Atlas of Genetics and Cytogenetics
in Oncology and Haematology

OPEN ACCESS JOURNAL

INIST-CNRS

Gene Section
Review

EPHA2 (EPH receptor A2)

Elisavet T Gatzidou, Stamatios Theocharis, Constantinos Giaginis

Department of Biology, School of Medicine, Democritus University of Thrace, Alexandroupolis, Greece (ETG), First Department of Pathology, Medical School, University of Athens, Athens, Greece (ST), Department of Food Science and Nutrition, University of the Aegean, Myrina, Lemnos, Greece (CG)

Published in Atlas Database: March 2012

Online updated version : http://AtlasGeneticsOncology.org/Genes/EPHA2ID40462ch1p36.html
DOI: 10.4267/2042/47529

Identity

Other names: ARCC2, CTPA, CTPP1, ECK

HGNC (Hugo): EPHA2

Location: 1p36.13

Note

EPHA2 was identified in 1990 by the screening of human epithelial cells (HeLa cells) cDNA library using degenerate probes designed to hybridize to highly conserved regions of protein tyrosine kinases. EPHA2 was initially referred to as Eck (epithelial cell kinase) for its expression in the majority of epithelial cells.

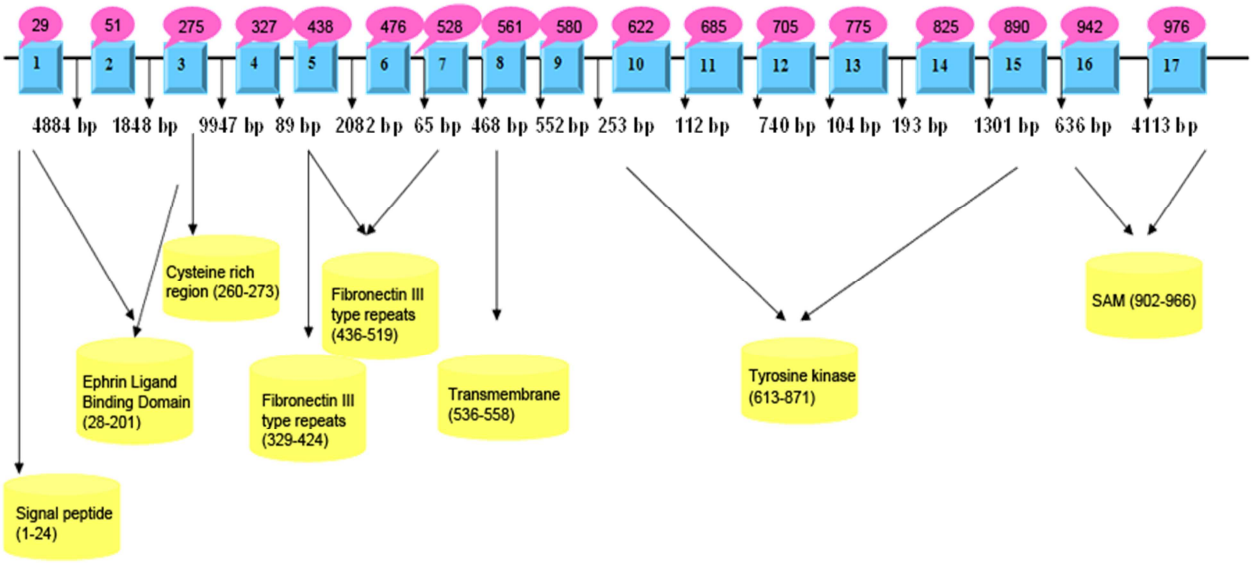
DNA/RNA

Description

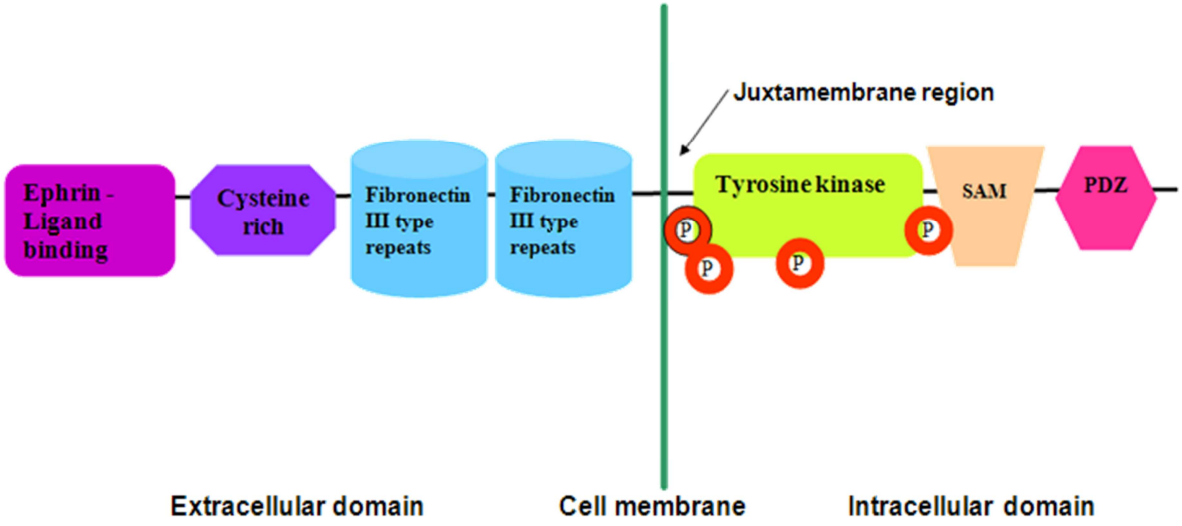
The EPHA2 is composed of 17 exons and 16 intervening introns spanning in a region of 31,73 kb.

Transcription

The transcribed mRNA was 3970 bp (NM_004431).



EPHA2 gene structure. This diagram presents exon as blue boxes, introns as connecting lines with bp, codons are numbered in pink boxes and the location of structural motifs of EPHA2 protein as yellow boxes.



Structure of EPHA2 protein.

Protein

Description

EPHA2 receptor is a transmembrane glycoprotein composed of 976 amino acid residues, with a calculated molecular mass of 130 kDa and an isoelectric point 6.1398. It is one member of the largest EPH (erythropoietin-producing hepatoma amplified sequence) family receptor tyrosine kinases. The family of Eph kinases binds ligands (known as ephrins) that are anchored to the membrane adjacent cells and consists of 16 known members across species, 14 of which are found in mammals and characterized by shared features in both the extracellular and intracellular domains.

EPH class receptors contain a single transmembrane spanning domain. Like other receptor tyrosine kinases, the extracellular domain of EPHA2 mediates ligand binding whereas the intacellular domain possesses intrinsic enzymatic activity.

The extracellular domain is glycosylated and is composed of globular, amino terminal domain followed by a cysteine-rich region with an epidermal growth factor-like motif and two fibronectin III-type repeats. The globular, amino-terminal domain contains immunoglobulin-like motifs and is both necessary and sufficient for ephrin-binding.

The intracellular domain includes a juxtamembrane region, a tyrosine kinase domain, a sterile alpha motif (SAM) and a PDZ-binding motif in the carboxy terminal end. The kinase domain and juxtamembrane region contain tyrosine residues and phosphorylation of these tyrosine residues creates docking sites for interaction with signalling proteins containing SH2/SH3 (Src - homology - 2/3) domains. SAM domain forms homodimers and may regulate receptor dimerization. The PDZ-binding motif binds to PDZ domain-containing proteins, which are though to serve as scaffolds for the assembly of multi-protein signalling complexes at the membrane.

EPHA2 shows 25-35% sequence homologies with other EPH receptors, and the tyrosine residues are conserved within the juxtamembrane and kinase domain.

Expression

EPHA2 is largely restricted at low levels on adult proliferating epithelial cells and enriched within sites of cell-cell adhesion in normal epithelial cells. EPHA2 expression has been detected in the brain, skin, bone marrow, lung, thymus, small intestine, colon, urinary bladder, kidney, liver, spleen, uterus, testis and prostate. EPHA2 expression levels in the colon, skin, kidney and lung were over 10-fold compared to those of the bone marrow. EPHA2 is also expressed during gastrulation in the ectodermal cells and early embryogenesis in the developing hind brain. In the skin, EphA2 is present in keratinocytes of epidermis and hair follicles but not in dermal cells, such as fibroblasts, vascular cells and inflammatory cells. EPHA2 has also been detected in proliferating mammary glands in female mice at puberty and differentially expressed during the estrous cycle. EPHA2 is widely unregulated and functionally altered in a variety of carcinomas and is implicated in cell transformation, primary tumor initiation, angiogenesis and metastasis in advanced cancer models. Overexpression has been shown both at the mRNA and protein level in established cell lines and human clinical specimens. Consistent findings indicate the prevalence of EPHA2 overexpression in many cancers, including glioblastoma, colorectal, gastric, esophageal, breast, thyroid, ovarian, endometrial, cervical, pancreatic, prostate, melanoma, bladder, renal cell, lung and hepatocellular carcinoma.

Localisation

The EPHA2 is localized to the cell membrane.

Function

The ligands for the EPH receptors are ephrins, which are 9 members and also fall into 2 subclasses: the GPI (glycosylphosphatidylinositol) anchored A-class of ligands (Ephrin A1-6) and the transmembrane B-class of ligands (B1-3).
EPH receptors interact with their cognate membrane anchored ligands at cell-cell contact sites to activate bidirectional signaling pathways effecting diverse physiologic processes including cell adhesion, repulsion, morphology, migration, differentiation and proliferation. Specifically, EPHA2 is activated by the ligand ephrin A1/EFNA1 and regulates migration, proliferation, integrin-mediated adhesion and differentiation of cells.
EPH receptor signaling has been implicated in many biological processes such as axon guidance and fasciculation, tissue border formation, neuronal targeting and angiogenesis during embryonic development. Especially, EPHA2 is involved in angiogenesis, in early hindbrain development and epithelial proliferation and branching morphogenesis during mammary gland development. EPHA2 with ephrin A2/EFNA2 may play a role in bone remodeling through regulation of osteoclastogenesis and osteoblastogenesis. It also engaged with the ephrin A5/EFNA5 and may regulate lens fiber cells shape and interactions and be critical for lens transparency development and maintenance.
Emerging evidence implicates EPHA2 overexpression in cell transformation, primary tumor initiation, progression, angiogenesis and metastasis in a variety of cancer models.

Homology

Human EPHA2 shares 96% amino acid identity with the chimpanzee, 95% amino acid identity with dogs, 94% with cows, 93% with mouse, 92% with rats and 56% amino acid identity with zebrafish.

Mutations

Note

Congenital cataract (CC) is one of the most significant causes of visual impairment and blidness in childhood. Approximately, up to 25% of all CC could be inherited, most often transmitting as an autosomal dominant trait and showing considerable inter- and intra-familial phenotypic variation.

Germinal

Loci for autosomal dominant posterior polar CC and total CC have both been mapped to chromosom 1p36 harboring the EPHA2 gene. Two missense mutations and one frameshift in the EPHA2 gene have been linked with posterior polar CC and one splicing mutation have been associated with total CC.
The c.2819 C>T (p.T940I) missense mutation changes an oligomerization interface of the SAM domain, most likely inactivating the EPHA2 signalling function by destroying its SAM domain.
The c.2842 G>T (p.G648W) missense mutation identified in exon 17 and occured at the first base of codon 948 and was predicted to result in substitution of glycine to tryptophan at the level of translation, placing it in the cytoplasmic SAM domain of EPHA2 gene.
The c.2915_2916delTG deletion of 2 bp discovered in exon 7 of EPHA2 gene and was predicted to result in a frameshift mutation creating a mutant protein with a novel C-terminal polypeptide of 39 amino acid residues.
The c.2826-9G>A is a splicing mutation with a single base substitution in intron 16 which creates a novel splice acceptor site causing an intronic sequence of 7 bp to be included in the processed transcript. This aberrant splicing is predicted to result in translational of a novel C-terminal polypeptide of 71 amino acid residues of which the last 39 are identical to that of the nove polypeptide produced bt the c.2915_2916delTG.

Implicated in

Various cancers

Note

EphA2 has been reported to be overexpressed in several cancers and a high level of EphA2 has been detected in malignant cancer-derived cell lines and advanced forms of cancer.

Prognosis

Eph-A2 overexpression was significantly associated with poor prognosis in several types of malignant tumors, including oral tongue, oesophageal, lung, renal, ovarian, cervical and endometrial carcinoma, as well as glioblastoma and melanoma. In human epidermal growth factor receptor 2 (Her2) positive breast cancer patients, increased levels of EphA2 mRNA were correlated to a decreased potential for overall and disease-free survival.

Epithelial ovarian carcinoma

Note

High EphA2 expression was evident in clinical specimens of invasive ovarian tumors, while little or no staining was observed in normal ovaries. Moreover, EphA2 overexpression was significantly associated with higher grade, advanced disease stage and with factors involved in invasion and angiogenesis. A relationship between EphA2 overexpression and the status of tumor suppressor p53 was noted. High EphA2 expressing tumors exhibited increased microvessel density when stained for CD31 as a measure of angiogenesis. In addition, the matrix metalloproteinase

expression, which degrades the extracellular matrix during cancer progression, was also associated with EphA2 expression.

Prostate cancer

Note

In clinical prostate carcinoma specimens, EphA2 immunoreactivity was increased with a positive staining in 60-100% of cells. EphA2 was overexpressed more in metastatic cells compared to non-invasive prostatic epithelial cells and its levels as increased as prostatic epithelial cells moved toward a more aggressive phenotype.

Breast cancer

Note

In breast carcinoma specimens, 92% of the cases showed moderate to high staining for EphA2. EphA2 overexpression in breast cancer was negatively associated with estrogen receptor expression. In clinical specimens of benign mammary epithelia, 75% of the specimens were negative, while 25% were weak positive.

Pancreatic carcinoma

Note

EphA2 was overexpressed in about 95% of pancreatic cancer specimens, being associated with metastatic disease, increased cellular invasiveness and patients' age.

Lung cancers

Note

In non-small cell lung cancer specimens, moderate to high EphA2 immunostaining was observed in the membrane and cytoplasm in more than 70% of the examined carcinomas. This increase was comparable in adenocarcinoma, squamous cell carcinoma and large cell carcinomas. EphA2 was also associated with clinically advanced stages of disease, the presence of brain metastasis and smoking status.

Brain cancers

Note

EphA2 was found to be overexpressed but not to be tyrosine phosphorylated in glioblastoma multiforme cells or tumors. In surgically resected human malignant glioma tissues, a heterogeneous and variable EphA2 staining pattern was observed. Although normal brain tissues exhibited minimal EphA2 staining, the cases of anaplastic astrocytoma and glioblastoma multiforme exhibited variable staining patterns. In astrocytic tumors, EphA2 overexpression was also correlated with the pathological grade and the proliferation status of tumors.

Urinary bladder carcinoma

Note

Clinical specimens of urinary bladder carcinoma when examined by a semi-quantitative immunostaining showed a differential staining pattern than normal specimens. Of all urinary bladder specimens with Ta grade lesions, 30% showed moderately strong staining, while in the T3 and T4 lesions, 75% and 90% of the samples showed strong staining, respectively. In sharp contrast, 85% of normal tissues showed weak staining, while the remaining 15% showed moderate staining for EphA2. Notably, EphA2 staining intensity was associated with advanced stage of urothelial carcinoma.

Melanoma

Note

EphA2 was found to be phosphorylated in aggressive melanoma-derived cells and was associated with vasculogenic mimicry, i.e. the formation of endothelial cell-like network. In a tissue microarray of melanomas, strong cytoplasmic EphA2 staining was present in 16% of the cases, being associated with histological thickness of melanomas and tumors proliferation status. A correlation of metastatic potential and high EphA2 expression was also observed in human melanoma cell lines derived from patients, while EphA2 overexpression changed cellular migration from the mesenchymal- to the amoeboid-type.

Oesophageal squamous cell carcinoma

Note

EphA2 overexpression was detected in esophageal carcinoma-derived cells and in 50% of clinical specimens. EphA2 expression was correlated with lymph node metastases, whereas no significant association with patients' age, tumour location, tumour size, histological differentiation and clinical stage was noted.

Colorectal carcinoma

Note

Increased expression of EphA2 was observed in over 59% of clinical specimens from colorectal cancer patients. EphA2 expression was increased in early-stage tumors compared to those of advanced stage, as well as in smaller tumors than large tumors. Microvessel count was also correlated with overexpression of EphA2. In human colon cancer-derived HCT116 cells, a dose and time-dependent upregulation of EphA2 was noticed after treatment with deoxycholic acid, a component of bile acids and promoter of colon cancer. The upregulation of EphA2 was p53-independent, but it was linked to the activation of MAP kinase pathway.

Renal cell carcinoma

Note

Higher levels of EphA2 expression were correlated with tumors that were of higher grade, larger and more highly vascularized in patients with renal cell carcinoma.

Vulvar carcinoma

Note

In vulvar cancers, more than 50% of vulvar squamous cell carcinomas expressed elevated levels of EphA2.

Malignant and benign thyroid malignancies

Note

Eph-A2 receptor was associated with increased proliferative activity of malignant thyroid lesions. Eph-A2 was significantly overexpressed in malignant compared to benign thyroid lesions. Papillary carcinoma cases also presented significantly increased Eph-A2 expression compared to those with hyperplasia nodules.

Squamous cell cervical carcinomas

Note

In early squamous cell cervical carcinomas, EphA2 expression was classified as negative in 21 tumors (10%), weak positive in 108 tumors (50%), moderate positive in 69 (32%) and strong positive in 19 tumors (9%).

Oral tongue squamous cell carcinoma

Note

In oral tongue SCC specimens, Eph-A2 expression was significantly correlated with tumor size, clinical stage, lymph invasion, recurrence and distant metastasis.

References

Lindberg RA, Hunter T. cDNA cloning and characterization of eck, an epithelial cell receptor protein-tyrosine kinase in the eph/elk family of protein kinases. Mol Cell Biol. 1990 Dec;10(12):6316-24

Ruiz JC, Robertson EJ. The expression of the receptor-protein tyrosine kinase gene, eck, is highly restricted during early mouse development. Mech Dev. 1994 May;46(2):87-100

Nakamoto M, Bergemann AD. Diverse roles for the Eph family of receptor tyrosine kinases in carcinogenesis. Microsc Res Tech. 2002 Oct 1;59(1):58-67

Kinch MS, Carles-Kinch K. Overexpression and functional alterations of the EphA2 tyrosine kinase in cancer. Clin Exp Metastasis. 2003;20(1):59-68

Kinch MS, Moore MB, Harpole DH Jr. Predictive value of the EphA2 receptor tyrosine kinase in lung cancer recurrence and survival. Clin Cancer Res. 2003 Feb;9(2):613-8

Miyazaki T, Kato H, Fukuchi M, Nakajima M, Kuwano H. EphA2 overexpression correlates with poor prognosis in esophageal squamous cell carcinoma. Int J Cancer. 2003 Feb 20;103(5):657-63

Fox BP, Kandpal RP. Invasiveness of breast carcinoma cells and transcript profile: Eph receptors and ephrin ligands as molecular markers of potential diagnostic and prognostic application. Biochem Biophys Res Commun. 2004 Jun 11;318(4):882-92

Kataoka H, Igarashi H, Kanamori M, Ihara M, Wang JD, Wang YJ, Li ZY, Shimamura T, Kobayashi T, Maruyama K, Nakamura T, Arai H, Kajimura M, Hanai H, Tanaka M, Sugimura H. Correlation of EPHA2 overexpression with high microvessel count in human primary colorectal cancer. Cancer Sci. 2004 Feb;95(2):136-41

Thaker PH, Deavers M, Celestino J, Thornton A, Fletcher MS, Landen CN, Kinch MS, Kiener PA, Sood AK. EphA2 expression is associated with aggressive features in ovarian carcinoma. Clin Cancer Res. 2004 Aug 1;10(15):5145-50

Han L, Dong Z, Qiao Y, Kristensen GB, Holm R, Nesland JM, Suo Z. The clinical significance of EphA2 and Ephrin A-1 in epithelial ovarian carcinomas. Gynecol Oncol. 2005 Nov;99(2):278-86

Herrem CJ, Tatsumi T, Olson KS, Shirai K, Finke JH, Bukowski RM, Zhou M, Richmond AL, Derweesh I, Kinch MS, Storkus WJ. Expression of EphA2 is prognostic of disease-free interval and overall survival in surgically treated patients with renal cell carcinoma. Clin Cancer Res. 2005 Jan 1;11(1):226-31

Landen CN, Kinch MS, Sood AK. EphA2 as a target for ovarian cancer therapy. Expert Opin Ther Targets. 2005 Dec;9(6):1179-87

Nakamura R, Kataoka H, Sato N, Kanamori M, Ihara M, Igarashi H, Ravshanov S, Wang YJ, Li ZY, Shimamura T, Kobayashi T, Konno H, Shinmura K, Tanaka M, Sugimura H. EPHA2/EFNA1 expression in human gastric cancer. Cancer Sci. 2005 Jan;96(1):42-7

Pasquale EB. Eph receptor signalling casts a wide net on cell behaviour. Nat Rev Mol Cell Biol. 2005 Jun;6(6):462-75

Wykosky J, Gibo DM, Stanton C, Debinski W. EphA2 as a novel molecular marker and target in glioblastoma multiforme. Mol Cancer Res. 2005 Oct;3(10):541-51

Abraham S, Knapp DW, Cheng L, Snyder PW, Mittal SK, Bangari DS, Kinch M, Wu L, Dhariwal J, Mohammed SI. Expression of EphA2 and Ephrin A-1 in carcinoma of the urinary bladder. Clin Cancer Res. 2006 Jan 15;12(2):353-60

Mudali SV, Fu B, Lakkur SS, Luo M, Embuscado EE, Iacobuzio-Donahue CA. Patterns of EphA2 protein expression in primary and metastatic pancreatic carcinoma and correlation with genetic status. Clin Exp Metastasis. 2006;23(7-8):357-65

Holm R, Knopp S, Suo Z, Tropè C, Nesland JM. Expression of EphA2 and EphrinA-1 in vulvar carcinomas and its relation to prognosis. J Clin Pathol. 2007 Oct;60(10):1086-91

Castaño J, Davalos V, Schwartz S Jr, Arango D. EPH receptors in cancer. Histol Histopathol. 2008 Aug;23(8):1011-23

Holm R, de Putte GV, Suo Z, Lie AK, Kristensen GB. Expressions of EphA2 and EphrinA-1 in early squamous cell cervical carcinomas and their relation to prognosis. Int J Med Sci. 2008 Jun 5;5(3):121-6

Shao Z, Zhang WF, Chen XM, Shang ZJ. Expression of EphA2 and VEGF in squamous cell carcinoma of the tongue: correlation with the angiogenesis and clinical outcome. Oral Oncol. 2008 Dec;44(12):1110-7

Shiels A, Bennett TM, Knopf HL, Maraini G, Li A, Jiao X, Hejtmancik JF. The EPHA2 gene is associated with cataracts linked to chromosome 1p. Mol Vis. 2008;14:2042-55

Vaught D, Brantley-Sieders DM, Chen J. Eph receptors in breast cancer: roles in tumor promotion and tumor suppression. Breast Cancer Res. 2008;10(6):217

Wang LF, Fokas E, Bieker M, Rose F, Rexin P, Zhu Y, Pagenstecher A, Engenhart-Cabillic R, An HX. Increased expression of EphA2 correlates with adverse outcome in primary and recurrent glioblastoma multiforme patients. Oncol Rep. 2008 Jan;19(1):151-6

Wykosky J, Debinski W. The EphA2 receptor and ephrinA1 ligand in solid tumors: function and therapeutic targeting. Mol Cancer Res. 2008 Dec;6(12):1795-806

Kamat AA, Coffey D, Merritt WM, Nugent E, Urbauer D, Lin YG, Edwards C, Broaddus R, Coleman RL, Sood AK. EphA2 overexpression is associated with lack of hormone receptor expression and poor outcome in endometrial cancer. Cancer. 2009 Jun 15;115(12):2684-92

Parri M, Taddei ML, Bianchini F, Calorini L, Chiarugi P. EphA2 reexpression prompts invasion of melanoma cells shifting from mesenchymal to amoeboid-like motility style. Cancer Res. 2009 Mar 1;69(5):2072-81

Taddei ML, Parri M, Angelucci A, Onnis B, Bianchini F, Giannoni E, Raugei G, Calorini L, Rucci N, Teti A, Bologna M, Chiarugi P. Kinase-dependent and -independent roles of EphA2 in the regulation of prostate cancer invasion and metastasis. Am J Pathol. 2009 Apr;174(4):1492-503

Zhang T, Hua R, Xiao W, Burdon KP, Bhattacharya SS, Craig JE, Shang D, Zhao X, Mackey DA, Moore AT, Luo Y, Zhang J, Zhang X. Mutations of the EPHA2 receptor tyrosine kinase gene cause autosomal dominant congenital cataract. Hum Mutat. 2009 May;30(5):E603-11

Cui XD, Lee MJ, Yu GR, Kim IH, Yu HC, Song EY, Kim DG. EFNA1 ligand and its receptor EphA2: potential biomarkers for hepatocellular carcinoma. Int J Cancer. 2010 Feb 15;126(4):940-9

Giaginis C, Tsourouflis G, Zizi-Serbetzoglou A, Kouraklis G, Chatzopoulou E, Dimakopoulou K, Theocharis SE. Clinical significance of ephrin (eph)-A1, -A2, -a4, -a5 and -a7 receptors in pancreatic ductal adenocarcinoma. Pathol Oncol Res. 2010 Jun;16(2):267-76

Karidis NP, Giaginis C, Tsourouflis G, Alexandrou P, Delladetsima I, Theocharis S. Eph-A2 and Eph-A4 expression in human benign and malignant thyroid lesions: an immunohistochemical study. Med Sci Monit. 2011 Sep;17(9):BR257-65

Tandon M, Vemula SV, Mittal SK. Emerging strategies for EphA2 receptor targeting for cancer therapeutics. Expert Opin Ther Targets. 2011 Jan;15(1):31-51

Ishikawa M, Miyahara R, Sonobe M, Horiuchi M, Mennju T, Nakayama E, Kobayashi M, Kikuchi R, Kitamura J, Imamura N, Huang CL, Date H. Higher expression of EphA2 and ephrin-A1 is related to favorable clinicopathological features in pathological stage I non-small cell lung carcinoma. Lung Cancer. 2012 Jun;76(3):431-8

This article should be referenced as such:

Gatzidou ET, Theocharis S, Giaginis C. EPHA2 (EPH receptor A2). Atlas Genet Cytogenet Oncol Haematol. 2012; 16(9):614-619.