Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Review

DEFB1 (defensin, beta 1)

Ernesto Prado Montes de Oca

Medical and Pharmaceutical Biotechnology Unit, Research Center in Technology and Design Assistance of Jalisco State (CIATEJ, A.C.), National Council of Science and Technology (CONACYT), Av. Normalistas 800, Col. Colinas de la Normal, C.P. 44270, Guadalajara, Jalisco, Mexico (EPMdO)

Published in Atlas Database: May 2010

Online updated version : http://AtlasGeneticsOncology.org/Genes/DEFB1ID44352ch8p23.html
DOI: 10.4267/2042/44957

Identity

Other names: BD1, DEFB-1, DEFB101, HBD1, MGC51822

HGNC (Hugo): DEFB1

Location: 8p23.1

Local order: AGPAT5-XKR5-DEFB1-DEFA6-DEFA4 (reverse strand, according to www.ensembl.org).

Note: DEFB1 is a peptide expressed mainly in epithelia with an antimicrobial function against viruses, Gram-positive, Gram-negative bacteria and Mycobacterium tuberculosis. It also functions as immunomodulator and as a tumor supressor gene. Single Nucleotide Polymorphisms (SNPs) in this gene have been associated with cancer, allergic and infectious diseases as well as with DEFB1 downregulation (Prado-Montes de Oca, 2010).

DNA/RNA

Description

DEFB1 is a gene composed of 2 exons and a ~7 kb intron. DEFB1 spans 7488 bp, two exons and one intron of 6962 bp (Liu et al., 1997).

Transcription

The transcript is of 207 nt (www.kegg.org). No variants are produced by alternative splicing, the entire mature peptide coding sequence is in exon 1, however several hBD-1 amino-terminal processed forms are found in urine (Valore et al., 1998), probably cleaved by chymotrypsin (Zucht et al., 1998) or matrix metalloproteinase 7 (matrylisin) (Wilson et al., 2009) each showing different microbicidal potencies (Valore et al., 1998). The functions and tissue of origin of these processed forms are unknown (Prado-Montes de Oca, 2010).

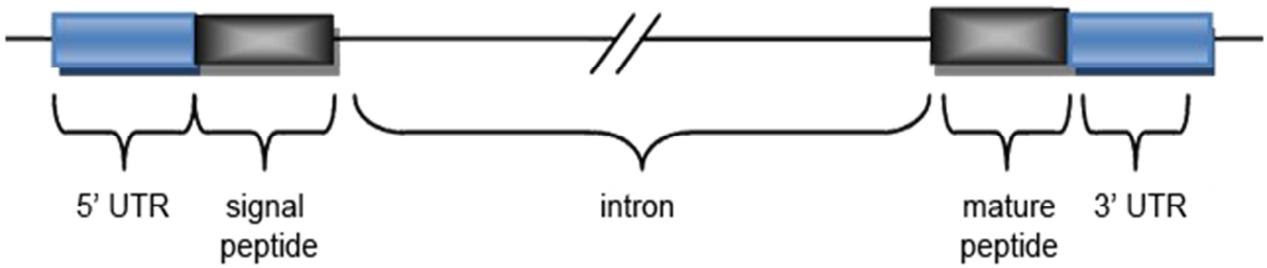

Figure 1. DEFB1 gene. The diagram shows pre-propeptide coding sequence (black rectangles) and unstranslated regions (blue rectangles). Signal peptide coding sequence is comprised of 60 bases. Mature peptide coding sequence spans 144 bases (www.ensembl.org). The pro-peptide segment is in exon 1 and not in exon 2 as in the rest of beta-defensins known to date (Pazgier et al., 2006).

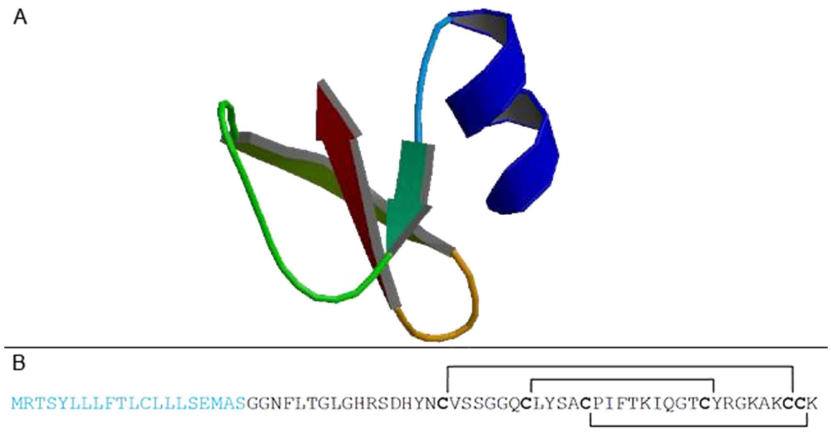

Figure 2. (A) Model of hBD-1 peptide (according to PDB:1IJU, www.pdb.org). **(B) Sequence of hBD-1 pro-peptide.** Signal peptide sequence (blue), mature peptide (black) with cysteine residues (bold) and disulfide bridges (brackets) are shown.

Pseudogene

None reported. DEFB1 is considered as a unique copy gene, although rare duplicons in some individuals have been reported (Linzmeier et al., 2005).

Protein

Note

Human beta-defensins are produced mainly by various epithelia and secreted in mature forms by the producing cells. The hBD-1 shows three disulfide bridges (with the pro-peptide nomenclature) are formed at cysteines 37-66 (1-5), 44-59 (2-4) and 49-67 (3-6). The disulfide bridge pattern on cysteines 1-5, 2-4 and 3-6 is a hallmark of beta-defensins (Prado-Montes de Oca, 2010).

Description

The prepropeptide has 68 aa and the mature peptide is of 48 amino acids. As quaternary structure hBD-1 shows in vitro dimerization by weak intermolecular salt bridges, but if dimers are formed in vivo or if they perform any different function is unknown (Prado Montes de Oca, 2010).

Expression

The highest concentrations of hBD-1 are found in the kidney (epithelial layes of the loops of Henle, distal tubules, collecting tubes) and female reproductive tract (layers of vagina, ectocervix, endocervix, uterus, fallopian tubes), especially in pregnant women. It is also expressed in astrocytes, mammary gland, cornea, small intestine, gingival tissue, epithelial cells of testis, mature dendritic cells (for a more complete information of DEFB1-expressing cells see www.ebi.ac.uk/microarray-as/atlas and www.ncbi.nlm.nih.gov/geo/).

Localisation

The hBD-1 peptide resides in the cytoplasm of normal cells and in the nucleus of several cancer cells (Bick et al., 2007; Wenghoefer et al., 2008). In normal skin, hBD-1 is localized to the perinuclear region of keratinocytes and in burned skin in dermal glandular structures and hair shafts (Poindexter et al., 2006).

Function

hBD-1 functions as an antimicrobial peptide against viruses as HIV, Av1CF2, Gram-positive and Gram-negative bacteria, Mycobacterium tuberculosis. It functions as a chemoattractant to immature dendritic cells and T cells acts as a tumor suppressor inducing caspase-mediated apoptosis. In addition it could be involved as transcription factor in epithelia reorganization (Prado Montes de Oca, 2010).

Homology

Homolog genes to human beta-defensin 1 are found in Mus musculus (mouse) (Morrison et al., 1998), Pan troglodytes (chimpanzee) (Prado-Montes de Oca et al., 2009), Macaca mulatta (Rhesus monkey), Canis familiaris (dog), Rattus norvegicus (rat), Sus scrofa (pig, named beta defensin 2), Bos taurus (cow, named protein similar to beta defensin) among other species (www.kegg.org; www.ensembl.org).

Mutations

Note

There are 214 annotated polymorphisms in DEFB1, most of them are SNPs (bdSNP build 130, www.genome.ucsc.edu). Insertions and deletions are less frequently found (López Campos and Prado Montes de Oca, in process). There are reports of 10 SNPs in DEFB1 with disease association. The most relevant SNPs are those located on 5' unstranslated region namely -52A (higher HIV load and higher risk of perinatal HIV infection, gastritis, asthma), -44C (atopic dermatitis, chronic obstructive pulmonar disease, Crohn's disease, cancer, lepromatous leprosy) and -20 A/G (infections in cystic fibrosis) (gene RIF at www.ncbi.nlm.nih.gov; Prado-Montes de Oca, 2010). The variant -44C correlates with lower constitutive expression and -44G correlates with lower IFN-gamma-dependent induction.

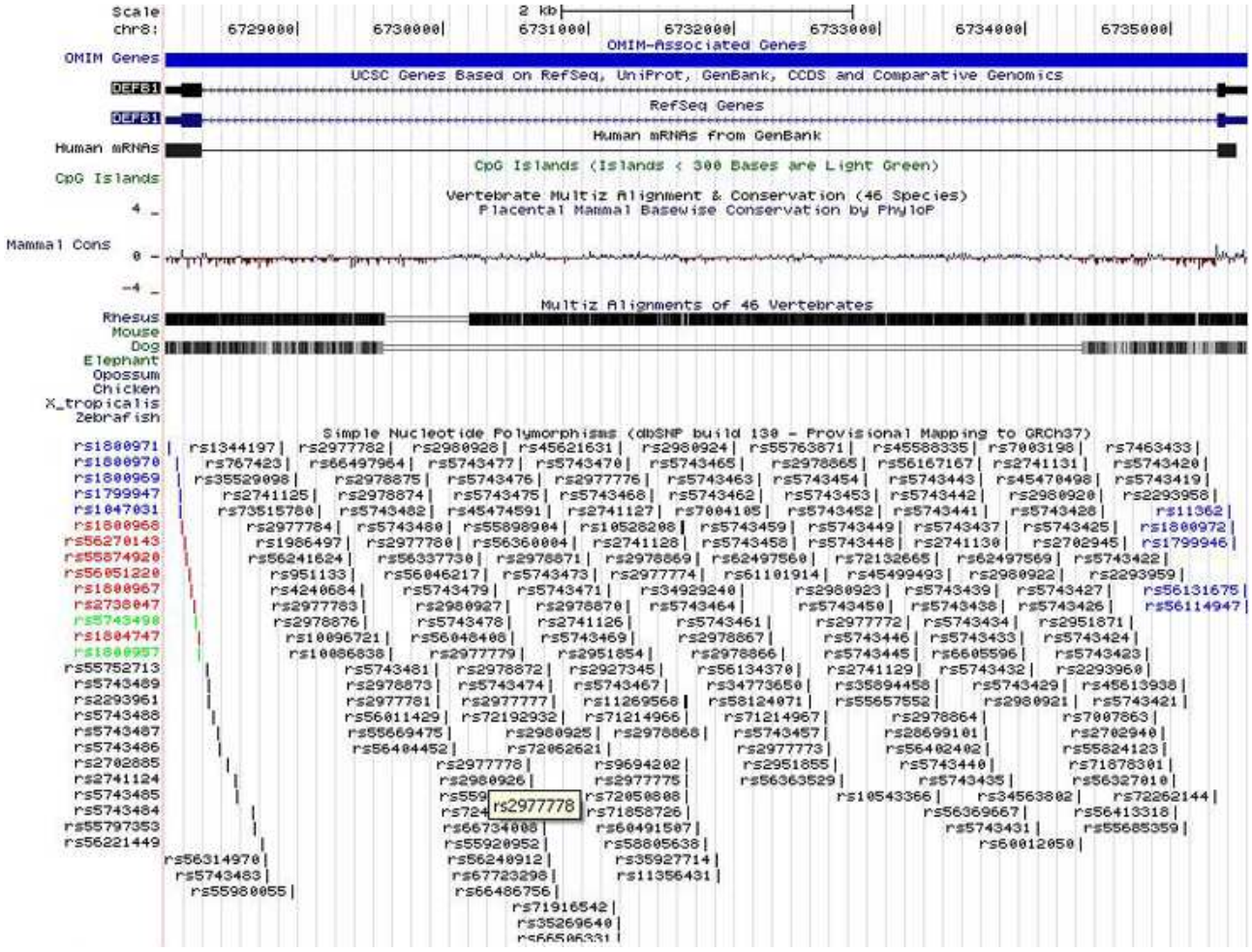

Figure 3. The 214 polymorphisms annotated in both strands of DEFB1 gene according to UCSC Genome Browser (www.genome.ucsc.edu, hg19, Feb 2009). Most polymorphisms are located in intron (black), fewer are located in UTRs (blue) and exons. Those polymorphisms located in exons could be either synonymous (green) or non-synonymous (red).

This could explain the extremely rare heterozygote advantage in this region (Figuera et al., 2005; Prado Montes de Oca, 2010).

Implicated in

The 8p23.1 duplication syndrome

Note

Associate with variable phenotype that may include one or more of the following: developmental delay, mild dysmorphism and heart defects (Barber et al., 2010).

Cytogenetics

The 8p23.1 duplication syndrome and copy number variation of the 8p23.1 defensin gene cluster are cytogenetically indistinguishable but distinct at the molecular level (Barber et al., 2010).

Copy number variation of the 8p23.1 defensin gene cluster

Note

From 1 to 12 copies of 8p23.1 defensin gene cluster are normally found per diploid genome (Hollox et al., 2003). The null allele is very rare (allele frequency 0.2%) (Hollox et al., 2008). Predisposition to Crohn's disease and sporadic prostate cancer is higher at low copy number (Huse et al., 2008) and to psoriasis at high copy number (Hollox, 2008).

Oral squamous cell carcinoma (OSCC)

Note

DEFB1 basal expression is 50-fold lower in OSCC, and inducibility is significantly reduced (Wenghoefer et al., 2008). Genotypes in DEFB1 gene tend to loss of heterozygosity in OSCC (Joly et al., 2009).

Malignant melanoma

Note

It was found weak evidence that genotype -44 GG in DEFB1 increases risk for malignant melanoma in a Spanish population (OR= 2.78, CI 95%= 0.88-8.82, p=0.08) (Fernandez et al., 2009).

Prostate and renal cancers

Note

DEFB1 has been proposed as a tumor suppressor because it promotes cancer cells apoptosis and is absent

in most tumor samples (Sun et al., 2006; Bullard et al., 2008). There is a marked down-regulation of DEFB1 in 82% of prostate cancers and 90% of renal cell carcinomas (Donald et al., 2003) and this DEFB1 downregulation is associated with malignancy (Wenghoefer et al., 2008; Pantelis et al., 2009). Furthermore, oncogene PAX2 binds to DEFB1 promoter and suppresses its expression independent of p53 (Bose et al., 2009). Parvalbumin and DEFB1 expression could be useful to differentiate papillary renal cell carcinoma (RCC) from conventional RCC (Young et al., 2003).

Leukoplakia

Note

DEFB1 is downregulated 2.5 fold in leukoplakia but their role in the disease, if any, is unknown (Wenghoefer et al., 2008).

Several allergic and infectious diseases

Note

For allergic and infectious diseases where DEFB1 is implicated see Prado Montes de Oca, 2010.

To be noted

Note

Gene regulation of DEFB1 is not well known. More experimental data is needed to differentiate the constitutive from the inducible pathways (Kalus et al., 2009; Prado Montes de Oca et al., 2009) in order to propose alternative therapies to diseases where DEFB1 is implicated (Prado Montes de Oca, 2010).

This work was supported by the Fondos Sectoriales de Ciencia Basica SEP-CONACYT (CB-2008-01-105813) and CIATEJ A.C. The author receives a research stimulus from the Sistema Nacional de Investigadores (SNI 41290, CONACYT, Mexico) and wishes to thank the Editor for the kind invitation.

References

Liu L, Zhao C, Heng HH, Ganz T. The human beta-defensin-1 and alpha-defensins are encoded by adjacent genes: two peptide families with differing disulfide topology share a common ancestry. Genomics. 1997 Aug 1;43(3):316-20

Morrison GM, Davidson DJ, Kilanowski FM, Borthwick DW, Crook K, Maxwell AI, Govan JR, Dorin JR. Mouse beta defensin-1 is a functional homolog of human beta defensin-1. Mamm Genome. 1998 Jun;9(6):453-7

Valore EV, Park CH, Quayle AJ, Wiles KR, McCray PB Jr, Ganz T. Human beta-defensin-1: an antimicrobial peptide of urogenital tissues. J Clin Invest. 1998 Apr 15;101(8):1633-42

Zucht HD, Grabowsky J, Schrader M, Liepke C, Jürgens M, Schulz-Knappe P, Forssmann WG. Human beta-defensin-1: A urinary peptide present in variant molecular forms and its putative functional implication. Eur J Med Res. 1998 Jul 20;3(7):315-23

Donald CD, Sun CQ, Lim SD, Macoska J, Cohen C, Amin MB, Young AN, Ganz TA, Marshall FF, Petros JA. Cancer-specific loss of beta-defensin 1 in renal and prostatic carcinomas. Lab Invest. 2003 Apr;83(4):501-5

Hollox EJ, Armour JA, Barber JC. Extensive normal copy number variation of a beta-defensin antimicrobial-gene cluster. Am J Hum Genet. 2003 Sep;73(3):591-600

Young AN, de Oliveira Salles PG, Lim SD, Cohen C, Petros JA, Marshall FF, Neish AS, Amin MB. Beta defensin-1, parvalbumin, and vimentin: a panel of diagnostic immunohistochemical markers for renal tumors derived from gene expression profiling studies using cDNA microarrays. Am J Surg Pathol. 2003 Feb;27(2):199-205

Figuera L, Prado Montes de Oca E, Gallegos-Arreola MP, Sandoval L.. Natural selection and/or gametic drift probably favours genotype of the beta defensin 1 in a Mexican population. X Human Genome Meeting 2005, Kyoto, Japan.

Linzmeier RM, Ganz T. Human defensin gene copy number polymorphisms: comprehensive analysis of independent variation in alpha- and beta-defensin regions at 8p22-p23. Genomics. 2005 Oct;86(4):423-30

Poindexter BJ, Bhat S, Buja LM, Bick RJ, Milner SM. Localization of antimicrobial peptides in normal and burned skin. Burns. 2006 Jun;32(4):402-7

Sun CQ, Arnold R, Fernandez-Golarz C, Parrish AB, Almekinder T, He J, Ho SM, Svoboda P, Pohl J, Marshall FF, Petros JA. Human beta-defensin-1, a potential chromosome 8p tumor suppressor: control of transcription and induction of apoptosis in renal cell carcinoma. Cancer Res. 2006 Sep 1;66(17):8542-9

Bick RJ, Poindexter BJ, Buja LM, Lawyer CH, Milner SM, Bhat S. Nuclear localization of HBD-1 in human keratinocytes. J Burns Wounds. 2007 Aug 24;7:e3

Pazgier M, Prahl A, Hoover DM, Lubkowski J. Studies of the biological properties of human beta-defensin 1. J Biol Chem. 2007 Jan 19;282(3):1819-29

Bullard RS, Gibson W, Bose SK, Belgrave JK, Eaddy AC, Wright CJ, Hazen-Martin DJ, Lage JM, Keane TE, Ganz TA, Donald CD. Functional analysis of the host defense peptide Human Beta Defensin-1: new insight into its potential role in cancer. Mol Immunol. 2008 Feb;45(3):839-48

Hollox EJ. Copy number variation of beta-defensins and relevance to disease. Cytogenet Genome Res. 2008;123(1-4):148-55

Hollox EJ, Barber JC, Brookes AJ, Armour JA. Defensins and the dynamic genome: what we can learn from structural variation at human chromosome band 8p23.1. Genome Res. 2008 Nov;18(11):1686-97

Huse K, Taudien S, Groth M, Rosenstiel P, Szafranski K, Hiller M, Hampe J, Junker K, Schubert J, Schreiber S, Birkenmeier G, Krawczak M, Platzer M. Genetic variants of the copy number polymorphic beta-defensin locus are associated with sporadic prostate cancer. Tumour Biol. 2008;29(2):83-92

Wenghoefer M, Pantelis A, Dommisch H, Götz W, Reich R, Bergé S, Martini M, Allam JP, Jepsen S, Merkelbach-Bruse S, Fischer HP, Novak N, Winter J. Nuclear hBD-1 accumulation in malignant salivary gland tumours. BMC Cancer. 2008 Oct 7;8:290

Wenghoefer M, Pantelis A, Dommisch H, Reich R, Martini M, Allam JP, Novak N, Bergé S, Jepsen S, Winter J. Decreased gene expression of human beta-defensin-1 in the development of squamous cell carcinoma of the oral cavity. Int J Oral Maxillofac Surg. 2008 Jul;37(7):660-3

Bose SK, Gibson W, Bullard RS, Donald CD. PAX2 oncogene negatively regulates the expression of the host defense peptide human beta defensin-1 in prostate cancer. Mol Immunol. 2009 Mar;46(6):1140-8

Fernandez LP, Milne RL, Pita G, Floristan U, Sendagorta E, Feito M, Aviles JA, Martin-Gonzalez M, Lázaro P, Benítez J, Ribas G. Human beta-defensins (HBD1 and HBD3) and malignant melanoma susceptibility. Melanoma Res. 2009 Oct;19(5):340-1

Joly S, Compton LM, Pujol C, Kurago ZB, Guthmiller JM. Loss of human beta-defensin 1, 2, and 3 expression in oral squamous cell carcinoma. Oral Microbiol Immunol. 2009 Oct;24(5):353-60

Kalus AA, Fredericks LP, Hacker BM, Dommisch H, Presland RB, Kimball JR, Dale BA. Association of a genetic polymorphism (-44 C/G SNP) in the human DEFB1 gene with expression and inducibility of multiple beta-defensins in gingival keratinocytes. BMC Oral Health. 2009 Aug 27;9:21

Pantelis A, Wenghoefer M, Haas S, Merkelbach-Bruse S, Pantelis D, Jepsen S, Bootz F, Winter J. Down regulation and nuclear localization of human beta-defensin-1 in pleomorphic adenomas of salivary glands. Oral Oncol. 2009 Jun;45(6):526-30

Prado-Montes de Oca E, Velarde-Félix JS, Ríos-Tostado JJ, Picos-Cárdenas VJ, Figuera LE. SNP 668C (-44) alters a NF-kappaB1 putative binding site in non-coding strand of human beta-defensin 1 (DEFB1) and is associated with lepromatous leprosy. Infect Genet Evol. 2009 Jul;9(4):617-25

Wilson CL, Schmidt AP, Pirilä E, Valore EV, Ferri N, Sorsa T, Ganz T, Parks WC. Differential Processing of {alpha}- and {beta}-Defensin Precursors by Matrix Metalloproteinase-7 (MMP-7). J Biol Chem. 2009 Mar 27;284(13):8301-11

Barber JC, Bunyan D, Curtis M, Robinson D, Morlot S, Dermitzel A, Liehr T, Alves C, Trindade J, Paramos AI, Cooper C, Ocraft K, Taylor EJ, Maloney VK. 8p23.1 duplication syndrome differentiated from copy number variation of the defensin cluster at prenatal diagnosis in four new families. Mol Cytogenet. 2010 Feb 18;3:3

Prado-Montes de Oca E. Human beta-defensin 1: a restless warrior against allergies, infections and cancer. Int J Biochem Cell Biol. 2010 Jun;42(6):800-4

This article should be referenced as such:

Prado Montes de Oca E. DEFB1 (defensin, beta 1). Atlas Genet Cytogenet Oncol Haematol. 2011; 15(2):136-140.