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Gene Section
Review

RAD51L3 (RAD51-like 3 (S. cerevisiae))

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Identity

Other names: HsTRAD; R51H3; RAD51D; Trad

HGNC (Hugo): RAD51D

Location: 17q12

Note

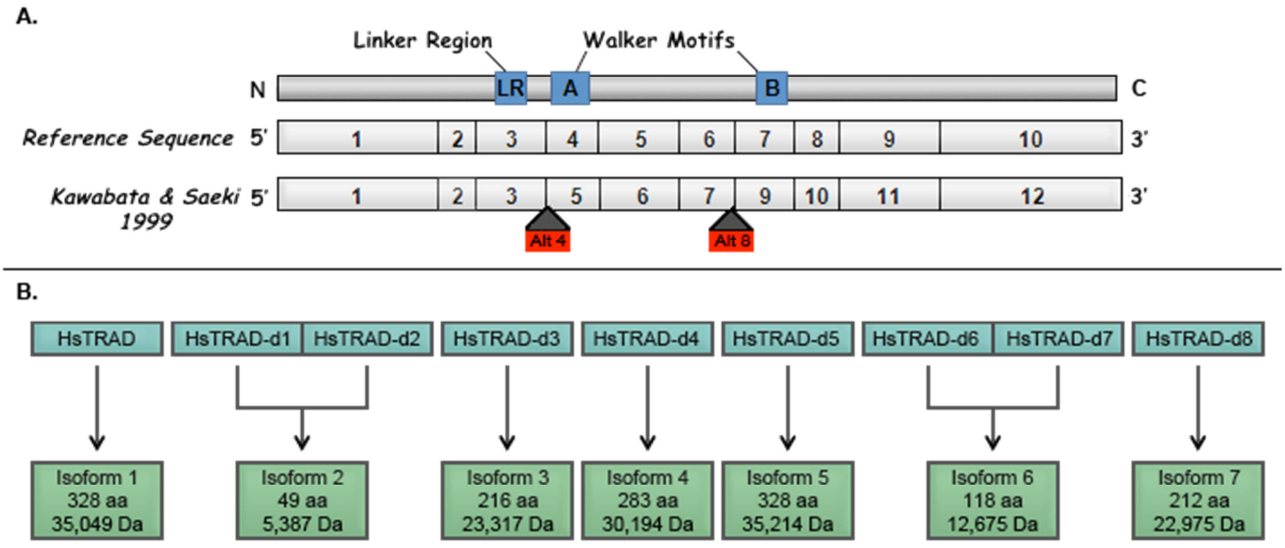
Of the five RAD51 paralog proteins, four come together to form the BCDX2 complex, which includes RAD51L1 (RAD51B; chromosome 14), RAD51L2 (RAD51C; chromosome 17), RAD51L3 (RAD51D; chromosome 17), and XRCC2 (chromosome 14). The protein complex is involved in homologous recombination repair of double-stranded breaks that result during DNA replication or from DNA-damaging agents, e.g., cisplatin (Masson et al., 2001).

The RAD51L3 protein directly interacts with RAD51L2 (RAD51C) and XRCC2. It does not directly interact with RAD51L1 (RAD51B) (Schild et al., 2000).

DNA/RNA

Note

The human gene is composed of 10 exons. The study by Kawabata and Saeki (1999) describes alternative splicing of the human gene using a numbering scheme of 12 alternatively spliced exons. The exon alignment is illustrated below.



Human RAD51D alternative splicing. A. Exons 4 and 8 of the Kawabata and Saeki numbering scheme are considered "alternative exons" and not included in the reference sequence. **B.** Summary of splice variants and predicted translation products (for further details see the annexed document below).

Further descriptions of mouse alternatively spliced variants are described in Gruver et al., 2009 and Kawabata et al., 2004.

Transcription

The HsTRAD transcript is the predominant variant. It is the full-length transcript and is made up of 2418 base pairs. This transcript will be used as the reference for the information that follows. There are multiple splice variants for the RAD51L3 gene that translate into one of seven putative protein isoforms.

Protein

Note

The Saccharomyces cerevisiae Rad51 protein is homologous to the RecA protein of Escherichia coli. The RecA protein is known to promote repair via ATP-dependent mechanisms and is responsible for pairing and strand transfer between homologous DNA sequences. This is similar to the actions of the RAD51 protein in repair pathways. There are 5 members of the RAD51 family that share similar roles in recombination and DNA repair. RAD51D is one of these RecA-like genes (Pittman et al., 1998; Cartwright et al., 1998).

The RAD51D gene is predicted to encode seven different protein isoforms through alternative splicing. Isoform 1 is the predominant protein and is translated from the HsTRAD transcript mentioned previously (Kawabata and Saeki, 1999). The diagram below is based on this predominant form.

Description

The RAD51D protein contains regions necessary for interactions with other RAD51 paralogs as well as those that are required for proper function of the protein. RAD51D contains an ATP binding domain with highly conserved Walker A and B motifs (Pittman et al., 1998; Cartwright et al., 1998). Mutations targeting the conserved residues of glycine and lysine within the Walker A motif region resulted in a reduction in RAD51C binding ability and were shown to be required for DNA repair (Gruver et al., 2005). The Walker B motif contains a "GGQRE" sequence between residues 219-223 that is also required for DNA repair (Wiese et al., 2006). Furthermore, RAD51D-XRCC2 complex formation is significantly reduced with mutations targeting a highly conserved aspartate residue within the Walker B motif (Wiese et al., 2006).

A carboxyl terminal domain spanning amino acids 77-329 has been identified to be required for RAD51D to interact with RAD51C.

In addition, the "linker region" located between residues 54-77 in the amino terminus is required for proper interactions with XRCC2. Together, these interactions aid in the repair of DNA damage (Miller et al., 2004; Gruver et al., 2009).

Expression

According to the study by Kawabata and Saeki (1999), RAD51L3 transcripts are expressed to varying degrees in the colon, prostate, spleen, testis, ovaries, thymus, small intestine and leukocytes.

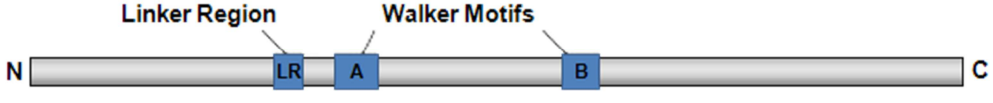
Localisation

Located in the nucleus. Specifically, RAD51L3 localizes to the telomeres during both mitosis and meiosis (Tarsounas et al., 2004). There is evidence that RAD51L3 is found in the cytoplasm as well (Gruver et al., 2005).

Function

RAD51D is one of five members of the RAD51 gene family that is known to participate in repair of double stranded DNA breaks via homologous recombination. Without repair, the DNA damage can result in cell death or chromosomal aberrations that can ultimately lead to cancer (Thacker, 2005). Knockout studies with mice have shown a dramatic increase in levels of chromosomal aberrations, most notably, chromatid and chromosome breaks that occur through unrepaired replication forks (Smiraldo et al., 2005; Hinz et al., 2006). Proteomic studies have identified an interaction between RAD51D with the SFPQ protein (Rajesh et al., 2011). Exposure of mouse RAD51D-deficient cells to a strong alkylating agent results in G2/M cell cycle arrest and ultimately apoptosis (Rajesh et al., 2010). RAD51D has recently been shown to play a diverse role in cellular processes through its interaction with proteins involved in cell division, embryo development, protein and carbohydrate metabolism, cellular trafficking, protein synthesis, modification or folding, and cellular structure (Rajesh et al., 2009).

RAD51L3 is directly associated with telomeres prevents their dysfunction (Tarsounas et al., 2004). In mouse studies, RAD51L3 foci were present at telomeres in both meiosis and mitosis. Knockout studies showed that "RAD51D-deficient" mice exhibited an increase in end-to-end fusion and telomere attrition (Smiraldo et al., 2005). In addition, human studies using RAD51D-deficient cells have shown repeated shortening of the telomeric DNA, leading to chromosomal instability. This suggests a role for "RAD51D" in telomere capping. Failure to provide this function can lead to chromosomal aberrations (Tarsounas and West, 2005).



RAD51L3 protein structure. Isoform 1 (from full-length transcript).

Homology

Canis lupus familiaris [Dog]	**Official gene name:** RAD51-like 3 (S. cerevisiae) **Genomic location:** chromosome 9	Reference material: no primary references found
Pan troglodytes [Chimpanzee]	**Official gene name:** RAD51-like 3 (S. cerevisiae) **Genomic location:** chromosome 17	Reference material: no primary references found
Bos taurus [Cow]	**Official gene name:** RAD51-like 3 (S. cerevisiae) **Genomic location:** chromosome 19	Reference material: Zimin et al., 2009
Gallus gallus [Chicken]	**Official gene name:** RAD51-like 3 (S. cerevisiae) **Genomic location:** chromosome 19	Reference material: no primary references found
Rattus norvegicus [Rat]	**Official gene name:** RAD51-like 3 (S. cerevisiae) **Genomic location:** chromosome 10	Reference material: Strausberg et al., 2002
Mus musculus [Mouse]	**Official gene name:** RAD51-like 3 (S. cerevisiae) **Genomic location:** chromosome 11	**Reference material:** Pittman et al., 1998 Cartwright et al., 1998
Arabidopsis thaliana [Thale cress]	**Official gene name:** RAD51D (ARABIDOPSIS HOMOLOG OF RAD51D) **Genomic location:** chromosome 1	Reference material: Durrant et al., 2007
Oryza sativa [Rice]	Official gene name: Os09g0104200 Genomic location: chromosome 9 **Hypothetical protein**	Reference material: no primary references found
Danio rerio [Zebrafish]	Official gene name: zgc:77165 Genomic location: chromosome 5	Reference material: no primary references found

** Protein alignments and protein sequences are available at the HomoloGene database.

Mutations

Note

Single nucleotide polymorphisms have been identified in RAD51L3. However, only a small number of the major mutations occur in coding regions. The majority of the other mutations are present in various locations within the introns. Of the mutations affecting the gene, only one has an observed clinical association. It is observed that a mutation of the mRNA position 954 (SNP ID: rs28363284) results in an allele change to GGG (from the wild type GAG). This point mutation affects the 233rd amino acid as a glycine residue is observed in this particular mutation rather than the natural glutamic acid. This particular variation in amino acid sequence has been implicated as a precursor to breast cancer (see "Implicated In" section below). Another mutation observed in the coding region is at mRNA position 188 (SNP ID: rs1871892), resulting in a change in the sequence to TCA (from the wild type

CCA). This particular substitution results in the insertion of proline at the 36th protein position rather than a serine.
A third mutation observed is noted to occur at mRNA positions 810 (SNP ID: rs4796033). A mutation at this location results in a sequence of CAG (from the natural CGG). The effect of this substitution is the insertion of a glutamine residue at the 185th amino acid position rather than the arginine observed in the wild type gene. It is noted, that this particular mutation also occurs in 2 additional transcripts of the gene at the mRNA positions 750 and 414 affecting the 165th and 53rd amino acid residues respectively. Other mutations in the coding region include E237K (SNP ID: rs115031549), R252Q (SNP ID: rs28363283), A245T (SNP ID: rs28363282), A210T (SNP ID: rs80116829), E177D (SNP ID: rs55942401), and R24S (SNP ID: rs28363257).

Implicated in

Cancer

Disease

Cancer arises in part due to the accumulation of genetic damage. Furthermore, such damage has a greater tendency to be found in significant levels when genetic repair pathways such as DNA mismatch repair and homologous recombination (HR) are defective. Involved in the pathway of HR are numerous proteins that are known as the RAD51 paralogs (RAD51L1, RAD51L2, RAD51L3, XRCC2 and XRCC3). It is believed that the lack of genetic stability created from the loss of this pathway, HR, is significant in initiation and potentially the progression of cancer. In particular, defects in the HR pathway have been noted to be associated with breast and ovarian cancer (Thacker, 2005); however, it is plausible that such a defect could potentially lead to multiple forms of cancer due to the accumulation of genetic mutations (although it takes significant damage accumulation to lead to tumor formation). A RAD51L3 variant does have an association with increased familial breast cancer risk (Rodríguez-López et al., 2004).

Breast cancer

Note

Although conflicting data exist, the RAD51D-E233G variant allele has been identified as a potential precursor to breast cancers in women with high familial risk but do not possess a BRCA1/BRCA2 mutation (Rodríguez-López et al., 2004; Dowty et al., 2008).

Disease

In an initial study that screened for possible breast cancer alleles, it was determined that the exon 8 mutation led to an increased frequency of breast cancer in a specific group of cases (familial cancer cases) versus the control group (Rodríguez-López et al., 2004). Additionally, individuals expressing the RAD51D-E233G variant have been shown to have higher proliferative indices and a less favorable clinical immunohistochemical pattern (Rodríguez-López et al., 2004). However, another study found no statistically significant evidence that this variant is associated with breast cancer risk. Yet, this study did find that it was plausible that the variable could lead to a small increase in the risk of breast cancer and that a small, yet insignificant, effect was made by the variant on the risk of breast cancer (approximately 30%) (Dowty et al., 2008).

Prognosis

It has been noted that the RAD51D-E223G variant confers increased resistance to DNA damaging agents such as: mitomycin C, cisplatin, ultraviolet light, and methyl methane sulfonate, and taxol. This presents clinical implications as these are commonly utilized therapies. Furthermore, the variant has increased cellular proliferation and telomere maintenance compared to the wild-type and exhibits reduced interaction with the binding partner RAD51C but does not affect binding to XRCC2 (Nadkarni et al., 2009b).

Bloom's syndrome

Disease

Bloom's syndrome is an autosomal recessive disorder of rare occurrence. Characteristics include short stature, immunodeficiency, fertility defects, and increased risk for the development of various types of cancer. Cells associated with this disorder are noted for their genomic instability. They exhibit an increase in sister chromatid and homologous chromosome exchanges. In normal, healthy cells, BLM, a helicase of the RecQ family, interacts with the RAD51L3 portion of the RAD51L3-XRCC2 heteromeric complex. Upon joining with the complex, BLM disrupts synthetic 4-way junctions that resemble Holliday junctions suggesting an important role for the protein-protein interaction in DNA repair. The mutated form of the gene encoding for this protein, which occurs in Bloom's syndrome, results in the inability for BLM to bind to RAD51L3. Absence of normal BLM function leads to the characteristic elevation in recombination events seen in Bloom's syndrome (Braybrooke et al., 2003).

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