BRCA2 card

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BRCA1 and BRCA2 Hereditary Breast/Ovarian Cancer

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Last revision: 5 December 2005

Disease characteristics. Mutations in both BRCA1 and BRCA2 are characterized by predisposition to breast cancer and ovarian cancer as well as prostate cancer (BRCA1) and other cancers (BRCA2). The risk of developing cancer that is associated with BRCA1 and BRCA2 cancer-predisposing mutations is not known and appears to be variable even within families of similar ethnic background with the same mutation. Estimates of breast cancer and ovarian cancer risks have been derived from families with multiple affected individuals as well as from families with few affected individuals and from population-based studies. Prognosis for breast cancer survival depends upon the stage at which breast cancer is diagnosed and may not be different between individuals with BRCA1 or BRCA2 cancer-predisposing mutations and controls.

Normal allelic variants: The BRCA2 gene encodes a 10.4-kb transcript composed of 27 exons.
There are eight repeats (34 aa) in BRCA2 designated as BRC1 to BRC8. BRC1, BRC2, BRC3, BRC4, BRC7, and BRC8 are highly conserved and bind to Rad51, whereas BRC5 and BRC6 are less well conserved and do not bind to Rad51 PUBMED:10551859.

Pathologic allelic variants: As with BRCA1, hundreds of BRCA2 mutations have been identified, although the number is somewhat lower than for BRCA1 (~450 vs >600). However, BRCA2 was cloned later than BRCA1 and is more difficult to screen. It is likely that the range of mutations in BRCA2 will be found to be comparable to that in BRCA1.

Mutations of unknown clinical significance: About a third of mutations identified in BRCA1 and BRCA2 sequencing studies are of uncertain clinical significance [Shattuck-Eidens et al 1997]. As research proceeds, some of these mutations will likely be proven to be normal variants without clinical significance, while others may be associated with an increased cancer risk.

Normal gene product: BRCA2 codes for a protein of 3,418 amino acids, making a 380-kd protein. The breast cancer type 2 susceptibility protein is normally located in the nucleus and contains phosphorylated residues [Bertwistle et al 1997]. The breast

cancer type 2 susceptibility protein has no apparent relation to the breast cancer type 1 susceptibility protein. Nonetheless, the breast cancer type 1 susceptibility protein and the breast cancer type 2 susceptibility protein appear to share a number of functional similarities that may suggest why mutations in these genes lead to a specific hereditary predisposition to breast and ovarian cancer. Like BRCA1, **BRCA2 is expressed in most tissues and cell types analyzed**, indicating that gene expression does not account for the tissue-restricted phenotype of breast and ovarian cancer. BRCA2 transcription is induced late in the G1 phase of the cell cycle and remains elevated during the S phase, indicating **some role in DNA synthesis** [Rajan et al 1996, Vaughn et al 1996]. **BRCA2 appears to be involved in the DNA repair process**. The breast cancer type 2 susceptibility protein **interacts with the RAD51 protein**, a key component in homologous recombination and double-strand break repair [Sharan et al 1997 , Wong et al 1997]. Perhaps through this mutual association with RAD51, BRCA1 and BRCA2 associate with each other at sites of DNA synthesis after the induction of DNA damage [Chen J et al 1998]. In order to study the function of BRCA2, homozygous knockout mice have been created. In most cases, the **complete loss of function of BRCA2 results in embryonic lethality** characterized by a lack of cell proliferation [Ludwig et al 1997 , Sharan et al 1997 , Suzuki et al 1997]. Cells derived from mouse embryos lacking BRCA2 are defective in their repair of DNA damage, [Connor et al 1997 , Chen PL et al 1998] and are hypersensitive to radiation and radiomimetics [Abbott et al 1998 , Biggs & Bradley 1998 , Chen PL et al 1998 , Morimatsu et al 1998] which may have implications for both mammographic screening and treatment modalities. Finally, BRCA2 knockout mice can be partially rescued by crossing with a p53 knockout strain suggesting that these genes interact with the p53-mediated DNA damage checkpoint [Brugarolas & Jacks 1997]. Therefore, **the available evidence indicates that BRCA2 is a "caretaker," like p53, which serves to maintain genomic integrity** [Zhang et al 1998]. When this function is lost, it probably allows for the accumulation of other genetic defects that are themselves directly responsible for cancer formation. Additional studies have attempted to attribute specific biochemical functions to the BRCA2 gene product. The breast cancer type 2 susceptibility protein contains regions that are capable of inducing transcription [Milner et al 1997] and has histone acetyltransferase activity potentially supporting its role in DNA repair and/or RNA transcription [Siddique et al 1998]. It is likely that the breast cancer type 2 susceptibility protein will eventually be implicated in a variety of cellular processes, only some of which will be related to their role in the etiology of breast and ovarian cancer.

Abnormal gene product: Most BRCA2 mutations reported to date consist of frameshift deletions, insertions, or nonsense mutations leading to **premature truncation** of protein transcription, consistent with the **loss of function** that is expected with clinically significant mutations in tumor suppressor genes.

BRCA2 cancer-predisposing mutations. The prevalence of cancer-predisposing BRCA2 mutations in the general population is unknown. From the prevalence of cancer-prone families, BRCA1 and BRCA2 cancer-predisposing mutations have been estimated to occur in approximately **one to two persons per thousand**. The following describes specific BRCA2 cancer-predisposing mutations in two ethnic groups:

Icelanders. The BRCA2 cancer-predisposing mutation 999del5 occurs in 0.6% of the Icelandic population and in 7.7% of women and 40% of men with breast cancer from Iceland [Thorlacius et al 1996 , Thorlacius et al 1997]. The mutation was seen in 17% of women diagnosed with breast cancer by age 50 years and in 4% of women diagnosed at later ages. Among individuals with the 999del5 mutation, 17 of 44 (39%) had no first or second degree relatives with cancer, suggesting incomplete penetrance of the mutation [Thorlacius et al 1996].

Ashkenazi Jews. **The BRCA2 mutation 6174delT occurs with a frequency of about 1% in individuals of Ashkenazi Jewish descent** [Struewing et al 1995 , Oddoux et al 1996 , Roa et al 1996 , Struewing et al 1997]. This mutation was initially observed in high-risk families. In persons of Ashkenazi Jewish heritage, three founder mutations are observed: 187delAG (BRCA1), 5385insC (BRCA1), and 6174delT (BRCA2). As many as one in 40 Ashkenazim has one of these three founder mutations [Struewing et al 1997].
They concluded that over 2% of Ashkenazi Jews carried mutations in BRCA1 or BRCA2 that conferred increased risks of breast, ovarian, and prostate cancer.