# **Proteomics Insights**



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#### ORIGINAL RESEARCH

# A Survey of Membrane Proteins in Human Serum

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Abstract: Serum and membrane proteins are two of the most attractive targets for proteomic analysis. Previous membrane protein studies tend to focus on tissue sample, while membrane protein studies in serum are still limited. In this study, an analysis of membrane proteins in normal human serum was carried out. Nano-liquid chromatography-electrospray ionization mass spectrometry (NanoLC-ESI-MS/MS) and bioinformatics tools were used to identify membrane proteins. Two hundred and seventeen membrane proteins were detected in the human serum, of which 129 membrane proteins have at least one transmembrane domain (TMD). Further characterizations of identified membrane proteins including their subcellular distributions, molecular weights, post translational modifications, transmembrane domains and average of hydrophobicity, were also implemented. Our results showed the potential of membrane proteins in serum for diagnosis and treatment of diseases.

**Keywords:** membrane proteins, proteomics, serum, NanoLC-ESI-MS/MS

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### Introduction

As the most easily obtained sample from patients, blood plasma is the primary specimen used to diagnose and monitor many diseases. Because changes in certain components of the plasma are indicative of abnormalities in the body system, many researches have been carried out in search for disease biomarkers in the plasma since the early history of clinical study. After proteomics emerged as a major discipline at the end of the 20th century, plasma study was launched in this new research direction, which could potentially analyze hundreds of proteins at the same time, instead of the one-protein study allowed by traditional genetic/biochemical approach.

The plasma contains thousands of proteins, including those originating from most, if not all kinds of cells and tissues. 1 The plasma is considered one of the most promising proteomes for proteomic research, and many proteomic techniques and methods have been utilized and modified to analyze the human plasma.<sup>2</sup> In an early study of human plasma, Pieper et al could identify 325 proteins using two-dimensional gel electrophoresis (2-DE) and mass spectrometry (MS).3 Advancements in the field of proteomics in the past decade have assisted plasma studies in both breadth and depth, exemplified by the forming of a human plasma Peptide Atlas by researchers participating in the Plasma Proteome Project of the Human Proteome Organization (HUPO).4 Comparative studies of the plasma have revealed many potential markers and some insights into the mechanisms of tissue specific diseases, such as cancers,<sup>5</sup> Alzheimer's disease,<sup>6</sup> and myocardial infarction.7

Membrane proteomics is a highly focused branch of proteomics. Approximately 30% of proteins encoded by the mammalian genome are transmembrane proteins. Membrane proteins play an important part in many important cellular processes, including cross-membrane transportation, cell adhesion, signal transduction, immune response, etc. Due to their roles as transporters, receptors and structural proteins as well as their impacts on intracellular processes, they are the usual candidates for drug development: about 60% of approved drugs target membrane proteins. Many membrane proteins were also found to directly associate with various human diseases, such as Alzheimer's disease, diabetes, Hodgkin's disease

and liver cirrhosis.<sup>12</sup> Thus, researches on membrane proteins also hold promises for developments of diagnosis and disease treatment.

The recent studies on human and mammalian membrane proteins tend to focus on cell/tissue samples. 13-15 Using carbonate extraction, trypsin digestion and NanoLC-MS/MS, a multilaboratory project has been found to profile membrane proteins from mouse liver. 16,17 Another study based on similar approaches, more than 200 proteins were detected in pancreatic cancer cells.<sup>18</sup> Furthermore, a large number (862) of membrane proteins were identified in the brain cortex. 19 However, we have not found any independent research that focus only on membrane proteins in serum. As a subset of the plasma, serum contains thousands of proteins, including the proteins of membrane origin, even though their abundance can be low. In this study, some results of profiling and characterization of membrane proteins in human serum by using combination of NanoLC-ESI-MS/MS methods and bioinformatics tools are shown. The present study was approved by the Ethics Committee of the Institute of Biotechnology (IBT), Vietnam Academy of Science and Technology (VAST).

# **Materials and Methods**

#### **Materials**

Dithiothreitol (DTT), iodoacetamide (IAA), ammonium bicarbonate, ammonium acetate, trypsin (proteomics sequencing grade), sodium bicarbonate and Triton X-100 were purchased from Sigma-Aldrich (St. Louis, MO, USA). Formic acid (FA) and triflouracetate (TFA) were obtained from Fluka (Fluka Chemie GmbH, Buchs, Switzerland). Acetonitrile (ACN, chromatogram grade) and other chemicals (analytical grade) were obtained from Barker (Pittsburgh, USA). The Bradford assay kit, Aurum serum protein mini kit, acrylamide, bis-acrylamide, urea, glycine, Tris, CHAPS, and SDS were purchased from Bio-Rad (Hercules, CA, USA). All equipment and standard reagents used directly should be clean as necessary.

## Sample preparation

Sera from healthy middle-aged individuals (20–40 years old) were supplied by Bach Mai Hospital, Hanoi, Vietnam, and stored at –80 °C until analysis. After that, albumin and IgG were depleted from the samples using the Aurum serum protein mini kit (Bio-Rad



Laboratories, Hercules, CA, USA). Briefly, serum protein column was washed with 1 ml of serum protein binding buffer. For each sample, 60  $\mu$ l of serum was diluted with 180  $\mu$ l serum protein binding buffer and then, 200  $\mu$ l of diluted serum was loaded onto the column. Subsequently, the depleted serum – unbound fraction was collected by centrifugation at 10,000  $\times$  g for 20 sec. The removal of albumin and IgG was evaluated by 12.6% SDS-PAGE.

## In-solution trypsin digestion

The depleted sera containing approximately 30 µg of total protein were dried by vacuum centrifugation and then dissolved in 50 mM NH<sub>4</sub>HCO<sub>3</sub>. The samples were reduced by 10 mM dithiothreitol (DTT) at 56 °C for 30 min and alkylated by 5 mM iodoacetamide (IAA) at room temperature for 1 hr. Proteins in the samples were digested using trypsin (Sequencing grade, Sigma-Aldrich, St. Louis, MO, USA) at ratio of 1:50 (w/w) enzyme to protein at 37 °C for 12 hrs. The digestion was stopped by formic acid with final concentration of 0.1%.

# Nano two-dimensional chromatography and mass spectrometry

Tryptic peptides were dissolved in 0.1% formic acid and loaded onto Strong Cation Exchange (SCX) Chromatography Column (LC Packing, Dionex, The Netherlands) for separation in the first dimension. The second dimension was performed using a C18 Reversed Phase (RP) Column (Grace Vydac, Hesperia, CA, USA) with mobile phase consisting of 0.1% formic acid in water (A) and 0.1% formic acid in 85% acetonitrile (B). Peptides were eluted in a linear gradient from 0% to 100% mobile phase B at a flow rate of 0.2 µl/min for 90 min.

Tandem mass spectrometry analysis were performed using an ABI QSTAR®XL hybrid quadrupole/TOF MS/MS instrument (Applied Biosystems/MDS Sciex, Ontario, Canada) equipped with a nanoelectrospray source (Protana XYZ manipulator). Positive mode nanoelectrospray was generated from fused-silica PicoTip emitters with a 10 µm aperture (New Objective, Woburn, MA) at 2.5 kV. MS and MS/MS spectra were recorded and processed in IDA mode (Information Dependent Acquisition) controlled by Analyst QS software. The range of the MS full scan was from

200 to 1500 amu followed by MS/MS fragmentation of the three most intense precursor ions. The dynamic ion selection threshold for MS/MS experiments was set to 45 counts.

## Identification of membrane proteins

The obtained MS and MS/MS spectra were searched against the NCBInr and the Swiss-Prot protein sequence database using Mascot<sup>TM</sup> V1.8 software (Matrix Science Ltd., London, UK). The parameters for searching were set as following: enzymatic digestion with trypsin with one potential missed cleavage; a peptide and fragment mass tolerance of ±0.5; carbamidomethyl (cysteine) as fixed modification; oxidation (methionine) as variable modification. Protein identifications were performed using a Mowse scoring algorithm with a confidence level of 95% and with at least two matched peptides. For further verification, proteins were validated using the open-source software MSQuant v 1.5 (http://msquant.sourceforge.net/).

Membrane proteins were sorted from total identified serum proteins based on UniProt protein database (http://www.uniprot.org). SOSUI prediction algorithm was used to predict transmembrane domains and average values of hydrophobicity of those membrane proteins.<sup>20</sup>

### Results

# Identification of membrane proteins in serum

The major aim of this study is to detect and profile membrane proteins from human serum. With the strategy and methods described above, 217 membrane proteins were detected from 2778 matched peptides (see Table 1, Supplementary Data). It is interesting to note that more than 90% of the identifications were based on 3 or more matched peptides. From the total of 217 identified membrane proteins, 129 proteins have at least one transmembrane domain (TMD) based on SOSUI prediction algorithm (see Table 1, Supplementary Data).

# Evaluation of membrane protein molecular weight

The distribution of molecular weights of membrane proteins from serum was shown in Figure 1. Membrane



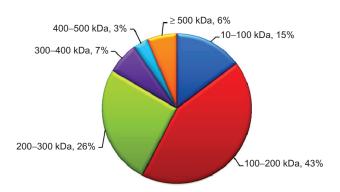


Figure 1. Distribution of molecular weights of membrane proteins found in human serum.

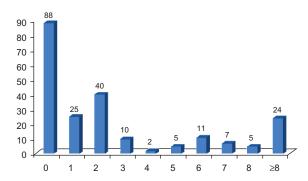
**Note:** Membrane protein identifications and molecular weights were obtained from MS and MS/MS data using Mascot software.

proteins in serum have a wide range of molecular weights. Proteins with molecular weights from 100–200 kDa make up the largest group, accounting for 43% the total of 217 identified membrane proteins. The second most abundant is the group of proteins with molecular weights in the range of 200–300 kDa (26%). It is also notable that several membrane proteins (6%) have molecular weights above 500 kDa.

# Transmembrane domains (TMDs) and average of hydrophobicity

TMD is one of the most distinguished features of membrane proteins. In our study, 129 (59.4%) proteins were predicted to have at least one TMD in the total of 217 membrane proteins according to SOSUI prediction algorithm. The majority of these 129 proteins have one TMD (25 proteins) and two TMDs (40 proteins), but a considerable number have more than 8 TMDs, which are often receptors, transporters or ion channels.

In this study, SOSUI prediction algorithm was also used to evaluate the hydrophobicity of membrane proteins from human serum. The average hydrophobicity values of all identified membrane proteins were calculated based on their amino acid sequences. It is notable that almost all proteins have average hydrophobicity values below zero. Only 17 proteins have positive average hydrophobicity values and most of them (16 proteins) are integral membrane proteins or transmembrane proteins. In addition, 7 UniProt annotated membrane proteins could not be analyzed by SOSUI prediction algorithm because their sizes have more than 5000 amino acids.



**Figure 2.** Prediction of transmembrane domains of identified membrane proteins.

**Notes:** Sequences of 217 membrane proteins indentified in human serum were processed by SOSUI prediction system for transmembrane domain (TMD) predictions. More than half (59.4%) of the identified membrane proteins have at least one TMD, and the rest (40.6%) with no TMD are membrane-associated proteins. The ordinate axis shows the protein number, whereas absciss axis shows the number of TMD.

# Subcellular distribution of membrane proteins

The subcellular distribution of 217 identified membrane proteins was determined using UniProt database according to their accession numbers. Analyzing the available information about the identified membrane proteins, we found that, these proteins have a certain distribution or are shuttled between organelles: 119 proteins are from plasma membrane and a range of proteins are from other cell components, such as nucleus (11 proteins), endoplasmic reticulum (16 proteins), Golgi apparatus (23 proteins), and mitochondrion (7 proteins).

# Post-translational modifications of membrane proteins

In this study, 359 post-translational modifications (PTMs) of membrane proteins were found in 187 proteins based on UniProt database; the other 30 membrane proteins do not have post translational modifications. Among the total of membrane proteins having PTMs, proteins with one PTM (77 proteins – 41.2%) and two PTMs (66 proteins – 35.3%) are the majority, while proteins with 5 PTMs make up the smallest group (4 proteins – 2.1%).

Among 359 modifications found in the identified membrane proteins, phosphorylation was the most common modification, with 136 phosphoproteins. Follow-up was glycosylation, with 96 glycoproteins. The third and fourth common groups were proteins with dilsufide bonds (48 proteins) and acetylation sites

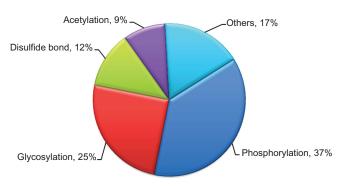


(34 proteins). Lipoproteins, palmitoylated proteins, nitrated proteins, ubiquitinated proteins... contributed to a small fraction of proteins with modifications (Fig. 3).

#### **Discussions**

In membrane proteomics, former studies are often inclined to use tissue/cell samples. Using membrane protein extraction by organic acid and NanoLC-MS/MS, Da Cruz et al found 182 membrane proteins from mouse liver mitochondrial inner membrane.21 Another study used membrane proteins extraction from pancreatic cancer cells, SDS-PAGE, in-gel digestion and NanoLC-ESI-MS/MS and detected more than 200 proteins. 18 In addition, a large number (862) of membrane proteins were found in the brain cortex. 19 The difference in the number of detected membrane proteins from various tissue types can be due to the specificity of each tissue, as well as fractionation and enrichment methods of each study. Combining data from four different sources, an early survey of the plasma by Anderson et al found 212 proteins with at least one TMD with multiple origins,1 which is similar to our results. Probably, there might be more membrane proteins in the serum that have not been detected yet because of their low abundance compared to other serum proteins.

Phosphorylation and glycosylation are the two most common modifications of protein in animal cells. Phosphorylation modifies the structure and function of many proteins. An upset balance between phosphorylation and dephosphorylation is the cause of many diseases.<sup>22</sup> Glycosylation was estimated



**Figure 3.** Components of post translational modifications (PTMs) of membrane proteins in human serum.

**Notes:** A total of 359 PTMs were found in 217 identified membrane proteins. The most common modifications are phosphorylation and glycosylation.

to be found in over 50% of human proteins,<sup>23</sup> and also of interest because some diseases were found to be related to glycan structural alterations.<sup>24,25</sup> Our results with the high proportion of phosphoproteins and glycoproteins showed the potential of membrane proteins in serum for diagnosis and treatment of disease.

### Conclusion

By using NanoLC-ESI-MS/MS technologies and bioinformatics tools, a data set of 217 membrane proteins from normal human serum was identified. Some characterization such as subcellular distribution, molecular weigh, post translational modification, transmembrane domain (TMD) and average of hydrophobicity of the identified proteins were also given. 129 proteins (59%) have at least one transmembrane domain, and 187 proteins (86%) have post-translational modifications.

### **Author Contributions**

Conceived and designed the experiments: PVC. Analysed the data: NTD. Wrote the first draft of the manuscript: PVC, NTD. Contributed to the writing of the manuscript: PVC, NTD. Agree with manuscript results and conclusions: PVC, NTD. Jointly developed the structure and arguments for the paper: PVC, NTD. Made critical revisions and approved final version: PVC, NTD. All authors reviewed and approved of the final manuscript.

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## **Competing Interests**

The author declares no conflicts of interest

#### **Disclosures and Ethics**

As a requirement of publication author(s) have provided to the publisher signed confirmation



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# **Supplementary Data**



**Table 1.** List of identified membrane proteins in human serum.

No.	Accession number	Protein name	Score	Peptide match	Molecular weight
1	Q8TC27	A disintegrin and metalloprotease domain 32	43	5	90328
2	Q9H2U9	A disintegrin and metalloproteinase 7	35	9	88036
3	Q9BZC7	ABC transporter ABCA2	61	16	272140
4	Q8IZY2	ABC transporter ABCA7	46	6	236328
5	Q99758	ABC3	41	23	192862
6	P00519	Abl protein	46	3	123852
7	000763	Acetyl-CoA carboxylase	60	6	281569
8	000763	Acetyl-CoA carboxylase 2	54	6	278361
9	O14617	Adapter-related protein complex 3 delta 1 subunit variant	62	9	145094
10	O95996	Adenomatosis polyposis coli 2	49	24	245966
11	Q13813	Alpha II spectrin	70	17	285689
12	P02763	Alpha-1-acid Glycoprotein 1 precursor	90	37	23579
13	Q9UHC3	Amiloride-sensitive cation channel 3 isoform c	48	8	61376
14	Q07837	Amino acid transport protein	56	11	79240
15	Q07075	Aminopeptidase A	50	15	109689
16	Q5Y190	Anchor protein	53	7	458487
17	Q96Q91	Anion exchanger AE4	47	4	105149
18	Q9P2R3	ANKHZN	54	7	129534
19	P02647	Apolipoprotein A-I preproprotein	245	45	30759
20	Q12797	Aspartyl(asparaginyl)beta-hydroxylase; HAAH	42	3	86294
21	Q86UQ4	ATP binding cassette, sub-family A (ABC1), member 13	50	12	580524
22	Q96J66	ATP-binding cassette protein C11 isoform A	40	18	151566
23	Q96J66	ATP-binding cassette transporter MRP8	47	5	155872
24	Q9HC28	ATP-binding cassette, sub-family A, member 2 isoform b	77	39	275244
25	Q92887	ATP-binding cassette, sub-family C (CFTR/MRP), member 2	36	68	175237
26	Q9UMD9	Autoantigen	55	8	154929
27	Q13563	Autosomal dominant polycystic kidney disease type II protein	47	4	110462
28	P50851	Beige-like protein; CDC4L protein	57	18	320076
29	Q76KP1	Beta-1,4-N-acetyl-galactosaminyl transferase 4	39	10	116954
30	Q01082	Beta-spectrin	43	10	275259
31	Q01082	Beta-spectrin 2 isoform 2	39	8	251948
32	Q15413	Brain ryanodine receptor	73	24	556937
33	O14514	Brain-specific angiogenesis inhibitor 1	51	14	176900
34	O60241	Brain-specific angiogenesis inhibitor 2	70	11	174738
35	O60242	Brain-specific angiogenesis inhibitor 3	59	7	176123
36	Q9HCU4	Cadherin EGF LAG seven-pass G-type receptor 2	44	7	322214
37	Q9NYQ7	Cadherin EGF LAG seven-pass G-type receptor 3	51	10	362937
38	Q9H251	Cadherin-23	74	6	370095
39	Q59FJ3	Calcium channel, voltage-dependent, N type, alpha 1B subunit	49	8	264553
40	Q9HCF6	Calcium-permeable store-operated channel TRPM3b	72	11	180008
			72 42		76872
41 42	Q08499 Q96P48	cAMP-specific phoshodiesterase HPDE4D3 variant Centaurin delta 2 isoform a variant	42 41	6 9	166159



Subcellular location	PTM	Hydrophobicity value	TMDs
Unclear	Disulfide bond, Glycoprotein, Phosphoprotein	-0.312452	2
Unclear	Disulfide bond, Glycoprotein	-0.414589	2
Membrane	Glycoprotein, Phosphoprotein	-0.065216	14
Plasma membrane, Endosome membrane,	Disulfide bond, Glycoprotein	0.055080	12
Golgi apparatus membrane	Bloding Bong, Clycoprotoin	0.000000	
Plasma membrane	Phosphoprotein	0.089026	13
Nucleus membrane	Lipoprotein, Myristate, Phosphoprotein	-0.597169	0
Endomembrane	Phosphoprotein	-0.227218	1
Endomembrane	Phosphoprotein	-0.227218	1
Golgi apparatus membrane	Phosphoprotein	-0.491761	1
•	Unknown		0
Golgi apparatus membrane		-0.529135	
Extracellular space	Acetylation, Phosphoprotein	-0.790330	0
Unclear	Disulfide bond, Glycoprotein, Lipoprotein, Palmitate, Phosphoprotein	-0.535821	1
Plasma membrane	Disulfide bond, Glycoprotein, Phosphoprotein	-0.265348	2
Plasma membrane	Disulfide bond, Glycoprotein	-0.441082	1
Plasma membrane	Disulfide bond, Glycoprotein, Phosphoprotein	-0.390491	1
Plasma membrane	Unknown	-0.188033	20
Plasma membrane	Glycoprotein, Phosphoprotein	0.143947	11
Endosome membrane	Acetylation	-0.154490	0
Plasma membrane	Glycation, Glycoprotein, Lipoprotein, Palmitate, Phosphoprotein	-0.717228	0
Endoplasmic reticulum membrane	Glycoprotein, Phosphoprotein	-0.788128	1
Plasma membrane	Unknown	-0.010508	14
Plasma membrane	Glycoprotein	0.191607	12
Plasma membrane	Glycoprotein	0.191607	12
Lysosome membrane	Unknown	-0.064204	14
Plasma membrane	Glycoprotein, Phosphoprotein	0.091068	13
Plasma membrane	Disulfide bond, Glycoprotein, Hydroxylation, Phosphoprotein	-0.573080	1
Endoplasmic reticulum membrane	Glycoprotein	-0.328512	8
Plasma membrane	Acetylation, Phosphoprotein	-0.201817	Ō
Golgi apparatus membrane	Glycoprotein	-0.597691	0
Plasma membrane	Acetylation, Glycoprotein, Phosphoprotein	-0.766116	Ö
Plasma membrane	Acetylation, Glycoprotein, Phosphoprotein	-0.766116	Ö
Endoplasmic reticulum	Glycoprotein	-0.278727	5
Plasma membrane	Disulfide bond, Glycoprotein, Phosphoprotein	-0.311806	8
Plasma membrane	Disulfide bond, Glycoprotein, Phosphoprotein	-0.211924	9
Plasma membrane	Disulfide bond, Glycoprotein, Phosphoprotein	-0.211863	9
Plasma membrane	Disulfide bond, Glycoprotein, Hydroxylation	-0.270751	8
Plasma membrane	Disulfide bond, Glycoprotein, Hydroxylation	-0.270751 -0.271258	8
Plasma membrane	Glycoprotein, Phosphoprotein		o 2
	Unknown	-0.142278	∠ 12
Unclear		-0.264964 0.303105	
Unclear	Unknown	-0.302195	6
Unclear	Phosphoprotein	-0.674043	0
Plasma membrane, Golgi apparatus, Membrane	Phosphoprotein	-0.422553	0



Table 1. (Continued)

No.	Accession number	Protein name	Score	Peptide match	Molecular weight
43	Q15700	Channel associated protein of synapse	35	8	97896
44	Q96QT4	Channel-kinase 1	65	11	214583
45	P51788	Chloride channel protein 2	41	8	99402
46	P00751	Complement factor B preproprotein	175	13	86847
47	P17927	Complement receptor 1	38	8	230417
48	P10606	COX5B	64	178	13914
49	Q7Z407	CUB and Sushi multiple domains 3 isoform 1	36	13	414007
50	Q8IY37	DEAH (Asp-Glu-Ala-His) box polypeptide 37	40	4	130547
51	Q6IC98	Death-inducing-protein	49	14	66766
52	Q14185	Dedicator of cytokinesis 1	52	6	216208
53	Q5VWQ8	Disabled homolog 2 interacting protein isoform 2	37	8	118547
54	O75923	Dysferlin isoform 8	43	4	239254
55	P22413	Ectonucleotide pyrophosphatase/phosphodiesterase 1	36	6	107024
56	Q8WYP5	ELYS transcription factor-like protein TMBS62	43	4	258191
57	Q541P7	EPH receptor B4 precursor	35	4	109741
58	Q15375	Ephrin receptor EphA7	55	10	113735
59	Q15375	Ephrin receptor EphA7 variant	61	10	113994
60	P54762	Ephrin receptor EphB1 precursor	45	20	111297
61	P29323	Ephrin type-B receptor 2	36	11	119128
62	Q9NZJ5	Eukaryotic translation initiation factor 2-alpha kinase 3	48	11	126095
63	Q16099	Excitatory amino acid receptor 1; kainate receptor subunit EAA1	41	9	108529
64	Q86XX4	Extracellular matrix protein FRAS1	45	10	453936
65	Q9NYQ8	FAT tumor suppressor 2 precursor	44	7	482097
66	Q6V0I7	Fat-like cadherin FATJ protein	43	10	354108
67	Q9NZM1	Fer-1 like protein 3	66	11	234737
68	Q59F30	Fibroblast growth factor receptor 4 variant	38	5	114772
69	P42345	FK506 binding protein 12-rapamycin associated protein 1	40	10	290759
70	Q9Y2I7	FYVE finger-containing phosphoinositide kinase	66	18	239581
71	Q86SQ6	G protein-coupled receptor 123	35	6	139868
72	Q5T848	G protein-coupled receptor 158	53	8	136886
73	O75899	GABBR2 protein	42	5	100861
74	Q14789	Giantin	44	13	377273
75	P42261	Glutamate receptor type 1	42	7	102270
76	Q9Y3R0	Glutamate receptor-interacting protein 1	46	5	123203
77	Q14789	Golgi antigen gcp372	44	8	373440
78	Q08378	Golgi autoantigen, golgin subfamily a, 3	69	17	167765
79	Q08378	Golgin-160	57	16	167810
80	Q6PRD1	GPR158-like 1 receptor	54	11	260635
81	Q8WXG9	G-protein coupled receptor 98	69	21	694181
82	Q8IWJ2	GRIP and coiled-coil domain-containing 2 isoform a	53	15	196873
83	O15068	Guanine nucleotide exchange factor DBS	37	4	129340
84	P52272	Heterogeneous nuclear ribonucleoprotein M isoform a	44	13	77749
85	O43166	High-risk human papilloma viruses E6 oncoproteins targeted protein E6TP1 alpha; putative GAP protei	59	12	198570



Subcellular location	PTM	Hydrophobicity value	TMDs
Plasma membrane	Lipoprotein, Palmitate, Phosphoprotein	-0.519310	0
Plasma membrane	Phosphoprotein	-0.270456	6
Plasma membrane	Unknown	0.132517	11
Plasma membrane	Acetylation	-0.501047	0
Plasma membrane	Disulfide bond, Glycoprotein, Pyrrolidone carboxylic acid	-0.320010	3
Mitochondrion membrane	Acetylation	-0.297674	0
Plasma membrane	Disulfide bond, Glycoprotein	-0.260239	1
Unclear	Unknown	-0.415385	0
Mitochondrion membrane	Phosphoprotein	-0.431833	3
Unclear	Phosphoprotein	-0.430617	0
Plasma membrane	Phosphoprotein	-0.578302	0
Vesicle	Phosphoprotein	-0.400145	1
Plasma membrane	Disulfide bond, Glycoprotein	-0.456000	1
Nuclear membrane	Acetylation, Phosphoprotein	-0. <del>4</del> 30000 -0.448765	Ö
Plasma membrane	Unknown	-0.446763 -0.235562	2
Plasma membrane	Glycoprotein, Phosphoprotein	-0.284268	2
Plasma membrane	Glycoprotein, Phosphoprotein	-0.284268 -0.284268	2
Plasma membrane	Glycoprotein, Phosphoprotein	-0.214431	2
Plasma membrane			2
	Lipoprotein, Myristate,Palmitate, Phosphoprotein	-0.293460	
Endoplasmic reticulum membrane	Glycoprotein, Phosphoprotein	-0.450717	2
Plasma membrane	Glycoprotein	-0.046653	4
Plasma membrane	Glycoprotein	-0.295608	2
Plasma membrane	Disulfide bond, Glycoprotein, Phosphoprotein	-0.249645	2
Plasma membrane	Disulfide bond, Glycoprotein, Phosphoprotein	-0.262940	2
Nuclear membrane, plasma membrane	Acetylation, Phosphoprotein	-0.456091	1
Unclear	Unknown	0.017312	6
Golgi membrane, endoplasmic reticulum membrane, mitochondrial outer membrane	Acetylation, Phosphoprotein	-0.192586	0
Endosome membrane	Acetylation, Phosphoprotein	-0.534366	0
Plasma membrane	Glycoprotein	-0.317749	6
Plasma membrane	Glycoprotein, Isopeptide bond, Phosphoprotein, Ubl conjugation	-0.480988	7
Plasma membrane	Glycoprotein, Phosphoprotein	-0.149734	8
Golgi apparatus membrane	Disulfide bond, Phosphoprotein	-0.936847	1
Plasma membrane, Endoplasmic reticulum membrane	Glycoprotein, Lipoprotein, Palmitate, Phosphoprotein	-0.199227	5
Plasma membrane, Endoplasmic reticulum membrane	Phosphoprotein	-0.362500	0
Golgi apparatus membrane	Disulfide bond, Phosphoprotein	-0.936847	1
Golgi apparatus membrane	Acetylation, Phosphoprotein	-0.834781	0
Golgi apparatus membrane	Acetylation, Phosphoprotein	-0.834781	0
Plasma membrane	Glycoprotein	-0.583101	7
Plasma membrane	Unknown	Too long	0
Golgi apparatus membrane	Phosphoprotein	-0.918825	0
Plasma membrane	Phosphoprotein	-0.552067	0
Plasma membrane	Acetylation, Phosphoprotein, Ubl conjugation	-0.341643	0
Plasma membrane	Phosphoprotein	-0.671840	0



Table 1. (Continued)

No.	Accession number	Protein name	Score	Peptide match	Molecular weight
86	P35523	Human CIC-1 muscle chloride channel	37	7	109696
87	Q14643	Human type 1 inositol 1,4,5-trisphosphate receptor	43	8	309942
88	Q9HCF6	Hypothetical protein	72	10	175211
89	Q9P1Z9	Hypothetical protein	43	14	199652
90	A6NI73	Immunoglobulin-like transcript 11 protein	39	4	27186
	Q14571				311074
91		Inositol 1,4,5-trisphosphate receptor type 2	50	6	
92	Q6P9B9	Integrator complex subunit 5	38	5	109239
93	Q15811	Intersectin long form	40	7	196293
94	Q9H4E7	IRF4-binding protein	48	7	74422
95	Q92508	KIAA0233	50	17	234888
96	Q13023	KIAA0311	40	7	259702
97	Q96P48	KIAA0782 protein	45	4	145325
98	Q9Y2H9	KIAA0973 protein	61	34	173192
99	Q96RV3	KIAA0995 protein	42	7	109401
100	Q9BZ29	KIAA1058 protein	42	7	241774
101	Q5T848	KIAA1136 protein	49	11	66642
102	Q5T4S7	KIAA1307 protein	53	7	188524
103	Q9BZ72	KIAA1457 protein	43	11	151395
103	Q9P1Z9	KIAA1529 protein	46	6	196058
105	Q6KCM7		45	7	63937
		KIAA1896 protein			
106	Q16787	Laminin alpha 3 subunit isoform 1	45	7	375652
107	P11047	Laminin B2 chain	54	7	183195
108	Q9Y6N6	Laminin gamma 3 chain precursor	40	6	177756
109	Q13449	LAMP	41	13	37798
110	P42704	Leucine-rich PPR-motif containing protein	52	7	146306
111	Q86UK5	Limbin	41	5	148825
112	P50851	Lipopolysaccharide-responsive and beige-like anchor protein	63	10	321639
113	Q9HCF6	Long transient receptor potential channel 3	75	10	196157
114	Q9NZR2	Low density lipoprotein receptor related protein-deleted in tumor	51	9	534844
115	Q5JRA6	Melanoma inhibitory activity family, member 3	52	7	214255
116	Q86UL8	Membrane associated guanylate kinase, WW and PDZ domain	39	5	159454
117	Q13421	containing 2 Mesothelin	45	4	68652
118	A1L467	Met proto-oncogene isoform b precursor	48	6	157779
119	Q8IWA4	Mitofusin 1 precursor	38	10	84892
120	Q6UVY6	Monooxygenase X	36	9	63474
121	Q8WXI7	Mucin 16	38	7	747071
122	O75970	Multiple PDZ domain protein	60	7	222792
123	Q9NZM1	Myoferlin	42	6	231092
124	B2RTY4	Myosin-IXa	54	9	294918
125	Q8NFP9	Neurobeachin	53	6	330066
126	P21359	Neurofibromin isoform 1	43	10	322760
127	Q9H2E3	Neuropilin-2b(5)	53	6	102975
					114564
128 129	Q13423 Q59GR1	Nicotinamide nucleotide transhydrogenase Niemann-Pick disease, type C1 variant	85 36	9 5	11456 14593



Subcellular location	РТМ	Hydrophobicity value	TMDs
Plasma membrane	Unknown	0.034919	11
Endoplasmic reticulum membrane	Glycoprotein, Phosphoprotein	-0.315448	6
Unclear	Unknown	-0.300924	6
Unclear	Phosphoprotein	-0.647996	2
Unclear	Disulfide bond, Glycoprotein	-0.267224	2
Plasma membrane	Acetylation, Phosphoprotein	-0.266755	7
Nucleus membrane	Phosphoprotein	0.109029	2
Plasma membrane	Acetylation, Phosphoprotein	-0.668043	0
Plasma membrane	Acetylation, Phosphoprotein	-0.946435	0
Endoplasmic reticulum membrane	Glycoprotein	-0.002357	23
Nucleus membrane	Unknown	-0.675982	0
Plasma membrane,	Phosphoprotein	-0.422553	0
Golgi apparatus membrane		0.122000	
Plasma membrane	Phosphoprotein	-0.569363	0
Plasma membrane	Glycoprotein	-0.284538	13
Plasma membrane	Phosphoprotein	-0.349204	0
Plasma membrane	Glycoprotein, Isopeptide bond,	-0.480988	7
r lacina mombrano	Phosphoprotein, Ubl conjugation	0.400000	•
Unclear	Acetylation, Phosphoprotein	Too long	0
Plasma membrane	Phosphoprotein	-0.405561	Ö
Unclear	Phosphoprotein	-0.647996	2
Mitochondrial membrane	Unknown	-0.099147	0
Unclear	Disulfide bond, Glycoprotein	-0.381368	0
Unclear	Disulfide bond, Glycoprotein	-0.615042	0
Unclear	Disulfide bond, Glycoprotein	-0.465018	0
Plasma membrane	Disulfide bond, GPI-anchor, Glycoprotein,	-0.278106	2
	Lipoprotein, Phosphoprotein	0.270100	_
Nuclear inner membrane	Acetylation	-0.206097	0
Plasma membrane	Glycoprotein	-0.445185	2
Plasma membrane	Acetylation, Phosphoprotein	-0.201817	0
Plasma membrane	Unknown	-0.300924	6
Plasma membrane	Disulfide bond, Glycoprotein	-0.489888	2
Endoplasmic reticulum membrane	Glycoprotein, Phosphoprotein	-0.887466	3
Plasma membrane	Phosphoprotein	-0.668455	0
		0.000100	
Plasma membrane	Cleavage on pair of basic residues, GPI-anchor, Glycoprotein, Lipoprotein	-0.105714	2
Plasma membrane	Unknown	-0.144388	2
Mitochondrial membrane	Unknown	-0.267476	2
Endoplasmic reticulum membrane	Disulfide bond, Glycoprotein	-0.260848	2
Plasma membrane	Disulfide bond, Glycoprotein, Phosphoprotein	Too long	1
Plasma membrane	Phosphoprotein	-0.233203	0
Vesicle membrane, nuclear membrane, plasma membrane	Acetylation, Phosphoprotein	-0.456091	1
Unclear	Phosphoprotein	-0.623980	0
Plasma membrane	Phosphoprotein	-0.188358	2
Plasma membrane	Disulfide bond, GPI-anchor, Glycoprotein, Lipoprotein	-0.136950	4
Plasma membrane	Unknown	-0.440066	2
Mitochondrial membrane	Acetylation	0.299079	13
Plasma membrane	Unknown	0.216447	13



Table 1. (Continued)

No.	Accession number	Protein name	Score	Peptide match	Molecular weight
130	Q13224	N-methyl-D-aspartate receptor subunit NR3	53	16	168067
131	Q13813	Nonerythroid alpha-spectrin	59	7	284905
132	Q9UM47	Notch homolog 3	43	8	256640
133	Q5STG5	Notch homolog 4 (Drosophila)	51	7	221594
134	P46531	Notch1 preproprotein	38	11	286350
135	Q92823	NrCAM protein	37	11	144138
136	Q8WXH0	NUANCE	104	29	801683
137	Q5VU65	Nucleoporin 210 kDa-like isoform 1	43	10	211668
138	Q13017	p190-B	45	6	173000
139	Q5T4S7	p600	121	21	580607
140	O60245	PCDH7 (BH-Pcdh)c	40	4	130999
141	Q9BXM0	Periaxin	59	8	155248
142	O75747	Phosphatidylinositol-4-phosphate 3-kinase C2 domain-containing gamma polypeptide	38	9	167814
143	O00443	Phosphoinositide 3-kinase	43	9	192271
144	O00750	PI-3 kinase	46	5	184101
145	Q6T4P5	Plasticity-related protein 2	43	12	79523
146	O75051	Plexin A2	37	13	214220
147	Q9Y4D7	Plexin-D1	48	9	215381
148	Q15142	Polycystic kidney disease-associated protein	57	5	396273
149	Q8TDX9	Polycystin-1 L1	35	4	319453
150	P13942	Pro-a2(XI)	51	10	160545
151	P08123	Pro-alpha 2(I) collagen	51	9	129858
152	P02647	Proapolipoprotein	664	75	28944
153	Q07954	Prolow-density lipoprotein receptor-related protein 1	66	13	523119
154	Q05655	Protein kinase C-delta 13	37	4	78624
155	Q8TF72	Protein Shroom 3	41	8	218125
156	Q96QU1	Protocadherin 15	59	13	217261
157	Q96QU1	Protocadherin 15 isoform CD1-4 precursor	48	12	217303
158	Q9UN70	Protocadherin 43	45	5	98230
159	Q14517	Protocadherin Fat 1	52	9	509384
160	Q9NYQ8	Protocadherin Fat 2	59	7	482172
161	Q86V60	PTPRM protein	39	8	158434
162	Q8WZA2	RAPGEF4 protein	53	13	100339
163	P23467	Receptor-type tyrosine-protein phosphatase beta	50	26	225497
164	Q13332	Receptor-type tyrosine-protein phosphatase S	43	9	218155
165	Q86UR5	Regulating synaptic membrane exocytosis 1	40	6	190154
166	Q5T4S7	Retinoblastoma-associated factor 600	124	20	580547
167	Q5T5U3	Rho GTPase-activating protein 21	41	8	218567
168	Q13464	Rho-associated, coiled-coil containing protein kinase 1	48	6	159102
169	Q5T5U3	Rho-GTPase activating protein 10	41	5	218563
170	Q5JTH9	Ribosomal RNA processing 12 homolog (S. cerevisiae)	56	9	145067
171	Q86UR5	RIM long form	48	7	164927
172	P21817	Ryanodine receptor 1	61	, 11	55204
	. 21017	Tyunoumo roooptor r			00204



Subcellular location	PTM	Hydrophobicity value	TMDs
Plasma membrane	Disulfide bond, Glycoprotein, Phosphoprotein	-0.388342	6
Unclear	Acetylation, Phosphoprotein	-0.790330	0
Plasma membrane	Disulfide bond, Glycoprotein, Phosphoprotein	-0.304826	3
Unclear	Unknown	-0.287183	3
Plasma membrane	Disulfide bond, Glycoprotein, Phosphoprotein	-0.420119	3
Plasma membrane	Disulfide bond, Glycoprotein, Phosphoprotein	-0.379601	2
Nuclear membrane	Acetylation, Phosphoprotein	Too long	0
Unclear	Glycoprotein	0.050265	3
Unclear	Nitration, Phosphoprotein	-0.592345	0
Unclear	Acetylation, Phosphoprotein	Too long	0
Plasma membrane	Glycoprotein, Phosphoprotein	-0.390365	2
Plasma membrane	Phosphoprotein	-0.225736	0
Unclear	Phosphoprotein	-0.322423	1
Plasma membrane	Acetylation, Phosphoprotein	-0.302136	0
Plasma membrane	Phosphoprotein	-0.363037	0
Membrane	Glycoprotein	-0.178273	6
Cell membrane	Glycoprotein, Phosphoprotein	-0.181468	3
Cell membrane, Membrane	Glycoprotein	-0.159013	2
Integral to membrane	Unknown	0.022760	14
Integral to membrane	Glycoprotein	-0.136856	7
Cell membrane	Disulfide bond, Glycoprotein, Sulfation	-0.805186	0
Plasma membrane	Glycoprotein, Hydroxylation, Pyrrolidone carboxylic acid	-0.648098	0
Plasma membrane	Glycation, Glycoprotein, Lipoprotein, Palmitate, Phosphoprotein	-0.717228	0
Plasma membrane	Disulfide bond, Glycoprotein, Phosphoprotein	-0.510386	2
Plasma membrane	Phosphoprotein	-0.377958	0
Plasma membrane	Phosphoprotein	-0.801652	0
Plasma membrane	Phosphoprotein	-0.245473	2
Plasma membrane	Phosphoprotein	-0.245473	2
Plasma membrane	Glycoprotein	-0.261670	2
Plasma membrane	Disulfide bond, Glycoprotein, Phosphoprotein	-0.294946	2
Plasma membrane	Disulfide bond, Glycoprotein, Phosphoprotein	-0.249645	2
Unclear	Unknown	-0.385540	1
Unclear	Phosphoprotein	-0.333927	0
Plasma membrane	Glycoprotein, Phosphoprotein	-0.372159	2
Plasma membrane	Disulfide bond, Glycoprotein	-0.401798	2
Plasma membrane	Phosphoprotein	-0.922459	0
Unclear	Acetylation, Phosphoprotein	Too long	0
Golgi apparatus membrane, vesicle membrane	Phosphoprotein	-0.827338	0
Golgi apparatus membrane	Unknown	-0.909454	0
Golgi apparatus membrane, vesicle membrane	Phosphoprotein	-0.827338	0
Nuclear membrane	Phosphoprotein	-0.225366	1
			0
Plasma membrane	Phosphoprotein	-0.922459	0



Table 1. (Continued)

No.	Accession number	Protein name	Score	Peptide match	Molecular weight
173	Q92736	Ryanodine receptor 2	70	10	569626
174	Q15413	Ryanodine receptor 3	71	24	557794
175	O15027	SEC16 homolog A	36	5	115891
176	A4QN19	SEC16A protein	40	2	116196
177	Q9H2E6	Sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6A	36	4	115608
178	O94921	Serine/threonine protein kinase PFTAIRE-1	41	8	53609
179	Q8NGB0	Seven transmembrane helix receptor	49	10	157779
180	Q9Y566	SH3 and multiple ankyrin repeat domains protein 1	49	7	225738
181	Q9UPX8	SH3 and multiple ankyrin repeat domains protein 2	54	6	135115
182	Q7Z5N4	Sidekick-like protein 1	39	4	242926
183	P21817	Skeletal muscle ryanodine receptor	78	9	570517
184	O94813	Slit homolog 2	47	13	175803
185	O94813	SLIT2	40	7	175329
186	Q9C0H9	SNAP-25-interacting protein	42	6	127182
187	Q9Y6M7	Sodium bicarbonate cotransporter2	44	8	115215
188	Q53ZR1	Solute carrier family 12 (sodium/potassium/chloride transporters), member 2	64	13	132048
189	Q9HBR0	Solute carrier family 38, member 10 isoform b	40	5	84069
190	Q9NRC6	Spectrin beta chain, brain 4	72	14	419259
191	Q01082	Spectrin, beta, non-erythrocytic 1 isoform 1 variant	48	8	276797
192	Q8WWQ8	Stabilin 2 precursor	57	9	288323
193	Q8WWQ8	Stabilin-2	46	9	288329
194	Q8IVL0	Steerin3 protein	37	5	256885
195	Q4LDE5	Sushi, von Willebrand factor type A, EGF and pentraxin domain containing 1	52	10	401915
196	Q9Y4G6	Talin-2	50	11	273723
197	Q9H2K2	Tankyrase, TRF1-interacting ankyrin-related ADP-ribose polymerase 2	41	4	128492
198	O60343	TBC1 domain family, member 4	36	5	148068
199	Q15643	Thyroid receptor-interacting protein 11	38	7	228184
200	P12270	Tpr	54	10	265840
201	Q9BX84	Transient receptor potential cation channel subfamily M member 6	79	20	232975
202	00NCO4	variant c	47	_	24405
202	Q8N6Q1	Transmembrane and coiled-coil domains 5A	47	5	34495
203	O95271	TRF1-interacting ankyrin-related ADP-ribose polymerase	47	12	143690
204	Q15643	Trip230	92	12	228116
205	Q9BX84	Truncated transient receptor potential cation channel subfamily M member 6 variant a	57	13	224977
206	Q8NFA0	Ubiquitin specific protease 32	47	8	183821
207	P55916	Uncoupling protein 3 isoform UCP3S	36	15	30219
208	P17927	Unnamed protein product	41	10	230401
209	P53420	Unnamed protein product	65	10	126774
210	P11717	Unnamed protein product	48	14	281089
211	Q6ZUB1	Unnamed protein product	36	10	158870
212	O75110	Unnamed protein product	39	10	108198



Subcellular location	PTM	Hydrophobicity value	TMDs
Plasma membrane	Glycoprotein, Phosphoprotein	-0.324300	7
Endoplasmic reticulum membrane	Glycoprotein	-0.278727	5
Endoplasmic reticulum membrane,	Acetylation, Phosphoprotein	-0.606607	0
Golgi apparatus membrane	Acotylication, 1 Hoophoprotoin	0.000001	Ü
Endoplasmic reticulum membrane,	Acetylation, Phosphoprotein	-0.606607	0
Golgi apparatus membrane	Acceptation, a moophoprotein	-0.000007	O
Plasma membrane	Disulfide bond, Glycoprotein	-0.448543	2
Plasma membrane	Phosphoprotein	-0.470362	0
Unclear	Unknown	-0.275069	6
Plasma membrane	Phosphoprotein	-0.539239	0
Plasma membrane	Glycoprotein, Phosphoprotein	-0.608572	0
Plasma membrane	Disulfide bond, Glycoprotein	-0.314144	1
Plasma membrane	Glycoprotein, Phosphoprotein,		0
Plasma membrane	S-nitrosylation	Too long	U
Plasma membrane	Disulfide bond, Glycoprotein	-0.323414	0
Plasma membrane	Disulfide bond, Glycoprotein	-0.323414	0
Plasma membrane	Phosphoprotein	-0.644456	0
Plasma membrane	Glycoprotein, Phosphoprotein	-0.130725	10
Plasma membrane	Unknown	0.069720	11
Unclear	Phosphoprotein	-0.363718	11
Unclear	Unknown	-0.576588	0
Plasma membrane	Acetylation, Glycoprotein, Phosphoprotein	-0.766116	0
Plasma membrane	Disulfide bond, Glycoprotein, Phosphoprotein, Proteoglycan	-0.268563	2
Plasma membrane	Disulfide bond, Glycoprotein,	-0.268563	2
	Phosphoprotein, Proteoglycan		•
Nuclear membrane	Phosphoprotein	-0.638784	0
Unclear	Disulfide bond, Glycoprotein	-0.320528	1
Plasma membrane	Acetylation, Phosphoprotein	-0.218412	0
Golgi apparatus membrane	ADP-ribosylation	-0.317066	0
Plasma membrane	Phosphoprotein	-0.553083	1
Golgi apparatus membrane	Phosphoprotein	-0.843506	0
Nuclear membrane	Acetylation, Phosphoprotein	-0.968726	0
Unclear	Phosphoprotein	-0.369882	5
Unclear	Unknown	-0.563888	1
Golgi apparatus membrane	ADP-ribosylation, Phosphoprotein	-0.327506	Ö
Unclear	Phosphoprotein		0
Plasma membrane	Phosphoprotein	-0.843506	5
Flasifia membrane	Phosphoprotein	-0.369882	5
Unclear	Lipoprotein, Phosphoprotein, Prenylation	-0.474689	0
Mitochondrion membrane	Unknown	0.074679	0
Plasma membrane	Disulfide bond, Glycoprotein, Pyrrolidone carboxylic acid	-0.320010	3
Vesicle membrane	Acetylation, Phosphoprotein	-0.659231	1
Plasma membrane	Acetylation, Disulfide bond, Glycoprotein, Phosphoprotein	-0.368528	3
	Glycoprotein	-0.709205	1
Unclear	Glycoprotein	-0.703203	



## Table 1. (Continued)

No.	Accession number	Protein name	Score	Peptide match	Molecular weight
213	Q9NRW7	Vacuolar protein sorting	41	6	65388
214	Q86Y38	Xylosyltransferase I	41	12	108357
215 216 217	Q13433 Q13439 Q8N1I0	Zinc transporter ZIP6 256 kD golgin Dedicator of cytokinesis protein 4	41 59 49	5 9 11	84685 256666 225206



Subcellular location	PTM	Hydrophobicity value	TMDs
Endosome membrane, Golgi apparatus membrane	Unknown	-0.310526	0
Endoplasmic reticulum membrane, Golgi apparatus membrane	Disulfide bond, Glycoprotein	-0.540564	0
Plasma membrane	Glycoprotein, Phosphoprotein	-0.421987	6
Golgi apparatus membrane	Phosphoprotein	-1.052981	0
Endomembrane	Phosphoprotein	-0.371464	0