

# Gene Section

## Review

## NPY1R (neuropeptide Y receptor Y1)

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### Identity

**Other names:** NPYR

**HGNC (Hugo):** NPY1R

**Location:** 4q32.2

### DNA/RNA

#### Note

**History:** The human NPY1R cDNA was cloned from a human brain cDNA library. The NPY1R was the first to be characterized, when the expression pattern of an orphan receptor was recognized to overlap with the distribution of NPY in brain. NPY receptors belong to the large superfamily of G-protein-coupled receptors. Many of these receptor genes lack introns, supporting the proposition that they were created via RNA-mediated transpositional events. Differently from the other NPY receptor isoforms NPY1R is the only one containing a single 97-base pairs (bp) intron in the coding region following the fifth transmembrane domain.

#### Description

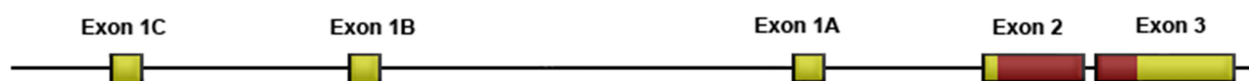
A 14-kilobase pair (kb) region of genomic DNA encoding the human neuropeptide Y Y1-receptor gene including 3'- and 5'- flanking sequences is localized to chromosome 4. It encompasses 8632 bp of DNA (4q32.2) between 164245117 and 164253748 bp. The

overall sequence of the gene consists of approximately 10 kb. The genomic structure presents a 6-kb intron situated approximately 150 bp upstream of the start codon within the 5'-untranslated region (5'UTR), as well as a small intron within the coding region.

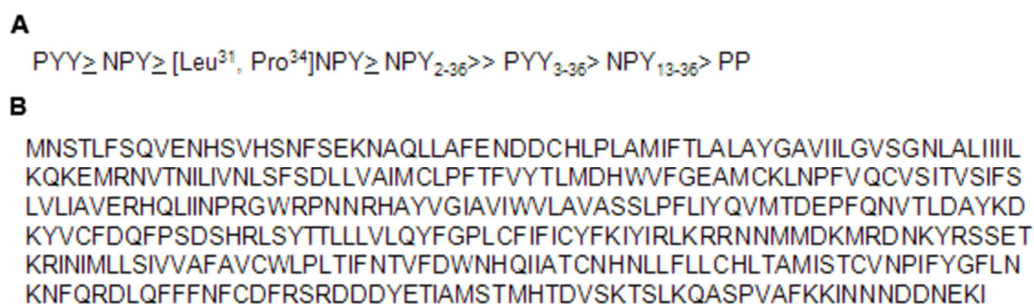
The human NPY1R gene is divided into three exons: exon 1 (115 bp), exon 2 (850 bp), and exon 3 (1749 bp). In particular, the NPY1R gene contains three alternative exon 1 sequences (80, 110, and 106 bp) located 6.4, 18.4, and 23.9 kb upstream of exon 2. Exon 1A is located 6.4 kb upstream of exon 2; exon 1B was found a further 12 kb upstream exon 1A, and exon 1C another 5.5 kb upstream of exon 1B. These alternative 5' exons allow the regulation of tissue-specific expression of the receptor. The first 57 nucleotides of the 5'UTR of the human NPY1R mRNA are separated by a 6-kb intron from the second exon. The second intron 97 bp, containing an in-frame stop codon, is located at nucleotide 908 in the protein coding region after the fifth transmembrane domain between exon 2 and 3. Moreover, as shown by Nakamura, mouse NPY1R gene contains an alternate exon 4 located over 15 kb downstream of exon 3.

#### Transcription

The human cDNA encodes a protein of 384 amino-acids (aa) in length that is preceded by approximately 200 bp of 5'UTR sequence.



Exon/intron structure and splice sites in the 5'UTR of the human NPY1R gene.



**Figure A.** Y1R affinity for various PP-family hormones and their C-terminal sequences.

**Figure B.** Homo sapiens Neuropeptide Y receptor type 1 (384 aa).

## Protein

### Note

The NPY Y1 receptor subtype (Y1R) was the first to be cloned in the rat, and subsequently in human and mouse. This receptor is as conserved as its ligand (NPY) throughout evolution and mammalian and non-mammalian species. The complete NPY<sub>1-36</sub> molecule is necessary for NPY to bind to Y1R. Any proteolytic process leading to alterations in the NH<sub>2</sub>-terminal domain essentially abolishes the ability of NPY to bind to Y1R. Therefore, NH<sub>2</sub>-terminally truncated NPY fragments such as NPY<sub>2-36</sub>, or NPY<sub>3-36</sub> have little or no affinity for the Y1R. Modification of COOH-terminal residues does not affect agonist binding. Thus, it has been established that the NH<sub>2</sub> terminus is essential for NPY to activate Y1R. The pharmacological profile of the Y1R is characterized by high affinity for NPY, PYY and the corresponding analogs containing Pro<sup>34</sup> and low affinity for the N-terminally truncated analogs and for PP.

### Description

Y1R has seven putative transmembrane domains associated with G-protein (GPCR). In the N-terminal portion Y1R presents potential sites of glycosylation and in the second extracellular loop, four extracellular cysteines in position 33, 113, 198 and 296 which may form two disulfide bridges (Cys 33 and 296; Cys 133 and 198). Phosphorylation sites are present in the intracellular domain (cysteine in the C-terminal portion at position 338). These cysteines may also explain the capability of palmitate residues to bind to the receptor. As observed for many GPCR, Y1R is internalized together with its ligand into endosomes and recycled to the cell surface within 60 minutes upon agonist stimulation. Moreover, Y1R is able to form homodimers.

### Expression

The expression of the human NPY Y1 receptor has been studied extensively by using immunohistochemical methods, in situ hybridization experiments and reverse-transcription polymerase chain reaction (RT-PCR; mRNA detection). The human

NPY1R is expressed in both central nervous system (i.e., cerebral cortex, thalamus and amigdala) and periphery (i.e., heart, kidneys, gastrointestinal tract, as well as blood vessels).

#### Nervous system

The NPY Y1R is widely distributed in the central nervous system. A study conducted on four normal human brains revealed that high levels of Y1R receptor mRNA were expressed in cortical areas and in the claustrum, while moderate levels were present in the nucleus accumbens, caudate nucleus, putamen, amygdaloid nuclei and arcuate and paraventricular nuclei of the hypothalamus. Moreover, a study conducted on prefrontal cortex of subjects affected by bipolar disorder, major depression, or schizophrenia revealed a progressive age-related decline in the expression of Y1R mRNA associated with a lack of coexpression with NPY neurons. Interestingly, there was no significant effect of suicide as a cause of death on Y1R mRNA expression levels. In fact, subjects with suicide as a cause of death tended to have higher Y1R mRNA expression levels, but these individuals were among the youngest ones (45 years old) in the population studied.

#### Periphery

Peripherally, Y1Rs are expressed mainly in arteries and veins, where they are associated with vasoconstriction and potentiation of other vasoconstrictors of neurogenic origin. Although limited, there is evidence of prejunctional Y1R inhibition of neurotransmitter release. Nonetheless, NPY Y1R is primarily located postjunctionally on vascular smooth muscle cells.

#### 1) Colon

In vitro receptor autoradiography ([<sup>125</sup>I]PYY) performed on normal human colonic tissue obtained from nine patients showed that Y1R is distributed only in vessels. No measurable levels of subtype Y1 was identified in smooth muscle, mucosa, muscularis mucosae, as well as in lymphoid follicles, myoenteric and submucosal plexus.

#### 2) Heart

A study conducted on 20-week old fetal human hearts showed that Y1R is present on right ventricular endocardial endothelial cells. In particular, it is highly

expressed at the level of the nucleus specifically at the perinucleoplasm and nuclear membrane levels, while lower levels were detected in the cytoplasm and the plasma membrane.

### 3) Dental pulp

NPY Y1R proteins were present in solubilized membrane preparations of both healthy and inflamed human gingival tissue by Western blotting. Major immunoreactive bands were detected at approximately 55 kDa due to a glycosylated form of the native receptor protein. By using the SwissProt glycosylation prediction packages NetNGlyc and NetOGly, authors confirmed that the human Y1R has potential N- and O-glycosylation sites. The expression of Y1R protein in both healthy and inflamed gingival tissue suggests that NPY could act via the Y1R to exert its tonic effects. Moreover, Y1R was expressed in human dental pulp with evidence of increased expression in carious compared with noncarious teeth. Y1R were localized to nerve fibres and inflammatory cells in the dental pulp of carious teeth.

### 4) Achilles tendons

Y1R is expressed in the tenocytes in the Achilles tendon. Specifically, Y1R is present within the smooth muscle of the blood vessel walls, but not in the endothelial layer of calcaneal tendons.

### 5) Skin

In human tissues, RT-PCR and immunocytochemistry studies suggested that Y1R is the primary receptor in human cutaneous circulation, supporting the findings that local non-noradrenergic mechanisms are entirely Y1R-based. Skin blood flow in humans is controlled through two branches of the sympathetic nervous system: a vasoconstrictor system and an active vasodilator system of uncertain neurotransmitter. In this context, NPY showed a vasoconstrictor effect in human subcutaneous arteries that had been dissected out of the abdominal regions from patients who underwent nonvascular disease surgeries (e.g., hernia). NPY decreased cutaneous blood flow via Y1R, with evidence for the additional involvement of postjunctional Y2R. This ability of NPY and Y1R to affect skin vascular conductance varies in accordance with relative innervations at specific sites.

### Localisation

NPY Y1R is a seven transmembrane receptor which has all the characteristics of the GPCR family including potential glycosylation sites in the N-terminal portion and in the second extra-cellular loop.

### Function

NPY has been demonstrated to be involved in mitogenic pathways and stimulate cell proliferation via the Y1R. The activation of Y1R is generally associated with reduction of cAMP accumulation, increase of intracellular free calcium concentration ( $[Ca^{2+}]_i$ ), and

modulation of the MAPK pathway via several signaling molecules, including the protein kinase C (PKC).

Y1R has been involved in several NPY-induced responses, such as activation of neuroendocrine axes, vasoconstriction, anxiolysis, as well as the stimulation of food intake. Moreover, Y1R mediates emotional behavior, stress response, and ethanol consumption.

The prototype of NPY Y1R-mediated responses is vasoconstriction. Specifically, the physiological role of the Y1R subtype was demonstrated in mice lacking Y1R expression, which show no blood pressure response to NPY, but a normal response to norepinephrine. Y1R knockout mice have normal blood pressure, suggesting that the Y1R does not play a crucial role in maintaining blood pressure homeostasis in unstimulated conditions. However, Y1R has been also involved in other NPY-induced responses, such as stimulation of food intake and activation of neuroendocrine axes. In particular, Y1R and Y5R, both expressed in hypothalamic regions involved in the control of feeding, represent the most likely candidates for mediating the appetite stimulatory capacity of NPY. Mice lacking Y1R showed an increased body weight due to a low-energy expenditure rather than high-energy intake. In fact, these mice had a decreased metabolic rate secondary to decreased locomotor activity and movement associated thermogenesis.

### Homology

The human Y1R subtype shares closest aa identity with the Y4R subtype (42%) and the non-active, human form of the y6 subtype (51%).

## Mutations

### Note

In 2004 Ramanathan described a case of autism in which a 19 megabase on chromosome 4q, spanning 4q32 to 4q34, was detected. Being involved in the deletion, those genes which are abundantly expressed in the brain, Y1R and Y5R resulted implicated. In this context, being the neuroproliferative effect of NPY in the hippocampus mediated through the neuropeptide Y Y1R, the authors postulate that the effect of NPY on learning and memory may be mediated through NPY neurogenesis.

Okahisa et al. described that genetic variants of rs7687423 of the NPY1R gene may alter the subjective effects of methamphetamine and result in susceptibility to dependence. Because NPY1R mRNA changes were observed in peripheral tissues and the brain in schizophrenia patients, these findings may also indicate that the NPY1R gene is involved in vulnerability to methamphetamine-induced psychosis because almost all of the analyzed subjects with methamphetamine dependence had comorbid methamphetamine psychosis.

## Implicated in

### Various tumors

#### Note

NPY receptors are mainly expressed in specific endocrine tumors and epithelial malignancies as well as in embryonal tumors. In endocrine tumors, NPY receptors are present in steroid hormone producing tumors, namely adrenal cortical adenomas, carcinomas, ovarian granulosa cell tumors, Sertoli-Leydig cell tumors, and in catecholamine producing tumors, i.e. pheochromocytomas and paragangliomas. Based on pharmacological displacement experiments, in addition to tumor cells, intra- and peritumoral blood vessels express Y1Rs. The Y1R-expressing blood vessels are mainly small and medium-sized arteries.

### Prostate cancer

#### Note

Prostate cancer represents one of the most common malignant diseases among men in the Western world. It is initially androgen dependent and it may later progress to the androgen-independent stage, which is associated with a lack of efficacy of the available hormonal therapy. This tumoral progression appears to be promoted at least in part by several growth factors and neurohormones. Within this context, we showed that Y1R protein is expressed in three human prostate cancer cell lines (LNCaP -androgen dependent-, DU145 and PC3 -androgen independent-) and that NPY treatment reduced the proliferation of LNCaP and DU145 cells and increased that of PC3 cells. Interestingly, the Y1R antagonist BIBP3226 abolished such effects, suggesting a mandatory role of Y1-R in this process. Moreover, these effects are associated with a clone-specific pattern of intracellular signaling activation, including a peculiar time-course of MAPK/ERK1/ERK2 phosphorylation (long-lasting in DU145 and transient in PC3 cells).

### Breast cancer

#### Note

Breast cancer accounts for almost 1/3 of all incident cases of cancer in women. Interestingly, the expression of NPY-Rs has been found in 85% of primary breast cancer in a series of 95 cases, and in 100% of lymph node metastases of receptor-positive primaries, where Y1R expression predominated and was often present in high density and great homogeneity. In normal breast tissue, however, Y1R was only found in a minority of the cases and concomitantly with Y2R, which seemed to be predominant in non-neoplastic breast. The neoplastic condition of breast tissue may thus induce a switch of expression from Y2R to Y1R.

Moreover, a functional interplay between estrogen and Y1R has been shown in a human breast cancer cell line responsive to this steroid, where estrogen was found to

increase Y1R expression, which in turn negatively regulated estrogen-stimulated cell proliferation.

### Pheochromocytoma and paraganglioma

#### Note

The frequency of NPY receptors (NPYRs) expression in pheochromocytomas and paragangliomas was found to be 35% and 61%, respectively. Both Y1R and Y2R are expressed, with a higher density of Y2R in paragangliomas than in pheochromocytomas, whereas the density of Y1R is comparably low in both tumor categories. NPYRs, mainly Y1R and Y5R, are also expressed in the Ewing's sarcoma family of tumors, other related neural crest-derived tumors, where activation of these receptors has been reported to regulate cell proliferation, as shown in the SK-N-MC cell line, an Ewing's sarcoma family of tumors expressing Y1R, where NPY has been shown to inhibit cell growth.

## References

- Soares MB, Schon E, Henderson A, Karathanasis SK, Cate R, Zeitlin S, Chirgwin J, Efstratiadis A. RNA-mediated gene duplication: the rat preproinsulin I gene is a functional retroposon. *Mol Cell Biol.* 1985 Aug;5(8):2090-103
- Wahlestedt C, Yanaihara N, Håkanson R. Evidence for different pre- and post-junctional receptors for neuropeptide Y and related peptides. *Regul Pept.* 1986 Feb;13(3-4):307-18
- Eva C, Oberto A, Sprengel R, Genazzani E. The murine NPY-1 receptor gene. Structure and delineation of tissue-specific expression. *FEBS Lett.* 1992 Dec 21;314(3):285-8
- Grundemar L, Jonas SE, Mörner N, Högestätt ED, Wahlestedt C, Håkanson R. Characterization of vascular neuropeptide Y receptors. *Br J Pharmacol.* 1992 Jan;105(1):45-50
- Larhammar D, Blomqvist AG, Yee F, Jazin E, Yoo H, Wahlestedt C. Cloning and functional expression of a human neuropeptide Y/peptide YY receptor of the Y1 type. *J Biol Chem.* 1992 Jun 5;267(16):10935-8
- Herzog H, Hort YJ, Shine J, Selbie LA. Molecular cloning, characterization, and localization of the human homolog to the reported bovine NPY Y3 receptor: lack of NPY binding and activation. *DNA Cell Biol.* 1993 Jul-Aug;12(6):465-71
- Ball HJ, Shine J, Herzog H. Multiple promoters regulate tissue-specific expression of the human NPY-Y1 receptor gene. *J Biol Chem.* 1995 Nov 10;270(45):27272-6
- Nakamura M, Sakanaka C, Aoki Y, Ogasawara H, Tsuji T, Kodama H, Matsumoto T, Shimizu T, Noma M. Identification of two isoforms of mouse neuropeptide Y-Y1 receptor generated by alternative splicing. Isolation, genomic structure, and functional expression of the receptors. *J Biol Chem.* 1995 Dec 15;270(50):30102-10
- Ammar DA, Eadie DM, Wong DJ, Ma YY, Kolakowski LF Jr, Yang-Feng TL, Thompson DA. Characterization of the human type 2 neuropeptide Y receptor gene (NPY2R) and localization to the chromosome 4q region containing the type 1 neuropeptide Y receptor gene. *Genomics.* 1996 Dec 15;38(3):392-8
- Jacques D, Tong Y, Dumont Y, Shen SH, Quirion R. Expression of the neuropeptide Y Y1 receptor mRNA in the human brain: an in situ hybridization study. *Neuroreport.* 1996 Apr 10;7(5):1053-6

- Blomqvist AG, Herzog H. Y-receptor subtypes--how many more? *Trends Neurosci.* 1997 Jul;20(7):294-8
- Cabrele C, Beck-Sickingler AG. Molecular characterization of the ligand-receptor interaction of the neuropeptide Y family. *J Pept Sci.* 2000 Mar;6(3):97-122
- Caberlotto L, Hurd YL. Neuropeptide Y Y(1) and Y(2) receptor mRNA expression in the prefrontal cortex of psychiatric subjects. Relationship of Y(2) subtype to suicidal behavior. *Neuropsychopharmacology.* 2001 Jul;25(1):91-7
- Rettenbacher M, Reubi JC. Localization and characterization of neuropeptide receptors in human colon. *Naunyn Schmiedebergs Arch Pharmacol.* 2001 Oct;364(4):291-304
- Reubi JC, Gugger M, Waser B, Schaer JC. Y(1)-mediated effect of neuropeptide Y in cancer: breast carcinomas as targets. *Cancer Res.* 2001 Jun 1;61(11):4636-41
- Balasubramaniam A. Neuropeptide Y (NPY) family of hormones: progress in the development of receptor selective agonists and antagonists. *Curr Pharm Des.* 2003;9(15):1165-75
- Dinger MC, Bader JE, Kobor AD, Kretschmar AK, Beck-Sickingler AG. Homodimerization of neuropeptide y receptors investigated by fluorescence resonance energy transfer in living cells. *J Biol Chem.* 2003 Mar 21;278(12):10562-71
- Pheng LH, Dumont Y, Fournier A, Chabot JG, Beaudet A, Quirion R. Agonist- and antagonist-induced sequestration/internalization of neuropeptide Y Y1 receptors in HEK293 cells. *Br J Pharmacol.* 2003 Jun;139(4):695-704
- Körner M, Waser B, Reubi JC. High expression of neuropeptide y receptors in tumors of the human adrenal gland and extra-adrenal paraganglia. *Clin Cancer Res.* 2004 Dec 15;10(24):8426-33
- Pedrazzini T. Importance of NPY Y1 receptor-mediated pathways: assessment using NPY Y1 receptor knockouts. *Neuropeptides.* 2004 Aug;38(4):267-75
- Ramanathan S, Woodroffe A, Flodman PL, Mays LZ, Hanouni M, Modahl CB, Steinberg-Epstein R, Bocian ME, Spence MA, Smith M. A case of autism with an interstitial deletion on 4q leading to hemizygoty for genes encoding for glutamine and glycine neurotransmitter receptor sub-units (AMPA 2, GLRA3, GLRB) and neuropeptide receptors NPY1R, NPY5R. *BMC Med Genet.* 2004 Apr 16;5:10
- Jemal A, Ward E, Thun MJ. Contemporary lung cancer trends among U.S. women. *Cancer Epidemiol Biomarkers Prev.* 2005 Mar;14(3):582-5
- Kitlinska J, Abe K, Kuo L, Pons J, Yu M, Li L, Tilan J, Everhart L, Lee EW, Zukowska Z, Toretsky JA. Differential effects of neuropeptide Y on the growth and vascularization of neural crest-derived tumors. *Cancer Res.* 2005 Mar 1;65(5):1719-28
- Amlal H, Faroqui S, Balasubramaniam A, Sheriff S. Estrogen up-regulates neuropeptide Y Y1 receptor expression in a human breast cancer cell line. *Cancer Res.* 2006 Apr 1;66(7):3706-14
- Ruscica M, Dozio E, Boghossian S, Bovo G, Martos Riaño V, Motta M, Magni P. Activation of the Y1 receptor by neuropeptide Y regulates the growth of prostate cancer cells. *Endocrinology.* 2006 Mar;147(3):1466-73
- Ruscica M, Dozio E, Motta M, Magni P. Relevance of the neuropeptide Y system in the biology of cancer progression. *Curr Top Med Chem.* 2007;7(17):1682-91
- El Karim IA, Lamey PJ, Linden GJ, Lundy FT. Neuropeptide Y Y1 receptor in human dental pulp cells of noncarious and carious teeth. *Int Endod J.* 2008 Oct;41(10):850-5
- Bjur D, Alfredson H, Forsgren S. Presence of the neuropeptide Y1 receptor in tenocytes and blood vessel walls in the human Achilles tendon. *Br J Sports Med.* 2009 Dec;43(14):1136-42
- Hodges GJ, Jackson DN, Mattar L, Johnson JM, Shoemaker JK. Neuropeptide Y and neurovascular control in skeletal muscle and skin. *Am J Physiol Regul Integr Comp Physiol.* 2009 Sep;297(3):R546-55
- Lundy FT, El Karim IA, Linden GJ. Neuropeptide Y (NPY) and NPY Y1 receptor in periodontal health and disease. *Arch Oral Biol.* 2009 Mar;54(3):258-62
- Okahisa Y, Ujike H, Kotaka T, Morita Y, Kodama M, Inada T, Yamada M, Iwata N, Iyo M, Sora I, Ozaki N, Kuroda S. Association between neuropeptide Y gene and its receptor Y1 gene and methamphetamine dependence. *Psychiatry Clin Neurosci.* 2009 Jun;63(3):417-22

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