

Gene Section

Review

EPHA1 (EPH receptor A1)

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Identity

Other names: EPH; EPHT; EPHT1; EphA1

HGNC (Hugo): EPHA1

Location: 7q34-35

Location (base pair): 7q35

Local order: (cen) ZYX ->, 8bp, <- EPHA1, 34.5kb, TASR60 -> (tel).

DNA/RNA

Description

EPHA1 consists of 18 exons and 17 introns and spans 17.78 kb of genomic DNA. EPHA1 is located within the human tilepath clone RP11-811J9.

Transcription

3,359 nucleotide mRNA. Two alternative splice variants, predicted to result in truncation within the extracellular domain of EphA1, have been reported.

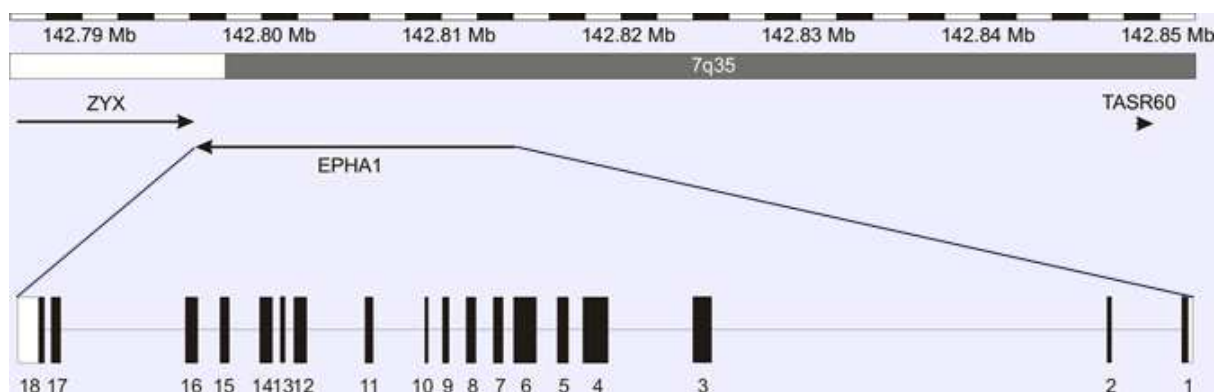
Pseudogene

None identified.

Protein

Note

EphA1 was isolated originally from an erythropoietin producing hepatoma cell line, from which its name, and the name of its gene family, derives.



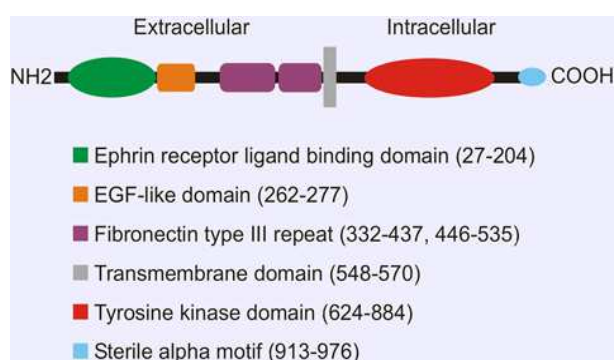
Genomic neighbourhood and organisation of EPHA1.

Description

The EPHA1 gene encodes a 976 amino acid protein with a calculated molecular weight of 108,126.89 and an isoelectric point of 6.6254. Amino acids 1-25 constitute a signal peptide.

EphA1 is the founding member of what is recognised as the largest subfamily of the receptor tyrosine kinases. This is an evolutionarily ancient protein group with members being present in sponges, worms and fruit flies. The expansion in the number of Eph receptor-encoding genes along with genes encoding their ligands, the ephrins (Eph receptor interacting proteins), is proposed to have contributed to the increase in complexity of the bilaterian body plan. Fourteen Eph receptors have been identified in vertebrates. These are subdivided into either EphA (EphA1, EphA2, EphA3, EphA4, EphA5, EphA6, EphA7, EphA8, EphA10) or EphB (EphB1, EphB2, EphB3, EphB4, EphB6) subclasses which differ primarily in the structure of their ligand binding domains. EphA receptors also exhibit greater affinity for binding GPI-linked ephrin-A ligands while EphB receptors bind transmembrane ephrin-B ligands. While interactions are somewhat promiscuous, and some cross-class binding occurs, each Eph receptor displays distinct affinity for the different ephrin ligands. Eph-ephrin binding involves cell-cell contact. Upon binding, both Eph and ephrin proteins on respective cells dimerise, and undergo higher order clustering. This results in signalling within both the Eph- and ephrin-bearing cells (bidirectional signalling) and either subsequent adhesion or repulsion of the interacting cells. Cell-cell contact, and thus Eph-ephrin signalling, may be terminated either by enzymatic cleavage of the extracellular domain of the Eph receptor or ephrin ligand or endocytosis of Eph-ephrin complexes.

The high affinity ligands for EphA1 are ephrin-A1 and ephrin-A3. EphA1 also binds fibronectin, a non-activating ligand.



Domain organisation of EphA1.

Expression

Embryonic stem (ES) cells and embryoid bodies differentiated from ES cells *in vitro*; dynamic and regionalised expression during murine embryogenesis (including epiblast, primitive streak,

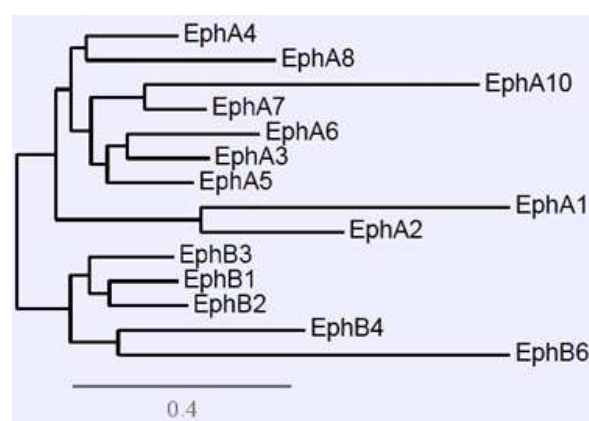
paraxial mesoderm, tail bud mesoderm, distal limb bud); human lung, small intestinal, kidney, bladder, thymus, skin and colon. Murine adult epithelial tissues (including epidermis of skin and vagina, endometrium, renal collecting system). Rat normal liver, kidney, lung. Human tumours and cell lines of epithelial origin.

Localisation

Membrane; single-pass type I membrane protein.

Function

Not yet entirely established. Generally repulsive interaction with its high affinity ligands ephrin-A1 and ephrin-A3. Transgenic expression of EphA1 in the blastula of pre-implantation mice is lethal (Duffy et al., unpublished). EphA1 homozygous null mice exhibit kinked tails (80%) and imperforate vagina (18% of females). The apparent absence of EphA1 in fish (zebrafish, medaka, fugu) and amphibia (*Xenopus*) and its emergence in vertebrates with reptiles (anole lizard) and birds (chicken) hints at an association with the transition of life from an aquatic to terrestrial environment. The presence of a membrane-embedded ionogenic Glu547 residue within the transmembrane domain of EphA1 also is unique among the Eph receptors. The structural-dynamic properties of the transmembrane domain have been shown to be dependent on the ionisation state of this residue, a finding that implies that the conformational flexibility and activation of the EphA1 receptor can be regulated by such external and local factors as pH and lipid composition of the membrane, a finding which may be of particular relevance to EphA1 function in the skin and kidney.



Homology

Phylogenetic tree for the Eph receptors. Amino acid sequences used for this compilation were EphA1 (NP_005223), EphA2 (NM_004431), EphA3 (NP_005224), EphA4 (NP_004429), EphA5 (NM_004439), EphA6 (ENSP00000374323), EphA7 (NP_004431), EphA8 (NP_065387), EphA10 (NP_001092909), EphB1 (NP_004432), EphB2 (NP_004433), EphB3 (NP_004434), EphB4 (NP_004435) and EphB6 (NP_004436).

Mutations

Germinal

No germinal mutations identified to be associated with cancer so far.

Somatic

Rare. A single heterozygous missense mutation E703K within the tyrosine kinase domain has been reported for a lobular breast carcinoma.

Implicated in

Colorectal cancer

Note

An immunohistochemical study of 20 colorectal adenomas and 111 colorectal carcinomas specimens detected EphA1 protein expression in all adenomas and reduced expression in 54% of colorectal cancers. Reduced expression of EphA1 was found more often in male patients ($P=0.028$) and in patients with poor differentiation ($P=0.027$), greater depth of wall invasion ($P=0.003$), lymph node metastasis ($P=0.034$), and advanced tumour stage ($P=0.003$).

Prognosis

Patients with colorectal cancer in this study with reduced EphA1 expression had a poor overall survival ($P=0.059$). Reduced EphA1 expression in patients over 55 years or with rectal cancers and sigmoid colon cancers was associated with a poor overall survival ($P=0.034$ and 0.015 , respectively).

Nonmelanoma skin cancer

Note

EphA1, which in human adults is expressed in the epidermis of the skin, is significantly downregulated at the protein level in basal cell and squamous cell carcinomas.

Glioblastoma

Note

EphA1 expression is significantly downregulated in human glioblastoma and glioblastoma cell lines.

Breast cancer

Note

Down regulation of EphA1 was associated with increased invasiveness in a breast cancer progression model using quantitative real time RT-PCR expression profiles of EphA1 mRNA in MCF-10A, MCF-7, and MDA-MB-231 cells, representing normal breast, non-invasive breast tumour, and invasive tumour, respectively, based on their characteristic phenotypes in Matrigel matrix.

Prostate cancer

Note

EphA1 mRNA transcript expression was found to decrease progressively in a panel of human prostate

cancer cell lines representative of the transition from normal prostate to primary prostate tumour to metastatic tumour.

Ovarian cancer

Note

Overexpression of EphA1 in the presence of elevated expression of its high affinity ligand ephrin-A1 was observed with more aggressive ovarian cancer phenotypes.

Head and neck squamous cell carcinoma (HNSCC)

Note

EphA1 was reported to be highly expressed in HNSCC using an approach that cloned receptor tyrosine kinases by RT-PCR using degenerate receptor tyrosine kinase primers from seven HNSCC specimens and confirmed abundant EphA1 protein expression by immunohistochemistry in eight independent HNSCC specimens.

References

- Hirai H, Maru Y, Hagiwara K, Nishida J, Takaku F. A novel putative tyrosine kinase receptor encoded by the eph gene. *Science*. 1987 Dec 18;238(4834):1717-20
- Maru Y, Hirai H, Yoshida MC, Takaku F. Evolution, expression, and chromosomal location of a novel receptor tyrosine kinase gene, eph. *Mol Cell Biol*. 1988 Sep;8(9):3770-6
- Maru Y, Hirai H, Takaku F. Overexpression confers an oncogenic potential upon the eph gene. *Oncogene*. 1990 Mar;5(3):445-7
- Owshalimpur D, Kelley MJ. Genomic structure of the EPHA1 receptor tyrosine kinase gene. *Mol Cell Probes*. 1999 Jun;13(3):169-73
- Castresana J. Selection of conserved blocks from multiple alignments for their use in phylogenetic analysis. *Mol Biol Evol*. 2000 Apr;17(4):540-52
- Boyd AW, Lackmann M. Signals from Eph and ephrin proteins: a developmental tool kit. *Sci STKE*. 2001 Dec 11;2001(112):re20
- Coulthard MG, Lickliter JD, Subanesan N, Chen K, Webb GC, Lowry AJ, Koblar S, Bottema CD, Boyd AW. Characterization of the EphA1 receptor tyrosine kinase: expression in epithelial tissues. *Growth Factors*. 2001;18(4):303-17
- Drescher U. Eph family functions from an evolutionary perspective. *Curr Opin Genet Dev*. 2002 Aug;12(4):397-402
- Guindon S, Gascuel O. A simple, fast, and accurate algorithm to estimate large phylogenies by maximum likelihood. *Syst Biol*. 2003 Oct;52(5):696-704
- Edgar RC. MUSCLE: multiple sequence alignment with high accuracy and high throughput. *Nucleic Acids Res*. 2004;32(5):1792-7
- 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
- Hafner C, Schmitz G, Meyer S, Bataille F, Hau P, Langmann T, Dietmaier W, Landthaler M, Vogt T. Differential gene

- expression of Eph receptors and ephrins in benign human tissues and cancers. *Clin Chem*. 2004 Mar;50(3):490-9
- Lin HS, Berry GJ, Fee WE Jr, Terris DJ, Sun Z. Identification of tyrosine kinases overexpressed in head and neck cancer. *Arch Otolaryngol Head Neck Surg*. 2004 Mar;130(3):311-6
- Stephens P, Edkins S, Davies H, Greenman C, Cox C, Hunter C, Bignell G, Teague J, Smith R, Stevens C, O'Meara S, Parker A, Tarpey P, Avis T, Barthorpe A, Brackenbury L, Buck G, Butler A, Clements J, Cole J, Dicks E, Edwards K, Forbes S, Gorton M, Gray K, Halliday K, Harrison R, Hills K, Hinton J, Jones D, Kosmidou V, Laman R, Lugg R, Menzies A, Perry J, Petty R, Raine K, Shepherd R, Small A, Solomon H, Stephens Y, Tofts C, Varian J, Webb A, West S, Widaa S, Yates A, Brasseur F, Cooper CS, Flanagan AM, Green A, Knowles M, Leung SY, Looijenga LH, Malkowicz B, Pierotti MA, Teh B, Yuen ST, Nicholson AG, Lakhani S, Easton DF, Weber BL, Stratton MR, Futreal PA, Wooster R. A screen of the complete protein kinase gene family identifies diverse patterns of somatic mutations in human breast cancer. *Nat Genet*. 2005 Jun;37(6):590-2
- Anisimova M, Gascuel O. Approximate likelihood-ratio test for branches: A fast, accurate, and powerful alternative. *Syst Biol*. 2006 Aug;55(4):539-52
- Chevenet F, Brun C, Bañuls AL, Jacq B, Christen R. TreeDyn: towards dynamic graphics and annotations for analyses of trees. *BMC Bioinformatics*. 2006 Oct 10;7:439
- Duffy SL, Steiner KA, Tam PP, Boyd AW. Expression analysis of the EphA1 receptor tyrosine kinase and its high-affinity ligands EfnA1 and EfnA3 during early mouse development. *Gene Expr Patterns*. 2006 Oct;6(7):719-23
- Fox BP, Tabone CJ, Kandpal RP. Potential clinical relevance of Eph receptors and ephrin ligands expressed in prostate carcinoma cell lines. *Biochem Biophys Res Commun*. 2006 Apr 21;342(4):1263-72
- Herath NI, Spanevello MD, Sabesan S, Newton T, Cummings M, Duffy S, Lincoln D, Boyle G, Parsons PG, Boyd AW. Overexpression of Eph and ephrin genes in advanced ovarian cancer: ephrin gene expression correlates with shortened survival. *BMC Cancer*. 2006 Jun 1;6:144
- Bocharov EV, Mayzel ML, Volynsky PE, Goncharuk MV, Ermolyuk YS, Schulga AA, Artemenko EO, Efremov RG, Arseniev AS. Spatial structure and pH-dependent conformational diversity of dimeric transmembrane domain of the receptor tyrosine kinase EphA1. *J Biol Chem*. 2008 Oct 24;283(43):29385-95
- Dereeper A, Guignon V, Blanc G, Audic S, Buffet S, Chevenet F, Dufayard JF, Guindon S, Lefort V, Lescot M, Claverie JM, Gascuel O. Phylogeny.fr: robust phylogenetic analysis for the non-specialist. *Nucleic Acids Res*. 2008 Jul 1;36(Web Server issue):W465-9
- Duffy SL, Coulthard MG, Spanevello MD, Herath NI, Yeadon TM, McCarron JK, Carter JC, Tonks ID, Kay GF, Phillips GE, Boyd AW. Generation and characterization of EphA1 receptor tyrosine kinase reporter knockout mice. *Genesis*. 2008 Oct;46(10):553-61
- Jin P, Zhang J, Sumariwalla PF, Ni I, Jorgensen B, Crawford D, Phillips S, Feldmann M, Shepard HM, Paleolog EM. Novel splice variants derived from the receptor tyrosine kinase superfamily are potential therapeutics for rheumatoid arthritis. *Arthritis Res Ther*. 2008;10(4):R73
- Masuda J, Usui R, Maru Y. Fibronectin type I repeat is a nonactivating ligand for EphA1 and inhibits ATF3-dependent angiogenesis. *J Biol Chem*. 2008 May 9;283(19):13148-55
- Pasquale EB. Eph-ephrin bidirectional signaling in physiology and disease. *Cell*. 2008 Apr 4;133(1):38-52
- Dong Y, Wang J, Sheng Z, Li G, Ma H, Wang X, Zhang R, Lu G, Hu Q, Sugimura H, Zhou X. Downregulation of EphA1 in colorectal carcinomas correlates with invasion and metastasis. *Mod Pathol*. 2009 Jan;22(1):151-60

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