Gene Section

Review

WWC1 (WW and C2 domain containing 1)

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Abstract

Review on WWC1, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: HBEBP3, HBEBP36, KIBRA
HGNC (Hugo): WWC1
Location: 5q34

DNA/RNA

Description

The gene of WWC1 locates on chromosome 5q34, with 23 exons crossing 180244bp (including untranslated regions) on the plus strand. In total 137 single nucleotide polymorphisms are present in ≥ 1% of samples according to UCSC database.

Transcription

The open reading frame of mRNA contains 3360bp. Three transcript variants encoding different isoforms have been found for this gene (provided by RefSeq, Mar 2010).

Pseudogene

No pseudogene of WWC1 is known.

Protein

Note

Preferred names: protein KIBRA
Names:
- protein KIBRA
- protein WWC1
- HBeAg-binding protein 3
- kidney and brain protein
- WW, C2 and coiled-coil domain containing 1

Description

KIBRA protein consists of 1119 amino acids (isoform 1), with a predicted molecular weight of 125kDa. It was first cloned and identified as a protein that interacts with the postsynaptic protein dendrin (Kremerskothen et al., 2003). KIBRA is constituted by two N-terminal WW domains, a C2 domain, a glutamic acid-rich domain and a PDZ binding motif. The WW domains which contain two conserved tryptophan residues are responsible for recognizing PPxY motifs in various proteins containing proline-rich sequences (PPxY).
Structure of human KIBRA. KIBRA contains two WW domains, a C2 domain, a glutamic acid-rich domain and a PDZ binding motif.

The C2 domain located between amino acids 655 and 783 is implied to be involved in binding phospholipids under assistance of two or three calcium ions. In addition to the WW and C2 domain, a glutamic acid-rich region can be found between amino acids 845 and 873 (Kremerskothen et al., 2003; Rayala et al., 2006) and a PDZ-binding motif is located between amino acids 1110 and 1113 at the C terminus (isoform 2) (Duning et al., 2008). Further, a conserved motif containing serine residue (Ser539) between the WW and C2 domains of KIBRA, is phosphorylated and regulated by aurora kinase and protein phosphatase 1 (Xiao et al., 2011b). Recently, KIBRA Ser542 and Ser931 have been identified as main phosphorylation sites for CDK1 (Ji et al., 2012).

Expression
KIBRA is predominately expressed in human kidney and brain (Kremerskothen et al., 2003). Gene expression studies and immunohistological staining have shown that KIBRA is mainly expressed in memory-related regions of the brain, such as hippocampus and cortex (Papassotiropoulos et al., 2006; Johannsen et al., 2008). In kidney, KIBRA is expressed in glomerular podocytes, tubules and some collecting ducts (Duning et al., 2008). KIBRA can also be detected in heart and colon.

Localisation
The localization of endogenously expressed KIBRA depends on the cell type. KIBRA localizes in the apical domain and at cell junctions in epithelial cells (Yoshihama et al., 2011). In brain, KIBRA co-localizes with protein kinase Mzeta (PKMzeta) in the mouse hippocampus (Yoshihama et al., 2009). In mouse kidney, KIBRA localizes in the distal tubular epithelial cells (Yoshihama et al., 2011). In migrating cells, KIBRA accumulates in the leading edge (Duning et al., 2008).

Function
KIBRA is a cytoplasmatic protein that is involved in various cellular processes and regulates a variety of cellular functions such as cell growth and apoptosis, directional cell migration, mitotic spindle assembly and mitogen-activated protein kinase (MAPK) activation.

In the field of neuroscience, KIBRA is associated with human memory performance (Papassotiropoulos et al., 2006). The single nucleotide polymorphism (SNP) of the ninth intron of KIBRA gene, rs17070145, is associated with human episodic memory performance. Carriers of the T to C nucleotide in the ninth intron have better performance on episodic memory tasks (Papassotiropoulos et al., 2006). After that, several other groups also reported the association of KIBRA with human memory performance in different subject populations (Almeida et al., 2008; Bates et al., 2009; Schaper et al., 2008). KIBRA gene is also associated with Alzheimer's disease and recurrent depressive disorders (Corneveaux et al., 2010; Galecki et al., 2010). Besides, KIBRA interacts with PKCzeta, which is involved in synaptic plasticity (Büther et al., 2004). Three recent studies independently identified KIBRA in Drosophila as a tumor suppressor that regulates Hippo signaling pathway, which controls tissue growth and organ size (Baumgartner et al., 2010; Genevet et al., 2010; Yu et al., 2010). This function of KIBRA seems to be conserved in mammals. Loss of KIBRA expression in immortalized breast epithelial cells exhibits epithelial-to-mesenchymal transition (EMT) features and reduced expression of KIBRA in breast cancer specimens correlates with poor prognosis (Moleirinho et al., 2013). However, a recent study reported that overexpression of KIBRA in gastric cancer correlates with lymphatic invasion and poor prognosis (Yoshihama et al., 2013). In podocytes, KIBRA interacts with PATJ and synaptopodin and positively modulates directional cell migration (Duning et al., 2008). Methylation status of KIBRA is correlated with prognosis of chronic lymphocytic leukemia and specific genetic event in B-cell acute lymphocytic leukemia (Shinawi et al., 2012; Hill et al., 2011). KIBRA also plays an important role in mitosis. KIBRA interacts with and regulates mitotic kinase aurora and is required for precise mitotic spindle assembly and chromosome alignment (Xiao et al., 2011b; Zhang et al., 2012). Additionally, KIBRA is also regulated by cyclin-dependent kinase 1 (CDK1) and cell division cycle 14A/B phosphatases (CDC14A, CDC14B) and thus regulates cell-cycle progression (Ji et al., 2012).
The KIBRA gene is conserved in chimpanzee, Rhesus monkey, dog, cow, mouse, rat, chicken, zebrafish, fruit fly, and mosquito (Provided by Pubmed). Two parologs of KIBRA have been discovered in human: WWC2 and WWC3. One ortholog of KIBRA (Kibra) has been identified in Drosophila. KIBRA and WWC3 exist in fish, and KIBRA and WWC2 are present in mice.

Mutations

No mutations of WWC1 are known.

Implicated in

Various cancers

Note

Genetic studies have identified Kibra as a tumor suppressor in Drosophila. Kibra functions together with Merlin and Expanded to regulate Hippo signaling pathway, which controls tissue growth and organ size (Baumgartner et al., 2010; Genevet et al., 2010; Yu et al., 2010). This function of KIBRA is also conserved in mammals. Methylation status of KIBRA is correlated with prognosis of chronic lymphocytic leukemia and specific genetic event in B-cell acute lymphocytic leukemia (Shinawi et al., 2012; Hill et al., 2011).

Cell cycle

Note

KIBRA is regulated by cyclin-dependent kinase 1 (CDK1) and cell division cycle 14A/B phosphatases (CDC14) and thus regulates cell-cycle progression (Ji et al., 2012). Besides, KIBRA interacts and regulates mitotic kinase aurora during mitosis and is required for precise mitotic spindle assembly and chromosome alignment (Xiao et al., 2011a; Zhang et al., 2012).

Epithelial-mesenchymal transition

Note

Loss of KIBRA expression induces features of epithelial-to-mesenchymal transition (EMT) in mammary epithelial cells. Decreased expression of KIBRA in breast cancer specimens correlates with poor prognosis (Moleirinho et al., 2013).

Memory performance

Note

The single nucleotide polymorphism (SNP) of the ninth intron of KIBRA gene, rs17070145, is associated with human episodic memory performance (Papassotripoulos et al., 2006). A recent study using KIBRA-knockout mice showed that KIBRA is necessary for the contextual and trace fear memory in adult mice (Makuch et al., 2011). KIBRA is also associated with Alzheimer's disease and recurrent depressive disorders (Corneveaux et al., 2008; Galecki et al., 2010).

References


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