

Gene Section

Review

PYGO2 (pygopus family PHD finger 2)

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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.

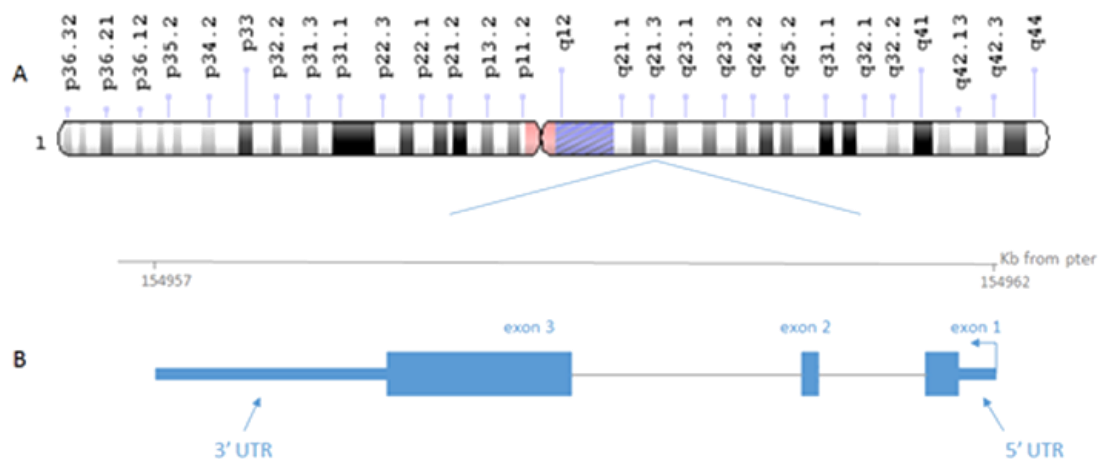


Figure 1: A) Location of PYGO2 gene on chr1. B) Schematic representation of PYGO2 gene, with its three exons.

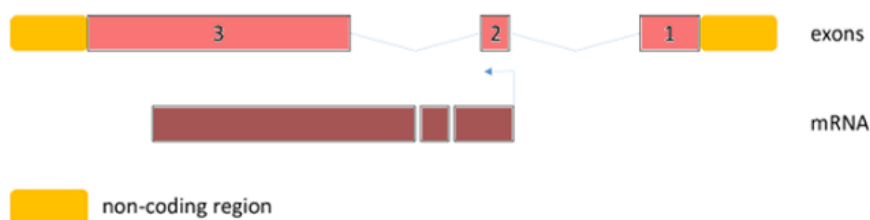


Figure 2: Schematic representation of PYGO2 gene.



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 (Townsend 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.

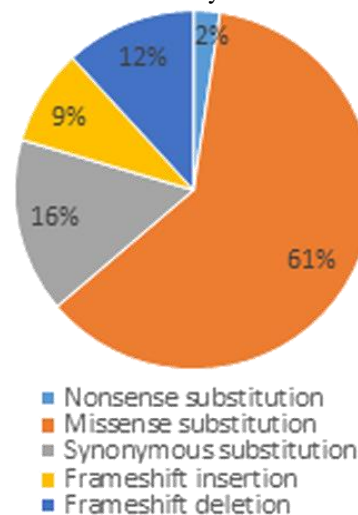


Figure 4: Overview of the major types of mutations occurring in PYGO2.

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).

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