KSR1 (kinase suppressor of ras 1)

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Identity

Other names: KSR; RSU2
HGNC (Hugo): KSR1
Location: 17q11.1
Local order: From centromere to telomere on 17q11.2, the KSR1 gene is flanked by: EOE1, EVI2A, JJAZ1, KNO3, KRT24, KSR1, LGALS9, LYZL6, MIR144, MIR451 (NCBI).

DNA/RNA

Description

The KSR1 gene was discovered in D. melanogaster and is highly conserved along the evolutionary tree through H. sapiens.

Transcription

Transcription can produce two different mRNA transcripts. The KSR1 is expressed in the thymus, bone marrow, brain, heart, kidney, lung, liver, pancreas, mammary gland, ovary, testis and muscle.

Pseudogene

No known pseudogenes.

Protein

Note

Belongs to the KSR family of proteins.

Description

The KSR1 protein is 921 kDa. There have been 15 phosphorylation sites identified.

Expression

Brain, kidney, lung, pancreas, ovaries, testis, breast.

Localization

Sequestered in the cytoplasm in quiescents cells. Upon stimulation, KSR1 protein localizes to the plasma membrane.

Function

Acts as a scaffold for the Raf/MEK/ERK kinase cascade.

Homology

R. norvegicus KSR1 (91.85%), M. musculus KSR1 (91.3%), C. familiars KSR1 (93.62%), G. gallus KSR1 (76.39%), D. reno KSR1 (67.85%), D. Melanogaster KSR (41.06%), C. elegans KSR1 (35.37%), X. laevis KSR1 (76.06%).
The KSR1 protein contains five conserved areas (CA). The CA1 region is unique to KSR1 protein; the CA2 region is a proline-rich region; the CA3 region is implicated in the Ras-induced plasma membrane localization; the CA4 region is a serine/threonine rich region and contains the MAPK docking site (FXFP); and the putative kinase domain (CA5), which contains an amino acid variation in subdomain II that suggests that this protein is catalytically inert. The KSR1 protein is composed of 921 amino acids.

Mutations

Note

There have been no prominent germinal or somatic mutations identified.

Implicated in

Cancer

Note

KSR1 has not been found to be upregulated or downregulated in tumors. However, studies in KSR1 knockout mice showed that the mice were less susceptible to papilloma virus driven tumors, indicating that KSR1 is required for Ras-mediated oncogenesis.

To be noted

Note

KSR1 is primarily recognized as a scaffold for the Raf/MEK/ERK kinase cascade. However, there are several published studies that sustain that KSR1 has catalytic activity. KSR1 is recognized as a pseudokinase, since mammalian KSR1 does not possess the lysine responsible for ATP orientation and hydrolysis in the putative kinase domain. This lysine is present in C. elegans and D. melanogaster, but mutation of this site did not affect activation of the Raf/MEK/ERK pathway. A recent publication (Rajakulendran et al., 2009) showed that KSR1 dimerization via its kinase domain to Raf facilitated the activation of Raf without KSR1 catalytic activity. It remains possible that KSR1 proteins have catalytic activity based on a yet to be identified novel mechanism.

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