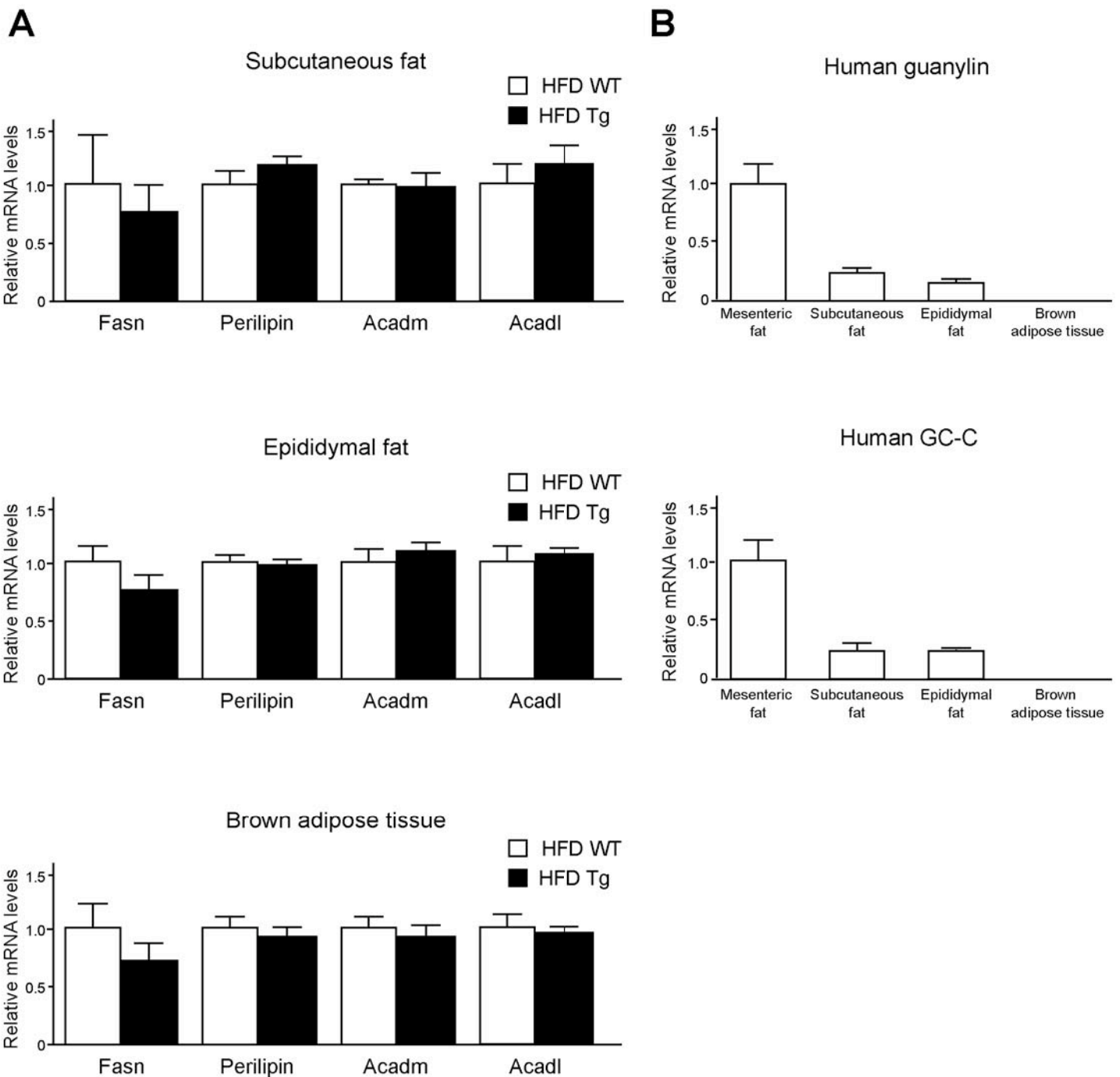
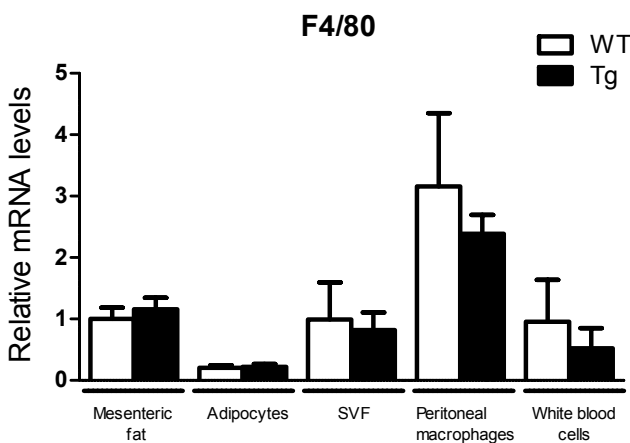
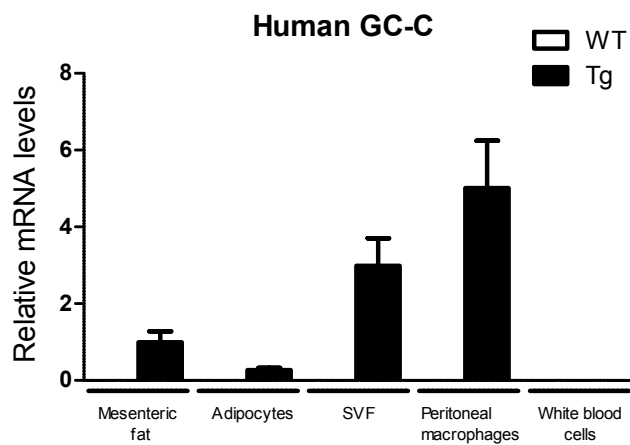
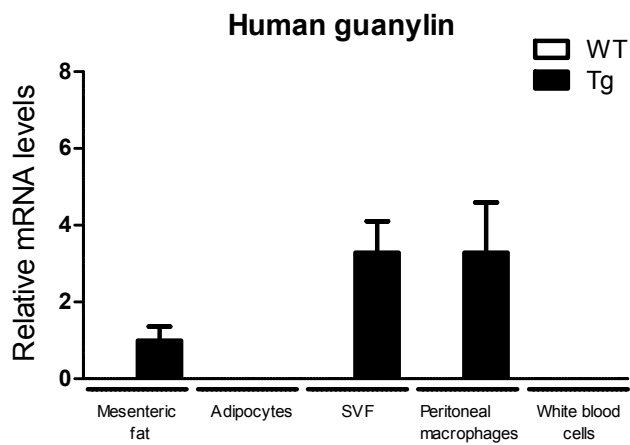


Supplementary Figure 1. (A) Immunostaining of mesenteric fat with anti-guanylin, anti-GC-C, and anti-CD68 antibodies in high-fat diet-induced obesity (DIO) rats and control rats. Left panel, guanylin; Middle panel, GC-C; Right panel, CD68 (brown), Scale bar, 50 μ m. **(B)** Western blot analysis of guanylin, GC-C, and CD68 in extracts of the Tg mesenteric fat.



Supplementary Figure 2. (A) mRNA expression in the subcutaneous fat, epididymal fat, and brown adipose tissue of WT and guanylin-GC-C double-Tg rats. Data were normalized against GAPDH mRNA levels and are presented as means \pm SEM ($n = 4$ or 5). **(B)** mRNA levels of human guanylin and human GC-C in the mesenteric fat, subcutaneous fat, epididymal fat, and brown adipose tissue of HFD Tg rats. Data were normalized against GAPDH mRNA levels and were expressed as fold induction relative to that of mesenteric fat. Data are presented as means \pm SEM ($n = 4$ or 5).



Supplementary Figure 3. mRNA levels of human guanylin, human GC-C and F4/80 in the mesenteric fat, adipocytes, stromal vascular fraction (SVF), peritoneal macrophages, and peripheral white blood cells of WT rats and Tg rats. Data were normalized against the 36B4 mRNA levels and were expressed as fold induction relative to that of mesenteric fat derived from Tg rats. Data are presented as means \pm SEM (n = 4).

Supplementary Table 1. Top 100 specifically up-regulated genes in guanylin/GC-C high expressed rats compared with control, DIO, and guanylin/GC-C low expressed rats.

Fold change ([gua/GC-C high expressed DR] vs [control])	Fold change ([DIO] vs [control])	Fold change ([gua/GC-C low expressed DR] vs [control])	Affymetrix probe set ID	Gene Symbol	Gene Title
147.14474	-1.0964204	-1.1947889	1369111_at	Fabp1	fatty acid binding protein 1, liver
112.548615	-1.0358278	-1.0658016	1372922_at	LOC691259	hypothetical protein LOC691259
111.325096	-1.0411407	1.0087899	1368269_at	Lgals4	lectin, galactoside-binding, soluble, 4
102.0206	1.0039177	-1.0883106	1390238_at	Clca3	chloride channel calcium activated 3
82.202194	1.1993738	-1.0115223	1368586_at	Zg16	zymogen granule protein 16
79.03206	1.0580212	-1.0815662	1378658_at	Clca4	chloride channel calcium activated 4
65.94027	-1.01929	-1.0763283	1369195_at	Fabp2	fatty acid binding protein 2, intestinal
60.74142	1.0563285	-1.030266	1395853_at	Clca3	chloride channel calcium activated 3
59.37088	1.3294017	-1.0127926	1388199_at	Epcam	epithelial cell adhesion molecule
55.99972	1.0454261	1.0495839	1368471_at	Guca2a	guanylate cyclase activator 2a (guanylin)
49.29587	1.0665547	1.1531565	1369224_at	Cdh17	cadherin 17
48.559757	1.138888	1.1120383	1370387_at	Cyp3a9	cytochrome P450, family 3, subfamily a, polypeptide 9
47.14064	2.2939198	1.0279789	1368413_at	Abp1	amiloride binding protein 1 (amine oxidase, copper-containing)
43.845566	1.1020275	1.014531	1370894_at	Cldn7	claudin 7
43.73931	-1.0783587	1.0489403	1383970_at		
43.222485	-1.0001742	1.006014	1368236_at	Mep1a	meprin 1 alpha
43.218243	-1.0690651	-1.0886675	1371099_at		
43.172997	1.0454063	1.1495814	1387314_at	Sult1b1	sulfotransferase family, cytosolic, 1B, member 1
42.597134	-1.1121064	-1.0289764	1390566_a_at	Ckmt1	creatine kinase, mitochondrial 1, ubiquitous
40.36157	1.0091859	-1.0251019	1368697_at	Fabp6	fatty acid binding protein 6, ileal
37.10351	-1.1901146	1.0773925	1386947_at	Cdh1	cadherin 1
32.467396	1.0329326	1.0187325	1388006_at	Muc13	mucin 13, cell surface associated

Fold change ([gua/GC-C high expressed DR] vs [control])	Fold change ([DIO] vs [control])	Fold change ([gua/GC-C low expressed DR] vs [control])	Affymetrix probe set ID	Gene Symbol	Gene Title
32.34029	-1.1132804	-1.0956278	1393121_at	Agr2	anterior gradient homolog 2 (<i>Xenopus laevis</i>)
32.223553	-1.0268033	1.0024045	1376359_at	Ms4a8a	membrane-spanning 4-domains, subfamily A, member 8A
31.805708	1.0900272	1.0509607	1387158_at	Mep1b	meprin 1 beta
29.839527	1.0573514	1.059727	1392969_at		
29.29737	1.1641557	-1.1442182	1368335_at	Apoa1	apolipoprotein A-I
27.950108	-1.0981983	-1.1441199	1377928_at	Tm4sf20	transmembrane 4 L six family member 20
27.105555	-1.0730618	-1.0120633	1387994_at	Hsd17b6	hydroxysteroid (17-beta) dehydrogenase 6
26.922874	-1.0485338	1.0020348	1370631_at	Reg3g	regenerating islet-derived 3 gamma
26.785194	-1.0356189	-1.0601935	1394228_at	Tmigd1	transmembrane and immunoglobulin domain containing 1
26.169155	-1.0377495	-1.0428827	1388147_at	Muc3a	mucin 3A, cell surface associated
25.769123	-1.1599573	-1.1091313	1392647_at	LOC687992	similar to Serum amyloid A-3 protein precursor
24.612743	1.1779646	1.0691462	1374070_at	Gpx2	glutathione peroxidase 2
24.404602	1.3734003	-1.4059792	1369953_a_at	Cd24	CD24 molecule
23.50129	-1.0585811	1.0432423	1369162_at	Gucy2c	guanylate cyclase 2C
23.497313	-1.0114307	1.0466768	1379393_at	Vil1	villin 1
23.289286	-1.0369344	-1.0084523	1368467_at	Cyp4f1	cytochrome P450, family 4, subfamily f, polypeptide 1
23.148066	2.1113644	1.6362264	1376191_at	Hpgd	hydroxyprostaglandin dehydrogenase 15 (NAD)
22.584402	1.9620341	1.7251744	1387631_at	Hpgd	hydroxyprostaglandin dehydrogenase 15 (NAD)
21.965387	1.041887	1.1134773	1387218_at	Tff3	trefoil factor 3, intestinal
21.675919	1.0629786	-1.2024075	1388190_at	Apob	apolipoprotein B (including Ag(x) antigen)
21.61933	1.0133145	-1.019164	1387156_at	Hsd17b2	hydroxysteroid (17-beta) dehydrogenase 2
18.935299	-1.1307874	-1.0006355	1375936_at	Dsc2	desmocollin 2
18.829332	1.0771842	-1.0052332	1387972_at	Mucdhl	mucin and cadherin like
18.59812	-1.073345	1.0064859	1388074_at	Krt20	keratin 20
17.458109	1.0655547	1.0381142	1382996_at	RGD1566202	similar to RIKEN cDNA 1810007E14

Fold change ([gua/GC-C high expressed DR] vs [control])	Fold change ([DIO] vs [control])	Fold change ([gua/GC-C low expressed DR] vs [control])	Affymetrix probe set ID	Gene Symbol	Gene Title
17.073355	1.0848356	1.0663605	1370299_at	Aldob	aldolase B, fructose-bisphosphate
17.001299	1.0285859	-1.1787591	1376287_at	Capn13	calpain 13
16.988863	1.079287	-1.0633701	1381082_at	RGD1564357	RGD1564357
16.907627	-1.1312453	1.0144043	1389762_at	RGD1311906	similar to Fc fragment of IgG binding protein; IgG Fc binding protei
16.829556	1.1692319	1.0408734	1376117_at	Slc44a4	solute carrier family 44, member 4
16.274204	-1.8676562	1.0085442	1396304_at		
15.947679	-1.0584149	-1.016524	1385263_at	Myo7b	myosin VIIb
15.3980465	-1.3460321	-1.1136945	1370464_at	Abcb1	ATP-binding cassette, sub-family B (MDR/TAP), member 1
15.273306	-1.199337	-1.0246488	1389783_s_at	RGD1311906	similar to Fc fragment of IgG binding protein; IgG Fc binding protei
15.2423115	1.0139916	1.0040486	1394174_at	Defa-rs1	defensin alpha-related sequence 1
14.850895	-1.0454618	1.0328736	1393953_at	Eps8l3	EPS8-like 3
14.73513	-1.058516	-1.059321	1392694_at	RGD1562344	similar to Gm566 protein
13.712856	1.0693414	1.001088	1370503_s_at	Epb4.1l3	erythrocyte protein band 4.1-like 3
13.624498	1.0719824	-1.5570296	1371530_at	Krt8	keratin 8
13.324245	-1.2469163	-1.1546512	1389654_at	Pls1	Plastin 1 (I isoform)
12.838897	-1.0325505	-1.1085513	1385767_at	LOC304000	cell adhesion molecule JCAM
12.632386	-1.0495781	-1.3305156	1379656_a_at		
12.609954	1.1485777	1.0726142	1369100_at	Nlrp6	NLR family, pyrin domain containing 6
12.376696	-1.1055664	-1.0205555	1376292_at		
12.073219	1.012987	1.0429072	1374657_at	Anks4b	ankyrin repeat and sterile alpha motif domain containing 4B
11.937026	1.0187414	-1.0711844	1378690_at	Ly6al	lymphocyte antigen 6 complex, locus A-like
11.882774	1.1035506	1.1561176	1393241_at	Prss32	protease, serine, 32
11.833633	1.2895955	-1.1892283	1383554_at	Rnf128	ring finger protein 128
11.616765	1.0598674	1.1177361	1368520_at	Apoa4	apolipoprotein A-IV
11.400645	1.1164505	1.3468087	1380577_at	Abcg2	ATP-binding cassette, sub-family G (WHITE), member 2

Fold change ([gua/GC-C high expressed DR] vs [control])	Fold change ([DIO] vs [control])	Fold change ([gua/GC-C low expressed DR] vs [control])	Affymetrix probe set ID	Gene Symbol	Gene Title
11.0176115	-1.0725214	-1.2562748	1368339_at	S100g	S100 calcium binding protein G
10.982584	-1.1256068	-1.0199848	1383898_at	Fam3d	family with sequence similarity 3, member D
10.930318	1.0158699	-1.0956024	1368515_at	Epb4.1l3	erythrocyte protein band 4.1-like 3
10.864786	-1.184054	-1.1132499	1374095_at		
10.8537	-1.116913	1.0280777	1376248_at	Sult2b1	sulfotransferase family, cytosolic, 2B, member 1
10.723244	-1.0492104	1.0642967	1391707_at		
10.6501875	1.025223	1.0788774	1391936_a_at		
10.625221	1.1272062	-1.3189434	1378288_at	Ostalpha	organic solute transporter alpha
10.200327	-1.1107224	-1.0970387	1383855_at	Degs2	degenerative spermatocyte homolog 2, lipid desaturase (Drosophi
10.189022	-1.0674437	-2.1932821	1388051_at	Slc26a3	solute carrier family 26, member 3
9.919589	-1.0470651	-1.029085	1368278_at	Lgals2	lectin, galactoside-binding, soluble 2
9.916595	1.2640928	1.1027277	1377637_at		
9.696659	-1.0030786	-1.0898958	1393845_a_at	Tmc4	transmembrane channel-like 4
9.678709	1.1380019	-1.0333991	1380834_at	Btnl8	butyrophilin-like 8
9.634692	-1.0247678	1.061924	1376163_at	Clrn3	clarin 3
9.49958	1.0156207	-1.1236516	1378753_at	Ocln	occludin
9.479225	-1.0825157	-1.4942826	1394039_at	Klf5	Kruppel-like factor 5
9.261945	1.0101215	1.1424137	1388238_at	Defcr24	defensin related cryptdin 24
9.015608	1.2213624	-1.9454161	1370349_a_at	LOC680367 /// Rup2	similar to Urinary protein 3 precursor (RUP-3) /// urinary protein 2
8.999008	-1.1149011	-1.0723684	1371089_at	Yc2	glutathione S-transferase Yc2 subunit
8.97663	1.0723041	1.0575533	1368238_at	Reg3b	regenerating islet-derived 3 beta
8.947264	-1.000822	-1.0255433	1373330_at	LOC690323	similar to Myosin-15 (Myosin XV) (Unconventional myosin-15)
8.84533	1.1128107	1.0981957	1392209_at	Gcnt3	glucosaminyl (N-acetyl) transferase 3, mucin type
8.83832	-1.0337001	-1.0404627	1380967_at	Nts	neurotensin
8.806242	-1.0475233	-1.0580055	1373329_at	Tmprss2	transmembrane protease, serine 2

Fold change ([gua/GC-C high expressed DR] vs [control])	Fold change ([DIO] vs [control])	Fold change ([gua/GC-C low expressed DR] vs [control])	Affymetrix probe set ID	Gene Symbol	Gene Title
8.775939	1.1818664	1.0882225	1391279_at	Scin	Scinderin
8.612451	-1.150608	-1.2218848	1368121_at	Akr7a3	aldo-keto reductase family 7, member A3 (aflatoxin aldehyde redu
8.589368	-1.2017964	-1.2438842	1392547_at	MGC105649	hypothetical LOC302884

Supplementary Table 2. Primers used for quantitative PCR

Gene	Forward	Reverse
36B4	TCATTGTGGGAGCAGACAATGTG	AGGTCCTCCTTGGTGAACACAAA
Glyceraldehyde 3-phosphate dehydrogenase (GAPDH)	GGCACAGTCAAGGCTGAGAAT	GGTGGTGAAGACGCCAGTAGA
Guanylin (rat)	TCACTGTGCAGGATGGAGAC	TGTTTGGGTCCTGAGCAATG
Guanylyl cyclase C (GC-C) (rat)	TGCGACAGTGCAAATACGAC	ACTCGACCACCCCAAAGATC
Peroxisome proliferator-activated receptor gamma (PPAR γ)	AGTCTGCTGATCTGCGAGCC	CTTTCCTGTCAAGATCGCCC
PPAR γ 2	GGCACGAGCATCAGTGGGAA	AGTGCATCAGCGAAGGCACC
CCAAT/enhancer-binding protein alpha (C/EBP α)	ATAAAGCCAAACAGCGCAAC	CGGTCATTGTCACTGGTCAA
Adiponectin (Adipoq)	ATGGCAGAGATGGCACTCCT	CCTTCCGCTCCTGTCAATCCA
Glucose transporter 4 (GLUT4)	GGGCTGTGAGTGAGTGCTTTC	CAGCGAGGCAAGGCTAGA
Fatty acid synthase (Fasn)	AGTTCTGGGCCAACCTCATTG	AGGCGTCGAACTTGGACAGAT
Perilipin	GGTACACACCGTGCAGAAGA	GGGAAGCGGGACATAGTGTA
Acyl-Coenzyme A dehydrogenase, C-4 to C-12 straight chain (Acadm)	GATATTGCCAACCACTCGC	TGATAGATCTTGGCGTCCCG
Acyl-Coenzyme A dehydrogenase, long chain (Acadl)	GCCAAAAGGTCTGGGAGTGAT	TCGAGCTTCACGATTGGTGAC
Carnitine palmitoyltransferase 1A (Cpt1a)	TTGTGGGAGTATGTCATGGCC	CCATTGTAGCCTTGTGGGCTT
Acyl-Coenzyme A oxidase 1, palmitoyl (Acox1)	TTACGTCACTTTTACCCCGGC	ACCGCACCTGGTCGTAGATTT
F4/80	ACCAATGTACCAGTTCTACAACCT	AGGGAATCCTTTTGCATGTGA
Guanylin (human)	GGTCCCATCCTCTGTAGCA	CAGCGTAGGCACAGATTTCA
Guanylyl cyclase C (GC-C) (human)	TCGCATTGGAGTTCACCTCTG	ATTCTCAAAGGGAGGCCAGT