Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL

INIST-CNRS

Gene Section
Review

PYGO2 (pygopus family PHD finger 2)

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Published in Atlas Database: June 2019
Online updated version : http://AtlasGeneticsOncology.org/Genes/PYGO2ID45884ch1q21.html
Printable original version : http://documents.irevues.inist.fr/bitstream/handle/2042/70695/06-2019-PYGO2ID45884ch1q21.pdf
DOI: 10.4267/2042/70695

Abstract

PYGO2 is member of a conserved family of plant homeo domain (PHD)-containing proteins and takes part in a wide range of developmental and transcriptional processes.
The most relevant role played by PYGO2 is in Wnt signaling pathway, where it is required for β-catenin/TCF-dependent transcription, even if it has showed to have a crucial role also in absence of β-catenin in tissues such as eye and testis.
PYGO2 is also known as a chromatin effector because of its implication in chromatin remodelling processes through regulation of histones methylation.

Keywords
PYGO2, Pygopus, Wnt signaling pathway, transcription factor, chromatin remodelling

Identity

Other names
Pygopus Homolog 2 (Drosophila), Pygopus Homolog 2, 190004M21 Rik, Pygopus 2

HGNC (Hugo) PYGO2

Location
1q21.3 [link to chromosomal band 1q21. [http://atlasgeneticsoncology.org/Bands/1q21.html]

Local order
Starts at 154957026 and ends at 154961782 from pter (according to hg38-Dec_2013)

DNA/RNA

Note
The PYGO2 gene (6828 bp) contains a total of 3 exons and the PYGO2 transcript is 3146 bp.

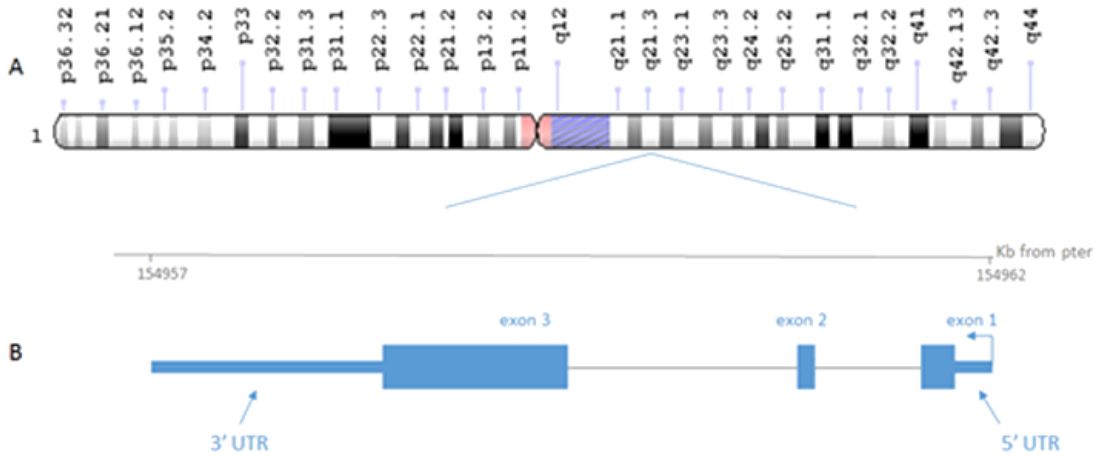

Figure 1: A) Location of PYGO2 gene on chr1. B) Schematic representation of PYGO2 gene, with its three exons.

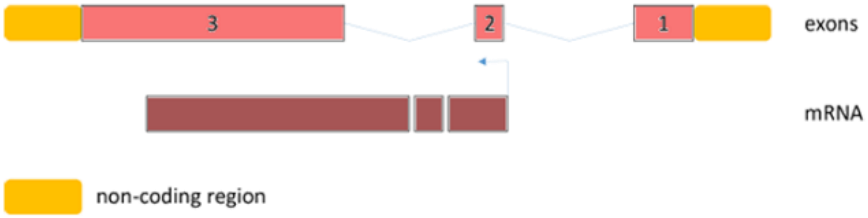

Figure 2: Schematic representation of PYGO2 gene.

Figure 3: Schematic illustration of domains of PYGO2 protein.

Description

Genomic size: 6828 bp. Exons count: 3. This gene has 3 transcript (splice variants), 112 orthologues and 1 paralogue

Transcription

3 transcript variants have been found for this gene (font. www.ensembl.org).
PYGO2-202 ENST00000368457.2 : mRNA 3146 bp, protein 406 aa
PYGO2-201 ENST00000368456.1 : mRNA 1306 bp, protein 369 aa
PYGO2-203 ENST00000483463.1 : mRNA 594 bp, no protein.

Protein

Description

PYGO2 protein, composed by 406 aa with a molecular mass of 41244 Da, is one of mammalian homologs of Drosophila Pygopus, essential for early embryonic development, moreover is known to be co-activator of the Wnt/β-catenin pathway transcriptional complex.
PYGO2 has two conserved domains, an N-terminal homology domain (NHD) and a C-terminal PHD zinc finger motif. The NHD domain plays an important role in transcriptional activation, taking part in the recruitment of histone modification factors and being involved in histone methylation (Gu et al., 2009). Deletion of NHD domain has been associated with 50% reduction of transcriptional activity (Liang et al., 2018). Moreover, in the N-terminal region, there is its nuclear localization signal-NLS (from aa 41 to aa 47) and a NPF (asparagine-proline-phenylalanine) sequence, which takes part in interactions with several proteins involved in chromatin remodelling. PYGO2 contains a plant homeodomain (PHD) finger, from aa 327 to aa 385, composed by 60 aminoacids organized in C4HC3 motives, which is important for the PYGO2 PHD-BCL9-HD1 complex formation (Miller et al., 2010).

Expression

The first molecular cloning and expression analysis of a mouse pygopus gene, mpygo2, were described by Li et al. (2004). Its transcripts were expressed in various adult mouse tissues, such as brain, heart, kidney, liver, lung, skin, small intestine, spleen, stomach, testis tissue and thymus; at the same manner, mpygo2 transcripts were detected in all embryos stages examined. The majority of tissues in which mpygo2 is expressed requires Wnt signaling activation for development, morphogenesis and maintenance and this is in line with the involvement of this gene in the Wnt signaling. Interestingly, since the hair follicle development is a well-known system which involves Wnt signaling, mpygo2 expression was detected both in developing and adult hair follicle (Li et al; 2004). The homologous Drosophila pygo gene is necessary to the binding with Lgs (legless) and for this reason Drosophila embryos homozygous for a pygo mutation, with any Pygo activity, die with a severe segment polarity phenotype (Kramps et al., 2002); this lethality is not found in mice. Mammals have two Pygopus homologues, Pygo1 and Pygo2, and the latter seems to be dominant (Schwab et al., 2007). The hPygo is expressed in a Wnt-dependent manner, in tissues such as kidney (Schwab et al., 2007), pancreas (Jonckheere et al., 2008), brain (Lake and Kao, 2003) and mammary gland (Gu et al., 2012); while is expressed in a Wnt-independent fashion for eye development (Song et al., 2007), spermiogenesis (Nair et al., 2008) and embryonic brain patterning (Lake and Kao, 2003). hPYGO2 shows high expression levels also in several types of cancer, in particular in epithelial ovarian cancer cell lines (Popadiuk et al., 2006), in several breast malignant tumours (Andrews et al., 2007), in gliomas and glioblastoma cells (Wang et al., 2010 14; Chen et al., 2011); recently hPYGO2 has been associated also

with adenomas and colon tumours (Brembeck et al., 2011) and esophageal squamous cell carcinoma (Moghbeli et al., 2013).

Localisation

PYGO2 is localized in the nucleus (UniProt Pygo2)

Function

PYGO2 protein is known to be implicated in chromatin remodelling and binding to methylated residues on lysine 4 of histone H3 (H3K4me), relevant for active transcription (Aasland et al., 1995). Has also been demonstrated that PYGO2 is involved in promoting trimethylation of the same residue (H3K4) and acetylation of H3K9/K14 (Gu et al., 2009; Chen et al., 2010). In addition, PYGO2 seems to act as scaffold protein between CTNNB1 (β-catenin), HNMT, TMPRSS11D (HAT) and the chromatin (Chen et al., 2010). This protein is also involved in signal transduction through the Wnt pathway and it showed a role in nuclear retention of β-catenin. Several studies reported that the NHD domain of Pygo regulates the transactivation activity, instead the PHD domain is responsible for the binding, through adaptor proteins, to the N-terminal domain of β-catenin (Townsley et al., 2004; Stadeli and Basler, 2005). Several studies reported not only the association with β-catenin to act as co-activators of the β-catenin/ LEF1/TCF complex (Kramps et al., 2002, Stadeli and Basler, 2005), but also the β-catenin independent association with LEF/TCF target genes (de la Roche and Bienz, 2007). In two of the most extensively characterized PYGO2-requiring tissues, testis and eye, its function is β-catenin independent. In the developing kidney PYGO2 shows wide expression in the ureteric bud and PYGO2 mutant phenotype resulted in reduced branching morphogenesis of this (Schwab et al., 2007). Similarly, a mutant phenotype has been observed also in pancreas, where lack of PYGO2 results in pancreas hypoplasia and defective endocrine cell differentiation (Jonckheere et al., 2008). PYGO2 demonstrated to play a role in development also in lung morphogenesis, because mpygo2$^{-/-}$ showed lungs pale and smaller than the wild type and with airways defects (Boan et al., 2007). Concerning the tissues where PYGO2 is not linked to the Wnt signalling, it showed to play a role in lens development, because of its expression in tissues of early eye such as optic vesicle and presumptive lens (Song et al., 2007), and during spermatogenesis, as a matter of fact its block leads to spermiogenesis arrest and infertility (Nair et al., 2008).

Homology

PYGO2 is conserved in human, mouse, rat, chimpanzee, cattle, dog and chicken.

Mutations

Somatic

Some somatic mutations have been identified and described by COSMIC (Catalogue of Somatic Mutation In Cancer) and they are listed mostly as substitutions and frameshift insertion or deletions; their role in disease has not yet been clarified.

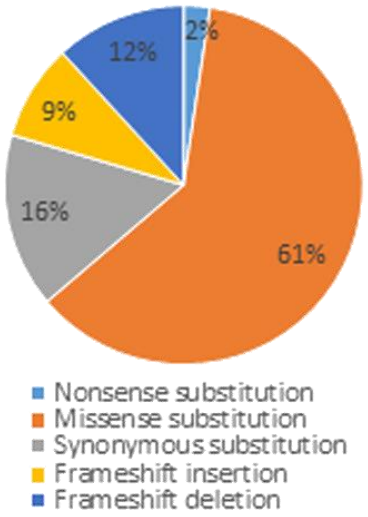

Figure 4: Overview of the major types of mutations occurring in PYGO2.

Implicated in

Metastatic prostate cancer

Prostate cancer (PrCa) is the most common malignancy in men. Since PYGO2 mRNA and protein show elevated levels in many androgen-dependent and androgen-independent PrCa cell lines (Kao et al., 2018), there could be evidences of his involvement in tumor progression. PYGO2 overexpression promotes prostate tumor growth and moreover regional lymph nodes invasion; instead its depletion results in cell cycle arrest, decreasing of cell proliferation and reduction of cell invasion (Lu et al., 2018).

Glioma

Glioma is one of the most common type of tumor that occurs in brain and spinal cord. Zhou et al (2016) found PYGO2 mRNA expression in the majority of primary glioma tissue of patients and this was increased compared to control. Interestingly, this overexpression correlates with some clinic-pathological features, such as the age and the tumor grade: it is present in patients over 50 years and in advanced tumors. Knockdown of PYGO2, in human brain glioma cell lines, leads to decreased mRNA and protein levels of some Wnt/β-catenin pathway downstream targets, acting through regulation of H2K4me3 level on their promoters.

Hepatic carcinoma

Hepatic carcinoma (HCC) is a primary malignancy of the liver. There are evidences (Zhang et al., 2015) that in HCC tissues PYGO2 mRNA and protein are highly expressed and it could play a role in HCC development and progression, showing positive regulation on cell migration. This positive regulation could be explained considering the fact that PYGO2 can bind to the promoter of CDH1 (E-cadherin) regulating its expression. Zhang and colleagues demonstrated that down-modulation of PYGO2 increased E-cadherin expression, resulting in increased cellular adhesion; indeed, a weak presence of PYGO2, and a subsequently wider presence of E-cadherin, leads to decreased invasion capability and metastasis formation.

Colon cancer

Colon cancer affects the large intestine and the primary source for the development of this type of cancer is the deregulation of Wnt/β-catenin signaling pathway, resulting in an overactivation of the entire pathway. Brembeck and colleagues (2011) demonstrated a PYGO2 overexpression in human colon cancer and for this reason has been investigated his oncogenic role. There are evidences that PYGO2 deletion decelerates tumor formation in chemically induced colon cancer, decreasing in a significant manner tumor number and size. This delay is caused by inhibition of Wnt signaling, because of the capability of PYGO2 to reduce overexpression of some Wnt/β-catenin target genes (Talla and Brembeck, 2016).

Non-small cell lung carcinoma

Non-small cell lung carcinoma (NSCLC) represents about 80% to 85% of lung cancers. Liu et al. (2013) demonstrated PYGO2 nuclear accumulation in more than half of the lung cancer samples analysed and determined a correlation between PYGO2 expression and some NSCLC clinic-pathological features, such as stages of tumor and survival. Moreover, viability assays demonstrated that PYGO2 silencing results in inhibition of lung cancer cells proliferation, via regulation of cell cycle and apoptosis.

Esophageal squamous cell carcinoma

Esophageal squamous cell carcinoma (ESCC) is a type of esophageal carcinoma that usually affects the upper or middle third part. For the first time Moghbeli et al. reported an association between the overexpression of PYGO2 and clinic-pathological features of ESCC, such as the grade of tumor differentiation, the tumor size and the age of patients. The exact role of PYGO2 in ESCC is unclear, but it has been demonstrated to have a significant correlation with EGFR, a type I transmembrane receptor which is broadly involved in various squamous cell carcinomas. Apparently, PYGO2 could act as transcriptional activator of EGFR, promoting the ESCC tumorigenesis

Epithelial ovarian cancer

Epithelial ovarian cancer is the most common type of ovarian cancer, almost 90% of ovarian cancers are epithelial. PYGO2 shows overexpression in six malignant epithelial ovarian cancer cell lines, compared to control. Interestingly it is overexpressed in both ovarian cancer tumors endometrioid and non-endometrioid, that differ from each other, respectively, for the activation and inactivation of Wnt pathway. Popadiuk et al. demonstrated that knockdown of Pygo2 results in reduction of mRNA and protein levels and it causes growth's inhibition.

Breast cancer

Breast cancer is the leading malignant female disease with a high percentage of chemoresistance. Watanabe et al. (2014) demonstrated that PYGO2 plays an important role in mammary tumorigenesis and its loss leads to delays in mammary tumors formation in mice, acting via both Wnt-dependent and independent mechanism. PYGO2 seems to play a role also in the onset of chemoresistance, activating a drug efflux transporter, ABCB1 (MDR1). To confirm this hypothesis, Zhang et al. (2016) demonstrated that knockdown of PYGO2 results in restoring sensitivity for chemotherapeutic drug.

Idiopathic azoospermia

Idiopathic azoospermia is a medical condition which implies the absence of sperm in semen. Two non-synonymous SNP mutations in PYGO2 have been reported to be implicated in this disease: rs61758740, M141I, has no effect on protein structure, and rs141722381, N240I, disrupts the protein structure and so it can be disease causing (Ge et al., 2015). These SNPs are reported in the National Center for Biotechnology Information SNP database (NCBI SNPdb).

References

Aasland R, Gibson TJ, Stewart AF. The PHD finger: implications for chromatin-mediated transcriptional regulation. Trends Biochem Sci. 1995 Feb;20(2):56-9

Andrews PG, Lake BB, Popadiuk C, Kao KR. Requirement of Pygopus 2 in breast cancer. Int J Oncol. 2007 Feb;30(2):357-63

Brembeck FH, Wiese M, Zatula N, Grigoryan T, Dai Y, Fritzmann J, Birchmeier W. BCL9-2 promotes early stages of intestinal tumor progression. Gastroenterology. 2011 Oct;141(4):1359-70, 1370.e1-3

Chen J, Luo Q, Yuan Y, Huang X, Cai W, Li C, Wei T, Zhang L, Yang M, Liu Q, Ye G, Dai X, Li B. Pygo2 associates with MLL2 histone methyltransferase and GCN5 histone acetyltransferase complexes to augment Wnt target gene

expression and breast cancer stem-like cell expansion. Molecular and cellular biology 30.24 (2010): 5621-5635.

Chen Y Y, Li B A, Wang H D, Liu X Y, Tan G W, Ma Y H, Shen S H, Zhu H W, Wang Z X. The role of Pygopus 2 in rat glioma cell growth. Medical Oncology 28.2 (2011): 631-640.

Ge SQ, Grifin J, Liu LH, Aston KI, Simon L, Jenkins TG, Emery BR, Carrell DT. Associations of single nucleotide polymorphisms in the Pygo2 coding sequence with idiopathic oligospermia and azoospermia Genet Mol Res 14.3 (2015): 9053-9061

Gu B, Sun P, Yuan Y, Moraes RC, Li A, Teng A, Agrawal A, Rhéaume C, Bilanchone V, Veltmaat JM, Takemaru K, Millar S, Lee EY, Lewis MT, Li B, Dai X. Pygo2 expands mammary progenitor cells by facilitating histone H3 K4 methylation. The Journal of cell biology 185.5 (2009): 811-826.

Gu B, Watanabe K, Dai X. Pygo2 regulates histone gene expression and H3 K56 acetylation in human mammary epithelial cells. Cell cycle 11.1 (2012): 79-87.

Jonckheere N, Mayes E, Shih HP, Li B, Lioubinski O, Dai X, Sander M. Analysis of mPygo2 mutant mice suggests a requirement for mesenchymal Wnt signaling in pancreatic growth and differentiation. Developmental biology 318.2 (2008): 224-235.

Kao KR, Popadiuk P, Thoms J, Aoki S, Anwar S, Fitzgerald E, Andrews P, Voisey K, Gai L, Challa S, He Z, Gonzales-Aguirre P, Simmonds A, Popadiuk C. PYGOPUS2 expression in prostatic adenocarcinoma is a potential risk stratification marker for PSA progression following radical prostatectomy. Journal of clinical pathology 71.5 (2018): 402-411.

Kramps T, Peter O, Brunner E, Nellen D, Froesch B, Chatterjee S, Murone M, Züllig S, Basler K. Wnt/wingless signaling requires BCL9/legless-mediated recruitment of pygopus to the nuclear β-catenin-TCF complex. Cell 109.1 (2002): 47-60.

Lake BB, Kao KR. Pygopus is required for embryonic brain patterning in Xenopus. Developmental biology 261.1 (2003): 132-148.

Li B, Mackay DR, Ma J, Dai X. Cloning and developmental expression of mouse pygopus 2, a putative Wnt signaling component. Genomics 84.2 (2004): 398-405.

Li B, Rhéaume C, Teng A, Bilanchone V, Munguia JE, Hu M, Jessen S, Piccolo S, Waterman ML, Dai X. Developmental phenotypes and reduced Wnt signaling in mice deficient for pygopus 2. Genesis 45.5 (2007): 318-325.

Liang Y, Wang C, Chen A, Zhu L, Zhang J, Jiang P, Yue Q, De G. Immunohistochemistry analysis of Pygo2 expression in central nervous system tumors. Journal of cell communication and signaling (2018): 1-10.

Liu Y, Dong QZ, Wang S, Fang CQ, Miao Y, Wang L, Li MZ, Wang EH. Abnormal expression of Pygopus 2 correlates with a malignant phenotype in human lung cancer. BMC cancer 13.1 (2013): 346.

Lu X, Pan X, Wu CJ, et al. An in vivo screen identifies PYGO2 as a driver for metastatic prostate cancer. Cancer research (2018): canres-3564.

Miller TC, Rutherford TJ, Johnson CM, Fiedler M, Bienz M. Allosteric remodelling of the histone H3 binding pocket in the Pygo2 PHD finger triggered by its binding to the B9L/BCL9 co-factor. Journal of molecular biology 401.5 (2010): 969-984.

Moghbeli M, Abbaszadegan MR, Farshchian M, Montazer M, Raeisossadati R, Abdollahi A, Forghanifard MM. Association of PYGO2 and EGFR in esophageal squamous cell carcinoma. Medical Oncology 30.2 (2013): 516.

Nair M, Nagamori I, Sun P, Mishra DP, Rhéaume C, Li B, Sassone-Corsi P, Dai X. Nuclear regulator Pygo2 controls spermiogenesis and histone H3 acetylation. Developmental biology 320.2 (2008): 446-455.

Popadiuk CM, Xiong J, Wells MG, Andrews PG, Dankwa K, Hirasawa K, Lake BB, Kao KR. Antisense suppression of pygopus2 results in growth arrest of epithelial ovarian cancer. Clinical Cancer Research 12.7 (2006): 2216-2223.

Schwab KR, Patterson LT, Hartman HA, Song N, Lang RA, Lin X, Potter SS. Pygo1 and Pygo2 roles in Wnt signaling in mammalian kidney development. BMC biology 5.1 (2007): 15.

Song N, Schwab KR, Patterson LT, Yamaguchi T, Lin X, Potter SS, Lang RA. pygopus 2 has a crucial, Wnt pathway-independent function in lens induction. Development 134.10 (2007): 1873-1885.

Städeli R, Basler K. Dissecting nuclear Wingless signalling: recruitment of the transcriptional co-activator Pygopus by a chain of adaptor proteins. Mechanisms of development 122.11 (2005): 1171-1182.

Talla SB, Brembeck FH. The role of Pygo2 for Wnt/β-catenin signaling activity during intestinal tumor initiation and progression. Oncotarget 7.49 (2016): 80612.

Townsley FM, Thompson B, Bienz M. Pygopus residues required for its binding to Legless are critical for transcription and development. Journal of Biological Chemistry 279.7 (2004): 5177-5183.

Wang ZX, Chen YY, Li BA, Tan GW, Liu XY, Shen SH, Zhu HW, Wang HD. Decreased pygopus 2 expression suppresses glioblastoma U251 cell growth. Journal of neuro-oncology 100.1 (2010): 31-41.

Watanabe K, Fallahi M, Dai X. Chromatin effector Pygo2 regulates mammary tumor initiation and heterogeneity in MMTV-Wnt1 mice. Oncogene 33.5 (2014): 632.

Zhang S, Li J, Liu P, Xu J, Zhao W, Xie C, Yin Z, Wang X. Pygopus-2 promotes invasion and metastasis of hepatic carcinoma cell by decreasing E-cadherin expression. Oncotarget 6.13 (2015): 11074.

Zhang ZM, Wu JF, Luo QC, Liu QF, Wu QW, Ye GD, She HQ, Li BA. Pygo2 activates MDR1 expression and mediates chemoresistance in breast cancer via the Wnt/β-catenin pathway. Oncogene 35.36 (2016): 4787.

Zhou C, Zhang Y, Dai J, Zhou M, Liu M, Wang Y, Chen XZ, Tang J. Pygo2 functions as a prognostic factor for glioma due to its up-regulation of H3K4me3 and promotion of MLL1/MLL2 complex recruitment. Scientific reports 6 (2016): 22066.

de la Roche M, Bienz M. Wingless-independent association of Pygopus with dTCF target genes. Current biology 17.6 (2007): 556-561.

This article should be referenced as such:

Esposito I., Cassaro A. PYGO2 (pygopus family PHD finger 2). Atlas Genet Cytogenet Oncol Haematol. 2020; 24(4):159-163.