-33. doi:10.1002/cncr.24012

nt J Mol Sci. 2021 Feb; 22(3): 1266.

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PMID: 33525353

Sarkisian, C J et al. “Analysis of murine Brca2 reveals conservation of protein-protein interactions but differences in nuclear localization signals.” *The Journal of biological chemistry* vol. 276,40 (2001): 37640-8. doi:10.1074/jbc.M106281200