The Evolution, Functions, and Applications of the Breast Cancer Genes BRCA1 and BRCA2

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Abstract

BRCA1 and BRCA2 are both tumor suppressors whose mutations are the cause of most hereditary breast cancers. Both genes are highly involved in ensuring genome stability. BRCA1 homologs are found in the plant and animal kingdoms while BRCA2 homologs are additionally found in the fungi kingdom. The initial origin of both genes remains unknown, however it is expected that the common ancestors originated around 1.6 billion years ago prior to the kingdoms diverging. There has been a great amount of divergence between homologs that is not observed in other tumor suppressors with only functionally important domains conserved. This divergence continues today with evidence of primate BRCA1/2 evolution. Cancer-associated mutations have been found to occur at conserved sites, indicating that conserved sites are important for function. In this study, we present a review on the phylogenesis of BRCA1 and BRCA2.

Function

• BRCA1 is involved in homologous recombination and cell cycle checkpoints
• BRCA2 is involved in DNA repair through homologous recombination

Phylogenesis

BRCA1
• 2.8% fixed overall
• 8.6% conserved
• Exon 11
  • 7.95% fixed
  • 22.4% conserved
• Mouse to human BRCA1: 56% identity
• RAD51: 99%; MSH2: 92%; XPA: 86%

BRCA2
• Chicken to human BRCA2
  • Overall: 37% identity
  • Exons 2, 4, 7, 16-20: 70% identity

Role in Cancer

Most mutations that cause cancer are in the domains
• Mutations that occur at conserved sites are the most likely to cause cancer
• It remains unknown why breast cancer remains the most prevalent cancer type with BRCA1/2 mutations

Continued Evolution

• There is evidence that both BRCA1 and BRCA2 are still evolving in primates

BRCA1
• 22 nonsynonymous mutations since divergence from chimpanzees and bonobos
• 2 SNPs in chimpanzees not in Hardy-Weinberg equilibrium
• Positive selection observed
• Selection force in only found in primates

BRCA2
• 3 sites in exon 11 that are under positive selection

Hypothesis

• Viral infections are driving rapid evolution
• Viruses must impede the DNA damage response
• Mutations cause the gene to be less susceptible to the virus

Domain Structure

BRCA1
• RING: Interacts with BARD1 and has E3 ligase activity
• P300/CBP: Transcriptional regulatory activity
• Coiled-coil: Binding site during homologous recombination
• BRCT: Binds to Abraxas, BRIP1, or CIP

BRCA2
• N-terminus: Binds to PALB2
• BRC: Binds to RAD51
• DDB: Binds DNA
• C-terminus: Binds to RAD51

Figure 1. The three complexes that BRCA1 forms. Complex A is involved in homologous recombination, complex B occurs in G2/M cell-cycle checkpoint, and complex C plays a role in G2/M cell-cycle checkpoint. BRCA2 is involved in complex A. Image from Trapp et al. 2001.

Figure 2. Phylogenetic tree of exon 11 of BRCA1. Image from Fleming et al. 2003.

Figure 3. Domains and binding sites of BRCA1 and BRCA2. Image from Roy et al. 2016.

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References