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#### Bone morphogenetic protein 4 inhibits insulin secretion from rodent beta cells through regulation of calbindin1 expression and reduced voltage-dependent calcium currents

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LUND UNIVERSITY

**PO Box 117** 221 00 Lund +46 46-222 00 00 Bone Morphogenetic Protein 4 inhibits insulin secretion from rodent beta cells through regulation of Calbindin1 expression and reduced voltage dependent calcium currents.

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Abbreviations:

- BMP: Bone Morphogenetic protein
- CDF: Chip definition file
- ECM: Extracellular matrix
- FDR: False discovery rate
- GSIS: Glucose stimulated insulin secretion
- HBSS: Hanks' balanced salt solution
- Id1: Inhibitor of differentiation 1
- Ins1: Insulin 1
- KO: Knock out
- KRHB: Krebs Ringer Hepes Buffer
- NCS: Newborn calf serum
- TGF-β: Transforming Growth Factor-β
- VDCC: Voltage dependent calcium channel
- WT: Wild type

#### Abstract

**Aims/hypothesis:** Type 2 diabetes is characterized by progressive loss of pancreatic beta cell mass and function. Therefore, it is of therapeutic interest to identify factors with potential to improve beta cell proliferation and insulin secretion. Bone morphogenetic protein 4 (BMP4) expression is increased in diabetic animals and BMP4 reduce glucose-stimulated insulin secretion (GSIS). Here we investigate the molecular mechanism behind this inhibition.

**Methods:** The BMP4 mediated inhibition of GSIS was investigated in detail using single cell electrophysiological measurements and live calcium imaging. BMP4 mediated gene expression changes were investigated with microarray profiling, q-pcr and western blotting.

**Results:** Prolonged exposure to BMP4 reduced GSIS from rodent pancreatic islets. This inhibition was associated with decreased exocytosis due to a reduced  $Ca^{2+}$ -current through voltage-dependent  $Ca^{2+}$ -channels. To identify proteins involved in the observed inhibition of GSIS we investigated the global gene expression changes induced by BMP4 in neonatal rat pancreatic islets. The expression of the  $Ca^{2+}$ -binding protein Calbindin1 was induced significantly by BMP4. Overexpression of Calbindin1 in primary islet cells reduced GSIS and the effect of BMP4 on GSIS was lost in islets from Calbindin1 knock out mice.

**Conclusions/interpretation:** We find BMP4 treatment to markedly inhibit GSIS from rodent pancreatic islets in a Calbindin1-dependent manner. Calbindin1 is suggested to mediate the effect of BMP4 by buffering Ca<sup>2+</sup> and decreasing Ca<sup>2+</sup>-channel activity resulting in diminished insulin exocytosis. BMP4 and Calbindin1 are both potential pharmacological targets for the treatment of beta cell dysfunction.

In response to insulin resistance, the pancreatic beta cells will initially compensate by increasing mass and function to maintain normal blood glucose levels [1]. In individuals who progress to develop type 2 diabetes the beta cells eventually fail to adapt and progressive loss of functional beta cells starts [1]. Although current type 2 diabetes drugs targeting insulin resistance or insulin secretion are initially efficient, beta cell mass and function tends to decline over time [2, 3]. Unidentified factors may limit the ability of the beta cells to adapt to insulin resistance. In our search for factors, with inhibitory effects on beta cells, we have recently described the inhibition of beta cell proliferation and insulin secretion by bone morphogenetic protein 4 (BMP4) [4].

BMPs belong to the Transforming Growth Factor- $\beta$  (TGF- $\beta$ ) protein family, known to play central roles in pancreas and islet development [5-10]. While the role of BMPs in the developing pancreas and beta cell has gained much attention [8, 11, 12], less is known about their function in the postnatal pancreas. Increasing evidence indicates BMP2 and 4 to be inflammatory markers in various tissues under diabetic conditions [13-15]. We have recently shown that BMP2 and 4 are expressed in pancreatic islets, and are upregulated during diabetes progression in islets from *db/db* mice and by proinflammatory cytokines *in vitro* [4]. Although culture of pancreatic islets in the presence BMP2 and 4 negatively affects beta cell function, it appears that the effect of BMPs *in vivo* is more complex. Beta cell specific deletion of the BMP receptor 1A (BMPR1A) results in impaired glucoseinduced insulin secretion (GSIS), whereas transgene BMP4 expression increase GSIS [16]. In contrast, deficiency of ID1, a central BMP regulated transcription factor, resulted in enhanced insulin secretion and protect from diet-induced glucose intolerance, suggesting that BMPs and ID1 normally exert inhibitory effects on adult beta cell function [17]. BMPs are released from and affect several metabolic relevant tissues, including fat, liver and kidney adding to the complexity of the role of BMPs in metabolism [14, 18, 19]. To characterize the direct effects of BMPs on beta cells we have recently reported BMP4

mediated inhibition of beta cell proliferation and repression of GSIS from mouse, rat and human islets [4]. Here, we further characterize the effects of BMP4 on insulin secretion by single cell electrophysiological measurements and evaluation of gene regulation to identify the molecular mechanism behind the observed inhibition of insulin secretion.

#### **Research Design and Methods**

#### Rat islet isolation and culture

Neonatal rat islets of Langerhans were isolated from 4-day-old Wistar rat pups (Taconic, Lille Skensved, Denmark) as previously described [20]. The isolated islets were precultured for 7-10 days in RPMI 1640 with ultraglutamine (Lonza, Vallensbaek, Denmark) supplemented with 10% newborn calf serum (NCS) (Biological Industries, Kibbutz Beit Haemek, Israel), 100 U/ml penicillin and 100 µg/ml streptomycin (Gibco, Life Technologies, Taastrup, Denmark), in 5% CO<sub>2</sub> at 37°C. For experimental setups, rat islets cultured as intact and free-floating in medium supplemented with 2% human serum (Lonza (BioWhittaker) or as islets dispersed into single cells by 0.2% trypsin (Gibco), 10 mmol/L EDTA (Gibco) in HBSS. Dispersed islets were cultured on coverslips coated with bovine corneal extracellular matrix (ECM), (Biological Industries, Kibbutz Beit, Haemek, Israel) in the medium described above containing 2% human serum.

#### Mouse islet isolation and culture

Pancreatic islets from 10-12 weeks old female NMRI mice where isolated using collagenase digestions as previously described [21]. The islets were handpicked in albumin-coated Petri dishes (1 mg albumin/ml HBSS) and cultured for 1 day in medium I (RPMI 1640 with 10 mmol/L glucose and 10% fetal calf serum, 100 IU/ml penicillin, and 100  $\mu$ g/ml streptomycin) and further 3 days in medium II (RPMI 1640 with 10 mM glucose and 2% fetal calf serum, 100 IU/ml penicillin, and 100  $\mu$ g/ml streptomycin) in the

absence or presence of BMP4 (50 ng/ml). After culture, mouse islets were fixated for transmission electron microscopy (TEM) or dispersed into single cells, using  $Ca^{2+}$ -free buffer, for electrophysiological experiments.

Pancreatic islets from 12-19 week old 129SV/C57/6crl WT and Calbindin1 KO mice [22] were isolated by bileduct perfusion of the pancreas with liberase (Roche, Hvidovre, Denmark). Digestion was stopped by addition of HBSS buffer containing  $Mg^{2+}$  and  $Ca^{2+}$  (Gibco) and 3 g/L BSA and 0.5 g/L D-glucose. Islets were filtered through a 400 µm pore size mesh, followed by 100 µm and 70 µm mesh strainers (BD Falcon, Albertslund, Denmark). Retained islets were handpicked under a dissection microscope. Islets were cultured for 1 day in medium I. The following day islets were transferred to medium II, in which they were kept throughout stimulation. Female mice were used for electrophysiological experiments and male mice for insulin secretion assays.

#### Microarray analysis

800 intact, free-floating rat islets were cultured in 5.5 cm Sterilin dishes for 5-10 days and exposed to BMP4 for 96 hrs. Total RNA was extracted using TRIzol (Gibco). One microgram of total RNA was labelled by One-Cycle Target labeling kit (Affymetrix, Santa Clara, Ca, USA) following the instructions of the manufacturer. Hybridization cocktails were hybridised to Rat Genome 230 2.0 GeneChip® arrays (Affymetrix) at 45°C for 17 hours (60 RPM) in a Hybridization Oven 640 (Affymetrix). GeneChips® were washed and stained in a GeneChip® fluidics station 450 using the fluidics protocol "EukGE-WS2v5\_450" (Affymetrix). Chips were scanned in a GeneChip® scanner 3000 (Affymetrix). Microarray data were normalized and gene expression measures derived using the RMA algorithm and the Bioconductor package "Affy" (http://www.bioconductor.org). Custom CDF (chip definition file) from brainarray.mbni.med.umich.edu was used. Qlucore Omics Explorer 3.0 (Qlucore AB, Sweden) was used for the statistical analysis of the normalized data. For comparing BMP4 to vehicle treatment, the microarray data were variance filtered  $(\sigma/\sigma(max)>0.1)$ , and the two groups compared (t-test, FDR=5% (Benjamini Hochberg correction for multiple testing)).

#### Analysis of Calbindin1 and Insulin1 mRNA expression by real-time qPCR

800 intact neonatal rat islets cultured for five days were exposed to 50 ng/ml BMP4 for the indicated time periods and total RNA extracted using TRIzol (LifeTechnologies). cDNA synthesis was performed by TaqMan Reverse Transcription Reagents (Applied Biosystems, CA, USA). TaqMan Gene Expression probes against rat *Calbindin1* (Rn00583140\_m1), *Insulin 1* (Rn02121433\_g1) and *Ppia* (Rn\_00690933\_m1) were from Applied Biosystems. The samples were run on ABI PRISM 7900 HT Taqman (Applied Biosystems). Each sample was run in duplicates or triplicates and expression was normalized to the internal control, *Ppia*.

#### Analysis of Calbindin1 protein expression by western blotting

1000 intact neonatal rat islets were cultured for 5-10 days prior to exposure to 50 ng/ml BMP4 for 24, 48, 72 or 96 hrs. SDS-PAGE and western blotting was performed as described previously [23]. Primary antibodies were rabbit anti-Calbindin1 (Cell Signaling Technology, AH Diagnostics, Aarhus, DK) and mouse-anti-β-actin ( Abcam, Cambridge, UK). Chemiluminiscense was detected by Lumi-GLO (Cell Signaling Technology) and visualized by use of Las 3000 (Fuji Film). Densitometric scannings were performed in Image J (Freeware, NIH, Bethesda, Maryland, USA).

#### Glucose stimulated insulin secretion

7-10 days after isolation, forty neonatal rat islets were transferred to medium containing 2% human serum, 100 IU/ml penicillin, and 100  $\mu$ g/ml streptomycin and stimulated with

50 ng/ml BMP4 for 0-96 hours. Mouse islets were stimulated the day after isolation. For each condition 20 islets were transferred to Krebs Ringer Hepes buffer (KRHB) (115 mmol/L NaCl, 4.7 mmol/L KCl,2.6 mmol/L CaCl<sub>2</sub>, 1.2 mmol/L KH<sub>2</sub>PO<sub>4</sub>, 1.2 mmol/L MgSO<sub>4</sub>, 10 mmol/L HEPES, 0.2% BSA, 2 mmol/L glutamine, 5 mmol/L NaHCO<sub>3</sub>, 1% P/S, pH 7.4), Containing 2 mmol/L glucose and incubated for 90 minutes prior to the GSIS experiment. Islets were sequentially exposed to 2 mmol/L glucose, 20 mmol/L glucose and 20 mmol/L glucose plus 10µmol/L forskolin (Sigma-Aldrich, Brøndby, Denmark) for 30 minutes and buffer was collected from each condition. Insulin content was determined using an in-house insulin Elisa assay. Results were corrected for DNA content using Quant-IT<sup>TM</sup> PicoGreen ® dsDNA Reagent and Kit (Invitrogen, Life Technologies).

#### Production of Calbindin1 lenti virus

Mouse Calbindin1 cDNA in entry vector pENTR(tm) 221 (Invitrogen) was transferred to the pLenti6.2/v5DEST Gateway® Vector (Invitrogen). Lenti virus was produced in HEK293ft cells using the ViraPower<sup>™</sup> Lenti viral Expression Systems (Invitrogen, Carlsbad, CA, USA) and lenti virus was harvested by ultra centrifugation. Titers were determined in HT1080 cells (Invitrogen). The virus was used at a MOI 5 for 6 hours.

#### Insulin release in single cells overexpressing Calbindin1 using lenti virus

Dispersed rat islet cells were cultured on coverslips coated with bovine corneal extracellular matrix (ECM) in 4 well containers for 4 days prior to transduction with Calbindin1 or GFP lenti virus for 6 hours at a MOI of 5. 96 hours after transduction, GSIS was evaluated as described above.

#### Electrophysiology

Capacitance measurements and ion-current measurements were performed on single beta cells in a mixture of dispersed islets cells using the patch-clamp technique as previously described [21]. Beta cells where identified by size and inactivation properties of the voltage dependent Na<sup>+</sup> channel [24, 25]. Exocytosis was evoked by a train of ten 500-ms depolarization from -70 mV to 0 mV with a frequency of 1Hz and measured as changes in membrane capacitance. The VDCC-currents to voltage relationship was determined by employing a protocol where the membrane was depolarized from -70 mV to between -40 mV to +40 mV for 50 ms.

#### Live calcium imaging

Islets were loaded with 4  $\mu$ M Fura 2-AM (TefLabs) for 40 minutes followed by 30 minutes de-esterification in imaging buffer at pH 7.4 (mM: KCl 3.6, MgSO<sub>4</sub> 0.5, CaCl<sub>2</sub> 2.5, NaCl 140, NaHCO<sub>3</sub>, NaH<sub>2</sub>PO<sub>3</sub> 0.5, HEPES 5). Imaging was performed with a Polychrome V monochromator (TILL Photonics, Graefeling, Germany) and a Nikon Eclipse Ti Microscope (Nikon, Tokyo, Japan) with a ER- BOB-100 trigger on an iXON3 camera and iQ2 (Andor Technology, Belfast, UK) software. Recording was performed at one frame per second at 37°C under perfusion 1ml/min. A region was marked around each islet and the light intensity was recoded in that region to get the integrated light intensity per unit area ( $\mu$ m<sup>2</sup>) at 340nm (exposure 150 ms) and 380 nm (exposure 100 ms). These measured intensities were then used to calculate the ratio of Fura-2 bound (340 nm) and unbound (380 nm) to calcium at one frame per second.

#### **Results:**

### BMP4 inhibits glucose stimulated insulin secretion

The effect of BMP4 on GSIS was investigated using neonatal rat islets. Pretreatment with 50 ng/ml BMP4 for 0-4 days resulted in a decrease in GSIS observed after 48 hours (Fig.

1a). Acute stimulation with BMP4 (0h) or pre-stimulation for up to 24 hours had no effect on insulin secretion. In addition doses as low as 2 ng/ml inhibits insulin secretion [4].
BMP4 stimulation had no effect on total islet insulin content (Fig. 1b) or *Ins1* mRNA levels (Fig. 1c). We did not observe any effect on the number, size or insulin granule proximity to the cell membrane using high resolution electron microscopy of adult mouse islets (Supplementary figure 1).

# BMP4 inhibits exocytosis and voltage dependent Ca<sup>2+</sup>-channel current

The fact that BMP4 inhibits GSIS without affecting total insulin content or total number of insulin granules, indicates that BMP4 may affect the secretory machinery. For further detailed electrophysiological analysis of insulin secretion we used dispersed primary mouse islet cells. We investigated exocytosis measured as an increase in membrane capacitance and found reduced depolarization-evoked increase in membrane capacitance in BMP4 treated primary mouse beta cells (Fig. 2a-e). The most pronounced effect was observed during the latter depolarizations (Depol 2-10; Fig 2d). This was further confirmed by a continued reduced exocytotic response to a second train of depolarizations performed 2 minutes later (Fig. 2e). Exocytosis is highly dependent on Ca<sup>2+</sup>-influx through voltagedependent Ca<sup>2+</sup>-channels (VDCC) [26]. We therefore determined the VDCC-influx to voltage relationship (Fig. 2f-g). Beta cells exposed to BMP4 show  $\sim$ 50% reduced Ca<sup>2+</sup>influx at 0 mV. BMP4 increased the Ca<sup>2+</sup>-sensitivity, i.e. the increase in membrane capacitance per Ca<sup>2+</sup>-charge unit entering the cell, which suggests that the BMP4dependent decrease in exocytosis is caused by a reduced  $Ca^{2+}$ -current rather than through a direct effect on exocytosis (Figure 2h). Moreover, BMP4 can be suggested to have a direct stimulatory effect on exocytosis that is less pronounced than the effect on the  $Ca^{2+}$ -current. To gain further insight into the mechanism on how BMP4 may cause reduced exocytosis we performed live calcium imaging in primary adult mouse islets. Evaluation of calcium

fluctuations was determined by differences in the Fura-2 340/380 ratio. Representative traces are shown in Figure 2i-j. All traces can be seen in supplementary Figure 1. Temporal fluctuation of intracellular calcium in response to glucose were organized into 2 classes: class 1 islets represent islets with separate  $1^{st}$  and  $2^{nd}$  phases with a clear  $1^{st}$  phase peak followed by a lowering of calcium and a  $2^{nd}$  phase with distinct regularly spaced calcium oscillations; class 2 islets present a rise in calcium with no clear first and second phases and no distinct oscillation in  $2^{nd}$  phase. In control islets we observed 64% and in BMP4 treated islets 26% to have a distinct  $1^{st}$  peak and  $2^{nd}$  phase oscillation in presence of high glucose (see Supplementary Table 1). In addition, there was a significant reduction in the first lowering of  $Ca^{2+}$  (Figure 2j and k) and the  $1^{st}$  phase peak amplitude at 16.7 mM glucose (Figure 2j and m) and the response to depolarizing K<sup>+</sup> (Figure 2j and o). The response time after increasing glucose concentrations was decreased by BMP4 treatment (Figure 2 j and 1) whereas the response time to lowering of glucose was increased (Figure 2n). We did not observe significant changes in the amplitude or frequency of calcium oscillations.

#### BMP4 mediates upregulation of Calbindin1

Since the effects of BMP4 on GSIS are first observed after 48 hours exposure, we hypothesize that gene regulation is required for this effect. To unravel the mechanism of BMP4 mediated inhibition of GSIS we therefore performed a gene expression array comparing 3 independent set of vehicle and BMP4 (96h) treated neonatal rat islets. With a false discovery rate (FDR) of 5%, we find 102 genes to be regulated by BMP4 (Supplementary Table 2). The genes with more than 2-fold up- or downregulation are shown in Table 1. Seven of the gene regulations have been verified on independent rat islet samples (denoted with a \* in Table 1).

We paid particular attention to genes known to be involved in hormone secretion and  $Ca^{2+}$ -handling based on the effects of BMP4 on insulin secretion, exocytosis and  $Ca^{2+}$ -channel

activity. We observed no regulation of the BMP receptors or L-type calcium channel subunits. One of the most regulated genes is Calbindin1, an EF-hand  $Ca^{2+}$ -binding protein which has previously been shown to regulate  $Ca^{2+}$ -currents through VDCC and inhibit GSIS in beta cells [27-29]. BMP4 increased the expression of Calbindin1 mRNA 6-fold in neonatal rat islets resulting in a 2.5 fold increase in Calbindin1 protein level after 96 hours (Figure 3a and b) As in primary neonatal rat islets, BMP4 increased the expression of Calbindin1 mRNA in adult mouse islets (Figure 3c).

#### Overexpression of Calbindin1 impairs GSIS

To determine the role of Calbindin1 in the BMP4 mediated effect on GSIS we induced overexpression of Calbindin1 in dispersed neonatal rat islet cells. Overexpression of Calbindin1 significantly reduced GSIS (Fig. 4a). Transfection efficiency was more than 80%, resulting in a robust upregulation of Calbindin1 protein (Fig. 4b).

#### BMP4 inhibition of GSIS and exocytosis is dependent on Calbindin1 upregulation

We further investigated the effect of BMP4 on GSIS from pancreatic islets isolated from Calbindin1 knock out (KO) mice and wild type (WT) littermates. Like in neonatal rat islets, we observed significant inhibition of GSIS by BMP4 treatment in WT adult mouse islets (Fig. 4c), whereas no inhibition was observed in islets from Calbindin KO mice (Fig. 4c). In accordance with this, we find that BMP4 does not reduce exocytosis in islets from Calbindin1 KO mice, but rather showed a non-significant increase in exocytosis (Fig. 4df).

#### **Discussion:**

Here we investigate the mechanism behind BMP4 mediated inhibition of GSIS in neonatal rat and adult mouse islets of Langerhans. This effect is not caused by decreased *Insulin1* 

mRNA expression or protein content, or by number, size or localization of insulin granules, but rather seems to be due to diminished Ca<sup>2+</sup>-influx through VDCC resulting in decreased exocytosis. Metabolism of glucose increase intracellular ATP levels resulting in closure of ATP dependent K<sup>+</sup> channels and membrane depolarization. Consequential opening of VDCC trigger Ca<sup>2+</sup>-entry which elicits insulin exocytosis (reviewed in [30, 31]). Hence,  $Ca^{2+}$ -entry is essential for the amount of insulin released. We observe a BMP4 dependent decrease in VDCC Ca<sup>2+</sup>-current leading to a reduction in depolarisation induced exocytosis and GSIS. Ca<sup>2+</sup>-sensitivity of exocytosis was not decreased, rather increased, indicating that the reduced  $Ca^{2+}$  current is the main determinant of the reduced exocytosis. The reduced  $Ca^{2+}$ -influx was also confirmed by lack of response to K<sup>+</sup> in live Ca<sup>2+</sup>-measurements. Both observations are indicative of reduced depolarization evoked Ca<sup>2+</sup> -influx or increased Ca<sup>2+</sup>-buffering after BMP4 treatment. An increased buffering would agree with the continued and more pronounced reduction in late exocytosis evoked by the latter depolarizations and the second train (Figure 2d-e). Interestingly, our microarray analysis identified the  $Ca^{2+}$ -binding protein Calbindin1 to be upregulated by BMP4. We refind this regulation on independent samples and in mouse islets. Although neonatal and adult islets have been suggested to respond different to glucose and other stimuli, BMP4 inhibit GSIS and upregulate Calbindin1 in both model systems. Overexpression of Calbindin1 reduced GSIS. The effect of BMP4 on GSIS was lost in islets from Calbindin1 KO mice (Fig. 4c). The exocytotic response to BMP4 in wild type islets showed the same trend as previously observed (Fig 4d and 2a-e), whereas this regulation was lost in islets from KO mice. There was a trend towards an increased exocytosis in response to BMP4 in the Calbindin1 KO mice, but this was not significant neither was it reflected in the GSIS. The observation that BMP induced inhibition of GSIS is not observed in islets from Calbindin1 KO mice points to the increased Calbindin1 expression being causative to the observed BMP4 mediated decline in GSIS. Indeed, the

BMP4 induced decrease in VDCC-influx is remarkably similar to the effect observed upon overexpression of Calbindin1 in a pancreatic beta cell line (Figure 2b-h and [29]). In addition to a  $Ca^{2+}$ -scavenging effect, accumulating evidence suggests that Calbindin1 reduce  $Ca^{2+}$ -currents through an association to L-type VDDCs [29]. A glucose and  $Ca^{2+}$ dependent translocation of Calbindin1 to the plasma membrane has previously been suggested to facilitate the interaction with the L-type  $Ca^{2+}$ -channel [28, 29]. This could explain the lack of effect on the capacitance increase evoked by the first depolarisation (Figure 2c and 4e), as the first influx of  $Ca^{2+}$  would induce translocation of Calbindin1 to the plasma membrane.

Glucose induced  $Ca^{2+}$ -oscillations occur in fewer BMP4 treated islets compared to control cells possibly due to reduced  $Ca^{2+}$ -influx through VDCC. This is further supported by the blunted  $Ca^{2+}$  -response to high glucose and depolarizing K<sup>+</sup> after BMP4 treatment (Fig. 3io and Supplementary Table 1). The lack of K<sup>+</sup>-induced  $Ca^{2+}$ -influx was also observed in a Calbindin1 overexpressing cell line, indicating that this is an effect caused by the increased Calbindin1 expression [27, 29]. Finally, the oscillations persist longer in BMP4 treated islets when glucose is lowered back to 2.8 mM (Figure 2n and Supplementary Table 1), indicating a failure of the beta cells to repolarize to baseline; again suggesting dysfunctional  $Ca^{2+}$  handling after BMP4 treatment.

Interestingly, Calbindin1 expression is increased in pancreatic islets from diabetic rats and mice [32, 33]. Concomitant upregulation of BMP2 (but not BMP4) and Calbindin1 in islets of Langerhans has been observed in a type 2 diabetic mouse model [33]. BMP2 also upregulate the expression of Calbindin1 and reduce GSIS in rat islets (data not shown). Generally BMP2 and 4 may be considered as inflammatory markers in several metabolic tissues. Under diabetic conditions the expression of BMP2 or 4 have been reported to increase in arteries, kidney, bones and islets [4, 14, 18, 19]. The increased expression is reflected by increased circulating levels of BMP4 in type 2 diabetic patients in one study

[13]. Thus, systemic inhibition of BMP2 and 4 appear as a possible strategy for broad targeting of a mediator of low grade inflammation associated with type 2 diabetes. Interestingly, it was recently reported that systemic administration of the natural BMP inhibitor noggin lowered blood glucose in db/db mice [14].

In conclusion, we have provided insight into mechanisms involved in BMP4 mediated inhibition of insulin secretion and gene regulation in islets of Langerhans and identified Calbindin1 as a mediator of BMP4 induced beta cell dysfunction.

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#### **Dualty of interest:**

MLBJ, CB and KSF are employees of Novo Nordisk A/S.

#### **Contribution statement:**

NB, GLC, MLBJ, CB and LE designed the study. GLC, MLBJ, AW, IM, JF, KSF, MM, CB, NB and LE participated in acquisition, analysis and interpretation of data. GLC, NB and LE

drafted the manuscript. GLC, MLBJ, AW, IM, JF, KSF, MM, CB, NB and LE revised the

manuscript critically for important intellectual content and approved the final version to be

published. NB is the guarantor of this work.

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#### Figure legends.

# Figure 1 BMP4 inhibits glucose stimulated insulin secretion without affecting total insulin content.

a) Neonatal rat islets were pre-exposed to 50 ng/ml BMP4 for 0-96 hours and GSIS was performed as described. b) Insulin content of islets post-assay. DNA content was used for normalization in a) and b). c) 8000 intact neonatal rat islets were exposed to 50 ng/ml BMP4 for 0-96 hours. *Ins1* mRNA expression is shown as relative values normalized against *Ppia* expression. All data are shown as mean +SEM. Statistical significance was evaluated using Anova followed by Dunnets t-test. \* indicates p<0.05

# Figure 2 BMP4 diminish capacitance and Ca<sup>2+</sup> influx through voltage dependent Ca<sup>2+</sup> channels

a) Example trace of depolarization-induced exocytosis, measured as changes in cell membrane capacitance ( $\Delta C_m$ ) in a single mouse beta cell. b) Mean increase in membrane capacitance evoked by a train of ten depolarizations, c) the first depolarization and d) depolarizations 2 to 10. e) Mean capacitance increase evoked by a second train applied 2 minutes later. f) Example trace from a VDCC in a beta cell incubated in the absence (grey) and presence of BMP4 (black). g) The measured charge (Q) as a function of the membrane voltage ( $V_m$ ) during a 50 ms depolarization. Open squares; Ctrl cells, Black squares; BMP4 treated cells. h) The Ca<sup>2+</sup>-sensitivity of the exocytotic response measured as the capacitance increase during the first depolarization of the train ( $\Delta C_m$ ) in c) divided by the Ca<sup>2+</sup>-influx (Charge; Q) during the same 500 ms-depolarization. Data presented in b-e and g-h are mean ± SEM of n=9 to 16 experiments in each group. \*p<0.05, \*\*p<0.01. i) Representative example of a calcium trace obtained from one islet pre-treated for 3 days with vehicle (control) or j) BMP4. C<sub>0</sub> - calcium dip occurring when 16.7 mM glucose reach the islets; **D**<sub>0</sub> - time delay between 16.7 mM glucose exposure and the first calcium peak; C<sub>1</sub> - amplitude of first phase peak; **D**<sub>1</sub> - time delay in response to low glucose; C<sub>K</sub> - amplitude of high potassium peak. The staircase indicates the glucose concentration: 2.8 mmol/L glucose (2.8) and 16.7 mmol/L glucose (16.7). The line with  $K^+$  indicate the addition of 70 mmol/L KCl. Summary statistics of calcium imaging traces shown in k) C<sub>0</sub>, l) D<sub>0</sub>, m)C<sub>1</sub>, n) D<sub>1</sub> o) C<sub>K</sub>

#### Figure 3 BMP4 stimulate the expression of Calbindin1

Islets were stimulated with 50 ng/ml BMP4 for 0-96 hours. a) Calbindin1 mRNA expression in neonatal rat islets is shown in relative values and normalized against the expression on *Ppia*. b) Protein expression in neonatal rat islets was determined by western blotting using primary antibodies against Calbindin1 and  $\beta$ -actin. A representative western blot is shown and quantification of densitometry of 3 blots was performed in image J. c) Isolated mouse islets were stimulated with 50 ng/ml BMP4 for 0-96 hours. *Calbindin1* mRNA expression is shown in relative amounts and normalized against the expression of *Ppia*. All data are presented as mean + SEM. n=3-4

#### Figure 4 Calbindin1 expression affects islet glucose and BMP4 responsiveness.

a) GSIS from dispersed neonatal rat islet cells overexpressing Calbindin1 or GFP. Insulin secretion is depicted as % of control cells exposed to high glucose. b) Western blot showing lentiviral overexpression of Calbindin1. c) Islets from Calbindin1 KO mice (KO) and littermate wild type controls (WT) were exposed to 50 ng/ml BMP4 for 96 hours and subsequently GSIS was determined, n=3. All data are presented as mean+SEM. d) Mean increase in membrane capacitance evoked by the full train, e) the first depolarization and f) 2-10th depolarizations in single mouse beta cells isolated from Calbindin1 KO mice (KO) and littermate wild type controls (WT).



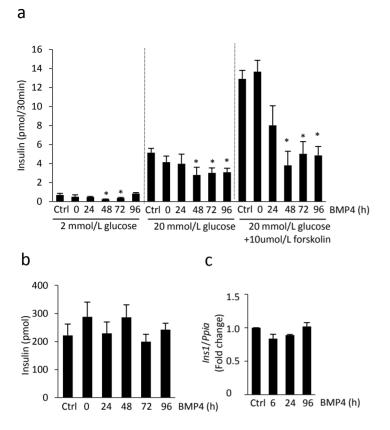


Figure 2

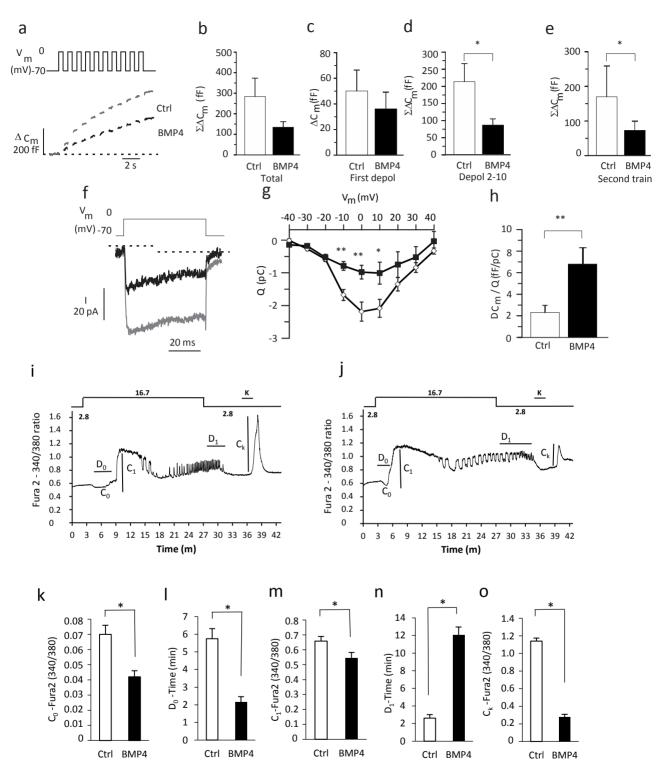


Figure 3

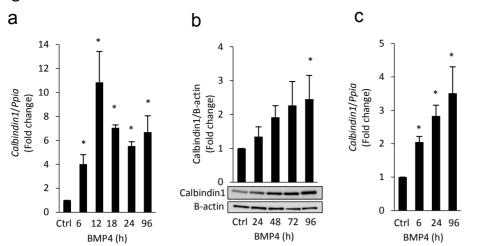
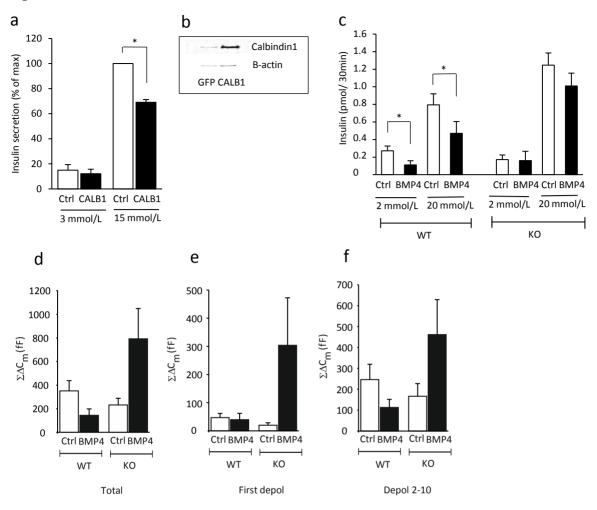


Figure 4



# Table 1

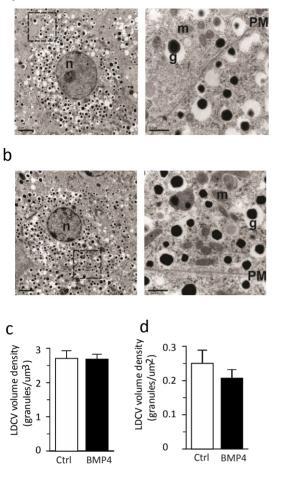
Genes regulated  $\geq$  2-fold in neonatal rat islets exposed to 50 ng/ml BMP-4 for 96 hrs.

		Fold
Gene	Protein name	change
Id3	DNA-binding protein inhibitor ID-3	17.92*
Id I	DNA-binding protein inhibitor ID-1	16.52*
Lypd8	Ly6/PLAUR domain containing protein 8 precursor	9.66
Irx-3	Iroquois-class homeodomain protein IRX-3	5.40
Calb1	Calbindin 1	4.62*
Id2	DNA-binding protein inhibitor ID-2	4.25*
Micalcl	MICAL C-terminal-like protein	4.06
Fam101a	Family with sequence similarity 101. member A (Fam101a)	3.85
Lgals4	Galectin-4	3.72
Bambi	BMP and activin membrane-bound inhibitor homolog	3.25*
Atoh8	Protein atonal homolog 8	3.13
Arc	Activity-regulated cytoskeleton-associated protein	3.08
Mlph	Melanophilin	2.90
Camklg	Calcium/calmodulin-dependent protein kinase type 1G	2.82
Chst10	Carbohydrate sulfotransferase 10	2.81
Dlk1	Protein delta homolog 1	2.75
Тррр3	Tubulin polymerization-promoting protein family member 3	2.72
Tmem100	Transmembrane protein 100	2.68
Ckb	Creatine kinase B-type	2.63
Ppp1r36	Protein phosphatase 1 regulatory subunit 36	2.59
Tmem100	Transmembrane protein 100	2.51
Rtn4rl1	Reticulon-4 receptor-like 1	2.44
St5	Suppression of tumorigenicity 5 protein	2.34
Akap12	A-kinase anchor protein 12	2.30
Vash2	Vasohibin-2	2.20
Ddx31	Probable ATP-dependent RNA helicase DDX31	2.07
Fads I	Fatty acid desaturase 1	0.45
Nod3l	NOD3-like protein	0.44
Bmp3	Bone morphogenetic protein 3	0.43*
Htr5b	5-hydroxytryptamine (serotonin) receptor 5B	0.33
Gpr6	G protein-coupled receptor 6	0.28*

\* Regulation have been verified by q-pcr on independent neonatal rat islet samples

# Supplementary Figure 1

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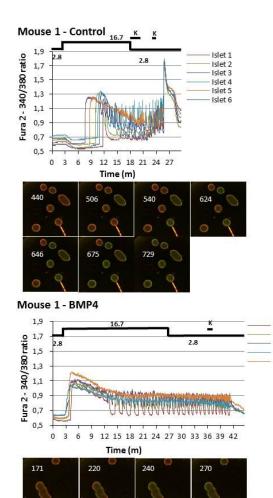


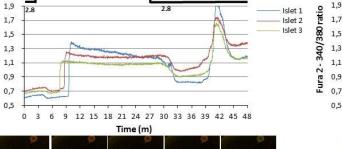
Supplementary figure 1 BMP4 does not affect the ultrastructure of mouse beta cells

a Transmission electron micrograph of a single beta cell within an islet that has been cultured in the absence of BMP4 (left: scale bar 2 um). The area within the square is highlighted to the right (scale bar 0.5 µm). PM-plasma membrane; g-granule; m-mitochondria; nnucleus. b As in a, but showing a single beta cell within an islet that have been cultured for 3 days in the presence of 50 ng/ml BMP4. C Histogram summarizing the total number of granules within beta cells after the different culture conditions presented as the volume density (granules/µm<sup>3</sup>). d Histogram summarizing the number of docked granules within beta cells after the different culture conditions presented as the surface density  $(granules/\mu m^2)$ . Granules were considered docked if the center of the granule was < 200 nm from the plasma membrane. Data in c and d is presented as mean + SEM of n=30 (Ctrl) and 32 (BMP4) treated cells.

#### Method: Transmission electron microscopy

Mouse islets where fixed in 2.5% glutaraldehyde in freshly prepared Millonig and post-fixed in 1% osmium tetroxide before being dehydrated and embedded in AGAR 100 (Oxford Instruments Nordiska AB) and cut into ultrathin sections (70-90 nm). The sections were put on Cu-grids and contrasted using uranyl acetate and lead citrate. The islet containing sections were examined in a JEM 1230 electron microscope (JEOL-USA. Inc.). Micrographs were analysed with respect to the intracellular distribution as described elsewhere in as described elsewhere in Olofsson CS, et al 2002: Fast insulin secretion reflects exocytosis of docked granules in mouse pancreatic B-cells. Pflügers Arch 444:43-51"



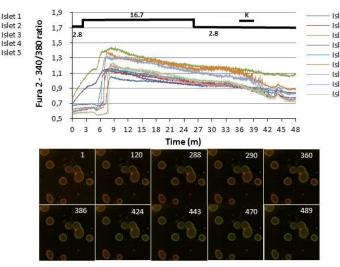




Mouse 2 - BMP4

Mouse 2 - Control

Fura 2 - 340/380 ratio



Mouse 3 - BMP4

453

Mouse 3 - Control

0 3 6

16.

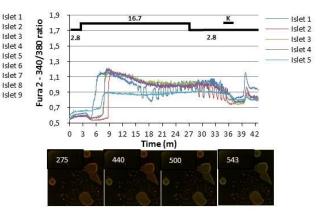
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9 12 15 18 21 24 27 30 33 36 39 42

592

Time (m)



Islet 1

Islet 2

#### Figure 2

Traces of all islets imaged for each NMRI mouse under control or BMP4 conditioning. Below each trace are selected snapshots showing the relative position of the islets and the moment at which the first response to 16.7mM glucose can be visualized at 340nm (frame identified by number on image: 1 frame per second; 60 frames = 1 min). The position of each change in buffer perfusion: 2.8mM glucose (2.8), 16.7mM glucose (16.7), and 2.8mM glucose in 70mM KCl buffer (2.8 + K) are indicated by arrows above each set of traces.

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Condition	Ctrl	BMP4	Ctrl	BMP4	Ctrl	BMP4	Ctrl	BMP4	Ctrl	BMP4	Ctrl	BMP4	Ctrl	BMP4	Ctrl	BMP4	Ctrl	BMP4
Number of islets	11	19	7	5	4	14	11	19	7	5	4	14	11	19	7	5	4	14
Mean	0.070	0.042	0.077	0.059	0.058	0.037	5.745	2.149	6.552	1.560	4.333	2.360	0.658	0.547	0.692	0.570	0.598	0.539
SEM	0.006	0.004	0.008	0.008	0.005	0.004	0.571	0.315	0.706	0.801	0.447	0.321	0.031	0.035	0.023	0.028	0.072	0.047
p-value	<b>5.63E-04</b> 0.15		15	1.50E-02		1.78E-06		9.19E-04		8.05E-03		4.39E-02		7.04E-03		0.56		

	F	Ч	Рм							PA				
Parameter	(peak	s/min)		(F	Fura2 34	0/380 rati	0)	(Fura2 340/380 ratio)						
Islet Class	Cla	ss 1	A	All		Class 1		Class 2		Class 1		Class 2		
Condition	Ctrl	BMP4	Ctrl	BMP4	Ctrl	BMP4	Ctrl	BMP4	Ctrl	BMP4	Ctrl	BMP4		
Number of islets	7	5	11	19	7	5	4	14	7	5	4	14		
Mean	1.357	0.940	0.962	0.997	0.884	0.892	1.100	1.035	0.168	0.126	0.030	0.031		
SEM	0.248	0.234	0.046	0.029	0.032	0.033	0.079	0.033	0.019	0.027	0.002	0.002		
p-value	0.27		0.51		0.87		0.39		0.22		0.84			

				<b>D</b> 1		Ск						
Parameter			(m	in) #				(Fi	ura2 340	/380 rat	io)	
Islet Class	A	11	Cla	ss 1	Cla	ass 2	A	.11	Class 1		Class 2	
Condition	Ctrl	Ctrl BMP4		BMP4	Ctrl	BMP4	Ctrl	BMP4	Ctrl	BMP4	Ctrl	BMP4
Number of islets	5	14	1	2	4	12	11	19	7	5	4	14
Mean	2.610	12.077	3.200	7.134	2.463	12.900	1.140	0.279	1.145	0.381	1.132	0.242
SEM	0.402	0.885	na	0.264	0.746	0.941	0.035	0.031	0.021	0.062	0.098	0.031
p-value	6.02E-05		na		5.90E-05		8.03E-17		1.09E-07		2.97E-09	

### Supplementary Table 1 – Summary statistics of calcium imaging traces

Temporal fluctuation of intracellular calcium response to 16.7mM glucose were organized into 2 classes: class 1 islets present separate  $1^{st}$  and  $2^{nd}$  phases with a clear  $1^{st}$  phase peak followed by a lowering of calcium and a  $2^{nd}$  phase with distinct regularly spaced calcium oscillations; class 2 islets present a rise in calcium with no clear first and second phases and no distinct oscillation in  $2^{nd}$  phase. Evaluation of calcium fluctuations was made by measuring differences in Fura-2 340/380 ration points.

Calcium was measured in a total of 30 islets from 2-3 mice: 11control and 19 BPM4 treated islets. In control islets we observed 7/11 class islets (64%) and in BMP4 treated islets we observed 5/19 class 1 islets (26%). This reduction in the number of class 1 islets may represent a loss of first phase insulin secretion in the BMP4 treated islets.

 $C_0$  - calcium dip occurring when 16.7 mM glucose reach the islets and before 1<sup>st</sup> phase peak;  $D_0$  - time delay between the moment 16.7 mM glucose reached the islet and the first calcium peak;  $C_1$  - amplitude of first phase peak response to 16.7 mM glucose;  $F_H$  - frequency of 2<sup>nd</sup> phase oscillations (in category 1 islets);  $P_M$  - mean ratio of oscillations during 2<sup>nd</sup> phase;  $P_A$  - mean amplitude of oscillations during 2<sup>nd</sup> phase;  $D_1$  - time delay in response to low glucose;  $C_K$  - amplitude of high potassium peak.

## Supplementary table 2. Genes regulated by 96h treatment with 50 ng/ml BMP4 (FDR<5%)

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Bissimologoocces         Wits Just         Parties writes horizing softma 1 [Source Rinking partitic Acc PP 355401]         OU0128         I           Bissimologoocces         Apt 2         Partial software shows in the 2 Source Rinking partitic Acc PP 255401]         OU011301         O		LOC498368			1,62
InSIGN000000000000000000000000000000000000					1,62
PRSNB000000000000000000000000000000000000					1,61
HISHNO000000000000000000000000000000000000					1,59
DRSND00000000000000000000000000000000000					1,56 1,56
DISBND000000000000000000000000000000000000					1,55
DISBND000000000000000000000000000000000000					1,55
eNSH00000002002         Ten/20         Tanomerikan protein IOA/C         0,00078         1           ENSN00000000721, al.         Gaim         Altos 1-guinzanza [Gource Lin/ProtRA/Suiss-ProtAcc.08403]         0,00013         1           ENSN00000000721, al.         Gaim         Altos 1-guinzanza [Gource Lin/ProtRA/Suiss-ProtAcc.08403]         0,00013         1           ENSN00000000128, al.         INSN         Team Protein ST. Montal, [Gource Lin/ProtRA/Suiss-ProtAcc.08403]         0,00013         0,00013           ENSN0000000128, al.         INSN         Team Protein ST. Montal, [Gource Lin/ProtRA/Suiss-ProtAcc.08403]         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064         0,00064					1,52
INSEND0000000191         Tenen TAb         Tenen Poten 170A         0.0198         1           INSEND00000001222.at         Galm         Allos 1 exploressa [Success University]/sixes/PotAcc.068460]         0.0013         1           INSEND000000012583.at         Smad 7         Mohers against decapentagies; honolog 7 [Sucress University]/sixes/PotAcc.068460]         0.00017         1           INSEND000000012583.at         MoteSa         membrane-spanning 4-domains, subfamily A member AB. [Sucres Refseg pedia/Acc.NP 00110580]         0.00057           INSEND000000012577.at         R00311805         samilar to RERA ONA 240010015 (Fold)311803, mAN. [Sucres Refseg pedia/Acc.NP 00112530]         0.000581           INSEND0000001557.at         Lant         Lant         Exploression Diversion Diversio	ENSRNOG0000036692_at	Gcgr	Glucagon receptor [Source:UniProtKB/Swiss-Prot;Acc:P30082]	0,002636	1,50
ENSIND 60000000202, at BNSN050000002383, at         Gaim         Adots 1-ppinzes [Source UniversitAl/Souis-Prod_Acc.0806]         0.00178         1           ENSIND 60000002383, at         MotaBa         mintafageliar transport protein 57 homoling. [Source UniversitAl/Souis-Prod_Acc.0806]         0.000178         1           ENSIND 60000002383, at         MotaBa         member apainting 4-portains. Submit/n A mother AL Source Enfortes peritube/Acc.NP (0110189]         0.000187         1           ENSIND 60000002386, at         Rash Ba         Ras association domain- containing protein 5 [Source UniversitAl/Souis-Prod_Acc.NP (0110189]         0.000187         1           ENSIND 60000001591, at         Sarc13         safk-related (at [string 11110/string string related (at [string 11110/string string related (at [string 11110/string related (at [string 111110/string related (at [string 11110/string related (at [string 11					1,50
INSHI00000000000000000000000000000000000					1,49
INSHR00000000398_at         Misbala         mitraflage/air range/origination protein 37 homolog         Bource MeRes peptide/cc:Pk 001098]         0,00176           INSRN00000002038_at         Misbala         Reas association domain-containing protein 6 [Source UniProtKIS/Waiss ProtAcc/MQ 001095]         0,00006         1           INSRN0000000039_at         Sauralia         Station domain-containing protein 3 [Source MeRes peptide/cc:Pk 0010530]         0,00006         1           INSRN00000000109_at         Sauralia         Station domain-containing protein 3 [Source MeRes peptide/cc:Pk 0010530]         0,00006         1           INSRN00000000109_at         Sauralia         Station domain-containing protein 3 [Source MeRes peptide/cc:Pk 0010530]         0,00006         1           INSRN000000001053_at         Lancil         Lancil kee protein 1 [Source MeRes peptide/cc:Pk 00101530]         0,00007         1           INSRN000000001032_at         Ge:         Gittamate-crystene ligate catalysis should. Source MeRes peptide/cc:Pk 00110200]         0,00007         1           INSRN00000000000132_at         Sauralia         Approtis regulatory protein Sin [Source MeRes peptide/cc:Pk 00110200]         0,00007         1           INSRN00000000000132_at         Sauralia         Approtis regulatory protein Sin [Source MeRes peptide/cc:Pk 00110200]         0,000000         1           INSRN00000000000000000000000000000000000					1,49 1,47
InstRes         Medda         membrane-spanning 4-domains, subfamily A, member R4: [Source:R4:R459:pptick.cx:P, 00110198]         0.000367           DISKING000000208         stafie         R5:R5:R5:R5:R5:R5:R5:R5:R5:R5:R5:R5:R5:R					1,47
INSNE000000286         Rasoff         Bits association domain-containing protein 6 [Source:LUPPORKJ/Wsis ProtAcc:Q40882]         0.002048         1           INSNE00000001397         AT         Troncol         Unamer tanker: Adv20010015 (R0113180), mRAH Spource:Refees puptideAccNP, 0.0129329)         0.00064         1           INSNE0000000109, at         Start31         StArtPretate [upid transmemtrare and colled-coll domain-containing protein 3 [Source:Refees puptideAccNP, 0.0129329]         0.001675           INSNE00000001557, at         Len1L         LunCile protein 1 [Source:LuPirotAK]/Swiss-ProtAccP19489]         0.000674           INSNE000000001582, at         Adamt515         Adiatingra and metallogrotelaxase With Introbuspondin monts 15 [Source:Refers puptideAccNP.00110289]         0.000674           INSNE000000002776, at         Fam92a1         Uncharacterized protein [Source:UniProtKS/Wsis-ProtAccP19488]         0.000627           INSNE000000027767, at         Sca8a5         Sodium:-coupled nextra1 amina acid transporter 5 [Source:UniProtKS/Wsis-ProtAccP1942AC/VSI]         0.00055         C           INSNE000000002778, at         Kr88         Kr881, [Source:UniProtKS/Wsis-ProtAccP102C/VSI]         0.000249         C           INSNE00000002776, at         Kr881         Kr881, [Source:UniProtKS/Wsis-ProtAccP102C/VSI]         0.00025         C           INSNE00000002776, at         Kr881         Kr881, [Source:UniProtKS/Wsis-ProtAccP102C/VSI]					1,45
INNEROGO000019346.jt         Traca3         transmethane and colled-coll domain-containing protein 3 [Source-Refse peptide/ac.NP.00112939]         0,000484         1           INNEROGO0000000.gt         Star13         Star13         Star14         Outpace         0,000483         1           INNEROGO00000553, at         Len11         Lan11         Lan11         Lan11         Decre UniProtKM/Swiss-Prot_Acc.P3968]         0,000249         1           INNEROGO00000582, at         Admits15         A diointegrina and metalloproteinase with thrombospond motifs 15         SparzeRefse peptide/acc.NP_00110280]         0,000249         1           INNEROGO000020757, at         Fam231         Uncharacterized protein [Source-UniProtKM/Swiss-Prot_Acc.P39692]         0,000121         0         0         0,00027         0,000121         0         0         0,00027         0,000123         0,000123         0,000123         0,000123         0,000123         0,000123         0,000124         0,000124         0,000124         0,000124         0,000124         0,000124         0,000124         0,000124         0,000124         0,000124         0,000124         0,000124         0,000124         0,000124         0,000124         0,000124         0,000124         0,000124         0,000124         0,000124         0,000124         0,000124         0,000124 <t< td=""><td></td><td></td><td></td><td></td><td>1,44</td></t<>					1,44
INNEROCOCOUNCESS, at         Pilp         Plannolpin [Source-IndPracK-P3782]         0.001675           INNEROCOCOUNCESS, at         Lanc1         Lanc1 (Lanc-Vile protein 1. [Source-IndPracK-P3782]         0.00226         D           INNEROCOCOUNCESS, at         Cdc         Gittamate-cyteine ligasc cata/utic submit [Source-IndPracK-P3787]         0.00226         D           INNEROCOCOUNCESS, at         Admits15         Admits16         Admits17         Admits16         Admits17	ENSRNOG0000012597_at	RGD1311805	similar to RIKEN cDNA 2400010D15 (RGD1311805), mRNA [Source:RefSeq DNA;Acc:NM_001009638]	0,000061	1,41
ENSING00000005658, at         Incl 1         Incl 1: Enc 1:					1,41
INNEROG000001357, at         Lanctli         Lanctlie protein 1 [Source UnProtA(X/swis-ProtAcc:020X89]         0.002269           INNEROG000000582, at         Golt         Ottimate-crystele ligase cativity souni [Source-UnProtA(X)/swis-ProtAcc:029X89]         0.000270           INNEROG000000582, at         Adamt51         Adjintegrin and metaloproteinase with thrombospondin motifs 15 [Source-UnProtA(X)/swis-ProtAcc:029X87]         0.000270           INNEROG000002854, at         Svia1         Apoptosis regulatory proteins is Na [Source-UnProtA(X)/swis-ProtAcc:21X77]         0.000155           INNEROG000002757, at         Sic38a5         Soulins-couple dentral annio acid transporter 5 [Source-UnProtA(X)/swis-ProtAcc:21X77]         0.000155           INNEROG0000002757, at         Artago A         Net arenti, type 11 (source-UnProtA(X)/swis-ProtAcc:01078]         0.000297           INNEROG000002057, at         Artago A         Net arenti, type 11 (source-UnProtA(X)/swis-ProtAcc:01072]         0.000320           INNEROG000002058, at         Net and type 11 (source-UnProtA(X)/swis-ProtAcc:01078]         0.000278         0.000235           INNEROG000002058, at         Net avuelenbindrin 2 (source-UnProtA(X)/swis-ProtAcc:01027]         0.000320         0.000235           INNEROG000002058, at         Net avuelenbindrin 2 (source-UnProtA(X)/swis-ProtAcc:01020]         0.000256         0.000278           INNEROG0000002058, at         Temmo Transmeriane protein 12 (Source					1,41
INSNEQ0000006302, #         Gdc         Glutamate-cystene ligase catalytic subant [Source:UniProtRK]/WskProtAcc:P3468]         0.000674           INSNEQ0000006392, #         Admints for anterlatorytenesis with thrombogonal months 15. [Source:Refees peptide/acc:NP_00100280]         0.001249           INSNEQ0000006392, #         FamSa1         Uncharacterized protein [Source:UniProtRK]/WskProtAcc:P32692]         0.001111         0.000527           INSNEQ0000002776, #         SIC385         Soduru-cupled neutral anino add transporter [Source:UniProtRK]/WskProtAcc:P3207         0.000238         0.001237           INSNEQ0000002776, #         SIC385         Soduru-cupled neutral anino add transporter [Source:UniProtRK]/WskProtAcc:P3207         0.000126           INSNEQ0000002978, #         Nrta         Keratin, bpcl I cytoskeltal [Source:UniProtRK]/WskProtAcc:P31071         0.000126           INSNEQ0000002095, #         Nrtag224         Not GPase-actin/ErotRK]/WskProtAcc:P31071         0.000247           INSNEQ0000002095, #         Nrtag224         Nucleabidine: 2 [Source:UniProtRK]/WskP-ProtAcc:P31071         0.000256           INSNEQ0000002095, #         Nrtag224         Nucleabidine: 2 [Source:UniProtRK]/NskP-ProtAcc:P31071         0.000256           INSNEQ0000020205, #         Nrtag22         Nucleabidine: 2 [Source:UniProtRK]/NskP-ProtAcc:P31071         0.000256           INSNEQ0000002058, #         Nrtag22         Nucleabididididididididididi					1,39
INSNEQCO00000892         Adamts15         A datategin and metallopoteniase with thrombospondin motifs [S Jource: Refesp patide,Acc.NP_001100280]         0.001249           INSNEQCO000028560, at         Sinal         Appotosis regulatory protein Siva [Source:UniProtRS/Wiss-ProtAcc.A2VCVS]         0.001251           INSNEQCO00002757, at         Sicalas         Sodum: coupled metral anima cali transporter 5 [Source:UniProtRS/Wiss-ProtAcc.P2VCVS]         0.000105           INSNEQCO000020757, at         Sicalas         Sodum: couple metral anima cali transporter 5 [Source:UniProtRS/Wiss-ProtAcc.P2177]         0.000105           INSNEQCO0000202057, at         Krafts         Kerain, type I protein 24 [Source:UniProtRS/Wiss-ProtAcc:Q3U27]         0.00032           INSNEQCO000002026, at         Atlgs224         Rho GTPace-activating protein 24 [Source:UniProtRS/Wiss-ProtAcc:Q3U27]         0.00032           INSNEQCO000002056, at         Anlgs224         Rho GTPace-activating protein 24 [Source:UniProtRS/Wiss-ProtAcc:Q3U27]         0.000312           INSNEQCO000021454         Anlgs224         Nucleobandm: 2 [Source:UniProtRS/Wiss-ProtAcc:Q3U82]         0.000356           INSNEQCO000021454         Anlgs22         Nucleobandm: 2 [Source:UniProtRS/Wiss-ProtAcc:Q3U82]         0.000356           INSNEQCO000021559, at         Tubb3         Tubbi Returner UniProtRS/Wiss-ProtAcc:Q3U82]         0.000356           INSNEQCO0000017209, at         Tubba         Tubba Returne					1,38 1,37
INSNEQ00000016338         f=m82a1         Uncharacterized protein [Source:UniProtKR/Swiss-ProtAcc:P569]         0.000627           INSNEQ0000002767.jt         St2385         Sodium-coupled neutral amino acid transporter 5 [Source:UniProtKR/Swiss-ProtAcc:P569]         0.00156           INSNEQ0000002776.jt         Track3         Neuromelink-receptor [Source:UniProtKR/Swiss-ProtAcc:P1677]         0.000166           INSNEQ0000002755.jt         Art8         Keratin, type II cytoskeletal 8 [Source:UniProtKR/Swiss-ProtAcc:C91075]         0.002497           INSNEQ0000002055.jt         Art8.jt         Keratin, type II cytoskeletal 8 [Source:UniProtKR/Swiss-ProtAcc:C91027]         0.00152           INSNEQ0000002055.jt         Art8.jt         Keratin, type II cytoskeletal 8 [Source:UniProtKR/Swiss-ProtAcc:C91027]         0.000278           INSNEQ0000002055.jt         Art8.jt         Brotein [Source:UniProtKR/Swiss-ProtAcc:C91025]         0.00278           INSNEQ000000255.jt         Transmembrane protein 20 [Source:UniProtKR/Swiss-ProtAcc:C91085]         0.000556         0.00030           INSNEQ0000002128.jt         Them205         Transmembrane protein 20 [Source:UniProtKR/Swiss-ProtAcc:C91081]         0.00030         0.00030           INSNEQ0000003158.jt         Them205         Transmembrane protein 20 [Source:UniProtKR/Swiss-ProtAcc:C90901]         0.000356         0.00030           INSNEQ0000003158.jt         The315         Nuchosome assembl					1,37
[NSRN0000002864]         Siva1         Approtois regulatory protein Sia [Source UniProtR[Jswiss-Prot_Acc.29692]         0.001121         0.00125           [NSRN0000000027767]         si C38a5         Sodium-coupled neutral amino and transporter [Source UniProtR[Jswiss-Prot_Acc.21071]         0.00015         0.00015           [NSRN000000002776]         st Crist         Artypap 24         Rof CTP-se activating protein S2 [Source UniProtR[Jswiss-Prot_Acc.20072]         0.000132           [NSRN000000002600]         st Si Suppression of tumorgine(rit) Source-UniProtR[Jswiss-Prot_Acc.20072]         0.000132         0.000132           [NSRN000000002600]         st Si Suppression of tumorgine(rit) Source-UniProtR[Jswiss-Prot_Acc.209X2]         0.000132         0.000055           [NSRN00000000260]         st Si Suppression of tumorgine(rit) Source-UniProtR[Jswiss-Prot_Acc.209X2]         0.000132         0.000055           [NSRN000000000285]         at Nucl2         Nucleoindin 2 [Source-UniProtR[Jswiss-Prot_Acc.209X2]         0.00056         0.000056           [NSNN000000000285]         at Tubba Tubuin beta 3 chan [Source-UniProtR[Jswiss-Prot_Acc.209X2]         0.000056         0.000056           [NSNN000000000286]         at Red135         Uncharacterized protein [Source-UniProtR[Jswiss-Prot_Acc.209N01]         0.000056           [NSNN000000000286]         at Red135         Uncharacterized protein [Source-UniProtR[Jswiss-Prot_Acc.209N01]         0.000056 <td></td> <td></td> <td></td> <td></td> <td>0,73</td>					0,73
[INSRN00000000372] at         Tar.3         Neuromedin-Kreegor [Source-UniProtKB/Swiss-ProtAcc.29127]         0,00015         0           [INSRN00000000279] at         Kriß Kernin, UPU el troskield at [Source-UniProtKB/Swiss-ProtAcc.05U27]         0,00032         0           [INSRN00000002295] at         Arhgop24         Rho GTPase-activating protein 24 [Source-UniProtKB/Swiss-ProtAcc.05U27]         0,00032         0           [INSRN000000012459] at         Arhge26         Rho glanine nucleotide exchange factor (EFP 26         0,002784         0,002516         0           [INSRN000000002359] at         R60155000         Uncharacterized protein [Source-UniProtKB/Swiss-ProtAcc.030427]         0,000356         0           [INSRN000000000335] at         Tbbb3         Tubba3         Tubba3         Tubba3         0,000255         0         0,000255         0         0,000255         0         0,000255         0         0,000255         0         0,000255         0         0,000255         0         0,000255         0         0,000255         0         0,000255         0         0,000255         0         0,000255         0         0,000255         0         0,000255         0         0,000255         0         0,000255         0         0,000255         0         0,000255         0         0,000255         0					0,72
INSRN000000007293 at         Kriß         Keratin, type II cytoskeintä 8 [Source-UniProtK8/Swiss-Prot.Acc.201758]         0,002497         C           ENSRN0500000002050, at         Arbgap24         Rho GTPase-activating protein 24 [Source-UniProtK8/Swiss-Prot.Acc.2090X27]         0,000352         C           ENSRN050000000250, at         Still         Suppression of tumorigenicity 18 protein [Source-UniProtK8/Swiss-Prot.Acc.2090X27]         0,000132         C           ENSRN0500000002456, at         Nucb2         Nucb2         0,002286         0,002286         C           ENSRN05000000017209 at         ROD1555002         Uncharacterized protein [Source-UniProtK8/Swiss-Prot.Acc.2040R8]         0,0003956         C           ENSRN05000000017209 at         Tubba         Tubba         Tubba         0,0003956         C           ENSRN05000000017209 at         Tensmembrane protein 206 [Source-UniProtK8/Swiss-Prot.Acc.2040R8]         0,000320         C           ENSRN05000000017209 at         Ticohai         Stoldat         Stoldat         0,000325         C           ENSRN0500000017209 at         Ticohai         Stoldat         O,000320         C         ENSRN050000001720         0,000320         C           ENSRN0500000017209 at         Temmebrane associated GTPsas-activating protein 2 [Source-UniProtK8/Swiss-Prot.Acc.C099N01]         0,000366         C         ENSRN		SIc38a5	Sodium-coupled neutral amino acid transporter 5 [Source:UniProtKB/Swiss-Prot;Acc:A2VCW5]	0,002558	0,71
ENSRN00000002053, at         Arhgap24         Rho GTP:se-activating protein 24 [Source-UmProtKB/Swiss-Prot,Acc:Q5U227]         0,00005         0           ENSRN0000000200, at         S118         Suppression of tumorigenicity 18 protein [Source-UmProtKB/Swiss-Prot,Acc:Q5U227]         0,000132         0           ENSRN000000020454, at         Angef26         Nho gianne nucleotide exchange factor (GF) 26         0,0022186         0           ENSRN000000020455, at         Nucb2         Nucleobindin-2 [Source-UmProtKB/Swiss-Prot,Acc:Q6H28]         0,00053         0           ENSRN0000000020558, at         RoD1555002         Uncharacterized protein [Source-UmProtKB/Swiss-Prot,Acc:Q6H28]         0,000320         0           ENSRN0000000003150, at         Them205         Transmembara protein 2005 [Source-UmProtKB/Swiss-Prot,Acc:Q6H28]         0,000320         0           ENSRN0000000001280, at         StotAa1         Solute carrier organic anionity member AA1 [Source-UmProtKB/Swiss-Prot,Acc:Q99N01]         0,000365         0           ENSRN000000001280, at         Alg312         AFG3-like protein 2 [Source-UmProtKB/Swiss-Prot,Acc:Q99N01]         0,000365         0           ENSRN000000001282, at         Alg312         AFG3-like protein 2 [Source-UmProtKB/Swiss-Prot,Acc:Q99N01]         0,000436         0           ENSRN0000000002862, at         Alg312         AFG3-like protein 2 [Source-UmProtKB/Swiss-Prot,Acc:Q99N01]					0,71
ENSRNO2000000003 at         \$18         Suppression of tumorigencity 18 protein [Source:UniProttk/Swiss-Prot,Acc:Q9UX27]         0,000122         CI           ENSRNO2000000015450         Arbge726         Rho glanine nucleotide exchange factor (GEF) 26         0,002216         0,000238         CI           ENSRNO2000000000000000000000000000000000000					0,71
INSRNG00000024569         Arhge/26         Rho gianne nucleotide exchange factor (IGEF) 26         0,002788         0,002788           ENSRNG00000024056, at         Nuck2         Nuckobinin-2 [Source:UniProtKB/Swiss-Prot,Acc:QBIS]         0,00053         0           ENSRNG0000002709 at         Tubb3         Tubulin beta-3 chain [Source:UniProtKB/Swiss-Prot,Acc:QBE4]         0,000536         0           ENSRNG00000003515 at         Tmem206         Transmethrane protein 206 [Source:UniProtKB/Swiss-Prot,Acc:QBE41]         0,000536         0           ENSRNG00000003515 at         Tmem206         Transmethrane protein 206 [Source:UniProtKB/Swiss-Prot,Acc:QBE413]         0,000536         0           ENSRNG00000001421 at         Sico4a1         Solute carrier organic anion transporter family member 4A1 [Source:UniProtKB/Swiss-Prot,Acc:QB9N01]         0,000636         0           ENSRNG00000001768 at         Afg31ke protein 2 [Source:EnliProtKB/Swiss-Prot,Acc:QB9N6]         0,001111         0           ENSRNG0000000758 at         Napl15         Nucleosome assembly protein 1/ke [Source:UniProtKB/Swiss-Prot,Acc:QB9N6]         0,000112         0           ENSRNG0000000758 at         Napl15         Nucleosome assembly protein 1/ke [Source:UniProtKB/Swiss-Prot,Acc:QB9N2]         0,000112         0           ENSRNG0000000758 at         Pdrd3         Na+()+(+)+ exhange regulatory cofactor NHE-FRH [Source:UniProtKB/Swiss-Prot,Accc:QB9N2]					0,71 0,71
ENSRNGG0000020558 at         Nucle         Nucleobidine 2 [Source:UniProtK8/swiss-ProtAcc:Q40R8]         0.002516           ENSRNGG0000005589 at         RGD165002         Uncharacterized protein [Source:UniProtK8/swiss-ProtAcc:Q40R8]         0.000693         0.000693           ENSRNGG00000005589 at         Tubb3         Tubulin bet-3 chain [Source:UniProtK8/swiss-ProtAcc:Q40R84]         0.000320         0.000320         0.000320         0.000320         0.000320         0.000320         0.000320         0.000320         0.000320         0.000320         0.000320         0.000320         0.000320         0.000320         0.000320         0.000320         0.000320         0.000320         0.00002120         at         Stockal and intracterized protein [Source:UniProtK8/swiss-ProtAcc:Q99N01]         0.000320         0.000320         0.000320         0.000320         0.000320         0.000320         0.0001121         0.0000320         0.0001121         0.0001263         0.0001121         0.0004120         0.000430         0.0001121         0.000447         0.0001121         0.000447         0.0001121         0.000447         0.0001120         0.0001121         0.0001120         0.000447         0.0001121         0.000447         0.0001121         0.000447         0.0001121         0.000447         0.0001121         0.000447         0.000113         0.0001121         0.000447<					0,71
ENSRNG00000001329 at         ROL165002         Uncharacterized protein [Source:UniProtKB/Swiss-Prot,Acc:Q4R08]         0,000593         C           ENSRNG00000001320 at         Tubbia         Tubbia         Tubbia         0,000320         C           ENSRNG000000021870 at         Timerized         Transmembrane protein 206 [Source:UniProtKB/Swiss-Prot,Acc:Q6H28]         0,000320         C           ENSRNG00000021870 at         Proth15         Uncharacterized protein 206 [Source:UniProtKB/TrisBulk_Acc:E11T00]         0,000366         C           ENSRNG000000011765 at         April 5         Uncharacterized protein 2 [Source:Rel5eq peptide,Acc:NP_001094139]         0,003692         C           ENSRNG00000007808 at         Nap15         Nuclesome assembly protein 1-11ke pstide:Acc:NP_001128336]         0,000111         C           ENSRNG00000007808 at         Nap15         Nuclesome assembly protein 1-11ke pstide:Acc:NP_001178925]         0,00047         C           ENSRNG00000001827 at         Ptd3         Na(-)/H(+ exchange regulatory cofactor NHE-R4 [Source:Rel5eq peptide,Acc:NP_001178925]         0,000112         C           ENSRNG00000019587 at         Ptgm         Receptor-type tyrosine-protein phosphatase-like N [Source:UniProtKB/Swiss-Prot,Acc:Q63259]         0,000213         C           ENSRNG00000001215 at         TGG_BAT         DCTD_RAT         DCOTD_RAT         DCOTD_RAT <td< td=""><td></td><td></td><td></td><td></td><td>0,70</td></td<>					0,70
ENSRNG00000001351 at         Transmembrane protein 206 [Source:UniProtK8/Swiss-Prot_Acc:Q66H28]         0,000320         C           ENSRNG00000006066 at         Podh15         Uncharacterized protein [Source:UniProtK8/TrEMBL/Acc:Q6EH28]         0,000636         C           ENSRNG000000121870, at         Slco4a1         Solute carrier organic anion transporter family member 4A1 [Source:UniProtK8/Swiss-Prot_Acc:Q9P00]         0,000636         C           ENSRNG00000017850, at         Afg312         AFG31ke protein 2 [Source:RefSeq peptide/Acc:NP_00128336]         0,001111         C           ENSRNG00000017850, at         Nap15         Nucleosome assembly protein 1-like 5 [Source:UniProtK8/Swiss-Prot_Acc:Q5PP66]         0,000447         C           ENSRNG000000018827, at         Ptdrd3         Na(+)/H(+) exchange regulatory cofactor NH: RF4 [Source:UniProtK8/Swiss-Prot_Acc:Q9H29]         0,002477         C           ENSRNG00000015827, at         Ptpm         Receptor-type tyrosine-protein phosphatas-tike N [Source:UniProtK8/Swiss-Prot_Acc:Q9129]         0,0002130         C           ENSRNG0000001251, at         TGA18, androgen-induce gene 1 protein A [Source:UniProtK8/Swiss-Prot_Acc:Q9129]         0,000133         C           ENSRNG0000001252, at         Pcp4         Purkinje cell protein 4 [Source:UniProtK8/Swiss-Prot_Acc:Q9129]         0,000133         C           ENSRNG00000001252, at         DCTD_RAT         Deoxycytidyidate dasminase [Sou	ENSRNOG0000005589_at	RGD1565002	Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:D4A0T8]	0,000693	0,70
ENSRN0G000000666 atPcdh15Uncharacterized protein [Source:UniProtKB/TrEMBL;Acc:F11T00]0,0020550ENSRN0G0000011421 atSinde arrier organic anion transporter family member 4A1 [Source:UniProtKB/Swiss-Prot,Acc:Q99N01]0,0036360ENSRN0G0000011421 atSinap2stromal membrane-associated GTPase-activating protein 2 [Source:RefSeq peptide;Acc:NP_00109139]0,0036920ENSRN0G00000011421 atSinap2Stromal membrane-associated GTPase-activating protein 2 [Source:RefSeq peptide;Acc:NP_001078925]0,00011110ENSRN0G00000015825 atAfg312AFG311ke protein 2 [Source:RefSeq peptide;Acc:NP_001178925]0,0004470ENSRN0G00000015825 atPdzd3Na(+)/[+](+] exchange regulatory cofactor NHE-RF4 [Source:RefSeq peptide;Acc:NP_001178925]0,00024770ENSRN0G00000015827 atSIG38a3Sodium-coupled neutral amino acid transporter 3 [Source:UniProtKB/Swiss-Prot,Acc:0391429]0,00023400ENSRN0G00000012151 atTAGL3 RATTransgelin-3 [Source:UniProtKB/Swiss-Prot,Acc:03926]0,00023400ENSRN0G00000012152 atPcp4Purkinjc cell protein [Source:UniProtKB/Swiss-Prot,Acc:06325]0,0001330ENSRN0G00000012753 atAig1androgen-induced gene 1 protein [Source:UniProtKB/Swiss-Prot,Acc:069499]0,0002660ENSRN0G0000001283 atGistar edvini-I [Source:UniProtKB/Swiss-Prot,Acc:026549]0,0000670ENSRN0G0000001283 atGistar edvini-I [Source:UniProtKB/Swiss-Prot,Acc:026549]0,00006670ENSRN0G0000001283 atGistar edvini-I [Source:UniProtKB/Swiss-Prot,Acc:02540]0,00006670 </td <td></td> <td></td> <td></td> <td></td> <td>0,69</td>					0,69
ENSRNGG0000021370_atSico4a1Solute carrier organic anion transporter family member 4A1 [Source:UniProtKB/Swiss-Prot,Acc:Q99N01]0,0006660ENSRNGG0000011745_atAfG3-like protein 2 [Source:RefSeq peptide;Acc:NP_00128336]0,001110CDENSRNGG0000007808_atNap115Nucleosome assembly protein 1-like 5 [Source:UniProtKB/Swiss-Prot,Acc:Q5PPG6]0,000112CDENSRNGG0000001827_atPtdr3Nat(-)/(I+I) exchange regulatory cofactor NHE-RF4 [Source:RefSeq peptide;Acc:NP_001178325]0,000112CDENSRNGG0000001827_atPtdr3Nat(-)/(I+I) exchange regulatory cofactor NHE-RF4 [Source:RefSeq peptide;Acc:NP_001178325]0,000277CDENSRNGG00000018257_atPtprmReceptor-type tyrosine-protein phosphatase-like N [Source:UniProtKB/Swiss-Prot,Acc:Q3H29]0,000234CDENSRNGG00000013215_atTAGL3_RATTransgelin-3 [Source:UniProtKB/Swiss-Prot,Acc:Q5M9G0]0,000234CDENSRNGG00000013253_atPcp4Purkinje cell protein 4 [Source:UniProtKB/Swiss-Prot,Acc:Q5M9G0]0,000133CDENSRNGG0000015253_atAig1androgen-induced gene 1 protein [Source:UniProtKB/Swiss-Prot,Acc:Q6P9X9]0,000266CDENSRNGG0000012753_atAig1androgen-induced gene 1 protein [Source:UniProtKB/Swiss-Prot,Acc:Q6P9X9]0,000266CDENSRNGG0000012753_atGirx1Glutredoxin-1 [Source:UniProtKB/Swiss-Prot,Acc:Q6P9X9]0,000266CDENSRNGG0000012753_atGirx1Glutredoxin-1 [Source:UniProtKB/Swiss-Prot,Acc:Q6P3X6]0,000069CDENSRNGG0000012753_atCsf6cystain-M [Source:RefSeq peptide;Acc:NP_958250] <td< td=""><td></td><td></td><td></td><td></td><td>0,69</td></td<>					0,69
ENSRNOG0000011421_atSmap2stromal membrane-associated GTPase-activating protein 2 [Source:RefSeq peptide;Acc:NP_001094139]0,0036920ENSRNOG00000017865_atAfg312AfG31ike protein 2 [Source:RefSeq peptide;Acc:NP_01128336]0,0011110ENSRNOG0000007808_atNap115Nucleosome assembly protein 1/ike 5 [Source:UniProtK8/Swiss-ProtAcc:Q5PPG6]0,0004770ENSRNOG0000001582_atPdd3Na(+)/H(+) exchange regulatory cofactor NHE-RF4 [Source:RefSeq peptide;Acc:NP_001178925]0,0001120ENSRNOG0000001582_atPidd3Sodium-coupled neutral amino acid transporter 3 [Source:UniProtK8/Swiss-ProtAcc:Q3H29]0,00024770ENSRNOG0000001582_atPtpmReceptor-type (prosine-protein phosphatas-like N [Source:UniProtK8/Swiss-ProtAcc:Q3H29]0,00023940ENSRNOG0000001525_atDCTD_RATDeoxycytidylate deaminase [Source:UniProtK8/Swiss-ProtAcc:Q5M9G0]0,000150ENSRNOG0000001523_atAig1androgen-induced gene 1 protein 4 [Source:UniProtK8/Swiss-ProtAcc:Q5D5]0,0004760ENSRNOG0000001523_atAig1androgen-induced gene 1 protein [Source:UniProtK8/Swiss-ProtAcc:Q5D5]0,0004660ENSRNOG000001523_atGlotaredoxin-1 [Source:UniProtK8/Swiss-ProtAcc:Q5SH6]0,00025600ENSRNOG000001218_atGlotaredoxin-1 [Source:UniProtK8/Swiss-ProtAcc:Q5SH6]0,00004560ENSRNOG000002492_atNnatNeuronatin [Source:UniProtK8/Swiss-ProtAcc:Q5SH6]0,00004590ENSRNOG000002465_atC56cystatin-M [Source:UniProtK8/Swiss-ProtAcc:Q5SH6]0,00004590ENSRNO					0,68 0,68
ENSRNGG0000017955_atAfg312AFG3-like protein 2 [Source:RefSeq peptide;Acc:NP_001128336]0,001111ENSRNGG0000007808_atNap1J5Nucleosome assembly protein 1-like 5 [Source:UniProtK8/Swiss-Prot;Acc:OSPG6]0,000447ENSRNGG0000001582_atPdzd3Nat/l/(+) exchange regulatory cofactor NHE-R44 [Source:RefSeq peptide;Acc:NP_001178925]0,00012ENSRNGG0000001582_atPdzd3Sodium-coupled neutral amino acid transporter 3 [Source:UniProtK8/Swiss-Prot;Acc:Q3HZ9]0,0002477ENSRNGG00000012151_atTAGL3_RATTransgelin-3 [Source:UniProtK8/Swiss-Prot;Acc:Q3HZ9]0,0002394ENSRNGG00000012151_atTAGL3_RATTransgelin-3 [Source:UniProtK8/Swiss-Prot;Acc:Q63259]0,000133ENSRNGG00000012151_atDCTD_RATDeoxycytidylate deaminase [Source:UniProtK8/Swiss-Prot;Acc:Q63259]0,000133ENSRNGG00000012753_atAlg1androgen-induced gene 1 protein [Source:UniProtK8/Swiss-Prot;Acc:Q69259]0,0000486ENSRNGG0000001273_atAlg1androgen-regulated mucin-like protein 1 homolog [Source:UniProtK8/Swiss-Prot;Acc:Q6929]0,000067ENSRNGG000001283_atGix1Glutaredoxin-1 [Source:UniProtK8/Swiss-Prot;Acc:Q5546]0,000067ENSRNGG000001283_atGix1Glutaredoxin-1 [Source:UniProtK8/Swiss-Prot;Acc:Q5545]0,000056ENSRNGG000001283_atGix1Glutaredoxin-1 [Source:UniProtK8/Swiss-Prot;Acc:Q5546]0,000067ENSRNGG000001283_atGix1Glutaredoxin-1 [Source:UniProtK8/Swiss-Prot;Acc:Q5546]0,0000661ENSRNGG000001283_atC616crystati-M [Source:UniProtK8/Swiss-Prot;Acc:P54256]0,000061ENSRNGG0000002455_at <td></td> <td></td> <td></td> <td></td> <td>0,68</td>					0,68
ENSRNOG0000007808_atNucleosome assembly protein 1-like 5 [Source:UniProtKB/Swiss-Prot,Acc:Q5PPG6]0,000447CENSRNOG0000005826_atPdrd3Nu(+)(H) exchange regulatory cofactor NHE-RF4 [Source:RefSeq peptide;Acc:NP_00117825]0,000112CENSRNOG00000016827_atSIC3833Sodium-coupled neutral amino acid transporter 3 [Source:UniProtKB/Swiss-Prot,Acc:Q9H29]0,0002477CCENSRNOG0000015257_atPtpmReceptor-type tyrosine-protein phosphatase-like N [Source:UniProtKB/Swiss-Prot,Acc:Q6259]0,000613CCENSRNOG00000013215_atDCTD_RATDeoxycytidylate deaminase [Source:UniProtKB/Swiss-Prot,Acc:C35M9G0]0,000715CCENSRNOG0000001525_atPctp4Purkinje cell protein 4 [Source:UniProtKB/Swiss-Prot,Acc:Q5M9G0]0,000133CCENSRNOG0000001525_atAig1androgen-induced gene 1 protein [Source:UniProtKB/Swiss-Prot,Acc:Q6P9X9]0,000466CCENSRNOG0000001218_atGirx1Giutraedoxin-1 [Source:UniProtKB/Swiss-Prot,Acc:Q6P549]0,000266CCENSRNOG000001218_atGirx1Giutraedoxin-1 [Source:UniProtKB/Swiss-Prot,Acc:Q6E9X9]0,000266CCENSRNOG000002493_atNathNeuronatin [Source:UniProtKB/Swiss-Prot,Acc:Q6E549]0,000056CCENSRNOG000002493_atCstfaCystain-M [Source:UniProtKB/Swiss-Prot,Acc:Q6E549]0,000069CCENSRNOG000002495_atCstfaCystain-M [Source:UniProtKB/Swiss-Prot,Acc:Q2556]0,0001816CCENSRNOG000002455_atCstfaCystain-M [Source:UniProtKB/Swiss-Prot,Acc:Q2556]0,0001816CCENSRNOG0000002455_atCstfa <td></td> <td></td> <td></td> <td>.,</td> <td>0,68</td>				.,	0,68
ENSRNOG0000008526_at         Pdrd3         Na(+)/H(+) exchange regulatory cofactor NHE-RF4 [Source:RefSeq peptide;Acc:NP_001178925]         0,000112         C           ENSRNOG00000015827_at         SIc38a3         Sodium-coupled neutral amino acid transporter 3 [Source:UniProtKB/Swiss-Prot,Acc:Q3H29]         0,002477         C           ENSRNOG00000015857_at         Ptpm         Receptor-type tyrosine-protein phosphatas-like N [Source:UniProtKB/Swiss-Prot,Acc:Q3259]         0,00013         CC           ENSRNOG00000013215_at         TAGL3_RAT         Transgelin-3 [Source:UniProtKB/Swiss-Prot,Acc:Q3260]         0,00013         CC           ENSRNOG0000001528_at         Pcp4         Putrinjc cell protein 4 [Source:UniProtKB/Swiss-Prot,Acc:Q5305]         0,00013         CC           ENSRNOG0000001528_at         Pcp4         Putrinjc cell protein 4 [Source:UniProtKB/Swiss-Prot,Acc:Q5951]         0,000486         C           ENSRNOG0000001278_at         Aig1         androgen-induced gene 1 protein [Source:UniProtKB/Swiss-Prot,Acc:Q6593]         0,000667         C           ENSRNOG0000001278_at         Girla         Glitaredoxin-1 [Source:UniProtKB/Swiss-Prot,Acc:Q5546]         0,000056         C           ENSRNOG000000128_at         Girla         Glitaredoxin-1 [Source:UniProtKB/Swiss-Prot,Acc:Q5256]         0,000459         C           ENSRNOG0000002492_at         Nnat         Neuronatin [Source:UniProtKB/Swiss-Prot,Acc:Q5256] </td <td></td> <td></td> <td></td> <td></td> <td>0,68</td>					0,68
ENSRNOG0000019587_atPtpmReceptor-type tyrosine-protein phosphatase-like N [Source:UniProtKB/Swiss-Prot,Acc:Q62559]0,000613CCENSRNOG00000013215_atTAGL3_RATTransgelin-3 [Source:UniProtKB/Swiss-Prot,Acc:Q5M9G0]0,0002394CCENSRNOG00000013215_atDCTD_RATDexycytidylate deaminase [Source:UniProtKB/Swiss-Prot,Acc:Q5M9G0]0,000133CCENSRNOG000001525_atPCTD_RATDexycytidylate deaminase [Source:UniProtKB/Swiss-Prot,Acc:Q5M9G0]0,000133CCENSRNOG000001525_atAig1androgen-induced gene 1 protein [Source:RelFseq peptide,Acc:NP_001127897]0,000486CCENSRNOG0000001278_atGilx1Gilutaredoxin-1 [Source:UniProtKB/Swiss-Prot,Acc:Q6E9X9]0,000266CCENSRNOG0000012183_atGirx1Gilutaredoxin-1 [Source:UniProtKB/Swiss-Prot,Acc:Q6E9K9]0,000266CCENSRNOG0000012493_atHap1Huntingtin-associated protein 1 [Source:UniProtKB/Swiss-Prot,Acc:Q6E945]0,000061CCENSRNOG000002493_atNantNeuronatin [Source:UniProtKB/Swiss-Prot,Acc:Q6E949]0,000069CCENSRNOG000002455_atCst6cystatin-M [Source:UniProtKB/Swiss-Prot,Acc:Q2546]0,000485CCENSRNOG0000002455_atCst6cystatin-M [Source:UniProtKB/Swiss-Prot,Acc:Q2556]0,000485CCENSRNOG0000001201_atCmtm8CKLF-like MARVEL transmembrane domain-containing protein a [Source:UniProtKB/Swiss-Prot,Acc:Q2556]0,000485CCENSRNOG0000001210_atCmtm8CKLF-like MARVEL transmembrane domain-containing protein a [Source:UniProtKB/Swiss-Prot,Acc:Q25506]0,0003136CC <td></td> <td>Pdzd3</td> <td>Na(+)/H(+) exchange regulatory cofactor NHE-RF4 [Source:RefSeq peptide;Acc:NP_001178925]</td> <td>0,000112</td> <td>0,67</td>		Pdzd3	Na(+)/H(+) exchange regulatory cofactor NHE-RF4 [Source:RefSeq peptide;Acc:NP_001178925]	0,000112	0,67
ENSRNOG00000013151_at         TAGL3_RAT         Transgelin-3 [Source:UniProtKB/Swiss-Prot,Acc:P37805]         0,002394         0           ENSRNOG00000013151_at         DCTD_RAT         Deoxyrytidylate deaminase [Source:UniProtKB/Swiss-Prot,Acc:Q5050]         0,000715         0           ENSRNOG0000001282         Pcp4         Purkinjc cell protein 4 [Source:UniProtKB/Swiss-Prot,Acc:Q5050]         0,000133         0           ENSRNOG0000001528_at         Aig1         androgen-induced gene 1 protein [Source:RefSeq peptide;Acc:NP_001127897]         0,000486         0           ENSRNOG0000012783_at         Girx1         Glitaredoxin-1 [Source:UniProtKB/Swiss-Prot,Acc:Q65949]         0,00056         0           ENSRNOG0000012183         td Girat additrine_Source:UniProtKB/Swiss-Prot,Acc:P54256]         0,000056         0           ENSRNOG0000012183         tHap1         Huntingtin-associated protein 1 [Source:UniProtKB/Swiss-Prot,Acc:P54256]         0,000051         0           ENSRNOG00000024923_at         Nnat         Neuronatin [Source:UniProtKB/Swiss-Prot,Acc:P54256]         0,000459         0           ENSRNOG0000002495_at         C56         cystatin-M [Source:UniProtKB/Swiss-Prot,Acc:P17475]         0,000186         0           ENSRNOG0000002495_at         C516         cystatin-M [Source:UniProtKB/Swiss-Prot,Acc:Q25N6]         0,000485         0           ENSRNOG00000012045					0,67
ENSRNOG0000013215_at         DCTD_RAT         Deoxycytidylate deaminase [Source:UniProtKB/Swiss-Prot;Acc:Q5M9G0]         0,000715         CC           ENSRNOG00000013215_at         Drp4         Purkinje cell protein 4 [Source:UniProtKB/Swiss-Prot;Acc:Q5055]         0,000133         C           ENSRNOG0000001253_at         Aig1         androgen-induced gene 1 protein [Source:RelSeq peptide;Acc:NP_001127897]         0,000466         C           ENSRNOG0000001253_at         Parm1         Prostate androgen-regulated mucin-like protein 1 homolog [Source:UniProtKB/Swiss-Prot;Acc:Q6P9X9]         0,000667         C           ENSRNOG0000001253_at         Girx1         Glutaredoxin-1 [Source:UniProtKB/Swiss-Prot;Acc:Q6E546]         0,000056         C           ENSRNOG00000024923_at         Nat         Neuronatin [Source:UniProtKB/Swiss-Prot;Acc:Q6E549]         0,00069         C           ENSRNOG0000024955_at         Cst6         cystatin-M [Source:UniProtKB/Swiss-Prot;Acc:Q6E549]         0,000059         C           ENSRNOG00000024955_at         Cst6         cystatin-M [Source:UniProtKB/Swiss-Prot;Acc:Q6E549]         0,000059         C           ENSRNOG0000002455_at         Cst6         cystatin-M [Source:UniProtKB/Swiss-Prot;Acc:Q2E5N6]         0,000186         C           ENSRNOG0000001255_at         Gst71         Alpha-1-antiproteinase [Source:UniProtKB/Swiss-Prot;Acc:Q2S5N6]         0,0001869         C					0,66
ENSRNOG0000001628_at         Pcp4         Purkinje cell protein 4 [Source:UniProtKB/Swiss-Prot;Acc:P63055]         0,000133         CC           ENSRNOG0000001575_at         Aig1         androgen-induced gene 1 protein [Source:RefSeq peptide,Acc:NP_001127897]         0,000486         CC           ENSRNOG0000002579_at         Parn1         Prostate androgen-regulated mucin-like protein 1 homolog [Source:UniProtKB/Swiss-Prot;Acc:Q6P9X9]         0,000667         CC           ENSRNOG0000002579_at         Girx1         Glutaredoxin-1 [Source:UniProtKB/Swiss-Prot;Acc:Q9E5H6]         0,000256         CC           ENSRNOG0000024923_at         Nat         Neuronatin [Source:UniProtKB/Swiss-Prot;Acc:Q6E549]         0,000059         CC           ENSRNOG0000024923_at         Cst6         cystain-M [Source:UniProtKB/Swiss-Prot;Acc:Q6E549]         0,000069         CC           ENSRNOG0000002495_at         Cst6         cystain-M [Source:UniProtKB/Swiss-Prot;Acc:Q62549]         0,000069         CC           ENSRNOG0000002645_at         Serpina1         Alpha-1-antiproteinase [Source:UniProtKB/Swiss-Prot;Acc:Q255N6]         0,0001816         CC           ENSRNOG0000000000000_600_at         Igsf1         Immonglobulins superfamily member 1 [Source:UniProtKB/Swiss-Prot;Acc:Q252N6]         0,000485         CC           ENSRNOG00000012101_at         Cmtm8         CKLF-like MARVEL transmembrane domain-containing protein 8 [Source:RefSeq peptide;		-			0,66
ENSRNOG000000253_at         Aig1         androgen-induced gene 1 protein         [Source:RefSeq peptide;Acc:NP_001127897]         0,000486         0           ENSRNOG0000002579_at         Parm1         Prostate androgen-regulated mucin-like protein 1 homolog [Source:UniProtRB/Swiss-Prot;Acc:Q6P9X9]         0,000667         0           ENSRNOG00000012183_at         GIX1         Glutaredoxin-1 [Source:UniProtRB/Swiss-Prot;Acc:Q6SH6]         0,000265         0           ENSRNOG0000012183_at         Hap1         Huntingtin-associated protein 1 [Source:UniProtRB/Swiss-Prot;Acc:P54256]         0,00069         0           ENSRNOG000002493_at         Nnat         Neuronatin [Source:UniProtRB/Swiss-Prot;Acc:Q62649]         0,0000459         0           ENSRNOG000002465_at         C56         cystatin-M [Source:UniProtRB/Swiss-Prot;Acc:Q2576]         0,000069         0           ENSRNOG0000002645_at         C56         cystatin-M [Source:UniProtRB/Swiss-Prot;Acc:Q2576]         0,000485         0           ENSRNOG0000002645_at         C56         cystatin-M [Source:UniProtRB/Swiss-Prot;Acc:Q2576]         0,000485         0           ENSRNOG0000001201_at         Cfmtm         Gpf1         Immunoglobulin superfamily member 1 [Source:UniProtRB/Swiss-Prot;Acc:P5426]         0,000485         0           ENSRNOG0000001201_at         Cmtm8         CKLF-like MARVEL transmembrane domain-containing protein 8 [Source: InProtRB/					0,63 0,63
ENSRNOG0000002579_at         Parm1         Prostate androgen-regulated mucin-like protein 1 homolog [Source:UniProtKB/Swiss-Prot,Acc:Q6P9X9]         0,000667         0           ENSRNOG00000012579_at         Girx1         Glutaredoxin-1 [Source:UniProtKB/Swiss-Prot,Acc:Q9E5K6]         0,000256         0           ENSRNOG00000124923_at         Hap1         Huntingtin-associated protein 1 [Source:UniProtKB/Swiss-Prot,Acc:Q9E5K6]         0,000601         0           ENSRNOG00000124923_at         Nnat         Neuronatin [Source:UniProtKB/Swiss-Prot,Acc:Q62649]         0,000059         0           ENSRNOG00000024955_at         Cst6         cystatin-M [Source:UniProtKB/Swiss-Prot,Acc:Q62649]         0,000169         0           ENSRNOG00000024655_at         Serpinal         Alpha-1-antiproteinase [Source:UniProtKB/Swiss-Prot,Acc:Q625N6]         0,000169         0           ENSRNOG0000007600_at         Igs1         Immunoglobulin superfamily member 1 [Source:UniProtKB/Swiss-Prot,Acc:Q925N6]         0,000485         0           ENSRNOG0000001201_at         Cmtm8         CKLF-like MARVEL transmembrane domain-containing protein 8 [Source:RefSeq peptide;Acc:NP_942049]         0,0003136         0           ENSRNOG0000001261_at         Gadd45a         Growth arrest and DNA damage-inducible protein 6ADD45 alpha [Source:UniProtKB/Swiss-Prot,Acc:P48317]         0,000316         0           ENSRNOG00000015571_at         Sic12a2         solu					0,63
ENSRNOG0000012183 at         Girx1         Glutaredoxin-1 [Source:UniProtKB/Swiss-Prot;Acc:09E5H6]         0,000256         0           ENSRNOG0000012183 at         Hap1         Huntingtin-associated protein 1 [Source:UniProtKB/Swiss-Prot;Acc:09E5H6]         0,000051         0           ENSRNOG0000012483 at         Nat         Neuronatin [Source:UniProtKB/Swiss-Prot;Acc:09E5H6]         0,000059         0           ENSRNOG0000024923 at         Nnat         Neuronatin [Source:UniProtKB/Swiss-Prot;Acc:0925H6]         0,000069         0           ENSRNOG00000024955 at         Cst6         cystain-M [Source:UniProtKB/Swiss-Prot;Acc:0925N6]         0,000186         0           ENSRNOG00000026403 at         Iserpina1         Alpha-1-antiproteinase [Source:UniProtKB/Swiss-Prot;Acc:0925N6]         0,000485         0           ENSRNOG0000007600 at         Igsf1         Immunoglobulins uperfamily member 1 [Source:UniProtKB/Swiss-Prot;Acc:0925N6]         0,000485         0           ENSRNOG0000001201 at         Cmtm8         CKLF-like MARVEL transmembrane domain-containing protein 8 [Source:RefSeq peptide;Acc:NP_942049]         0,0003136         0           ENSRNOG0000001201 at         Gadd45a         Growth arrest and DNA damage-inducible protein 6AD045 alpha [Source:Prot;Acc:P48317]         0,000048         0           ENSRNOG0000001557_at         Sold45a         Growth arrest and DNA damage-inducible protein GAD045 alpha [Source:Pro					0,62
ENSRNOG0000024923_at         Nnat         Neuronatin [Source:UniProtKB/Swiss-Prot;Acc:Q62649]         0,000459         0           ENSRNOG00000024923_at         Cst6         cystatin-M [Source:UniProtKB/Swiss-Prot;Acc:Q62649]         0,000069         0           ENSRNOG00000024655_at         Cst6         cystatin-M [Source:UniProtKB/Swiss-Prot;Acc:Q727475]         0,001816         0           ENSRNOG0000007600_at         lsg1         Immunoglobulin superfamily member 1 [Source:UniProtKB/Swiss-Prot;Acc:Q225N6]         0,000485         0           ENSRNOG0000001201_at         Cmtm8         CKLF-like MARVEL transmembrane domain-containing protein 8 [Source:RefSeq peptide;Acc:NP_942049]         0,000689         0           ENSRNOG0000001201_at         Phactr1         Phosphatase and actin regulator 1 [Source:UniProtKB/Swiss-Prot;Acc:P2024]         0,003136         0           ENSRNOG00000015971_at         Gadd45a         Growth arrest and DNA damage-inducible protein GADD45 alpha [Source:UniProtKB/Swiss-Prot;Acc:P48317]         0,0003419         0		Girx1	Glutaredoxin-1 [Source:UniProtKB/Swiss-Prot;Acc:Q9ESH6]	0,000256	0,61
ENSRNOG0000020455_at         Cst6         cystatin-M [Source:RefSeq peptide;Acc:NP_598250]         0,000069         C           ENSRNOG0000020455_at         Serpina1         Alpha-1-antiproteinase [Source:UniProtKS/Wsiss-Prot;Acc:0255N6]         0,001816         C           ENSRNOG0000007600_at         Igs1         Immunoglobulins uperfamily member 1 [Source:UniProtKS/Wsiss-Prot;Acc:0255N6]         0,000485         C           ENSRNOG0000001201_at         Cmtm8         CKLF-like MARVEL transmembrane domain-containing protein 8 [Source:RefSeq peptide;Acc:NP_942049]         0,000489         C           ENSRNOG00000014201_at         Cmtm8         CKLF-like MARVEL transmembrane domain-containing protein 8 [Source:RefSeq peptide;Acc:NP_942049]         0,000316         C           ENSRNOG00000014264_at         Phactr1         Phosphatase and actin regulator 1 [Source:UniProtKB/Swiss-Prot;Acc:P62024]         0,003136         C           ENSRNOG00000015571_at         Gadd45a         Growth arrest and DNA damage-inducible protein GADD45 alpha [Source:UniProtKB/Swiss-Prot;Acc:P48317]         0,000044         C           ENSRNOG00000015571_at         Sic12a2         solute carrier family 12 member 2 [Source:RefSeq peptide;Acc:NP_113986]         0,00349         C					0,60
ENSRNGG0000002569_at         Serpinal         Alpha-1-antiproteinase [Source:UniProtK8/Swiss-Prot,Acc:197475]         0,001816         0           ENSRNGG000007600_at         Igs1         Immunoglobulin superfamily member 1 [Source:UniProtK8/Swiss-Prot,Acc:0925N6]         0,000485         0           ENSRNGG0000001201_at         Cmtm8         CKLF-like MARKVEL transmembrane domain-containing protein 8 [Source:NP_942049]         0,000386         0           ENSRNGG0000001201_at         Phatr1         Phosphatase and actin regulator 1 [Source:UniProtK8/Swiss-Prot,Acc:P62024]         0,003136         0           ENSRNGG00000015571_at         Gadd45a         Growth arrest and DNA damage-inducible protein GADD45 alpha [Source:NP_113986]         0,00044         0           ENSRNG00000015571_at         Solute carrier family 12 member 2 [Source:ReSeq peptide;Acc:NP_113986]         0,00349         0					0,60
ENSRNOG0000007600_at         Igsf1         Immunoglobulin superfamily member 1 [Source::UniProtKB/Swiss-Prot;Acc:Q925N6]         0,000485         0           ENSRNOG0000001210_at         Cmtm8         CKLF-like MARVEL transmembrane domain-containing protein 8 [Source::RefSeq peptide;Acc:NP_942049]         0,000689         0           ENSRNOG00000014264_at         Phactr1         Phosphatase and actin regulator 1 [Source::UniProtKB/Swiss-Prot;Acc:P62024]         0,003136         0           ENSRNOG0000005615_at         Gadd45a         Growth arrest and DNA damage-inducible protein GADD45 alpha [Source::UniProtKB/Swiss-Prot;Acc:P48317]         0,000048         0           ENSRNOG00000051591_at         Sic12a2         solute carrier family 12 member 2 [Source::RefSeq peptide;Acc:NP_113986]         0,003419         0					0,58
ENSRNOG0000011201_at         Cmtm8         CKLF-like MARVEL transmembrane domain-containing protein 8 [Source:RefSeq peptide;Acc:NP_942049]         0,000689         CC           ENSRNOG0000011201_at         Phactr1         Phosphatase and actin regulator 1 [Source:UniProtKB/Swiss-Prot;Acc:P62024]         0,003136         CC           ENSRNOG000000055615_at         Gadd45a         Growth arrest and DNA damage-inducible protein GADD45 alpha [Source:UniProtKB/Swiss-Prot;Acc:P48317]         0,000084         CC           ENSRNOG00000055971_at         Sic12a2         solute carrier family 12 member 2 [Source:RefSeq peptide;Acc:NP_113986]         0,00319         CC					0,56 0,54
ENSRNOG0000014264_at         Phactr1         Phosphatase and actin regulator 1 [Source:UniProtKB/Swiss-Prot;Acc:P62024]         0,003136         0           ENSRNOG0000005615_at         Gadd45a         Growth arrest and DNA damage-inducible protein GADD45 alpha [Source:UniProtKB/Swiss-Prot;Acc:P48317]         0,00084         0           ENSRNOG00000015971_at         Slc12a         solute carrier family 12 member 2 [Source:RefSeq peptide;Acc:NP_113986]         0,003419         0					0,54
ENSRNOG0000005615_at         Gadd45a         Growth arrest and DNA damage-inducible protein GADD45 alpha [Source:UniProtKB/Swiss-Prot;Acc:P48317]         0,00084         0           ENSRNOG0000005159_1at         Slc12a2         solute carrier family 12 member 2 [Source:RefSeq peptide;Acc:NP_113986]         0,003419         0					0,54
ENSRNOG0000015971_at         SIc12a2         solute carrier family 12 member 2 [Source:RefSeq peptide;Acc:NP_113986]         0,003419         0					0,51
	ENSRNOG0000015971_at	Slc12a2	solute carrier family 12 member 2 [Source:RefSeq peptide;Acc:NP_113986]	0,003419	0,50
					0,45
					0,44
					0,43
					0,33 0,29