

Gene Section

Review

EYA2 (EYA transcriptional coactivator and phosphatase 2)

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Abstract

EYA2 encodes a co-activator for the SIX family of homeobox transcription factors. The SIX/EYA transcriptional complex plays important roles in organogenesis, promoting the proliferation and survival of progenitor cells. Abnormal re-expression of EYA2 in adult tissue promotes tumorigenesis and metastasis in multiple tumor types. In addition to its role as a co-activator, the EYA Domain (ED) of EYA2 contains a unique HAD family Tyr phosphatase activity, which plays a role in ER β specific anti-tumor activity in breast cancer. The EYA2 Tyr phosphatase can also dephosphorylate H2AX, potentially playing a role in DNA damage repair. The N-terminal region of EYA2 also contains a Ser/Thr phosphatase activity, which may regulate the innate immune response.

Keywords: Transcriptional co-activator, phosphatase, organogenesis, oncogenesis.

Identity

Other names: EAB1

HGNC (Hugo): EYA2

Location : 20q13.12

DNA/RNA

Description

EYA2 gene is located at 20q13 (a frequently

amplified region (Zhang et al., 2005)) and has 16 exons.

Transcription

The transcript of EYA2 gene is 2702 bp long. Coding sequence of EYA2 starts at the 375th bp and ends at the 1991st bp of the mRNA.

Pseudogene

No pseudogene has been reported for EYA2.

Protein

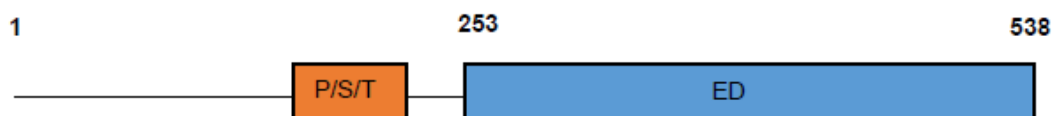
Description

The EYA2 gene encodes a 538 amino acid protein with a predicted molecular weight of 59 kDa.

It is composed of a flexible N-terminal region and a highly conserved C-terminal EYA domain (ED). The N-terminal region is poorly conserved among EYA family members (EYA1, EYA2, EYA3 and EYA4) and the lengths of the N-terminal region in EYA2 vary amongst species.

The N-terminal region contains a Pro/Ser/Thr rich transactivation domain that is responsible for activating SIX-mediated transcription (Xu et al., 1997a; Ohto et al., 1999).

The N-terminal region of all mouse EYA family members have been shown to possess Ser/Thr phosphatase activity, and this activity of EYA4 was shown to play a role in regulating the innate immune response (Okabe et al., 2009; Sano and Nagata, 2011).



A schematic representation of the EYA2 protein that contains a flexible N-terminal region and a highly conserved C-terminal EYA domain (ED).

The highly conserved C-terminal ED mediates the interaction between EYA2 and its protein partners, including SIX1 (Patrick et al., 2013). The ED of EYA2 also contains Mg^{2+} -dependent Tyr phosphatase activity (Krishnan et al., 2009; Yuan et al., 2014). Crystal structures of both the ED of human EYA2 and the SIX1/EYA2 ED complex have been determined, providing detailed structural information for the C-terminal half of EYA2 (Jung et al., 2010; Patrick et al., 2013).

Expression

To date, there has been no investigation of EYA2 protein levels in different developmental stages or tissues, but the mRNA transcripts of EYA2 have been examined by Northern blot, real time RT-PCR or in situ hybridization.

In general, EYA2 expression is high and widespread in embryo and is low and limited in adult tissues.

In situ hybridization in mouse embryo detected *Eya2* in facioacoustic ganglionic complex, epibranchial placodes, nasal placodes, somites, branchial arch ectoderm, the trigeminal, dorsal root ganglia, cranial placodes, central nervous system, neural retina, sclera, optic nerve sheath (Xu et al., 1997b), and the tendons and ligaments of the limb (Xu et al., 1997a). EYA2 expression in limb displayed a pattern similar to that of SIX1.

In newborn mice, EYA2 was detected using Northern blot in the eye, brain, and lung at high levels, but was not detected in the skin, liver, intestine, and kidney (Duncan et al., 1997).

In adult mice, EYA2 mRNA remains at high levels in the eye lens, and is decreased in the lung and brain based on Northern blot analyses (Duncan et al., 1997). EYA2 mRNA can also be detected in thymus and uterus (Zimmerman et al., 1997).

In adult humans, EYA2 was predominantly observed in muscle, and at lower levels in kidney, placenta, brain, and pancreas based on Northern blot analyses (Duncan et al., 1997). RT-PCR revealed EYA2 mRNAs in human testis, colon, thymus, thyroid and prostate (Zhang et al., 2005).

Localisation

EYA2 is localized in both the nucleus and cytoplasm (Ohto et al., 1999; Fougousse et al., 2002; Farabaugh et al., 2012). The SIX proteins actively translocate EYAs into the nucleus for SIX/EYA mediated transcriptional activation (Ohto et al., 1999).

Function

EYA2 functions both as a transcriptional co-activator and a protein phosphatase. Although EYA2 is best known for its role as a co-activator for the SIX family transcription factors, it can also form complexes with PAX6 (Xu et al., 1997b) and DACHSHUND (Heanue et al., 1999) to mediate transcriptional activation of downstream genes. SIX proteins promote cell proliferation and survival (Ford et al., 1998; Li et al., 2002; Li et al., 2003; Del Bene et al., 2004; Coletta et al., 2004; Zou et al., 2004; Zou et al., 2006), likely by collaborating with EYA proteins including EYA2. EYA2 is involved in the development of eye, kidney, ear, heart (Duncan et al., 1997), limb (Xu et al., 1997a), and cranial placodes (Xu et al., 1997b). An *Eya2* transgene can rescue the eyeless phenotype in a fly *eya* mutant, implicating EYA2 as an important regulator of eye development (Bui et al., 2000). EYA2 also controls muscle development during organogenesis by regulating the expression of c-MYC, GDNF, and muscle determination genes such as MYOD, MRF4, and MYOG (Fougousse et al., 2002; Grifone et al., 2007). EYA2 may also activate novel anti-hypertrophic signaling pathways to prevent cardiac hypertrophy and heart failure (Lee et al., 2009).

The EYA domain of EYA2 contains a HAD family Tyr phosphatase activity, which dephosphorylates the Y36 residue of ER β (Yuan et al., 2014). Since phosphorylated Y36 is required for ER β to recruit co-activators to its target promoters and subsequent activation of antitumor transcriptional pathways, EYA2-mediated dephosphorylation of Y36 counteracts ER β dependent antitumor activity in breast cancer cell culture and mouse xenograft models (Yuan et al., 2014). In addition, the Tyr phosphatase activity of EYA3 was shown to dephosphorylate H2AX and leads cells to the DNA repair instead of apoptosis pathway upon DNA damage (Cook et al., 2009). Although EYA2 is also able to dephosphorylate H2AX (Krishnan et al., 2009), its direct role in DNA damage response has not been experimentally proven. Furthermore, the N-terminal region of EYA2 contains a Ser/Thr phosphatase activity, similar to EYA4 whose Ser/Thr phosphatase activity has been shown to play a role in innate immune response (Okabe et al., 2009).

Homology

The EYA Domain (ED) of human EYA2 has 64% sequence identity (83% similarity) with *Drosophila* EYA (Tadjuidje and Hegde, 2013), and 99% sequence identity (97% similarity) with mouse EYA2 (calculated by Clustal W). Within the human EYA family, EYA2 displays 83% sequence identity (92% similarity) with EYA1; 68% sequence identity (83% similarity) with EYA3; and 80% sequence identity (91% similarity) with EYA4 (Tadjuidje and Hegde, 2013).

Mutations

Germinal

No EYA2 mutants were reported.

Somatic

A number of genomic variants in normal individuals (Redon et al., 2006; Mills et al., 2006; de Smith et al., 2007; McCarroll et al., 2008; Park et al., 2010; Teague et al., 2010; Xu et al., 2011; Genomes Project et al., 2012; Wong et al., 2013) and cancer patients (COSMIC (Forbes et al., 2008) and TCGA (Cerami et al., 2012; Gao et al., 2013)) have been reported, although the correlation between these variants and any disease phenotypes is not yet clear. In addition, EYA2 is amplified in 14.8% of ovarian carcinomas and its protein product was detected in 93.6% of ovarian cancer specimens (Zhang et al., 2005). Aberrant overexpression of EYA2 is observed in breast cancer (Zhang et al., 2005; Farabaugh et al., 2012), lung adenocarcinoma (Zhang et al., 2005; Guo et al., 2009), prostate cancer (Zhang et al., 2005), desmoid tumors (Bacac et al., 2006), and urinary tract cancers (Zhang et al., 2005). The Oncomine database reveals that EYA2 is significantly overexpressed in multiple other tumor types, including infiltrating bladder urothelial carcinoma, superficial bladder cancer, glioblastoma, high grade squamous intraepithelial neoplasia, cervical cancer, and parathyroid gland adenoma (Patrick et al., 2013). On the other hand, decreased level of EYA2 by silencing methylations has been reported in colorectal cancers (Zou et al., 2007) and pancreatic cancer (Vincent et al., 2014).

Implicated in

Various cancers

Note

EYA2 is heavily implicated in breast tumorigenesis and metastasis. Knock down of EYA2 in SIX1-overexpressing MCF7 cells inhibits the ability of SIX1 to induce TGF- β signaling, epithelial-mesenchymal transition (EMT), and tumor initiating cell (TIC) characteristics, properties that are all associated with SIX1-induced tumorigenesis

and metastasis (Farabaugh et al., 2012). Examination of the Wang and Van de Vijver public breast cancer microarray datasets demonstrated that over-expression of SIX1 and EYA2 together (but not either gene alone) is significantly associated with shortened time to relapse and metastasis and shortened survival (Farabaugh et al., 2012). Disruption of the SIX1-EYA2 interaction inhibits SIX1-EYA2 mediated breast tumor metastasis in mouse model (Patrick et al., 2013).

EYA2 has also been shown to dephosphorylate Y36 of ER β and reduces ER β -mediated growth inhibition of breast cancer cells (Yuan et al., 2014).

In addition, high SIX1/EYA2 expression correlates with decreased survival in large cell lung carcinoma and more advanced stage in ovarian serous adenocarcinoma (Patrick et al., 2013).

References

- Duncan MK, Kos L, Jenkins NA, Gilbert DJ, Copeland NG, Tomarev SI. Eyes absent: a gene family found in several metazoan phyla. *Mamm Genome*. 1997 Jul;8(7):479-85
- Xu PX, Cheng J, Epstein JA, Maas RL. Mouse Eya genes are expressed during limb tendon development and encode a transcriptional activation function. *Proc Natl Acad Sci U S A*. 1997a Oct 28;94(22):11974-9
- Xu PX, Woo I, Her H, Beier DR, Maas RL. Mouse Eya homologues of the *Drosophila* eyes absent gene require Pax6 for expression in lens and nasal placode. *Development*. 1997b Jan;124(1):219-31
- Zimmerman JE, Bui QT, Steingrímsson E, Nagle DL, Fu W, Genin A, Spinner NB, Copeland NG, Jenkins NA, Bucan M, Bonini NM. Cloning and characterization of two vertebrate homologs of the *Drosophila* eyes absent gene. *Genome Res*. 1997 Feb;7(2):128-41
- Ford HL, Kabingu EN, Bump EA, Mutter GL, Pardee AB. Abrogation of the G2 cell cycle checkpoint associated with overexpression of HSIX1: a possible mechanism of breast carcinogenesis. *Proc Natl Acad Sci U S A*. 1998 Oct 13;95(21):12608-13
- Heanue TA, Reshef R, Davis RJ, Mardon G, Oliver G, Tomarev S, Lassar AB, Tabin CJ. Synergistic regulation of vertebrate muscle development by Dach2, Eya2, and Six1, homologs of genes required for *Drosophila* eye formation. *Genes Dev*. 1999 Dec 15;13(24):3231-43
- Ohto H, Kamada S, Tago K, Tominaga SI, Ozaki H, Sato S, Kawakami K. Cooperation of six and eya in activation of their target genes through nuclear translocation of Eya. *Mol Cell Biol*. 1999 Oct;19(10):6815-24
- Bui QT, Zimmerman JE, Liu H, Bonini NM. Molecular analysis of *Drosophila* eyes absent mutants reveals features of the conserved Eya domain. *Genetics*. 2000 Jun;155(2):709-20
- Fougerousse F, Durand M, Lopez S, Suel L, Demignon J, Thornton C, Ozaki H, Kawakami K, Barbet P, Beckmann JS, Maire P. Six and Eya expression during human somitogenesis and MyoD gene family activation. *J Muscle Res Cell Motil*. 2002;23(3):255-64
- Li X, Perissi V, Liu F, Rose DW, Rosenfeld MG. Tissue-specific regulation of retinal and pituitary precursor cell proliferation. *Science*. 2002 Aug 16;297(5584):1180-3

- Li X, Oghi KA, Zhang J, Kronen A, Bush KT, Glass CK, Nigam SK, Aggarwal AK, Maas R, Rose DW, Rosenfeld MG. Eya protein phosphatase activity regulates Six1-Dach-Eya transcriptional effects in mammalian organogenesis. *Nature*. 2003 Nov 20;426(6964):247-54
- Coletta RD, Christensen K, Reichenberger KJ, Lamb J, Micomonaco D, Huang L, Wolf DM, Müller-Tidow C, Golub TR, Kawakami K, Ford HL. The Six1 homeoprotein stimulates tumorigenesis by reactivation of cyclin A1. *Proc Natl Acad Sci U S A*. 2004 Apr 27;101(17):6478-83
- Del Bene F, Tessmar-Raible K, Wittbrodt J. Direct interaction of geminin and Six3 in eye development. *Nature*. 2004 Feb 19;427(6976):745-9
- Zou D, Silviu D, Fritsch B, Xu PX. Eya1 and Six1 are essential for early steps of sensory neurogenesis in mammalian cranial placodes. *Development*. 2004 Nov;131(22):5561-72
- Zhang L, Yang N, Huang J, Buckanovich RJ, Liang S, Barchetti A, Vezzani C, O'Brien-Jenkins A, Wang J, Ward MR, Courreges MC, Fracchioli S, Medina A, Katsaros D, Weber BL, Coukos G. Transcriptional coactivator *Drosophila eyes absent* homologue 2 is up-regulated in epithelial ovarian cancer and promotes tumor growth. *Cancer Res*. 2005 Feb 1;65(3):925-32
- Bacac M, Migliavacca E, Stehle JC, McKee T, Delorenzi M, Coindre JM, Guillou L, Stamenkovic I. A gene expression signature that distinguishes desmoid tumours from nodular fasciitis. *J Pathol*. 2006 Mar;208(4):543-53
- Mills RE, Luttig CT, Larkins CE, Beauchamp A, Tsui C, Pittard WS, Devine SE. An initial map of insertion and deletion (INDEL) variation in the human genome. *Genome Res*. 2006 Sep;16(9):1182-90
- Redon R, Ishikawa S, Fitch KR, Feuk L, Perry GH, Andrews TD, Fiegler H, Shapero MH, Carson AR, Chen W, Cho EK, Dallaire S, Freeman JL, González JR, Gratacòs M, Huang J, Kalaitzopoulos D, Komura D, MacDonald JR, Marshall CR, Mei R, Montgomery L, Nishimura K, Okamura K, Shen F, Somerville MJ, Tchinda J, Valsesia A, Woodwark C, Yang F, Zhang J, Zerjal T, Zhang J, Armengol L, Conrad DF, Estivill X, Tyler-Smith C, Carter NP, Aburatani H, Lee C, Jones KW, Scherer SW, Hurles ME. Global variation in copy number in the human genome. *Nature*. 2006 Nov 23;444(7118):444-54
- Zou D, Silviu D, Rodrigo-Blomqvist S, Enerbäck S, Xu PX. Eya1 regulates the growth of otic epithelium and interacts with Pax2 during the development of all sensory areas in the inner ear. *Dev Biol*. 2006 Oct 15;298(2):430-41
- de Smith AJ, Tsalenko A, Sampas N, Scheffer A, Yamada NA, Tsang P, Ben-Dor A, Yakhini Z, Ellis RJ, Bruhn L, Laderman S, Froguel P, Blakemore AI. Array CGH analysis of copy number variation identifies 1284 new genes variant in healthy white males: implications for association studies of complex diseases. *Hum Mol Genet*. 2007 Dec 1;16(23):2783-94
- Grifone R, Demignon J, Giordani J, Niro C, Souil E, Bertin F, Laclef C, Xu PX, Maire P. Eya1 and Eya2 proteins are required for hypaxial somitic myogenesis in the mouse embryo. *Dev Biol*. 2007 Feb 15;302(2):602-16
- Zou H, Harrington JJ, Shire AM, Rego RL, Wang L, Campbell ME, Oberg AL, Ahlquist DA. Highly methylated genes in colorectal neoplasia: implications for screening. *Cancer Epidemiol Biomarkers Prev*. 2007 Dec;16(12):2686-96
- Forbes SA, Bhamra G, Bamford S, Dawson E, Kok C, Clements J, Menzies A, Teague JW, Futreal PA, Stratton MR. The Catalogue of Somatic Mutations in Cancer (COSMIC). *Curr Protoc Hum Genet*. 2008 Apr;Chapter 10:Unit 10.11
- McCarroll SA, Kuruvilla FG, Korn JM, Cawley S, Nemesh J, Wysoker A, Shapero MH, de Bakker PI, Maller JB, Kirby A, Elliott AL, Parkin M, Hubbell E, Webster T, Mei R, Veitch J, Collins PJ, Handsaker R, Lincoln S, Nizzari M, Blume J, Jones KW, Rava R, Daly MJ, Gabriel SB, Altshuler D. Integrated detection and population-genetic analysis of SNPs and copy number variation. *Nat Genet*. 2008 Oct;40(10):1166-74
- Cook PJ, Ju BG, Telese F, Wang X, Glass CK, Rosenfeld MG. Tyrosine dephosphorylation of H2AX modulates apoptosis and survival decisions. *Nature*. 2009 Apr 2;458(7238):591-6
- Guo JT, Ding LH, Liang CY, Zhou NK, Ye QN. [Expression of EYA2 in non-small cell lung cancer]. *Zhonghua Zhong Liu Za Zhi*. 2009 Jul;31(7):528-31
- Krishnan N, Jeong DG, Jung SK, Ryu SE, Xiao A, Allis CD, Kim SJ, Tonks NK. Dephosphorylation of the C-terminal tyrosyl residue of the DNA damage-related histone H2A.X is mediated by the protein phosphatase eyes absent. *J Biol Chem*. 2009 Jun 12;284(24):16066-70
- Lee SH, Yang DK, Choi BY, Lee YH, Kim SY, Jeong D, Hajjar RJ, Park WJ. The transcription factor Eya2 prevents pressure overload-induced adverse cardiac remodeling. *J Mol Cell Cardiol*. 2009 Apr;46(4):596-605
- Okabe Y, Sano T, Nagata S. Regulation of the innate immune response by threonine-phosphatase of Eyes absent. *Nature*. 2009 Jul 23;460(7254):520-4
- Patrick AN, Schiemann BJ, Yang K, Zhao R, Ford HL. Biochemical and functional characterization of six SIX1 Branchio-oto-renal syndrome mutations. *J Biol Chem*. 2009 Jul 31;284(31):20781-90
- Jung SK, Jeong DG, Chung SJ, Kim JH, Park BC, Tonks NK, Ryu SE, Kim SJ. Crystal structure of ED-Eya2: insight into dual roles as a protein tyrosine phosphatase and a transcription factor. *FASEB J*. 2010 Feb;24(2):560-9
- Park H, Kim JI, Ju YS, Gokcumen O, Mills RE, Kim S, Lee S, Suh D, Hong D, Kang HP, Yoo YJ, Shin JY, Kim HJ, Yavartanoo M, Chang YW, Ha JS, Chong W, Hwang GR, Darvishi K, Kim H, Yang SJ, Yang KS, Kim H, Hurles ME, Scherer SW, Carter NP, Tyler-Smith C, Lee C, Seo JS. Discovery of common Asian copy number variants using integrated high-resolution array CGH and massively parallel DNA sequencing. *Nat Genet*. 2010 May;42(5):400-5
- Teague B, Waterman MS, Goldstein S, Potamouis K, Zhou S, Reslewic S, Sarkar D, Valouev A, Churas C, Kidd JM, Kohn S, Runnheim R, Lamers C, Forrest D, Newton MA, Eichler EE, Kent-First M, Surti U, Livny M, Schwartz DC. High-resolution human genome structure by single-molecule analysis. *Proc Natl Acad Sci U S A*. 2010 Jun 15;107(24):10848-53
- Sano T, Nagata S. Characterization of the threonine-phosphatase of mouse eyes absent 3. *FEBS Lett*. 2011 Sep 2;585(17):2714-9
- Xu H, Poh WT, Sim X, Ong RT, Suo C, Tay WT, Khor CC, Seielstad M, Liu J, Aung T, Tai ES, Wong TY, Chia KS, Teo YY. SgD-CNV, a database for common and rare copy number variants in three Asian populations. *Hum Mutat*. 2011 Dec;32(12):1341-9
- Cerami E, Gao J, Dogrusoz U, Gross BE, Sumer SO, Aksoy BA, Jacobsen A, Byrne CJ, Heuer ML, Larsson E, Antipin Y, Reva B, Goldberg AP, Sander C, Schultz N. The cBio cancer genomics portal: an open platform for exploring

multidimensional cancer genomics data. *Cancer Discov.* 2012 May;2(5):401-4

Farabaugh SM, Micalizzi DS, Jedlicka P, Zhao R, Ford HL. Eya2 is required to mediate the pro-metastatic functions of Six1 via the induction of TGF- β signaling, epithelial-mesenchymal transition, and cancer stem cell properties. *Oncogene.* 2012 Feb 2;31(5):552-62

Abecasis GR, Auton A, Brooks LD, DePristo MA, Durbin RM, Handsaker RE, Kang HM, Marth GT, McVean GA. An integrated map of genetic variation from 1,092 human genomes. *Nature.* 2012 Nov 1;491(7422):56-65

Gao J, Aksoy BA, Dogrusoz U, Dresdner G, Gross B, Sumer SO, Sun Y, Jacobsen A, Sinha R, Larsson E, Cerami E, Sander C, Schultz N. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. *Sci Signal.* 2013 Apr 2;6(269):pl1

Patrick AN, Cabrera JH, Smith AL, Chen XS, Ford HL, Zhao R. Structure-function analyses of the human SIX1-EYA2 complex reveal insights into metastasis and BOR syndrome. *Nat Struct Mol Biol.* 2013 Apr;20(4):447-53

Tadjuidje E, Hegde RS. The Eyes Absent proteins in development and disease. *Cell Mol Life Sci.* 2013

Jun;70(11):1897-913

Wong LP, Ong RT, Poh WT, Liu X, Chen P, Li R, Lam KK, Pillai NE, Sim KS, Xu H, Sim NL, Teo SM, Foo JN, Tan LW, Lim Y, Koo SH, Gan LS, Cheng CY, Wee S, Yap EP, Ng PC, Lim WY, Soong R, Wenk MR, Aung T, Wong TY, Khor CC, Little P, Chia KS, Teo YY. Deep whole-genome sequencing of 100 southeast Asian Malays. *Am J Hum Genet.* 2013 Jan 10;92(1):52-66

Vincent A, Hong SM, Hu C, Omura N, Young A, Kim H, Yu J, Knight S, Ayars M, Griffith M, Van Seuning I, Maitra A, Goggins M. Epigenetic silencing of EYA2 in pancreatic adenocarcinomas promotes tumor growth. *Oncotarget.* 2014 May 15;5(9):2575-87

Yuan B, Cheng L, Chiang HC, Xu X, Han Y, Su H, Wang L, Zhang B, Lin J, Li X, Xie X, Wang T, Tekmal RR, Curiel TJ, Yuan ZM, Elledge R, Hu Y, Ye Q, Li R. A phosphotyrosine switch determines the antitumor activity of ER β . *J Clin Invest.* 2014 Aug 1;124(8):3378-90

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