Supporting Information

A Blinded Testing of Function Annotation for uPE1 Proteins by the I-TASSER/COFACTOR Pipeline Using the 2018-2019 Additions to neXtProt and CAFA3 Challenge

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Text S1. Retrieval of Fmax data for CAFA3 human targets. For Figure 2 in the main text, we plot the Fmax values of COFACTOR (Zhang-Freddolino lab), Naïve and BLAST using supplementary data accompanying the CAFA3 report (https://figshare.com/articles/Supplementary_data/8135393). Within the above-mentioned CAFA3 supplementary data folder, the six spreadsheets for these Fmax values are located within supplementary_data/cafa3/sheets/ and have the following filenames:

mfo_HUMAN_type1_mode1_all_fmax_sheet.csv

mfo_HUMAN_type2_mode1_all_fmax_sheet.csv

bpo_HUMAN_type1_mode1_all_fmax_sheet.csv

bpo_HUMAN_type2_mode1_all_fmax_sheet.csv

cco_HUMAN_type1_mode1_all_fmax_sheet.csv

cco_HUMAN_type2_mode1_all_fmax_sheet.csv

In the filenames, "type1" and "type2" are for "No knowledge" and "Limited Knowledge" targets, respectively. In each spreadsheet, the performance of COFACTOR (Zhang-Freddolino Lab), Naïve and BLAST are identified by the "M138", "BN7U", and "BB7U" labels, respectively. We did not show the performance of other CAFA3 teams because we were not informed of their respective labels in the spreadsheets, due to restrictions imposed by CAFA data anonymity policy.

For Figure 3, the Fmax for each target is calculated using ground truth GO terms listed under the cafa3/benchmark20171115.tar.

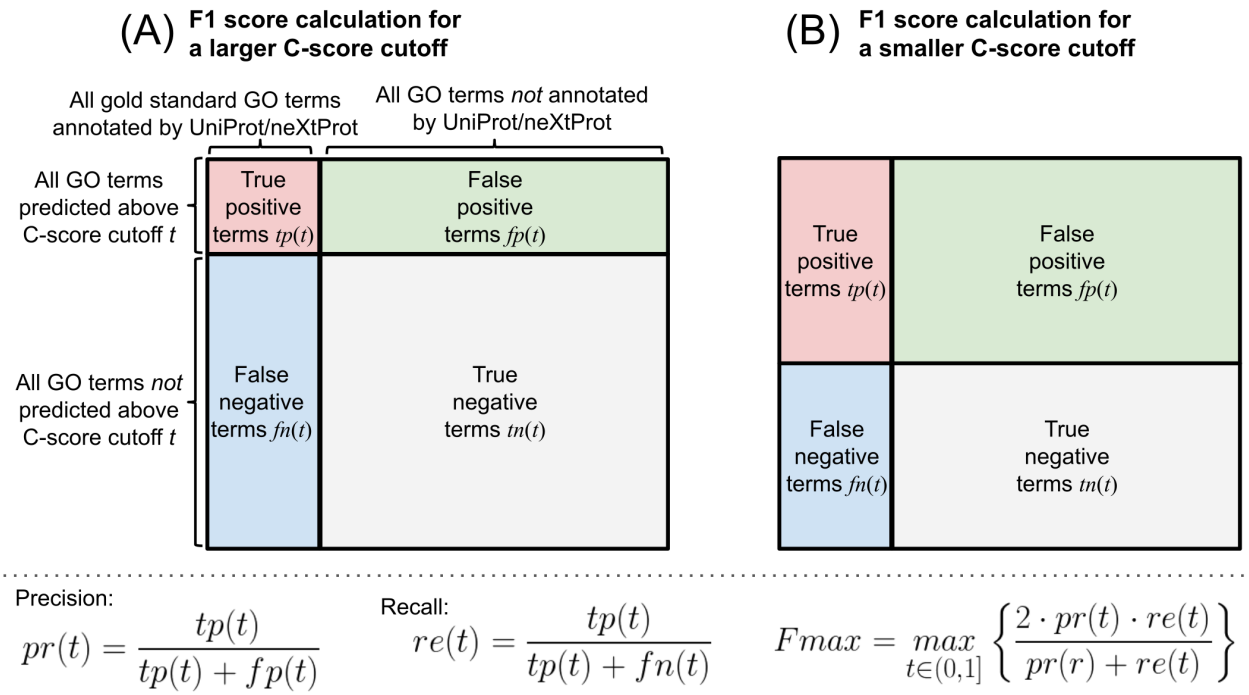

Figure S1. (A) Graphic explanation of Fmax, the standard metric for evaluating the overlap between of the set of predicted GO terms (the two red and green rectangles on the top) and the set of ground-truth GO terms (usually being experimental annotations in UniProt/neXtProt, the two red and cyan rectangles on the left). The big square represents all possible GO terms. Precision is the portion of predicted GO terms that are correct (the set of ground-truth GO terms), and recall is the portion of ground-truth standard terms that are predicted. **(B)** For the same protein, the set of "predicted" GO terms depends on the C-score cutoff *t* ranging between 0 and 1, and less stringent cutoff (smaller *t* value) results in larger set of predicted terms (bigger area for the two rectangles on the top), which makes both precision and recall dependent on the C-score cutoff *t* as well. The harmonic average of precision and recall is called F1 score, whose maximum over the entire range of *t* is Fmax.

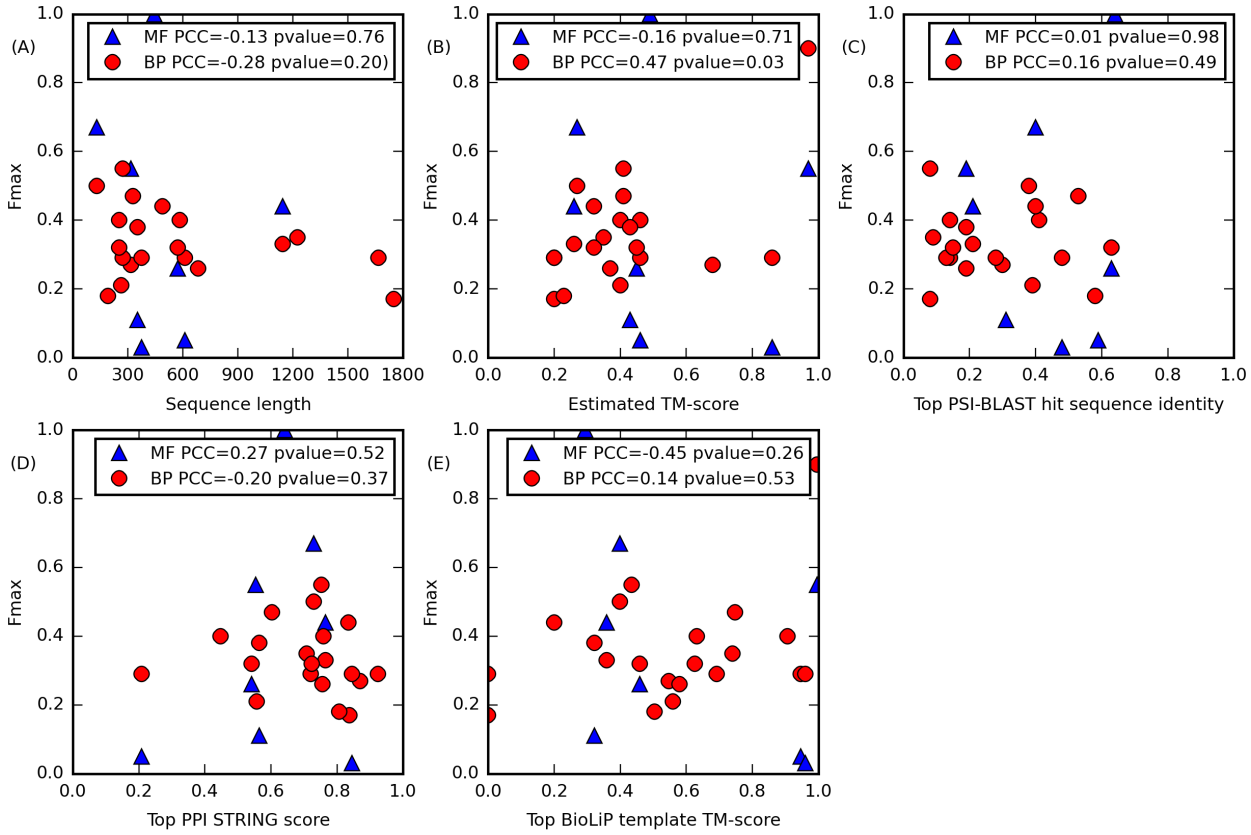

Figure S2. Fmax versus features of target protein in time-elapsed set of 8 and 22 proteins with MF and BP GO terms by UniProt/neXtProt. Inside each figure legend, the two numbers are the Pearson's correlation coefficient (PCC) between Fmax and target protein feature, followed by the *p*-value of PCC.

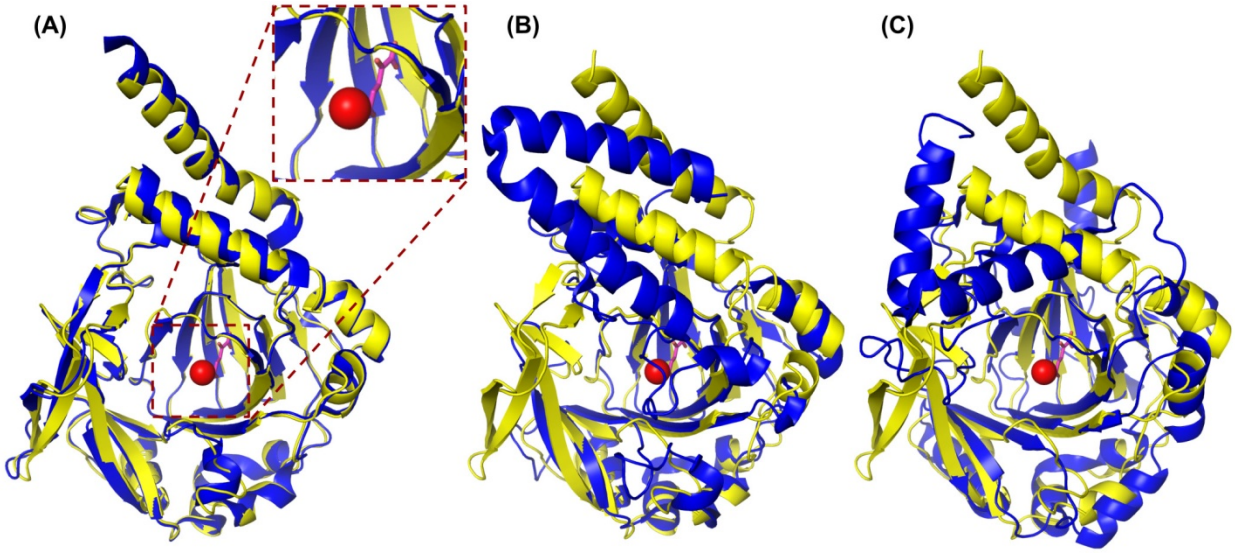

Figure S3. I-TASSER model of human JMJD7 (yellow cartoon) superposed to **(A)** its native structure (PDB ID 5nfn Chain A), **(B)** a human tRNA hydrolase (PDB ID 3al5 Chain B), and **(C)** a human hypoxia-inducible factor-asparagine dioxygenase (PDB ID 4b7e Chain A) in yellow blue cartoons. The JMJD7 ligand binding site (dashed inset) shows the COFACTOR predicted ligands, including Fe^{2+} ion (red sphere) and 2-oxoglutarate (magenta stick), both of which are known to participate in the catalytic activity of JMJD7.

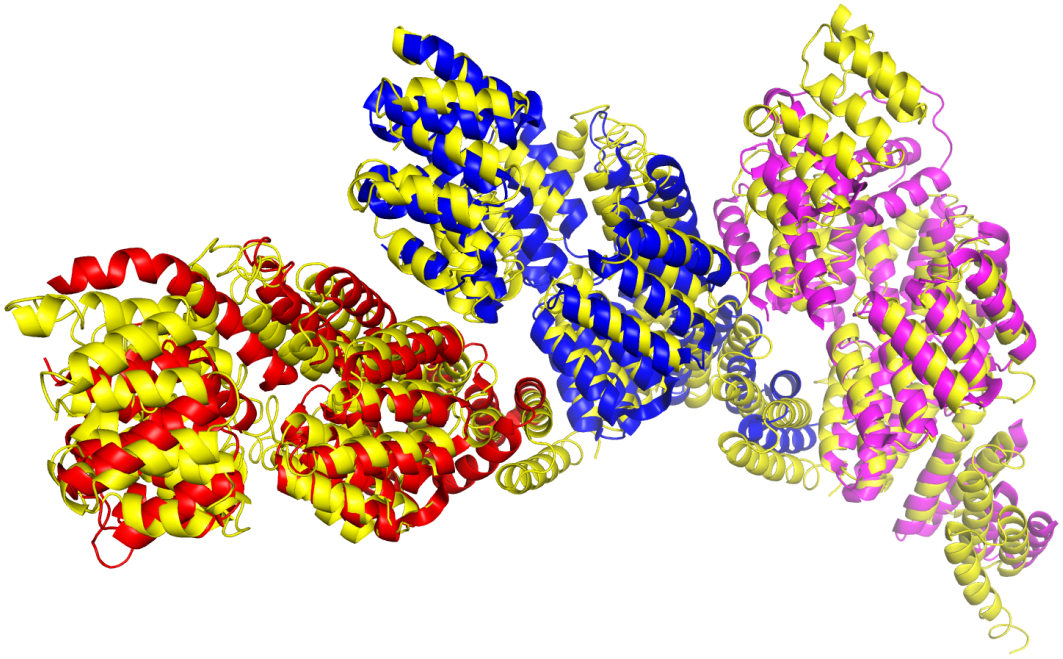

Figure S4. I-TASSER model of TTC39B (yellow cartoons) superposed to three subunits of Apc/C (5a31 Chain F, J, P in red, blue, and magenta cartoons, respectively) with TM-scores ranging from 0.66 to 0.76. Subunits of this complex are involved in regulation and catalysis of protein ubiquitination.

Table S1. Comparison of our function annotation by I-TASSER/COFACTOR and by UniProt/neXtProt curation for the 25 uPE1 proteins with newly provided function annotation in neXtProt release 2019-01-11.

(a) An asterisk (*) marks a target if our free-text annotation (see below) matches neXtProt free text annotation (obtained from release 2019-01-11). For each target, we manually assign a free-text annotation based on specific GO term predicted by our automatic I-TASSER/COFACTOR pipeline. #2, 3, 4, 7, 10, 11, 15, 19, 23 are marked by asterisks.

(b) A plus (+) marks a target whose Fmax for either MF or BP is >0.5 but the free-text annotation does not match. Fmax for MF/BP quantitatively measures the consistency between COFACTOR predicted GO terms and neXtProt curated GO terms. "NA", or not applicable, means neXtProt did not assign GO term for a target. #6 is marked by a plus. The table is ranked in descending order of Fmax.

(c) Since there are usually many GO terms predicted for a target protein by our pipeline, we only show the GO term used to derive our free-text annotation. The criteria for selection of these GO terms are explained in "Manual free-text function interpretation" section in the main text. These GO terms are not necessarily the same as the set of GO terms for Fmax calculation, which are shown at https://zhanglab.ccmb.med.umich.edu/COFACTOR2/nx2019addition/GOterm.html#2. Due to page limitation, the full set of predicted GO terms for each target is available separately at https://zhanglab.ccmb.med.umich.edu/COFACTOR/nx2019addition/GOterm.html#3.

(d) In the last column, phrases at top are free-text annotations, followed by MF and BP GO terms. Red shades indicate free-text phrases consistent between I-TASSER/COFACTOR prediction and neXtProt annotation.

#	Accession, Gene (Chromosome)	Match	Estimated TM-score	Fmax MF/BP	I-TASSER/COFACTOR prediction	neXtProt annotation
1	Q96M27-1, PRRC1 (Chr5)	*	0.49	1.00, 0.88	Protein kinase A regulation == MF == GO:0034237 0.65 protein kinase A regulatory subunit binding == BP == GO:0001934 0.67 positive regulation of protein phosphorylation GO:0034199 0.65 activation of protein kinase A activity	Activation of protein kinase A activity. Protein binding. Protein kinase A regulatory subunit binding. ==== MF ==== GO:0034237 protein kinase A regulatory subunit binding ==== BP ==== GO:0034199 activation of protein kinase A activity

2	P0C870-1, JMJD7 (Chr15)	*	0.97	0.55, 0.90	Histone demethylation == MF == GO:0016706 0.76 2-oxoglutarate-dependent dioxygenase activity GO:0032452 0.63 histone demethylase activity GO:0003682 0.51 chromatin binding == BP == GO:0016570 0.53 histone modification	Bifunctional enzyme that acts both as an endopeptidase and 2-oxoglutarate-dependent monoxygenase. Endopeptidase that cleaves histones N-terminal tails at the carboxyl side of methylated arginine or lysine residues, to generate 'tailless nucleosomes', which may trigger transcription elongation. Preferentially recognizes and cleaves monomethylated and dimethylated arginine residues of histones H2, H3 and H4. After initial cleavage, continues to digest histones tails via its aminopeptidase activity. Additionally, may play a role in protein biosynthesis by modifying the translation machinery. Acts as Fe2+ and 2-oxoglutarate-dependent monoxygenase, catalyzing (S)-stereospecific hydroxylation at C-3 of 'Lys-22' of DRG1 and 'Lys-21' of DRG2 translation factors (TRAFAC), promoting their interaction with ribonucleic acids (RNA). ==== MF ==== GO:0016706 2-oxoglutarate-dependent dioxygenase activity GO:0004177 aminopeptidase activity GO:0004175 endopeptidase activity GO:0046872 metal ion binding GO:0035064 methylated histone binding GO:0004497 monooxygenase activity ==== BP ==== GO:0018126 protein hydroxylation
3	Q7Z5A7-1, FAM19A5 (Chr22)	*	0.27	0.67, 0.50	Regulation of microglial cell activation == BP == GO:0031347 0.67 regulation of defense response GO:0002682 0.67 regulation of immune system process GO:1903980 0.66 positive regulation of microglial cell activation GO:1903979 0.66 negative regulation of microglial cell activation	Acts as a chemokine-like protein by regulating cell proliferation and migration through activation of G protein-coupled receptors (GPCRs), such as S1PR2 and FPR2. Stimulates chemotactic migration of macrophages mediated by the MAPK3/ERK1 and AKT1 pathway. Blocks TNFSF11/RANKL-induced osteoclast formation from macrophages by inhibiting up-regulation of osteoclast fusogenic and differentiation genes. Stimulation of macrophage migration and inhibition of osteoclast formation is mediated via GPCR FPR2. Acts as an adipokine by negatively regulating vascular smooth muscle cell (VSMC) proliferation and migration in response to platelet-derived growth factor stimulation via GPCR S1PR2 and G protein GNA12/GNA13-transmitted RHOA signaling. Inhibits injury-induced cell proliferation and neointima formation in the femoral arteries ==== MF ==== GO:0005125 cytokine activity ==== BP ==== GO:0010469 regulation of signaling receptor activity
4	Q5T0D9-1, TPRG1L (Chr1)	+	0.41	NA, 0.55	Phosphatidylinositol-4-phosphate phosphatase == MF == GO:0034596 0.70 phosphatidylinositol phosphate 4-phosphatase activity GO:0052833 0.68 inositol monophosphate 4-phosphatase activity == BP == GO:0048015 0.70 phosphatidylinositol-mediated signaling GO:0046856 0.70 phosphatidylinositol dephosphorylation GO:0031161 0.70 phosphatidylinositol catabolic process	Presynaptic protein involved in the synaptic transmission tuning. Regulates synaptic release probability by decreasing the calcium sensitivity of release ==== BP ==== GO:0051966 regulation of synaptic transmission, glutamatergic

5	Q96D15-1, RCN3 (Chr19)		0.41	NA, 0.47	Catalytic activity, acting on a protein == MF == GO:0140096 0.41 catalytic activity, acting on a protein	Probable molecular chaperone assisting protein biosynthesis and transport in the endoplasmic reticulum. Required for the proper biosynthesis and transport of pulmonary surfactant-associated protein A/SP-A, pulmonary surfactant-associated protein D/SP-D and the lipid transporter ABCA3. By regulating both the proper expression and the degradation through the endoplasmic reticulum-associated protein degradation pathway of these proteins plays a crucial role in pulmonary surfactant homeostasis. Has an anti-fibrotic activity by negatively regulating the secretion of type I and type III collagens. This calcium-binding protein also transiently associates with immature PCSK6 and regulates its secretion. ==== BP ==== GO:0009306 protein secretion GO:0010952 positive regulation of peptidase activity GO:0015031 protein transport GO:0032964 collagen biosynthetic process GO:0036503 ERAD pathway GO:0043129 surfactant homeostasis GO:0051896 regulation of protein kinase B signaling GO:0055091 phospholipid homeostasis GO:0060428 lung epithelium development
6	Q8WTR8-1, NTN5 (Chr19)	*	0.32	NA, 0.44	Anatomical structure morphogenesis == BP == GO:0048856 0.66 anatomical structure development GO:0009653 0.63 anatomical structure morphogenesis GO:0007411 0.48 axon guidance GO:0051960 0.45 regulation of nervous system development GO:0050767 0.44 regulation of neurogenesis GO:0045664 0.43 regulation of neuron differentiation GO:0010975 0.42 regulation of neuron projection development GO:0010769 0.41 regulation of cell morphogenesis involved in differentiation	Plays a role in neurogenesis. Prevents motor neuron cell body migration out of the neural tube. ==== BP ==== GO:0022008 neurogenesis
7	Q9C0D6-1, FHDC1 (Chr4)	*	0.26	0.44, 0.33	Binding of cytoskeleton == MF == GO:0008092 0.70 cytoskeletal protein binding == CC == GO:0044430 0.47 cytoskeletal part	Microtubule-associated formin which regulates both actin and microtubule dynamics. Induces microtubule acetylation and stabilization and actin stress fiber formation. Regulates Golgi ribbon formation. Required for normal cilia assembly. ==== MF ==== GO:0003779 actin binding GO:0008017 microtubule binding ==== BP ==== GO:0043149 stress fiber assembly GO:0060271 cilium assembly GO:0090161 Golgi ribbon formation
8	O75363-1, BCAS1 (Chr20)		0.46	NA, 0.40	(for CC: neuron part) == CC == GO:0097458 0.42 neuron part	Required for myelination. ==== BP ==== GO:0042552 myelination
9	P60827-1, C1QTNF8 (Chr16)	*	0.40	NA, 0.40	Signaling receptor binding	May play a role as ligand of relaxin receptor RXFP1. ==== BP ==== GO:2000147 positive regulation of cell motility

10	Q8IUY3-1, GRAMD2A (Chr15)		0.43	0.11, 0.38	Binding of GTPase from Ras superfamily == MF == GO:0017016 0.63 Ras GTPase binding GO:0005096 0.62 GTPase activator activity GO:0017137 0.61 Rab GTPase binding == BP == GO:0043087 0.74 regulation of GTPase activity GO:0090630 0.73 activation of GTPase activity	Participates in the organization of endoplasmic reticulum-plasma membrane contact sites (EPCS) with pleiotropic functions including STIM1 recruitment and calcium homeostasis. Constitutive tether that co-localize with ESYT2/3 tethers at endoplasmic reticulum-plasma membrane contact sites in a phosphatidylinositol lipid-dependent manner. Pre-marks the subset of phosphtidylinositol 4,5-biphosphate (PI(4,5)P2)-enriched EPCS destined for the store operated calcium entry pathway (SOCE). ==== MF ==== GO:0005546 phosphatidylinositol-4,5-bisphosphate binding GO:0035091 phosphatidylinositol binding ==== BP ==== GO:0061817 endoplasmic reticulum-plasma membrane tethering GO:2001256 regulation of store-operated calcium entry
11	Q9BZH6-1, WDR11 (Chr10)		0.35	NA, 0.35		Involved in the Hedgehog (Hh) signaling pathway, is essential for normal ciliogenesis. Regulates the proteolytic processing of GLI3 and cooperates with the transcription factor EMX1 in the induction of downstream Hh pathway gene expression and gonadotropin-releasing hormone production. WDR11 complex facilitates the tethering of Adaptor protein-1 complex (AP-1)-derived vesicles. WDR11 complex acts together with TBC1D23 to facilitate the golgin-mediated capture of vesicles generated using AP-1. ==== BP ==== GO:0006886 intracellular protein transport GO:0007507 heart development GO:0008589 regulation of smoothened signaling pathway GO:0035264 multicellular organism growth GO:0060271 cilium assembly GO:0060322 head development GO:0099041 vesicle tethering to Golgi
12	Q6ZNE9-2, RUFY4 (Chr2)		0.45	0.26, 0.32	Regulation of protein folding == MF == GO:0051082 0.44 unfolded protein binding GO:0044183 0.44 protein binding involved in protein folding == BP == GO:0061077 0.51 chaperone-mediated protein folding GO:0006458 0.51 'de novo' protein folding	Positively regulates macroautophagy in primary dendritic cells. Increases autophagic flux, probably by stimulating both autophagosome formation and facilitating tethering with lysosomes. Binds to phosphatidylinositol 3-phosphate (PtdIns3P) through its FYVE-type zinc finger. ==== MF ==== GO:0032266 phosphatidylinositol-3-phosphate binding ==== BP ==== GO:0000045 autophagosome assembly GO:0016239 positive regulation of macroautophagy GO:0071353 cellular response to interleukin-4
13	Q9GZU8-1, FAM192A (Chr16)		0.32	NA, 0.32	Hydrolase, probably hydrolase of protein == MF == GO:0016787 0.53 hydrolase activity GO:0140096 0.48 catalytic activity, acting on a protein == BP == GO:0019538 0.50 protein metabolic process	Promotes the association of the proteasome activator complex subunit PSME3 with the 20S proteasome and regulates its activity. Inhibits PSME3-mediated degradation of some proteasome substrates, probably by affecting their diffusion rate into the catalytic chamber of the proteasome ==== BP ==== GO:0032091 negative regulation of protein binding GO:1901799 negative regulation of proteasomal protein catabolic process

14	Q494U1-1, PLEKHN1 (Chr1)		0.46	0.05, 0.29	Transmembrane transport of small molecules, such as nucleotide == MF == GO:0008028 0.59 monocarboxylic acid transmembrane transporter activity == BP == GO:0015780 0.53 nucleotide-sugar transmembrane transport == CC == GO:0016020 0.62 membrane	Controls the stability of the leptin mRNA harboring an AU-rich element (ARE) in its 3' UTR, in cooperation with the RNA stabilizer ELAVL1 ==== MF ==== GO:0001786 phosphatidylserine binding GO:0070300 phosphatidic acid binding GO:1901612 cardiolipin binding GO:1901981 phosphatidylinositol phosphate binding ==== BP ==== GO:0001666 response to hypoxia GO:0043065 positive regulation of apoptotic process GO:0061158 3'-UTR-mediated mRNA destabilization
15	Q8IUW5-1, RELL1 (Chr4)	*	0.20	NA, 0.29	Regulation of apoptosis through TNF == MF == GO:0005031 0.40 tumor necrosis factor-activated receptor activity == BP == GO:0097190 0.51 apoptotic signaling pathway GO:0042981 0.51 regulation of apoptotic process GO:0042127 0.51 regulation of cell proliferation GO:0006955 0.51 immune response GO:0006954 0.51 inflammatory response	Induces activation of MAPK14/p38 cascade, when overexpressed ==== BP ==== GO:1900745 positive regulation of p38MAPK cascade
16	Q8NDM7-1, CFAP43 (Chr10)		0.20	NA, 0.29		Flagellar protein involved in sperm flagellum axoneme organization and function. ==== BP ==== GO:0007288 sperm axoneme assembly
17	Q8TDG2-1, ACTRT1 (ChrX)		0.86	0.03, 0.29	Regulation of chromosome organization either though histone acetylation or binding of cytoskelton used in chromsome segregation == MF == GO:0004402 0.61 histone acetyltransferase activity GO:0008092 0.59 cytoskeletal protein binding == BP == GO:0006325 0.64 chromatin organization GO:0018193 0.61 peptidyl-amino acid modification GO:0016570 0.61 histone modification GO:0016573 0.60 histone acetylation GO:0006281 0.60 DNA repair GO:0000916 0.59 actomyosin contractile ring contraction GO:0006355 0.53 regulation of transcription, DNA-templated == CC == GO:0005856 0.66 cytoskeleton GO:0044430 0.60 cytoskeletal part	Negatively regulates the Hedgehog (SHH) signaling. Binds to the promoter of the SHH signaling mediator, GLI1, and inhibits its expression. ==== MF ==== GO:0003682 chromatin binding ==== BP ==== GO:0008589 regulation of smoothened signaling pathway GO:0045892 negative regulation of transcription, DNA-templated
18	O75677-1, RFPL1 (Chr22)	*	0.68	NA, 0.27	Ubiquitin-protein transferase activity == MF == GO:0004842 0.78 ubiquitin-protein transferase activity == BP == GO:0016567 0.55 protein ubiquitination	Negatively regulates the G2-M phase transition, possibly by promoting cyclin B1/CCNB1 and CDK1 proteasomal degradation and thereby preventing their accumulation during interphase. ==== BP ==== GO:0007049 cell cycle GO:0008285 negative regulation of cell proliferation GO:0010972 negative regulation of G2/M transition of mitotic cell cycle GO:0032436 positive regulation of proteasomal ubiquitin-dependent protein catabolic process GO:0043065 positive regulation of apoptotic process GO:0045930 negative regulation of mitotic cell cycle GO:0051782 negative regulation of cell division GO:2001272 positive regulation of cysteine-type endopeptidase activity involved in execution phase of apoptosis

19	Q5VTQ0-1, TTC39B (Chr9)	*	0.37	NA, 0.26	Protein ubiquitination regulation == MF == GO:0019899 0.52 enzyme binding == BP == GO:0006508 0.52 proteolysis GO:0016567 0.50 protein ubiquitination GO:0051603 0.49 proteolysis involved in cellular protein catabolic process GO:0043632 0.49 modification-dependent macromolecule catabolic process	Regulates high density lipoprotein (HDL) cholesterol metabolism by promoting the ubiquitination and degradation of the oxysterols receptors LXR (NR1H2 and NR1H3). ==== BP ==== GO:0006629 lipid metabolic process GO:0010874 regulation of cholesterol efflux GO:0010887 negative regulation of cholesterol storage GO:0042632 cholesterol homeostasis GO:0090181 regulation of cholesterol metabolic process
20	Q96S16-1, JMJD8 (Chr16)		0.40	NA, 0.21	Histone demethylation == MF == GO:0016705 0.87 oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen GO:0016706 0.79 2-oxoglutarate-dependent dioxygenase activity GO:0032452 0.75 histone demethylase activity GO:0003682 0.50 chromatin binding == BP == GO:0018193 0.63 peptidyl-amino acid modification GO:0006325 0.63 chromatin organization GO:0016570 0.61 histone modification GO:0016577 0.52 histone demethylation == CC == GO:0005634 0.86 nucleus GO:0044428 0.79 nuclear part GO:0005654 0.61 nucleoplasm	Functions as a positive regulator of TNF-induced NF-kappa-B signaling. Regulates angiogenesis and cellular metabolism through interaction with PKM. ==== BP ==== GO:0006110 regulation of glycolytic process GO:0043123 positive regulation of I-kappaB kinase/NF-kappaB signaling GO:1903302 regulation of pyruvate kinase activity GO:1903672 positive regulation of sprouting angiogenesis
21	Q9H9L7-1, AKIRIN1 (Chr1)		0.23	NA, 0.18	By binding to RNA polymerase, regulate expression of genes such as cytokines == MF == GO:0019899 0.77 enzyme binding == BP == GO:0045944 1.00 positive regulation of transcription by RNA polymerase II GO:0001819 0.68 positive regulation of cytokine production GO:0032755 0.67 positive regulation of interleukin-6 production == CC == GO:0005634 1.00 nucleus	Functions as signal transducer for MSTN during skeletal muscle regeneration and myogenesis. May regulates chemotaxis of both macrophages and myoblasts by reorganising actin cytoskeleton, leading to more efficient lamellipodia formation via a PI3 kinase dependent pathway. ==== BP ==== GO:0010592 positive regulation of lamellipodium assembly GO:0010759 positive regulation of macrophage chemotaxis GO:0014839 myoblast migration involved in skeletal muscle regeneration GO:0045663 positive regulation of myoblast differentiation GO:1902723 negative regulation of skeletal muscle satellite cell proliferation GO:1902725 negative regulation of satellite cell differentiation
22	Q96KV7-1, WDR90 (Chr16)		0.20	NA, 0.17	Regulation of transcription by nucleic acid binding == MF == GO:0140110 0.46 transcription regulator activity == BP == GO:0010468 0.60 regulation of gene expression GO:0051252 0.58 regulation of RNA metabolic process GO:0006355 0.57 regulation of transcription, DNA-templated GO:0006357 0.43 regulation of transcription by RNA polymerase II == CC == GO:0005634 0.75 nucleus GO:0044428 0.56 nuclear part	Required for efficient primary cilium formation. ==== BP ==== GO:0060271 cilium assembly
23	Q6AI39-1, BICRAL (Chr6)		0.33	NA, NA	Sodium:potassium ion transporter == MF == GO:0005391 0.54 sodium:potassium-exchanging ATPase activity == BP == GO:0010248 0.54 establishment or maintenance of transmembrane electrochemical gradient == CC == GO:0005886 0.55 plasma membrane	Component of SWI/SNF chromatin remodeling subcomplex GBAF that carries out key enzymatic activities, changing chromatin structure by altering DNA-histone contacts within a nucleosome in an ATP-dependent manner.

					GO:0005886 0.55 plasma membrane	
24	Q96J88-1, EPSTI1 (Chr13)		0.42	NA, NA	Cytoskeleton binding == MF == GO:0008092 0.43 cytoskeletal protein binding == BP == GO:0007010 0.54 cytoskeleton organization GO:0032185 0.47 septin cytoskeleton organization GO:0007017 0.47 microtubule-based process == CC == GO:0044430 0.55 cytoskeletal part	Plays a role in M1 macrophage polarization and is required for the proper regulation of gene expression during M1 versus M2 macrophage differentiation. Might play a role in RELA/p65 and STAT1 phosphorylation and nuclear localization upon activation of macrophages.
25	Q9BZD6-1, PRRG4 (Chr11)		0.32	NA, NA	Serine-type endopeptidase == MF == GO:0070011 0.89 peptidase activity, acting on L-amino acid peptides GO:0004175 0.84 endopeptidase activity GO:0008236 0.79 serine-type peptidase activity GO:0004252 0.74 serine-type endopeptidase activity == BP == GO:0030193 0.56 regulation of blood coagulation	May control axon guidance across the CNS. Prevents the delivery of ROBO1 at the cell surface and downregulates its expression.