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Gene Section
Review

VHL (von Hippel-Lindau tumor suppressor)

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Identity

HGNC (Hugo): VHL

Location: 3p25-26

Note
Tumour suppressor.

DNA/RNA

Description

The VHL gene spans 10 kb and is composed of three exons.

Transcription

The VHL gene encodes a 4.7 kb mRNA which is widely expressed in both foetal and adult tissues. An alternatively spliced VHL transcript has been detected reflecting the absence of exon 2 (isoform II) but no endogenous associated protein has been reported.

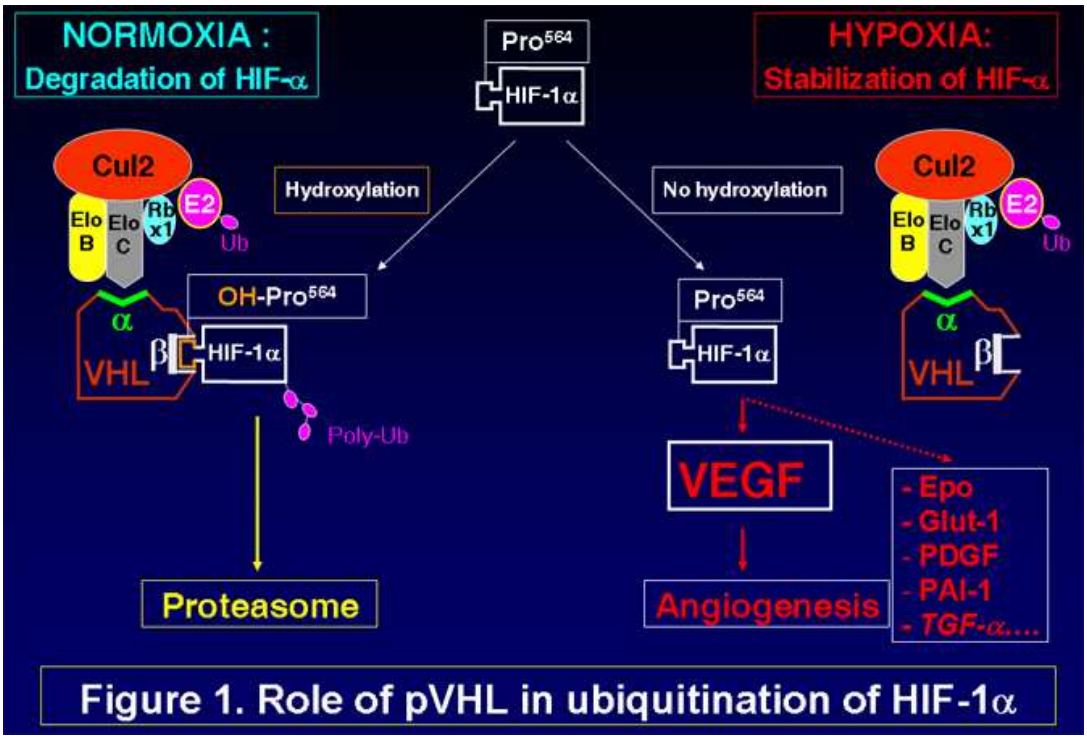

Figure 1. Role of pVHL in ubiquitination of HIF-1α

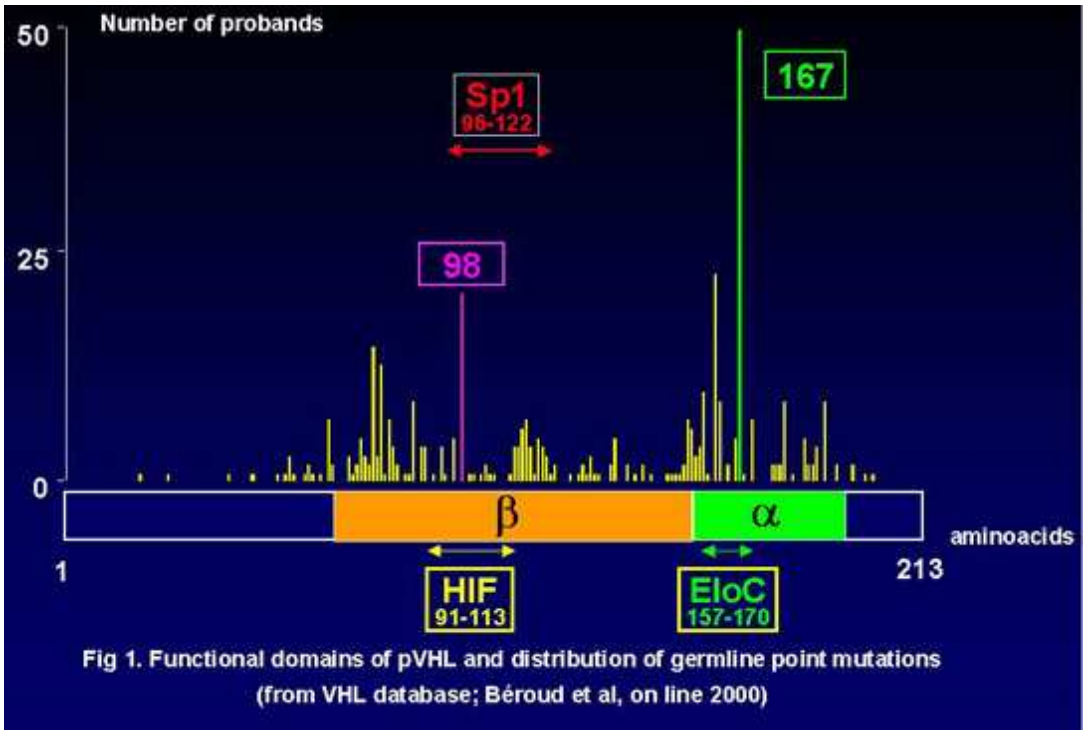

Fig 1. Functional domains of pVHL and distribution of germline point mutations (from VHL database; Béroud et al, on line 2000)

Protein

Description

The full-length VHL protein, pVHL, contains 213 amino-acids (28-30 kDa) ("pVHL30") A second major VHL-gene product arises by internal translation initiation from the codon 54 methionine, producing a 160 amino-acid protein (18-19 kDa) ("pVHL19").

Expression

pVHL is widely expressed in both foetal and adult human tissues.

Localisation

The pVHL is largely a cytoplasmic protein but appears to shuttle between the cytoplasm and nucleus.

Function

pVHL interacts with three other proteins, elongin C and B and Cullin 2 (CUL2), in a complex referred to as VCB-CUL2. pVHL has two main structural domains: an N-terminal domain composed mainly of b-sheets (the b domain) and a smaller C-terminal domain between aminoacids 155-192 composed mainly of a helices (a-domain). The a domain consists of three a helices that combines with a fourth a helice donated by elongin C. The b-domain is on the opposite side of the a domain and is free to contact other protein.

VHL and angiogenesis- A main function of the pVHL is to negatively regulate hypoxia-inducible mRNAs such as the mRNA encoding VEGF, EPO, PDGF and the glucose-transporter GLUT-1. pVHL plays a critical role in targeting the hypoxia-inducible transcription factor HIF-1a for degradation by the proteasome. HIF-1a contributes to form the HIF-1 transcriptional complex responsible for activation of genes involved in metabolism, angiogenesis and apoptosis. The VCB-CUL2 complex has been demonstrated as a ubiquitin-ligase system presenting many similarities with the SCF system ("Skp1-CUL1-Fbox protein"). HIF is normally degraded under normoxic conditions and binding to VHL is dependent on hydroxylation of Pro 564 in HIF-1a (Figure 1). When the VHL gene is mutated, absence of HIF degradation is responsible for abnormal accumulation of VEGF and other hypoxia-inducible mRNA explaining the angiogenic phenotype of VHL tumours. pVHL may also downregulate VEGF production by direct binding and inhibiting to the transcriptional activator SP1.

In homozygous VHL knock-out mice, embryos will die early because of a major disorder of placental vasculogenesis.

Other functions

pVHL plays a role in:

ability of cells to exit the cell cycle and enter the quiescent state.

assembly of extracellular fibronectin matrix.

degradation of TGFa LYT10, TGFb, and carbonic anhydrases CA9 and CA12.

regulation of the urokinase-type plasminogen activator system.

inhibition of the hepatocyte growth factor-induced invasion in renal cell carcinoma.

a direct interaction with atypical protein kinase C (PKC) z and l has also recently been demonstrated.

Thus, VHL appears as a multifunctional gene and may play a gatekeeper role especially in kidney.

Homology

The primary sequence structure of pVHL shows minimal homology to any knows protein but evolutionary conservation of the pVHL is very strong except for the first 53 amino acids.

Mutations

Germinal

Germline mutations cause von Hippel-Lindau disease. VHL mutations are heterogeneous and distributed widely throughout the coding sequence except 5' for the translation initiation site for pVHL19. There is a few recurrent mutations and only one founder effect is known, originating from Germany (T292C resulting in a Tyr98His substitution).
Point mutations occur in about 60% of cases (Figure 2) and large deletions in about 40%. VHL 1 (without pheochromocytoma) is mainly produced by mutations responsible for truncated protein (deletions, frameshift mutations and nonsense mutations). VHL type 2 (with high risk of pheochromocytoma) is mainly produced by missense mutations. Type 2B is the potentially "full" form of the disease (frequent mutations: Arg167Gln, Arg167Trp). Type 2A is associated with a very low risk of clear cell renal cell cancer (RCC) (common mutation: Tyr98His). Type 2C is characterized by the occurrence of pheochromo-cytoma only (example: Leu188Val).
Between 10 and 15% of cryptic VHL cases could be explained by de novo mutations and there are some cases of germline mosaicism.
There is some evidence that genetic modifiers may influence the phenotypic expression of the disease.

Somatic

Mutations are encountered in 60 % of sporadic clear cell RCC. In addition, 15% of tumours show evidence of inactivation by methylation. VHL alterations have been associated with occupational exposure to trichlorethylene.
Somatic mutations are also frequent in CNS sporadic hemangioblastoma but rarer in sporadic endolymphatic sac tumours, pancreatic serous cystadenomas and endocrine tumours, epididymal cystadenomas and pheochromocytomas.

Implicated in

von Hippel-Lindau disease

Disease

Von Hippel-Lindau (VHL) disease is a hereditary devastating cancer syndrome, predisposing to the development of various benign and malignant tumours (Central nervous system hemangio-blastomas and Retinal hemangioblastomas, endolymphatic sac tumours, clear cell renal cell cancer and/or renal cysts, pheochromocytoma, pancreatic cysts and neuroendocrine tumours, epididymal and broad ligament cystadenomas). VHL disease is the first cause of hereditary kidney cancer.

Sporadic renal cell carcinomas

Sporadic hemangioblastomas

References

Latif F, Tory K, Gnarra J, Yao M, Duh FM, Orcutt ML, Stackhouse T, Kuzmin I, Modi W, Geil L. Identification of the von Hippel-Lindau disease tumor suppressor gene. Science. 1993 May 28;260(5112):1317-20

Brauch H, Kishida T, Glavac D, Chen F, Pausch F, Höfler H, Latif F, Lerman MI, Zbar B, Neumann HP. Von Hippel-Lindau (VHL) disease with pheochromocytoma in the Black Forest region of Germany: evidence for a founder effect. Hum Genet. 1995 May;95(5):551-6

Neumann HP, Lips CJ, Hsia YE, Zbar B. Von Hippel-Lindau syndrome. Brain Pathol. 1995 Apr;5(2):181-93

Iliopoulos O, Levy AP, Jiang C, Kaelin WG Jr, Goldberg MA. Negative regulation of hypoxia-inducible genes by the von Hippel-Lindau protein. Proc Natl Acad Sci U S A. 1996 Oct 1;93(20):10595-9

Los M, Jansen GH, Kaelin WG, Lips CJ, Blijham GH, Voest EE. Expression pattern of the von Hippel-Lindau protein in human tissues. Lab Invest. 1996 Aug;75(2):231-8

Zbar B, Kishida T, Chen F, Schmidt L, Maher ER, Richards FM, Crossey PA, Webster AR, Affara NA, Ferguson-Smith MA, Brauch H, Glavac D, Neumann HP, Tisherman S, Mulvihill JJ, Gross DJ, Shuin T, Whaley J, Seizinger B, Kley N, Olschwang S, Boisson C, Richard S, Lips CH, Lerman M. Germline mutations in the Von Hippel-Lindau disease (VHL) gene in families from North America, Europe, and Japan. Hum Mutat. 1996;8(4):348-57

Decker HJ, Weidt EJ, Brieger J. The von Hippel-Lindau tumor suppressor gene. A rare and intriguing disease opening new insight into basic mechanisms of carcinogenesis. Cancer Genet Cytogenet. 1997 Jan;93(1):74-83

Maher ER, Kaelin WG Jr. von Hippel-Lindau disease. Medicine (Baltimore). 1997 Nov;76(6):381-91

Prowse AH, Webster AR, Richards FM, Richard S, Olschwang S, Resche F, Affara NA, Maher ER. Somatic inactivation of the VHL gene in Von Hippel-Lindau disease tumors. Am J Hum Genet. 1997 Apr;60(4):765-71

Béroud C, Joly D, Gallou C, Staroz F, Orfanelli MT, Junien C. Software and database for the analysis of mutations in the VHL gene. Nucleic Acids Res. 1998 Jan 1;26(1):256-8

Ivanov SV, Kuzmin I, Wei MH, Pack S, Geil L, Johnson BE, Stanbridge EJ, Lerman MI. Down-regulation of transmembrane carbonic anhydrases in renal cell carcinoma cell lines by wild-type von Hippel-Lindau transgenes. Proc Natl Acad Sci U S A. 1998 Oct 13;95(21):12596-601

Kaelin WG Jr, Maher ER. The VHL tumour-suppressor gene paradigm. Trends Genet. 1998 Oct;14(10):423-6

Knebelmann B, Ananth S, Cohen HT, Sukhatme VP. Transforming growth factor alpha is a target for the von Hippel-Lindau tumor suppressor. Cancer Res. 1998 Jan 15;58(2):226-31

Neumann HP, Bender BU, Berger DP, Laubenberger J, Schultze-Seemann W, Wetterauer U, Ferstl FJ, Herbst EW,

Schwarzkopf G, Hes FJ, Lips CJ, Lamiell JM, Masek O, Riegler P, Mueller B, Glavac D, Brauch H. Prevalence, morphology and biology of renal cell carcinoma in von Hippel-Lindau disease compared to sporadic renal cell carcinoma. J Urol. 1998 Oct;160(4):1248-54

Ohh M, Yauch RL, Lonergan KM, Whaley JM, Stemmer-Rachamimov AO, Louis DN, Gavin BJ, Kley N, Kaelin WG Jr, Iliopoulos O. The von Hippel-Lindau tumor suppressor protein is required for proper assembly of an extracellular fibronectin matrix. Mol Cell. 1998 Jun;1(7):959-68

Olschwang S, Richard S, Boisson C, Giraud S, Laurent-Puig P, Resche F, Thomas G. Germline mutation profile of the VHL gene in von Hippel-Lindau disease and in sporadic hemangioblastoma. Hum Mutat. 1998;12(6):424-30

Pause A, Lee S, Lonergan KM, Klausner RD. The von Hippel-Lindau tumor suppressor gene is required for cell cycle exit upon serum withdrawal. Proc Natl Acad Sci U S A. 1998 Feb 3;95(3):993-8

Stolle C, Glenn G, Zbar B, Humphrey JS, Choyke P, Walther M, Pack S, Hurley K, Andrey C, Klausner R, Linehan WM. Improved detection of germline mutations in the von Hippel-Lindau disease tumor suppressor gene. Hum Mutat. 1998;12(6):417-23

Webster AR, Richards FM, MacRonald FE, Moore AT, Maher ER. An analysis of phenotypic variation in the familial cancer syndrome von Hippel-Lindau disease: evidence for modifier effects. Am J Hum Genet. 1998 Oct;63(4):1025-35

Brauch H, Weirich G, Hornauer MA, Störkel S, Wöhl T, Brüning T. Trichloroethylene exposure and specific somatic mutations in patients with renal cell carcinoma. J Natl Cancer Inst. 1999 May 19;91(10):854-61

Cohen HT, Zhou M, Welsh AM, Zarghamee S, Scholz H, Mukhopadhyay D, Kishida T, Zbar B, Knebelmann B, Sukhatme VP. An important von Hippel-Lindau tumor suppressor domain mediates Sp1-binding and self-association. Biochem Biophys Res Commun. 1999 Dec 9;266(1):43-50

Gallou C, Joly D, Méjean A, Staroz F, Martin N, Tarlet G, Orfanelli MT, Bouvier R, Droz D, Chrétien Y, Maréchal JM, Richard S, Junien C, Béroud C. Mutations of the VHL gene in sporadic renal cell carcinoma: definition of a risk factor for VHL patients to develop an RCC. Hum Mutat. 1999;13(6):464-75

Iwai K, Yamanaka K, Kamura T, Minato N, Conaway RC, Conaway JW, Klausner RD, Pause A. Identification of the von Hippel-lindau tumor-suppressor protein as part of an active E3 ubiquitin ligase complex. Proc Natl Acad Sci U S A. 1999 Oct 26;96(22):12436-41

Koochekpour S, Jeffers M, Wang PH, Gong C, Taylor GA, Roessler LM, Stearman R, Vasselli JR, Stetler-Stevenson WG, Kaelin WG Jr, Linehan WM, Klausner RD, Gnarra JR, Vande Woude GF. The von Hippel-Lindau tumor suppressor gene inhibits hepatocyte growth factor/scatter factor-induced invasion and branching morphogenesis in renal carcinoma cells. Mol Cell Biol. 1999 Sep;19(9):5902-12

Kroll SL, Paulding WR, Schnell PO, Barton MC, Conaway JW, Conaway RC, Czyzyk-Krzeska MF. von Hippel-Lindau protein induces hypoxia-regulated arrest of tyrosine hydroxylase transcript elongation in pheochromocytoma cells. J Biol Chem. 1999 Oct 15;274(42):30109-14

Los M, Zeamari S, Foekens JA, Gebbink MF, Voest EE. Regulation of the urokinase-type plasminogen activator system by the von Hippel-Lindau tumor suppressor gene. Cancer Res. 1999 Sep 1;59(17):4440-5

Maxwell PH, Wiesener MS, Chang GW, Clifford SC, Vaux EC, Cockman ME, Wykoff CC, Pugh CW, Maher ER, Ratcliffe PJ. The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. Nature. 1999 May 20;399(6733):271-5

Ohh M, Kaelin WG Jr. The von Hippel-Lindau tumour suppressor protein: new perspectives. Mol Med Today. 1999 Jun;5(6):257-63

Ohh M, Takagi Y, Aso T, Stebbins CE, Pavletich NP, Zbar B, Conaway RC, Conaway JW, Kaelin WG Jr. Synthetic peptides define critical contacts between elongin C, elongin B, and the von Hippel-Lindau protein. J Clin Invest. 1999 Dec;104(11):1583-91

Okuda H, Hirai S, Takaki Y, Kamada M, Baba M, Sakai N, Kishida T, Kaneko S, Yao M, Ohno S, Shuin T. Direct interaction of the beta-domain of VHL tumor suppressor protein with the regulatory domain of atypical PKC isotypes. Biochem Biophys Res Commun. 1999 Sep 24;263(2):491-7

Pack SD, Zbar B, Pak E, Ault DO, Humphrey JS, Pham T, Hurley K, Weil RJ, Park WS, Kuzmin I, Stolle C, Glenn G, Liotta LA, Lerman MI, Klausner RD, Linehan WM, Zhuang Z. Constitutional von Hippel-Lindau (VHL) gene deletions detected in VHL families by fluorescence in situ hybridization. Cancer Res. 1999 Nov 1;59(21):5560-4

Stebbins CE, Kaelin WG Jr, Pavletich NP. Structure of the VHL-ElonginC-ElonginB complex: implications for VHL tumor suppressor function. Science. 1999 Apr 16;284(5413):455-61

Zbar B, Kaelin W, Maher E, Richard S. Third International Meeting on von Hippel-Lindau disease. Cancer Res. 1999 May 1;59(9):2251-3

Brauch H, Weirich G, Brieger J, Glavac D, Rödl H, Eichinger M, Feurer M, Weidt E, Puranakanitstha C, Neuhaus C, Pomer S, Brenner W, Schirmacher P, Störkel S, Rotter M, Masera A, Gugeler N, Decker HJ. VHL alterations in human clear cell renal cell carcinoma: association with advanced tumor stage and a novel hot spot mutation. Cancer Res. 2000 Apr 1;60(7):1942-8

Couch V, Lindor NM, Karnes PS, Michels VV. von Hippel-Lindau disease. Mayo Clin Proc. 2000 Mar;75(3):265-72

Murgia A, Martella M, Vinanzi C, Polli R, Perilongo G, Opocher G. Somatic mosaicism in von Hippel-Lindau Disease. Hum Mutat. 2000 Jan;15(1):114

Richard S, David P, Marsot-Dupuch K, Giraud S, Béroud C, Resche F. Central nervous system hemangioblastomas, endolymphatic sac tumors, and von Hippel-Lindau disease. Neurosurg Rev. 2000 Mar;23(1):1-22; discussion 23-4

Sgambati MT, Stolle C, Choyke PL, Walther MM, Zbar B, Linehan WM, Glenn GM. Mosaicism in von Hippel-Lindau disease: lessons from kindreds with germline mutations identified in offspring with mosaic parents. Am J Hum Genet. 2000 Jan;66(1):84-91

Vortmeyer AO, Huang SC, Koch CA, Governale L, Dickerman RD, McKeever PE, Oldfield EH, Zhuang Z. Somatic von Hippel-Lindau gene mutations detected in sporadic endolymphatic sac tumors. Cancer Res. 2000 Nov 1;60(21):5963-5

Woodward ER, Buchberger A, Clifford SC, Hurst LD, Affara NA, Maher ER. Comparative sequence analysis of the VHL tumor suppressor gene. Genomics. 2000 May 1;65(3):253-65

Baba M, Hirai S, Kawakami S, Kishida T, Sakai N, Kaneko S, Yao M, Shuin T, Kubota Y, Hosaka M, Ohno S. Tumor suppressor protein VHL is induced at high cell density and mediates contact inhibition of cell growth. Oncogene. 2001 May 17;20(22):2727-36

Blancher C, Moore JW, Robertson N, Harris AL. Effects of ras and von Hippel-Lindau (VHL) gene mutations on hypoxia-inducible factor (HIF)-1alpha, HIF-2alpha, and vascular endothelial growth factor expression and their regulation by the phosphatidylinositol 3'-kinase/Akt signaling pathway. Cancer Res. 2001 Oct 1;61(19):7349-55

Bonicalzi ME, Groulx I, de Paulsen N, Lee S. Role of exon 2-encoded beta -domain of the von Hippel-Lindau tumor suppressor protein. J Biol Chem. 2001 Jan 12;276(2):1407-16

Clifford SC, Astuti D, Hooper L, Maxwell PH, Ratcliffe PJ, Maher ER. The pVHL-associated SCF ubiquitin ligase complex: molecular genetic analysis of elongin B and C, Rbx1 and HIF-1alpha in renal cell carcinoma. Oncogene. 2001 Aug 16;20(36):5067-74

Clifford SC, Cockman ME, Smallwood AC, Mole DR, Woodward ER, Maxwell PH, Ratcliffe PJ, Maher ER. Contrasting effects on HIF-1alpha regulation by disease-causing pVHL mutations correlate with patterns of tumourigenesis in von Hippel-Lindau disease. Hum Mol Genet. 2001 May 1;10(10):1029-38

Davidowitz EJ, Schoenfeld AR, Burk RD. VHL induces renal cell differentiation and growth arrest through integration of cell-cell and cell-extracellular matrix signaling. Mol Cell Biol. 2001 Feb;21(3):865-74

de Paulsen N, Brychzy A, Fournier MC, Klausner RD, Gnarra JR, Pause A, Lee S. Role of transforming growth factor-alpha in von Hippel--Lindau (VHL)(-/-) clear cell renal carcinoma cell proliferation: a possible mechanism coupling VHL tumor suppressor inactivation and tumorigenesis. Proc Natl Acad Sci U S A. 2001 Feb 13;98(4):1387-92

Friedrich CA. Genotype-phenotype correlation in von Hippel-Lindau syndrome. Hum Mol Genet. 2001 Apr;10(7):763-7

Gallou C, Longuemaux S, Deloménie C, Méjean A, Martin N, Martinet S, Palais G, Bouvier R, Droz D, Krishnamoorthy R, Junien C, Béroud C, Dupret JM. Association of GSTT1 non-null and NAT1 slow/rapid genotypes with von Hippel-Lindau tumour suppressor gene transversions in sporadic renal cell carcinoma. Pharmacogenetics. 2001 Aug;11(6):521-35

Haase VH, Glickman JN, Socolovsky M, Jaenisch R. Vascular tumors in livers with targeted inactivation of the von Hippel-Lindau tumor suppressor. Proc Natl Acad Sci U S A. 2001 Feb 13;98(4):1583-8

Hoffman MA, Ohh M, Yang H, Klco JM, Ivan M, Kaelin WG Jr. von Hippel-Lindau protein mutants linked to type 2C VHL disease preserve the ability to downregulate HIF. Hum Mol Genet. 2001 May 1;10(10):1019-27

Ivan M, Kaelin WG Jr. The von Hippel-Lindau tumor suppressor protein. Curr Opin Genet Dev. 2001 Feb;11(1):27-34

Ivanov S, Liao SY, Ivanova A, Danilkovitch-Miagkova A, Tarasova N, Weirich G, Merrill MJ, Proescholdt MA, Oldfield EH, Lee J, Zavada J, Waheed A, Sly W, Lerman MI, Stanbridge EJ. Expression of hypoxia-inducible cell-surface transmembrane carbonic anhydrases in human cancer. Am J Pathol. 2001 Mar;158(3):905-19

Ivanova AV, Ivanov SV, Danilkovitch-Miagkova A, Lerman MI. Regulation of STRA13 by the von Hippel-Lindau tumor suppressor protein, hypoxia, and the UBC9/ubiquitin proteasome degradation pathway. J Biol Chem. 2001 May 4;276(18):15306-15

Karumanchi SA, Jiang L, Knebelmann B, Stuart-Tilley AK, Alper SL, Sukhatme VP. VHL tumor suppressor regulates Cl-/HCO3- exchange and Na+/H+ exchange activities in renal carcinoma cells. Physiol Genomics. 2001 Apr 2;5(3):119-28

Kim MS, Kwon HJ, Lee YM, Baek JH, Jang JE, Lee SW, Moon EJ, Kim HS, Lee SK, Chung HY, Kim CW, Kim KW. Histone deacetylases induce angiogenesis by negative regulation of tumor suppressor genes. Nat Med. 2001 Apr;7(4):437-43

Klein B, Weirich G, Brauch H. DHPLC-based germline mutation screening in the analysis of the VHL tumor suppressor gene: usefulness and limitations. Hum Genet. 2001 May;108(5):376-84

Kondo K, Kaelin WG Jr. The von Hippel-Lindau tumor suppressor gene. Exp Cell Res. 2001 Mar 10;264(1):117-25

Ma X, Yang K, Lindblad P, Egevad L, Hemminki K. VHL gene alterations in renal cell carcinoma patients: novel hotspot or founder mutations and linkage disequilibrium. Oncogene. 2001 Aug 30;20(38):5393-400

Mahon PC, Hirota K, Semenza GL. FIH-1: a novel protein that interacts with HIF-1alpha and VHL to mediate repression of HIF-1 transcriptional activity. Genes Dev. 2001 Oct 15;15(20):2675-86

Maxwell PH, Pugh CW, Ratcliffe PJ. Insights into the role of the von Hippel-Lindau gene product. A key player in hypoxic regulation. Exp Nephrol. 2001;9(4):235-40

Moore PS, Missiaglia E, Antonello D, Zamò A, Zamboni G, Corleto V, Falconi M, Scarpa A. Role of disease-causing genes in sporadic pancreatic endocrine tumors: MEN1 and VHL. Genes Chromosomes Cancer. 2001 Oct;32(2):177-81

Pioli PA, Rigby WF. The von Hippel-Lindau protein interacts with heteronuclear ribonucleoprotein a2 and regulates its expression. J Biol Chem. 2001 Oct 26;276(43):40346-52

Velickovic M, Delahunt B, Störkel S, Grebem SK. VHL and FHIT locus loss of heterozygosity is common in all renal cancer morphotypes but differs in pattern and prognostic significance. Cancer Res. 2001 Jun 15;61(12):4815-9

Wiesener MS, Münchenhagen PM, Berger I, Morgan NV, Roigas J, Schwiertz A, Jürgensen JS, Gruber G, Maxwell PH, Löning SA, Frei U, Maher ER, Gröne HJ, Eckardt KU. Constitutive activation of hypoxia-inducible genes related to overexpression of hypoxia-inducible factor-1alpha in clear cell renal carcinomas. Cancer Res. 2001 Jul 1;61(13):5215-22

Wykoff CC, Pugh CW, Harris AL, Maxwell PH, Ratcliffe PJ. The HIF pathway: implications for patterns of gene expression in cancer. Novartis Found Symp. 2001;240:212-25; discussion 225-31

Yu F, White SB, Zhao Q, Lee FS. Dynamic, site-specific interaction of hypoxia-inducible factor-1alpha with the von Hippel-Lindau tumor suppressor protein. Cancer Res. 2001 May 15;61(10):4136-42

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