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# **Gene Section**

Review

# DEFB1 (defensin, beta 1)

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# **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, Grampositive, 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).

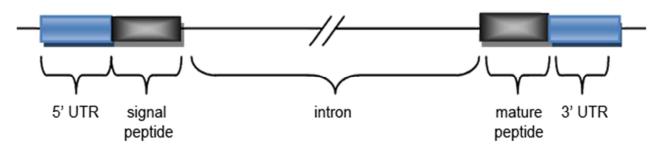
# DNA/RNA

# 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).

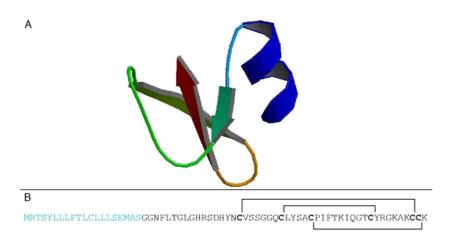


Figure 2. (A) Model of hBD-1 peptide (according to PDB:1IJU, www.pdb.org). (B) Sequence of hBD-1 pro-peptide. Signal peptide sequence (blue), mature peptide (black) with cysteine residues (bold) and disulfide bridges (brackets) are shown.

# 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 Gramnegative 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 IFNgamma-dependent induction.

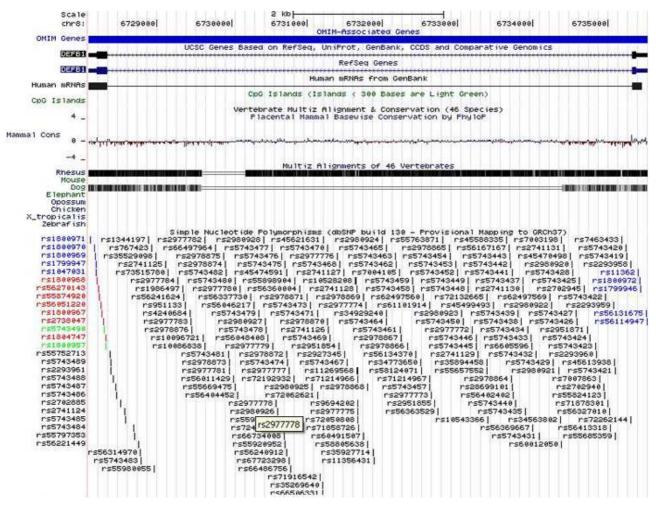


Figure 3. The 214 polymorphisms annotated in both strands of DEFB1 gene according to UCSC Genome Browser (www.genome.ucsc.edu, hg19, Feb 2009). Most polymorphisms are located in intron (black), fewer are located in UTRs (blue) and exons. Those polymorphisms located in exons could be either synonymous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

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