**Table S1.** The eights proteins ranked on top 50 by all three methods—forward, reverse, and non-directional.

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| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Protein Name*a* | Kegg ID*b* | IPI Number | Gene name | Definition | Pathway | Bits | E-value | a.a. No. |
| ACVR1 | hsa:90 | IPI00029219 | ACVR1, ACTRI, ACVR1A, ACVRLK2, ALK2, FOP, SKR1, TSRI | activin A receptor, type I | Cytokine-cytokine receptor interaction;TGF-beta signaling pathway. | 242 | 2.00E-64 | 509 |
| CDC42 | hsa:998 | IPI00007189 | CDC42, CDC42Hs, G25K | cell division cycle 42 (GTP binding protein, 25kDa) | MAPK signaling pathway;Chemokine signaling pathway;Endocytosis;Axon guidance;VEGF signaling pathway;Focal adhesion;Adherens junction;Tight junction;T cell receptor signaling pathway;Fc gamma R-mediated phagocytosis;Leukocyte transendothelial migration;Neurotrophin signaling pathway;Regulation of actin cytoskeleton;GnRH signaling pathway;Bacterial invasion of epithelial cells;Epithelial cell signaling in Helicobacter pylori infection;Pathogenic *Escherichia coli* infection;Shigellosis;Salmonella infection;Pathways in cancer;Renal cell carcinoma;Pancreatic cancer. | 353 | 2.00E-98 | 191 |
| RAC1 | hsa:5879 | IPI00010271 | RAC1, Rac-1, TC-25, p21-Rac1 | ras-related C3 botulinum toxin substrate 1 (rho family, small GTP binding protein Rac1) | MAPK signaling pathway;Chemokine signaling pathway;Phagosome;Wnt signaling pathway;Axon guidance;VEGF signaling pathway;Osteoclast differentiation;Focal adhesion;Adherens junction;Toll-like receptor signaling pathway;Natural killer cell mediated cytotoxicity;B cell receptor signaling pathway;Fc epsilon RI signaling pathway;Fc gamma R-mediated phagocytosis;Leukocyte transendothelial migration;Neurotrophin signaling pathway;Regulation of actin cytoskeleton;Pancreatic secretion;Amyotrophic lateral sclerosis (ALS);Bacterial invasion of epithelial cells;Epithelial cell signaling in Helicobacter pylori infection;Shigellosis;Salmonella infection;Pathways in cancer;Colorectal cancer;Renal cell carcinoma;Pancreatic cancer;Viral myocarditis.  | 306 | 4.00E-84 | 192 |
| RAF1 | hsa:5894 | IPI00021786 | RAF1, CRAF, NS5, Raf-1, c-Raf | v-raf-1 murine leukemia viral oncogene homolog 1 | MAPK signaling pathway;ErbB signaling pathway;Chemokine signaling pathway;Vascular smooth muscle contraction;VEGF signaling pathway;Focal adhesion;Gap junction;Natural killer cell mediated cytotoxicity;T cell receptor signaling pathway;B cell receptor signaling pathway;Fc epsilon RI signaling pathway;Fc gamma R-mediated phagocytosis;Long-term potentiation;Neurotrophin signaling pathway;Serotonergic synapse;Long-term depression;Regulation of actin cytoskeleton;Insulin signaling pathway;GnRH signaling pathway;Progesterone-mediated oocyte maturation;Melanogenesis;Tuberculosis;Hepatitis C;Influenza A;Pathways in cancer;Colorectal cancer;Renal cell carcinoma;Pancreatic cancer;Endometrial cancer;Glioma;Prostate cancer;Melanoma;Bladder cancer;Chronic myeloid leukemia;Acute myeloid leukemia;Non-small cell lung cancer.  | 360 | 1.00E-99 | 648 |
| RHOA | hsa:387 | IPI00478231 | RHOA, ARH12, ARHA, RHO12, RHOH12 | ras homolog gene family, member A | Chemokine signaling pathway;Endocytosis;Vascular smooth muscle contraction;Wnt signaling pathway;TGF-beta signaling pathway;Axon guidance;Focal adhesion;Adherens junction;Tight junction;T cell receptor signaling pathway;Leukocyte transendothelial migration;Neurotrophin signaling pathway;Regulation of actin cytoskeleton;Pancreatic secretion;Bacterial invasion of epithelial cells;Pathogenic Escherichia coli infection;Pertussis;Tuberculosis;Pathways in cancer;Colorectal cancer. | 344 | 1.00E-95 | 193 |
| TGFBR1 | hsa:7046 | IPI00005733 | TGFBR1, AAT5, ACVRLK4, ALK-5, ALK5, LDS1A, LDS2A, MSSE, SKR4, TGFR-1 | transforming growth factor, beta receptor 1 | MAPK signaling pathway;Cytokine-cytokine receptor interaction;Endocytosis;TGF-beta signaling pathway;Osteoclast differentiation;Adherens junction;Chagas disease (American trypanosomiasis);HTLV-I infection;Pathways in cancer;Colorectal cancer;Pancreatic cancer;Chronic myeloid leukemia. | 249 | 2.00E-66 | 426 |
| TRAF2 | hsa:7186 | IPI00030278 | TRAF2, MGC:45012, TRAP, TRAP3 | TNF receptor-associated factor 2 | MAPK signaling pathway;Protein processing in endoplasmic reticulum;Apoptosis;Osteoclast differentiation;RIG-I-like receptor signaling pathway;Adipocytokine signaling pathway;Hepatitis C;Herpes simplex infection;Pathways in cancer;Small cell lung cancer. | 126 | 2.00E-29 | 501 |
| TRAF6 | hsa:7189 | IPI00743663 | TRAF6, MGC:3310, RNF85 | TRAF6, MGC:3310, RNF85 | MAPK signaling pathway;Ubiquitin mediated proteolysis;Endocytosis;Osteoclast differentiation;Toll-like receptor signaling pathway;NOD-like receptor signaling pathway;RIG-I-like receptor signaling pathway;Neurotrophin signaling pathway;Pertussis;Leishmaniasis;Chagas disease (American trypanosomiasis);Toxoplasmosis;Tuberculosis;Hepatitis C;Measles;Herpes simplex infection;Pathways in cancer;Small cell lung cancer. | 124 | 1.00E-28 | 522 |

*a*:Further information of these proteins can be found in File S10.

*b*: The information of these eight proteins are summarized from Kegg: www.genome.jp/kegg/