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Gene Section
Review

BUB1 (budding uninhibited by benzimidazoles 1 homolog (yeast))

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Identity

Other names: BUB1A, BUB1L, hBUB1

HGNC (Hugo): BUB1

Location: 2q13

Note

The multidomain protein kinase BUB1 is a central component of the mitotic checkpoint for spindle assembly (SAC). This evolutionary conserved and essential self-monitoring system of the eukaryotic cell cycle ensures the high fidelity of chromosome segregation by delaying the onset of anaphase until all chromosomes are properly bi-oriented on the microtubule spindle.

DNA/RNA

Description

The gene spans 40.2 kb and is composed of 25 exons.

Transcription

NM_004336.3

Protein

Note

Uniprot accession number: NP_004327.1.
ENZYME entry (serine/threonine protein kinase): EC 2.7.11.1.

Amino acid sequence (FASTA format).

Description

1085 amino acids, 122.37 kDa.

Expression

Ubiquituously expressed.

Localisation

Cytoplasmic in interphase cells. It is localized in nuclear kinetochores in cells with an unsatisfied mitotic checkpoint in a process that requires BUB1 binding to Blinkin and BUB3.

Function

BUB1 is required for chromosome congression, kinetochore localization of BUBR1, CENP-E, CENP-F and Mad2 in cells with mitotic checkpoint unsatisfied and for the establishment and/or maintenance of efficient bipolar attachment to spindle microtubules (Johnson et al., 2004; Lampson and Kapoor, 2005; McGuinness et al., 2009). Deletion of Bub1 from S. pombe increases the rate of chromosome missegregation (Bernard et al., 1998) while deletion of Bub1 from S. cerevisiae results in slow growth and elevated chromosome loss (Warren et al., 2002).
BUB1 is recruited very early in prophase (Wong and Fang, 2006) and is essential for assembly of the functional inner centromere (Taylor et al., 1998; Boyarchuk et al., 2007).

Figure 1. Schematic representation of the human bub1 gene demonstrating the relative size of each of the 25 exons (introns are not drawn to scale).

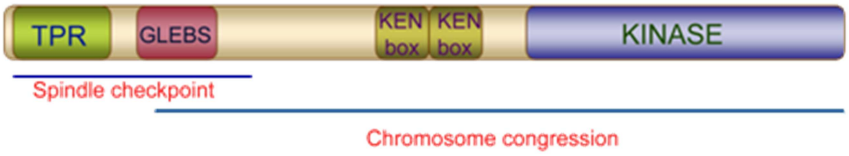

Figure 2. Domain organization of BUB1. Three main regions can be identified in the BUB1 gene product: a conserved N-terminal region, which contains the kinetochore localization domain; an intermediate, non-conserved region, which is required for Bub3 binding; and a C-terminal region containing a catalytic serine/threonine kinase domain. The main functions associated with the different BUB1 regions are also indicated.

It accumulates at the kinetochore in SAC-activated cells and assures the correct kinetochore formation.
The N-terminal region mediates the binding of BUB1 to the mitotic kinetochore protein Blinkin (a protein also commonly referred to as KNL1/Spc105/AF15q14); the interaction is essential for the kinetochore localization of BUB1 induced in cells with an unsatisfied mitotic checkpoint (Kiyomitsu et al., 2007). N-terminal BUB1 is organised as a triple tandem of the TPR motif (Bolanos-Garcia et al., 2009). In fission yeast, the Bub1 N-terminal residues 1-179 are required for targeting the protein Shugoshin 1 (SGO1) to centromeres (Vaur et al., 2005) while deletion of residues 28-160 results in a truncated protein unable to recruit Bub3 and Mad3/BUB1B to kinetochores (Vanoosthuyse et al., 2004). The C-terminal region contains a catalytic, serine threonine kinase domain that resembles the mechanism of activation of CDKs by cyclins (Kang et al., 2008).

Homology

The bub1 gene is conserved in chimpanzee, cow, mouse, rat, chicken, and zebrafish. Homology exists with the gene encoding for the mitotic checkpoint kinase BUBR1 (a BUB1 paralogue) (Bolanos-Garcia and Blundell, 2011).

Mutations

The following somatic mutations have been reported to date: A130->S (Shichiri et al., 2002); deletion delta76-141 (Cahill et al., 1998); 140, transition of the splicing donor site (Cahill et al., 1998); S492->Y (Cahill et al., 1998); deletion delta827 (Ouyang et al., 2002); G250->N (Ohshima et al., 2000); S950->G (Imai et al., 1999); Y259->C (Hempen et al., 2003); H265->N (Hempen et al., 2003). It could not be determined whether the R209->Q substitution was the result of a somatic mutation or due to a rare polymorphism because constitutional DNA from the patient harbouring this mutation was not available (Sato et al., 2000). The clinical condition associated to each mutation is described in Table 1. The mapping of residues substitutions onto the BUB1 domains is depicted in Figure 3.

Bub1 region	Mutation	Residue	Domain	Clinical condition	Reference
N-terminal	GAG→GAT	E36→D	TPR domain	Colorectal cancer	Cahill et al., 1999
	Deletion	Δ76-141, frameshift		Colorectal cancer	Cahill et al., 1998
	GCT→TCT	A130→S		Lymph node metastasis	Shichiri et al., 2002
	G→A	140, transition of the splicing donor site		Colorectal cancer	Cahill et al., 1998
GLEBS motif	CGA→CAA	R209→Q		Lung cancer	Sato et al., 2000
	GGT→GAT	G250→N		ATLL	Ohshima et al., 2000*
	TAT→TGT	Y259→C		Pancreatic cancer	Hempen et al., 2003
	CAC→AAC	H265→N		Pancreatic cancer	Hempen et al., 2003
Middle region of low structural complexity	TCC→TTC	S375→F		Colorectal cancer	Saeki et al., 2002
	TCT→TAT	S492→Y		Colorectal cancer	Cahill et al., 1998
	AAG→AGG	K566→R		Colorectal cancer	Saeki et al., 2002
	CCC→CGC	P648→R		Colorectal cancer	Cahill et al., 1999
C-terminal	Deletion	Δ827, frameshift		Tyroid follicular adenoma	Ouyang et al., 2002
		S950→G	Kinase domain	Colorectal cancer	Imai et al., 1999

Table 1. Human bub1 mutations associated with cancer. *These authors incorrectly number these residues; the numbering shown here is the correct.

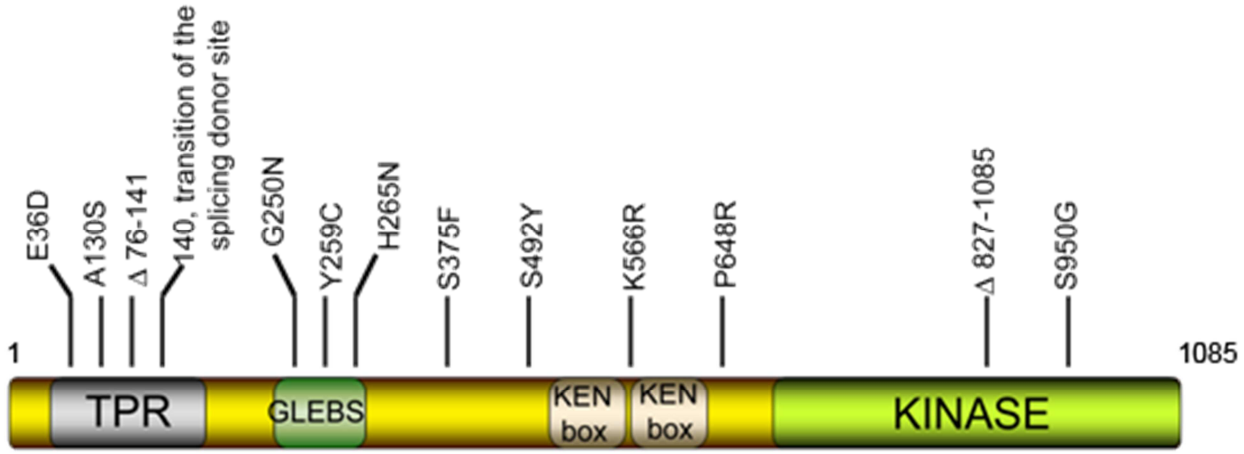

Figure 3. Mapping of cancer associated substitutions onto the amino acid sequence of human BUB1.

Implicated in

Colorectal cancer

Disease

Colorectal cancer, also referred to as bowel cancer, is characterized by neoplasia in the colon, rectum, or vermiform appendix. Colorectal cancer is the third most commonly diagnosed cancer in the world and fourth most frequent cause of cancer death in males. More than half of the people who die of colorectal cancer live in a developed region of the world.

Cytogenetics

RT-PCR mediated amplification and direct sequencing of the entire BUB1 coding region in the colorectal cancer cell line V400 revealed an internal deletion of 197 bp of this gene (Cahill et al., 1998). The deletion results in the remotion of codons 76 to 141 and creates a frameshift immediately thereafter. Sequence analysis of cDNA from another colorectal cancer cell line, V429, revealed a missense mutation at codon 492 that resulted in the substitution of tyrosine for a conserved serine (Cahill et al., 1998). The V400 and V429 mutations were heterozygous, somatic and present in primary tumours but not in normal tissues. Another heterozygous BUB1 missense mutation (AGT to GGT) at codon 950 has been identified (Imai et al., 1999).

Hepatocellular carcinoma (HCC)

Disease

Hepatocellular carcinoma (HCC) is one of the most common tumors worldwide and it accounts for most liver cancers. HCC occurs more often in men than women and is more common in people ages 30-50. Hepatitis virus infection, alcohol consumption, and dietary exposure to toxins such as aflatoxin B1 are associated with the occurrence of HCC.

Cytogenetics

Two BUB1 gene variants have been identified in HCC specimens (Saeki et al., 2002). The expression product of one variant has a serine (TCC) substituted for phenylalanine (TTC) at codon 375 while the other has a lysine (AAG) substituted for arginine (AGG) at codon 566 (Saeki et al., 2002). S375F showed a well-differentiated HCC in cirrhotic liver caused by hepatitis B virus, whereas K566R showed a moderately differentiated HCC in hepatitis C virus induced cirrhotic liver. Genomic DNA extracted from nontumorous liver tissue revealed the same variants in both cases.

Lung cancer

Disease

Lung cancer is the most frequently diagnosed cancer among men. The mortality rate is the highest among men and the second highest among women worldwide. The main types of lung cancer are small-cell lung carcinoma and non-small-cell lung carcinoma. Non-small-cell lung carcinoma is sometimes treated with surgery, while small-cell lung carcinoma usually responds better to chemotherapy and radiation. Lung cancer cells harbour many cytogenetic abnormalities suggestive of allele loss, including non-reciprocal translocations and aneuploidy. The stage of the disease is a strong predictor of survival, suggesting that early detection is needed for improvement in treatment outcomes.

Cytogenetics

A nucleotide change of the BUB1 gene that results in the substitution of Arginine by Glutamine R209Q has been identified in the cell line NCI-H345 (Sato et al., 2000). Unfortunately, it was not possible to determine whether the change was a somatic mutation or a rare polymorphism because constitutional DNA from this patient was not available.

Adult T-cell leukaemia/lymphoma (ATLL)

Disease

Lymphomas, malignancies of the lymphoid cells, are divided on the basis of their pathologic features into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma

(NHL). Adult T-cell leukemia/lymphoma (ATLL) is usually a highly aggressive non-Hodgkin's lymphoma of the patient's own T-cells with no characteristic histologic appearance except for a diffuse pattern and a mature T-cell phenotype. The frequent isolation of HTLV-1 from patients with this disease and the detection of HTLV-1 proviral genome in ATLL leukemic cells suggest that HTLV-1 causes ATLL.

Cytogenetics

A BUB1 missense mutation of G to A at codon 250 (GGT to GAT) has been reported (Ohshima et al., 2000).

Pancreatic cancer

Disease

The term pancreatic cancer usually refers to adenocarcinoma that arises within the exocrine component of the pancreas. Pancreatic cancer is one of the most aggressive diseases with most cancers and often has a poor prognosis: for all stages combined, the 1- and 5-year relative survival rates are 25% and 6%, respectively; for local disease the 5-year survival is approximately 20% while the median survival for locally advanced and for metastatic disease, which collectively represent over 80% of individuals, is about 10 and 6 months respectively.

Cytogenetics

Two missense variants in the BUB1 gene have been identified in the aneuploid pancreatic cell line Hs766T (Hempen et al., 2003). These mutations are found in the same allele, accompanied by a wild-type BUB1 allele. Mutation of nucleotide 776 from an adenine to a guanine results in an amino acid change at codon 259 from tyrosine to cysteine (Y259C). A second mutation at nucleotide 793 changed a cytosine to an adenine (C to A) thus resulting in the mutant H265N (Hempen et al., 2003).

Thyroid follicular adenoma

Disease

Almost all thyroid adenomas are follicular adenomas. Follicular adenomas can be described as "cold", "warm" or "hot" depending on their level of function. Histopathologically, follicular adenomas can be classified according to their cellular architecture and relative amounts of cellularity and colloid into the following types:

- fetal (microfollicular), which have the potential for microinvasion,
- colloid (macrofollicular), which do not have any potential for microinvasion,
- embryonal (atypical), which have the potential for microinvasion.

Cytogenetics

A thyroid follicular carcinoma that has a 2-bp somatic deletion (G2480/A2481) of BUB1 has been reported by Ouyang and collaborators (2002).

Lymph node metastasis

Disease

Certain cancers spread in a predictable fashion from where the cancer started. Because the flow of lymph is directional, if the cancer spreads it will spread first to lymph nodes close to the tumor before it spreads to other parts of the body.

Cytogenetics

A BUB1 missense somatic mutation (nucleotide 437 GCT to TCT transition) that replaces Ala to Ser at codon 130 has been identified in an ascending colorectal carcinoma (Shichiri et al., 2002).

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