BRCA2 (breast cancer 2, early onset)

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Identity

Other names: BRCC2, BROVCA2, FACD, FAD, FAD1, FANCB, FANCD, FANCD1, GLM3
HGNC (Hugo): BRCA2
Location: 13q13.1

DNA/RNA

Description

The BRCA2 gene is composed of 27 exons and spans approximately 84.2 kb of genomic DNA.

Transcription

The BRCA2 gene encodes a 11386 bp mRNA transcript. Transcription site is located 227 bp upstream the first ATG of the BRCA2 ORF. The translation start site is located in exon 2.

Pseudogene

No pseudogene reported.

Protein

Description

Human BRCA2 protein is composed of 3418 amino acids (384 kDa).

The N-terminal part of the BRCA2 protein contains a transcriptional activation domain (aa 18-105).
BRCA2 exon 11 encodes eight conserved motifs termed BRC repeats. Each of these repeats is composed of about 30 residues.
A DNA-binding domain has been located in the C-terminal region of the BRCA2 protein (aa 2478-3185). It is composed of a conserved helical domain and three OB folds.
Two nuclear localization signals (NLS) have been identified in the C-terminal region of BRCA2.

Expression

BRCA2 expression is proportional to the rate of cell proliferation. Non-dividing cells do not express BRCA2 while wide expression of BRCA2 was observed in actively dividing tissues, including the epithelium of the breast during puberty and pregnancy.
The BRCA2 expression is regulated during the cell cycle, with highest expression during the S phase of the cell cycle.
Most of the BRCA2 proteins are associated to DSS1. The presence of DSS1 was demonstrated to stabilize the BRCA2 protein.

Localisation

BRCA2 is a nuclear protein.

Structure of BRCA2. BRCA2 is a 3418 aa protein. BRC repeats: BRCA C-terminal repeats; NLS: Nuclear localization signals.
**Function**

BRCA2 has been implicated in maintenance of genomic integrity and in the cellular response to DNA damage. The BRCA2 protein interacts with the RAD51 recombinase to regulate homologous recombination (HR). BRCA2 regulates the intracellular localization of RAD51. It also targets the RAD51 to ssDNA and inhibits dsDNA binding, thus regulating/enhancing DNA strand exchange activity of RAD51. CHEK1 and CHEK2 both phosphorylate the RAD51/BRCA2 complex and regulate the functional association of this complex in response to DNA damage.

BRCA2 is also implicated in cell cycle checkpoints. Following exposure to X-rays or UV light, cells expressing truncated BRCA2 protein exhibit arrest in the G1 and G2/M phases. BRCA2 protein plays a role in mitotic spindle assembly checkpoints through modulation of the level of spindle assembly checkpoint proteins including Aurora A and Aurora B.

A role in regulation of transcription has been attributed to BRCA2. BRCA2 binding to the DSS1 protein appears to be required for proper completion of cell division in yeast.

The BRCA2 protein demonstrated the ability to stimulate transcription. For example, exogenous expression of BRCA2 can stimulate transcription of androgen receptor-regulated genes. This function of BRCA2 is regulated by the binding of the EMSY protein to the region of BRCA2 responsible for transcriptional activation. An excess of EMSY results in silencing of BRCA2-driven transcriptional activation.

BRCA2 localizes to meiotic chromosomes during early meiotic prophase I when homologous chromosomes undergo synopsis. Moreover, BRCA2 interacts with the meiosis-specific recombinase DMC1, thus implicating BRCA2 in meiotic recombination.

**Homology**

BRCA2 homologs have been found in a diverse range of organisms. In addition to zebrafish and C. elegans, homologs exist in diverse eukaryotes, from plants to parasitic organisms.

Low general conservation is found in BRCA2. Higher level of homology is observed for several segments, including transactivation domain, BRCA2 repeats and nuclear localization signals located within C-terminal region.

**Mutations**

**Germinal**

High risk of breast and ovarian cancer is associated with germline BRCA2 mutations. Cumulative risk of breast cancer in BRCA2 mutation carriers was estimated to 45% by the age of 70 years while ovarian cancer risk in carriers was estimated to 11%. Increased risk of several other cancers are associated with BRCA2 mutations, especially for prostate and pancreatic cancer.

**Somatic**

Somatic mutations in BRCA2 are infrequent in sporadic breast cancer. Methylation of the BRCA2 promoter has not been detected in normal tissues nor in breast and ovarian cancers. Loss of heterozygosity at the BRCA2 locus has been frequently found in sporadic breast and ovarian tumors.

**Implicated in**

**Breast cancer**

**Note**

Informations regarding breast cancer and BRCA2 mutations and polymorphisms are available in a central repository formed by the National Human Genome Research; National Institute of Health. This repository, named Breast Cancer Information Core (BIC) - NHGRI, is available at the following address: http://research.nhgri.nih.gov/bic/.

**Disease**

Breast tumors in BRCA2 carriers are found at higher histologic grade (2 and 3) than sporadic tumors. Tumors from BRCA2 carriers are more commonly found to be stage IV than sporadic control tumors and BRCA2-associated breast cancer cases are more often node-positive than control breast cancer cases.

**Prognosis**

BRCA2 mutation carriers show younger mean age at diagnosis than sporadic breast cancer cases. Bilateral breast cancer is found more commonly in BRCA2-associated breast cancer than in sporadic breast cancer. ER and PR expression in BRCA2 tumors are similar than in control tumors, which contrasts with ER and PR expression found in BRCA1 tumors.

**Oncogenesis**

It was suggested that genomic rearrangements account for 7.7% of the BRCA2 mutation spectrum. Loss of the wild-type allele is not required for breast tumorigenesis in BRCA2 mutation carriers.

Somatic mutations of the BRCA2 gene are an infrequent event in sporadic breast cancer tumors. Loss of heterozygosity at the BRCA2 locus on chromosome 13q12-q13 was observed in approximately 30% of sporadic breast cancer. Methylation of the CpG dinucleotide within the BRCA2 promoter is not found in normal and neoplastic breast tissues.

**Male breast cancer**

**Note**

A cumulative risk of 6% and 7% of developing breast cancer by the age of 70 and 80, respectively, has been estimated for male BRCA2 mutation carriers. BRCA2 mutations have been found in 14% of familial male breast cancer and 4% of unselected male breast cancer cases.
**Disease**

Male breast cancers are mostly ductal or unclassified carcinomas. Papillary, mucinous and lobular carcinomas each represent less than 3% of male breast cancers. Estrogen receptor and progesterone receptor expression is found in approximately 90% and 81% of male breast cancers, respectively.

**Prognosis**

Overall survival rates for male breast cancers are lower than for female breast cancers due to the older age and more advanced disease at the time of diagnosis. Male breast cancers associated with BRCA2 mutation are diagnosed at younger age than sporadic male breast cancer cases.

**Ovarian cancer**

**Note**

Carriers of mutations in the central portion of BRCA2, termed OCCR (ovarian cancer cluster region; aa 1012-2210), are at higher risk of ovarian cancer and lower breast cancer risk than carriers of mutations outside the OCCR.

**Disease**

Ovarian cancer is mostly epithelial tumors (90%) and lifetime risk of ovarian cancer in the general population is estimated to be 1-1.5%. Risk of ovarian cancer in BRCA2 mutation carriers is estimated to be 10%.

**Prognosis**

BRCA2 ovarian tumors are similar to BRCA1 ovarian tumors as these two types of tumors are more likely to be serous adenocarcinomas and higher grade than control tumors. BRCA2-associated ovarian cancers occur later in life than BRCA1-related or control ovarian tumors.

**Oncogenesis**

Complete loss of the wild-type BRCA2-allele is observed in BRCA2-associated ovarian cancers. Loss of heterozygosity at 13q12-q14 is also observed in sporadic epithelial ovarian cancers. On the other hand, CpG dinucleotide methylation of the BRCA2 promoter is not found in sporadic ovarian cancers.

**Prostate cancer**

**Note**

Different studies conducted on BRCA2 mutation carriers revealed an increased risk of prostate cancer in BRCA2 mutation carriers. Relative risk associated with BRCA2 mutations is estimated to be approximately 2.5 to 5.

Protein-truncating BRCA2 mutations are associated with early-onset prostate cancer. Different studies revealed that BRCA2 mutations are responsible for less than 1% of early-onset prostate cancer in the US Caucasian population while such mutations are responsible for 2.3% of early-onset prostate cancer diagnosed in United Kingdom.

Most studies conducted on hereditary prostate cancer families did not revealed a contribution of BRCA2 truncating mutations in these families. However, a small study conducted on a limited number of families found BRCA2 mutations in two families. Incomplete segregation of the mutation with the disease was found in these families as affected brothers did not carry these mutations.

**Prognosis**

BRCA2 mutation carriers have a significantly lower mean age at diagnosis of prostate cancer and shorter mean survival time than non-carriers. BRCA2 mutation carriers show more advanced tumor stage and higher grade at diagnosis. Prostate cancer carriers of a BRCA2 mutation show poorer survival than BRCA1 carriers. Prostate cancer patients which are carriers of the 999del5 Icelandic founder mutation appear to have worse prognosis than non-carriers of this mutation. Histopathological features of prostate cancer in BRCA2 mutation carriers revealed that prostate cancer developed in mutation carriers show higher Gleason scores than non-carriers.

**Stomach cancer**

**Note**

Stomach cancer was reported in family members of women with ovarian cancer carrying a BRCA2 mutation within the OCCR. On the other hand, the presence of stomach cancer in relatives of ovarian cancer cases is strongly predictive of the presence of a BRCA2 mutation. Specifically, the BRCA2 999del5 mutation is associated with an increased risk of stomach cancer in first- and second-degree relatives. Assessment of the presence of non-breast or ovarian cancers in BRCA2 mutation carriers estimated a relative risk of stomach cancer of 2.59 to be associated with BRCA2 mutations. Meta-analysis of published studies latter confirmed increased risk of stomach cancer in BRCA2 carriers.

**Pharyngeal cancer**

**Note**

An increased risk of buccal cavity and pharynx cancer was suggested during the assessment of cancers other than breast and ovarian cancer in BRCA2 mutation carriers. This was thereafter confirmed in a cohort of BRCA2 mutation carriers leading to the estimation of a relative risk of 7.3 (95% CI = 2.0 - 18.6). Higher relative risk of pharyngeal cancer is found for carriers younger than 65 years old.

**Gallbladder and bile duct cancer**

**Note**

Evaluation of risks of cancers other than breast and
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ovarian cancers in BRCA2 carriers found a higher risk of gallbladder and bile duct cancer in BRCA2 carriers (RR = 4.97; 95% CI = 1.50-16.52). Specifically, the 6167delT Jewish Ashkenazi founder BRCA2 mutation was observed at significantly higher rate in bile duct cancer cases than in population controls.

**Colon cancer**

**Note**

It was reported that risk of colorectal cancer in first-degree relatives of BRCA2 mutation carriers affected with ovarian cancer is increased by threefold for BRCA2 mutations located within the OCCR. Analysis of a BRCA2 mutation in different families led to the suggestion that BRCA2 mutations predispose to colon cancer. It was thereafter reported that BRCA2 mutation carriers are at increased risk of colon cancer before the age of 65 years old. The association of BRCA2 mutations with colon cancer was latter confirmed in a meta-analysis.

**Pancreas cancer**

**Note**

Different studies suggested that BRCA2 mutations are associated with less than 1% of sporadic pancreatic cancer in Caucasians while such mutations could account for 10% of sporadic pancreatic cancer in Ashkenazi Jewish population. Approximately 10% of patients developing pancreatic cancer show patterns of hereditary predisposition. Screening of BRCA2 mutations in familial pancreatic cancer cases suggested that BRCA2 mutations account for 6-17% of these families. Following the identification of germline BRCA2 mutations in pancreatic cancer, it was evaluated that BRCA2 mutations confer roughly a 3.5-folds increased risk. Relative risk of pancreatic cancer was found to be higher at younger age (younger than 65 years old). Different studies evaluated the lifetime risk of pancreatic cancer in BRCA2 mutation carriers to be approximately 5%.

**Prognosis**

Among human malignancies, pancreatic cancer has one of the worst prognoses.

**Oncogenesis**

Pancreatic intraepithelial neoplasia (PanIN) analysis in BRCA2 mutation carriers revealed that loss of the wild type BRCA2 allele is found solely in high-grade PanIN, thus suggesting that biallelic inactivation of the BRCA2 gene is a late event in pancreatic tumorigenesis in patients with germline BRCA2 mutation.

**Malignant melanoma**

**Note**

BRCA2 mutation carriers were estimated to be at higher risk of developing malignant melanoma (RR = 2.58; 95% CI = 1.28-5.17). Despite many studies reported malignant melanoma in mutation carriers or in their relatives, other studies did not confirm this association.

**Bone cancer**

**Note**

An excess risk of bone cancer (RR = 14.4; 95% CI = 2.9 - 42.1) was observed in a cohort of BRCA2 mutation carriers from the Netherlands.

**Fanconi anemia (complementation group D1)**

**Note**

Biallelic mutations of the BRCA2 gene are responsible for Fanconi anemia subgroup D1 (FA-D1).

**Disease**

Fanconi anemia (FA) is a rare recessive disease characterized by various clinical features. Many developmental defects are found in FA patients. Radial aplasia, microcephaly, microphthalmia, small stature, skin hyperpigmentation and malformation of the kidneys are encountered in FA patients. Very high frequency of bone marrow failure, leukemia and squamous cell carcinoma of the head and neck as well as gynecological squamous cell carcinoma are associated with FA. Bone marrow failure generally leads to aplastic anemia during the first decade of life. Esophageal carcinoma and liver, brain, skin and renal tumors are also found in FA patients.

**Prognosis**

The FA-D1 and FA-N subgroups are clinically different from other FA subgroups as these subgroups are associated with increased predisposition to solid childhood malignancies such as medullloblastoma and Wilms tumor.

**Cytogenetics**

At the cellular level, FA is a chromosomal fragility syndrome. FA cells are hypersensitive to DNA interstrand crosslinking agents such as mitomycin C, diepoxybutane and cisplatin. In addition to hypersensitivity to these agents, FA cells show an increased number of spontaneous breaks.

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