

## Gene Section

### Mini Review

# EGLN1 (egl nine homolog 1 (*C. elegans*))

Terhi Jokilehto, Panu M Jaakkola

Hypoxia group, Turku centre for Biotechnology, Tykistokatu 6, 20520 Turku, Finland

Published in Atlas Database: January 2008

Online updated version: <http://AtlasGeneticsOncology.org/Genes/EGLN1ID44140ch1q42.html>

DOI: 10.4267/2042/38569

This work is licensed under a Creative Commons Attribution-Non-commercial-No Derivative Works 2.0 France Licence.

© 2008 Atlas of Genetics and Cytogenetics in Oncology and Haematology

## Identity

**Hugo:** EGLN1

**Other names:** C1orf12; DKFZp761F179; ECYT3; HIFPH2; HPH-2; PHD2; SM-20; SM20; ZMYND6

**Location:** 1q42.2

## DNA/RNA

### Description

EGLN1 gene is located on chromosome 1, location 229568054-229627413. Gene spans 61293 bases and has 5 exons.

### Transcription

PHD2 expression is strongly induced in hypoxia by the HIF-1alpha transcription factor. Primary transcript length is 5936 bases. On mRNA level two splice variants have been proposed, lacking exons 3 or 4, but these have not been confirmed on protein level.

## Protein

### Description

PHD2 protein is 426 amino acids long and approximately 46 kDa. It has a zf-MYND domain (aa 21-58) and a 2-OG-FeII-oxygenase domain (aa 205-391).

### Expression

Ubiquitous.

### Localisation

Predominantly cytoplasmic.

### Function

PHD2 is a member of the 2-oxoglutarate-dependent, non-haem iron binding dioxygenases.

PHD2 post-translationally regulates the levels of

hypoxia-inducible factor-alpha (HIF-alpha) subunits in normoxic conditions by hydroxylating them in an oxygen-dependant manner on specific proline residues. This enables recognition of HIF by the VHL ubiquitin ligase complex and subsequent degradation of HIF by the proteasome. In hypoxic conditions the hydroxylation is significantly decreased, and the HIF-alpha subunits are stabilized. PHD2 is considered the main HIF-1alpha regulator in normoxic and mildly hypoxic conditions.

### Homology

EGLN1 has two paralogs: EGLN2 and EGLN3 homologs have been found in all multicellular organisms investigated.

## Mutations

**Note:** Homozygous deletion confers embryonic lethality in mouse.

### Germinal

Heterozygous mutations have been associated with familial erythrocytosis. Currently three point mutations: G1112A → Arg371His, C950G → Pro317Arg, C1129T → Gln377X, one deletion: 606delG → frameshift, and one insertion: 840\_841insA → frameshift have been reported.

## Implicated in

### Familial erythrocytosis (ECYT3)

**Note:** ECYT3 is characterized by increased serum hemoglobin and hematocrit, but with normal serum erythropoietin levels.

### Disease

Characterized EGLN1 mutations result in the loss of catalytic function and thereby aberrant erythropoietin expression.

## Head and neck squamous cell carcinoma

**Note:** Increased expression levels and nuclear translocation have been associated with the aggressiveness of the carcinoma.

## References

Dupuy D, Aubert I, Dupérat VG, Petit J, Taine L, Stef M, Bloch B, Arveiler B. Mapping, characterization, and expression analysis of the SM-20 human homologue, c1orf12, and identification of a novel related gene, SCAND2. *Genomics* 2000;69:348-354.

Epstein AC, Gleadle JM, McNeill LA, Hewitson KS, O'Rourke J, Mole DR, Mukherji M, Metzzen E, Wilson MI, Dhanda A, Tian YM, Masson N, Hamilton DL, Jaakkola P, Barstead R, Hodgkin J, Maxwell PH, Pugh CW, Schofield CJ, Ratcliffe PJ. C. elegans EGL-9 and mammalian homologs define a family of dioxygenases that regulate HIF by prolyl hydroxylation. *Cell* 2001;107:43-54.

Ivan M, Kondo K, Yang H, Kim W, Valiando J, Ohh M, Salic A, Asara JM, Lane WS, Kaelin WG Jr. HIF $\alpha$  targeted for VHL-mediated destruction by proline hydroxylation: implications for O<sub>2</sub> sensing. *Science* 2001;292(5516):464-468.

Jaakkola P, Mole DR, Tian YM, Wilson MI, Gielbert J, Gaskell SJ, Kriegsheim AV, Hebestreit HF, Mukherji M, Schofield CJ, Maxwell PH, Pugh CW, Ratcliffe PJ. Targeting of HIF- $\alpha$  to the von Hippel-Lindau ubiquitylation complex by O<sub>2</sub>-regulated prolyl hydroxylation. *Science* 2001;292:468-472.

Taylor MS. Characterization and comparative analysis of the EGLN gene family. *Gene* 2001 275:125-132.

Berra E, Benizri E, Ginouvès A, Volmat V, Roux D, Pouyssegur J. HIF prolyl-hydroxylase 2 is the key oxygen sensor setting low steady-state levels of HIF-1 $\alpha$  in normoxia. *EMBO J* 2003;22:4082-4090.

Hirsilä M, Koivunen P, Günzler V, Kivirikko KI, Myllyharju J. Characterization of the human prolyl 4-hydroxylases that modify the hypoxia-inducible factor. *J Biol Chem* 2003;278:30772-30780.

Metzen E, Berchner-Pfannschmidt U, Stengel P, Marxsen JH, Stolze I, Klinger M, Huang WQ, Wotzlaw C, Hellwig-Bürgel T,

Jelkmann W, Acker H, Fandrey J. Intracellular localisation of human HIF-1  $\alpha$  hydroxylases: implications for oxygen sensing. *J Cell Sci* 2003;116:1319-1326.

Appelhoff RJ, Tian YM, Raval RR, Turley H, Harris AL, Pugh CW, Ratcliffe PJ, Gleadle JM. Differential function of the prolyl hydroxylases PHD1, PHD2, and PHD3 in the regulation of hypoxia-inducible factor. *J Biol Chem* 2004;279:38458-38465.

Metzen E, Stiehl DP, Doege K, Marxsen JH, Hellwig-Bürgel T, Jelkmann W. Regulation of the prolyl hydroxylase domain protein 2 (phd2/egln-1) gene: identification of a functional hypoxia-responsive element. *Biochem J* 2005;387:711-717.

Jokilehto T, Rantanen K, Luukka M, Heikkinen P, Grenman R, Minn H, Kronqvist P, Jaakkola PM. Overexpression and nuclear translocation of hypoxia-inducible factor prolyl hydroxylase PHD2 in head and neck squamous cell carcinoma is associated with tumor aggressiveness. *Clin Cancer Res* 2006;12:1080-1087.

Percy MJ, Zhao Q, Flores A, Harrison C, Lappin TR, Maxwell PH, McMullin MF, Lee FS. A family with erythrocytosis establishes a role for prolyl hydroxylase domain protein 2 in oxygen homeostasis. *PNAS* 2006;103:654-659.

Takeda K, Ho VC, Takeda H, Duan LJ, Nagy A, Fong GH. Placental but not heart defects are associated with elevated hypoxia-inducible factor  $\alpha$  levels in mice lacking prolyl hydroxylase domain protein 2. *Mol Cell Biol* 2006;22:8336-8346.

Al-Sheikh M, Moradkhani K, Lopez M, Wajzman H, Préhu C. Disturbance in the HIF-1 $\alpha$  pathway associated with erythrocytosis: Further evidences brought by frameshift and nonsense mutations in the prolyl hydroxylase domain protein 2 (PHD2) gene. *Blood Cells Mol Dis* 2007;.

Percy MJ, Furlow PW, Beer PA, Lappin TR, McMullin MF, Lee FS. A novel erythrocytosis-associated PHD2 mutation suggests the location of a HIF binding groove. *Blood* 2007;110:2193-2196.

---

*This article should be referenced as such:*

Jokilehto T, Jaakkola PM. EGLN1 (egl nine homolog 1 (C. elegans)). *Atlas Genet Cytogenet Oncol Haematol*.2008;12(5):365-366.

---