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Transcriptional Profiling of Native Inner Medullary Collecting Duct Cells from Rat Kidney

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Abstract

Vasopressin acts on the inner medullary collecting duct (IMCD) in the kidney to regulate water and urea transport. To obtain a ‘parts list’ of gene products expressed in the IMCD, we carried out mRNA profiling of freshly isolated rat IMCD cells using Affymetrix Rat 230 2.0 microarrays with approximately 31,000 features. 7913 annotated transcripts were found to be expressed above background in the IMCD cells. We have created a new online database (the “IMCD Transcriptome Database” †) to make the results publicly accessible. Among the 30 transcripts with the greatest signals on the arrays were three water channels: aquaporin-2, aquaporin-3, and aquaporin-4, all of which have been reported to be targets for regulation by vasopressin. In addition, the transcript with the greatest signal among members of the solute carrier (SLC) family of genes was the UT-A urea transporter (*Slc14a2*), which is also regulated by vasopressin. The V2 vasopressin receptor was strongly expressed, but the V1a and V1b vasopressin receptors did not produce signals above background. Among the 200 protein kinases expressed, the serum-glucocorticoid regulated kinase (*Sgk1*) had the greatest signal intensity in the IMCD. WNK1 and WNK4 were also expressed in the IMCD with a relatively high signal intensity as was protein kinase A (β -catalytic subunit). In addition, a large number of transcripts corresponding to AKAPs and 14-3-3 proteins (phospho-S/T binding proteins) were expressed. Altogether, the results combine with proteomics studies of the IMCD to provide a framework for modeling complex interaction networks responsible for vasopressin action in collecting duct cells.

Index words

Oligonucleotide array; vasopressin; aquaporin-2; urea transport; kinases

INTRODUCTION

The inner medullary collecting duct (IMCD) is the terminal portion of the collecting duct system of the kidney. The collecting duct system represents the final site of adjustment of urinary composition and volume, and therefore is critical for extracellular fluid homeostasis. An important regulator of collecting duct transport function is vasopressin, which controls both water and urea transport (21;53)

To address the mechanisms of vasopressin signaling in the renal IMCD, we have been following a “systems–biology” approach consisting of identification of the component proteins via protein mass spectrometry-based analysis (2;29;30;62;71;102), and antibody-based quantification of protein abundance (41), coupled to computational analysis of the identified

†<http://dir.nhlbi.nih.gov/papers/lkem/imcdtr/>

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proteins to discover signaling networks involved in IMCD regulation (30). An important product of these studies is the generation of a ‘parts list’, the IMCD proteome, that includes the signaling apparatus (http://dir.nhlbi.nih.gov/labs/lkem/rm/proteomics_db.asp). The IMCD proteome database currently is made up of 2338 proteins identified at high stringency.

Despite the success so far of the proteomics approach, proteomics methodologies have limitations that make it unlikely that all of the proteins that play important roles in vasopressin signaling will be found. Limited sensitivity is the chief factor. In the present study, in order to augment our enumeration of an ‘IMCD parts list’, we have pursued an analysis of the IMCD transcriptome using Affymetrix oligonucleotide arrays. The studies were carried out in native IMCD cells freshly isolated from rat inner medullas. The arrays contain approximately 31,000 features representing most of the expressed genes in the rat genome. Although the approach is comprehensive, the chief objective is to determine what transcripts are expressed in functional categories most relevant to vasopressin signaling related to short- and long-term regulation of water and urea transport in the IMCD.

The new data from the present study add to transcriptomic data obtained in microdissected cortical and outer medullary collecting ducts using a micro-SAGE technique (9). SAGE data, however, are not available for the IMCD. Early approaches to transcriptional profiling in IMCD involved large-scale sequencing of cDNAs prepared from microdissected IMCD segments, an approach that was informative but not comprehensive (78). A number of studies have also reported transcriptional profiling of whole inner medulla (7;8;51;66;80), which contain IMCDs as well as loops of Henle, vasa recta, capillaries and interstitial cells. IMCDs make up about 40% of the inner medullary tissue by volume (40). In the present study, we carry out transcriptional analysis of biochemically enriched IMCD cells isolated from rat renal inner medulla.

METHODS

Animals

Pathogen-free male Sprague-Dawley rats weighing 100–120 grams (Taconic Farms Inc. Germantown, NY) were maintained on an autoclaved pelleted rodent diet and *ad libitum* drinking water (NHLBI Animal Care and Use Committee approved protocol number H-0110). The age of the rats was chosen to match the age of rats typically used for our isolated perfused tubule studies (12).

Preparation of IMCD and non-IMCD cell suspensions

IMCD and non-IMCD cells were prepared from whole inner medullas as previously described (62) with slight modification (Figure 1 and Supplementary Methods).

In order to assess purity of IMCD samples, aliquots from each cell suspension were loaded onto SDS-polyacrylamide gels and immunoblotting was carried out as described (12). An immunoblot for a collecting duct marker AQP2 (Figure 2 panel A) demonstrated that AQP2 was indeed highly enriched in the IMCD fraction and depleted from the non-IMCD fraction (Band densities: IMCD fraction, 412; non-IMCD fraction, 45). An immunoblot for AQP1, a marker of vasa recta and thin descending limbs of Henle (Figure 2 panel B), demonstrated that there was relatively little contamination of the IMCD fraction from non-IMCD elements (Band densities: IMCD fraction, 1.4; non-IMCD fraction, 29.4). Lack of contamination by outer medullary cells was demonstrated by immunoblotting using an antibody to NKCC2, a marker of the outer medullary thick ascending limb (Figure 2 panel C) (Band densities: IMCD fraction, 0.9; non-IMCD fraction, 0.4; OMCD fraction, 11.3).

Total RNA extraction

Total RNA of IMCD and non-IMCD cells was extracted using Trizol reagent (Invitrogen, Carlsbad, CA) following the manufacturer's protocol. Full details are reported in the Supplementary Methods. Typically, for IMCD, the yield was 1 µg per kidney and, for non-IMCD, the yield was 0.7 µg per kidney.

Oligonucleotide microarrays

Hybridization probes (labeled cDNAs corresponding to the transcripts) were prepared and hybridized to the Affymetrix Rat Genome 230 2.0 microarrays (Affymetrix Inc, Santa Clara, CA) according to the manufacturer's protocols. See Supplementary Methods for full details.

Microarray data analysis and identification of IMCD and non-IMCD transcribed genes

The total number of genes with the Affymetrix Detection p-value consistent with a "Present Call" (*detected*) was about 17,000 from 31,000 features in the Affymetrix Rat Genome 230 2.0 array for both IMCD and non-IMCD samples. These 17,000 features corresponded to about 10,200 distinct genes. The remaining 14,000 features were identified to have "Absent" (not detected) or "Marginal" Calls based on the Detection p-value from Affymetrix GCOS software. Intensities of each probe set were normalized by median-transformed normalization.

The IMCD and non-IMCD samples contain a relatively small amount of contaminating cells from non-IMCD elements and IMCD elements, respectively (see AQP1 and AQP2 immunoblots in Figure 2). We calculated corrected values for mRNA signals using estimates of cross contamination. The appropriate equations are (see Supplementary Methods for derivation):

$$\text{IMCD}_{\text{corrected}} = (d \cdot \text{IMCD}_{\text{observed}} - b \cdot \text{non-IMCD}_{\text{observed}}) / (ad - bc) \quad (\text{Equation 1})$$

$$\text{non-IMCD}_{\text{corrected}} = (a \cdot \text{non-IMCD}_{\text{observed}} - c \cdot \text{IMCD}_{\text{observed}}) / (ad - bc) \quad (\text{Equation 2})$$

where,

$\text{IMCD}_{\text{observed}}$ = the normalized signal intensity for a given feature for IMCD sample;

and

$\text{non-IMCD}_{\text{observed}}$ = the normalized signal intensity for the same feature for the corresponding non-IMCD sample;

and

a = fraction of the total signal in IMCD samples from IMCD cells

b = fraction of the total signal in IMCD samples from non-IMCD cells

c = fraction of the total signal in non-IMCD samples from IMCD cells

d = fraction of the total signal in non-IMCD samples from non-IMCD cells.

Note also that $a + b = 1$ and $c + d = 1$.

The cross contamination values a, b, c, and d could in principle be estimated from the AQP1 and AQP2 immunoblots but a more general approach is to use the array data to determine the required cross contamination correction. Supplementary Figure 3 shows a histogram of the ratios of normalized, but uncorrected, IMCD-to-non-IMCD signal ratios for individual features

on the array. In theory, the maximum and minimum ratios should be bounded at a distinct value determined by the degree of cross contamination. The maximum and minimum ratios in principle could then be used to estimate the degree of cross contamination. However, as seen in Supplementary Figure 3, there is considerable splay in the tails of the ratio histogram, indicating that a direct choice of single unique values for cross contamination is not feasible. Consequently, we chose an alternative approach in which we chose a set of transcripts corresponding to IMCD and non-IMCD marker proteins. These are transcripts known to be exclusively or predominantly expressed in the IMCD (“IMCD markers”) and transcripts known to be expressed in non-IMCD structures but not in the IMCD itself (“non-IMCD markers”). Thus, we choose values for a, b, c, and d such that the mean value for [non-IMCD_{corrected}] is zero for a selected set of IMCD markers and the mean value for [IMCD_{corrected}] is zero for a selected set of non-IMCD markers. For IMCD markers, we have chosen aquaporin-3 (*Aqp3*), gamma ENaC (*Scnn1g*), ClC-K2 (*Clcnkb*), the vasopressin V2 receptor (*Avpr2*) and frizzled receptor 1 (*Fzd1*). For non-IMCD markers, we have chosen UT-B (*Slc14a1*, expressed in vasa recta), NHE3 (*Slc9a3*, expressed in thin descending limb of Henle), von Willebrand’s factor (*Vwf*, expressed in endothelial cells of vasa recta) and EEAC1 (*Slc1a1*, expressed in thin limbs of Henle’s loop). Calculated in this way, the resulting values for b, c, and d were: $a = 0.80 \pm 0.00$, $b = 0.20 \pm 0.00$, $c = 0.27 \pm 0.01$ and $d = 0.73 \pm 0.01$.

Equations 1 and 2 were applied to each feature to gain corrected signal intensities that would be expected if the samples were pure IMCD and non-IMCD suspensions. The signal intensities for IMCD and non-IMCD are reported as mean $\pm$ SE for all replicates.

RESULTS AND DISCUSSION

The general strategy employed in this study was to use Affymetrix microarrays to profile gene expression at an mRNA level in rat IMCD cells, focusing on the general question: What gene products can be identified in the IMCD that could be components of the pathways and networks involved in regulation of aquaporin-2 and osmotic water permeability in the IMCD? The data presented are calculated from the results of 6 microarray chip sets, i.e. 3 pairs of IMCD vs. non-IMCD transcripts. Total RNA samples for each pair were isolated from 7 rats (14 inner medullas). A full listing of the results is shown in Supplementary Table S1 and the full results have also been deposited in the GEO database (GSE7891: at <http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?token=rbyjrsiskikmeze&acc=GSE7891>). 7913 annotated transcripts (compared to 10,206 total transcripts above background) were found to be expressed above background in the IMCD cells.

We have created a new online database (the “IMCD Transcriptome Database” at <http://dir.nhlbi.nih.gov/papers/lkem/imcdtr/>) to provide ready access to these data. This site also includes the data in a downloadable format and a BLAST facility for searching for a particular transcript in the database.

The variability of the normalized, corrected signals for the three experiments is shown as scattergrams in Supplementary Figure 4. As can be seen, the distribution of IMCD and non-IMCD signals were reproducible with more than 85% of IMCD features and more than 80% of non-IMCD features showing coefficients of variation ($CV = \text{variance}/\text{mean} \times 100\%$) less than 15%. Supplementary Figure 5 shows mean corrected, normalized signals for IMCD plotted against the non-IMCD values for the same features. Values that deviate from the diagonal indicate transcripts selectively expressed in IMCD (above line) or non-IMCD elements of inner medulla (below line). Supplementary Figure 6 shows the corrected values for IMCD plotted against the corresponding non-corrected values. As can be seen, the corrections were generally relatively small. Only 0.8 percent of the values had correction factors of 50% or more of the uncorrected values.

In the following, we present a series of tables showing, for specific categories of gene products, what transcripts in IMCD cells are associated with the highest signals on the microarrays along with comments regarding gene products that are thought to be involved in vasopressin action in the IMCD. We also include significant negatives in which corrected signals in the IMCD were indistinguishable from zero. The classification of expressed genes in each table was based on classification terms from the PANTHER Database (83) and the Rat Genome Database (87). We emphasize that the signals from the array provide a general index of relative expression levels for individual transcripts but do not necessarily correlate with the absolute level of the specific mRNA in the cells. Furthermore, transcript level does not necessarily correlate with protein expression level owing to differences in translation rate and protein stability among various proteins (7).

G-protein coupled receptors

Table 1 summarizes the microarray results for G-protein coupled receptors. Normalized and corrected intensity values reported in all tables are calculated from the raw data as described in the Methods section. The value of 1.0 represents the median value for all positive transcripts in the IMCD. A number of receptors with well established roles in the IMCD were identified and had substantial signals on the arrays. These were the vasopressin V2 receptor, the frizzled receptor 1, the PGE₂ receptor EP1, the endothelin B receptor, the adenosine A1 receptor, the adrenergic receptor 2a, the frizzled receptor 6, the adrenergic receptor 1d, the PGE₂ receptor EP4, and the nucleotide receptor P2Y2. Of these, only the vasopressin V2 receptor (53) and the prostaglandin E₂ receptor EP4 (5) are known to be coupled to the heterotrimeric G-protein G_s and to generate cyclic AMP when bound to ligand. Presumably, PGE₂ does not increase water permeability in the IMCD because of the prevailing inhibitory effect of the EP1 receptor, which signals via G_{aq}. In addition to receptors with well-established roles, a number of other G-protein coupled receptors were identified in the IMCD (Table 1), providing hypotheses for further study. For example, the chemokine orphan receptor 1 (Cmkr1) is the highest ranked receptor from the point of view of normalized intensity.

In our previous study, vasopressin-induced cAMP production was inhibited by epinephrine or the α 2-agonist clonidine, but not by the α 1-agonist, phenylephrine (46). This finding is consistent with the present finding of dominant expression of the α 2a-adrenergic receptor relative to the α 1-adrenergic receptor as shown in Table 1. In contrast, β -adrenergic receptor expression was below background.

The adenosine receptor A1 is associated with a high signal intensity on the IMCD arrays (Table 1). It has been shown that adenosine analogues can decrease water permeability induced by arginine vasopressin (18). Our previous experiments using the adenosine A1 agonist NPEA (N⁶-2-phenylethyladenosine) showed an increase in intracellular Ca²⁺ concentration and this effect was inhibited by the selective adenosine A1 antagonist 8-phenyltheophylline (17).

Endothelin-1 can induce diuresis in part by inhibiting water reabsorption induced by arginine vasopressin in the IMCD (60). In the IMCD, it has been demonstrated by immunofluorescence and RT-PCR that the endothelin B receptor is the predominant endothelin receptor subtype in agreement with our microarray data (42;81).

Purinergic P2Y2 receptors have been demonstrated in the rat IMCD (38). Binding of ATP or UTP to P2Y2 receptors increase intracellular calcium in the IMCD, decreasing water permeability (17). This inhibition of water permeability might occur through activation of protein kinase C and reduction of cellular cAMP levels (37).

Arginine vasopressin receptors are of two types, V1 and V2 receptors. From the microarray analysis, the signal intensity corresponding to the V1a and V1b receptors in the IMCD cells

was negligible. In contrast, V2 receptor signal intensity was relatively high. This evidence supports our previous finding that V2 receptors, but not V1a receptors, are expressed in the IMCD (16;45).

Heterotrimeric G-proteins

Table 2 shows heterotrimeric G-protein subunits expressed in the IMCD. The α subunits expressed include three inhibitory α subunits ($G_{\alpha i}$) which regulate adenylyl cyclases in an inhibitory fashion, the stimulatory α subunit ($G_{\alpha s}$) which stimulates adenylyl cyclases, $G_{\alpha q}$ which couples to phospholipase C β (PLC β) isoforms and $G_{\alpha 12}$, an activator of Rho-GEF (43) and a regulator of the actin cytoskeleton. All are potentially involved in vasopressin signaling.

Nucleotide cyclases

Only 3 adenylyl cyclase transcripts of the 10 known genes were identified in the IMCD samples, namely *Adcy6* and *Adcy3* previously identified in the IMCD (28), as well as *Adcy9* as shown in Table 3. In addition, soluble guanylyl cyclase 1 was identified, which functions as a nitric oxide receptor and transducer. Interestingly, there was no significant signal for any of the three nitric oxide synthase (NOS) isoforms in the IMCD samples, although NOS3 (endothelial NOS) was detected in the non-IMCD samples (Table 16). However, previous qualitative RT-PCR studies in microdissected IMCD segments demonstrated the presence of NOS1, 2 and 3 mRNA (96). Furthermore, both NOS1 (102) and NOS2 (91) protein has been detected in the IMCD by protein mass spectrometry.

Cyclic nucleotide phosphodiesterases

As shown in Table 4, the predominant cyclic nucleotide phosphodiesterase transcripts correspond to the type 4 and type 1 classes, consistent with pre-existing findings (15;75). Type 4 phosphodiesterases (PDE4A, PDE4B, PDE4C, and PDE4D, coded by separate genes) are cAMP-specific and inhibitable by rolipram. Type 1 phosphodiesterases hydrolyze both cAMP and cGMP and are calmodulin-dependent. No significant signal was found for PDE5, which has been implicated in regulation of aquaporin-2 trafficking in more proximal collecting duct segments (4).

Protein kinases

There are more than 500 genes coding for protein kinases in mammalian genomes (48). As shown in Table 5, a large number of these are expressed in the IMCD. There were 93 serine/threonine kinases with signals above the median value in the IMCD (corrected signal above 1.0, Table 5A). Serum-glucocorticoid regulated kinase, *sgk1*, a serine/threonine kinase closely related to protein kinase B (*Akt1*), is the kinase with greatest signal intensity in the IMCD (Table 5A). This kinase is strongly regulated by the mineralocorticoid hormone aldosterone (11). WNK1 and WNK4, two kinases implicated in regulation of ion transport in more proximal parts of the renal tubule (95;99), are also expressed in the IMCD with a relatively high signal intensity. Protein kinase A (catalytic β subunit), long recognized as a major element of vasopressin signaling, is also associated with a high signal intensity on the IMCD arrays. Additional protein kinases with proposed roles in vasopressin signaling have relatively high signal intensities including protein kinase B (*Akt1*), protein kinase C (iota, zeta, nu and epsilon), casein kinase isoforms, calmodulin-dependent kinases, myosin light chain kinase, Rho-kinase, two G-protein coupled receptor kinases (GRK2 and GRK6), various kinases in MAP kinase pathways, and cyclic-GMP-dependent kinases. Obviously, a large number of kinases were detected whose roles in the IMCD have not been investigated.

Relative to the number of serine/threonine kinases in IMCD, There are relatively few tyrosine kinases (Table 5B and 5C). Tyrosine kinases are of two types: non-receptor tyrosine kinases

and receptor tyrosine kinases. Of the non-receptor tyrosine kinases, Frk (a src-family homolog) is strongly expressed in IMCD relative to non-IMCD elements. Also strongly represented is Janus kinase 1 (Jak1), which regulates transcription through activation of Stat1 and/or Stat2. Of the receptor tyrosine kinases, two are heavily expressed in the IMCD relative to non-IMCD elements, namely fibroblast growth factor receptor 2 (Fgfr2) and epidermal growth factor receptor (Egfr). Most of the detectable tyrosine kinases in the IMCD have been identified previously in fetal kidney including Jak1, Frk, Ptk2, Fgfr2, Egfr, Ryk, Ddr1 and Fgfr1 (36). Tyrosine kinases are associated with regulation of cell proliferation and differentiation.

Protein phosphatases

The serine/threonine phosphatases found in the IMCD are listed in Table 6A. Focusing on the catalytic subunits, the highest signal intensities in the IMCD appear to be the PP1 phosphatases of which three different isoforms are represented namely, α , β and γ . The catalytic subunit of calcineurin, a Ca^{2+} -calmodulin dependent phosphatase (PPP3CA), is also expressed as is the catalytic subunit of the magnesium-dependent phosphatase, PP2C. For all of these catalytic subunits, significant expression was found in both the IMCD and non-IMCD fractions, consistent with their ubiquitous roles in cell signaling (69). In contrast, the PP2A catalytic subunit signal on the IMCD arrays was indistinguishable from background, although several of its regulatory subunits were present. Calcineurin has been reported to be expressed in the IMCD and to be colocalized with PKC ζ , the RII subunit of PKA, and AQP2 in endosomes of the IMCD (35). It has been reported that the α isoform of the calcineurin catalytic subunit is required for normal intracellular trafficking of AQP2 (23). Finally, there are many more genes in the genome that code for Ser/Thr phosphatase regulatory subunits than for catalytic subunits, a number of which were found to be expressed in the IMCD.

Table 6B summarizes the protein tyrosine phosphatases (PTPs) found in the IMCD. The protein tyrosine phosphatases can be classified into transmembrane receptor-like protein tyrosine phosphatases and cytosolic protein tyrosine phosphatases (84). There are 16 PTP transcripts identified in the IMCD samples with signal intensity above median. Ten coded for cytosolic PTPs and 5 for transmembrane receptor-like PTPs.

Dual specificity phosphatases in the IMCD are summarized in Table 6C. These phosphatases dephosphorylate a phosphotyrosine and a neighboring phosphothreonine. Among these, the transcript corresponding to Dusp1 displays the strongest intensity in the IMCD. Its function is to dephosphorylate the MAP kinases ERK1 and ERK2 at the sites phosphorylated by dual specificity kinases (MAP kinase kinases or MEKs) (73). Two dual specificity phosphatases are expressed in the IMCD but not in non-IMCD cell types, namely Dusp2 and Dusp5.

AKAPs

A-kinase anchoring proteins (AKAPs) are scaffold proteins that facilitate localized signaling through creation of binding complexes that bring enzymes (mainly kinases and phosphatases) into the vicinity of their targets. Table 7 shows the AKAPs whose signal intensity in the IMCD samples were above background. Those expressed at highest levels were AKAP-7, -8, -9, -11 and -13. AKAP7 (aka AKAP18 δ) has been shown to be colocalized with AQP2 intracellularly in the IMCD (27). Both AKAP7 and AQP2 were localized predominantly at the apical plasma membrane when the IMCD cells were stimulated with dDAVP.

14-3-3 proteins

14-3-3 proteins are phospho-serine/phospho-threonine binding proteins. By virtue of their binding specificities, they have been proposed to play various phosphorylation-dependent regulatory roles. There are seven isoforms of 14-3-3, viz. β , γ , ϵ , η , σ , τ and ζ (Note: α and δ are phosphorylated forms of β and ζ isoforms (97;98)). In the present study, 5 of 7 isoforms of

14-3-3 were identified in the IMCD with high signal intensity (Table 15). Functional roles of 14-3-3 in the IMCD have not been elucidated yet. However, 14-3-3 proteins have been found to modulate the function of the ubiquitin ligase Nedd4-2 in cultured collecting duct cells by binding to Nedd4-2 after sgk1-mediated phosphorylation (3).

Phospholipases

Table 8 shows the phospholipases in IMCD with signals above background for either IMCD or non-IMCD samples. Among the phospholipases with the highest signal intensities was cytosolic phospholipase A2 (PLA₂) which hydrolyzes the ester bond in SN-2 position of the core glycerol. This reaction is important because it liberates arachidonic acid, an unsaturated fatty acid that is the substrate for prostaglandin synthesis. Vasopressin has been seen to be variably associated with stimulation of prostaglandin E2 synthesis in collecting ducts, which provides a modulating influence on water permeability (68). Prostaglandin E2 synthesis depends on expression of one of two cyclooxygenases (COX-1 and COX-2). COX-1 exhibited a very high signal on the arrays, with a signal that is in the top 100 among transcripts in the IMCD. Both COX-1 and COX-2 are selectively expressed in the IMCD. As noted above, three different PGE₂ receptors are expressed in the IMCD consistent with the view that PGE₂ works as an autocrine.

As shown in Table 8, several isoforms of phospholipase C (PLC) are also expressed in the IMCD. PLC cleaves phosphatidylinositol 4,5-bisphosphate (PIP₂) to yield two second messengers, diacylglycerol and inositol 1,4,5 tris-phosphate (IP₃). The beta isoforms are activated by heterotrimeric G-protein alpha subunits Gα_q and Gα₁₁. There are two PLC-β isoforms expressed in the IMCD, PLCβ1 and PLCβ4. PLCβ1 is expressed selectively in IMCD cells versus non-IMCD cells. PLCγ isoforms are regulated via tyrosine phosphorylation, typically following growth factor receptor activation (65). PLCγ1, but not PLCγ2, appears to be expressed in IMCD substantially above background. PLCδ4 is also selectively expressed in the IMCD over non-IMCD cell types.

Small GTP-binding proteins

Table 9 lists transcripts corresponding to small GTP-binding proteins expressed on the IMCD arrays including Rab proteins, Arf/Sar proteins, Rho/Rac/CDC42 proteins, Ras and Ras-like proteins, and Ran proteins (77).

Members of the Rab family of proteins play a critical role in intracellular membrane trafficking. Large numbers of transcripts corresponding to Rab proteins were identified on the IMCD expression arrays (Table 9A) including many of those previously identified in a proteomic analysis of aquaporin-2-containing vesicles in IMCD cells (2). Most of the Rab proteins were found both in IMCD and non-IMCD cells, although Rab15 and Rab31 appear to be selectively expressed in the IMCD. Based on studies in non-renal cells, Rab15 is believed to be expressed in early endosomes and recycling endosomes (74). Rab31 is thought to be an early endosomal Rab based on its similarity to Rab5 (72).

ADP-ribosylation factors (Arfs) regulate coat protein-mediated vesicle budding, vesicular trafficking, and actin cytoskeleton assembly. Transcripts corresponding to most of the known Arf and Arl (ADP-ribosylation factor-like) proteins are expressed in the IMCD (Table 9B). Arf1 has been shown to be important for Golgi to ER transport. Arf6 is important for endocytosis (10;14). Both Arf1 and Arf6 displayed high signal intensity on the arrays. Transcripts for the Arf-like proteins Sar1a and Sar1b were also found in the IMCD.

Rho/Rac/CDC42 GTPases are involved in regulation of the actin cytoskeleton and cell mobility. CDC42, Rnd1, Rac1, and RhoA are the four members of this family with the greatest

signals on the arrays (Table 9C). In IMCD cells in primary culture, cAMP was found to inhibit Rho activation, thereby stimulating actin depolymerization and aiding translocation of aquaporin-2 to the plasma membrane (90). Rnd1 is expressed at a very high level in IMCD relative to other inner medullary cell types, specifically about 20-fold higher. Rnd1 has also been reported to promote disassembly of actin filaments (55). However, whether it plays a role in aquaporin-2 regulation has not yet been reported. A number of other Rho-like GTPases were also associated with high signal intensities in the IMCD including RhoB, RhoC, RhoG, RhoQ, RhoT2, and Rnd3.

The Ras-like protein family of small GTPases includes Rap, Rheb and Ral as well as Ras itself. They play an important role in regulating cell proliferation and differentiation. Among the Ras and Ras-like protein transcripts expressed in the IMCD, Rheb was associated with the greatest signal on the arrays (Table 9D). Rheb is a small GTPase that binds and activates the mTOR kinase (1). Another transcript with a relatively high signal intensity was K-Ras. This isoform of Ras has been shown to be an aldosterone-stimulated protein in collecting duct cells (93). Transcripts corresponding to other Ras-like proteins expressed in the IMCD include RalA, RalB, Rap1a, Rap1b, Rasd1, and Rras2. The Ral proteins have been found in aquaporin-2 containing intracellular vesicles in the IMCD (2). These proteins are associated with the so-called 'exocyst complex' involved in basolateral targeting of proteins. We have identified RalA in the basolateral plasma membrane of IMCD cells (unpublished data). Rap1 is involved in cell morphogenesis, cell differentiation, cell adhesion and cytoskeleton organization. It has been demonstrated that SPA-1 (signal-induced proliferation-associated 1), a GTPase-activating protein specific to Rap1, binds to AQP2 in the renal medulla (56). We identified SPA-1 in the IMCD in this study (Supplementary Table S1). Studies in SPA-1 knockout mice showed a defect in AQP2 trafficking to the apical plasma membrane (58). Rap1 is also a target of Epac, a RapGEF, that is activated by cAMP. Epac has been found to be important for regulation of vasopressin-stimulated calcium mobilization in collecting duct cells (101), which is necessary for AQP2 trafficking (13). Transcripts corresponding to Epac1 but not Epac2 were identified in the IMCD in our array studies (Supplementary Table S1). One of Rap1's targets is Raf1, a kinase in the MAP kinase pathway (see above). A full listing of transcripts corresponding to small GTP-binding protein GEFs, GAPs and interacting proteins found in the IMCD is reported in (Supplementary Table S4).

SNARE proteins and SNARE-related proteins

SNARE proteins play an important role in membrane fusion in eukaryotic cells. Syntaxin 7 and 12 were the SNARE protein transcripts with the greatest signals in the IMCD as shown in Table 10. Syntaxin 7 is present in the late endosome while syntaxin 12 is present in the recycling endosome (63), an organelle that may be important in AQP2 recycling to the plasma membrane. Plasma membrane syntaxins include syntaxins 2, 3 and 4. Among these, only syntaxin 4 was associated with a strong signal in the IMCD. This syntaxin is present in the apical plasma membrane and has been proposed to be involved in AQP2 trafficking (47). In the current study, VAMP3 (cellubrevin) had the strongest signal intensity among VAMP/synaptobrevin transcripts. This protein was previously identified in the IMCD by immunogold electron microscopy (22). VAMP2 and VAMP4 transcripts were also found to be expressed in the IMCD above the median value. VAMP2 colocalizes with aquaporin-2 in AQP2-containing intracellular vesicles (2;54). An additional subfamily of SNARE proteins is the SNAP25 homologues. SNAP25 is neural-specific and its expression level was very low in the IMCD. SNAP23 protein has previously been identified in the IMCD on the basis of immunorecognition (32) and in the present study we found that it is expressed in the IMCD above the median expression level for all IMCD transcripts.

Clathrin and clathrin adaptors

Both clathrin heavy chain and light chain polypeptides were identified in the IMCD (Table 11). The clathrin adaptors, AP1, AP2 and AP3 are also expressed in the IMCD. These clathrin adaptor proteins function in post-Golgi trafficking pathways. AP1 regulates vesicle transport between the trans-Golgi network and endosomes. AP2 regulates endocytosis (6) and AP3 is involved in vesicle trafficking from early endosomes to late endosomes or lysosomes (59). In addition, three clathrin adaptors called epsins are strongly expressed in the IMCD namely epsin 4 (enthoprotein), epsin 3 and epsin 2. These proteins bind both to ubiquitylated integral membrane proteins and to PIP2 (in addition to clathrin) and may be involved in regulated endocytosis of apical plasma membrane transporters in the collecting duct (94). Finally, an adaptor called phosphatidylinositol binding clathrin assembly protein or CALM, a PIP2-binding clathrin adaptor was found at a relatively high signal intensity level on the IMCD arrays.

Dynamin-like GTPases

Dynamins are GTPases (although not 'small' GTPases) that are associated with clathrin-coated pits and are involved in the abscission process forming clathrin-coated vesicles. In this study, dynamin-1 was expressed below background and dynamin-2 and -3 were expressed at very low levels only (0.21 and 0.45, respectively, Table 15). In contrast, the dynamin-like GTPases Mx1 and Mx2 were associated with high signal intensities in the IMCD (7.60 and 16.14, respectively). Their locations and roles in the IMCD cell have not been reported.

Actin and actin-binding proteins

γ - and β -actin, the two chief forms of non-muscle actin were associated with the highest actin signals on the IMCD arrays. These forms have been seen previously in proteomic studies of the IMCD (2;62). Vasopressin induces actin filament depolymerization in the IMCD (70), a process that has been shown to be required for AQP2 translocation from intracellular to apical plasma membrane in cultured CD8 cells (79).

ERM proteins (ezrin, radixin, and moesin) are actin-binding proteins that link actin to the plasma membrane and are involved in signal transduction and cytoskeleton remodeling (85). In the present study, ezrin (Vil2) and radixin (Rdx) were found to be expressed in IMCD at high signal intensity. On the contrary, moesin mRNA was not detected. A previous study (66) reported a marked increase in the expression of ezrin mRNA in the inner medullas of lithium-treated rats, which was associated with an increase in ezrin protein in the IMCD. The authors proposed that this protein plays a role in the nephrogenic diabetes insipidus seen in response to lithium. Moesin has been reported to mediate trafficking of AQP2 to plasma membrane in rabbit CD8 cells (79). Our finding of low or nonexistent levels of moesin mRNA in the IMCD suggests that moesin's role in AQP2 trafficking may not be universal.

Several actin-binding proteins have been identified that are AQP2-binding partners in rat inner medulla including α 2-spectrin, α -tropomyosin 5b (tropomyosin 3 γ), gelsolin, and α -actinin (57). Transcripts corresponding to all of these proteins showed high signal intensity on our microarrays.

Myosins

Myosin regulatory light chain B and non-muscle myosin II-B (heavy chain 10) were associated with the greatest signals among myosin gene products. Also associated with relatively high signals in IMCD were myosin II-A (heavy chain 9) and unconventional myosins 1B, 1C, 1D, and 1E, as well as myosin 5B. Myosin regulatory light chain has been demonstrated to be phosphorylated in the IMCD in response to vasopressin (12). This protein regulates the non-

muscle myosins II-A and II-B, both of which are expressed in the IMCD. As demonstrated previously, myosin II-B is collecting duct selective in the inner medulla (12). Myosin II-A has been demonstrated to be bound to AQP2 in cell lysates of kidney inner medulla (57). Recently myosin 5B has been reported to be associated with Rab11-positive AQP2-containing endosomes, presumably recycling endosomes (52).

Microtubules and microtubule-associated proteins

Table 12C shows the transcripts corresponding to the microtubule proteins and microtubule-associated proteins including molecular motors that are expressed above background on the arrays. Microtubule disruption with colchicine and other agents reduces the hydro-osmotic action of vasopressin in collecting ducts (61) through effects on AQP2 trafficking (67). In addition, it has been shown that both dyneins (microtubule-based molecular motors) and dynactin in the inner medulla were associated with trafficking of AQP2-containing vesicles to the apical plasma membrane (49). In the present study, multiple dynein and dynactin isoforms were found in the rat IMCD. Cytoplasmic dyneins are multi-subunit proteins consisting of a combination of light chains, heavy chains, and intermediate chains. The predominant dyneins in the IMCD are cytoplasmic dyneins with signal intensity of light chain-1 > intermediate chain-1 > heavy chain-2 polypeptides. Cytoplasmic dynein heavy polypeptide-2 is selectively expressed in IMCD over non-IMCD elements of the inner medulla.

Transporters and channels

The transcripts corresponding to transport proteins found in the IMCD above background are reported in Table 13. As can be seen in Table 13A, three water channels are associated with extremely high signal intensities, namely AQP4, AQP2 and AQP3. The signal intensities for these aquaporins were ranked 3rd, 10th and 14th, respectively, among the 7913 annotated transcripts found in the IMCD. In contrast, AQP1 was present only in the non-IMCD samples from the inner medulla.

Table 13B shows the ion channels and transporters expressed in the IMCD. The chloride channel CIC-Kb is expressed in the basolateral plasma membrane of cells throughout the distal nephron from thick ascending limb to the collecting duct and is mutated in some forms of Bartter's Syndrome (92). Its transcript was found at a moderate level in IMCD but not in non-IMCD components of the inner medulla. Note that the levels of the epithelial sodium channel (ENaC) α , β , and γ transcripts are relatively low, consistent with the low level of ENaC protein expressed in this segment (24).

Table 13C shows the non-mitochondrial solute carrier (SLC) transcripts found in the IMCD. Among these, the transcript with the highest signal was the vasopressin-regulated urea transporter UT-A (*Slc14a2*). This protein is key to the accumulation of urea in the renal inner medulla (19; 20). Its manner of regulation by vasopressin is controversial with one group claiming that the protein undergoes regulated trafficking (39) while another finds an absence of regulated trafficking by vasopressin (33).

Supplementary Table S6 reports the mitochondrial transporters and carriers detected. As may be expected, many of these were components of the F0-F1 ATP synthase responsible for proton gradient-driven ATP synthesis.

Transcription factors

We identified about 824 transcription factors expressed in IMCD above background. A list of the transcription factors identified with signal intensity above median is shown in Supplementary Table S7. Only a few of these have been studied in the context of AQP2 regulation.

The 5' flanking region of AQP2 has been sequenced and putative transcription factor binding sites have been identified including AP1, AP2, CRE, GATA, and Sp1 motifs in human, mouse and rat (64;88).

Leucine zipper transcription factors including CREB-like factors

Long-term increases in ambient vasopressin in animals or cultured cells results in increased AQP2 protein abundance that is mediated at least in part by enhanced AQP2 gene transcription rates (53). A cAMP responsive element (CRE) plays a critical role (31;50;100). It has been widely assumed that regulation of AQP2 transcription involves the transcription factor CREB. However, in this study, we found that CREB itself (now called Creb1) is associated with an extremely low signal intensity on the arrays (Table 14A). This finding raises the possibility that other CREB-family members may be responsible for the long-term regulation of AQP2 gene transcription. The CREB-like transcriptional factors in the IMCD associated with high signal intensities are Atf3 and Atf4 (Creb2). All of these factors share the same recognition site TGACGTCA, which is present in the AQP2 promoter region. Atf3 is thought to be a stress-response transcription factor (25). We hypothesize that Atf4 (Creb2) mediates the effects of cAMP on AQP2 gene expression.

Previous studies have demonstrated that Fos expression is markedly increased in rat inner medulla in response to vasopressin (7). Furthermore, c-Jun phosphorylation was found to be increased in the same study. These two proteins together constitute the transcription factor AP1. They were both found on our arrays with very high signal intensity (Table 14A)

Zinc finger transcription factors

Kruppel-like factors (KLF) are transcription factors in the zinc finger family that regulate cell differentiation, cell proliferation and development with a DNA-binding site motif of CACCC (34;86). KLF12 was found to be expressed in the IMCDs of young mouse kidneys (76). In the current study in mature rats, the KLF12 intensity on the arrays was, however, below background. Other KLF transcription factors are expressed in the IMCD including KLF5, KLF6, KLF9, and KLF10.

Rat GATA3 but not GATA2 can be amplified by RT-PCR from the collecting ducts of rat kidneys (89). Overexpression of rat GATA3 in primary culture of mouse OMCD cells can increase AQP2 activities, indicating that GATA3 could interact with GATA motifs in the AQP-2 promoter (89). Also, both GATA2 and GATA3 were detected at high signal intensity in the IMCD, but not in the non-IMCD portions of the inner medulla (Table 14B). GATA1 signal intensity was below background. Sp1 is also a member of the KLF transcription factor family. In the present study, Sp1 showed a moderate signal intensity in the IMCD.

Rel/Dorsal transcription factors

TonEBP (Nfat5) is a Rel/Dorsal transcription factor that regulates cellular accumulation of organic osmolytes and HSP70. These mechanisms are critical to the process that protects cells from the hypertonic stress of the renal medulla. In the present study, TonEBP was indeed found to be expressed in the IMCD at a transcript level, although, the signal intensity was below the median on the arrays (Supplementary Table S1). Mice deficient in the TonEBP gene display severe atrophy of the renal medulla, presumably because the cells failed to adapt to the hyperosmolality (44). In response to long term hypertonicity in mpkCCD cells, TonEBP mediates expression of UT-A and possibly AQP2 independent of vasopressin level (26). However, AQP2 was not found to be strongly regulated by local osmolality in the renal inner medulla (82).

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Figure 1.
Isolation scheme for rat IMCD and non-IMCD cell fractions.

Figure 2.

Immunoblots illustrating purity of fractions. A. Immunoblot of IMCD and non-IMCD fractions probed with aquaporin-2 (AQP2) antibody, 10 μ l/lane. B: immunoblot probed with aquaporin-1 (AQP1) antibody, 10 μ l protein loaded/lane. C: Immunoblot probed with NKCC2 antibody, 10 μ l protein loaded/lane. Protein concentrations in samples were: IMCD, 1.25 μ g/ μ l, non-IMCD, 1.1 μ g/ μ l. OMCD, 0.8 μ g/ μ l.

Table 1

G-protein coupled receptors.

Gene Name	Gene Symbol	IMCD-Signal Mean $\pm$ SE	non-IMCD-Signal Mean $\pm$ SE
chemokine orphan receptor 1	Cmkor1	17.40 $\pm$ 1.13	1.55 $\pm$ 0.33
arginine vasopressin receptor 2	Avpr2	14.20 $\pm$ 0.34	-1.89 $\pm$ 0.22
endothelial differentiation, lysophosphatidic acid G-protein-coupled receptor, 2	Edg2	8.74 $\pm$ 0.31	3.73 $\pm$ 0.43
frizzled homolog 1 (Drosophila)	Fzd1	8.62 $\pm$ 0.13	-0.87 $\pm$ 0.24
thrombin receptor	F2r	7.42 $\pm$ 0.14	4.80 $\pm$ 0.45
prostaglandin E receptor 1 (subtype EP1)	Ptger1	6.78 $\pm$ 0.27	-1.27 $\pm$ 0.17
progesterone and adipoQ receptor family member V	Paqr5	6.69 $\pm$ 0.19	2.83 $\pm$ 0.09
taste receptor, type 1, member 2	Tas1r2	5.10 $\pm$ 0.21	1.62 $\pm$ 0.16
endothelin receptor type B	Ednrb	4.74 $\pm$ 0.21	7.58 $\pm$ 0.75
γ -aminobutyric acid B receptor 1	Gabbr1	3.80 $\pm$ 0.30	-0.96 $\pm$ 0.12
adenosine A1 receptor	Adora1	3.50 $\pm$ 0.05	0.64 $\pm$ 0.10
cadherin EGF LAG seven-pass G-type receptor 2	Celsr2	2.66 $\pm$ 0.17	2.99 $\pm$ 0.15
leucine-rich repeat-containing G protein-coupled receptor 4	Lgr4	2.28 $\pm$ 0.31	1.01 $\pm$ 0.14
adrenergic receptor, alpha 2a	Adra2a	2.26 $\pm$ 0.12	-0.23 $\pm$ 0.12
G protein-coupled receptor, family C, group 5, member A	Gprc5a	2.18 $\pm$ 0.25	5.93 $\pm$ 0.35
lanC-like 1	Lanc11	1.64 $\pm$ 0.07	2.46 $\pm$ 0.52
G protein-coupled receptor, family C, group 5, member C	Gprc5c	1.44 $\pm$ 0.08	1.42 $\pm$ 0.13
frizzled homolog 6 (Drosophila)	Fzd6	1.36 $\pm$ 0.13	1.15 $\pm$ 0.07
latrophilin 2	Lphn2	1.35 $\pm$ 0.17	0.74 $\pm$ 0.12
cadherin EGF LAG seven-pass G-type receptor 1	Celsr1	1.18 $\pm$ 0.07	0.93 $\pm$ 0.13
G protein-coupled receptor 116	Gpr116	1.13 $\pm$ 0.34	6.77 $\pm$ 0.43
prostaglandin E receptor 4 (subtype EP4)	Ptger4	1.09 $\pm$ 0.21	3.54 $\pm$ 0.23
purinergic receptor P2Y, G-protein coupled 2	P2ry2	0.90 $\pm$ 0.03	2.81 $\pm$ 0.20
adrenergic receptor, alpha 1d	Adra1d	0.90 $\pm$ 0.06	-0.28 $\pm$ 0.03
thrombin receptor-like 1	F2rl1	0.89 $\pm$ 0.02	0.70 $\pm$ 0.07
frizzled homolog 4 (Drosophila)	Fzd4	0.85 $\pm$ 0.08	0.38 $\pm$ 0.16
G protein-coupled receptor 37	Gpr37	0.69 $\pm$ 0.07	-0.11 $\pm$ 0.04
G protein-coupled receptor 176	Gpr176	0.48 $\pm$ 0.10	0.47 $\pm$ 0.02
frizzled homolog 3 (Drosophila)	Fzd3	0.37 $\pm$ 0.04	0.14 $\pm$ 0.03
purinergic receptor P2Y, G-protein coupled, 14	P2ry14	0.36 $\pm$ 0.06	2.37 $\pm$ 0.17
adrenomedullin receptor	Admr	0.30 $\pm$ 0.05	0.91 $\pm$ 0.24
G protein-coupled receptor 64	Gpr64	0.27 $\pm$ 0.02	0.74 $\pm$ 0.07
angiotensin receptor-like 1	Agtrl1	0.25 $\pm$ 0.01	0.51 $\pm$ 0.11
G protein-coupled receptor 37-like 1	Gpr37l1	0.23 $\pm$ 0.05	0.18 $\pm$ 0.07
G protein-coupled receptor kinase 2, groucho gene related (Drosophila)	Gprk2l	0.22 $\pm$ 0.01	0.31 $\pm$ 0.02
G protein-coupled receptor 19	Gpr19	0.20 $\pm$ 0.04	0.27 $\pm$ 0.07
calcium-sensing receptor like 1	Casr1	0.18 $\pm$ 0.03	0.16 $\pm$ 0.03
5-hydroxytryptamine (serotonin) receptor 2A	Htr2a	0.17 $\pm$ 0.02	0.20 $\pm$ 0.04
endothelial differentiation, sphingolipid G-protein-coupled receptor, 5	Edg5	0.16 $\pm$ 0.02	0.38 $\pm$ 0.01
cholinergic receptor, muscarinic 3	Chrm3	0.15 $\pm$ 0.03	0.37 $\pm$ 0.04
parathyroid hormone receptor 1	Pthr1	0.14 $\pm$ 0.05	0.18 $\pm$ 0.05
adenosine A2B receptor	Adora2b	0.14 $\pm$ 0.03	0.17 $\pm$ 0.01
endothelin receptor type A	Ednra	0.14 $\pm$ 0.01	0.21 $\pm$ 0.03
prostaglandin E receptor 3 (subtype EP3)	Ptger3	0.12 $\pm$ 0.04	0.44 $\pm$ 0.05
growth hormone releasing hormone receptor	Ghrhr	0.11 $\pm$ 0.0	0.45 $\pm$ 0.05
latrophilin 1	Lphn1	0.10 $\pm$ 0.03	0.20 $\pm$ 0.01
luteinizing hormone/choriogonadotropin receptor	Lhcgr	0.07 $\pm$ 0.03	0.27 $\pm$ 0.06
calcitonin receptor-like	Calcl	0.07 $\pm$ 0.01	0.43 $\pm$ 0.10
galanin receptor 2	Galr2	0.06 $\pm$ 0.01	0.38 $\pm$ 0.02
adrenergic receptor, beta 2	Adrb2	0.05 $\pm$ 0.01	0.19 $\pm$ 0.02
chemokine (C-C motif) receptor 5	Ccr5	0.03 $\pm$ 0.03	0.49 $\pm$ 0.07
EGF, latrophilin and seven transmembrane domain containing 1	Eltid1	0.03 $\pm$ 0.03	5.65 $\pm$ 0.17
smoothened homolog (Drosophila)	Smo	0.02 $\pm$ 0.03	0.48 $\pm$ 0.04
chemokine (C-X-C motif) receptor 3	Cxcr3	-0.02 $\pm$ 0.04	0.54 $\pm$ 0.03
thrombin receptor-like 2	F2rl2	-0.04 $\pm$ 0.01	0.46 $\pm$ 0.03
G protein-coupled receptor 109A	Gpr109a	-0.05 $\pm$ 0.01	0.68 $\pm$ 0.03
purinergic receptor P2Y, G-protein coupled, 13	P2ry13	-0.06 $\pm$ 0.01	0.55 $\pm$ 0.06
prostaglandin E receptor 2 (subtype EP2)	Ptger2	-0.06 $\pm$ 0.01	0.37 $\pm$ 0.02
complement component 3a receptor 1	C3ar1	-0.09 $\pm$ 0.01	0.71 $\pm$ 0.05
platelet-activating factor receptor	Ptafr	-0.10 $\pm$ 0.06	3.47 $\pm$ 0.32
neuropeptide Y	Npy	-0.17 $\pm$ 0.01	1.88 $\pm$ 0.33
CD97 antigen	Cd97	-0.27 $\pm$ 0.03	2.51 $\pm$ 0.20
pyrimidinergic receptor P2Y, G-protein coupled, 6	P2ry6	-0.39 $\pm$ 0.05	2.14 $\pm$ 0.09
arginine vasopressin receptor 1A	Avpr1a	-0.59 $\pm$ 0.02	4.33 $\pm$ 0.18
chemokine (C-X-C motif) receptor 4	Cxcr4	-0.84 $\pm$ 0.01	4.18 $\pm$ 0.13
complement component 5, receptor 1	C5r1	-0.90 $\pm$ 0.03	4.15 $\pm$ 0.24
endothelial differentiation sphingolipid G-protein-coupled receptor 1	Edg1	-1.07 $\pm$ 0.17	16.70 $\pm$ 1.39

Gene Name	Gene Symbol	IMCD-Signal Mean $\pm$ SE	non-IMCD-Signal Mean $\pm$ SE
EGF-like module containing, mucin-like, hormone receptor-like sequence 1	Emr1	-1.60 $\pm$ 0.05	6.91 $\pm$ 0.63

Table 2

Heterotrimeric G-proteins.

Gene Name	Gene Symbol	IMCD-Signal Mean $\pm$ SE	non-IMCD-Signal Mean $\pm$ SE
GNAS complex locus	Gnas	34.30 $\pm$ 01.16	22.86 $\pm$ 00.42
gamma 5 subunit	Gng5	11.34 $\pm$ 0.26	8.60 $\pm$ 0.41
beta polypeptide 2	Gnb2	8.81 $\pm$ 0.12	6.54 $\pm$ 0.41
beta 1	Gnb1	8.01 $\pm$ 0.35	3.41 $\pm$ 0.29
transducin (beta)-like 1X-linked receptor 1 (predicted)	Tbl1xr1_predicted	6.49 $\pm$ 0.14	1.98 $\pm$ 0.14
gamma 10	Gng10	5.79 $\pm$ 0.23	5.04 $\pm$ 0.75
alpha inhibiting 3	Gnai3	3.20 $\pm$ 0.05	0.67 $\pm$ 0.23
similar to RIKEN cDNA 5730596K20 (predicted)	RGD1309871_predicted	2.04 $\pm$ 0.12	1.62 $\pm$ 0.05
alpha q polypeptide	Gnaq	1.92 $\pm$ 0.11	1.88 $\pm$ 0.18
beta 5	Gnb5	1.85 $\pm$ 0.02	0.22 $\pm$ 0.05
alpha inhibiting 2	Gnai2	1.39 $\pm$ 0.21	6.03 $\pm$ 1.07
alpha inhibiting 1	Gnai1	1.31 $\pm$ 0.03	1.34 $\pm$ 0.20
alpha 12	Gna12	0.77 $\pm$ 0.05	0.49 $\pm$ 0.13
similar to hypothetical protein FLJ12681	RGD1310180	0.55 $\pm$ 0.08	5.57 $\pm$ 0.46

Table 3

Nucleotide cyclases.

Gene Name	Gene Symbol	IMCD-Signal Mean $\pm$ SE	non-IMCD- Signal Mean $\pm$ SE
adenylate cyclase 6	Adcy6	7.98 $\pm$ 0.02	3.26 $\pm$ 0.63
guanylate cyclase 1, soluble, beta 3	Gucy1b3	1.95 $\pm$ 0.04	2.03 $\pm$ 0.22
adenylate cyclase 3	Adcy3	1.21 $\pm$ 0.21	0.29 $\pm$ 0.11
adenylate cyclase 9 (predicted)	Adcy9_predicted	0.66 $\pm$ 0.02	0.77 $\pm$ 0.07
guanylate cyclase 2g	Gucy2g	0.08 $\pm$ 0.03	1.27 $\pm$ 0.16
natriuretic peptide receptor 2	Npr2	0.03 $\pm$ 0.06	0.89 $\pm$ 0.08
CD38 antigen	Cd38	0.02 $\pm$ 0.04	0.49 $\pm$ 0.06
natriuretic peptide receptor 1	Npr1	-0.01 $\pm$ 0.03	1.60 $\pm$ 0.14
adenylate cyclase 4	Adcy4	-0.03 $\pm$ 0.03	2.03 $\pm$ 0.14
adenylate cyclase 2	Adcy2	-0.04 $\pm$ 0.02	0.62 $\pm$ 0.07
bone marrow stromal cell antigen 1	Bst1	-2.02 $\pm$ 0.09	10.08 $\pm$ 0.82

Table 4

Phosphodiesterases.

Gene Name	Gene Symbol	IMCD-Signal Mean $\pm$ SE	non-IMCD-Signal Mean $\pm$ SE
phosphodiesterase 4C, cAMP-specific	Dpde1	9.97 $\pm$ 0.21	1.75 $\pm$ 0.44
phosphodiesterase 1A, calmodulin-dependent	Pde1a	4.33 $\pm$ 0.09	-1.09 $\pm$ 0.13
phosphodiesterase 4B, cAMP specific	Pde4b	1.95 $\pm$ 0.25	0.95 $\pm$ 0.18
cyclic nucleotide phosphodiesterase 1	Cnp1	1.87 $\pm$ 0.04	1.38 $\pm$ 0.04
phosphodiesterase 4A, cAMP specific	Pde4a	1.23 $\pm$ 0.03	0.31 $\pm$ 0.08
phosphodiesterase 3B	Pde3b	0.96 $\pm$ 0.14	0.19 $\pm$ 0.12
phosphodiesterase 7B	Pde7b	0.83 $\pm$ 0.03	0.69 $\pm$ 0.17
phosphodiesterase 8A	Pde8a	0.66 $\pm$ 0.07	-0.07 $\pm$ 0.07
phosphodiesterase 2A, cGMP-stimulated	Pde2a	0.52 $\pm$ 0.01	3.71 $\pm$ 0.09
phosphodiesterase 1C	Pde1c	0.17 $\pm$ 0.02	0.59 $\pm$ 0.04
phosphodiesterase 4D, cAMP specific	Pde4d	0.11 $\pm$ 0.03	0.26 $\pm$ 0.04
phosphodiesterase 7A	Pde7a	-0.36 $\pm$ 0.06	3.85 $\pm$ 0.22

Table 5

Protein kinases

Table 5A. Serine/threonine kinases with IMCD signals above median.

Table 5B. Non-receptor tyrosine kinases with IMCD signals above median.

Table 5C. Tyrosine kinase receptors with IMCD signals above median.

Gene Name	Gene Symbol	IMCD-Signal Mean $\pm$ SE	non-IMCD-Signal Mean $\pm$ SE
serum/glucocorticoid regulated kinase	Sgk1	34.33 $\pm$ 0.30	8.30 $\pm$ 0.71
transglutaminase 2, C polypeptide	Tgm2	18.36 $\pm$ 0.19	4.36 $\pm$ 0.44
receptor-interacting serine-threonine kinase 4 (predicted)	Ripk4_predicted	13.71 $\pm$ 0.09	0.81 $\pm$ 0.15
casein kinase 1, alpha 1	Csnk1a1	12.81 $\pm$ 0.68	4.67 $\pm$ 0.63
CDC-like kinase 1	Clk1	12.76 $\pm$ 0.16	5.39 $\pm$ 0.20
mitogen-activated protein kinase 6	Mapk6	12.73 $\pm$ 0.71	-0.39 $\pm$ 0.51
wee 1 homolog (S. pombe)	Wee1	11.25 $\pm$ 0.86	-1.83 $\pm$ 0.30
CDP-diacylglycerol synthase 1	Cds1	10.28 $\pm$ 0.44	1.48 $\pm$ 0.11
receptor-interacting serine-threonine kinase 3	Ripk3	9.99 $\pm$ 0.17	7.15 $\pm$ 0.62
polo-like kinase 2 (Drosophila)	Plk2	8.95 $\pm$ 0.56	2.75 $\pm$ 0.28
protein kinase, cAMP dependent, catalytic, beta (predicted)	Prkacb_predicted	7.53 $\pm$ 0.22	4.14 $\pm$ 0.17
homeodomain interacting protein kinase 1 (predicted)	Hipk1_predicted	6.66 $\pm$ 0.09	4.07 $\pm$ 0.27
protein kinase C, iota	Prcki	6.45 $\pm$ 0.16	7.42 $\pm$ 0.17
large tumor suppressor 2 (predicted)	Lats2_predicted	5.71 $\pm$ 0.25	9.07 $\pm$ 0.56
protein kinase C, zeta	Prkcz	5.43 $\pm$ 0.07	0.25 $\pm$ 0.12
PCTAIRE-motif protein kinase 2	Petk2	5.40 $\pm$ 0.17	2.58 $\pm$ 0.10
integrin linked kinase	Ilk	5.35 $\pm$ 0.34	6.82 $\pm$ 0.40
dystrophia myotonica-protein kinase (predicted)	Dmpk_predicted	5.21 $\pm$ 0.45	3.0 $\pm$ 0.31
eukaryotic translation initiation factor 2 alpha kinase 1	Eif2ak1	5.14 $\pm$ 0.23	1.58 $\pm$ 0.30
MAP/microtubule affinity-regulating kinase 3	Mark3	4.71 $\pm$ 0.05	3.34 $\pm$ 0.15
v-raf-1 murine leukemia viral oncogene homolog 1	Raf1	4.69 $\pm$ 0.10	3.35 $\pm$ 0.05
calcium/calmodulin-dependent protein kinase II, delta	Camk2d	4.68 $\pm$ 0.23	4.05 $\pm$ 0.16
mitogen activated protein kinase 3	Mapk3	4.68 $\pm$ 0.30	2.76 $\pm$ 0.37
protein kinase, cGMP-dependent, type 1 (mapped)	Prkg1_mapped	4.64 $\pm$ 0.25	3.36 $\pm$ 0.28
WNK lysine deficient protein kinase 4	Wnk4	4.45 $\pm$ 0.16	2.51 $\pm$ 0.72
casein kinase II, alpha 1 polypeptide	Csnk2a1	4.02 $\pm$ 0.06	3.83 $\pm$ 0.09
protein kinase N2	Pkn2	4.02 $\pm$ 0.18	2.23 $\pm$ 0.08
MAP kinase-activated protein kinase 2	Mapkapk2	4.01 $\pm$ 0.07	3.68 $\pm$ 0.09
cyclin G associated kinase	Gak	3.98 $\pm$ 0.14	2.51 $\pm$ 0.17
doublecortin and CaM kinase-like 3 (predicted)	Dcamk13_predicted	3.86 $\pm$ 0.19	0.30 $\pm$ 0.02
thymoma viral proto-oncogene 1	Akt1	3.81 $\pm$ 0.06	3.32 $\pm$ 0.12
CDC42 binding protein kinase beta	Cdc42bpb	3.69 $\pm$ 0.07	0.70 $\pm$ 0.23
conserved helix-loop-helix ubiquitous kinase (predicted)	Chuk_predicted	3.64 $\pm$ 0.09	3.36 $\pm$ 0.19
protein kinase N1	Pkn1	3.56 $\pm$ 0.59	-0.58 $\pm$ 0.25
phosphorylase kinase, gamma 2 (testis)	Phkg2	3.48 $\pm$ 0.14	2.40 $\pm$ 0.05
cyclin-dependent kinase 4	Cdk4	3.26 $\pm$ 0.10	3.17 $\pm$ 0.13
PCTAIRE-motif protein kinase 3	Petk3	3.25 $\pm$ 0.26	-0.35 $\pm$ 0.14
mitogen activated protein kinase 14	Mapk14	3.18 $\pm$ 0.05	4.35 $\pm$ 0.29
casein kinase 1, delta	Csnk1d	3.15 $\pm$ 0.10	1.46 $\pm$ 0.24
serine/arginine-rich protein specific kinase 2 (predicted)	Srpk2_predicted	3.07 $\pm$ 0.06	1.17 $\pm$ 0.07
myosin, light polypeptide kinase (predicted)	Mylk_predicted	3.01 $\pm$ 0.16	2.10 $\pm$ 0.06
serine/threonine kinase 3 (STE20 homolog, yeast)	Stk3	3.01 $\pm$ 0.18	2.20 $\pm$ 0.25
NUAK family, SNF1-like kinase, 2	Nuak2	2.99 $\pm$ 0.15	1.60 $\pm$ 0.50
protein kinase, X-linked	Prkx	2.89 $\pm$ 0.21	1.24 $\pm$ 0.11
MAP/microtubule affinity-regulating kinase 2	Mark2	2.72 $\pm$ 0.02	2.66 $\pm$ 0.20
receptor (TNFRSF)-interacting serine-threonine kinase 2	Ripk2	2.59 $\pm$ 0.08	0.83 $\pm$ 0.07
Rho-associated coiled-coil forming kinase 1	Rock1	2.59 $\pm$ 0.02	3.85 $\pm$ 0.29
death-associated protein kinase 3	Dapk3	2.52 $\pm$ 0.07	1.85 $\pm$ 0.13
protein kinase, lysine deficient 1	Prkwk1	2.47 $\pm$ 0.25	7.39 $\pm$ 0.51
unc-51-like kinase 1 (mapped)	Ulk1_mapped	2.46 $\pm$ 0.08	2.23 $\pm$ 0.26
leucine-rich repeat kinase 1 (predicted)	Lrk1_predicted	2.44 $\pm$ 0.19	2.88 $\pm$ 0.15
CDC like kinase 4	Clk4	2.41 $\pm$ 0.19	2.88 $\pm$ 0.10
protein kinase C, nu	Prkcn	2.41 $\pm$ 0.22	2.96 $\pm$ 0.16
mitogen activated protein kinase kinase kinase 12	Map3k12	2.37 $\pm$ 0.26	2.17 $\pm$ 0.27
receptor (TNFRSF)-interacting serine-threonine kinase 1 (predicted)	Ripk1_predicted	2.22 $\pm$ 0.06	0.85 $\pm$ 0.18
tousled-like kinase 1 (predicted)	Tlk1_predicted	1.98 $\pm$ 0.05	1.49 $\pm$ 0.20
mitogen activated protein kinase kinase kinase 7 (predicted)	Map3k7_predicted	1.90 $\pm$ 0.04	1.70 $\pm$ 0.14
vaccinia related kinase 3	Vrk3	1.87 $\pm$ 0.04	1.31 $\pm$ 0.23
V-raf murine sarcoma 3611 viral oncogene homolog	Araf	1.86 $\pm$ 0.05	1.51 $\pm$ 0.14
Fms interacting protein	Fmip	1.82 $\pm$ 0.18	1.63 $\pm$ 0.21
MAP kinase-interacting serine/threonine kinase 2	Mknk2	1.76 $\pm$ 0.03	2.22 $\pm$ 0.17
cyclin-dependent kinase 9 (CDC2-related kinase)	Cdk9	1.70 $\pm$ 0.08	2.27 $\pm$ 0.06
PCTAIRE-motif protein kinase 1	Petk1	1.64 $\pm$ 0.08	1.36 $\pm$ 0.27
thymoma viral proto-oncogene 2	Akt2	1.63 $\pm$ 0.01	0.91 $\pm$ 0.15
casein kinase 1, gamma 2	Csnk1g2	1.61 $\pm$ 0.02	2.57 $\pm$ 0.19
serine/threonine kinase 16	Stk16	1.60 $\pm$ 0.04	1.54 $\pm$ 0.08

Gene Name	Gene Symbol	IMCD-Signal Mean $\pm$ SE	non-IMCD-Signal Mean $\pm$ SE
similar to TANK-binding kinase 1	LOC299827	1.57 $\pm$ 0.05	1.97 $\pm$ 0.08
serine/threonine kinase 38	Stk38	1.54 $\pm$ 0.01	1.47 $\pm$ 0.07
casein kinase II, alpha 2, polypeptide (predicted)	Csnk2a2_predicted	1.53 $\pm$ 0.01	1.02 $\pm$ 0.04
protein kinase, interferon-inducible double stranded RNA dependent	Prkr	1.52 $\pm$ 0.05	0.84 $\pm$ 0.12
G protein-coupled receptor kinase 6	Gprk6	1.46 $\pm$ 0.01	4.55 $\pm$ 0.28
FK506 binding protein 12-rapamycin associated protein 1	Frap1	1.44 $\pm$ 0.06	1.35 $\pm$ 0.09
protein kinase C, delta	Prkd	1.44 $\pm$ 0.18	2.92 $\pm$ 0.22
PRP4 pre-mRNA processing factor 4 homolog B (yeast)	Prpf4b	1.40 $\pm$ 0.06	0.88 $\pm$ 0.12
serine/threonine kinase 17b (apoptosis-inducing)	Stk17b	1.35 $\pm$ 0.20	3.70 $\pm$ 0.27
tousled-like kinase 2 (Arabidopsis) (predicted)	Tlk2_predicted	1.32 $\pm$ 0.03	0.79 $\pm$ 0.06
intestinal cell kinase	Ick	1.32 $\pm$ 0.08	0.36 $\pm$ 0.03
cyclin-dependent kinase 7 (homolog of Xenopus MO15 cdk-activating kinase)	Cdk7	1.31 $\pm$ 0.05	1.36 $\pm$ 0.04
protein kinase, DNA activated, catalytic polypeptide (predicted)	Prkdc_predicted	1.23 $\pm$ 0.12	1.26 $\pm$ 0.04
microtubule associated serine/threonine kinase 2 (predicted)	Mast2_predicted	1.21 $\pm$ 0.01	1.07 $\pm$ 0.12
similar to CDC-like kinase 2	LOC365842	1.15 $\pm$ 0.18	1.79 $\pm$ 0.16
RIO kinase 3 (yeast) (predicted)	RioK3_predicted	1.13 $\pm$ 0.13	1.64 $\pm$ 0.28
similar to nemo like kinase (predicted)	LOC365949	1.11 $\pm$ 0.16	0.49 $\pm$ 0.02
SNF1-like kinase	Snf1lk	1.09 $\pm$ 0.09	2.53 $\pm$ 0.81
eukaryotic translation initiation factor 2 alpha kinase 3	Eif2ak3	1.08 $\pm$ 0.18	0.67 $\pm$ 0.17
G protein-coupled receptor kinase 2, groucho gene related (Drosophila)	Gprk2l	1.08 $\pm$ 0.14	0.32 $\pm$ 0.07
calcium/calmodulin-dependent protein kinase I	Camk1	1.06 $\pm$ 0.04	1.01 $\pm$ 0.09
cyclin-dependent kinase (CDC2-like) 10	Cdk10	1.06 $\pm$ 0.02	0.93 $\pm$ 0.13
mitogen activated protein kinase 13	Mapk13	1.05 $\pm$ 0.01	0.09 $\pm$ 0.01
mitogen activated protein kinase 1	Mapk1	1.04 $\pm$ 0.0	0.60 $\pm$ 0.06
mitogen-activated protein kinase-activated protein kinase 3	Mapkapk3	1.03 $\pm$ 0.05	0.93 $\pm$ 0.09
cyclin-dependent kinase 5	Cdk5	1.02 $\pm$ 0.03	0.42 $\pm$ 0.03
protein kinase C, epsilon	Prkce	1.01 $\pm$ 0.05	0.58 $\pm$ 0.11
G protein-coupled receptor kinase 5	Gprk5	1.0 $\pm$ 0.09	0.82 $\pm$ 0.01
Gene Name	Gene Symbol	IMCD-Signal Mean $\pm$ SE	non-IMCD-Signal Mean $\pm$ SE
Janus kinase 1	Jak1	9.69 $\pm$ 0.05	9.42 $\pm$ 0.26
fyn-related kinase	Frk	5.58 $\pm$ 0.34	0.24 $\pm$ 0.14
PTK2 protein tyrosine kinase 2	Ptk2	2.28 $\pm$ 0.05	2.23 $\pm$ 0.16
dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 2 (predicted)	Dyrk2_predicted	2.06 $\pm$ 0.12	2.29 $\pm$ 0.15
similar to tyrosine kinase Fps/Fes (predicted)	RGD1564385_predicted	1.53 $\pm$ 0.14	1.08 $\pm$ 0.13
tec protein tyrosine kinase	Tec	1.52 $\pm$ 0.09	0.96 $\pm$ 0.08
c-src tyrosine kinase	Csk	1.16 $\pm$ 0.08	3.0 $\pm$ 0.15
Gene Name	Gene Symbol	IMCD-Signal Mean $\pm$ SE	non-IMCD-Signal Mean $\pm$ SE
fibroblast growth factor receptor 2	Fgfr2	10.09 $\pm$ 0.24	-0.29 $\pm$ 0.24
Met proto-oncogene	Met	5.55 $\pm$ 0.10	4.83 $\pm$ 0.33
epidermal growth factor receptor	Egfr	3.41 $\pm$ 0.35	0.57 $\pm$ 0.07
receptor-like tyrosine kinase	Ryk	3.26 $\pm$ 0.26	1.76 $\pm$ 0.19
Eph receptor A2 (predicted)	Epha2_predicted	2.91 $\pm$ 0.18	2.37 $\pm$ 0.65
discoidin domain receptor family, member 1	Ddr1	1.78 $\pm$ 0.07	0.75 $\pm$ 0.11
fibroblast growth factor receptor 1	Fgfr1	1.62 $\pm$ 0.06	0.94 $\pm$ 0.15
insulin receptor	Insr	1.61 $\pm$ 0.10	0.72 $\pm$ 0.05
v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian)	ErbB2	1.43 $\pm$ 0.08	0.93 $\pm$ 0.09

Table 6**Protein phosphatases**

Table 6A. Serine/threonine phosphatases with IMCD signals above median.

Table 6B. Tyrosine phosphatases with IMCD signals above median.

Table 6C. Dual specificity phosphatases with IMCD signals above median.

Gene Name	Gene Symbol	IMCD-Signal Mean ± SE	non-IMCD-Signal Mean ± SE
protein phosphatase 1, catalytic subunit, beta isoform	Ppp1cb	18.11±0.06	9.36±0.60
protein phosphatase 1, catalytic subunit, gamma isoform	Ppp1cc	17.59±0.77	9.94±0.52
protein phosphatase 1, catalytic subunit, alpha isoform	Ppp1ca	15.14±0.03	10.81±0.15
protein phosphatase 2, regulatory subunit A (PR 65), alpha isoform	Ppp2r1a	8.46±0.05	3.37±0.10
protein phosphatase 3, regulatory subunit B, alpha isoform (calcineurin B, type I)	Ppp3r1	6.79±0.12	1.89±0.10
protein phosphatase 2C, magnesium dependent, catalytic subunit	Ppm2c	6.22±0.43	-0.63±0.17
protein phosphatase 2, regulatory subunit B", alpha isoform	Ppp2r3a	5.76±0.26	0.12±0.27
protein phosphatase 1B, magnesium dependent, beta isoform	Ppm1b	4.40±0.05	3.17±0.14
protein phosphatase 2, regulatory subunit A (PR 65), beta isoform	Ppp2r1b	4.05±0.28	1.51±0.02
protein phosphatase 2, regulatory subunit B (B56), alpha isoform (predicted)	Ppp2r5a_predicted	3.98±0.13	18.52±0.62
protein phosphatase 2, regulatory subunit B (PR 52), alpha isoform	Ppp2r2a	3.47±0.13	2.46±0.14
protein phosphatase 2, regulatory subunit B (B56), epsilon isoform (predicted)	Ppp2r5e_predicted	3.16±0.15	3.37±0.36
protein phosphatase 1G, magnesium-dependent, gamma isoform	Ppm1g	2.88±0.06	2.78±0.40
protein phosphatase 3, catalytic subunit, alpha isoform	Ppp3ca	2.55±0.21	5.57±0.30
protein phosphatase 4, regulatory subunit 1	Ppp4r1	2.46±0.01	1.15±0.07
protein phosphatase 1D magnesium-dependent, delta isoform (predicted)	Ppm1d_predicted	2.36±0.22	1.26±0.01
protein phosphatase 2, regulatory subunit B, delta isoform	Ppp2r2d	1.81±0.05	2.21±0.11
protein phosphatase 2, regulatory subunit B (PR 52), beta isoform	Ppp2r2b	1.77±0.03	0.28±0.09
protein phosphatase 2, regulatory subunit B (B56), beta isoform	Ppp2r5b	1.68±0.07	1.04±0.13
integrin-linked kinase-associated serine/threonine phosphatase 2C	Ilkap	1.27±0.07	1.63±0.10
protein phosphatase 3, catalytic subunit, beta isoform	Ppp3cb	1.24±0.14	1.72±0.03
protein phosphatase 1A, magnesium dependent, alpha isoform	Ppm1a	1.04±0.02	0.69±0.05
Gene Name	Gene Symbol	IMCD-Signal Mean ± SE	non-IMCD-Signal Mean ± SE
protein tyrosine phosphatase 4a1	Ptp4a1	21.24±0.28	9.22±1.20
protein tyrosine phosphatase 4a2	Ptp4a2	17.65±0.11	9.17±0.47
protein tyrosine phosphatase, receptor type, F myotubularin related protein 2 (predicted)	Ptpnf2_predicted	9.97±0.05	9.45±0.47
protein tyrosine phosphatase, non-receptor type 18	Ptpn18	6.80±0.10	3.79±0.25
protein tyrosine phosphatase, non-receptor type 2	Ptpn2	5.04±0.40	4.23±0.67
protein tyrosine phosphatase, mitochondrial 1 similar to protein Tyr phosphatase	Ptpmt1	4.54±0.23	0.79±0.06
protein tyrosine phosphatase, non-receptor type 3	LOC498331	4.45±0.18	3.0±0.28
protein tyrosine phosphatase, non-receptor type 21	Ptpn3	3.69±0.30	6.30±0.29
protein tyrosine phosphatase, non-receptor type 11	Ptpn21	3.24±0.20	0.64±0.07
protein tyrosine phosphatase, non-receptor type 11	Ptpn11	2.61±0.08	1.10±0.02
protein tyrosine phosphatase, receptor type, J	Ptpn11	2.39±0.17	2.55±0.05
protein tyrosine phosphatase, receptor type, G	Ptpnj	1.60±0.06	0.51±0.10
protein tyrosine phosphatase domain containing 1 (predicted)	Ptpng	1.51±0.19	1.91±0.13
protein tyrosine phosphatase, receptor type, K, extracellular region	Ptpdc1_predicted	1.17±0.11	1.08±0.02
protein tyrosine phosphatase, receptor type, M	Ptpnk	1.16±0.02	1.26±0.11
	Ptpnm	1.14±0.13	1.16±0.20
Gene Name	Gene Symbol	IMCD-Signal Mean ± SE	non-IMCD-Signal Mean ± SE
dual specificity phosphatase 1	Dusp1	21.46±1.65	30.23±1.48
dual specificity phosphatase 6	Dusp6	10.80±0.29	7.69±0.62
dual specificity phosphatase 2	Dusp2	10.31±0.79	0.45±0.53
dual specificity phosphatase 5	Dusp5	8.52±0.33	0.45±0.18
dual specificity phosphatase 14 (predicted)	Dusp14_predicted	2.49±0.34	0.77±0.11

Gene Name	Gene Symbol	IMCD-Signal Mean ± SE	non-IMCD-Signal Mean ± SE
dual specificity phosphatase 22 (predicted)	Dusp22_predicted	1.65±0.05	2.47±0.09
dual specificity phosphatase 7	Dusp7	1.45±0.07	1.85±0.11
slingshot homolog 3 (Drosophila)	Ssh3	1.03±0.02	1.08±0.07

Table 7

A kinase anchor proteins (AKAP).

Gene Name	Gene Symbol	IMCD-Signal Mean $\pm$ SE	non-IMCD-Signal Mean $\pm$ SE
A kinase (PRKA) anchor protein 11	Akap11	21.87 $\pm$ 01.39	-1.63 $\pm$ 0.41
A kinase (PRKA) anchor protein (yotiao) 9	Akap9	2.81 $\pm$ 0.12	2.50 $\pm$ 0.22
A kinase (PRKA) anchor protein 8	Akap8	2.29 $\pm$ 0.01	2.66 $\pm$ 0.31
A kinase (PRKA) anchor protein 13	Akap13	1.52 $\pm$ 0.05	2.27 $\pm$ 0.05
A kinase (PRKA) anchor protein 7	Akap7	1.05 $\pm$ 0.08	1.33 $\pm$ 0.08
A kinase (PRKA) anchor protein 10 (predicted)	Akap10_predicted	0.82 $\pm$ 0.02	1.0 $\pm$ 0.12
A kinase (PRKA) anchor protein 1	Akap1	0.54 $\pm$ 0.02	0.35 $\pm$ 0.02
A kinase (PRKA) anchor protein 5	Akap5	0.21 $\pm$ 0.01	0.23 $\pm$ 0.02
A kinase (PRKA) anchor protein 2	Akap2	0.09 $\pm$ 0.03	1.42 $\pm$ 0.12
A kinase (PRKA) anchor protein (gravin) 12	Akap12	0.04 $\pm$ 0.13	6.07 $\pm$ 1.46

Table 8

Phospholipases.

Gene Name	Gene Symbol	IMCD-Signal Mean $\pm$ SE	non-IMCD-Signal Mean $\pm$ SE
lysophospholipase 1	Lypla1	5.96 $\pm$ 0.17	3.62 $\pm$ 0.31
monoglyceride lipase	Mgll	5.78 $\pm$ 0.22	2.35 $\pm$ 0.13
phospholipase A2, group IVA (cytosolic, calcium-dependent)	Pla2g4a	3.85 $\pm$ 0.27	3.15 $\pm$ 0.14
phospholipase C, beta 4	Plcb4	3.60 $\pm$ 0.17	2.18 $\pm$ 0.28
phospholipase C, beta 1	Plcb1	2.49 $\pm$ 0.20	-0.05 $\pm$ 0.15
lysophospholipaseLysophospholipase-like 1 (predicted)	Lypla1_predicted	2.36 $\pm$ 0.09	1.12 $\pm$ 0.08
lysophospholipase 2	Lypla2	1.85 $\pm$ 0.04	0.65 $\pm$ 0.04
phospholipase C, delta 4	Plcd4	1.31 $\pm$ 0.10	-0.25 $\pm$ 0.06
DDHD domain containing 1	Ddhd1	1.19 $\pm$ 0.06	0.59 $\pm$ 0.10
phospholipase D family, member 3	Pld3	1.16 $\pm$ 0.02	0.79 $\pm$ 0.04
phospholipase D2	Pld2	1.0 $\pm$ 0.02	1.02 $\pm$ 0.12
phospholipase C, gamma 1 1	Plcg1	0.83 $\pm$ 0.04	2.28 $\pm$ 0.27
phospholipase A2, group VI	Pla2g6	0.68 $\pm$ 0.07	0.47 $\pm$ 0.04
hypothetical protein LK44	RGD735140	0.62 $\pm$ 0.05	1.07 $\pm$ 0.01
SEC23 interacting protein	Sec23ip	0.58 $\pm$ 0.03	0.85 $\pm$ 0.04
similar to FLJ0414 protein (predicted)	RGD1304675_predicted	0.34 $\pm$ 0.04	0.40 $\pm$ 0.09
phospholipase D1	Pld1	0.18 $\pm$ 0.04	0.38 $\pm$ 0.07
phospholipase C, delta 3 (predicted)	Plcd3_predicted	0.08 $\pm$ 0.03	0.64 $\pm$ 0.08
phosphatidylserine-specific phospholipase A1	Pspla1	-0.03 $\pm$ 0.05	0.68 $\pm$ 0.08
phospholipase C, delta 1	Plcd1	-0.05 $\pm$ 0.02	0.48 $\pm$ 0.04
phospholipase C, gamma 2	Plcg2	-0.05 $\pm$ 0.03	0.85 $\pm$ 0.01
similar to phospholipase D family, member 4	LOC362792	-1.02 $\pm$ 0.04	4.53 $\pm$ 0.17

Table 9**Small GTP-binding proteins**

Table 9A. Rab small GTP-binding proteins (Rab family) with IMCD signals above median.

Table 9B. Arf small GTP-binding proteins (Arf/Sar1 family) with IMCD signals above median.

Table 9C. Rho small GTP-binding proteins (Rho/Rac/Cdc42 family) with IMCD signals above median.

Table 9D. Ras and Ras-related small GTP-binding proteins (Ras family) with IMCD signals above median.

Gene Name	Gene Symbol	IMCD-Signal Mean ± SE	non-IMCD-Signal Mean ± SE
Rab1, member Ras oncogene family	Rab1	33.86±1.16	13.73±1.06
Rab12, member Ras oncogene family	Rab12	20.91±0.41	14.23±1.32
Rab2, member Ras oncogene family	Rab2	20.38±0.90	9.82±0.14
Rab7, member Ras oncogene family	Rab7	18.79±0.27	10.85±0.23
Rab6A, member Ras oncogene family	Rab6a	17.13±0.39	6.54±0.45
Rab11A, member Ras oncogene family	Rab11a	14.80±0.26	3.99±0.24
Rab10, member Ras oncogene family	Rab10	11.99±0.14	6.46±0.09
Rab9, member Ras oncogene family	Rab9	9.26±1.10	1.58±0.13
Rab18, member Ras oncogene family	Rab18	7.88±0.29	2.77±0.44
Rab28, member Ras oncogene family	Rab28	7.56±0.19	4.46±0.28
Rab11B, member Ras oncogene family	Rab11b	7.37±0.03	4.41±0.20
Rab5B, member Ras oncogene family (predicted)	Rab5b_predicted	7.27±0.14	3.29±0.13
Rab21, member Ras oncogene family	Rab21	5.46±0.12	1.78±0.16
Rab15, member Ras oncogene family	Rab15	5.23±0.41	-1.03±0.13
Rab31, member Ras oncogene family	Rab31	5.16±0.05	0.27±0.20
Rab5A, member Ras oncogene family	Rab5a	4.83±0.03	3.41±0.31
Rab8A, member Ras oncogene family	Rab8a	4.02±0.08	2.62±0.40
Rab25, member Ras oncogene family (predicted)	Rab25_predicted	3.87±0.33	0.47±0.15
Rab7, member Ras oncogene family-like 1	Rab711	3.55±0.08	1.92±0.27
Rab2B, member Ras oncogene family	Rab2b	3.30±0.32	2.85±0.47
Rab14, member Ras oncogene family	Rab14	2.96±0.20	4.33±0.42
Rab5C, member Ras oncogene family (predicted)	Rab5c_predicted	2.31±0.06	4.89±0.54
Rab8B, member Ras oncogene family	Rab8b	1.85±0.03	5.07±0.53
Rab34, member of Ras oncogene family	Rab34	1.68±0.07	2.07±0.10
Rab35, member Ras oncogene family	Rab35	1.43±0.18	1.19±0.23
Rab4B, member Ras oncogene family	Rab4b	1.24±0.07	0.86±0.10
TBC1 domain family, member 7 (predicted)	Tbc1d7_predicted	1.17±0.10	0.51±0.12
Gene Name			
Gene Symbol			
IMCD-Signal Mean			
± SE			
non-IMCD-Signal			
Mean ± SE			
ADP-ribosylation factor 1	Arf1	30.88±0.79	16.78±1.37
ADP-ribosylation factor 3	Arf3	16.48±0.34	3.71±0.43
ADP-ribosylation factor 4	Arf4	16.21±0.64	5.78±0.82
ADP-ribosylation factor 4-like (predicted)	Arf4l_predicted	10.63±0.90	2.47±0.22
ADP-ribosylation factor-like 1	Arf1	8.73±0.38	16.81±1.47
SAR1 gene homolog A (S. cerevisiae)	Sar1a	6.46±0.21	2.65±0.39
ADP-ribosylation factor 6	Arf6	5.66±0.18	3.44±0.46
SAR1 gene homolog B (S. cerevisiae)	Sar1b	5.13±0.02	3.10±0.25
ADP-ribosylation factor-like 6 (predicted)	Arf6_predicted	3.07±0.02	0.42±0.01
ADP-ribosylation factor-like 4A	Arf4a	2.62±0.04	2.62±0.33
ADP-ribosylation factor 2	Arf2	2.44±0.08	1.07±0.18
ADP-ribosylation factor related protein 1	Arfrip1	2.05±0.04	1.42±0.16
ADP-ribosylation factor 5	Arf5	2.03±0.07	1.72±0.17
ADP-ribosylation factor-like 3	Arf3	2.0±0.09	1.71±0.09
Gene Name			
Gene Symbol			
IMCD-Signal Mean			
± SE			
non-IMCD-Signal			
Mean ± SE			
cell division cycle 42 homolog (S. cerevisiae)	Cdc42	35.87±0.87	30.81±2.06
Rho family GTPase 1	Rnd1	18.88±0.33	0.51±0.53
Ras-related C3 botulinum toxin substrate 1	Rac1	18.65±0.19	13.62±0.67
Ras homolog gene family, member A	Rhoa	16.56±0.73	16.01±1.92
Ras homolog gene family, member B	Rhob	8.01±0.42	33.09±2.67
Rho family GTPase 3	Rnd3	5.22±0.17	1.37±0.43
Ras homolog gene family, member C (predicted)	Rhoc_predicted	4.86±0.08	0.62±0.13
Ras homolog gene family, member Q	Rhoq	3.24±0.13	1.70±0.20
Ras homolog gene family, member G	Rhog	1.79±0.05	4.67±0.40
Ras homolog gene family, member T2	Rhot2	1.62±0.10	0.90±0.06
Gene Name			
Gene Symbol			
IMCD-Signal Mean			
± SE			
non-IMCD-Signal			
Mean ± SE			
Ras homolog enriched in brain	Rheb	16.36±0.31	11.12±0.64
Ras related protein 1B	Rap1b	14.03±0.4	8.61±0.76
Ras-related associated with diabetes	Rrad	12.16±0.92	-2.06±0.12
Ras, dexamethasone-induced 1	Rasd1	10.88±1.23	1.57±0.84

Gene Name	Gene Symbol	IMCD-Signal Mean ± SE	non-IMCD-Signal Mean ± SE
related Ras viral (r-Ras) oncogene homolog 2	Rras2	8.78±0.14	5.86±0.4
Ras-related GTP binding A	Rraga	6.68±0.23	5.32±0.35
Ras-related protein 1A	Rap1a	5.74±0.14	5.45±0.4
V-Ral simian leukemia viral oncogene homolog A (Ras related)	Rala	5.42±0.41	2.69±0.62
v-Ki-Ras2 Kirsten rat sarcoma viral oncogene homolog	Kras	3.5±0.19	4.86±0.29
Ras-related GTP binding C (predicted)	Rragc_predicted	2.75±0.25	4.19±0.13
Ras-related GTP binding D (predicted)	Rragd_predicted	2.63±0.22	-0.42±0.08
muscle and microspikes Ras	Mras	1.62±0.04	1.63±0.13
Harvey rat sarcoma viral (v-Ha-Ras) oncogene homolog	Hras	1.57±0.04	1.56±0.13
v-Ral simian leukemia viral oncogene homolog B	Ralb	1.4±0.1	1.12±0.01
neuroblastoma Ras oncogene	Nras	1.34±0.1	0.7±0.05
Harvey rat sarcoma oncogene, subgroup R (predicted)	Rras_predicted	1.08±0.18	1.45±0.13

Table 10

SNAREs and SNARE-related proteins.

Gene Name	Gene Symbol	IMCD-Signal Mean $\pm$ SE	non-IMCD-Signal Mean $\pm$ SE
syntaxin 7	Stx7	24.43 $\pm$ 1.36	8.32 $\pm$ 0.40
vesicle-associated membrane protein 8	VAMP8	9.12 $\pm$ 0.25	6.46 $\pm$ 0.09
N-ethylmaleimide-sensitive factor attachment protein, gamma	Napg	8.06 $\pm$ 0.07	1.15 $\pm$ 0.07
similar to NipSnap2 protein (Glioblastoma amplified sequence)	LOC498174	6.27 $\pm$ 0.19	3.55 $\pm$ 0.34
syntaxin 12	Stx12	6.27 $\pm$ 0.21	3.09 $\pm$ 0.11
vesicle-associated membrane protein 3	Vamp3	5.73 $\pm$ 0.14	3.33 $\pm$ 0.35
syntaxin binding protein 3	Stxbp3	5.61 $\pm$ 0.17	3.10 $\pm$ 0.12
SNAP-associated protein	Snapp	5.0 $\pm$ 0.35	2.58 $\pm$ 0.06
Golgi SNAP receptor complex member 2	Gosr2	3.99 $\pm$ 0.16	0.74 $\pm$ 0.13
syntaxin 4A (placental)	Stx4a	3.78 $\pm$ 0.09	4.39 $\pm$ 0.09
blocked early in transport 1 homolog (S. cerevisiae)	Bet1	2.86 $\pm$ 0.18	1.62 $\pm$ 0.02
Golgi SNAP receptor complex member 1	Gosr1	2.47 $\pm$ 0.09	1.07 $\pm$ 0.22
similar to T-Brain-1	LOC311078	2.44 $\pm$ 0.08	1.75 $\pm$ 0.15
SEC22 vesicle trafficking protein-like 1 (S. cerevisiae)	Sec22l1	2.13 $\pm$ 0.12	0.95 $\pm$ 0.13
syntaxin binding protein 2	Stxbp2	2.02 $\pm$ 0.04	0.56 $\pm$ 0.05
syntaxin 8	Stx8	1.98 $\pm$ 0.04	1.36 $\pm$ 0.04
syntaxin 5a	Stx5a	1.98 $\pm$ 0.05	1.52 $\pm$ 0.13
synaptosomal-associated protein 29	Snapp29	1.95 $\pm$ 0.06	1.11 $\pm$ 0.07
vesicle-associated membrane protein 4 (predicted)	Vamp4_predicted	1.94 $\pm$ 0.04	1.19 $\pm$ 0.04
synaptosomal-associated protein 23	Snapp23	1.86 $\pm$ 0.03	3.15 $\pm$ 0.36
N-ethylmaleimide sensitive fusion protein	Nsf	1.72 $\pm$ 0.0	0.83 $\pm$ 0.13
prenylated SNARE protein	Ykt6	1.53 $\pm$ 0.08	1.06 $\pm$ 0.13
vesicle-associated membrane protein 2	Vamp2	1.53 $\pm$ 0.03	1.88 $\pm$ 0.19
4-nitrophenylphosphatase domain and non-neuronal SNAP25-like protein homolog 1 (C. elegans)	Nipsnap1	1.43 $\pm$ 0.15	0.60 $\pm$ 0.02
vesicle transport through interaction with t-SNAREs homolog 1A (yeast)	Vti1a	1.23 $\pm$ 0.06	3.08 $\pm$ 0.18
vesicle-associated membrane protein 1	Vamp1	0.85 $\pm$ 0.07	0.76 $\pm$ 0.07
synaptotagmin-like 4	Sytl4	0.51 $\pm$ 0.04	0.0 $\pm$ 0.02
blocked early in transport 1 homolog (S. cerevisiae) like	Bet1l	0.44 $\pm$ 0.03	0.57 $\pm$ 0.04
nipsnap homolog 3A (C. elegans)	Nipsnap3a	0.40 $\pm$ 0.06	0.85 $\pm$ 0.10
syntaxin 11	Stx11	0.40 $\pm$ 0.02	0.50 $\pm$ 0.05
synaptotagmin-like 2 (predicted)	Sytl2_predicted	0.36 $\pm$ 0.10	4.60 $\pm$ 0.11
syntaxin binding protein 5 (tomosyn)	Stxbp5	0.29 $\pm$ 0.02	0.58 $\pm$ 0.03
syntaxin 3	Stx3	0.22 $\pm$ 0.03	0.19 $\pm$ 0.03
syntaxin 1A (brain)	Stx1a	0.21 $\pm$ 0.02	0.14 $\pm$ 0.03
syntaxin binding protein 1	Stxbp1	0.12 $\pm$ 0.04	0.25 $\pm$ 0.02

Table 11

Coat proteins and clathrin adaptors.

Gene Name	Gene Symbol	IMCD-Signal Mean $\pm$ SE	non-IMCD- Signal Mean $\pm$ SE
clathrin, light polypeptide (Lca)	Clta	19.43 $\pm$ 0.65	12.23 $\pm$ 0.20
clathrin, heavy polypeptide (Hc)	Cltc	15.16 $\pm$ 0.22	13.10 $\pm$ 0.95
adaptor-related protein complex 2, mu 1 subunit	Ap2m1	14.70 $\pm$ 0.49	14.54 $\pm$ 0.40
coatamer protein complex subunit alpha	Copa	10.76 $\pm$ 0.16	8.53 $\pm$ 0.47
phosphatidylinositol binding clathrin assembly protein	Picalm	10.41 $\pm$ 0.28	19.58 $\pm$ 0.40
coatamer protein complex, subunit beta 2 (beta prime)	Copb2	7.12 $\pm$ 0.03	4.32 $\pm$ 0.27
enthoprotein (epsin 4)	Enth	6.83 $\pm$ 0.08	2.36 $\pm$ 0.38
coatamer protein complex, subunit beta 1	Copb1	5.82 $\pm$ 0.14	3.88 $\pm$ 0.21
adaptor protein complex AP-1, sigma 1 (predicted)	Ap1s1_predicted	5.29 $\pm$ 0.12	1.21 $\pm$ 0.16
archain 1	Arcn1	4.69 $\pm$ 0.11	3.18 $\pm$ 0.06
coatamer protein complex, subunit zeta 1 (predicted)	Copz1_predicted	4.55 $\pm$ 0.16	4.55 $\pm$ 0.21
coatamer protein complex, subunit epsilon (predicted)	Cope_predicted	3.69 $\pm$ 0.05	3.04 $\pm$ 0.15
epsin 3	Epn3	3.53 $\pm$ 0.13	1.02 $\pm$ 0.15
adaptor-related protein complex 3, sigma 1 subunit (predicted)	Ap3s1_predicted	3.22 $\pm$ 0.14	1.92 $\pm$ 0.10
NECAP endocytosis associated 2	Necap2	2.90 $\pm$ 0.20	2.34 $\pm$ 0.16
adaptor-related protein complex 3, mu 1 subunit	Ap3m1	2.82 $\pm$ 0.24	1.22 $\pm$ 0.19
adaptor-related protein complex 2, sigma 1 subunit	Ap2s1	2.67 $\pm$ 0.01	2.82 $\pm$ 0.08
coatamer protein complex, subunit gamma	Copg	2.65 $\pm$ 0.03	2.06 $\pm$ 0.10
hypothetical LOC308765 (predicted)	RGD1311021_predicted	2.46 $\pm$ 0.12	1.22 $\pm$ 0.11
clathrin, light polypeptide (Lcb)	Cltb	1.42 $\pm$ 0.06	2.15 $\pm$ 0.11
epsin 2	Epn2	1.19 $\pm$ 0.06	1.73 $\pm$ 0.07
adaptor-related protein complex AP-1, mu subunit 1	Ap1m1	1.01 $\pm$ 0.06	1.64 $\pm$ 0.13
epsin 1	Epn1	0.69 $\pm$ 0.10	0.42 $\pm$ 0.16
Golgi associated, gamma adaptin ear containing, ARF binding protein 1	Ggal	0.69 $\pm$ 0.01	0.74 $\pm$ 0.09
adaptor-related protein complex 3, mu 2 subunit	Ap3m2	0.66 $\pm$ 0.05	0.24 $\pm$ 0.03
SEC31-like 1 (<i>S. cerevisiae</i>)	Sec31l1	0.60 $\pm$ 0.04	0.60 $\pm$ 0.02
coatamer protein complex, subunit zeta 2 (predicted)	Copz2_predicted	0.38 $\pm$ 0.02	0.34 $\pm$ 0.03
similar to TICAM-1	LOC363328	0.27 $\pm$ 0.01	0.26 $\pm$ 0.06
adaptor-related protein complex 1, sigma 2 subunit (predicted)	Ap1s2_predicted	-0.52 $\pm$ 0.02	3.60 $\pm$ 0.30

Table 12

Cytoskeletal proteins and cytoskeletal regulators

Table 12A. Actin and actin-binding proteins.

Table 12B. Myosin and myosin-like proteins.

Table 12C. Microtubule and microtubule-related proteins.

Table 12D. Intermediate filaments and related proteins.

Gene Name	Gene Symbol	IMCD-Signal Mean $\pm$ SE	non-IMCD-Signal Mean $\pm$ SE
thymosin, beta 4	Tmsb4x	66.99 $\pm$ 1.02	71.67 $\pm$ 7.80
actin, gamma, cytoplasmic 1	Actg1	60.72 $\pm$ 1.74	53.20 $\pm$ 6.33
actin, beta	Actb	53.14 $\pm$ 1.80	45.18 $\pm$ 7.59
desrin	Dstn	50.35 $\pm$ 2.15	13.86 $\pm$ 0.49
catenin (cadherin-associated protein), alpha 1	Catna1	39.85 $\pm$ 0.76	21.23 $\pm$ 2.29
plastin 3 (T-isoform)	Pls3	36.0 $\pm$ 0.35	7.36 $\pm$ 1.29
spectrin beta 3	Spnb3	34.18 $\pm$ 0.72	-4.57 $\pm$ 0.40
calponin 3, acidic	Cnn3	33.23 $\pm$ 1.03	3.85 $\pm$ 0.20
mucin 1, transmembrane	Muc1	29.01 $\pm$ 0.48	11.23 $\pm$ 0.73
cortactin	Cttn	27.53 $\pm$ 0.47	0.32 $\pm$ 0.41
actin related protein 2/3 complex, subunit 2 (predicted)	Arpc2_predicted	24.33 $\pm$ 0.29	17.32 $\pm$ 1.19
tropomyosin 4	Tpm4	24.31 $\pm$ 0.53	2.69 $\pm$ 0.91
spectrin beta 2	Spnb2	23.76 $\pm$ 0.12	22.34 $\pm$ 1.75
alpha-spectrin 2	Spna2	22.14 $\pm$ 0.95	22.93 $\pm$ 0.41
tropomyosin 1, alpha	Tpm1	21.92 $\pm$ 0.41	10.75 $\pm$ 1.26
capping protein (actin filament), gelsolin-like	Capg	21.54 $\pm$ 0.10	14.33 $\pm$ 0.49
actin related protein 2/3 complex, subunit 3 (predicted)	Arpc3_predicted	20.79 $\pm$ 0.21	12.33 $\pm$ 0.46
transgelin 2	Tagln2	19.69 $\pm$ 0.66	9.54 $\pm$ 0.52
plastin 1 (I isoform) (predicted)	Pls1_predicted	18.08 $\pm$ 0.99	-2.60 $\pm$ 0.83
ARP2 actin-related protein 2 homolog (yeast)	Actr2	17.65 $\pm$ 0.37	22.10 $\pm$ 1.52
capping protein (actin filament) muscle Z-line, beta	Capzb	15.87 $\pm$ 0.18	11.06 $\pm$ 0.56
villin 2	Vil2	15.76 $\pm$ 0.51	13.41 $\pm$ 0.38
tropomyosin 3, gamma	Tpm3	15.53 $\pm$ 0.65	7.57 $\pm$ 0.71
actin related protein 2/3 complex, subunit 1B	Arpc1b	15.26 $\pm$ 0.19	8.73 $\pm$ 0.65
actinin alpha 4	Actn4	14.90 $\pm$ 0.64	8.07 $\pm$ 1.06
catenin (cadherin associated protein), alpha-like 1 (predicted)	Cttna11_predicted	14.72 $\pm$ 0.23	1.38 $\pm$ 0.23
LIM and SH3 protein 1	Laspl	12.92 $\pm$ 0.14	6.41 $\pm$ 0.57
kelch domain containing 8A	Klhd8a	12.17 $\pm$ 0.92	5.16 $\pm$ 0.19
GABA(A) receptor-associated protein like 2	Gabarapl2	12.16 $\pm$ 0.29	7.52 $\pm$ 0.88
WD repeat protein 1	Wdr1	11.64 $\pm$ 0.16	5.67 $\pm$ 0.81
vinculin (predicted)	Vcl_predicted	11.37 $\pm$ 0.98	4.10 $\pm$ 0.84
protein tyrosine kinase 9	Ptk9	11.18 $\pm$ 0.45	1.30 $\pm$ 0.44
cofilin 1, non-muscle	Cfl1	10.19 $\pm$ 0.87	11.61 $\pm$ 1.99
ARP3 actin-related protein 3 homolog (yeast)	Actr3	9.80 $\pm$ 0.23	10.79 $\pm$ 1.12
actin related protein 2/3 complex, subunit 5	Arpc5	9.09 $\pm$ 0.53	9.75 $\pm$ 0.57
capping protein (actin filament) muscle Z-line, alpha 2	Capza2	8.58 $\pm$ 0.10	4.07 $\pm$ 0.26
filamin, beta (predicted)	Flnb_predicted	8.57 $\pm$ 0.15	7.53 $\pm$ 0.23
actin related protein 2/3 complex, subunit 1A	Arpc1a	8.16 $\pm$ 0.05	1.67 $\pm$ 0.01
adducin 1 (alpha)	Add1	7.54 $\pm$ 0.28	5.48 $\pm$ 0.40
ectodermal-neural cortex 1	Enc1	7.09 $\pm$ 0.11	2.07 $\pm$ 0.47
erythrocyte protein band 4.9 (predicted)	Epb4.9_predicted	6.29 $\pm$ 0.45	2.18 $\pm$ 0.33
gelsolin	Gsn	5.84 $\pm$ 0.43	6.03 $\pm$ 0.65
SH3 domain YSC-like 1 (predicted)	Sh3yl1_predicted	4.97 $\pm$ 0.09	1.02 $\pm$ 0.39
ARP10 actin-related protein 10 homolog (S. cerevisiae)	Actr10	4.69 $\pm$ 0.05	4.21 $\pm$ 0.43
kelch-like 2, Mayven (Drosophila) (predicted)	Klhl2_predicted	4.62 $\pm$ 0.23	0.25 $\pm$ 0.23
actinin, alpha 1	Actn1	4.53 $\pm$ 0.08	2.16 $\pm$ 0.12
huntingtin interacting protein 1	Hip1	4.51 $\pm$ 0.25	3.56 $\pm$ 0.24
flightless 1 homolog (Drosophila)	Fliih	4.36 $\pm$ 0.12	3.52 $\pm$ 0.30
similar to KIAA1749 protein (predicted)	RGD1304623_predicted	3.99 $\pm$ 0.23	32.69 $\pm$ 0.56
Golgi autoantigen, Golgin subfamily b, macroGolgin 1	Golgb1	3.91 $\pm$ 0.38	2.42 $\pm$ 0.06
coronin, actin-binding protein, 1B	Coro1b	3.88 $\pm$ 0.08	3.42 $\pm$ 0.33
drebrin-like	Dbnl	3.58 $\pm$ 0.12	1.79 $\pm$ 0.21
kelch-like 7 (Drosophila)	Klhl7	3.55 $\pm$ 0.23	2.41 $\pm$ 0.24
formin binding protein 4	Fbnp4	3.09 $\pm$ 0.31	2.92 $\pm$ 0.06
PDZ and LIM domain 1 (elfin)	Pdlim1	2.84 $\pm$ 0.22	2.09 $\pm$ 0.13
actin-like 6A	Actl6a	2.73 $\pm$ 0.05	1.64 $\pm$ 0.08
similar to PDZ domain actin binding protein Shroom	RGD1310470	2.72 $\pm$ 0.04	-0.29 $\pm$ 0.06
parvin, alpha	Parva	2.70 $\pm$ 0.07	0.35 $\pm$ 0.29
cofilin 2, muscle (predicted)	Cfl2_predicted	2.53 $\pm$ 0.18	2.34 $\pm$ 0.29
ARP8 actin-related protein 8 homolog (S. cerevisiae) (predicted)	Actr8_predicted	2.39 $\pm$ 0.04	1.26 $\pm$ 0.03
dishevelled associated activator of morphogenesis 1 (predicted)	Daam1_predicted	2.23 $\pm$ 0.06	1.81 $\pm$ 0.13

Gene Name	Gene Symbol	IMCD-Signal Mean $\pm$ SE	non-IMCD-Signal Mean $\pm$ SE
ARP6 actin-related protein 6 homolog (yeast)	Actr6_predicted	2.12 $\pm$ 0.11	1.57 $\pm$ 0.14
(predicted)			
actin related protein 2/3 complex, subunit 4 (predicted)	Arpc4_predicted	2.10 $\pm$ 0.16	3.78 $\pm$ 0.76
filamin, alpha (predicted)	Flna_predicted	2.06 $\pm$ 0.18	6.48 $\pm$ 0.34
kelch-like 5 (Drosophila)	Klhl5	1.65 $\pm$ 0.09	1.69 $\pm$ 0.09
Nebulette (predicted)	Neb1_predicted	1.59 $\pm$ 0.27	0.35 $\pm$ 0.14
ankyrin 3, epithelial	Ank3	1.51 $\pm$ 0.29	1.05 $\pm$ 0.19
syntrophin, acidic 1	Snta1	1.43 $\pm$ 0.04	0.65 $\pm$ 0.07
A disintegrin and metalloprotease domain 8 (predicted)	Adam8_predicted	1.42 $\pm$ 0.03	2.0 $\pm$ 0.05
smooth muscle alpha-actin	Acta2	1.35 $\pm$ 0.13	0.67 $\pm$ 0.09
dystrobrevin, beta	Dtnb	1.30 $\pm$ 0.07	4.53 $\pm$ 0.16
ARP1 actin-related protein 1 homolog B (yeast)	Actr1b	1.25 $\pm$ 0.08	0.93 $\pm$ 0.10
ARP1 actin-related protein 1 homolog A (yeast)	Actr1a_predicted	1.21 $\pm$ 0.10	2.09 $\pm$ 0.25
(predicted)			
diaphanous homolog 1 (Drosophila) (predicted)	Diap1_predicted	1.16 $\pm$ 0.05	1.19 $\pm$ 0.10
enabled homolog (Drosophila)	Enah	1.14 $\pm$ 0.07	0.80 $\pm$ 0.06
tensin like C1 domain containing phosphatase	Tenc1_predicted	0.89 $\pm$ 0.08	1.71 $\pm$ 0.16
(predicted)			
supervillin (predicted)	Svil_predicted	0.87 $\pm$ 0.01	1.63 $\pm$ 0.03
cappuccino homolog (mouse)	Cno	0.85 $\pm$ 0.09	1.92 $\pm$ 0.11
similar to CG32384-PA (predicted)	RGD1311955_predicted	0.83 $\pm$ 0.03	0.25 $\pm$ 0.09
spectrin alpha 1	Spna1	0.82 $\pm$ 0.11	0.42 $\pm$ 0.04
huntingtin interacting protein 1 related	Hip1r	0.79 $\pm$ 0.03	0.97 $\pm$ 0.02
villin-like (predicted)	Vill_predicted	0.68 $\pm$ 0.02	1.64 $\pm$ 0.0
caldesmon 1	Cald1	0.63 $\pm$ 0.08	-0.01 $\pm$ 0.01
PDZ and LIM domain 5	Pdlim5	0.61 $\pm$ 0.04	0.16 $\pm$ 0.08
calponin 1	Cnn1	0.55 $\pm$ 0.13	1.18 $\pm$ 0.17
adducin 3 (gamma)	Add3	0.52 $\pm$ 0.04	0.77 $\pm$ 0.10
coronin 7	Coro7	0.49 $\pm$ 0.05	1.35 $\pm$ 0.07
IAP promoted placental gene (predicted)	Ipp_predicted	0.45 $\pm$ 0.02	0.19 $\pm$ 0.05
kelch-like 8 (Drosophila) (predicted)	Klhl8_predicted	0.37 $\pm$ 0.03	0.31 $\pm$ 0.02
drebrin 1	Dbn1	0.36 $\pm$ 0.08	0.44 $\pm$ 0.11
kelch-like 25 (Drosophila)	Klhl25	0.31 $\pm$ 0.03	0.60 $\pm$ 0.06
ARP5 actin-related protein 5 homolog (yeast)	Actr5_predicted	0.27 $\pm$ 0.01	0.41 $\pm$ 0.04
(predicted)			
coronin, actin binding protein 2A	Coro2a	0.26 $\pm$ 0.03	0.13 $\pm$ 0.04
ankyrin 2, neuronal	Ank2	0.22 $\pm$ 0.01	1.10 $\pm$ 0.11
coronin, actin binding protein 6	Coro6	0.18 $\pm$ 0.04	0.23 $\pm$ 0.02
parvin, beta (predicted)	Parvb_predicted	0.16 $\pm$ 0.01	0.58 $\pm$ 0.09
WAS protein family, member 2	Wasf2	0.15 $\pm$ 0.01	0.57 $\pm$ 0.04
actin related protein 2/3 complex, subunit 5-like	Arpc5l	0.15 $\pm$ 0.02	0.12 $\pm$ 0.01
PDZ and LIM domain 2	Pdlim2	0.12 $\pm$ 0.02	0.30 $\pm$ 0.05
tensin	Tns	0.09 $\pm$ 0.03	0.49 $\pm$ 0.07
WAS protein family, member 1	Wasf1	0.04 $\pm$ 0.01	0.35 $\pm$ 0.05
asp (abnormal spindle)-like, microcephaly associated	Aspm_predicted	0.04 $\pm$ 0.01	0.25 $\pm$ 0.05
(Drosophila) (predicted)			
transgelin	Tagln	-0.04 $\pm$ 0.02	0.49 $\pm$ 0.08
llymphocyte cytosolic protein 1	Lcp1	-0.18 $\pm$ 0.06	18.16 $\pm$ 0.82
Ena-vasodilator stimulated phosphoprotein	Evl	-0.23 $\pm$ 0.03	3.18 $\pm$ 0.13
formin-like 1 (predicted)	Fmn1l_predicted	-0.35 $\pm$ 0.08	3.96 $\pm$ 0.29
coronin, actin binding protein 1A	Coro1a	-2.54 $\pm$ 0.04	11.01 $\pm$ 0.22
Gene Name	Gene Symbol	IMCD-Signal Mean $\pm$ SE	non-IMCD-Signal Mean $\pm$ SE
myosin light chain, regulatory B	Mrlcb	27.64 $\pm$ 0.84	22.96 $\pm$ 1.85
myosin, heavy polypeptide 10, non-muscle	Myh10	26.57 $\pm$ 0.37	-1.92 $\pm$ 0.73
myosin ID	Myo1d	7.85 $\pm$ 0.02	4.03 $\pm$ 0.08
myosin, heavy polypeptide 9, non-muscle	Myh9	7.27 $\pm$ 0.13	9.73 $\pm$ 1.98
myosin Ib	Myo1b	3.79 $\pm$ 0.11	-0.33 $\pm$ 0.16
myosin 5B	Myo5b	2.42 $\pm$ 0.09	3.83 $\pm$ 0.18
similar to myosin XVIIIa	LOC360570	2.30 $\pm$ 0.14	2.12 $\pm$ 0.15
myosin IE	Myo1e	1.88 $\pm$ 0.23	1.77 $\pm$ 0.34
myosin IC	Myo1c	1.84 $\pm$ 0.08	1.83 $\pm$ 0.09
myosin binding protein H	Mybph	1.51 $\pm$ 0.16	0.59 $\pm$ 0.07
myosin VC (predicted)	Myo5c_predicted	1.46 $\pm$ 0.03	1.97 $\pm$ 0.08
myosin X (predicted)	Myo10_predicted	0.56 $\pm$ 0.0	0.55 $\pm$ 0.04
myosin, heavy polypeptide 14	Myh14	0.54 $\pm$ 0.02	1.59 $\pm$ 0.02
myosin IXA	Myo9a	0.50 $\pm$ 0.02	0.43 $\pm$ 0.07
myosin Va	Myo5a	0.49 $\pm$ 0.09	0.71 $\pm$ 0.02
myosin IXb	Myo9b	0.36 $\pm$ 0.04	1.76 $\pm$ 0.12
myosin, heavy polypeptide 7, cardiac muscle, beta	Myh7	0.07 $\pm$ 0.01	0.11 $\pm$ 0.01
myosin, light polypeptide 9, regulatory (predicted)	Myl9_predicted	-0.13 $\pm$ 0.06	1.08 $\pm$ 0.17
myosin VIIA and Rab interacting protein	Myrip	-0.14 $\pm$ 0.01	0.63 $\pm$ 0.08
myosin IG	Myo1g	-0.15 $\pm$ 0.02	1.20 $\pm$ 0.03

Gene Name	Gene Symbol	IMCD-Signal Mean $\pm$ SE	non-IMCD-Signal Mean $\pm$ SE
myosin IF (predicted)	Myo1f_predicted	-0.46 $\pm$ 0.0	2.13 $\pm$ 0.07
Gene Name	Gene Symbol	IMCD-Signal Mean $\pm$ SE	non-IMCD-Signal Mean $\pm$ SE
tumor protein, translationally-controlled 1	Tpt1	44.78 $\pm$ 1.48	53.40 $\pm$ 5.56
gamma-aminobutyric acid receptor associated protein	Gabarap	17.51 $\pm$ 0.52	12.0 $\pm$ 1.02
dynein light chain LC8-type 1	Dynll1	11.85 $\pm$ 0.38	20.26 $\pm$ 0.37
dynein light chain LC8-type 2	Dynll2	10.28 $\pm$ 0.31	4.38 $\pm$ 0.26
dynein, cytoplasmic, light chain 2A	Dncl2a	10.10 $\pm$ 0.08	6.78 $\pm$ 0.32
T-complex associated-testis-expressed 1-like (Protein 91/23)	Tcte11	8.26 $\pm$ 0.70	2.15 $\pm$ 0.25
dynein, cytoplasmic, intermediate chain 2	Dncic2	7.51 $\pm$ 0.20	4.01 $\pm$ 0.35
microtubule-associated protein 7 (predicted)	Mtap7_predicted	7.48 $\pm$ 0.03	0.53 $\pm$ 0.09
microtubule-associated protein, RP/EB family, member 1	Mapre1	6.20 $\pm$ 0.22	3.86 $\pm$ 0.10
cytoskeleton-associated protein 1 (predicted)	Ckap1_predicted	6.13 $\pm$ 0.45	3.52 $\pm$ 0.31
tubulin, beta 2c	Tubb2c	5.36 $\pm$ 0.22	4.79 $\pm$ 0.31
dynein, cytoplasmic, heavy polypeptide 2	Dnch2	5.05 $\pm$ 0.07	-0.21 $\pm$ 0.13
kinesin-associated protein 3 (predicted)	Kifap3_predicted	4.93 $\pm$ 0.19	1.27 $\pm$ 0.26
MAP/microtubule affinity-regulating kinase 3	Mark3	4.71 $\pm$ 0.05	3.34 $\pm$ 0.15
microtubule-associated protein 1b	Map1b	4.64 $\pm$ 0.77	1.22 $\pm$ 0.12
doublecortin and CaM kinase-like 3 (predicted)	Dcamk13_predicted	3.86 $\pm$ 0.19	0.30 $\pm$ 0.02
microtubule-associated protein 1 light chain 3 beta	Map1lc3b	3.80 $\pm$ 0.12	1.95 $\pm$ 0.19
dynactin 6 (predicted)	Dctn6_predicted	3.77 $\pm$ 0.17	5.16 $\pm$ 0.33
dynactin 1	Dctn1	3.52 $\pm$ 0.06	3.86 $\pm$ 0.10
dynein cytoplasmic 1 heavy chain 1	Dync1h1	3.48 $\pm$ 0.05	6.86 $\pm$ 0.29
t-complex testis expressed 1	Tctex1	3.42 $\pm$ 0.20	2.77 $\pm$ 0.05
tubulin, alpha 4	Tuba4	3.37 $\pm$ 0.03	2.63 $\pm$ 0.18
microtubule-associated protein 1 light chain 3 alpha	Map1lc3a	3.31 $\pm$ 0.13	2.97 $\pm$ 0.23
dynactin 2	Dctn2	3.26 $\pm$ 0.35	3.29 $\pm$ 0.25
kinesin family member 16B (predicted)	Kif16b_predicted	3.23 $\pm$ 0.21	1.68 $\pm$ 0.24
microtubule-associated protein 2	Mtap2	3.23 $\pm$ 0.05	1.99 $\pm$ 0.16
nuclear distribution gene C homolog (Aspergillus)	Nude	3.03 $\pm$ 0.06	2.91 $\pm$ 0.13
similar to KIAA0980 protein (predicted)	RGD1306152_predicted	2.96 $\pm$ 0.40	0.19 $\pm$ 0.14
dynein cytoplasmic 2 light intermediate chain 1	Dync2li1	2.89 $\pm$ 0.18	0.79 $\pm$ 0.18
tubulin, beta 5	Tubb5	2.88 $\pm$ 0.15	5.05 $\pm$ 0.39
kinesin family member 12	Kif12	2.81 $\pm$ 0.06	4.65 $\pm$ 0.35
dynein, cytoplasmic, light intermediate polypeptide 2	Dncli2	2.81 $\pm$ 0.17	2.95 $\pm$ 0.10
kinesin light chain 2 (predicted)	Klc2_predicted	2.76 $\pm$ 0.04	1.85 $\pm$ 0.02
kinesin family member 1A	Kif1a	2.73 $\pm$ 0.11	-0.33 $\pm$ 0.10
MAP/microtubule affinity-regulating kinase 2	Mark2	2.72 $\pm$ 0.02	2.66 $\pm$ 0.20
dynamain 1-like	Dnm11	2.34 $\pm$ 0.19	1.11 $\pm$ 0.20
dynactin 5	Dctn5	2.26 $\pm$ 0.03	2.46 $\pm$ 0.03
cytoskeleton associated protein 5	Ckap5	2.04 $\pm$ 0.06	1.88 $\pm$ 0.11
kinesin light chain 4	Klc4	1.88 $\pm$ 0.02	1.70 $\pm$ 0.14
kinesin family member C3	Kifc3	1.83 $\pm$ 0.14	4.57 $\pm$ 0.47
kinesin 2	Kns2	1.80 $\pm$ 0.08	2.13 $\pm$ 0.23
cytoplasmic linker 2	Cyln2	1.69 $\pm$ 0.15	1.27 $\pm$ 0.20
amyloid beta precursor protein (cytoplasmic tail)	Appbp2	1.55 $\pm$ 0.05	0.95 $\pm$ 0.04
binding protein 2			
tetratricopeptide repeat domain 23	Ttc23	1.44 $\pm$ 0.02	0.40 $\pm$ 0.15
kinesin family member 3C	Kif3c	1.44 $\pm$ 0.06	0.43 $\pm$ 0.05
A disintegrin and metalloprotease domain 8 (predicted)	Adam8_predicted	1.42 $\pm$ 0.03	2.0 $\pm$ 0.05
kinesin family member 21A (predicted)	Kif21a_predicted	1.40 $\pm$ 0.04	0.68 $\pm$ 0.05
tubulin, gamma 1	Tubg1	1.29 $\pm$ 0.07	1.39 $\pm$ 0.08
dynactin 4	Dctn4	1.19 $\pm$ 0.05	1.0 $\pm$ 0.17
kinesin family member 3B (predicted)	Kif3b_predicted	1.15 $\pm$ 0.10	0.79 $\pm$ 0.04
dynein, axonemal, light chain 4	Dnalc4	1.13 $\pm$ 0.07	0.78 $\pm$ 0.13
optic atrophy 1 homolog (human)	Opal	1.07 $\pm$ 0.04	0.81 $\pm$ 0.07
kinesin family member 1B	Kif1b	1.05 $\pm$ 0.07	1.28 $\pm$ 0.11
kinesin heavy chain family, member 2	Kif2	0.97 $\pm$ 0.01	1.14 $\pm$ 0.01
tubulin, beta 2b	Tubb2b	0.93 $\pm$ 0.06	1.48 $\pm$ 0.10
katanin p60 (ATPase-containing) subunit A1	Katna1	0.90 $\pm$ 0.03	0.86 $\pm$ 0.13
spastin (predicted)	Spast_predicted	0.89 $\pm$ 0.03	1.50 $\pm$ 0.10
dynein-like protein 2	DLP2	0.83 $\pm$ 0.09	0.26 $\pm$ 0.04
kinesin family member 3a	Kif3a	0.75 $\pm$ 0.02	0.38 $\pm$ 0.10
WD repeat domain 34	Wdr34	0.73 $\pm$ 0.02	0.62 $\pm$ 0.08
NudC domain containing 2	Nudcd2	0.72 $\pm$ 0.05	0.55 $\pm$ 0.03
similar to hypothetical protein FLJ1030 (predicted)	RGD1306493_predicted	0.70 $\pm$ 0.04	0.35 $\pm$ 0.08
tubulin tyrosine ligase	Ttl	0.70 $\pm$ 0.01	0.66 $\pm$ 0.05
kinesin family member C2	KIFC2	0.69 $\pm$ 0.03	0.33 $\pm$ 0.05
BPY2 interacting protein 1 (predicted)	Bpy2ip1_predicted	0.67 $\pm$ 0.08	0.43 $\pm$ 0.09
restin (Reed-Steinberg cell-expressed intermediate filament-associated protein)	Rsn	0.61 $\pm$ 0.07	0.91 $\pm$ 0.12

Gene Name	Gene Symbol	IMCD-Signal Mean $\pm$ SE	non-IMCD-Signal Mean $\pm$ SE
adenomatosis polyposis coli	Apc	0.57 $\pm$ 0.04	0.32 $\pm$ 0.05
tubulin, gamma complex associated protein 6 (predicted)	Tubgcp6_predicted	0.49 $\pm$ 0.03	0.63 $\pm$ 0.15
MAP/microtubule affinity-regulating kinase 1	Mark1	0.47 $\pm$ 0.02	0.19 $\pm$ 0.03
dynamain 3	Dnm3	0.45 $\pm$ 0.01	0.45 $\pm$ 0.03
tubulin, gamma complex associated protein 3	Tubgcp3	0.44 $\pm$ 0.02	0.27 $\pm$ 0.02
tubulin, beta 6	Tubb6	0.42 $\pm$ 0.06	1.25 $\pm$ 0.10
double cortin and calcium/calmodulin-dependent protein kinase-like 1	Dcamk11	0.38 $\pm$ 0.09	0.32 $\pm$ 0.08
similar to hypothetical protein FLJ32871	RGD1307081	0.36 $\pm$ 0.07	0.32 $\pm$ 0.04
tubulin, beta 4	Tubb4	0.35 $\pm$ 0.02	0.18 $\pm$ 0.07
tubulin, epsilon 1 (predicted)	Tube1_predicted	0.34 $\pm$ 0.06	0.32 $\pm$ 0.03
pleckstrin homology-like domain, family B, member 1	Phldb1	0.32 $\pm$ 0.05	0.85 $\pm$ 0.23
microtubule-associated protein, RP/EB family, member 3	Mapre3	0.30 $\pm$ 0.02	0.55 $\pm$ 0.09
dynein light chain roadblock-type 2 (predicted)	Dynlrb2_predicted	0.29 $\pm$ 0.01	0.16 $\pm$ 0.02
Unc-84 homolog A (C. elegans)	Unc84a	0.28 $\pm$ 0.01	0.65 $\pm$ 0.07
protein regulator of cytokinesis 1 (predicted)	Prc1_predicted	0.26 $\pm$ 0.04	0.70 $\pm$ 0.05
similar to RIKEN cDNA 6330415M09 (predicted)	RGD1308384_predicted	0.26 $\pm$ 0.03	0.77 $\pm$ 0.03
kinesin family member 13A (predicted)	Kif13a_predicted	0.26 $\pm$ 0.02	0.20 $\pm$ 0.03
kinesin family member 15	Kif15	0.22 $\pm$ 0.03	0.31 $\pm$ 0.07
dynamain 2	Dnm2	0.21 $\pm$ 0.01	0.65 $\pm$ 0.05
kinesin family member 11	Kif11	0.20 $\pm$ 0.02	0.27 $\pm$ 0.03
kinesin light chain 3	Klc3	0.18 $\pm$ 0.01	0.40 $\pm$ 0.11
kinesin family member 23 (predicted)	Kif23_predicted	0.16 $\pm$ 0.05	0.44 $\pm$ 0.08
Katanin p60 subunit A-like 1	Katnal1	0.15 $\pm$ 0.02	0.15 $\pm$ 0.04
kinesin family member C1	Kifc1	0.07 $\pm$ 0.02	0.48 $\pm$ 0.04
dynein cytoplasmic 1 light intermediate chain 1	Dync1li1	0.05 $\pm$ 0.0	0.22 $\pm$ 0.06
kinesin family member 22	Kif22	-0.03 $\pm$ 0.02	0.66 $\pm$ 0.06
microtubule-associated protein tau	Mapt	-0.15 $\pm$ 0.01	0.78 $\pm$ 0.06
Gene Name	Gene Symbol	IMCD-Signal Mean $\pm$ SE	non-IMCD-Signal Mean $\pm$ SE
keratin complex 1, acidic, gene 18	Krt1-18	25.16 $\pm$ 0.62	7.99 $\pm$ 0.30
keratin complex 2, basic, gene 8	Krt2-8	18.28 $\pm$ 0.19	3.91 $\pm$ 0.59
lamin A	Lmna	7.11 $\pm$ 0.47	1.32 $\pm$ 0.14
plakophilin 4 (predicted)	Pkp4_predicted	5.65 $\pm$ 0.63	4.12 $\pm$ 0.27
keratin complex 1, acidic, gene 19	Krt1-19	4.98 $\pm$ 0.50	-0.34 $\pm$ 0.18
plakophilin 2	Pkp2	1.54 $\pm$ 0.04	1.53 $\pm$ 0.14
keratin complex 2, basic, gene 7	Krt2-7	1.49 $\pm$ 0.31	12.10 $\pm$ 0.54
Desmuslin	Dmn	1.42 $\pm$ 0.15	0.36 $\pm$ 0.18
plakophilin 3 (predicted)	Pkp3_predicted	0.80 $\pm$ 0.02	0.57 $\pm$ 0.08
lamin B1	Lmnb1	0.48 $\pm$ 0.09	0.11 $\pm$ 0.10
plakophilin 1 (predicted)	Pkp1_predicted	0.31 $\pm$ 0.06	0.53 $\pm$ 0.03
beaded filament structural protein 1	Bfsp1	0.21 $\pm$ 0.01	0.11 $\pm$ 0.01
Nestin	Nes	0.15 $\pm$ 0.02	0.94 $\pm$ 0.05
peripherin 1	Prph1	0.10 $\pm$ 0.01	0.21 $\pm$ 0.04
desmin	Des	0.08 $\pm$ 0.06	0.41 $\pm$ 0.07
envoplakin (predicted)	Evpl_predicted	-0.51 $\pm$ 0.03	4.43 $\pm$ 0.12
vimentin	Vim	-4.23 $\pm$ 0.11	24.68 $\pm$ 0.50

Table 13**Transporters and channels**

Table 13A. Water channels.

Table 13B. Ion channels and transporters excluding SLC proteins.

Table 13C. Solute carrier proteins (SLCs).

Gene Name	Gene Symbol	IMCD-Signal Mean $\pm$ SE	non-IMCD-Signal Mean $\pm$ SE
aquaporin 4	Aqp4	68.09 $\pm$ 0.98	5.77 $\pm$ 6.48
aquaporin 2	Aqp2	59.01 $\pm$ 1.67	32.22 $\pm$ 7.6
aquaporin 3	Aqp3	58.08 $\pm$ 3.95	3.87 $\pm$ 2.74
aquaporin 1	Aqp1	-9.62 $\pm$ 2.09	58.23 $\pm$ 14.91
Gene Name	Gene Symbol	IMCD-Signal Mean $\pm$ SE	non-IMCD-Signal Mean $\pm$ SE
ATPase, Na ⁺ /K ⁺ transporting, beta 1 polypeptide	Atp1b1	56.73 $\pm$ 0.84	33.13 $\pm$ 2.26
ATPase, Na ⁺ /K ⁺ transporting, alpha 1 polypeptide	Atp1a1	34.84 $\pm$ 0.50	11.43 $\pm$ 0.27
chloride intracellular channel 1	Clc1	23.54 $\pm$ 0.39	18.78 $\pm$ 0.96
ATPase, H ⁺ transporting, lysosomal V0 subunit c	Atp6v0c	18.38 $\pm$ 0.32	15.65 $\pm$ 0.82
ATPase, H ⁺ transporting, V0 subunit E isoform 1	Atp6v0e1	16.72 $\pm$ 0.04	8.6 $\pm$ 1.46
ATPase, Na ⁺ /K ⁺ transporting, beta 3 polypeptide	Atp1b3	13.60 $\pm$ 0.51	18.79 $\pm$ 0.83
ATPase, H ⁺ transporting, lysosomal V1 subunit F	Atp6v1f	13.51 $\pm$ 0.42	6.65 $\pm$ 0.50
chloride channel calcium activated 6	Clca6	13.03 $\pm$ 1.51	-3.14 $\pm$ 0.33
ATPase, H ⁺ transporting, V1 subunit D	Atp6v1d	12.11 $\pm$ 0.19	5.17 $\pm$ 0.29
inositol 1,4,5-triphosphate receptor 1	Itpr1	12.02 $\pm$ 0.68	1.23 $\pm$ 0.39
ATPase, Ca ⁺⁺ transporting, cardiac muscle, slow twitch 2	Atp2a2	11.79 $\pm$ 0.13	6.37 $\pm$ 0.54
ATPase, H ⁺ transporting, lysosomal accessory protein 1	Atp6ap1	11.09 $\pm$ 0.61	10.44 $\pm$ 1.01
ATPase, H ⁺ transporting, V1 subunit E isoform 1	Atp6v1e1	8.58 $\pm$ 0.50	3.27 $\pm$ 0.26
ATP-binding cassette, sub-family G (WHITE), member 1	Abcg1	7.12 $\pm$ 0.34	3.75 $\pm$ 0.36
sodium channel, nonvoltage-gated 1 gamma	Scnn1g	6.63 $\pm$ 0.58	-1.33 $\pm$ 0.31
ATPase, H ⁺ transporting, V0 subunit D isoform 1	Atp6v0d1	6.18 $\pm$ 0.22	5.88 $\pm$ 0.56
ATPase, H ⁺ transporting, lysosomal V1 subunit G3 (predicted)	Atp6v1g3_predicted	6.10 $\pm$ 1.32	0.94 $\pm$ 0.41
ATPase, H ⁺ transporting, lysosomal V1 subunit G1 (predicted)	Atp6v1g1_predicted	5.70 $\pm$ 0.34	1.89 $\pm$ 0.04
potassium channel tetramerisation domain containing 12 (predicted)	Kctd12_predicted	5.64 $\pm$ 0.19	4.09 $\pm$ 0.92
vacuolar ATPase subunit H	Atp6v1h	5.54 $\pm$ 0.05	2.51 $\pm$ 0.24
ATPase, Ca ⁺⁺ -sequestering	Atp2c1	5.32 $\pm$ 0.06	2.23 $\pm$ 0.17
potassium channel tetramerisation domain containing 14 (predicted)	Kctd14_predicted	4.94 $\pm$ 0.19	-0.42 $\pm$ 0.12
chloride channel 3	Clcn3	4.76 $\pm$ 0.14	3.43 $\pm$ 0.22
ATPase, H ⁺ transporting, V1 subunit C, isoform 1	Atp6v1c1	4.18 $\pm$ 0.05	3.38 $\pm$ 0.44
potassium channel, subfamily K, member 1	Kcnk1	4.03 $\pm$ 0.15	0.40 $\pm$ 0.27
ATPase, Class I, type 8B, member 1 (predicted)	Atp8b1_predicted	3.97 $\pm$ 0.27	1.08 $\pm$ 0.33
tweety homolog 3 (Drosophila) (predicted)	Ttyh3_predicted	3.90 $\pm$ 0.36	1.49 $\pm$ 0.25
transmembrane 9 superfamily member 1	Tm9sf1	3.73 $\pm$ 0.08	3.68 $\pm$ 0.10
ATPase, H ⁺ transporting, V0 subunit B (predicted)	Atp6v0b_predicted	3.66 $\pm$ 0.03	4.32 $\pm$ 0.22
ATPase, H ⁺ transporting, V0 subunit E isoform 2	Atp6v0e2	3.64 $\pm$ 0.27	2.61 $\pm$ 0.40
ATP-binding cassette, sub-family B (MDR/TAP), member 10	Abcb10	3.51 $\pm$ 0.14	1.26 $\pm$ 0.09
ATP-binding cassette, sub-family D (ALD), member 3	Abcd3	3.25 $\pm$ 0.01	1.51 $\pm$ 0.2
chloride channel, nucleotide-sensitive, 1A	Clns1a	3.16 $\pm$ 0.13	1.93 $\pm$ 0.16
inositol 1,4,5-triphosphate receptor 3	Itpr3	3.14 $\pm$ 0.05	0.3 $\pm$ 0.10
potassium voltage-gated channel, Isk-related subfamily, member 3	Kcne3	3.11 $\pm$ 0.1	-0.46 $\pm$ 0.08
ATP-binding cassette, sub-family C (CFTR/MRP), member 4	Abcc4	3.07 $\pm$ 0.07	5.52 $\pm$ 0.43
transient receptor potential cation channel, subfamily V, member 4	Trpv4	3.02 $\pm$ 0.21	0.9 $\pm$ 0.12
ATPase, H ⁺ transporting, lysosomal V1 subunit B2	Atp6v1b2	3 $\pm$ 0.13	1.88 $\pm$ 0.24
chloride channel Kb	Clcnkb	2.93 $\pm$ 0.72	0.22 $\pm$ 0.20
ATPase, H ⁺ transporting, lysosomal V0 subunit A isoform 4 (predicted)	Atp6v0a4_predicted	2.74 $\pm$ 0.28	0.17 $\pm$ 0.06
ATP-binding cassette, sub-family C (CFTR/MRP), member 5	Abcc5	2.69 $\pm$ 0.24	1.12 $\pm$ 0.07
arsA arsenite transporter, ATP-binding, homolog 1 (bacterial)	Asna1	2.4 $\pm$ 0.04	0.85 $\pm$ 0.06
Kv channel interacting protein 4	Kcnip4	2.37 $\pm$ 0.31	-0.17 $\pm$ 0.16
ATPase, Ca ⁺⁺ transporting, plasma membrane 1	Atp2b1	2.32 $\pm$ 0.2	4.71 $\pm$ 0.36
ATP-binding cassette, sub-family A (ABC1), member 2	Abca2	2.26 $\pm$ 0.03	1.06 $\pm$ 0.18
Rhesus blood group-associated C glycoprotein	Rhcg	2.16 $\pm$ 0.11	0.64 $\pm$ 0.05
transmembrane 9 superfamily protein member 4	Tm9sf4	2.15 $\pm$ 0.05	1.00 $\pm$ 0.21
ATP-binding cassette, sub-family C (CFTR/MRP), member 1	Abcc1	2.13 $\pm$ 0.12	2.12 $\pm$ 0.08
potassium voltage-gated channel, subfamily Q, member 1	Kcnq1	2.12 $\pm$ 0.03	-0.25 $\pm$ 0.05
transient receptor potential cation channel, subfamily C, member 1	Trpc1	2.08 $\pm$ 0.09	0.18 $\pm$ 0.02
potassium channel tetramerisation domain containing 5 (predicted)	Kctd5_predicted	1.96 $\pm$ 0.18	1.28 $\pm$ 0.34
ATP-binding cassette, sub-family F (GCN20), member 3	Abcf3	1.95 $\pm$ 0.05	1.45 $\pm$ 0.09

Gene Name	Gene Symbol	IMCD-Signal Mean ± SE	non-IMCD-Signal Mean ± SE
sodium channel, nonvoltage-gated 1 beta	Scnn1b	1.94±0.23	-0.14±0.11
ATP-binding cassette, sub-family F (GCN20), member 2 (predicted)	Abcf2_predicted	1.91±0.04	1.60±0.14
inositol 1,4,5-triphosphate receptor 2	Itpr2	1.83±0.11	0.39±0.03
ATP-binding cassette, sub-family A (ABC1), member 3	Abca3	1.81±0.08	2.50±0.10
ATPase type 13A1 (predicted)	Atp13a1_predicted	1.55±0.24	2.13±0.34
transporter 1, ATP-binding cassette, sub-family B (MDR/TAP)	Tap1	1.55±0.04	1.06±0.07
potassium channel tetramerisation domain containing 6 (predicted)	Kctd6_predicted	1.52±0.21	0.62±0.08
potassium channel tetramerisation domain containing 9 (predicted)	Kctd9_predicted	1.51±0.01	0.81±0.17
ATPase, H ⁺ transporting, V1 subunit C, isoform 2	Atp6v1c2	1.5±0.05	0.50±0.13
chloride intracellular channel 3	Clc3	1.3±0.08	-0.23±0.03
ATPase type 13A2 (predicted)	Atp13a2_predicted	1.17±0.14	2.24±0.15
similar to potassium channel TASK2	LOC364241	1.08±0.01	1.26±0.04
ATPase, H ⁺ transporting, lysosomal V0 subunit a isoform 2 (predicted)	Atp6v0a2_predicted	1±0.02	1.01±0.09
ATP-binding cassette, sub-family A (ABC1), member 7	Abca7	1±0.1	0.95±0.2
transient receptor potential-related protein, ChaK	Trpm7	0.99±0.07	0.95±0.06
purinergic receptor P2X, ligand-gated ion channel 4	P2rx4	0.99±0.13	1.75±0.23
ATP-binding cassette, sub-family A (ABC1), member 5	Abca5	0.99±0.02	0.33±0.07
similar to sodium/calcium exchanger protein	LOC498185	0.91±0.19	1.48±0.24
gamma-aminobutyric acid A receptor, pi	Gabrp	0.83±0.11	-0.22±0.05
potassium inwardly-rectifying channel, subfamily J, member 16	Kcnj16	0.82±0.02	1.67±0.15
two pore channel 1	Tpcn1	0.80±0.16	5.71±0.12
mucolipin 1 (predicted)	Mcoln1_predicted	0.76±0.08	1.04±0.16
glutamate receptor, ionotropic, kainate 5	Grik5	0.74±0.07	0.12±0.01
calcium channel, voltage-dependent, beta 3 subunit	Cacnb3	0.73±0.03	0.16±0.01
transporter 2, ATP-binding cassette, sub-family B (MDR/TAP)	Tap2	0.71±0.07	0.37±0.09
ATPase, aminophospholipid transporter (APLT), class I, type 8A, member 1 (predicted)	Atp8a1_predicted	0.71±0.03	0.52±0.04
chloride channel calcium activated 3 (predicted)	Clca3_predicted	0.68±0.09	-0.04±0.01
glutamate receptor, ionotropic, kainate 2	Grik2	0.67±0.21	-0.02±0.02
ATPase, H transporting, lysosomal V1 subunit B1 (predicted)	Atp6v1b1_predicted	0.67±0.06	0.03±0.16
hyperpolarization activated cyclic nucleotide-gated potassium channel 2	Hcn2	0.66±0.01	0.28±0.11
ATP-binding cassette, sub-family A (ABC1), member 1	Abca1	0.63±0.10	1.09±0.26
cholinergic receptor, nicotinic, beta polypeptide 1 (muscle)	Chrnbl	0.60±0.02	0.48±0.08
ATPase, H ⁺ transporting, lysosomal V0 subunit A1	Atp6v0a1	0.60±0.04	0.69±0.06
sodium channel, nonvoltage-gated 1 alpha	Scnn1a	0.58±0.03	0.02±0.03
potassium channel, subfamily K, member 6	Kcnk6	0.57±0.05	0.23±0.05
ATP-binding cassette, sub-family B (MDR/TAP), member 6	Abcb6	0.54±0.05	0.25±0.07
chloride intracellular channel 4	Clc4	0.54±0.09	1.47±0.43
chloride intracellular channel 2	Clc2	0.5±0.10	7.03±0.87
potassium voltage-gated channel, subfamily H (eag-related), member 3	Kcnh3	0.47±0.03	0.52±0.15
potassium channel tetramerisation domain containing 11 (predicted)	Kctd11_predicted	0.47±0.10	0.24±0.11
ATP-binding cassette, sub-family D (ALD), member 4	Abcd4	0.46±0.01	0.45±0.06
ATP-binding cassette, sub-family G (WHITE), member 3	Abcg3	0.46±0.04	0.40±0.07
transient receptor potential cation channel, subfamily M, member 4	Trpm4	0.41±0.11	0.41±0.11
Gene Name	Gene Symbol	IMCD-Signal Mean ± SE	non-IMCD-Signal Mean ± SE
solute carrier family 14 (urea transporter), member 2	Slc14a2	39.31±0.15	20.34±3.51
solute carrier family 5 (inositol transporters), member 3	Slc5a3	23.46±1.13	12.07±0.57
solute carrier family 19 (thiamine transporter), member 2	Slc19a2	13.95±0.2	-0.67±0.17
solute carrier family 2 (facilitated glucose transporter), member 1	Slc2a1	11.38±0.4	3.3±0.21
solute carrier family 7 (cationic amino acid transporter, y ⁺ -system), member 1	Slc7a1	10.59±0.1	-0.26±0.04
solute carrier organic anion transporter family, member 4a1	Slco4a1	8.86±0.58	15.9±1.88
solute carrier family 11 (proton-coupled divalent metal ion transporters), member 2	Slc11a2	8.71±0.88	-0.65±0.19
solute carrier family 35, member B3 (predicted)	Slc35b3_predicted	6.5±0.18	2.4±0.29
solute carrier family 4, member 1	Slc4a1	6.22±1.37	1.14±0.72
solute carrier family 6 (neurotransmitter transporter), member 17	Slc6a17	5.98±0.78	-0.5±0.28
solute carrier family 4, sodium bicarbonate transporter-like, member 11 (predicted)	Slc4a11_predicted	5.8±0.57	16.44±2.35
solute carrier family 44, member 2 (predicted)	Slc44a2_predicted	4.68±0.20	3.85±0.15

Gene Name	Gene Symbol	IMCD-Signal Mean $\pm$ SE	non-IMCD-Signal Mean $\pm$ SE
solute carrier family 9 (sodium/hydrogen exchanger), member 6 (predicted)	Slc9a6_predicted	4.65 $\pm$ 0.18	1.2 $\pm$ 0.12
solute carrier family 9, member 4	Slc9a4	4.25 $\pm$ 0.25	-1.16 $\pm$ 0.12
solute carrier family 25, member 1	Slc25a1	4.11 $\pm$ 0.05	0.8 $\pm$ 0.06
solute carrier family 35 (CMP-sialic acid transporter), member 1 (predicted)	Slc35a1_predicted	3.68 $\pm$ 0.16	0.64 $\pm$ 0.16
solute carrier family 20 (phosphate transporter), member 1	Slc20a1	3.25 $\pm$ 0.24	9.84 $\pm$ 0.39
solute carrier family 22 (organic cation transporter), member 18	Slc22a18	3.05 $\pm$ 0.1	0.05 $\pm$ 0.04
solute carrier family 39 (zinc transporter), member 10 (predicted)	Slc39a10_predicted	2.91 $\pm$ 0.07	1.74 $\pm$ 0.26
solute carrier family 31, member 2	Slc31a2	2.73 $\pm$ 0.14	12.5 $\pm$ 2.12
solute carrier family 9 (sodium/hydrogen exchanger), isoform 3 regulator 1	Slc9a3r1	2.68 $\pm$ 0.15	3.37 $\pm$ 0.69
solute carrier family 12, member 2	Slc12a2	2.64 $\pm$ 0.4	4.95 $\pm$ 0.23
solute carrier family 16 (monocarboxylic acid transporters), member 3	Slc16a3	2.42 $\pm$ 0.06	0.46 $\pm$ 0.13
solute carrier family 33 (acetyl-CoA transporter), member 1	Slc33a1	2.41 $\pm$ 0.02	2.38 $\pm$ 0.26
solute carrier family 16 (monocarboxylic acid transporters), member 1	Slc16a1	2.32 $\pm$ 0.05	0.46 $\pm$ 0.04
solute carrier family 37 (glycerol-3-phosphate transporter), member 1	Slc37a1	2.23 $\pm$ 0.08	1.09 $\pm$ 0.15
solute carrier family 4, member 2	Slc4a2	2.17 $\pm$ 0.02	1.63 $\pm$ 0.17
solute carrier family 39 (zinc transporter), member 13	Slc39a13	2.09 $\pm$ 0.11	2.32 $\pm$ 0.07
solute carrier family 22 (organic cation transporter), member 17	Slc22a17	1.8 $\pm$ 0.49	2.66 $\pm$ 0.39
solute carrier family 22 (organic cation transporter), member 5	Slc22a5	1.75 $\pm$ 0.08	4.07 $\pm$ 0.52
solute carrier family 37 (glycerol-6-phosphate transporter), member 4	Slc37a4	1.7 $\pm$ 0.09	1.55 $\pm$ 0.16
solute carrier family 30 (zinc transporter), member 6 (predicted)	Slc30a6_predicted	1.7 $\pm$ 0.11	1.19 $\pm$ 0.1
solute carrier family 30 (zinc transporter), member 5 (predicted)	Slc30a5_predicted	1.64 $\pm$ 0.14	1.12 $\pm$ 0.06
solute carrier family 31 (copper transporters), member 1	Slc31a1	1.6 $\pm$ 0.09	0.6 $\pm$ 0.13
solute carrier family 7 (cationic amino acid transporter, y+ system), member 6 (predicted)	Slc7a6_predicted	1.58 $\pm$ 0.08	1.42 $\pm$ 0.19
solute carrier family 30 (zinc transporter), member 2	Slc30a2	1.51 $\pm$ 0.02	0.01 $\pm$ 0.05
solute carrier family 5 (sodium-dependent vitamin transporter), member 6	Slc5a6	1.46 $\pm$ 0.02	2.96 $\pm$ 0.14
solute carrier family 27 (fatty acid transporter), member 4	Slc27a4	1.39 $\pm$ 0.13	1.07 $\pm$ 0.26
solute carrier family 17 (anion/sugar transporter), member 5	Slc17a5	1.37 $\pm$ 0.15	1.49 $\pm$ 0.05
solute carrier family 7 (cationic amino acid transporter, y+ system), member 8	Slc7a8	1.35 $\pm$ 0.03	0.16 $\pm$ 0.13
solute carrier family 7, (cationic amino acid transporter, y+ system) member 13	Slc7a13	1.26 $\pm$ 0.07	0.57 $\pm$ 0.15
solute carrier family 26 (sulfate transporter), member 1	Slc26a1	1.24 $\pm$ 0.06	2.42 $\pm$ 0.06
solute carrier family 4 (anion exchanger), member 1, adaptor protein (predicted)	Slc4a1ap_predicted	1.23 $\pm$ 0.08	0.98 $\pm$ 0.14
solute carrier family 30 (zinc transporter), member 1	Slc30a1	1.21 $\pm$ 0.11	0.25 $\pm$ 0.06
solute carrier family 35, member A4	Slc35a4	1.19 $\pm$ 0.04	1.06 $\pm$ 0.08
solute carrier family 35 (UDP-N-acetylglucosamine (UDP-GlcNAc) transporter), member 3	Slc35a3	1.18 $\pm$ 0.04	0.1 $\pm$ 0.15
solute carrier family 35, member B4 (predicted)	Slc35b4_predicted	1.17 $\pm$ 0.05	1.4 $\pm$ 0.03
solute carrier family 9, member 1	Slc9a1	1.15 $\pm$ 0.06	0.77 $\pm$ 0.02
solute carrier family 6 (neurotransmitter transporter, betaine/GABA), member 12	Slc6a12	1.14 $\pm$ 0.05	2.86 $\pm$ 0.18
solute carrier family 35, member C1 (predicted)	Slc35c1_predicted	1.12 $\pm$ 0.05	0.9 $\pm$ 0.07
solute carrier family 39 (metal ion transporter), member 6	Slc39a6	1.1 $\pm$ 0.03	1.37 $\pm$ 0.22
solute carrier family 34 (sodium phosphate), member 1	Slc34a1	1.02 $\pm$ 0.09	1.42 $\pm$ 0.28
solute carrier family 12, member 1	Slc12a1	1.01 $\pm$ 0.34	3.15 $\pm$ 0.42
solute carrier family 4, member 3	Slc4a3	1 $\pm$ 0.04	0.31 $\pm$ 0.06
solute carrier family 6 (neurotransmitter transporter, creatine), member 8	Slc6a8	0.93 $\pm$ 0.09	0.82 $\pm$ 0.11
solute carrier family 12 (potassium/chloride transporters), member 7	Slc12a7	0.9 $\pm$ 0.1	3.49 $\pm$ 0.07
solute carrier family 4, sodium bicarbonate cotransporter, member 7	Slc4a7	0.88 $\pm$ 0.05	0.65 $\pm$ 0.13
solute carrier family 15, member 4	Slc15a4	0.88 $\pm$ 0.09	1.03 $\pm$ 0.11
solute carrier family 16 (monocarboxylic acid transporters), member 10	Slc16a10	0.87 $\pm$ 0.05	0.33 $\pm$ 0.04
solute carrier family 20, member 2	Slc20a2	0.86 $\pm$ 0.07	0.75 $\pm$ 0.11
solute carrier family 22 (organic cation transporter), member 15 (predicted)	Slc22a15_predicted	0.83 $\pm$ 0.03	1.27 $\pm$ 0.12

Gene Name	Gene Symbol	IMCD-Signal Mean $\pm$ SE	non-IMCD-Signal Mean $\pm$ SE
solute carrier family 16 (monocarboxylic acid transporters), member 7	Slc16a7	0.73 $\pm$ 0.05	1.47 $\pm$ 0.12
solute carrier family 9 (sodium/hydrogen exchanger), member 8	Slc9a8	0.69 $\pm$ 0.02	0.44 $\pm$ 0.07
solute carrier family 2, (facilitated glucose transporter) member 8	Slc2a8	0.65 $\pm$ 0.07	0.55 $\pm$ 0.12
solute carrier family 4 (anion exchanger), member 8	Slc4a8	0.65 $\pm$ 0.02	0.69 $\pm$ 0.05
solute carrier family 1 (neutral amino acid transporter), member 5	Slc1a5	0.61 $\pm$ 0.08	1.89 $\pm$ 0.37
solute carrier family 12 (potassium/chloride transporters), member 9	Slc12a9	0.6 $\pm$ 0.02	0.6 $\pm$ 0.07
solute carrier family 23 (nucleobase transporters), member 2	Slc23a2	0.58 $\pm$ 0.01	0.06 $\pm$ 0.03
solute carrier family 13 (sodium-dependent dicarboxylate transporter), member 2	Slc13a2	0.57 $\pm$ 0.12	0.17 $\pm$ 0.07
solute carrier family 9 (sodium/hydrogen exchanger), member 2	Slc9a2	0.56 $\pm$ 0.04	-0.01 $\pm$ 0.07
solute carrier family 15 (H ⁺ /peptide transporter), member 2	Slc15a2	0.53 $\pm$ 0.03	0.47 $\pm$ 0.03
solute carrier family 39 (zinc transporter), member 3	Slc39a3	0.49 $\pm$ 0.04	0.41 $\pm$ 0.08
solute carrier family 30 (zinc transporter), member 7	Slc30a7	0.46 $\pm$ 0.02	0.44 $\pm$ 0.1
solute carrier organic anion transporter family, member 3a1	Slco3a1	0.46 $\pm$ 0.06	0.53 $\pm$ 0.05
solute carrier family 7 (cationic amino acid transporter, y ⁺ -system), member 5	Slc7a5	0.41 $\pm$ 0.01	0.31 $\pm$ 0.11
solute carrier family 35, member D2 (predicted)	Slc35d2_predicted	0.41 $\pm$ 0.02	0.28 $\pm$ 0.03
solute carrier family 5 (sodium iodide symporter), member 5	Slc5a5	0.37 $\pm$ 0.03	0.01 $\pm$ 0.01
solute carrier family 24 (sodium/potassium/calcium exchanger), member 2	Slc24a2	0.36 $\pm$ 0.01	0.19 $\pm$ 0.02
solute carrier family 35, member C2	Slc35c2	0.34 $\pm$ 0	0.78 $\pm$ 0.08
solute carrier family 35, member E4	Slc35e4	0.32 $\pm$ 0.02	0.65 $\pm$ 0.03
solute carrier family 29 (nucleoside transporters), member 3	Slc29a3	0.32 $\pm$ 0.02	1.1 $\pm$ 0.01
solute carrier family 30 (zinc transporter), member 4	Slc30a4	0.32 $\pm$ 0.01	2.22 $\pm$ 0.17
solute carrier family 1 (glial high affinity glutamate transporter), member 3	Slc1a3	0.25 $\pm$ 0.01	0.13 $\pm$ 0.02
solute carrier family 16 (monocarboxylic acid transporters), member 6	Slc16a6	0.24 $\pm$ 0.05	1.42 $\pm$ 0.1
solute carrier family 6 (neurotransmitter transporter, taurine), member 6	Slc6a6	0.24 $\pm$ 0.02	0.25 $\pm$ 0.04
solute carrier family 29 (nucleoside transporters), member 1	Slc29a1	0.23 $\pm$ 0.01	0.35 $\pm$ 0.04
solute carrier family 41, member 3	Slc41a3	0.18 $\pm$ 0.01	0.28 $\pm$ 0.06
solute carrier family 7 (cationic amino acid transporter, y ⁺ -system), member 4 (predicted)	Slc7a4_predicted	0.18 $\pm$ 0.02	0.31 $\pm$ 0.04
solute carrier family 4, sodium bicarbonate cotransporter, member 5	Slc4a5	0.18 $\pm$ 0.03	0.16 $\pm$ 0.05
solute carrier family 39 (zinc transporter), member 14 (predicted)	Slc39a14_predicted	0.17 $\pm$ 0.01	0.08 $\pm$ 0.03
solute carrier family 23 (nucleobase transporters), member 3 (predicted)	Slc23a3_predicted	0.17 $\pm$ 0.01	0.09 $\pm$ 0.01
solute carrier family 9 (sodium/hydrogen exchanger), member 3	Slc9a3	0.16 $\pm$ 0.05	0.78 $\pm$ 0.02
solute carrier family 35 (UDP-glucuronic acid/UDP-N-acetylgalactosamine dual transporter), member D1 (predicted)	Slc35d1_predicted	0.1 $\pm$ 0.03	0.55 $\pm$ 0.05
solute carrier family 2 (facilitated glucose transporter), member 4	Slc2a4	0.1 $\pm$ 0.01	0.18 $\pm$ 0.01
solute carrier family 22 (organic anion/cation transporter), member 9	Slc22a9	0.08 $\pm$ 0.01	0.06 $\pm$ 0
solute carrier family 9 (sodium/hydrogen exchanger), isoform 3 regulator 2	Slc9a3r2	0.05 $\pm$ 0.04	1.59 $\pm$ 0.2
solute carrier family 16 (monocarboxylic acid transporters), member 13	Slc16a13	0.04 $\pm$ 0.02	0.43 $\pm$ 0.05
solute carrier family 12, member 4	Slc12a4	0.01 $\pm$ 0.03	1.71 $\pm$ 0.07
solute carrier organic anion transporter family, member 1a4	Slco1a4	-0.04 $\pm$ 0.04	0.78 $\pm$ 0.07
solute carrier organic anion transporter family, member 2a1	Slco2a1	-0.1 $\pm$ 0.05	1.47 $\pm$ 0.14
solute carrier family 2 (facilitated glucose transporter), member 13	Slc2a13	-0.12 $\pm$ 0.06	1.61 $\pm$ 0.11
solute carrier family 14 (urea transporter), member 1	Slc14a1	-0.16 $\pm$ 0.12	3.12 $\pm$ 0.94
solute carrier family 22 (organic cation transporter), member 4	Slc22a4	-0.18 $\pm$ 0	1.47 $\pm$ 0.08
solute carrier organic anion transporter family, member 2b1	Slco2b1	-0.2 $\pm$ 0.01	1.46 $\pm$ 0.09
solute carrier family 1 (neuronal/epithelial high affinity glutamate transporter, system Xag), member 1	Slc1a1	-0.2 $\pm$ 0.14	4.33 $\pm$ 0.23
solute carrier family 39 (metal ion transporter), member 8	Slc39a8	-0.24 $\pm$ 0.02	1.55 $\pm$ 0.14
solute carrier family 6 (neurotransmitter transporter), member 18	Slc6a18	-0.41 $\pm$ 0.05	2.11 $\pm$ 0.24
solute carrier family 28 (sodium-coupled nucleoside transporter), member 2	Slc28a2	-0.41 $\pm$ 0.02	2.07 $\pm$ 0.13

Gene Name	Gene Symbol	IMCD-Signal Mean $\pm$ SE	non-IMCD-Signal Mean $\pm$ SE
solute carrier family 7 (cationic amino acid transporter, y+ system), member 7	Slc7a7	-0.58 $\pm$ 0.04	3.86 $\pm$ 0.07
solute carrier family 6 (neurotransmitter transporter, glycine), member 9	Slc6a9	-0.66 $\pm$ 0.03	3.26 $\pm$ 0.1
solute carrier family 15, member 3	Slc15a3	-0.85 $\pm$ 0.04	3.92 $\pm$ 0.56

Table 14**Transcription factors**

Table 14A. Leucine zipper transcription factors.

Table 14B. Zinc finger transcription factors (partial).

Gene Name	Gene Symbol	IMCD-Signal Mean $\pm$ SE	Non-IMCD-Signal Mean $\pm$ SE
activating transcription factor 3	Atf3	48.17 $\pm$ 1.59	28.0 $\pm$ 2.15
FBJ murine osteosarcoma viral oncogene homolog	Fos	35.64 $\pm$ 1.12	36.71 $\pm$ 2.65
Jun oncogene	Jun	33.72 $\pm$ 1.03	20.84 $\pm$ 3.18
activating transcription factor 4 (CREB2)	Atf4	23.41 $\pm$ 0.21	12.61 $\pm$ 0.33
Jun D proto-oncogene	Jund	22.05 $\pm$ 0.44	16.91 $\pm$ 2.84
Jun-B oncogene	Junb	12.66 $\pm$ 1.15	7.51 $\pm$ 1.50
cAMP responsive element modulator	Crem	4.0 $\pm$ 0.10	0.28 $\pm$ 0.41
activating transcription factor 1	Atf1	3.54 $\pm$ 0.10	4.57 $\pm$ 0.30
cAMP responsive element binding protein 3	Creb3	1.64 $\pm$ 0.02	1.17 $\pm$ 0.02
cAMP responsive element binding protein-like 1	Creb1	1.43 $\pm$ 0.14	1.01 $\pm$ 0.03
cAMP responsive element binding protein 3-like 2	Creb3l2	0.40 $\pm$ 0.09	0.24 $\pm$ 0.02
cAMP responsive element binding protein 3-like 1	Creb3l1	0.28 $\pm$ 0.01	0.29 $\pm$ 0.03
cAMP responsive element binding protein 1	Creb1	0.25 $\pm$ 0.01	0.24 $\pm$ 0.06
basic leucine zipper transcription factor, ATF-like (predicted)	Batf_predicted	0.09 $\pm$ 0.03	0.90 $\pm$ 0.03
Gene Name	Gene Symbol	IMCD-Signal $\pm$ SE	non-IMCD- Signal $\pm$ SE
early growth response 1	Egr1	46.05 $\pm$ 1.21	37.53 $\pm$ 1.21
Kruppel-like factor 6	Klf6	19.18 $\pm$ 0.18	9.8 $\pm$ 0.18
GATA binding protein 3	Gata3	13.98 $\pm$ 1.9	-2.15 $\pm$ 1.9
Kruppel-like factor 5	Klf5	9.8 $\pm$ 0.25	-0.06 $\pm$ 0.25
Kruppel-like factor 9	Klf9	9.44 $\pm$ 0.94	6.66 $\pm$ 0.94
GATA binding protein 2	Gata2	5.31 $\pm$ 0.42	-0.59 $\pm$ 0.42
Kruppel-like factor 3 (basic) (mapped)	Klf3_mapped	4.13 $\pm$ 0.45	2.31 $\pm$ 0.45
sp1 transcription factor	Sp1	1.93 $\pm$ 0.07	3.29 $\pm$ 0.07
Kruppel-like factor 2 (lung) (predicted)	Klf2_predicted	0.63 $\pm$ 0.04	2.1 $\pm$ 0.04
Kruppel-like factor 15	Klf15	0.53 $\pm$ 0.01	0.94 $\pm$ 0.01

Table 15

Miscellaneous

Gene Name	Gene Symbol	IMCD-Signal Mean ± SE	non-IMCD-Signal Mean ± SE
myxovirus (influenza virus) resistance 2	Mx2	16.14±1.72	11.22±2.14
myxovirus (influenza virus) resistance 1	Mx1	7.60±0.51	2.09±0.42
dynamin 1-like	Dnm1l	2.34±0.19	1.11±0.20
GTP binding protein (gene overexpressed in skeletal muscle) (predicted)	Gem_predicted	0.88±0.02	5.73±0.34
dynamin 3	Dnm3	0.45±0.01	0.45±0.03
GTP binding protein 3	Gtpbp3	0.39±0.01	0.36±0.05
dynamin 2	Dnm2	0.21±0.01	0.65±0.05
nitric oxide synthase 3, endothelial cell	Nos3	-0.13±0.02	1.24±0.07
nitric oxide synthase interacting protein (predicted)	Nosip_predicted	1.11±0.09	1.32±0.15
prostaglandin-endoperoxide synthase 1	Ptgs1	38.69±0.48	-2.44±0.89
prostaglandin-endoperoxide synthase 2	Ptgs2	10.54±0.34	-1.73±0.05
tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, theta polypeptide (14-3-3 tau, 14-3-3 theta)	Ywhaq	37.49±1.88	26.40±2.08
tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon polypeptide (14-3-3 epsilon)	Ywhae	19.73±0.23	10.66±1.66
tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta polypeptide (14-3-3 zeta)	Ywhaz	18.58±0.47	8.01±1.48
tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, beta polypeptide (14-3-3 beta)	Ywhab	9.76±0.17	11.95±0.54
tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, eta polypeptide (14-3-3 eta)	Ywhah	8.75±0.10	8.03±0.53
tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, gamma polypeptide (14-3-3 gamma)	Ywhag	8.07±0.23	5.01±0.58