Bombesin Receptor Structure and Expression in Human Lung Carcinoma Cell Lines

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Abstract Mammalian bombesin-like peptides gastrin-releasing peptide (GRP) and neuromedin B (NMB) are regulatory neuropeptides involved in numerous physiologic processes, and have been implicated as autocrine and/or paracrine growth factors in human lung carcinoma. Three structurally and pharmacologically distinct bombesin receptor subtypes have been isolated and characterized: the gastrin releasing peptide receptor (GRP-R), the neuromedin B receptor (NMB-R), and bombesin receptor subtype-3 (BRS-3). The three receptors are structurally related, sharing about 50% amino acid identity. They are members of the G-protein coupled receptor superfamily with a seven predicted transmembrane segment topology characteristic of receptors in this family. The signal transduction pathway for GRP-R and NMB-R involves coupling to a pertussis-toxin insensitive G-protein, activation of phospholipase C (PLC), generation of inositol trisphosphate (IP3), release of intracellular calcium, and activation of protein kinase C. While all three bombesin receptor subtypes are activated by bombesin agonists, GRP-R, NMB-R, and BRS-3 have very different affinities for the mammalian bombesin-like peptides GRP and NMB, as well as bombesin receptor antagonists. The three bombesin receptor subtypes are expressed in an overlapping subset of human lung carcinoma cell lines. Any therapeutic strategy based on modulation of bombesin growth responses in human lung carcinoma would be well served to take into account the pharmacologic heterogeneity of the relevant receptors. (1996 Wiley-Liss, Inc.*

Key words: bombesin receptor, gastrin releasing peptide receptor, neuromedin B receptor, bombesin, autocrine growth

Bombesin is a tetradecapeptide originally purified from the skin of the European frog Bombina bombina [1]. Many bombesin-like peptides with related C-terminal octapeptide structures were subsequently isolated from various amphibians and classified into three subfamilies (bombesin, ranatensin, and phyllolitorin) based on the sequence of the last three residues in their amidated C-terminal domain [2]. Two mammalian bombesin-like peptides been identified and characterized: gastrin-releasing peptide (GRP) [3] in the bombesin subfamily, and neuromedin B (NMB) [4] in the ranatensin subfamily. As yet, no mammalian counterpart to the amphibian phyllolitorin peptides has been identified at either the gene or peptide level.

Mammalian bombesin-like peptides have been associated with a wide spectrum of physiologic

effects, including regulation of secretion, growth, and neuromodulation [reviewed in ref. 5]. In normal tissues, bombesin-related peptides stimulate growth of normal bronchial epithelial cells [6] and endometrial stromal cells [7]. The growth stimulatory properties of bombesin in Swiss 3T3 fibroblasts [8] have been used to great advantage as a model system, providing significant insights into the biochemical and genetic changes leading to cell proliferation. Furthermore, bombesin can regulate reorganization of the actin cytoskeleton, an important component of many cellular processes including cell division, by stimulating accumulation of the small GTPbinding proteins Rho and Rac in the active GTPbound state. Accumulation of activated Rac leads to membrane ruffling, while activated Rho results in stress fiber formation [9].

Several observations indicate that growth stimulation by mammalian bombesin-like peptides plays a significant role in human neoplasia. Immunocytochemical studies demonstrated the presence of bombesin-like immunoreactivity [10,11] and gastrin-releasing peptide mRNA [12]

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in many human small cell lung cancer (SCLC) tumors and cell lines. The clonal growth of some SCLC cell lines in soft agar was increased by addition of bombesin and gastrin-releasing peptide [13]. A neutralizing monoclonal antibody (2A11) directed against the C-terminal domain of bombesin, the peptide domain critical for receptor binding, attenuated growth of some human SCLC cells both as soft agar clones in vitro and nude mouse xenografts in vivo [14]. Potent bombesin receptor antagonists inhibited the growth of bombesin-receptor positive, but not receptor negative, SCLC cells in vivo and in vitro [15–17]. These findings indicate that mammalian bombesin-like peptides can function as autocrine growth factors of potential importance in the pathogenesis and progression of some human lung carcinomas.

Bombesin-mediated growth may also be relevant in other malignancies besides lung cancer. Immunohistochemical analysis of human prostate tumors revealed that about half of the specimens showed features of neuroendocrine differentiation, many of which were positive for bombesin-like immunoreactivity [18]. In a study of the human prostate cancer cell line PC-3, GRP receptors and bombesin-dependent growth stimulation were observed [19]. A bombesin receptor antagonist inhibited growth of nude mouse xenografts established using the prostate cancer cell line PC-82 [20].

Bombesin was also shown to stimulate the proliferation of human breast carcinoma cells in culture [21,22], or as nude mouse xenografts [23]. Expression of the gastrin releasing peptide gene [24] and GRP receptors [25] were reported in human breast cancer cell lines. The bombesin receptor antagonist RC-3095 was also shown to inhibit the growth of human breast cancer cell lines [26], suggesting the possibility that gastrinreleasing peptide may function as an autocrine or paracrine growth factor in some breast cancer cells. Given these findings, attenuation of bombesin-mediated responses, or intracellular pathways which mediate these growth-regulatory responses, may provide a means for interfering with the growth of bombesin-dependent cells in several different tumor types.

It has proven difficult to analyze the functional properties of bombesin receptors mediating these effects in the context of a human tumor cell. Typically, the number of receptors per cell is low, and often there is more than one receptor subtype expressed by the same cell. Both of these variables complicate functional and pharmacologic studies of the bombesin signalling pathway. To precisely determine the functional and pharmacologic properties of a specific receptor, it is very useful to design model systems where the receptor is expressed at uniformly high levels in the absence of other receptor subtypes with overlapping functional properties that could complicate the study. These model systems are developed by obtaining cDNA clones for the family of mammalian bombesin receptors, and expressing the receptors in appropriate host cells that do not express their own endogenous bombesin receptors.

Recently, we [27–30] and others [31,32] have cloned and characterized three structurally and pharmacologically distinct human bombesin peptide receptor subtypes: GRP-R, NMB-R, and bombesin receptor subtype-3 (BRS-3). In this study, the properties of these three bombesin receptor subtypes are summarized, and the pattern of expression in a panel of human lung carcinoma cell lines was studied using a very sensitive and specific assay involving reverse transcription of mRNA followed by polymerase chain reaction (RT/PCR) [33].

MATERIALS AND METHODS Isolation and Characterization of Bombesin Receptor cDNAs

Procedures used for isolation and characterization of cDNA and genomic clones encoding the murine GRP-R [27,30], rat NMB-R [28], human GRP-R and NMB-R [29], and human BRS-3 [30] are found in the indicated references.

Reverse Transcription/Polymerase Chain Reaction (RT/PCR) Assay to Detect Bombesin Receptor mRNAs Expressed in Human Lung Cancer Cell Lines

Lung cancer cell lines were kindly provided by Drs. J. Minna and A. Gazdar, and their histological typing summarized in Corjay et al. [29]. Total RNA was isolated from cultured cells as described [34]. Total RNA was reverse transcribed using gene-specific antisense oligonucleotide primers complementary to 3' untranslated sequences in receptor mRNAs (huGRP-R: 5'TTCCTGTCTAGCCATAAAGC 3'; huNMB-R: 5'GTTCTCTCCAGGTAGTGAGTT 3'; huBRS-3: 5'CCTGCACACAGCTTAGAGTC 3'). One microgram total RNA, 100 ng gene specific primer, and water were combined in 10 µl volume, incubated at 70°C for 2 min, and placed on ice. The following reagents were added to the primer and RNA: 4 μ l 5 × RT buffer (250 mM Tris pH 8.3, 375 mM KCl, 15 mM MgCl₂; Bethesda Research Labs, Gaithersburg, MD), 2 μ l 0.1 M DTT, 4 μ l 2.5 mM dGTP, dATP, dTTP, dCTP, 1 μ l RNasin (Promega, Madison, WI), 1 μ l Moloney-MLV⁽³⁾) reverse transcriptase (200 U/ μ l; Bethesda Research Labs). The reverse transcription reaction was incubated at 42°C for 1 h, and the enzyme heat inactivated by incubation at 70°C for 5 min. This cDNA served as template for the polymerase chain reaction (PCR).

In the PCR reaction, the gene-specific PCR primers for each receptor mRNA were resuspended at 100 ng/µl in water: GRP-R sense primer, 5'TTAAAGAAGGCAAAGAGC 3'; GRP-R antisense primer, 5'ATCTTCATCAGGGCATGGGA 3'; NMB-R sense primer, 5'GTGGGCGTTCAGTCCT-CAGG 3'; NMB-R antisense primer, 5'ACTTCT-GAAAACACCGCTTC 3'; BRS-3 sense primer, 5'GGCTCAAAGGCAGCCTCACT 3'; BRS-3 antisense primer, 5'AGTCTTCAGGATGGCATTGG 3'. The PCR sense and antisense primer pairs were chosen such that they spanned an intron, so that only a cDNA template, and not genomic DNA, could be successfully amplified to give a PCR product of the predicted size.

The PCR reaction was performed essentially as described, using a commercially available kit (GeneAmp[®], US Biochemicals, Cleveland, OH). The reactions were assembled as follows: 1 µl cDNA from the reverse transcription reaction, $10 \times PCR$ buffer (100 mM Tris, pH 8.3, 500 mM KCl, 15 mM MgCl₂, 0.01% [w/v] gelatin [Type A porcine]), 8 µl 2.5 mM dGTP, dATP, dTTP, dCTP, 1 μ l each of the gene specific sense and antisense primers, 78 µl water, 1 µl Amplitaq[®] Tag DNA polymerase (US Biochemicals), overlayed with 50 µl mineral oil. The reaction was cycled using a DNA Thermal Cycler (Perkin Elmer, Norwalk, CT) for 35 rounds of: 94°C, 1 min; 50°C, 1 min, 72°C, 1 min. The reaction was extended for 5 min at 72°C at the end of the last cycle.

Ten microliter PCR product from each sample was analyzed by agarose gel electrophoresis using established methods [34]. The predicted sizes of the PCR products were: GRP-R, 586 bp; NMB-R, 617 bp; BRS-3, 489 bp. Agarose gels were blotted to nitrocellulose membranes using established methodology [34], and were baked at 80°C for 30 min to fix the transferred DNA. Membranes were hybridized to gene-specific oligonucleotide probes complementary to cDNA sequences located between the PCR primers (GRP-R, 5'-CCTGGCTGACAGATGGCTATTT-3'; NMB-R, 5'-CCCAGCAAGCCCACGGTGAT-3'; BRS-3, 5'-TCCTTCTGCAAGGTAGTGAG-3'). The primers were end-labelled using gamma-³²P-ATP (3,000 Ci/mMol) and T4 polynucleotide kinase as described [34]. Membranes were hybridized in 40% (v/v) formamide, 0.6 M NaCl, 60 mM NaCitrate, 20 mM Tris pH 7.4, $20 \mu g/ml$ denatured herring sperm DNA, 10% (w/v) dextran sulfate, 0.02% (w/v) bovine serum albumin, 0.02% (w/v) Ficoll 400, 0.02% (w/v) polyvinylpyrrolidone, 5 \times 10⁵ cpm/ml labelled oligonucleotide probe at room temperature (22°C) overnight. After hybridization, the filters were washed twice for 10 min each in several hundred ml of 0.3 M NaCl, 30 mM NaCitrate, pH 7.0, 0.1% (w/v) SDS, and twice in several hundred ml of 15 mM NaCl, 1.5 mM NaCitrate, pH 7.0, 0.1% (w/v) SDS for 10 min each at 32°C. After washing, the filters were exposed to Kodak X-AR film for several hours to generate autoradiograms.

RESULTS

Figure 1 shows an amino acid comparison of the amphibian peptides bombesin and ranatensin with their mammalian counterparts gastrin releasing peptide and neuromedin B, respectively. Gastrin-releasing peptide is most similar to bombesin, while neuromedin B is more similar to ranatensin. Note the structural similarity of all four peptides at their amidated C-termini (Trp-Ala-Val/Thr-Gly-His-Leu/Phe-Met-NH₂), and the lack of conserved sequence over the amino terminal domain of the peptides. The conserved C-terminus appears to be the critical domain for binding to high affinity receptors [35], conferring biological activity in mammalian systems; the remarkable conservation of this domain explains why the amphibian bombesin-like peptides elicit potent responses in mammals.

The nucleotide sequence of the coding regions of five mammalian bombesin receptor cDNAs is shown in Figure 2, with the sequences aligned to maximize homology. The corresponding predicted coding sequences of the same five receptor cDNAs are aligned in Figure 3. As expected, mammalian homologs of the same receptor (mouse GRP-R and human GRP-R, 90% identity; rat NMB-R and human GRP-R; 89% identity) are more similar in amino acid sequence

BOMBESIN	Bombesin:	E Q R L G N Q WA V GH	L M-NH2
SUBFAMILY	Human GRP:	V P L P A G G G T V L T K M Y P R G N H WA V GH	L M-NH2
RANATENSIN	Ranatensin:	EVPQ WA V GH	F M-NH2
SUBFAMILY	Human NMB:	APLSWDLPEPRSRASKIRVHSRGNL WA T GH	

Fig. 1. Amino acid comparison of the amphibian peptides bombesin and ranatensin with their mammalian relatives GRP and NMB, respectively. Note the remarkable sequence identity over the seven C-terminal amino acids (boxed), the peptide region critical for receptor binding.

than two distinct receptor subtypes from the same species (human GRP-R and human NMB-R; 55% identity) (Fig. 3). The five receptors show the greatest degree of similarity in the seven hydrophobic transmembrane domains (TM I-VII), while the predicted extracellular domains (e1-e4) are less well conserved. These observations are consistent with the hypothesis that conserved residues in these domains may play an important role in determining the ligand binding pocket. Three conserved sites for potential phosphorylation by protein kinase C are also noted in intracellular domains 3 and 4 (vertical boxes with asterisks, Fig. 3).

The signal transduction pathway utilized by GRP-R (Benya et al., manuscript in preparation) and NMB-R expressed after transfection into Balb 3T3 fibroblasts [36,37] has been studied in detail. For both receptors, ligand binding results in activation of a pertussis toxin insensitive guanine nucleotide binding protein (Gprotein), which activates phospholipase C resulting in an increase in inositol trisphosphate, followed rapidly by transient elevation in intracellular calcium. Due to the lack of a high affinity agonist, detailed characterization of the signal transduction properties of BRS-3 has not been performed. The bombesin-dependent BRS-3 electrophysiologic assay performed in Xenopus oocytes [30] monitors the opening of a calcium dependent chloride channel, suggesting that the BRS-3 signal transduction pathway also involves a transient elevation in intracellular calcium.

The binding properties of GRP-R and NMB-R transfected into Balb 3T3 fibroblasts are compared in Table I. Quantitative ligand displacement of [¹²⁵I]Tyr⁴bombesin shows the distinct binding properties of these two receptors, with the rank order of affinity for binding to GRP-R (GRP, [D-Phe⁶]bombesin (6–13) ethyl ester antagonist > NMB) differing from NMB-R (NMB > GRP, [D-Phe⁶]bombesin (6–13) ethyl ester antagonist). Bombesin binds both receptors with high affinity ($K_i = 1-3$ nM). Neither GRP nor NMB appear to be high affinity ligands for BRS-3 [30,32]. Micromolar levels of GRP, NMB, or BN are needed to elicit responses from BRS-3 expressed in *Xenopus* oocytes [30], while nanomolar concentrations of high affinity ligands for GRP-R and NMB-R elicit responses in the same assay [27–29].

The pattern of expression of these three pharmacologically distinct bombesin receptors was examined in a panel of human small cell lung carcinoma cell lines. The expression of transcripts encoding the three human bombesin receptor subtypes (huGRP-R, huNMB-R, hu-BRS-3) was assayed by reverse transcription followed by polymerase chain reaction using gene-specific primers (RT/PCR). This assay is the most sensitive assay available for mRNA detection [33], and was chosen because the levels of GRP-R and NMB-R mRNAs detected in bombesin responsive cell lines were shown to be very low using a less sensitive but quantitative RNase protection assay in an earlier study [29]. Representative results are shown in Figure 4, and results from a panel of cell lines are summarized in Table II. Expression of GRP-R, NMB-R, and BRS-3 mRNA is widespread in human lung carcinoma cell lines, with most cell lines expressing at least one of the three receptors and many cell lines expressing more than one receptor (H345, for example).

Bombesin Receptors in Human Lung Cancer

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Mogrp-R	• • • • • • • • • • •	ATGGCTCCAA	ATAATIGTIC	CCACCTGAAC	TTGGACGTGG	ACCCTTTCCT	GTCCTGCAAC	GACACCITCA	ATCAAAGTCT	GAGTCCCCCC
Hugrp-R		ATGGCTCTAA	ATGACTGTTT	CCTTCTGAAC	TTGGAGGTGG	ACCATTICAT	GCACTGCA	ACATCTCCA	GTCACAGTGC	GGATCTCCCC
Hubrs-3	AIGGUICAAA	ADCCCCTCA	ACTORCOTART	CAGACTITIAA	CITCLATCAC	AAATGACACA	GAATCATCAA	GCTCTGTGGT	TICTAACGAT	AACACAAATA
Ratomb-R		ATGCCCCCCA	GGTCTCTCCC	CAACCTCTCC	TTECCCACCO	ACCCCARIGA	CACCCACTTC	GINCCCGAGG	GGIGGGAAAG	GGATTTCCTG
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Mogrp-R	AAGATGGACA	ACTGGTTT	CACCCGGGC .	TTCAT	CTATGTCATC	CCTGCAGTTT	ATGGGCTTAT	CATCGTGATA	GGTCTTATIG	GCAACATCAC
Hugrp-R	GTGAACGATG	ACTGGTCC	CACCCGGGG.	ATCCT	CTATGTCATC	CCTGCAGTTT	ATGGGGTTAT	CATTCTGATA	GGCCTCATTG	GCAACATCAC
Hubrs-3	AAGGATGGAG	CGGGGACAAC	TCTCCAGGAA	TAGAAGCATT	GTGTGCCATC	TATATTACTT	ATGCTGTGAT	CATTTCAGTG	GGCATCCTTG	GAAATGCTAT
Hunmb-R	CCGGCCTCGG	ACGGGACC	ACCACGGAGT	TGGTGATCCG	CTGTGTGTGATC	CCGTCCCTCT	ACCTGCTCAT	CATCACCGTG	GGCTTGCTGG	GCAACATCAT
Rathmo-R	CCIGACICAG	ACGGGACC	ACCECGGAGT	IGGTAATCCG	CIGIGIGATA	CCATCCCTCT	ACCTAATCAT	CATCICGGIG	GGCTIGCTGG	GCAACATCAT
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Mogrp-R	GCTCATCAAG	ATCTTCTGCA	CGGTCAAGTC	CATGCGAAAC	GTOCCAAACC	TGTTCATCTC	TAGCCTGGCT	TTGGGAGACC	TGCTGCTGCT	GGTGACATGC
Hugrp-R	TTTGATCAAG	ATCTTCTGTA	CAGTCAAGTC	CATGCGAAAC	GTICCAAACC	TGTTCATTTC	CAGTCTGGCT	TTGGGAGACC	TGCTCCTCCT	AATAACGTGT
Hubrs-3	TCTCATCAAA	GTCTTTTTCA	AGACCAAATC	CATGCAAACA	GTICCAAATA	TTTTCATCAC	CAGCCTGGCT	TTTGGAGATC	TTTTACTTCT	GCTAACTTGT
Hunmb-R	GCTGGTGAAG	ATCTTCATCA	CCAACAGCGC	CATGAGGAGC	GTOCCCAACA	TCTTCATCTC	TAACCTGGCG	GCCGGGGGACT	TGCTGCTGCT	GCTCACCTGC
Racrimb~R	GCIGGIGAAG	ATAPICCICA	CCAACAGCAC	CAIGCGGAGT	GIQUCCAACA	TCTTCATCTC	TAACCIGGCT	GCGGGGAGACC	TGCIGCTGCT	GCTGACCTGC
	301								TN	//- 400
Mogrp-R	GCCCCTGTGG	ATGCCAGCAA	GTACCTGGCT	GACAGGTGGC	TATTIGCCAG	AATTIGGCTGC	AAACTGATCC	COTTATACA	እርማካል ርማጥና እ	CTCCCCCTCT
Hugrp-R	GCTCCAGTGG	ATGCCAGCAG	GTACCTGGCT	GACAGATGGC	TATTTGGCAG	GATTGGCTGC	AAACTGATCC	CCTTTATACA	GCTTACCTCT	GTTGGGGGTGT
Hubrs-3	GTGCCAGTCG	ATGCAACTCA	CTACCTTGCA	GAAGGATGGC	TGTTCGGAAG	AATTGGTTGT	AAGGTGCTCT	CTITCATCCG	GCTCACTTCT	GTTGGTGTGT
Hunmb-R	GTCCCGGTGG	ACGCCTCGCG	CTACTTCTTC	GACGAGTGGA	TGTTTGGCAA	GGTGGGCTGC	AAACTGATCC	CTGTCATCCA	GCTCACTTCC	GTGGGGGTTT
Ratnmb-R	GTCCCAGTCG	ATGCCTCCCG	ATACTICTIT	GATGAATGGG	TGTTCGGCAA	GCTGGGCTGC	AAACTCATCC	CAGCCATCCA	GCTCACCTCG	GTCGCGGTTT
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Mogrp-R	CIGICITICAC	ACTIACGGCA	CIGICAGCIG	ACAGGTACAA	AGCCATTGTA	CGGCCAATGG	ATATECAGGC	ATCCCATGCC	CIGAIGAAGA	TCIGICICAA
Hubrs-3	CAGTOTTCAC	ATTAACAATT	CTCAGOGCTG	ACAGATACAA	GCCACTIGIC	AAGCCACTTG	AGCGACAGGC	CTCCANTGCC	ATCOTOAAGA	CURCUCICAA
Hunmb-R	CCGTGTTCAC	TCTCACTGCC	CTCAGGCCG	ACAGGTACAG	AGCCATCGTT	AACCCCATGG	ACATGCAGAC	GTCAGGGGCA	TTGCTGCGG	CONGIGIGAA
Ratnmb-R	CCGTGTTCAC	TCTCACGGCC	CTCAGCGCTG	ACAGGTACAG	AGCTATCGTG	AACCCCATGG	ACATGCAGAC	GTCTGGTGTG	GTGCTGTGGA	CCAGTTTGAA
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Mogrp-K	AGCIGCITIG	ATCIGGATIG	TCTCTATGTT	GTIGGCCAIC	CCAGAGGCIG	TGIPPITCIGA	COTCCACCCC	TICCATGIGA	AAGATACCAA	CCAAACCTTC
Hubre-3	AGCCGCCTTT	GTCTCGATCA	TOTOCATGOT	AUTOCCATT	CCHGAGGCCG	TATTTTCTGA	TOTATACACT	TICCAIGAGG	CONTRACCA	CCAGACCITC
Hunmb-R	GGCCATGGGT	ATCTGGGTGG	TCTCCGTGTT	GCTGGCAGTT	CCCGAAGCGG	TOTTTCAGA	AGTGGCTCGC	ATCAGTAGCT	TCCATAATAA	C ACCTTC
Ratnmb-R	GGCCGTGGGC	ATCTGGGTGG	TCTCTGTGCT	GTTGGCTGTC	CCTGAGGCTG	TGITTTCGGA	AGTAGCACGC	ATCGGTAGCT	CGGATAACAG	CAGTTTC
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Mogrp-R	ATTAGTTGTG	CCCCCTACCC	ACACTCCAAT	GAGCTACACC	стаааатсса	TTCCATGGCT	ICCTTICIGG	TTTTCTACGT	TATCCCACTG	GCGATCATCT
Mogrp-R Hugrp-R	ATTAGTTGTG ATTAGCTGTG	CCCCCTACCC CCCCATACCC	ACACTCCAAT ACACTCTAAT	GAGCTACACC GAGCTTCACC	CTAAAATCCA CCAAAATCCA	TTCCATGGCT TTCTATGGCT	TCCTTTCTGG TCCTTTCTGG	TTTTCTACGT TCTTCTACGT	TATCCCACTG CATCCCACTG	GCGATCATCT TCGATCATCT
Mogrp-R Hugrp-R Hubrs-3 Hupph-R	ATTAGTTGTG ATTAGCTGTG GAATCATGTA	CCCCCTACCC CCCCATACCC CCTCTTATCC	ACACTCCAAT ACACTCTAAT TGTCTCTAAG	GAGCTACACC GAGCTTCACC AAGCTCTTGC	CTAAAATCCA CCAAAATCCA AAGAAATACA CAAACATTCA	TTCCATGGCT TTCTATGGCT TTCTCTGCTG	TCCTTTCTGG TCCTTTCTGG TGCTTCTTAG	TTTTCTACGT TCTTCTACGT TGTTCTACAT	TATCCCACTG CATCCCACTG TATTCCACTC	GCGATCATCT TCGATCATCT TCTATTATCT
Mogrp-R Hugrp-R Hubrs-3 Hunmb-R Batnmb-R	ATTAGTTGTG ATTAGCTGTG GAATCATGTA ACAGCATGTA ACAGCATGCA	CCCCCTACCC CCCCATACCC CCTCTTATCC TCCCATACCC TACCCTACCC	ACACTCCAAT ACACTCTAAT TGTCTCTAAG TCAAACAGAT ACAAACAGAT	GAGCTACACC GAGCTTCACC AAGCTCTTGC GAATTACATC GAGTTACATC	СТААААТССА ССААААТССА ААДАААТАСА САААДАТТСА САААДАТССА	TTCCATGGCT TTCTATGGCT TTCTCTGCTG TTCAGTGCTC CTCAGTGCTC	TCCTTTCTGG TCCTTTCTGG IGCTTCTTAG ATTTTCTTGG ATTTTCTTGG	TTTTCTACGT TCTTCTACGT TGTTCTACAT TCTATTTCCT	TATCCCACTG CATCCCACTG TATTCCACTC CATACCACTT CATACCACTT	СССАТСАТСТ ТССАТСАТСТ ТСТАТТАТСТ ССТАТТАТСТ СТТАТТАТСА
Mogrp-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R	ATTAGTTGTG ATTAGCTGTG GAATCATGTA ACAGCATGTA ACAGCATGCA	CCCCCTACCC CCCCATACCC CCTCTTATCC TCCCATACCC TACCCTACCC	АСАСТССААТ АСАСТСТААТ ТСТСТСТААС ТСАААСАСАТ АСАААСАСАТ	GAGCTACACC GAGCTTCACC AAGCTCTTGC GAATTACATC GAGTTACATC	СТААААТССА ССААААТССА ААДАААТАСА САААДАТТСА САААДАТССА	TTCCATGGCT TTCTATGGCT TTCTCTGCTG TTCAGTGCTC CTCAGTGCTC	TCCTTTCTGG TCCTTTCTGG TGCTTCTTAG ATTTTCTTGG ATTTTTCTTG	TTTTCTACGT TCTTCTACGT TGTTCTACAT TCTATTTCCT TCTATTTCCT	TATCCCACTG CATCCCACTG TATTCCACTC CATACCACTT CATACCCCTT	GCGATCATCT TCGATCATCT TCTATTATCT GCTATTATTA GTTATCATCA
Mogrp-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R	ATTAGTTGTG ATTAGCTGTG GAATCATGTA ACAGCATGTA ACAGCATGCA 701	CCCCCTACCC CCCCATACCC CCTCTTATCC TCCCATACCC TACCCTACCC	ACACTCCAAT ACACTCTAAT TGTCTCTAAG TCAAACAGAT ACAAACAGAT	GAGCTACACC GAGCTTCACC AAGCTCTTGC GAATTACATC GAGTTACATC	СТАЛАЛТССА ССАЛАЛТССА АЛБАЛТТСА САЛАБАТТСА САЛАБАТТСА	TTCCATCGCT TTCTATCGCT TTCTCTCGCTG TTCAGTGCTC CTCAGTGCTC	ICCTITIC TGG ICCTITIC TGG IGCTICTTAG ATTITICTIGG ATTITICTIGG	TITTCTACGT TCTTCTACGT TGTTCTACAT TCTATTTCCT TCTATTTCCT	TATECCACEG CATECCACEG TATECCACEG CATACCACET CATACCACET	СССАТСАТСТ ТССАТСАТСТ ТСТАТТАТСТ ССТАТТАТСТ ССТАТТАТТА СТТАТСАТСА 2 800
Mogrp-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Mogrp-R	ATTAGTTGTG ATTAGCTGTG GAATCATGTA ACAGCATGTA ACAGCATGCA 701 CTGTCTACTA	CCCCCTACCC CCCCATACCC CCTCTTATCC TCCCATACCC TACCCTACCC CTACTTCATT	АСАСТССААТ АСАСТСТААТ ТСТСТСТААС ТСАЛАСАСАТ АСАЛАСАСАТ СССССАЛАТС	GAGCTACACC GAGCTTCACC AAGCTCTTGC GAATTACATC GAGTTACATC TGATTCAGAG	СТААААТССА ССААААТССА ААДАААТАСА САААДАТТСА САААДАТТСА ТGCCTACAAT	TTCCATGGCT TTCTATGGCT TTCTCTGCTG TTCAGTGCTC CTCAGTGCTC CTTCCCGTGG	AAGGCAATAT	TTTTCTACGT TCTTCTACGT TGTTCTACAT TCTATTTCCT TCTATTTCCT ACATGTCAAG	TATCCCACTG CATCCCACTG TATTCCACTC CATACCACTT CATACCCCTT NTRON AAGCACTCG	GCGATCATCT TCGATCATCT TCTATTATCT GCTATTATCA GTTATCATCA 2 800 AATCCCGGAA
Mogrp-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Mogrp-R Hugrp-R	ATTAGTIGTG ATTAGCTGTG GAATCATGTA ACAGCATGTA ACAGCATGCA 701 CTGTCTACTA CTGTTTACTA	CCCCCTACCC CCCCATACCC CCTCTTATCC TCCCATACCC TACCCTACCC CTACTTCATT CTACTTCATT	АСАСТССААТ АСАСТСТААТ ТОТСТСТААТ ТСАААСАДАТ АСАААСАДАТ ССССДАААТС GCCCGAAATC GCTAAAAATC	GAGCTACACC GAGCTTCACC AAGCTCTTGC GAATTACATC GAGTTACATC TGATTCAGAG TGATCCAGAG	СТААААТССА ССААААТССА ААДААТАСА САААДАТТСА САААДАТТСА ТGCCTACAAT TGCCTACAAT	TTCCATGGCT TTCTATGGCT TTCTCTGCTG TTCAGTGCTC CTCAGTGCTC CTCCCGTGG CTTCCCGTGG	TCCTTTCTGG TCCTTTCTGG TGCTTCTTAG ATTTTCTTGG ATTTTTCTTG AAGGCAATAT AAGGCAATAT	TTTTCTACGT TCTTCTACGT TGTTCTACAT TCTATTTCCT TCTATTTCCT TCTATTTCCT ACATGTCAAG ACATGTCAAG	TATCCCACTG CATCCCACTG TATTCCACTC CATACCACTT CATACCCCTT NTRON AAGCACTTCG AAGCACTTCG	GCGATCATCT TCGATCATCT TCTATTATCT GCTATTATCA GTTATCATCA 2 800 AATCCCCGGAA AATCCCGGAA
Mogrp-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Mogrp-R Hugrp-R Hubrs-3	ATTAGTTGTG ATTAGCTGTG GAATCATGTA ACAGCATGTA ACAGCATGTA ACAGCATGCA 701 CTGTCTACTA CTGTTTACTA	CCCCCTACCC CCCCATACCC CCTCTTATCC TCCCATACCC TACCCTACCC CTACTTCATT TTCCTTGATT	АСАСТССААТ АСАСТСТААТ ТСЯТСТСТААС ТСАЛАСАСАТ АСАААСАСАТ ССОССАЛАТС СССССАЛАТС ССТАЛАЛАТС	GAGCTACACC GAGCTTCACC AAGCTCTTGC GAATTACATC GAGTTACATC TGATTCAGAG TTGATTCAGAG TTTACAAAAG	СТААЛАТССА ССАЛАТССА АЛБАЛТСА САЛАБАТТСА САЛАБАТТСА САЛАБАТССА ТБССТАСАЛТ ТБССТАСАЛТ САССТБААС	TTCCATGGCT TTCTATGGCT TTCTCGCTG TTCAGTGCTC CTCAGTGCTC CTTCCCGTGG CTTCCCGTGG ATACCTACTG	TCCTTTCTGG TCCTTTCTGG TGCTTCTTAG ATTTTCTTGG ATTTTTCTTGG AAGGCAATAT AAGGCAATAT AGGGAACAAAG	TTTTCTACGT TCTTCTACGT TGTTCTACAT TCTATTTCCT TCTATTTCCT TCTATTTCCT ACATGTCAAG ACATGTCAAG CCATGCCCGT	TATCCCACTG CATCCCACTG TATTCCACTC CATACCACTT CATACCCCTT NTRON AAGCACTTCG AAGCACTTCG AAGCACTTG	GCGATCATCT TCGATCATCT TCTATTATCT GCTATTATATCT GTTATCATCA 2 800 AATCCCCGGAA AATCCCCGAAA
Mogrp-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Mogrp-R Hugrp-R Hubrs-3 Hunmb-R	ATTAGTTGTG ATTAGCTGTG GAATCATGTA ACAGCATGTA ACAGCATGTA ACAGCATGCA CTGTCTACTA CTGTCTACTA CTGTCTACTA GCATTTACTA	CCCCCTACCC CCCCATACCC CCTCTTATCC TCCCATACCC TACCCTACCC CTACTTCATT TTCCTTGATT TTCCTTGATT TTATCATATT	АСАСТССААТ АСАСТСТААТ ТСТАСТСТААС ТСАЛАСАGАТ АСАААСАGАТ АСАААСАGАТ СССССАААААТС ССТАААААТС ССТАДАДАССС ССТААДАССС	GAGCTACACC GAGCTTCACC AAGCTCTGC GAATTACATC GAGTTACATC TGATTCAGAG TGATCCAGAG TTACAAAAG TAATTAAAAG	ΟΤΆΑΑΑΤΟCΑ ΟCΑΑΑΑΤΟCΑ ΑΑGΑΑΤΑCΑ CAAAGATTCA CAAAGATCCA TGCCTACAAT TGCTTACAAT CACCCTGAAC CGCACACAAT	TTCCATGGCT TTCTATGGCT TTCATGGTG TTCAGTGCTC CTCAGTGCTC CTTCCCGTGG ATACCTACTG CTTCCCGGGG CTTCCCGGGAG	TCCTTTCTGG TCCTTTCTGG IGCTTCTTAG ATTTTCTTGG ATTTTCTTGG AAGGCAATAT AAGGGAATAT AGGAACAAAG AATACAATGA	TTTTCTACGT TCTTCTACGT TGTTCTACAT TCTATTTCCT TCTATTTCCT ACATGTCAAG ACATGTCAAG ACATGCCGT ACATGCCCGT ACATACCAAA	TATCCCACTG CATCCCACTG TATTCCACTG CATACCACTT CATACCCCTT NTRON AAGCACATTG AAGCACATTG AAGCACATTG	GCGATCATCT TCGATCATCT TCTATTATCT GCTATTATTA GTTATCATCA 800 AATCCCGGAA AATCCCGGAA AAACCCGGAA
Mogrp-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R	ATTAGTTGTG ATTAGCTGTG GAATCATGTA ACAGCATGTA ACAGCATGTA ACAGCATGCA TOT CTGTCTACTA CTGTTTACTA CTGTTTACTA GCATTTATTA GCATTTATTA	CCCCCTACCC CCCCTACCC TCCCATACCC TCCCATACCC TACCTACC	АСАСТССААТ АСАСТСТААТ ТБТСТСТААБ ТСАААСАБАТ АСАААСАБАТ ССССБААТС ССТАААААТС GCTAGACCC GCTAGGACCC GCCAAGACCT	GAGCTACACC GAGCTTCACC AAGCTCTTGC GAATTACATC GAGTTACATC TGATTCAGAG TGATCCAGAG TTTACAAAAG TAATTAAAAG TAATTAAAAG	СТАЛЛАТССА ССАЛАТССА АЛБАЛТСА САЛАБАТТСА САЛАБАТТСА ТБССТАСАЛТ ТБССТАСАЛТ ТБССТАСАЛТ САССТБАСА СБСАСАСАЛТ ТБСАСАСАЛТ	TTCCATGGCT TTCTATGGCT TTCCTGCTG TTCCAGTGCTC CTCCCGTGG CTTCCCGTGG CTTCCCGTGG CTTCCTGGAG CTTCCTGGAG	TCCTTTCTGG TCCTTTCTGG TCCTTCTTAG ATTITCTTGG ATTITCTTGG ATTITCTTG AAGGCAATAT AAGGACAAAA AATACAATGA AATACAATGA	ТТТТСТАССТ ТСТТСТАССТ ТСТТСТАСАТ ТСТАТТТССТ ТСТАТТТССТ АСАТСТСААС АСАТСТСААС АСАТСТСААС АСАТСССАТ АСАТАССААА АСАТАССААА	TATCCCACTG CATCCCACTG TATTCCACTC CATACCACTT CATACCACTT NTRON AAGCACTTG AAGCACTTG AAGCACTTG AAGCACTTG AAGCACTTG AAGCACTTG	GCGATCATCT TCGATCATCT TCTATTATCT GCTATTATTA GTTATCATCA 2 800 AATCCCGGAA AATCCCGGAA AATCCCGAA AAACACGGAA AGACACGGAA
Mogrp-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R	ATTAGTTGTG ATTAGCTGTG GAATCATGTA ACAGCATGTA ACAGCATGTA ACAGCATGCA 701 CTGTCTACTA CTGTTTACTA CTGTTTACTA GCATTTATTA GCATTTATTA 801	CCCCTACCC CCCATACCC CCCATACCC TACCTACCC TACCTACC	АСАСТССААТ АСАСТСТААТ ТСТСТСТАА ТСАААСАБАТ АСАААСАБАТ ССССБАААТС GCTAAAAATC GCTAAAAATC GCTAAGAACC GCAAAGACT GCCAAGACT	GAGCTACACC GAGCTACACC GAATTACATC GATTACATC GAGTTACATC TGATTCAGAG TGATTCAGAG TTTACAAAAG TAATTAAAAG TAATTAAAAG	сталалтсса ссалалтсса саладаттса саладаттса саладаттса саладаттса саладаттса саладатсса тосстасалт сассстасалт сассстодалс сассстодалс сассстасалт тосстасалт сассостасалт тосстасалт сассостасалт тосстасалт сассостасалт тосстасалт тосстасалт сассостасалт тосстасалт сассостасалт	TTCCATGGCT TTCTATGCTT TTCATGCTG TTCAGTGCTC CTCAGTGCTC CTTCCCGTGG CTTCCCGTGG ATACCTACTG ATACCTACTG CTTCCTGGAG	TCCTTTCTGG TCCTTTCTGG ISCTTCTTAG ATTTTCTTGG ATTTTCTTGG AAGGCAATAT AAGGCAATAT AGGAACAAGA AATACAATGA	ТГТТСТАССТ ТСТТСТАССТ ТСТАТТТССТ ТСТАТТТССТ ТСТАТТТССТ АСАТСТСАА АСАТСТСАА ССАТСССАА АСАТСССАА АСАТАССААА	TATCCCACTG CATCCCACTG TATTCCACTC CATACCACTT CATACCCCTT NTRON AAGCACTTG AAGCACTTG AAGCACTTG AAGCACTGG AAGCACTGG	GCGATCATCT TCCATCATCAT TCTATTATCT GCTATTATCA GCTATTATCA Q 800 AATCCCGGAA AATCCCGGAA AATCCCGGAA AACCCCGGAA AACCCCGGAA AACCCCGGAA AACCCCGGAA AACCCCGAA AACCCCGAA
Mogrp-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Hugrp-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R	ATTAGTTGTG ATTAGCTGTG GAATCATGTA ACAGCATGTA ACAGCATGTA ACAGCATGTA CTGTTTACTA CTGTTTACTA CTGTTTACTA GCATTTATTA 801 801	CCCCCTACCC CCCCATACCC TCCCATACCC TCCCATACCC TACCTACTCATT CTACTTCATT TTCCTACTTCATT TTATCACATT TATCACATT	АСАСТССААТ АСАСТСТААТ ТGTCTCTAAG TCAAACAGAT АСАААСАGAT АСАААСАGAT GCCGGAAATC GCTAAGAACT GCCAAGACTT TGGTGTTTGT	GAGCTACACC GAGCTACACC AAGCTCTTGC GAATTACATC GAGTTACATC TGATTCAGAG TGATCCAGAG TTTACAAAAG TAATTAAAAG TAATTAAAAG	сталалтсса ссалаатсса аладалтаса саладаттса саладатсса тосстасалт тосстасалт сассстоалс сосасасталт тосассасалт тосассасалт тосасасалт TM-V	TTCCATGGCT TTCTATGGCT TTCATCGCTG TTCAGTGCTC CTCAGTGCTC CTTCCCGTGG ATACCTACTG ATACCTACTG CTTCCTGGAG CTTCCTGGAG CTTCCTGGAG	TCCTTTCTGG TCCTTTCTGG IGCTTCTTAG ATTITCTTGG ATTITCTTGG ATTITTCTTG AAGGCAATAT AAGGCAATAT AAGGAACAAG AATACAATGA AATACAATGA CCATGTCATC	ТТТТСТАССТ ТСТТСТАССТ ТСТТСТАСАТ ТСТАТТТССТ ТСТАТТТССТ СТАТТТССТ АСАТСТСАА АСАТСТСАА АСАТСТСАА АСАТСССАА АСАТАССААА ТАССТСРАСС	TATCCCACTG CATCCCACTG TATTCCACTC CATACCACTT CATACCACTT NTRON AAGCACTTG AAGCACTTG AAGCACTTG AAGCACTTG GTTCCTACCA	GCGATCATCT TCGATCATCT TCTATTATCT GCTATTATTATCA Q 800 AATCCCGGAA AATCCCGGAA AATCCCGGAA AACCCCGAA AACACGGAA AGACACGGAA 900 CTACTCT
Mogrp-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Ratnmb-R Ratnmb-R	ATTAGTTGTG ATTAGCTGTG GAATCATGTA ACAGCATGTA ACAGCATGTA ACAGCATGCA 701 CTGTCTACTA CTGTCTACTA CTGTCTACTA GCATTTATTA GCATTTATTA 801 GCGGCTTGCC GCGACTTGCC	CCCCTACCC CCCCTACCC CCCCTATACC TACCTACCC TACCTCATT TTACCATATT TTATCATATT TTATCACATT AAGACA <u>STAC</u> AAGACASTAC	ACACTCCAAT ACACTCCTAAT TGTCTCTAAG TCAAACAGAT ACAAACAGAT GCCGCAAATC GCTAAAAATC GCTAAGAACC GCTAAGAACC GCCAAAGACCT GCCGAAGACCT TGGTGTTTGT TGGTGTTTGT	GAGCTACACC GAGCTACACC GAGCTACACC GAATTACATC GATTACATC GATTCAGAG TGATTCAGAG TTACAAAAG TAATTAAAAG GGGCCTCTTT GGGCCTCTTT	сталалтсса ссалалтсса ладалатаса саладаттса саладаттса саладаттса твосттасалт сассетасалт твостасалт твосасасалт твосасасалт твосасасалт восстетаст	TTCCATGGCT TTCTATGGCT TTCTATGGCTG TTCCAGTGGCTC CTCAGTGCTC CTCCCGTGG ATACCTACTG CTTCCCGGAG CTTCCCGGAG CTTCCCGGAG GGCTCCCCAA GGCTCCCCAA	TCCTTTCTGG TCCTTTCTGG ATTTTCTTGG ATTTTCTTGG ATTTTCTTGG AAGGCAATAT AAGGAACAATAT AAGGAACAATGA AATACAATGA AATACAATGA CCATGTCATC TCATGTCATC	ТГТТСТАССТ ТСТТСТАСАТ ТСТАТТТССТ ТСТАТТТССТ ТСТАТТТССТ АСАТСТСАА ССАТССАА ССАТССАА ССАТССССТ АСАТАССАА АСАТАССАА ТАССТСРАСС ТАССТСРАСС	TATCCCACTG CATCCCACTG TATTCCACTC CATACCACTT CATACCCCTT NTRON AAGCAGTTG AAGCAGTTG AAGCAGTTG AAGCAGTTG GTTCCTACCA GCTCCTACCA	GCGATCATCT TCGATCATCT TCTATTATCT GCTATTATCA GCTATTATCA Q 800 AATCCCGGAA AATCCCGGAA AATCCCGGAA AATCCCGGAA AATCCCGGAA AGACACGGAA 900 CT ACTCT CT ACTCT
Mogrp-R Hugrp-R Hubra-3 Hunmb-R Ratnmb-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Ratnmb-R Hugrp-R Hugrp-R Hubrs-3	ATTAGTTGTG ATTAGCTGTG GAATCATGTA ACAGCATGTA ACAGCATGTA ACAGCATGTA CTGTTTACTA CTGTTTACTA CTGTTTACTA GCATTTATTA 801 GCGGCTTGCC GCGACTTGCC GAGAATTGCC	CCCCTACCC CCCATACCC CCCATACCC TCCTATATCC TCCCATACCC TACCTACATT TTACCATATT TTATCATATT TTATCATATT TATCACATT AAGACATTAC AGAACATTAC	ACACTCCAAT ACACTCCAAT TGTCTCTAAG TCAAACAGAT ACAAACAGAT ACAAACAGAT GCCCGAAATC GCTAGAAATC GCTAGACACCT GCCGAAGACCT TGGTGTTTGT TGGTGTTTGT TGGTGTTGGT	САССТАСАСС САССТТСАСС САССТТСАСС САСТТАСАТС САСТТАСАТС САСТТАСАТС САССТАСА САССТСАТА САССССТТТ СССССТТТ СССССТТТ СССССТТТ	сталалтсса ссалалтсса ладалатаса саладаттса саладаттса саладаттса твестасалт твестасалт твестасалт твесасасалт твесасасалт TM-V	TTCCATGGCT TTCTATGGCT TTCTATGGCTG TTCAGTGCTC CTCAGTGCTC CTTCCCGTGG CTTCCCGTGG CTTCCCGTGGA CTTCCTGGAG CTTCCTGGAG CTTCCTGGAG GCTCCCCAA GGCTCCCCAA	TCCTTTCTGG TCCTTTCTGG ATTTTCTTGG ATTTTCTTGG ATTTTCTTGG AAGGCAATAT AAGGACAAAA AAGGACAAAA AATACAATGA AATACAATGA AATACAATGA CCATGTCATC TCATGTCATC TCATGTCATC TCACCTCCTG	ТГТТСТАССТ ТСТТСТАСАТ ТСТАТТТССТ ТСТАТТТССТ ТСТАТТТССТ АСАТСТСААС АСАТСТСААС АСАТСТСАА АСАТССААА АСАТАССААА АСАТАССААА ТАССТСРАСС ТАССТСРАСС ТАССТСРАСС	TATCCCACTG CATCCCACTG TATTCCACTC CATACCACTT CATACCCCTT NTRON AAGCACTTG AAGCACTTG AAGCACTTG AAGCACTTG GTTCCTACCA ATTCATCACCACTACCA	GCGATCATCT TCGATCATCT TCTATTATCT GCTATTATTA GTTATCATCA 2 800 AATCCCGGAA AATCCCGGAA AATCCCGGAA AACACGGAA GCTACTCT CTACTCT CTACTCT TTCTCAAAACC
Mogrp-R Hugrp-R Hubra-3 Hunmb-R Ratnmb-R Mogrp-R Hubrs-3 Hunmb-R Ratnmb-R Mogrp-R Hugrp-R Hugrp-R Hugrp-R Hubrs-3 Hunmb-R	ATTAGTTGTG ATTAGCTGTG GAATCATGTA ACAGCATGTA ACAGCATGTA ACAGCATGCA CTGTTTACTA CTGTTTACTA CTGTTTACTA GCATTTATTA GCATTTATTA B01 GCGGCTTGCC GCGACTTGCC ACGCCTGGCT	ССССТАССС ССССТАТАСС ССТСТТАТСС ТСССАТАССС ТАССТСАТС СТАСТТСАТТ СТАСТТСАТТ ТТАТСАТАТТ ТТАТСАТАТТ ТТАТСАСАТТ ААGACAБТЭС АGAACAБТЭС АGAACAБТЭС	ACACTCCAAT ACACTCCTAAT TGTCTCTAAG TCAAACAGAT ACAAACAGAT ACAAACAGAT GCCGGAAATC GCTAGGAACCC GCTAGGACCC GCCAAGACCT TGGTGTTTGT TGGTGTTTGT TGGTGTTTGT TGGTGTTTGT	GAGCTACACC GAGCTACACC GAGCTACACC GAATTACATC GAGTTACATC GAGTTACATC TGATTCAGAG TGATCCAGAG TATTACAAAAG TAATTAAAAAG TAATTAAAAAG GGGCCTCTTT GGGCCTCTTT GGGCTGTTTC	сталалтсса ссалалтсса саладаттса саладаттса саладаттса саладаттса саладаттса саладаттса сасстасалт сасстасалт сассстасалт сассстабас сассасалт тасаласалат тасаласалат тасаласалат сасстатстаст сасстастаст	ТТССАТСВСТ ТТСТАТСВСТ ТТСТАТСВСТС ТТСАТСВСТС СТТССССТСС СТТССССТСВ СТТССССТСВ СТТССССТСВ СТТССТСВАВ СТТССТСВАВ СТТССТСВАВ СТТССССАА ВСТТССССАА ВСТССССАА ВСТТСССАА ВСТТСССАА ВСТТСССАА	TCCTTTCTGG TCCTTTCTGG TCCTTTCTGG ATTTTCTTGG ATTTTCTTGG AGGACAATAT AAGGACAATAG AATACAATGA AATACAATGA AATACAATGA CCATGTCATC TCATGTCATC CCACTCCTG CCACTCCTT	ТГТТСТАССТ ТСТТСТАССТ ТСТАТТТССТ ТСТАТТТССТ ТСТАТТТССТ АСАТСТСААС АСАТСТСААС АСАТССССС АСАТАСССАА АСАТАССААА ТАССТСТАСС ТАССТСТАСС ТАССТСТАСС ТАСАТСТААС	TATCCCACTG CATCCCACTG TATTCCACTC CATACCACTT CATACCCCTT NTRON AAGCACTTG AAGCACTTG AAGCACTTG AAGCACTTG GTTCCTACCA GTTCCTACCA GTTCCTACCA GTTCCTACCA	GCGATCATCT TCCATCATCAT TCTATTATCT GCTATTATCA GCTATTATCA Q 800 AATCCCGGAA AATCCCGGAA AATCCCGGAA AACACGGAA GCTACTCT CTACTCT TTCTCAAACC CTACTCT CTATCATC
Mogrp-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Hugrp-R Hugrp-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R	ATTAGTTGTG ATTAGCTGTG GAATCATGTA ACAGCATGTA ACAGCATGTA ACAGCATGCA TOT CTGTCTACTA CTGTCTACTA CTGTCTACTA GCATTTATTA GCATTTATTA B01 GCGGCTTGCC GCGACTTGCC GAGAATTGCC ACGCCTGGCC	CCCCTACCC CCCCATACCC CCCCTTATCC TCCCATACCC TACCTTCATT CTACTTCATT TTCCTTGATT TTATCATATT TTATCATATT TTATCACATTC AAGACAETAC AAGACAETAC AAGACGTAT AAGATETTCC AAGATCGTTC	ACACTCCAAT ACACTCTAAT TGTCTCTAAG TCAAACAGAT ACAAACAGAT ACAAACAGAT GCCGGAAATC GCTAGGACCC GCTAGGACCC GCCAAGACCT TGCTGTTTGT TGGTGTTTGT TGGTGTTTGT TGGTGTTTGT TGGTGTTTGT	GAGCTACACC GAGCTACACC GAGCTACACC GAGTTACATC GAGTTACATC GAGTTACATC TGATTCAGAG TGATCCAGAG TTACAAAAG TAATTAAAAG TAATTAAAAG GGGCCTCTTTC GGGCCTGTTTC GGGCTGCTTTC GGGCTGCTTTC	сталалтсса ссалалтса ладалтаса саладаттса саладаттса саладаттса саладаттса саладаттса саладаттса саладаттса сасстасталт сассстасталт сассстасалт TM-V GCCTTCTGCT GCCTTCTGCT GCCTTCTGCT GCCTTCTGCT	TTCCATGGCT TTCTATGGCT TTCATGCTGCTG TTCAGTGCTC CTCAGTGCTC CTCCCGTGG CTTCCCGTGG CTTCCCGTGG CTTCCTGGAG CTTCCTGGAG GCTCCCCAA GGCTCCCCAA GGTTCCCAA GGTTCCCAA	TCCTTTCTGG TCCTTTCTGG TGCTTCTTAG ATTTTCTTGG ATTTTCTTGG ATTTTTCTTG AAGGCAATAT AAGGCAATAT AAGGAACAATGA AATACAATGA AATACAATGA CCATGTCÄTC TCACGTCCTG CCACGTCCTT CCACGTCCTC	ТГТТСТАССТ ТСТТСТАССТ ТСТАТТТССТ ТСТАТТТССТ ТСТАТТТССТ АСАТСТСАА АСАТСТСАА ССАТСССАА АСАТССАА АСАТАССАА АСАТАССАА ТАССТСРАСС ТАССТСРАСС ТАССТСРАСС ТАСАТСТААС	TATCCCACTG CATCCCACTG TATTCCACTC CATACCACTT CATACCCCTT NTRON AAGCACTTG AAGCACTTG AAGCACTTG AAGCACTG AAGCACTG GTTCCTACCA GCTCCTACCA ATTCATTCAA GGTCTTTCAA	GCGATCATCT TCCATCATCATCT TCTATTATCT GCTATTATCA Q 800 AATCCCGGAA AATCCCGGAA AATCCCGGAA AATCCCGGAA AACCCCGGAA AACCCCGGAA CTACTCT CTACTCT CTACTCT CTACTCT CTACTCT CTACAACC ATCAAACC
Mogrp-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Ratnmb-R	ATTAGTTGTG ATTAGCTGTG GAATCATGTA ACAGCATGTA ACAGCATGTA ACAGCATGCA 701 CTGTCTACTA CTGTCTACTA CTGTCTACTA GCATTTATTA 801 GCGGCTTGCC GCGACTTGCC GCGACTTGCC ACGCCTGGCC 201	ССССТАССС СССАТАССС ССТСТТАТСС ТСССАТАССС ТАССТСАТТ СТАСТТСАТТ ТТССТТСАТТ ТТССТТСАТТ ТТАТСАТАТТ ТТАТСАТАТТ ТТАТСАТАТТ ТТАТСАСАТТ ААGACAETAC АAGACAETAC АAGACAETAC АAGACCETAT	ACACTCCAAT ACACTCCAAT TGTCTCTAAG TCAAACAGAT ACAAACAGAT GCCGCAAATC GCTAAAAATC GCTAGGACCC GCAAAGACCT GCCGAAGACCT TGGTGTTTGT TGGTGTTTGT TGGTGTTTGT TGGTGTTGT	GAGCTACACC GAGCTACACC GAGCTACACC GAATTACATC GATTACATC GATTCAGAG TGATCCAGAG TTACAAAAG TAATTAAAAG TAATTAAAAG GGGCCTCTTT GGGCCTCTTT GGGCCTCTTT GGGCCTGTTC GGGCTGTTTC	сталалтсса ссалалтсса аладалтаса саладаттса саладаттса саладаттса саладаттса саладаттса саладатса сасстасалт сасстасалт сассстасалт сассасалт TM-V GCCTTCTGCT gccCTTCTGCT gccCTTCTGCT gccCTTCTGCT	TTCCATGGCT TTCTATGGCT TTCTATGGCTG TTCCAGTGGCTC CTCAGTGCTC CTTCCCGGGG ATACCTACTG CTTCCCGGGG CTTCCCGGAG CTTCCCGGAG GGCTCCCCAA GGCTCCCCAA GGTTCCCAAA GGTTCCCAAA	ГССТТТСТВС ГССТТТСТВС ПССТТСТТАС АТТТТСТТОС АТТТТСТТОС АТТТТСТТОС АТТТТСТТОС ААСССАТАТАТ ААСССАТАТАТ ААССААТАТ ААССААТАТ ССАТСТСТС ССАСАТССТС ССАСАТССТС ТМ-1	ТТТТСТАСЯТ ТСТТСТАСАТ ТСТАТТТССТ ТСТАТТТССТ ТСТАТТТССТ АСАТЯСТСАА ССАТЯССАА ССАТЯССАА ССАТЯССАА АСАТАССАА АСАТАССАА АСАТАССАА ТАССТСТАСС ТАССТСТАСС ТАССТСТАСС ТАССТСТАСС ТАСАТСТАТАС ТАСАТЯТАСА АСАТЯТСАА АСАТАССАА АСАТЯТАТА АСАТЯТАТА АСАТЯТАТА АСАТЯТАТАТАТАТАТАТАТАТАТАТАТАТАТАТАТАТАТ	TATCCCACTG CATCCCACTG TATTCCACTC CATACCACTT CATACCCCTT NRON AAGCAGTTG AAGCAGTTG AAGCAGTTG AAGCAGTTG GATCCTACCA GTTCCTACCA GTTCCTACCA GGTCTTTCAA GGTCTTTCAA	GCGATCATCT TCCATCATCATCT TCTATTATCT GCTATTATCA Q 800 AATCCCGGAA AATCCCGGAA AATCCCGGAA AACCCCGAA AACCCCGAA AACCCCGAA CTACTCT CTACTCT TTCTCAAACC CTACTCT TTCTCAAACC CTACAAG
Mogrp-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Mogrp-R Hubrs-3 Hunmb-R Ratnmb-R Ratnmb-R Ratnmb-R	ATTAGTTGTG ATTAGCTGTG GAATCATGTA ACAGCATGTA ACAGCATGTA ACAGCATGCA 701 CTGTCTACTA CTGTCTACTA CTGTCTACTA GCATTTATTA B01 GCGGCTTGCC GCGACTTGCC ACGCCTGGCC 901 GAAGTGGACA	CCCCTACCC CCCCTACCC CCCCTACCC CCCCTACCC TACCTCATT CTACTTCATT TTCCTTGATT TTATCATATT TTATCACATT AAGACASTGC AGACASTGC AGACCSTAT AAAATISTIGC AAGACSTTAC CCTCCATGCT	ACACTCCAAT ACACTCCAAT TGTCTCTAAG TCAAACAGAT ACAAACAGAT ACAAACAGAT GCCGGAAATC GCTAGAAATC GCTAGAAATC GCTAGACCT GCCGAAAACCT GCCGAAAACCT TGGTGTTTGT TGGTGTTTGT TGGTGTTTGT TGGTGTTTGT CCACTTTGT	САССАССТАСАСС САССТАСАСС САСТАСАСС САСТАСАСС САСТАСАСС САСТАСАСА СОССССТАТТ СОСССССТАТТ СОСССССТАТТ СОССССТАТТ СОСССССТАТТ СОСССССТАТТ СОССССТАТТ СОСССССТАТТ СОССССТАТТ СОСССССТАТТТ СОСССССТАТТ СОСССССТАТТ СОСССССТАТТ СОСССССТАТТ СОСССССТАТТ СОСССССТАТТ СОСССССТАТТ СОСССССТАТТ СОСССССТАТТ СОСССССТАТТ СОССССТАТТТ СОСССССТАТТ СОСССССТАТТ СОСССССТАТТ СОСССССТАТТ СОСССССТАТТ СОСССССТАТТ СОСССССТАТТ СОСССССТАТТ СОСССССТАТТ СОСССССТАТТТ СОСССССТАТТТ СОСССССТАТТТ СОСССССТАТТТ СОСССССТАТТТ СОСССССТАТТТ СОССССССТАТТТ СОСССССССТАТТТ СОССССССТАТТТ СОСССССТАТТТ СОСССССТАТТТ СОСССССТАТТТ СОССССССТАТТТ СОСССССТАТТТ СОССССССТАТТТ СОССССССТАТТТ СОССССССТАТТТ СОССССССТАТТТ СОССССССТАТТТ СОССССССТАТТТ СОССССССТАТТТ СОСССССССТАТТТ СОСССССССТАТТТ СОССССССТАТТТ СОССССССССССССССССССССССССССССССССС	сталалтсса ссалалтсса аладалтса саладаттса саладаттса саладаттса саладатса твестасалт сасстасалт твестасалт сасстасалт твестасалт сасстасалт	TTCCATGGCT TTCTATGGCT TTCTATGGCTG TTCCATGGCTG CTTCCCGTGG ATACCTACTG CTTCCCGGAG CTTCCCGGAG GCTTCCCGAA GGCTCCCCAA GGTTCCCCAA GGTTCCCCAA	ГССТТТСТВС ГССТТТСТВС АТТТТСТТВС АТТТТСТТВС АТТТТСТТВС АЛССААТАТ АЛССААТАТ ССАТСТСАТС ССАТСТСТС ССАТСТСТС ССАСТССТССС ССАСТССТС ССАСТССТС ССАСТСССС ССАСТСССС ССАСТСССС ССАСТССС ССАСТСССС ССАСТСССС ССАСТССС ССАСТССС ССАСТССС ССАСТССС ССАСТССС ССАСТССС ССАСТССС ССАСТССС ССАСТСС ССАСТСС ССАСТСС ССАСТСС ССАСТСС ССАСТСС ССАСТСС ССАСТСС ССАСТСС ССАСТСС ССАСТСС ССАСТСС ССАСТСС ССАСТСС ССАСТСС ССАСТСС ССАСТСС ССАСТСС ССАСТСС ССАССС ССАСТСС ССАСТСС ССАССС ССАСТС ССАСТСС СССС ССС	ТТТТСТАСЯТ ТСТТСТАСЯТ ТСТТСТАСАТ ТСТАТТТССТ ТСТАТТТССТ ТСТАТТТССТ АСАТGТСААG АСАТGТСААG АСАТGТСААG АСАТАССАРА АСАТАССАРА ТАССТСРАСС ТАССТСРАСС ТАССТСРАСС ТАССТСРАСС ТАСТСРАСС ТАСТСРАСС	TATCCCACTG CATCCCACTG TATTCCACTC CATACCACTT CATACCACTT CATACCCCTT NTRON AAGCACTTG AAGCACTTG AAGCACTTG AAGCACTTG GATCCTACCA GCTCCTACCA GGTCTTTCAA GGTCTTTCAA	GCGATCATCT TCGATCATCT TCTATTATCT GCTATTATCA GCTATTATCA Q 800 AATCCCGGAA AATCCCGGAA AACACGGAA AGACACGGAA GCTACTCT TTCTCAAACC CTACTCT TTCTCCAAAC CTACTCT TTCTCCAAAC CTACTCT TTCTCCAAACC CTACATCT TTCTCCAAACC TACTCCCT
Mogrp-R Hugrp-R Hubra-3 Hunmb-R Ratnmb-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Ratnmb-R Rugrp-R Hubrs-3 Hunmb-R Ratnmb-R Ratnmb-R	ATTAGTTGTG ATTAGCTGTG GAATCATGTA ACAGCATGTA ACAGCATGTA ACAGCATGTA CTGTTTACTA CTGTTTACTA CTGTTTACTA CTGTTTACTA GCATTTATTA B01 GCGGCTTGCC GCGACTTGCC GAGAATTGCC ACGCCTGGCC 901 GAAGTGGACA GAGTGGACA	CCCCTACCC CCCCTACCC CCCCTATACC TCCCTATACC TCCCTACCTA	ACACTCCAAT ACACTCCTAAT TGTCTCTTAAG TCAAACAGAT ACAAACAGAT ACAAACAGAT GCCCGAAATC GCTAAGACCT GCTAGGACCC GCTAAGACCT TGCTGTTTGT TGGTGTTTGT TGGTGTTTGT TGGTGTTTGT TGGTGTTTGT TGGTGTTTGT CCACTTTGTC CCACTTTGTC	САССАССТАСАСС САСТТАСАСС САСТТАСАСТ САСТТАСАТТС САСТТАСАТС САСТТАСАТС САСССАСАТСТ САССССТТТ СССССТТТ СССССТТТ СССССТТТ СССССТТТ СССССТТТ СССССТТТ СССССТТТ СССССТТТ СССССТТТ СССССССТТТ СССССССТТТ ССССССТТТ ССССССТТТ ССССССТТТ ССССССТТТ ССССССТТТ ССССССТТТ ССССССТТТ ССССССТТТ ССССССТТТ ССССССТТТ ССССССТТТ ССССССТТТ ССССССТТТ ССССССТТТ ССССССТТТ ССССССТТТ ССССССТТТ СССССССТТТ СССССССТТТ СССССССТТТ СССССССТТТ СССССССТТТ СССССССТТТ СССССССТТТ	сталалтсса ссалалтсса сладалтса сладаттса сладаттса сладаттса сладаттса сасстаслалт тостаслалт тосстаслалт тослесатобас сосстетобас оссететобас оссететобас оссететобас ассетобас ассеттетобас ассетобас ассетстобас	TTCCATGGCT TTCTATGGCT TTCTATGGCTG TTCCCGTGG CTTCCCGTGG CTTCCCGTGG CTTCCCGTGG CTTCCCGTGG CTTCCCGGGG CTTCCTGGAG CTTCCTGGAG CTTCCTGGAG GCTTCCCAA GGTTCCCAA GGTTCCCAA GGTTCCCAA GGTTCCCAA	ГССТТТСТВС ГССТТТСТВС АТТТСТТКС АТТТСТТВС АТТТСТТСТВС АТТТТСТТСВ АТТТТСТТСВ АТТТТСТТСВ АТТТТСТТСВ АТТСАТАТА ААССААТАСАТА ССАТССТССТС ССАСАТССТТ ССАСАТССТТ АССААСТССТ	ТТТТСТАССТ ТСТАТСТАСАТ ТСТАТТТССТ ТСТАТТТССТ АСАТСТСАС АСАТСТСАС ССАТССССС ССАТССССС АСАТАСССА АСАТАСССА АСАТАСССА ТАССТСРАСС ТАССТСРАСС ТАССТСРАСС ТАССТСРАСС ТАССТСРАСС ТАССТСРАСС ТАССТСРАСС ТАССТСРАСС ТАССТСРАСС ТАССТСРАСС ТАССТСРАСС ТАССТСРАСС	ТАТСССАСТВ САТСССАСТВ ТАТТССАСТС САТАССАСТТ САТАССССТТ NTRON ААССАТТВ ААССАТТВ ААССАТТВ ААССАТТВ ААССАТТВ СТТССТАССА СТТССТАССА АТТСАТСАС СВТССТАССА СТТГВСТСТТ АССАСТТ САТССТАССА СТТГВСТСТТСА СТТГВСТСТТ	GCGATCATCT TCCATCATCAT TCTATTATCAT GCTATTATTA GCTATTATCA Q 800 AATCCCGGAA AATCCCCGAA AATCCCCGAA AACACGGAA AGACACGGAA CTACTCT CTACTCT CTACACG TTCTCAAACC CTACACGT TTCTCAAACC CTACACGT TACTGCTGCA
Mogrp-R Hugrp-R Hubra-3 Hunmb-R Ratnmb-R Mogrp-R Hubrs-3 Hunmb-R Ratnmb-R Ratnmb-R Rugrp-R Hubrs-3 Hunmb-R Ratnmb-R Ratnmb-R Ratnmb-R Rugrp-R Hubrs-3	ATTAGTTGTG ATTAGCTGTG GAATCATGTA ACAGCATGTA ACAGCATGTA ACAGCATGTA CTGTTTACTA CTGTTTACTA CTGTTTACTA CTGTTTACTA GCATTTATTA GCATTTATTA B01 GCGGCTTGCC GCGACTTGCC GCGACTTGCC ACGCCTGGCC 901 GAAGTGGACA GAGGTGGACA TATGTAGACC	CCCCCATACCC CCCCATACCC CCCCTTATCC TCCCATACCC TACCTTCATT CTACTTCATT TTATCATATT TTATCATATT TTATCACATT AAGACASTGC AGAACASTGC AGAACASTGC CCTCCATGCT CCTCCATGCT CCTCCATGCT	ACACTCCAAT ACACTCCTAAT TGTCTCTAAG TCAAACAGAT ACAAACAGAT ACAAACAGAT GCCGGAAATC GCTAGGAACCC GCTAGGACCC GCCAAGACCT TGGTGTTTGT TGGTGTTTGT TGGTGTTTGT TGGTGTTTGT TGGTGTTTGT CCACTTTGTC CCACTTTGTC CCACTTTGTC	GAGCTACACC GAGCTACACC GAGCTACACC GAATTACATC GAGTTACATC GAGTTACATC TGATTCAGAG TGATCCAGAG TATTACAAAAG TAATTAAAAAG TAATTAAAAAG GGGCCTCTTT GGGCCTGTTT GGGCTGTTTC GGGCTGCTTT ACCAGGATCT ACCAGGATCT	сталалтсса ссалалтсса саладаттса саладаттса саладаттса саладаттса саладаттса саладаттса саладаттса сасстастаса сасстабас сасстаба састаба састаба састаба састаба састаба састаба састаба састаба састаба састаба састаба састаба састаба састаба састаба састаба сасстаба састаба састаба сасстаба састаба с с с с с с с с с с с с с с с с с с	TTCCATGGCT TTCTATGGCT TTCATGGCTG TTCAGTGGTGCTC CTCCCGTGG CTTCCCGTGG CTTCCCGTGG CTTCCTGGAG CTTCCTGGAG GCTCCCCAA GGCTCCCCAA GGTTCCCAAA GGTTCCCAAA GGTTCCCAAA GGTTCCCAAA GGTTCCCAAA GGTTCCCCAA	ТССТТТСТВС ТССТТТСТВС АТТТСТТТСТВ АТТТСТТВС АТТТСТТВС АТТТТСТТВС АТТТТСТТВС АТТТТСТТВС АТТТСТТВС АТТТТСТВС АТТТСТТВС АТТТСТТВС АТТТСТТВС АТТТСТТВС АТТТСТТВС АТТТСТТВС АТТТСТТВС АТТТСТТВС АТТТСТТВС АССАСТССТ ССАТБТСАТС ССАТБТСАТССТ ССАСАТССТ АССААСТССТ АССААСТССТ	ТГТТСТАССТ ТСТТСТАССТ ТСТАТТТССТ ТСТАТТТССТ ТСТАТТТССТ АСАТСТСААС АСАТСТСААС АСАТССССС АСАТССССС АСАТАСССАА АСАТАССААА ТАССТСТАСС ТАССТСТАСС ТАССТСТАСС ТАССТСТАСС ТАССТСТАСС ТАССТСТАСС ТАССТСТАСС ТАССТСТАСС ТАССТСТАСС ТАССТСТАСС ТАССТСТАСС ТАССТСТАСС ТАССТСТАСС	TATCCCACTG CATCCCACTG TATTCCACTC CATACCACTT CATACCCCTT NTRON AAGCACTTG AAGCACTTG AAGCACTTG AAGCACTTG AAGCACTTG GTTCCTACCA GTTCCTACCA GTTCCTACCA GTTCCTTCCA GGTCTTTCAA GTTTTGCTCTC CTTTGCCTCTC	GCGATCATCT TCCATCATCAT TCTATTATCT GCTATTATTA GCTATTATCA 2 800 AATCCCGGAA AATCCCGGAA AATCCCGGAA AACACGGAA AGACACGGAA 900 CTACTCT CTACTCT CTACTCT CTACAAG 1000 TACCGCTGA TACCTGCTGA
Mogrp-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Mogrp-R Hubrs-3 Hunmb-R Ratnmb-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Hugrp-R Hubrs-3 Hunmb-R	ATTAGTTGTG ATTAGCTGTG GAATCATGTA ACAGCATGTA ACAGCATGTA ACAGCATGCA 701 CTGTCTACTA CTGTCTACTA CTGTCTACTA GCATTTATTA 801 801 802 GCGCTTGCC GCGACTTGCC GCGACTTGCC GCGACTTGCC GCGACTTGCC GCGACTTGCC GCGACTTGCC GCGACTTGCC GAGGTGGACA ACGCCTGGCC	CCCCTACCC CCCCTACCC CCCCTACCC CTACTTCATT TACCATACCC CTACTTCATT TTCCTTGATT TTATCATATT TTATCATATT TTATCATATT TATCACATT AAGACAETAC AGAACAETAC AAGACCETAT AAGATCETTC CCTCCATGCT CCTCCATGCT	ACACTCCAAT ACACTCCAAT TGTCTCTAAG TCAAACAGAT ACAAACAGAT ACAAACAGAT GCTGGAAATC GCTAGAACAGAT GCTAGGACCC GCTAAAAATC GCTAGGACCT GCTAGGACTT TGGTGTTTGT TGGTGTTTGT TGGTGTTTGT TGGTGTTTGT CCACTTTGTC CCACTTTGTC GCACTTCATT	GAGCTACACC GAGCTACACC GAGCTACACC GAATTACATC GATTACATC GATTCAGAG TGATCCAGAG TTACAAAAG TAATTAAAAG TAATTAAAAG GGGCCCCTTT GGGCCCGTTTC GGGCCGCTTT GGGCCGCTTT ACCAGCATCT TTCACCATTA	сталалтсса ссалалтсса аладалтаса саладаттса саладаттса саладаттса саладаттса саладаттса саладаттса саладаттса сасстасталт сассстасалт сассстасалт сассстасалт TM-V <u>GCCTTCTGCT</u> gCCTTCTGCT gCCCTTCTGCT gCCCTCTGCT GTCCTCGCT GTGCCCACCT GTGCCCACCT GTGCCCACCT	TTCCATGGCT TTCTATGGCT TTCTATGGCTG TTCCACTGGTGG TTCCACGTGGC CTTCCCGGTGG ATACCTACTG CTTCCCGGGG CTTCCCTGGAG GCTCCCCCAA GGCTCCCCAA GGCTCCCCAA GGCTCCCCAA GGCTCCCCAA GCTTCCCCAA CCTGGCCTTC CCTGGCCTTC TTTGGCTTTC	ГССТТТСТВЕ ГССТТТСТВЕ АТТТТСТТВЕ АТТТТСТТВЕ АТТТТСТТВЕ АТТТТСТТВЕ АТТТТСТТВЕ АТТТТСТТВЕ АТТТТСТТВЕ АТТТТСТТВЕ АТТТТСТТВЕ АТТСАТАТА АТТСАТАТА ССАЛЕТСТСТ ССАЛЕТССТС ССАЛЕТССТС АССАЛЕТССТ АССАЛЕТССТ АССАЛЕТССТ АССАЛЕТССТ АССАЛЕТССТ АССАЛЕТССТ АССАЛЕТССТ	ТТТТСТАСЭТ ТСТТСТАСЭТ ТСТТСТАСАТ ТСТАТТТССТ ТСТАТТТССТ ТСТАТТТССТ АСАТЭССАЭ ССАТЭССЭТ АСАТЭССАЭ ССАТЭССЭТ АСАТЭССАЭ	TATCCCACTG CATCCCACTG TATTCCACTC CATACCACTT CATACCACTT CATACCCCTT NRON AAGCAGTTG AAGCAGTTG AAGCAGTTG AAGCAGTTG GTCCTACCA GTCCTACCA GTCCTACCA GTCCTTCCA GTCTTTCCA GTCTTTCCA CTTTGCCTCCT	GCGATCATCT TCCATCATCATCT TCTATTATCT GCTATTATCAT Q 800 AATCCCGGAA AATCCCGGAA AATCCCGGAA AATCCCGGAA AATCCCGGAA AATCCCGGAA AATCCCGGAA CTACTCT CTACTCT CTACTCT CTACTCT CTACTCT CTACTGCT TACTGCTGCTGA TACCTGCTGA TACCTGCTGA TACCTGCTGA TACCTGCTGA
Mogrp-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Ratnmb-R Ratnmb-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Ratnmb-R Ratnmb-R	ATTAGTTGTG ATTAGCTGTG GAATCATGTA ACAGCATGTA ACAGCATGTA ACAGCATGCA 701 CTGTCTACTA CTGTCTACTA CTGTCTACTA GCATTTATTA GCATTTATTA 801 GCGGCTTGCC GCGACTTGCC GCGACTTGCC GCGACTTGCC GACATTGCC GACATGGCC 901 GAAGTCGACA ATATGTAGACC GACATCGATC	CCCCTACCC CCCCTACCC CCCCTACCC CCCCTACCC CTACTTCATT TTCCTGATT TTCCTGATT TTATCATATT TTATCATATT TTATCACATT AAGACASTAC AGACCSTAT AAAATISTGC CCTCCATGCT CCTCCATGCT CCTCCATGCT	ACACTCCAAT ACACTCCTAAT TGTCTCTTAAG TCAAACAGAT ACAAACAGAT ACAAACAGAT GCTGCGAAATC GCTAAGAACCC GCTAAGAACCC GCTAAGAACCC GCTAAGAACCT TGGTGTTTGT TGGTGTTTGT TGGTGTTTGT TGGTGTTTGT TGGTGTTTGT CCACTTTGTC CCACTTTGTC CCACTTTGTC ACACTGATT ACACTGATT	GAGCTACACC GAGCTACACC GAGCTACACC GAATTACATC GATTACATC GATTCAGAG TTACAAAAG TTACAAAAG TAATTAAAAG GGGCCCCTTTT GGGCCTGTTTC GGGCTGCTTT GGGCTGTTTC GGGCTGCTTT ACCAGCATCT TCACCCTTAG GTCACCTTAG GTCACCTTAG	СТАЛАЛТССА ССАЛАЛТССА АЛАДАЛТССА САЛАДАТТСА САЛАДАТТСА САЛАДАТТСА СССТАСАЛТ ТСССТАСАЛТ ТСССТСАСАТ ТСССТСТАСАТ ССССТСТАСАТ ССССТСТАСАТ ССССТСТСАТ СССТСТСТСТ	TTCCATGGCT TTCTATGGCT TTCTATGGCTG TTCCAGTGGCTC CTCAGTGCTC CTCCCGTGG ATACCTACTG CTTCCCGGGG ATACCTACTG CTTCCTGGAG CTTCCTGGAG GGCTCCCCAA GGCTTCCCCAA GGTTTCCAAA GGTTTCCAAA GGTTTCCCAA	ГССТТТСТВ ГССТТТСТВ ПССТТСТТА АЛОССАЛТАТ АЛОССАЛТАТ АДОССАЛТАТ АДОССАЛТАТ АДОССАЛТАТ ССАТСТСАТС ССАТСТСАТС ССАТСТСАТС ССАСТССТС СССАСТССТС ССССССССС СССАСТСССТСС СССАСТССТС СССАСТССТС СССАСТССТС СССАСТССТС СССАСТССС СССССССССС	ТТТТСТАСЭТ ТСТТСТАСЭТ ТСТТСТАСАТ ТСТАТТТССТ ТСТАТТТССТ ТСТАТТТССТ АСАТЭТСААЗ ССАТЭСССЭТ АСАТЭТСААЗ САТАССАЗА АСАТЭТСАЗА ТАССТСРАСС ТАССТСРАСС ТАССТСРАСС ТАСАТЭТАТС ТАССТСРАСС ТАСАТЭТАТС ТАССТСРАСС СССТСААСС СССТСААССС СССТСААССС СССТСААССС СССТСААССС СССТСААССС СССТСААССС СССТСААССС СССТСААССС СССТСААССС СССТСААССС	TATCCCACTG CATCCCACTG TATTCCACTC CATACCACTT CATACCACTT AAGCACTTG AAGCACTTG AAGCACTTG AAGCACTTG AAGCACTTG GTTCCTACCA GTTCCTACCA GTTCCTACCA GTTCCTTCCA GTTTTCCTCCA CTTTGCCTCT CTTTGCCTCT GTTTGCTCTT GTTTGCTCTT	GCGATCATCT TCGATCATCT TCTATTATCT GCTATTATTA GCTATTATCATCA 2 800 AATCCCGGAA AATCCCGGAA AACCCGGAA AACACGGAA AGACACGGAA GCTACTCT CTACTCT CTACTCT CTACTCT TCTCTCAAACC CTACATCT TACTGCTGCTGA TACCTGCTGA TACCTGCTGA TACCTGCTGA TACCTGCTGA TACCTGCTGA
Mogrp-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Ratnmb-R	ATTAGTTGTG ATTAGCTGTG GAATCATGTA ACAGCATGTA ACAGCATGTA ACAGCATGTA ACAGCATGCA 701 CTGTCTACTA CTGTCTACTA CTGTCTACTA GCATTTATTA GCATTTATTA B01 GCGGCTTGCC GCGACTTGCC GCGACTTGCC GCGACTTGCC GCGACTGGCC 901 GAAGTGGACA TATGTAGACC GAGATGGACA	CCCCTACCC CCCTTTATCC TCCATACCC TACCTTCATT TTCCTTCATT TTCCTTCATT TTATCATATT TTATCATATT TTATCATATT TATCACATT AAGACASTGC AGAACASTGC AGAACASTGC CCTCCATGCT CCTCCATGCT CATCCTCAGC CCTCCTCAGCG	ACACTCCAAT ACACTCCAAT TGTCTCTAAG TCAAACAGAT ACAAACAGAT ACAAACAGAT GCTGGAAAATC GCTAGAAAATC GCTAGAAAATC GCTAGACCT GCTAGACCT GCGAGACCT TGGTGTTGGT TGGTGTTGGT TGGTGTTGGT TGGTGTTGGT TGGTGTTGGT CCACTTTGTC CCACTTTGTC CCACTTTGTC CCACTGATT ACACATGATT	САССТАСАСС САССТАСАСС САССТАСАСС САСТАСАСС САСТАСАСС САСТАСАСА САСТАСАСА САССТСТТС САССТСТТТ САССТСТТТ СССССТТТ СССССТТТ СССССТАС ССССССТАС ССССССТАС СССССССССС	сталалтсса ссалалтсса сладалтса сладаттса сладаттса сладаттса сладаттса состтаслат сосстаслат тостастаса сосстстаст оссттетост осстетост осстетост осстетост осстетост отстетост отстетост отстетост отстетост отстетост отстетост отстетост отстетост отстетост отстетост отстетост отстетост отстетост отстетост	TTCCATGGCT TTCTATGGCT TTCTATGGCT TTCCATGGCT CTCAGTGCTC CTCAGTGCTC CTTCCCGGGG ATACCTACTG CTTCCTGGAG CTTCCTGGAG GCTTCCTGGAG GGTTCCCCAA GGTTCCCCAA GGTTCCCCAA GGTTCCCCAA CCTGGCCTTC CCTGGCCTTC TTCGCGTTTC TCTGAGTTTT TCTCAGTTTC	ГССТТТСТВС ГССТТТСТВС АТТТТСТТАС АТТТТСТТОС АТТТТСТТСВ АТТТТСТТСВ АТТТТСТТСВ АТТТТСТТСВ АТТТТСТТСВ АТТТТСТТСВ АТТСТАТССТСВ ССАТСВАСААА ССАТСВАСААССССТ ССАСАТССТС ССАСАТССТС ССАСАТССТС АССААСТССТ АССААСТССТ АССААСТССТ АССААСТССТ АССААСТССТ АССААСТССТ АССААСТССТ АССААСТССТ	ТГТТСТАСЭТ ТСТТСТАСЭТ ТСТТСТАСАТ ТСТАТТТССТ ТСТАТТТССТ ТСТАТТТССТ ССАТЭСССЭТ АСАТЭТСАЭА АСАТЭТСАЭА АСАТЭТСАЭА ТАССТСТАСС ТАССТСТАСС ТАССТСТАСС ТАССТСТАСС ТАССТСТАСС ТАССТСТАСС ТАССТСТАСС ТАССТСТАСС ТАССТСТАСС ТАССТСТАСС СТАСТСТАСС СТАСТСТАСС СТАСТСТАСС СССТЭЛАССС СССТЭЛАССС СССТЭЛАССС СССТЭЛАССС СССТЭЛАССС СССТААССС	TATCCCACTG CATCCCACTG TATTCCACTC CATACCACTT CATACCACTT CATACCACTTG AAGCACTTG AAGCACTTG AAGCACTTG AAGCACTTG CATCCTACCA GTTCCTACCA GTTCCTACCA GGTCTTTCCA GGTCTTTCCA GGTCTTTCCA GGTCTTTCCA GTTTGCCTCT CTTTGCCTCT CTTTGCCTCT GTTTGCCTCT	GCGATCATCT TCGATCATCT TCTATTATCT GCTATTATCA Q 800 AATCCCGGAA AATCCCGGAA AATCCCGGAA AATCCCGGAA AACACGGAA GCTACTCT TTCTCAAACC CTACTCT TTCTCAAACC TTCTCAAACC TACTGCTGAA 1000 TACTGCTGAT TACCTGCTGA TACCTGCTGA TACCTGCTGA TACCTGCTGA
Mogrp-R Hugrp-R Hubra-3 Hunmb-R Ratnmb-R Hubrs-3 Hunmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R	ATTAGTTGTG ATTAGCTGTG GAATCATGTA ACAGCATGTA ACAGCATGTA ACAGCATGCA 701 CTGTCTACTA CTGTTTACTA CTGTTTACTA CTGTTTACTA GCATTTATTA 801 GCGGCTTGCC GAGAATTGCC ACGCCTGGCC 901 GAAGTGGACA GAGGTGGACA GAGGTGGACA GAGATGACC GAGATCGATC	CCCCTACCC CCCCTACCC CCCCTATACC TCCCTATACC TCCCTACCTA	ACACTCCAAT ACACTCCAAT TGTCTCTAAG TGAAACAGAT ACAAACAGAT ACAAACAGAT GCCGGAAATC GCTAGGAACC GCTAGGACCC GCTAGGACCC GCCAAGACCT TGGTGTTIGT TGGTGTTIGT TGGTGTTIGT TGGTGTTIGT CCACTTIGTC CCACTTIGTC CCACTTIGTC CCACTTIGTC CCACTTIGTC CCACTTIGTC	GAGCTACACC GAGCTACACC GAGCTTCACC GAATTACATC GAATTACATC GATTACAATC TGATTCAGAG TGATCCAGAG TAATTAAAAG TAATTAAAAG TAATTAAAAG GGGCCTCTTT GGGCTGTTTC GGGCTGTTTC GGGCTGTTTC GGGCTGTTTC GGGCTGTTTC GGGCTGTTTC GGGCTGCTTT TCACCGTTTG GTCACCTTAG GTCACCTTAG	СТАЛАЛТССА ССАЛАЛТССА АЛБАЛАТССА САЛБАЛТССА САЛБАТТСА САЛБАТТСА САЛБАТТСА САССТЕЛСАЛТ ТЭССТАСАЛТ ТЭСАСАСАЛТ ТЭСАСАССАЛТ ТЭСАСАСАЛТ ТЭСАСАСАЛТ ССССТСТОСТ ССССТСТОСТ ССССТСТОСТ ССССТСТОСТ ССССТСТОСТ СТССССАССТ ТЭССССАССТ ТЭСССССОСТ	TTCCATGGCT TTCTATGGCT TTCTATGGCTG TTCCCGTGG TTCAGTGCTC CTCCCGTGG CTTCCCGTGG CTTCCCGTGG CTTCCTGGAG CTTCCTGGAG CTTCCTGGAG GCTTCCCCAA GGTTCCCAA GGTTCCCAA GGTTCCCAA GGTTCCCAA GGTTCCCAA CCTGGCCTTC CCTGGCCTTC TTGGCCTTC TCTGAGTTTC	ГССТТТСТВС ГССТТТСТВС АТТТТСТТВС АТТТТСТТВС АТТТТСТТВС АТТТТСТТВС АТТТТСТТВС АТТТТСТТВС АТТТТСТТВС АТТТТСТТВС АССАЗСАТСАТС ССАТССТСТС ССАСАТССТС АССААСТССТ АССААСТССТ АССААСТССТ АССААСТССТ АССААСТССТ	ТТТТСТАСЯТ ТСТТСТАСЯТ ТСТАТТТССТ ТСТАТТТССТ ТСТАТТТССТ АСАТСТСАЯ АСАТСТСАЯ АСАТСТСАЯ ССАТССССЯ ССАТССССЯ АСАТАССАЯ АСАТАССАЯ АСАТАССАЯ ТАССТСРАСС ТАССТСРАСС ТАССТСРАСС ТАССТСРАСС СССЯССАЯ ССЯТСААССС СТССААССС СТССААССС СТССААССС	TATCCCACTG CATCCCACTG TATTCCACTC CATACCACTT CATACCCCTT NTRON AAGCACTTG AAGCACTTG AAGCACTTG AAGCACTTG CATCCTACCA GTTCCTACCA GTTCCTACCA GTTCCTACCA GTTCCTACCA GTTCCTACCA GTTCCTACCA GTTCCTACCA CTTTGCTCTT CATTGCTCTT CTTTGCCCTC CTTTGCCCTC CTTTGCCCTCT	GCGATCATCT TCCATCATCAT TCTATTATCAT GCTATTATTA GCTATTATTA GTATTATCATCA 2 800 AATCCCGGAA AATCCCGGAA AATCCCGGAA AATCCCGGAA AATCCCGGAA CTACTCT CTACTCT CTACTCT CTACTCT CTACTCT CTACACGT TACTGCTGCTQA 1000 TACTGCTGA TACCTGCTQA TACCTGCTQA TACCTGCTQA
Mogrp-R Hugrp-R Hubra-3 Hunmb-R Ratnmb-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R	ATTAGTTGTG ATTAGCTGTG GAATCATGTA ACAGCATGTA ACAGCATGTA ACAGCATGTA CTGTTTACTA CTGTTTACTA CTGTTTACTA CTGTTTACTA CTGTTTACTA GCATTTATTA B01 GCGGCTTGCC GCGACTTGCC GAGAATTGCC ACGCCTGGCC 901 GAAGTGGACA GAGGTGGACA GAGGTGGACA TATGTAGACC GAGAATGATC GAGACTGATC	CCCCCTACCC CCCCTATACC TCCCTTATCC TCCCTACCC TACCTTCATT CTACTTCATT TTATCATATT TTATCATATT TTATCATATT TATCACATT AAGACASTGC AAGACASTGC CAGCACGTAT AAATTESGC AAGATOSTTC CCTCCATGCT CCTCCATGCT CCTCCATGCT CCTCCATGCT CCTCCATGCT CCTCCATGCT CCTCCATGCT CCTCCATGCT	ACACTCCAAT ACACTCCAAT ACAACCTAAG TGCTCTAAG TCAAACAGAT ACAAACAGAT ACAAACAGAT GCCGGAAATC GCTAGGAACC GCTAGGACCC GCGAAGACCT TGGTGTTTGT TGGTGTTTGT TGGTGTTTGT TGGTGTTTGT CCACTTTGTC CCACTTTGTC CCACTTTGTC CCACTTGTC CCACTTGTC CCACTTGTC CCACTTGTC CCACTTGTC TCCACACACTC	GAGCTACACC GAGCTACACC GAGCTACACC GAATTACATC GAATTACATC GATTACATC GATTACAACC TGATTCAGAG TGATCCAGAG TATTACAAAAG TAATTAAAAAG TAATTAAAAAG TAATTAAAAAG GGCCTCTTTT GGGCTGTTTC GGGCTGTTTC GGGCTGTTTT CGGCTGTTTT CGGCTGTTTT GTCACCTTAG GTCACCTTAG	СТАЛАЛТССА ССАЛАЛТССА АЛБАЛТТСА САЛАБАТТСА САЛАБАТТСА САЛАБАТТСА САЛАБАТТСА САССТБАСС СВССТАСАЛТ ТВССТАСАЛТ ТВССАССА ССССТСТАСА ССССТСАСА ССССТСТАСА ССССТСТАСА ССССТСТАСА ССССТСТАСА ССССТСТАСА ССССТСТАСА ССССТСТАСА ССССТСТАСА ССССТСТАСА ССССТСТАСА ССССТСТАСА ССССТСТАСА ССССТСТАСА ССССТСТАСА ССССТСТАСА ССССТСАСА ССССТСТСТАСА ССССТСТСТАСА ССССТСТСТАСА ССССТСТСТАСА ССССТСТСТАСА ССССТСТАСА ССССТСТАСА ССССТСТСТАСА СССССССС	TTCCATGGCT TTCTATGCT TTCTATGCT TTCAGTGCTC CTCAGTGCTC CTCCCGTGG CTTCCCGTGG CTTCCCGTGG CTTCCTGGAG CTTCCTGGAG CTTCCTGGAG GCTTCCCCAA GGTTCCCCAA GGTTCCCAA GGTTCCCAA GGTTCCCAA CCTGGCCTTC TTTGGCTTTC TCTCAGTTTT TCTCAGTTTC	ТССТТТСТВ ТССТТТСТВ АТТТСТТТСВ АТТТСТТВ АТТТСТТВ АЛОВСААТАТ ААОВСААТАТ ААОВСААТАТ ААОВСААТАТ АССАСТСТСТ ССАТБТСАТС ССАТБТСАТС ССАСБТССТС ССАСАТССТС АССААСТССТ АССААСТССТ АССААСТССТ АССААСТССТ АССАСТССТ АССАСТССТ	ТТТТСТАССТ ТСТТСТАССТ ТСТАТТТССТ ТСТАТТТССТ ТСТАТТТССТ АСАТСТСАС АСАТССССС ССАТСССССТ АСАТАСССАА АСАТАСССАА АСАТАСССАА ТАССТСТАСС ТАССТСТАСС ТАССТСТАСС ТАССТСТАСС ТАССТСТАСС СССССАСАС СССТСАССС СССТСАССС СССТСАССС СССТСАССС СССТСАССС СССТСАССС СССТСАССС СССТСАССС СССТСАССС СССТСАССС СССТСАССС СССТСАССС СССТСАССС ССССАСАСС ССССССАСАСС	ТАТСССАСТБ САТСССАСТБ ТАТТССАСТС САТАССАСТТ САТАССССТТ NTRON ААGCAGTTG ААGCAGTTG ААGCAGTTG САССАСТБ САССАСТБ ААGCAGTTG СТТССТАССА GTTCCTACCA GTTCCTACCA GTCTTTCCA GTCTTTCCA CTTTGCCTCT CTTTGCCTCT CTTTGCCTCT ACAGGCAGAA	GCGATCATCT TCCATCATCAT TCTATTATCT GCTATTATTA GCTATTATCA 2 800 AATCCCGGAA AATCCCGGAA AATCCCGGAA AACACGGAA AACACGGAA GCTACTCT CTACTCT CTACTCT CTACAGGAA J000 TATCTGCTGAA TACCAGCTA TACCTGCTGA TACCTGCTGA TACCTGCTGA TACCTGCTGA TACCTGCTGA TACCTGCTGA TACCTGCTGA TACCTGCTGA TACCTGCTGA TACCAGCACA
Mogrp-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R	ATTAGTTGTG ATTAGCTGTG GAATCATGTA ACAGCATGTA ACAGCATGTA ACAGCATGTA CTGTTCTACTA CTGTCTACTA CTGTCTACTA GCATTTATTA 801 GCGGCTTGCC GCGACTTGCC GCGACTGGCC 901 GAAGTGGACA GAGGTGGACA GAGGTGGACA GAGGTGGACA 1001 GCAAGAGCTT GCAAGAGCTT GCAAGAGCTT	CCCCTACCC CCCCTACCC CCCCTACCC CCACTTCATT TCCCTACTCATT TTCCTTGATT TTATCATATT TTATCATATT TTATCATATT TTATCATATT TATCACATT AAGACASTAC AGACASTAC AGACCSTAT AAAATISTGC CCTCCATGCT CCTCCATGCT CCTCCATGCT CCTCCATGCC CCTCCATGCC CCTCCATGCC CCTCCTTAGC CCTCCTTAGC CCTCCTTAGC CCTCCTTAGC CCTCCTTAGC CCTCCTTAGC CCTCCTTAGC CCTCCTTAGC CCTCCTTAGC	ACACTCCAAT ACACTCCTAAT TGTCTCTTAAG TCAAACAGAT ACAAACAGAT ACAAACAGAT GCCGCAAATC GCTAAAAATC GCTAAGAACC GCTAAGAACC GCTAAGAACCT TGGTGTTTGT TGGTGTTTGT TGGTGTTTGT TGGTGTTTGT CCACTTTGTC CCACTTTGTC CCACTTTGTC CCACTTTGTC CCACTTTGTC TCCAACACTC TTCAACACTC TTCAACACTC TTCAACACTC	GAGCTACACC GAGCTACACC GAGCTACACC GAATTACATC GATTACATC GATTACAAC TGATTCAGAG TTACAAAAG TAATTAAAAG TAATTAAAAG GGGCCCCTTTT GGGCTCTTTT GGGCTGCTTT GGGCTGCTTT ACCAGCATCT TCCACCTTAG GTCACCTTAG GTCACCTTAG AGCTGCTCTG	CTAAAATCCA CCAAAATCCA AAGAAATCCA AAGAATCCA CAAAGATTCA CAAAGATTCA CAAAGATTCA CAACCTGCAAC TGCCTACAAT TGCATACAAT TGCAACACAAT TGCACCTGGCT GCCTTCTGCT GCCTTCTGCT GTCTCCTGCT GTCTCCCGGGT TGCCCGGGT TGCCCGGGT CTGCCAGCCT TTGCCAGCCT	TTCCATGGCT TTCTATGGCT TTCTATGGCTG TTCCAGTGGCTC CTCAGTGCTC CTCCCGTGG ATACCTACTG CTTCCCGGGG ATACCTACTG CTTCCCGGAG GCTCCCCCAA GGCTCCCCAA GGCTTCCCCAA GGTTCCCCAA GGTTCCCCAA GGTTCCCCAA GGTTCCCCAA GGCTCCCCAA GGTTCCCCAA GGCTCCCCAA GGCTCCCCAA GGCTCCCCAA GGCCTGATCA	ГССТТТСТВС ГССТТТСТВС ПССТТТТТСТТВС АТТТТСТТВС АТТТТСТТВС АТТТТСТТВС АТТТТСТТВС АТТТТСТТВС АТТТТСТТВС АТТТТСТТВС АТТТТСТТВС АТТТТСТТВС АТТТТСТТВС АТТТТСТТВС АТТТТСТТВС АССАТАТСАТС ССАТСТСТСТС ССАТСТСТСТС ССАТСТСТС ССАСТССТСТ АССААСТССТ АССААСТССТ АССААСТССТ АССААСТССТ АССААСТССТ АССААСТССТ АССААСТССТ АССААСТССТ АССАСТССТ АССАСТССТ АССАСТССТ АССАСТССТ АССАСТССТ АССАСТССТ АССАСТССТ АССАСТССТ АССАСТССТ АССАСТССТ АССАСТССТ АССАСТССТ АССАСТССТ АССАСТССТ	ТТТТСТАСЭТ ТСТТСТАСЭТ ТСТТСТАСАТ ТСТАТТТССТ ТСТАТТТССТ ТСТАТТТССТ ТСТАТТТССТ АСАТЭССАЭ АСАТЭССАЭ АСАТЭССАЭ АСАТЭССАЭ АСАТЭССАЭ АСАТЭССАЭ ТАССТСТАСС ТАССТСТАСС ТАССТСТАСС ТАССТСТАСС СССТСТАСС СССТСТАСС СССТСТАСС СССТСТАСС СССТСТАСС СССТСТАССС СССТСТАССС СССТСТАССС СССТСТАССС СССТСТАССС СССТСТАССС СССТСТАССС СССТСАСАСС СССТССАСАСС СТСТССАСАСС СТССССАСАСС СТССССАСАСС	TATCCCACTG CATCCCACTG TATTCCACTC CATACCACTT CATACCACTT AACCACTTG AAGCACTTG AAGCACTTG AAGCACTTG AAGCACTTG CATCCTACCA GTTCCTACCA GTTCCTACCA GTTCTTCACA GTTCTTCACA GTTCTTCACA CTTTGCTCTT CTTTGCCTCT CTTTGCCTCTT CTTTGCCTCTT GTTTGCTCTTC AACAGCAGAAA ACTGGAAGAA	GCGATCATCT TCGATCATCT TCTATTATCT GCTATTATCA Q 800 AATCCCGGAA AATCCCGGAA AATCCCGGAA AATCCCGGAA AAACACGGAA AGACACGGAA CT ACTCT CT ACTCT CT ACTCT CT ACTCT TCCTGCAACACC 1000 TACCTGCTGA TACCTGCTGA TACCTGCTGA 11000 GTACCAC GTACCAC GTACCAC GTACCAC GTACCAC
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Mogrp-R Hugrp-R Hubra-3 Hunmb-R Ratnmb-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R	ATTAGTTGTG ATTAGCTGTG GAATCATGTA ACAGCATGTA ACAGCATGTA ACAGCATGTA ACAGCATGTA CTGTTTACTA CTGTTTACTA CTGTTTACTA CTGTTTACTA GCATTTATTA 801 GCGGCTTGCC GCGACTTGCC GCGACTTGCC GAGAATTGCC ACGCCTGGCC 901 GAAGTGGACA GAGGTGGACA GAGATGACC GAGATGACC GAGATGACC GCAACAGCTT GCAAGAGCTT GCAAGAGCTT GCAAGAGCTT GCAAGAGCTT	CCCCTACCC CCCTATACC CCCTTTATC TCCTTCATT TTCCTTCATT TTCCTTCATT TTTCTTCATT TTATCATATT TTATCATATT TTATCATATT TATCATATT AAGACBTAC AGAACGTAT AAGACGTAT AAGACGTAT CCTCCATGCT CCTCCATGCT CCTCCATGCT CCTCCATGCT CATCTTAGC CTTCTCTGG CAGGAAGCAG CAGGAAGCAT CAGGAAGCAT CAGGAAGCAT	ACACTCCAAT ACACTCCAAT ACACTCTAAT TGTCTCTTAAG TCAAACAGAT ACAAACAGAT ACAAACAGAT GCCGGAAATC GCTAGGACCC GCTAGGACCC GCCAAGACCT TGGTGTTGGT TGGTGTTGGT TGGTGTTGGT TGGTGTTGGT TGGTGTTGGT CCACTTTGTC CCACTTTGTC CCACTTTGTC CCACTTTGTC CCACTTTGTC CCACTTTGTC CCACTTTGTC CCACTTTGTC CCACTTTGTC CCACTTTGTC CCACTTTGTC CCACTTTGTC CCACTTTGTC CCACTTTGTC CCACTTTGTC CCACTGATT	GAGCTACACC GAGCTACACC GAGCTTCACC GAATTACATC GAATTACATC GATTACATC GATCAGAG TGATCCAGAG TGATCCAGAG TAATTAAAAG TAATTAAAAG TAATTAAAAG GGCCTCTTT GGGCTGTTC GGCCTGTTC GGCCTGTTT GGGCTGTTTC GGCCTGTTT GGGCTGCTTTG GTCACCTTAG GTCACCTTAG GTCACCTTAG ACTCTCTG ACTCTCTG ACTCTCTG ACTCTCTG ACTCTCTG GCCTCTTTG	CTAAAATCCA CCAAAATCCA AAGAAATCCA CAAGAATCCA CAAGAATCCA CAAGAATCCA TGCCTACAAT TGCTTACAAT TGCTTACAAT TGCACACCAAT TGCACACCAAT TGCACACCAAT TGCACACCAAT CTM-V GCCTTCTGCT GCCCTCTGCT GCCCTCTGCT GTCCTCGGGT TGCCCCGGGT TGCCCCGGGT TGCCCCGGCT TTGCAGCCG TGGCAGCAAG TGGCAGCAAG TGGCAGCAAG TGGCAGCAAG	TTCCATGGCT TTCTATGGCT TTCTATGGCTG TTCCTTGGCTG TTCCGCTGGCTC CTCCCGCTGG CTTCCCGTGG CTTCCCGTGG CTTCCCGGGG CTTCCTGGAG CTTCCTGGAG CTTCCTGGAG GGTTCCCAA GGTTCCCAA GGTTCCCAA GGTTCCCAA GGTTCCCAA GGTTCCCAA GGTTCCCAA GGTTCCCAA GGTTCCCAA GGTTCCCAA GGTTCCCAA GGTTCCCAA GGTTCCCAA GGTTCCCAA GGTTCCCAA CCTGGCCTTC TCTGAGTTTC TCTGAGTTTC CCTGGCCTGATGA GGCCTGATGA GGCCTGATCA GAGCGCCCTG TCCTATCAAG TCCTATCCTG	ICCTTTCTGG ICCTTTCTGG ATTTTCTTGG ATTTTCTTGG ATTTTCTTGG ATTTTCTTGG AAGGACAATAT AAGGACAATAT AAGGACAAAG AATACAATGA AATACAATGA AATACAATGA AATACAATGA AATACAATGA CCATGTCATC TCACGTCCTG CCACATCCTT GCCACTCCT GCCACTCCT GCCACTCCT GCCACTCCT GCCACTCCT ACCAACTCCT ACCAACTCCT ACCAACTCCT ACCAACTCCT ACCAACTCCT ACCAACTCCT ACCAACTCCT ACCAACTCCT ACCAACTCCT ACCAACTCCT ACCAACTCCT ACCACTCCTCT ACCACTCCT ACCACTCCT ACCACTCCT ACCACTCCT ACCACTCCT ACCACTCCT ACCACTCCT ACCACTCCT ACCACTCCT ACCACTCCTCT ACCACTCCTCT ACCACTCCTCTCT ACCACTCCTCT ACCACTCCTCT ACCACTCCTCT ACCACTCCT	ТТТТСТАССТ ТСТТСТАСАТ ТСТАТТТССТ ТСТАТТТССТ ТСТАТТТССТ АСАТСТСАСА АСАТСТСАСА ССАТСССССТ АСАТАСССАА АСАТАССАА АСАТАССАА ТАССТСРАСС ТАССТСРАСС ТАССТСРАСС ТАССТСРАСС ТАССТСРАСС СТССТСРАСС СТССТСРАСС ССССССАСА СССТСРАСС СССТСРАС СССТСРАС СССТСРАС СССТСРАС СССТСРАС СССТСРАС СССТСРАС СССТСРАС СССТСРАС СССТСРАС СССТСРАС СССТСРАС СССТСРАС СССТСРАС СССТСРАС С СССТСРАС С С С С С С С С С С С С С С С С С С	TATCCCACTG CATCCCACTG TATTCCACTC CATACCCCTT NTRON AAGCACTTG AAGCACTTG AAGCACTTG AAGCACTTG CATCCTACCA GTTCCTACCA GTTCCTACCA GTTCCTACCA GTTCCTACCA GGTCTTTCCA GGTCTTTCCA GGTCTTTCCA GGTCTTTCCA GGTCTTTCCA CTTTGCCCTC CTTTGCCCTC ATTTGCTCTT GTTTGCTCTT ACAGGCAGAA ACTCGAAGGA TCCTTACCA TACCTCCTCA	GCGATCATCT TCCATCATCAT TCTATTATCAT GCTATTATTA GCTATTATCA 2 800 AATCCCGGAA AATCCCGGAA AATCCCCGAA AATCCCCGAA AATCCCCGAA AATCCCCGAA AATCCCCGAA AATCCCCGAA AATCCCCGAA AATCCCCGAA AATCCCCGAA AACACGGAA J000 CTACTCT CTACTGCT TACTGCTGCTGA TACTGCTGCTGA TACCTGCTGA TACCTGCTGA 1100 GTACCAC CCCTGGCTGT GTACCACC CCCTGGCTGT GCTCTTCAGC
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Mogrp-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Hubrs-3 Hunmb-R Ratnmb-R	ATTAGTTGTG ATTAGCTGTG GAATCATGTA ACAGCATGTA ACAGCATGTA ACAGCATGTA ACAGCATGTA CTGTTTACTA CTGTCTACTA CTGTCTACTA GCATTTATTA B01 GCGGCTTGCC GCGACTTGCC GCGACTTGCC GCGACTTGCC GACATCGAC 901 GCACGCCTGGCC 901 GCACGCCTGGCC 901 GCACGCCTGGCC 1001 GCAAGAGCTT GCAAGAGCTT GCAAGAGCTT GCAAGAGCTT GCAAGAGCTT GTGAAAGCTT GTGAAAGCTT	CCCCTACCC CCCCTACCC CCCCTACCC CCCCTACCC CCCCTACCC CTACTTCATT TTCCTGATT TTCCTGATT TTATCATATT TTATCATATT TTATCATATT TTATCACATT AAGACAETAC AGGACAETAC AGGACAETAC AGGACCETAT CCTCCATGCT CCTCCATGCT CCTCCATGCT CCTCCATGCC CCTCCTTGCAT CAGGAGCAG CAGGAGCAG CAGGAGCAT CAGGAGCAT CAGGAGCAT	ACACTCCAAT ACACTCCAAT ACACTCTAAT TGTCTCTTAAG TCAAACAGAT ACAAACAGAT ACAAACAGAT GCTGAGAAATC GCTAAGAACCC GCTAAGAACCC GCTAAGACCT TGGTGTTTGT TGGTGTTTGT TGGTGTTTGT TGGTGTTTGT TGGTGTTGT	GAGCTACACC GAGCTACACC GAGCTACACC GAGTTACATC GATTACATC GATTACATC GATCAGAG TTACAAAG TAATTAAAAG TAATTAAAAG GGGCCCTCTTT GGGCTGCTTTC GGGCTGCTTTC GGGCTGCTTTC GGGCTGCTTTC GGGCTGCTTTC GGGCTGCTTTC GGGCTGCTTTC GGGCTGCTTTG GGCTGCTTTG GGCCCCTCG AACTTCTCTG AGCTGCTCG AGCTGCTCG GGCTGCTCG CACCCTCCTG CACCCTCCCTC CACCCTCCTCCCCCCCCCC	CTAAAATCCA CCAAAATCCA AAGAAATCCA CAAAGATTCA CAAAGATTCA CAAAGATTCA CAAAGATTCA CACCTACAAT CACCTGCAAC CGCACACAAT TGCATACAAT CGCCTCTGCT GCCTTCTGCT GCCTTCTGCT GTCTCTCGCT GTCTCCCGGT TGCCCGGGT TGCCCGGGT CTGCCAGCCT TTGCCAGCCT TTGCCAGCCT TTGCCAGCAA TGGGCAGAAG TGGGCAGAAG	TTCCATGGCT TTCTATGGCT TTCTATGGCT TTCCATGGTG TTCCAGTGGTC CTCCCGGTGG ATACCTACTG CTTCCCGGGG ATACCTACTG CTTCCTGGAG CTTCCTGGAG GCTCCCCAA GGTTCCCCAA GGTTCCCCAA GGTTCCCCAA GGTTCCCCAA GGTTCCCCAA GGTTCCCCAA GGTTCCCCAA GGTTCCCCAA GGTTCCCCAA GGCTCGCCTC TTGGCGTTC TCTCAGTTTT TCTGAGTTTC GGCCTGATCA GACCGCCCTG CCTATCCAG TCCTATCCAG	ГССТТТСТВ ГССТТТСТВ ПССТТТТТСТТВ АЛОВСАЛТАТ АЛОВСАЛТАТ АДОВСАЛТАТ АДОВСАЛТАТ АДОВАСЛАЛА АЛТАСАЛТАТ ССАТСТСТСТС ССАТСТСТС ССАТСТСТС ССАТСТСТС ССАТСТСТС ССАТСТСТС ССАТСТСТС ССАТССТСТ АССАЛССТСТ АССАЛСТССТ АССАЛСТССТ АССАЛСТССТ АССАЛСТССТ АССАЛСТССТ АССАЛСТССТ АССАЛСТССТ АССАЛСТССТ АССАЛСТССТ АССАЛСТССТ ССАЛСТССТ	TTTTCTACGT TCTTCTACGT TCTTCTACAT TCTATTTCCT TCTATTTCCT TCTATTTCCT TCTATTTCCT TCTATTTCCT TCTATTTCCT TCTATTTCCT TCTACTCAA ACATGCCAA ACATGCCAA ACATGCCAA TACCTCTACC TACCTCTACC TACCTCTACC TACCTCTACC GCGTGAACCC GCGTGAACCC GTGTCCACAGC GTCTCACAGC GTCTCACAGC GTCTCACAGC	TATCCCACTG CATCCCACTG TATTCCCACTC CATACCACTT CATACCACTT CATACCCCTT NTRON AAGCAGTTG AAGCAGTTG AAGCAGTTG GAGCAGTG GTTCCTACCA GGTCTTCCACA GGTCTTTCCA GGTCTTTCCA GGTCTTTCCA GGTCTTTCCA CTTTGCTCTC CTTTGCCTCT GTTTGCTCTT GTTTGCTCTT GTTTGCTCTT CACAGCAGAA ACTGGAAGA TCCTTTACCA	GCGATCATCT TCGATCATCT TCTATTATCT GCTATTATCAT GCTATTATACT GCTATTATCATCA Q 800 AATCCCGGAA AATCCCGGAA AAACACGGAA AAACACGGAA AAACACGGAA AAACACGGAA GCTACTCT CTACTCT TCTCTCAAACC CTACATCT TCTCTCAAACC CTACAAC 1000 TACCTGCTGA TACCTGCTGA TACCTGCTGA TACCTGCTGA TACCTGCTGA 1100 GTACCAC GCTCTTCAGC GCTCTTCAGC 1197 C
Mogrp-R Hugrp-R Hubra-3 Hunmb-R Ratnmb-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R	ATTAGTTGTG ATTAGTTGTG GAATCATGTA ACAGCATGTA ACAGCATGTA ACAGCATGTA ACAGCATGTA TGTTTACTA CTGTCTACTA CTGTCTACTA CTGTCTACTA GCATTTATTA B01 GCGGCTTGCC GCGACTTGCC GCGACTTGCC GAGATCGACA GAGGTGGACA TATGTAGACC GAGATCGACA 1001 GCAAGAGCTT GCAAGAGCTT GCAAGAGCTT GTGAAAGCTT GTGAAAGCTT 1101 CTGCATG	CCCCTACCC CCCATACCC CCCATACCC CCCCTTATCC TCCCATACCC TACCTTCATT TTCCTTGATT TTATCATATT TTATCATATT TTATCATATT TTATCACATT AAGACASTGC AGAACASTGC AGAACASTGC CCCCATGCT CCTCCATGCT CCTCCATGCT CCTCCATGCT CATCTCTAGG CCTCCATGCT CAGGAAGCAG CAGGAAGCAG CAGGAAGCAT CAGGAGCAT CAGGCCTTCA	ACACTCCAAT ACACTCCAAT ACACTCCAAT TGTCTCTTAAG TCAAACAGAT ACAAACAGAT ACAAACAGAT GCCGGAAATC GCTAGAGACCT GCTAGAGACCT GCGAGACCT GCGAGTTGGT TGGTGTTGGT TGGTGTTGGT TGGTGTTGGT TGGTGTTGGT CCACTTTGTC CCACTTTGTC CCACTTTGTC CCACTTTGTC CCACTTTGTC CCACTTTGTC CCACTTTGTC TCCACATCATT ACACATGATT TTCAACACTC TTCAACACCC TTCAACACCC TTCAACAGCC AGAGCAC AGAGCAC	GAGCTACACC GAGCTACACC GAGCTACACC GAGCTACACC GAATTACATC GATTACAAC GATTACAAC TGATCAGAG TTACAAAAG TAATTAAAAG TAATTAAAAG GGGCCTCTTT GGGCTGTTTC GGGCTGTTTC GGGCTGTTTC GGGCTGTTTC GGGCTGTTTC GGGCTGTTTC GGCTGTTTC GGCCTGTTTC GCCCGTAG TTACCACCTAG ACTACCTTAG ACTACCTG ACTACCTCAG ACTACCTCAG ACTACCTCAG ACTACCTCAG ACTACCTCAG ACTACCTCAG ACTACCTCAG ACTACCTCAG ACTACCTCAG ACTACCTCAG ACTACCTCAG ACTACCTCAG ACTACCTCAG ACTACCTCAG ACTACCTCAG ACTACCTCAG ACTACCTCAG ACTACCTCAG	CTAAAATCCA CCAAAATCCA AAGAAATCCA CAAAGATTCA CAAAGATTCA CAAAGATTCA CAAAGATTCA CACCTOCAAT TGCTTACAAT TGCAACACAAT TGCACACAAT TGCACCTOGCT GCCTTCTGCT GCCTTCTGCT GCCTCTGCT GTGCCCACCT GTGCCCACCT TGCCCGGGT TGCCCGGGT CTGCCAGCCA CTGCCAGCCA CTGCCAGCCA CTGCCAGCCA CTGCCAGCCA CTGCCAGCCA CTGCCAGCCA CTGCCAGCAAG CGGCACAAAG CGGCACCAAGCCA	TTCCATGGCT TTCTATGGCT TTCTATGGCTG TTCCATGGCTG CTTCCCGGGG ATACCTACTG CTTCCCGGGG ATACCTACTG CTTCCCGGGG CTTCCTGGAG CTTCCTGGAG GCTCCCCAA GGTTCCCCAA GGTTCCCCAA GGTTCCCCAA GGTTCCCCAA GGTTCCCCAA GGTTCCCCAA GGCTGGCCTTC TCTGGCTTTC TCTGAGTTTC CCTGGCCTCAT TTAGCCTCAT	ICCTITICING ICCTITICING ATTITICITIG AAGGCAATAT AAGGAACAATA AAGGAACAATA AAGGAACAATGA AATACAATGA AATACAATGA AATACAATGA AATACAATGA CCATGTCATC TCATGTCATC TCATGTCATC TCACCTCCTG GCAACTCCTT AGCAACTCCT AGCAACTCCT AGCAACTCCT AGCAACTCCT AGCACTCCTG AGCACTCCTGT AGCACTCCTGT AGCACTCCTGT AGCACTCCTGT AGCACTCCTGT AGCACTCCTGT AGCACTCCTGT AGCACTCCTGT AGCACTCCTGT AGCACTCCTGT AGCACTCCTGT AGCACTCCTGT AGCACCTCCTGT AGCACCTCCTGT AGCACCTCCTGT AGCACCTCCTGT AGCACCTCCTGT AGCACCTCCTGT AGCACCTCCTGT AGCACCTCCTGT AGCACCTCCTGT AGCACCTCCTGT AGCACCTCCTGT AGCACCTCCTGT	ΤΤΤΤΟΤΑCGΤ ΤΟΤΤΟΤΑCGΤ ΤΟΤΤΟΤΑCAΤ ΤΟΤΤΟΤΑCAΤ ΤΟΤΤΟΤΑCAΤ ΤΟΤΤΤΤΟCΟΤ ΤΟΤΤΤΤΟCΟΤ ΤΟΤΤΤΟCΟΤ ΑCATGTCAAG ΑCATGTCAAG ΑCATACCAAA ΑCATACCAAA ΑCATACCAAA ΑCATACCAAA ΤΑCCTOFACC ΤΑCCTOFACC ΤΑCCTOFACC ΤΑCCTOFACC ΤΑCCTOFACC ΤΑCCTOFACC ΟΤGTGAACCC GCGTGAACCC GTGTCACCAGC GTGTCACCAGC GTCTCACAGC GTCTCACAGC GTCTCACAGC ACTOFAACCAGC GTCTCACAGC	TATCCCACTG CATCCCACTG CATACCCACTT CATACCACTT CATACCACTT CATACCACTTG AAGCACTTG AAGCACTTG AAGCACTTG AAGCACTTG CATCCTACCA GTTCCTACCA GTTCCTACCA GTTCCTACCA GTTCCTACCA GTTCCTACCA GTTCCTACCA GTTCCTACCA GTTTGCTCTT CTTTGCCTCT CTTTGCCTCTT GTTTGCTCTT GTTTGCTCTT GTTTGCTCTT ACAGGCAGAA ACTGGAAGGA TCCTTACCA ACCGCACACA	GCGATCATCT TCGATCATCT TCTATTATCT GCTATTATCA Q 800 AATCCCGGAA AATCCCGGAA AATCCCGGAA AATCCCGGAA AATCCCGGAA AATCCCGGAA AATCCCGGAA AATCCCGGAA AACACGGAA 900 CTACTCT TTCTCAAACC CTACTCT TTCTCAAACC CTACACT TACTGCTGA TACTGCTGA TACTGCTGA TACTGCTGA TACTGCTGA TACTGCTGA TACTGCTGA 1100 GTACCAC GCTCTTCAGC 1100 GTACCAC GCTCTTCAGC 1197 C CACHTCACC
Mogrp-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Hubrs-3 Hunmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Rugrp-R Hubrs-3 Hunmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Hubrs-3 Hunmb-R Ratnmb-R Hubrs-3 Hunmb-R Ratnmb-R	ATTAGTTGTG ATTAGCTGTG GAATCATGTA ACAGCATGTA ACAGCATGTA ACAGCATGTA ACAGCATGTA CTGTCTACTA CTGTCTACTA CTGTCTACTA CTGTCTACTA GCATTTATTA B01 GCGGCTTGCC GCGACTTGCC GCGACTTGCC GAGAATTGCC ACGCCTGGCC 901 GAAGTGGACA GAGGTGGACA GAGGTGGACA GAGATGGACC 1001 GCAAGAGCTT GCAAGAGCTT GTGAAAGCTT GTGAAAGCTT GTGAAGCTT GTGCATG ACTGCATG GATCGATG CACTGCATG CACTGCATG	CCCCTACCC CCCATACCC CCCATACCC CCCCTTATCC TCCATATCC TCCATACCTACC	ACACTCCAAT ACACTCCAAT ACACTCTAAT TGTCTCTTAAG TCAAACAGAT ACAAACAGAT ACAAACAGAT GCCGGAAATC GCTAGGACCC GCTAGGACCC GCTAGGACCC GCCAAGACCT TGGTGTTGGT TGGTGTTGGT TGGTGTTGGT TGGTGTTGGT TGGTGTTGGT TGGTGTTGGT TGGCTTTGT CCACTTTGTC CCACTTGTC CCACTTTGTC CCACTTTGTC CCACTTTGTC CCACTGTC CCACTTGTC CCACTGTC CCACTTGTC CCACTTGTC CCACTGTC CCACTGTC CCACTTGTC CCACTTGTC CCACTGT	GAGCTACACC GAGCTACACC GAGCTACACC GAGTTACATC GAGTTACATC GAGTTACATC GAGTTACATC GATCAGAG TGATCCAGAG TGATCCAGAG TAATTAAAAG TAATTAAAAG GGGCTCTTTT GGGCTGTTTC GGGCTGTTTC GGGCTGTTTC GGGCTGTTTC GGGCTGTTTC GGGCTGCTTTG GGCCGCTTTG GTCACCTTAG GTCACCTTAG GTCACCTTAG GTCACCTTAG ACTTCTCTG AGCTGCTCTG AGCTGCTCTG AGCTGCTCTG AGCTGCTCTG AGCTGCTCTG AACCACCTCACC TAACCACCTC. CAACCCCTCC	CTAAAATCCA CCAAAATCCA AAGAAATCCA CAAGAATCCA CAAGAATCCA CAAGAATCCA CACCTCACAAT TGCCTACAAT TGCCTACAAT TGCCTACAAT TGCACACCAAT TGCACACCAAT TGCACACCAAT TGCCCACCT GCCCTCTGCT GCCCTCTGCT GCCCTCTGCT GTGCCCACCT TGCCCGGGT TGCCCGGGT TGCCCGGGT TGCCCGGGT TGCCCGGCA CTGCCAGCCT TGCCCAGCCT TGCCCAGCCT TGCCCAGCCT TGCCCAGCCT TGCCCAGCCT TGCCCAGCAT	TTCCATGGCT TTCTATGGCT TTCTATGGCT TTCCATGGTG TTCCCGTGG CTTCCCGTGG CTTCCCGTGG CTTCCCGTGG CTTCCTGGAG CTTCCTGGAG CTTCCTGGAG GCTTCCCCAA GGTTCCCAA GGTTCCCAA GGTTCCCAA GGTTCCCAA GGTTCCCAA GGTTCCCAA GGTTCCCAA GGTTCCCAA GGTTCCCAA GGCTGATGA GGCCTGATGA GGCCTGATGA GGCCTGATGA GGCCTGATCA CCTATCCTG TTAGCCTCAT TTAGCCTCAT	ICCTTTCTGG ICCTTTCTGG ATTTTCTTGG ATTTTCTTGG ATTTTCTTGG ATTTTCTTGG ATTTTCTTGG AAGGCAATAT AAGGAACAAAG AATACAATGA AATACAATGA AATACAATGA AATACAATGA AATACAATGA AATACAATGA AATACAATGA AATACAATGA AATACAATGA AATACAATGA AATACAATGA ACCAACTCCT ACCAACTCCT ACCAACTCCT ACCAACTCCT ACCAACTCCT ACCAACTCCT ACCAACTCCT ACCAACTCCT ACCAACTCCT ACCAACTCCT ACCAACTCCT ACCACTCCT ACCACTCCT ACCACTCCT ACCACTCCT ACCACTCCT CCACTCCTGT ACCACTCCTCT	ΤΤΤΤΟΤΑCGΤ ΤΟΤΤΟΤΑCGΤ ΤΟΤΤΟΤΑCAΤ ΤΟΤΤΟΤΑCAΤ ΤΟΤΤΤΤΟCΟΤ ΤΟΤΤΤΤΟCΟΤ ΤΟΤΤΤΤΟCΟΤ ΤΟΤΤΤΤΟCΟΤ ΑCΑΤΟΤΟΛΑC ΑCΑΤΟΤΟΛΑC ΑCΑΤΑCCAAA ΑCΑΤΑCCAAA ΑCΑΤΑCCAAA ΑCΑΤΑCCAAA ΑCΑΤΑCCAAA ΤΑCCTOPACC ΤΑCCTOPACC ΤΑCCTOTACC ΤΑCATOTAC ΤΑCCTOPACC GCGTGAAACCC GCGTGAAACCC GTGTCACAGC GTCTCACAGC GTCTCACAGC GTCTCACAGC GTCTCACAGC GTCTCACAGC GTCTCACAGC GTCTCACAGC GTCTCACAGC GTCTCACAGC GTCTCACAGC GTCTCACAGC GTCTCACAGC GTCTCACAGC GTCTCACAGC GTCTCACAGC GTCTCACAGC GTCTCACAGC GTCTCACAGC GTCTCACAGC	TATCCCACTG CATCCCACTG CATACCCCCTT CATACCCCCTT CATACCCCTT NTRON AAGCACATTG AAGCACATTG AAGCACATTG CATCCTACCA GTTCCTACCA GTTCCTACCA GTTCCTACCA GTTCCTACCA GTTCTTCCAC GGTCTTTCA GGTCTTTCA GGTCTTTCCA CTTTGCCTCT CTTTGCCTCT ATTGCCTCT ACAGGCAGAA ACTCGAAGGA ACTCGAAGGA ACTCCTACCA TACCTCCTCA AGGCGTATGT AGGCGAAGGA	GCGATCATCT TCGATCATCT TCTATTATCT GCTATTATTATCA Q 800 AATCCCGGAA AATCCCGGAA AATCCCGGAA AATCCCGGAA AATCCCGGAA AACACGGAA 900 CTACTCT CTACTCT CTACTCT CTACTCT CTACTCT TTCTCAAACC CTACAAG 1000 TACTGCTGA TACTGCTGA TACCTGCTGA TACCTGCTGA TACCTGCTGA 1100 GTACCAC GCTCTTCAGC GTACAGCAC CCTCTCAGC 1197 C C C C C C
Mogrp-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Ratnmb-R Hugrp-R Hubrs-3 Hunmb-R Ratnmb-R	ATTAGTTGTG ATTAGCTGTG GAATCATGTA ACAGCATGTA ACAGCATGTA ACAGCATGTA ACAGCATGTA CTGTCTACTA CTGTCTACTA CTGTCTACTA CTGTCTACTA GCATTTATTA 801 GCGGCTTGCC GCGACTTGCC GCGACTTGCC GCGACTTGCC GAGAATTGCC GAGATTGACC GAGATCGACC 1001 GCAAGAGCTT GCAAGAGCTT GCAAGAGCTT GCAAGAGCTT GCAAGAGCTT GCAAGAGCTT GCAAGAGCTT GCAAGAGCTT GCAAGAGCTT GCAAGAGCTT GCAAGAGCTT GCAAGAGCTT	CCCCTACCC CCCATACCC CCCATACCC CCCATACCC TACCTCATT CTACTTCATT TTATCATATT TTATCATATT TTATCATATT TTATCATATT TATCACATT AAGACAGTGC AGAACGTAC AGAACGTAC AGAACGTAC CCTCCATGCT CCTCCATGCT CCTCCATGCT CCTCCATGCT CCTCCATGCA CAGGAAGCAG CAGGAAGCAG CAGGAAGCAG CAGGAAGCAG CAGGAAGCAT CAGGAAGCAT CAGGAGCAT CAGGAGCAT CAGGAGCAT	ACACTCCAAT ACACTCCTAAT TGTCTCTTAAG TGTCTCTTAAG TCAAACAGAT ACAAACAGAT GCTGGAAATC GCTAGAAATC GCTAGAAATC GCTAGGACCT GCTAGGACCT GCGAGGACCT TGGTGTTGT TGGTGTTGT TGGTGTTGT TGGTGTTGT	GAGCTACACC GAGCTACACC GAGCTTCACC GAATTACATC GAATTACATC GATTACATC GATTACATC GATCAGAG TGATCCAGAG TGATCCAGAG TATTACAAAAG TAATTAAAAG TAATTAAAAAG GGCCTCTTTT GGGCTGTTC GGCCTGTTC GGCCTGTTTC GGCCTGTTTC GGCCTGTTTC GGCCTGTTTG GTCACCTTAG GTCACCTTAG GTCACCTTAG TCACCGTAG AACTTCTCTG AGCTGCTCTG AGCTCGTCTG TAACCCCTC. CAACCCCTC. CAACCCCTCC ACAGATGTC TAGAACATG	CTAAAATCCA CCAAAATCCA AAGAAATCCA CAAGAATCCA CAAGAATCCA CAAGAATCCA CAAGAATCCA CACCTCACAAT TGCTTACAAT TGCTACAAT TGCCACCACAAT TGCACACCAAT TGCACACCACAT TGCCCCCCCT CTCTCTCGGT CTGCCCGGGT TGCCCCGGGT TGCCCCGGGT TGCCCCGGCT TGCCCGGCT TGCCCGGCT TGCCCGGCT TGCCCGGCT TGCCCGGCT TGCCCGGCT TGCCCGCCT TGCCCGCCT TGCCCGCCT TGCCCGCCT TGCCCGCCT TGCCCGCCT TGCCCGCCT TGCCCGCCT TGCCCGCCT TGCCCCCCC GAATTACTG GTGCCCCACTT GTGCCCCACT	TTCCATGGCT TTCTATGGCT TTCTATGGCT TTCAGTGCTC CTCAGTGCTC CTCCCGTGG CTTCCCGTGG CTTCCCGTGG CTTCCCGGGG CTTCCTGGAG CTTCCTGGAG CTTCCTGGAG GCTCCCCAA GGTTCCCAA GGTTCCCAA GGTTCCCAA GGTTCCCAA GGTTCCCAA GGTTCCCAA GGTTCCCAA GGTTCCCAA CCTGGCCTTC TCTGAGTTTC CCTGGCCTGATGA GGCCTGATGA GGCCTGATGA GGCCTGATCA GAGCGCCCG TTAGCCTCAT TTAGCCTCAT TTAGCCTCAT	ICCTTTCTGG ICCTTTCTGG ATTTTCTTGG ATTTTCTTGG ATTTTCTTGG ATTTTCTTGG ATTTTCTTGG AAGGACAATAT AAGGACAATAG AATACAATGA AATACAATGA AATACAATGA AATACAATGA AATACAATGA AATACAATGA AATACAATGA CCATGTCATC TCATGTCATC TCACGTCCTG GCCACTCCTG GCCACTCCTG GCCACTCCTG GCCACTCCTG ACCAACTCCT ACCAACTCCT ACCAACTCCT ACCAACTCCT ACCAACTCCT ACCAACTCCT ACCAACTCCT ACCAACTCCT ACCAACTCCT ACCAACTCCT ACCACTCCTG AGAG AGCCTCCTGT AGAG AGCCTCCTGT AGAG AGCACCCTT AATGGAAAC CCATGGGACT	TTTTCACGT TCTTCTACGT TCTTCTACAT TCTATTTCCT TCTATTTCCT TCTATTTCCT ACATGTCAAG ACATGTCAAG CCATGCCCGT ACATACCAAA ACATACCAAA ACATACCAAA TACCTCPACC TACCTCPACC TACCTCPACC TACCTCTACC TACCTCTACC TACCTCTACC GCGTGAAACCC GCGTGAAACCC GTGTCACAGC GTCTCACAGC TGCTCACAGC TGCTCACAGC GTCTCACAGC GTCTCACAGC GTCTCACAGC GTCTCACAGC AGCATGAAGCA AGCATGAAAGC	TATCCCACTG CATCCCACTG TATTCCACTC CATACCCCTT CATACCCCTT NTRON AAGCACTTG AAGCACTTG AAGCACTTG AAGCACTTG CATCCTACCA GTTCCTACCA GTTCCTACCA GTTCCTACCA GTTCCTACCA GTTCTTCCCACG GTCTTTCCCACG GTCTTTCCCTCC CTTTGCCCTC CTTTGCCCTC CTTTGCCCTC CTTTGCCCTC CTTTGCCCTC ATTTGCCCTC CTTTGCCCTC ACTGGAAGA ACCGGAAGA ACCCGAAGA AGCGGTATGT AGGCGTATGT	GCGATCATCT TCCATCATCAT TCTATTATCAT GCTATTATTATA GTATTATCATCA Q 800 AATCCCCGGAA AATCCCCGGAA AATCCCCGGAA AATCCCCGAAA AATCCCCGAAA AATCCCCGAAA AACACGGAA GCT ACTCT CT ACTCT CT ACTCT CT ACTCT CT ACTCT CT ACACG 1000 TACTGCTCA 1100 GTACCAC CCCTGGCTGT GCTCTTCAGC 1197 C CAGTTC AATS ACTG

Fig. 2. Nucleotide sequence comparison of coding domains of five cloned mammalian bombesin receptors. The nucleotide sequences are aligned to maximize sequence identity at a givel position. Boxes designate sequences encoding the seven transmembrane protein domains characteristic of G protein-coupled receptors. The conserved location of two introns dividing the

coding regions is indicated. The receptor sequences shown are as follows: Mogrp-R, mouse gastrin releasing peptide receptor [27]; Hugrp-R, human gastrin releasing peptide receptor [29]; Hubrs-3, human bombesin receptor subtype 3 [30]; Hunmb-R, human neuromedin B receptor [29]; Ratnmb-R, rat neuromedin B receptor [28].

	1		e1			TM-i	60
Mogrp-R	MAPNNC	SHLNLDVDPF	LSCNDTFN	QSLSPPKMDN	WFHPGFIYVI	PAVYGL	IIVI
Hugrp-R	MALNDC	FLLNLEVDHF	MHCNISS	HSADLPVNDD	WSHPGILYVI	PAVYGV	IILI
Hubrs-3	MAQRQPHSPN	QTLISITNDT	ESSSSVVSND	NTNKGWSGDN	SPGIEALCAI	YITYAV	IISV
Hunmb-R	MPSKSL	SNLSVTTGAN	ESGSVPEGWE	RDFLPASDGT	TTELVIRCVI	PSLYLL	IITV
Ratnmb-R	MPPRSL	PNLSLPTEAS	ESELEPEVWE	NDFLPDSDGT	TAELVIRCVI	PSLYLI	IISV
	61	i1		TM-II		e2	120
Mogrp-R	GLIGNITLIK	IFCTVKSMRN	VPNLFISSLA	LGDLLLLVTC	APVDASKYLA	DRWLFGI	RIGC
Hugrp-R	GLIGNITLIK	IFCTVKSMRN	VPNLFISSLA	LGDLLLLITC	APVDASRYLA	DRWLFGI	RIGC
Hubrs-3	GILGNAILIK	VFFKTKSMQT	VPNIFITSLA	FGDLLLLLTC	VPVDATHYLA	EGWLFG	RIGC
Hunmb-R	GLIGNIMLVK	IFITNSAMRS	VPNIFISNLA	AGDLLLLLTC	VPVDASRYFF	DEWMFGI	KVGC
Ratnmb-R	<u>GLI</u> GNIMLVK	IFLTNSTMRS	VPNIFISNLA	AGDLLLLLTC	VPVDASRYFF	DEWVFGI	KLGC
	101	M-III		12		TM_IV	100
Mogrn-R	KI TERTOLUS	VOVSVETLTA	LGADRYKATV	REMOTORSHA	LMKTCLKAAL	TWTVSM	TTTAT
Hugrp-R	KI TPETOLTS	VGVSVETLTA	LSADRYKATV	REMOTORCHA	LMKICLKAAF	TWITCM	
Hubre-3	KVI.SETRLTS	VGVSVFTLTT	I.SADRYKAW	KDLEROPSNA	TIKECVKAGC	WILSH.	TENT.
Hupmb-B	KT.TPVIOLTS	VGVSVETLTA	LSADBYRATV	NPMDMOTSGA	LLRTCVKAMC	TWATAGM	T.T.AV
Ratnmb-R	KI TPATOLTS	VGVSVETLTA	LSADBYRATV	NPMDMOTSGV	VLWTSLKAVG	TWANGV	T.T.AV
Nuclinio IV	N <u>DIIINIQDID</u>	101011111	DenDRITATIV	MINDIQIDOV	TODIATO	100050	
	181		e3		-	TM-V	240
Mogrp-R	PEAVESDLHP	FHVKDTNOTF	ISCAPYPHSN	ELHPKIHSMA	SFLVFYVIPL	AIISVY	YYFI
Hugrp-R	PEAVFSDLHP	FHEESTNOTF	ISCAPYPHSN	ELHPKIHSMA	SFLVFYVIPL	SIISVY	YYFI
Hubrs-3	PEATFSNVYT	FRDPNKNMTF	ESCTSYPVSK	KLLQEIHSLL	CFLVFYIIPL	SIISVY	YSLI
Hunmb-R	PEAVFSEVAR	I.SSLDNSSF	TACIPYPQTD	ELHPKIHSVL	IFLVYFLIPL	AIISIY	YYHI
Ratnmb-R	<u>PEAV</u> FSEVAR	I.GSSDNSSF	TACIPYPQTD	ELHPKIHSVL	IFLVYFLIPL	VIISIY	YYHI
			.				
	241	13					300
Mogrp-R	ARNLIQSAYN	LPVEGNIHVK	KQIESRKRLA	KTVLVFVGLF	AFCWLPNHVI	YLYRSY	HYSE
Hugrp-R	AKNLIQSAYN	LPVEGNIHVK	KQIESRKRLA	KTVLVFVGLF	AFCWLPNHVI	YLYRSY	HYSE
Hubrs-3	ARTLYKSTLN	IPTEEQSHAR	KQIESRKRIA	RTVLVLVALF	ALCWLPNHLL	YLYHSF	TSQI
Hunmb-R	AKTLIKSAHN	LPGEYNEHTK	KQMEIRKRLA	KIVLVFVGCF	IFCWFPNHIL	YMYRSFI	NYNE
Ratnmb-R	AKTLIRSAHN	LPGEYNEHTK	KOMETRARLA	KIVLVFVGCF	VFCWFPNHIL	YLYRSF	NYKE
	301 e4		TM-VII	*	iД		360
Mogro-R	.VDTSMLHFV	TSICAHLLAF	TNSCVNPFAL	YLLSKSFRKO	FNTOLLCCOP	GLMNRS	HS .
Hugrp-R	.VDTSMLHFV	TSICARLLAF	TNSCVNPFAL	YLLSKSFRKO	FNTOLLCCOP	GLITES	HS
Hubrs-3	YVDPSAMHFI	FTIFSRVLAF	SNSCVNPFAL	YWLSKSFOKH	FKAOLECCKA	ERPEPP	v
Hunmb-R	. IDPSLGHMI	VILVARVLSF	GNSCVNPFAL	YLISESERRH	FNSOLCCGRK	SYOERG	TSYL
Ratnmb-R	. IDPSLGHMI	VTLVARVLSF	SNSCVNPFAL	YLLSESERKH	FNSOLCCGOK	SYPERS	TSYL
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	361	*			405		
Mogrp-R	TGRSTTCMTS	FKSTNPS.AT	FSLINRNICH	EGYV			
Hugrp-R	TGRSTTCMTS	LKSTNPSVAT	FSLINGNICH	ERYV			
Hubrs-3	ADTSLTT	LAVMGTVPGT	GSIQMSEISV	TSFTGCSVKQ	AEDRF		
Hunmb-R	LSSSAVRMTS	LKSNAKNMVT	NSVLLNGHSM	KQEMAM			
Ratnmb-R	LSSSAVRMTS	LKSNAKNVVT	NSVLLNGHST	KQEIAL			

Fig. 3. Amino acid sequence comparison of five cloned bombesin receptors. The amino acid sequences are aligned to maximize sequence similarity. Note the remarkable sequence similarity in regions of the seven putative transmembrane domains (TM-I to TM-VII). Four extracellular domains (e1–e4) and four intracellular domains (i1-i4) are indicated, as well as three consensus protein kinase C phosphorylation sites (boxed, with asterisks) in the i3 and i4 domains which may mediate receptor desensitization by interfering with coupling to G-proteins.

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TABLE I. Displacement of [125]]Tyr4 BombesinBinding by GRP, NMB, and the Antagonist[D-Phe6]Bombesin6-13 Ethyl Ester*

	K _i (nM)				
Subtype	GRP	NMB	Antagonist		
MoGRP-R	2	62	1.6		
RatNMB-R	43	2	>1,000		

Displacement of $[^{125}I]$ Tyr⁴bombesin binding by GRP, NMB, and the antagonist [D-Phe⁶]bombesin₆₋₁₃ ethyl ester. The whole cell binding assay was performed as described [28]. Note the remarkable difference in affinity for the antagonist seen when GRP-R and NMB-R are compared. BRS-3 does not bind the labelled bombesin tracer with sufficient affinity to accurately measure displacement above background in this assay.



Fig. 4. RT/PCR analysis of bombesin receptor expression in a panel of human lung carcinoma cell lines. Total RNA samples isolated from cell lines was reverse transcribed, and the resulting cDNA subjected to polymerase chain reaction amplification using gene-specific primers for GRP-R, NMB-R, or BRS-3. The PCR product was resolved by agarose gel electrophoresis, blotted, and hybridized to a gene-specific oligonucleotide probe to detect receptor mRNA expression in the individual cell lines. Representative data is shown in this figure, and a summary of the data from all cell lines examined can be found in Table II. Note that most cell lines express at least one of the three bombesin receptors. Details of the method are provided in Materials and Methods.

Cell line			
and morphological type	GRP-R	NMB-R	BRS-3
Small cell lung carcinoma			
NCI-H69	Tr	Tr	+
NCI-H82		+	
NCI-H209	-	+	+
NCI-H345	+	+	-
NCI-N417	_	+	+
NCI-H510	\mathbf{Tr}	+	_
NCI-N592	+	+	+
Carcinoid			
NCI-H720	÷	+	+
NCI-H727	-	+	+
Non-small cell lung			
carcinoma			
NCI-H23	-	\mathbf{Tr}	_
NCI-H125	+	+	+
NCI-H157	-	+	-
NCI-H226	\mathbf{Tr}	+	-
NCI-H322	+	+	\mathbf{Tr}
NCI-H358	\mathbf{Tr}	+	+
NCI-H441	-	\mathbf{Tr}	-
NCI-H460	-	\mathbf{Tr}	-
NCI-H520	+	+	+
NCI-H661	-	+	_
NCI-H810	_	\mathbf{Tr}	_
NCI-H1299	+	+	\mathbf{Tr}
NCI-H1373	\mathbf{Tr}	+	-

TABLE II. Bombesin Receptor Subtype mRNA Expression in Lung Cancer Cell Lines as Determined by RT/PCR*

*(+), (Tr), and (-) indicate high, trace, and non-detectable levels of mRNA expression respectively. Bombesin receptor mRNA expression detected by RT/PCR in human lung cancer cell lines. The presence or absence of a detectable PCR product is indicated by a +; barely detectable expression is designated trace (tr); no expression is indicated by a -. Both small cell and non-small cell lung cancer cell lines were examined. The assay was performed as indicated in Materials and Methods.

DISCUSSION

Human lung tumor cell lines have proven to be a reliable source for the identification, isolation, and structural characterization of human bombesin receptor subtype cDNAs, where, in some examples, they are reported to play an important role in the pathogenesis or progression of neoplasia. Curiously, bombesin receptor mRNA levels are invariably low in all the human lung cancer cell lines studied. The explanation for the low expression is not clearly understood at present, but may be an important feature for exhibiting an autocrine or paracrine growth response. In quiescent Balb 3T3 cells expressing high levels of transfected NMB-R $(8 \times 10^5 \text{ recep-})$ tors/cell), the growth response is biphasic with apparent growth stimulation at low levels of peptide (less than 10 nM) and growth inhibition at higher levels (10-100 nM) [37]. A similar biphasic growth effect was observed in Swiss 3T3 cells expressing endogenous GRP-R, indicating that this effect was not unique to the NMB-R. These studies indicate that constitutive occupation of bombesin receptors present in high numbers (>50,000 receptors/cell) inhibits, rather than stimulates, growth. Growth inhibition may result from an overstimulation of a physiologic signal transduction pathway or inappropriate activation of a secondary signal transduction pathway which results in decreased proliferation. If the dose-response of the growth inhibition effect depends on high receptor number, lung cancer cells may be selected to express sufficient receptors for growth stimulation, but not inhibition, at the available ligand concentration. Future studies will be needed to determine the effects of receptor number on the growth response to a range of concentrations of bombesin-like peptides.

Three conserved protein kinase C phosphorylation sites are found in the intracellular 3 and 4 domains of 4/5 bombesin receptor sequences (i3 and i4, boxed regions, Fig. 3). The location of these potential sites of protein kinase C phosphorylation are in domains known to be critical for G-protein coupling in other G-protein coupled receptors, including the beta-adrenergic [38], muscarinic [38], and TSH receptors [39]. In a previous study of bombesin receptor function in small cell lung cancer cell line H345, the phorbol compound 12-myristate 13-acetate, a protein kinase C activator, attenuated bombesin-stimulated increases in intracellular Ca++ [40], indicating a role for protein kinase C phosphorylation in receptor desensitization. Zachary and coworkers [41] have reported that the early cellular responses following stimulation of the Swiss 3T3 GRP-R by ligand include activation of protein kinase C. Taken together, these observations suggest that bombesin receptors may be phosphorylated by protein kinase C at conserved sites in i3 and i4 after ligand activation, and that this post-translational modification may serve to desensitize the receptor by interfering with G-protein coupling. Analysis of the desensitization properties of receptors with mutations altering one or more of these three conserved

sites should clarify the importance of this potential regulatory mechanism.

After expression of BRS-3 in Xenopus oocytes, the receptor is specifically activated by bombesinlike peptides, and not peptides from other neuropeptide families. However, in contrast to GRP-R and NMB-R, higher ligand concentrations (10^{-6}) vs. 10^{-8} M) were required to elicit responses. Several explanations are possible for this difference between BRS-3 and the other two receptors: (1) a specific G-protein and/or auxillary protein(s) not available in the Xenopus oocyte may be needed for high affinity ligand binding. For example, the secretion receptor shows a ten-fold increase in ligand affinity when coexpressed with a specific G-alpha subunit, G_s, in COS cells [42]; (2) a critical post-translational modification that does not occur in Xenopus oocytes may be required for BRS-3 to bind ligands at high affinity binding; (3) BRS-3 mRNA or protein may be unstable in *Xenopus* oocytes, resulting in a low number of receptors expressed on the oocyte membrane; or (4) the mammalian bombesin-like peptide specific for BRS-3 is neither GRP nor NMB, and remains to be identified. Future efforts will be directed towards expressing BRS-3 in host cells other than Xenopus oocytes, including a panel of murine fibroblast cell lines. In addition, we are actively attempting to identify and characterize additional mammalian bombesin-like peptide ligands. Potential sources of these novel peptides include human lung carcinoma cell lines or testis, which are cell or tissue types that express BRS-3 [30].

No pre-existing pharmacologic study predicted the existence of BRS-3, the third human bombesin receptor to be cloned and characterized. The third exon of BRS-3 was initially identified and cloned as a 3.0 kb Eco RI human genomic DNA fragment that hybridized at low stringency to GRP-R and NMB-R cDNA probes at low stringency [30]. Several other fragments with similar hybridization properties were also noted, none of which encode exons of GRP-R, NMB-R, or BRS-3. These unexplained genomic DNA fragments may encode exons of additional human bombesin receptor genes that are not characterized at present. Future efforts will be directed towards the characterization of these potentially interesting sequences, which may provide a means for obtaining new cDNAs encoding additional human bombesin receptors which are likely to possess their own unique pharmacologic properties and pattern of expression. Given the receptor heterogeneity observed to date, it is clear that further characterization of mammalian bombesin-like peptides and their receptors will provide additional useful information for the design of compounds and therapeutic regimens of potential importance in modulating bombesin-dependent growth in human neoplastic disease.

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