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Gene Section
Review

BRMS1 (breast cancer metastasis suppressor 1)

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Identity

Other names: DKFZP564A063

HGNC (Hugo): BRMS1

Location: 11q13.1

Local order: Chr 11: 65861380 - 65869158 (minus strand).

DNA/RNA

Description

BRMS1 is a functioning gene comprising 10 exons and spanning 7.8 kb of genomic DNA. Alternative splicing results in two mRNA transcripts, translating into two distinct proteins, 246 amino acids and 290 amino acids in length, respectively (Seraj et al., 2000). The longer transcript uses an alternative splice site in the 3' untranslated terminal exon which results in the use of a downstream stop codon. The encoded protein has a longer distinct C-terminus.

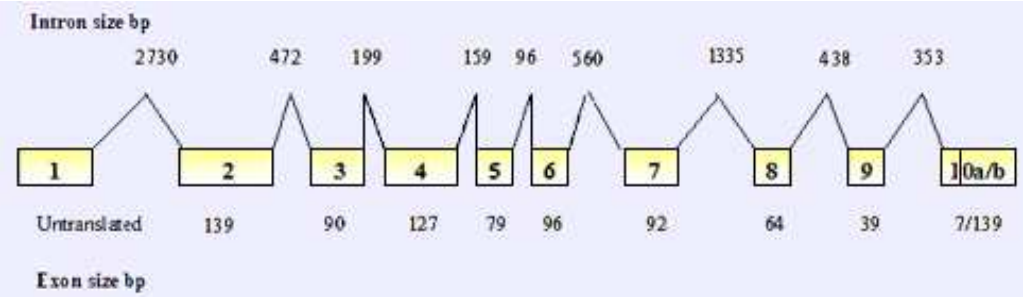
Transcription

Structural analysis of the BRMS1 promoter has revealed the presence of two hypermethylated cytosine-phosphoguanine (CpG) islands (Metge et al., 2008). Hypermethylation of CpG islands restricts the activity of the BRMS1 protein, mainly due the tightly packed nucleosomes (Metge et al., 2008). Gene expression can also be suppressed by blocking transcription factor binding.

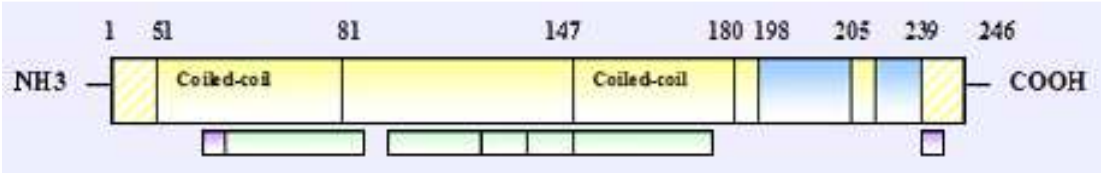
Protein

Note

1-246 amino acids;
Coiled-Coil Motifs: 51-81 and 147-180 amino acids;
Imperfect Leucine Zippers: 67-88, 131-152, 138-159, 153-174 and 160-181 amino acids;
Nuclear Localisation Signals: 198-205, 239-245 amino acids;
cAMP/cGMP Phosphorylation Sites: 55-58 and 240-243 amino acids.



Exon-Intron structure of human BRMS1.



Schematic representation of the BRMS1 protein. The coiled coil motifs are shown in yellow, nuclear localisation signals are shown in blue, the imperfect leucine zipper motifs are shown in green and the cAMP/cGMP phosphorylation sites are shown in purple.

Description

The BRMS1 protein consists of 246 amino acids, two coiled-coil motifs and a number of imperfect leucine zipper motifs at amino acids 67-88, 131-152, 138-159, 153-174 and 160-181, respectively. Several putative phosphorylation sites have also been identified (see diagram above) (Seraj et al., 2000). The full length protein is 2.8 kDa. In addition, a novel BRMS1-homologue protein (p40) has been identified, which may play a role in transcription repression by recruiting histone deacetylase complexes (Nikolaev et al., 2004).

Expression

BRMS1 was originally identified by differential display analysis. Transfection of BRMS1 cDNA into MDA-MB-435 and MDA-MB-231 breast cancer cell lines was shown to suppress formation of metastasis without affecting tumourigenicity (Samantet al., 2000). BRMS1 overexpression also inhibits lung and lymph node metastasis in experimental melanoma and ovarian cancer models (Shevde et al., 2002; Zhang et al., 2006). Reduced expression of BRMS1 has been correlated with poor prognosis in human breast cancer (Zhang et al., 2006). In addition, reduced expression of BRMS1 has been observed in breast cancer brain metastasis (Stark et al., 2005).

Localisation

The BRMS1 protein is predominantly located in the nucleus.

Function

Breast cancer metastasis suppressor gene 1 is a member of a growing family of metastasis suppressor genes which prevent the development of metastasis without affecting tumour growth (Welch et al., 2000). The main cause of mortality in cancer patients is the formation of metastasis, a multistep process, modulated largely by activators and suppressors of metastasis (Chambers et al., 2002; Duffy, 1996). BRMS1 has been shown to suppress metastasis of human breast cancer and melanoma cells in nude mice (Seraj et al., 2000; Samant et al., 2000; Samant et al., 2002). It maps to chromosome 11, a region of the genome which has been implicated in the progression and metastasis of human breast cancer (Seraj et al., 2000).

Recent studies suggest that BRMS1 inhibits metastasis through an interaction with histone deacetylase complexes, resulting in aberrant gene regulation (Hurst et al., 2006; Samant et al., 2007). It is a selective component of the mSin3a/histone deacetylase corepressor complex and when activated results in basal transcriptional repression (Meehan et al., 2004). In addition, BRMS1 has been shown to negatively regulate NF-kB activity, which is constitutively activated in many human cancers and plays an important role in apoptosis (Samant et al., 2007).

Metge et al. (2008) recently identified two hypermethylated CpG islands in the BRMS1 promoter. This group also observed reduced expression of BRMS1 in metastatic breast cancer cell lines. They hypothesized that promoter hypermethylation may be involved in this downregulation of BRMS1 expression (Metge et al., 2008). Methylation appears to be an important early event in the etiology of human breast cancer, resulting in the silencing of many tumour suppressor genes, including BRMS1 (Nephew et al., 2003). Metge et al. (2008) suggest that epigenetic silencing of BRMS1 may be an important prognostic indicator in human breast cancer.

Other functions of BRMS1 include restoring homotypic gap junctional intercellular communications (Samant et al., 2000; Shevde et al., 2002; Saunders et al., 2001), inhibiting expression of the metastasis-promoting chemokine osteopontin (Samant et al., 2007; DeWald et al., 2005). Furthermore, BRMS1 has been shown to play a role in phosphoinositide signaling.

Implicated in

Note

A growing number of human malignancies (breast, ovarian, melanoma) have been associated with a decrease in BRMS1 expression, leading to an increased risk of metastasis and a decreased overall disease-free survival and poor prognosis (Shevde et al., 2002; Zhang et al., 2006; DeWald et al., 2005; Kelly et al., 2005).

Breast cancer

Disease

Overexpression of BRMS1 has been shown to reduce the metastatic ability of human breast cancer cells injected into nude mice (Seraj et al., 2000; Samant et al., 2006). Loss of BRMS1 protein expression correlated with reduced disease-free survival in human breast cancer and also with estrogen and progesterone receptor negative and HER-2/neu positive tumours, suggesting that BRMS1 plays a role in the biology of these tumours (Hicks et al., 2006). However, Kelly et

al. (2005) showed expression of BRMS1 mRNA was independent of metastasis to lymph nodes, hormone receptor status and tumour size in human breast cancer. These conflicting findings suggest further investigations are necessary to elucidate the role of BRMS1 in the metastatic cascade.
Recently, Cicek et al. (2005) showed an inverse correlation between expression of BRMS1 and urokinase plasminogen activator (uPA) in metastatic breast cancer cell lines. The expression of uPA has long been associated with metastasis (Duffy et al., 1990). uPA catalyses the conversion of inactive plasminogen to plasmin, a broad spectrum protease, capable of catalyzing the degradation of most proteases in the extracellular matrix (Duffy et al., 1984). uPA was the first proteolytic enzyme shown to be associated with poor prognosis in breast cancer. In 1988, Duffy et al. showed that breast cancer patients with high levels of uPA had a significantly shorter disease-free survival compared with patients whose tumours expressed low levels of the enzyme. uPA is currently one of the best validated prognostic marker for breast cancer (Look et al., 2002; Nijziel et al., 2003).

Ovarian carcinoma

Disease

BRMS1 mRNA expression in ovarian carcinoma was found to be significantly lower than in normal ovarian tissue. Transfection of BRMS1 into the metastatic ovarian cancer cell line HO-8910PM significantly suppressed call adhesion to extracellular matrix components. In addition, when injected into nude mice the BRMS1-transfected cells had a reduced capacity to form lung colonies (Zhang et al., 2006). This suggests that BRMS1 may play a role in the metastatic potential of ovarian tumours.

Melanoma

Disease

BRMS1 mRNA expression has been observed in melanocytes, shown to be reduced in early melanoma-derived cell lines, and scarcely detectable in metastatic cell lines. Transfection of BRMS1 into metastatic melanoma cell lines significantly reduced the metastatic potential while having no effect on tumourigenicity (Shevde et al., 2002).

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