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Gene Section
Review

ROR2 (receptor tyrosine kinase-like orphan receptor 2)

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Identity

Other names: BDB, BDB1, MGC163394, NTRKR2

HGNC (Hugo): ROR2

Location: 9q22.31

Local order: Orientation: minus strand.

DNA/RNA

Description

ROR2 contains 9 exons and is 227561 base pairs (via GeneLoc).

Transcription

Five (5) alternative splice variants have been identified for ROR2.

Protein

Description

The ROR2 protein product is 943 amino acids with the molecular weight estimated to be 104.76 kDa.

Expression

ROR2 is a developmentally expressed kinase with high expression normally seen throughout the body including the face, limb buds, heart, lungs and brain (Takeuchi et al., 2000; Matsuda et al., 2001). Expression of ROR2 begins to abate at approximately day 16 of development (Yoda et al., 2003).

In adult tissues, ROR2 is normally undetectable or expressed at very low levels. Functional ROR2 expression has been confirmed in the mouse cycling and pregnant uterus (Hatta et al., 2010). In humans, ROR2 cDNA has been detected in the uterus as well as the parathyroid and testis (Katoh et al., 2005). ROR2 has further been found to be upregulated as pluripotent cells emerge as pre-osteoblasts, and to be downregulated again as cells differentiate into osteocytes (Billiard et al., 2005).

Localisation

ROR2 is a single-pass type I membrane protein (Masiakowski et al., 1992) with localization restricted to the membrane.

Extracellularly, ROR2 contains an Ig-like domain (Ig), a frizzled or cysteine-rich (CRD) domain shown to act as a receptor for Wnt and a kringle (Kr) domain. The extracellular and intracellular domains are separated by a transmembrane (TM) domain. Intracellularly, ROR2 contains a tyrosine kinase (TK) domain and a proline-rich domain (PR) flanked by serine/threonine (ST) rich domains.

Function

ROR2 is a tyrosine protein kinase receptor highly implicated in development. It has also been implicated in the early formation of chondrocytes (DeChiara et al., 2000; Takeuchi et al., 2000). ROR2 is thought to play a key role in cartilage and growth plate development (DeChiara et al., 2000). The Wnt signaling pathway has also emerged as a key target of ROR2 activity. More specifically, evidence suggests that Wnt5a utilizes ROR2 as a receptor or co-receptor for its noncanonical Wnt mediated signaling (Minami et al., 2010; Sato et al., 2010). Additionally, recent evidence suggests that ROR2 is expressed and plays a role in various cancer etiologies including gastric cancer, renal cell carcinoma, malignant melanoma, and prostate cancer.

Homology

ROR2 is highly conserved across several species - from C. elegans to D. melanogaster to M. musculus to H. sapiens. For example, there is a 92% amino acid identity between mouse and human ROR2 (Yoda et al., 2003).

Mutations

Note

Robinow syndrome and Brachydactyl type B (BDB) are two genetic disorders that arise from mutations in ROR2:

1) Robinow syndrome is an autosomal recessive disorder that arises from nonsense, missense and frameshift mutations in the kringle, CRD and kinase domains - and is thought to cause a loss of function of ROR2 (Afzal et al., 2000). Those that present with Robinow syndrome have skeletal development defects (van Bokhoven et al., 2000; Afzal et al., 2003; Schwabe et al., 2004). This is seen within developmentally regulated features such as the formation of bones in the face and limbs.

2) BDB is an autosomal dominant disorder that arises from truncations of the kinase domains - either truncation of the serine/threonine domains and proline rich domain just below the Tyr kinase domain; or truncation of the entire intracellular domain right just below the transmembrane domain (Oldridge et al., 2000). Patients that present with BDB have abnormally short digits with the 4^{th} and 5^{th} digits particularly affected and have malformed or absent finger and toe nails (Schwabe et al., 2000; Afzal et al., 2003).

Somatic

Kubo et al. has reported somatic mutations in ROR2 in invasive gastric cancers (Kubo et al., 2009).

Implicated in

Gastric cancers

Note

ROR2 has been identified in poorly differentiated invasive gastric cancer and in intestinal-type and diffuse-type gastric cancers. ROR2 is identified as a frequent target of somatic mutations in poorly differentiated invasive gastric cancers (Kubo et al., 2009). In intestinal-type and diffuse-type gastric cancers, ROR2 is shown to play a role in cell invasion and is also downstream of the crosstalk between the Hedgehog and Wnt signaling pathways (Ohta et al., 2009).

Metastatic melanoma

Note

ROR2 was found to be overexpressed in a majority of metastatic malignant melanomas and also found to have a dramatic impact on cell motility, cell invasion and metastasis. Additionally, ROR2 expression was found to be correlated with Wnt5a expression in metastatic melanoma (O'Connell et al., 2010).

Osteosarcoma

Note

ROR2 overexpression has been described in this adolescent bone cancer. ROR2 is transactivated in a majority of osteosarcoma and also plays a role in cell migration and cell proliferation (Morioka et al., 2009). Evidence links Wnt5a and ROR2 within osteosarcoma where ROR2 has additional ties to having a role in the degradation of the extracellular matrix and invadopia formation (Enomoto et al., 2009).

Prostate cancer

Note

ROR2 has also been linked to prostate cancer via Wnt5a interaction. In prostate cancer, evidence suggests that Wnt5a utilizes ROR2 or Frizzled 2 as a receptor for its invasive potential. Further, it was shown that the Wnt5a/ROR2 receptor complex has a role in cell invasion (Yamamoto et al., 2010).

Renal cell carcinoma

Note

ROR2 was found to be overexpressed in the majority of renal cell carcinoma primary tumors. This aberrantly overexpressed kinase was shown to support cell migration, affect anchorage independent growth and promote xenograft tumor growth in renal cell carcinoma cell lines (Wright et al., 2009).

Squamous cell carcinoma

Note

ROR2 has been shown to be more highly invasive in oral malignant cancer epithelial cells than normal mucosa. In this cancer, ROR2 is associated with increased cell polarity and cell motility (Kobayashi et al., 2009).

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