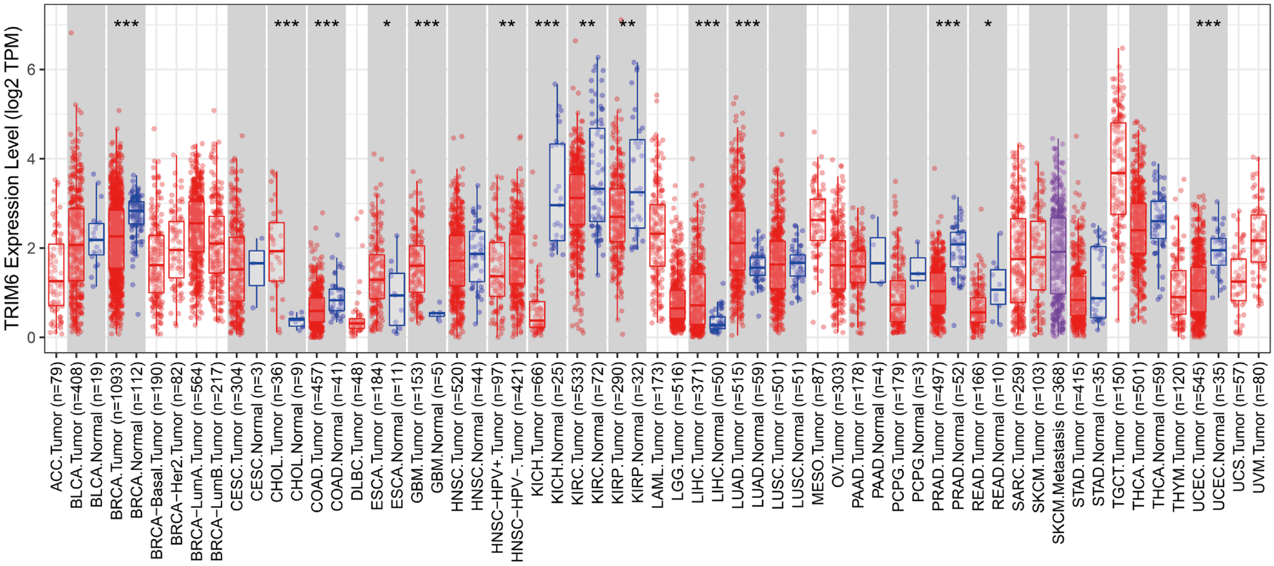


Figure S1 Abnormal expression of TRIM6 in pan-cancer tissues from the TIMER2 database. *, P<0.05; **, P<0.01; ***, P<0.001. TRIM6, tripartite motif containing 6.

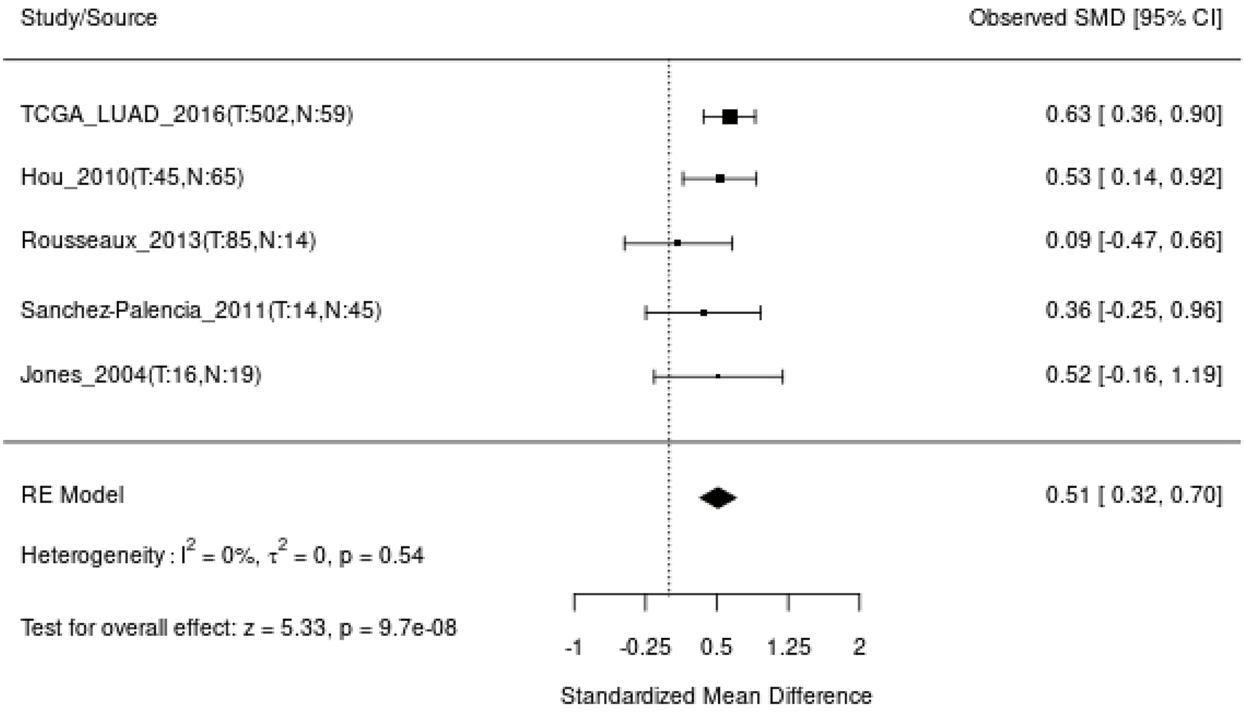


Figure S2 Overexpression of TRIM6 in LAC tissues via meta-analysis. TRIM6, tripartite motif containing 6; LAC, lung adenocarcinoma.

https://dx.doi.org/10.21037/tcr-21-2181

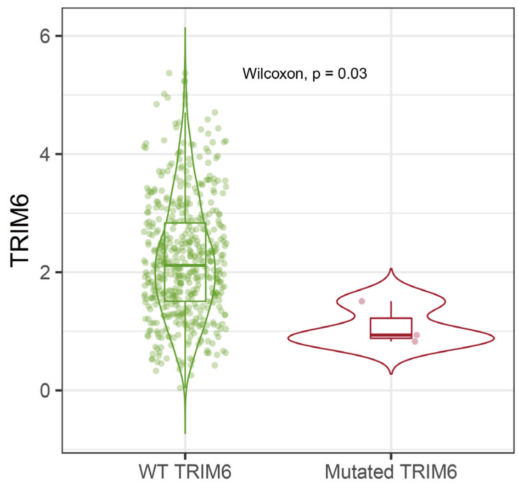
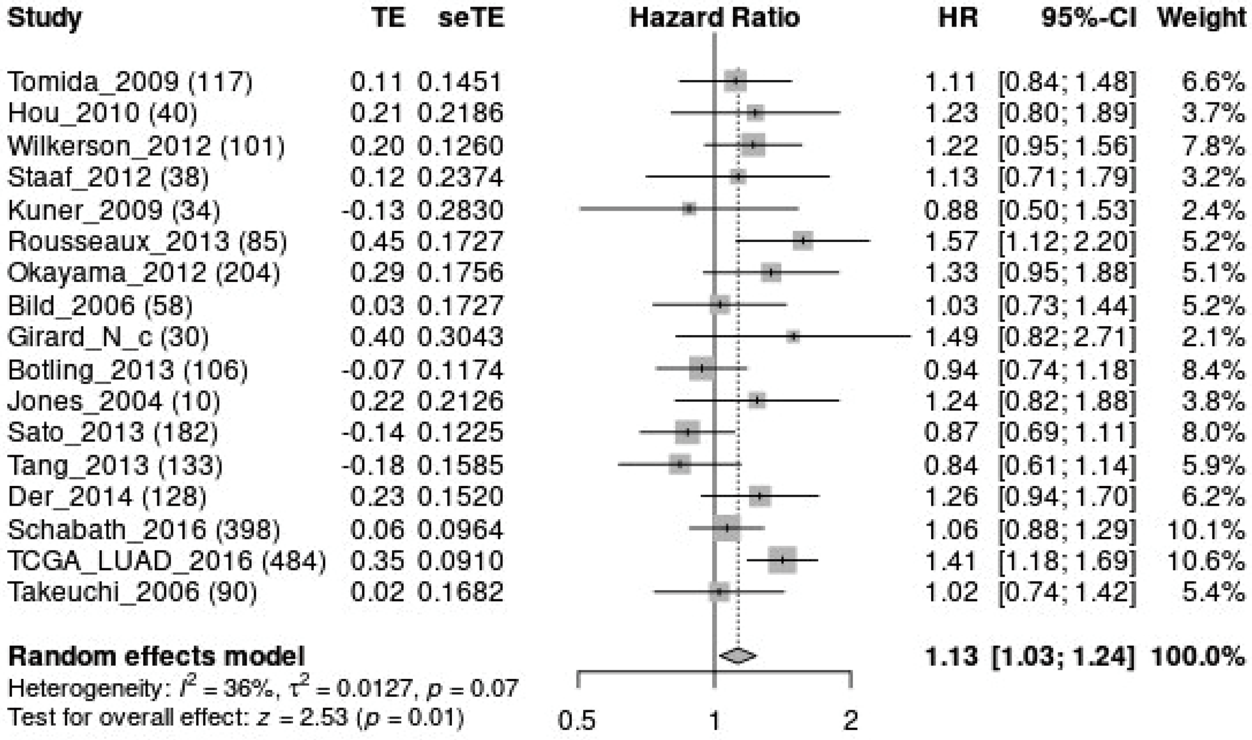


Figure S3 Statistical significance of TRIM6 expression level in wild- and mutant-types. TRIM6, tripartite motif containing 6.



Study	TE	seTE	HR	95%-CI	Weight
Tomida_2009 (117)	0.11	0.1451	1.11	[0.84; 1.48]	6.6%
Hou_2010 (40)	0.21	0.2186	1.23	[0.80; 1.89]	3.7%
Wilkerson_2012 (101)	0.20	0.1260	1.22	[0.95; 1.56]	7.8%
Staaf_2012 (38)	0.12	0.2374	1.13	[0.71; 1.79]	3.2%
Kuner_2009 (34)	-0.13	0.2830	0.88	[0.50; 1.53]	2.4%
Rousseaux_2013 (85)	0.45	0.1727	1.57	[1.12; 2.20]	5.2%
Okayama_2012 (204)	0.29	0.1756	1.33	[0.95; 1.88]	5.1%
Bild_2006 (58)	0.03	0.1727	1.03	[0.73; 1.44]	5.2%
Girard_N_c (30)	0.40	0.3043	1.49	[0.82; 2.71]	2.1%
Botling_2013 (106)	-0.07	0.1174	0.94	[0.74; 1.18]	8.4%
Jones_2004 (10)	0.22	0.2126	1.24	[0.82; 1.88]	3.8%
Sato_2013 (182)	-0.14	0.1225	0.87	[0.69; 1.11]	8.0%
Tang_2013 (133)	-0.18	0.1585	0.84	[0.61; 1.14]	5.9%
Der_2014 (128)	0.23	0.1520	1.26	[0.94; 1.70]	6.2%
Schabath_2016 (398)	0.06	0.0964	1.06	[0.88; 1.29]	10.1%
TCGA_LUAD_2016 (484)	0.35	0.0910	1.41	[1.18; 1.69]	10.6%
Takeuchi_2006 (90)	0.02	0.1682	1.02	[0.74; 1.42]	5.4%
Random effects model			**1.13**	**[1.03; 1.24]**	**100.0%**

Heterogeneity: $I^2 = 36\%$, $\tau^2 = 0.0127$, $p = 0.07$

Test for overall effect: $z = 2.53$ ($p = 0.01$)

Figure S4 Association of TRIM6 overexpression with dismal prognosis in LAC patients via meta-analysis. TRIM6, tripartite motif containing 6; LAC, lung adenocarcinoma.

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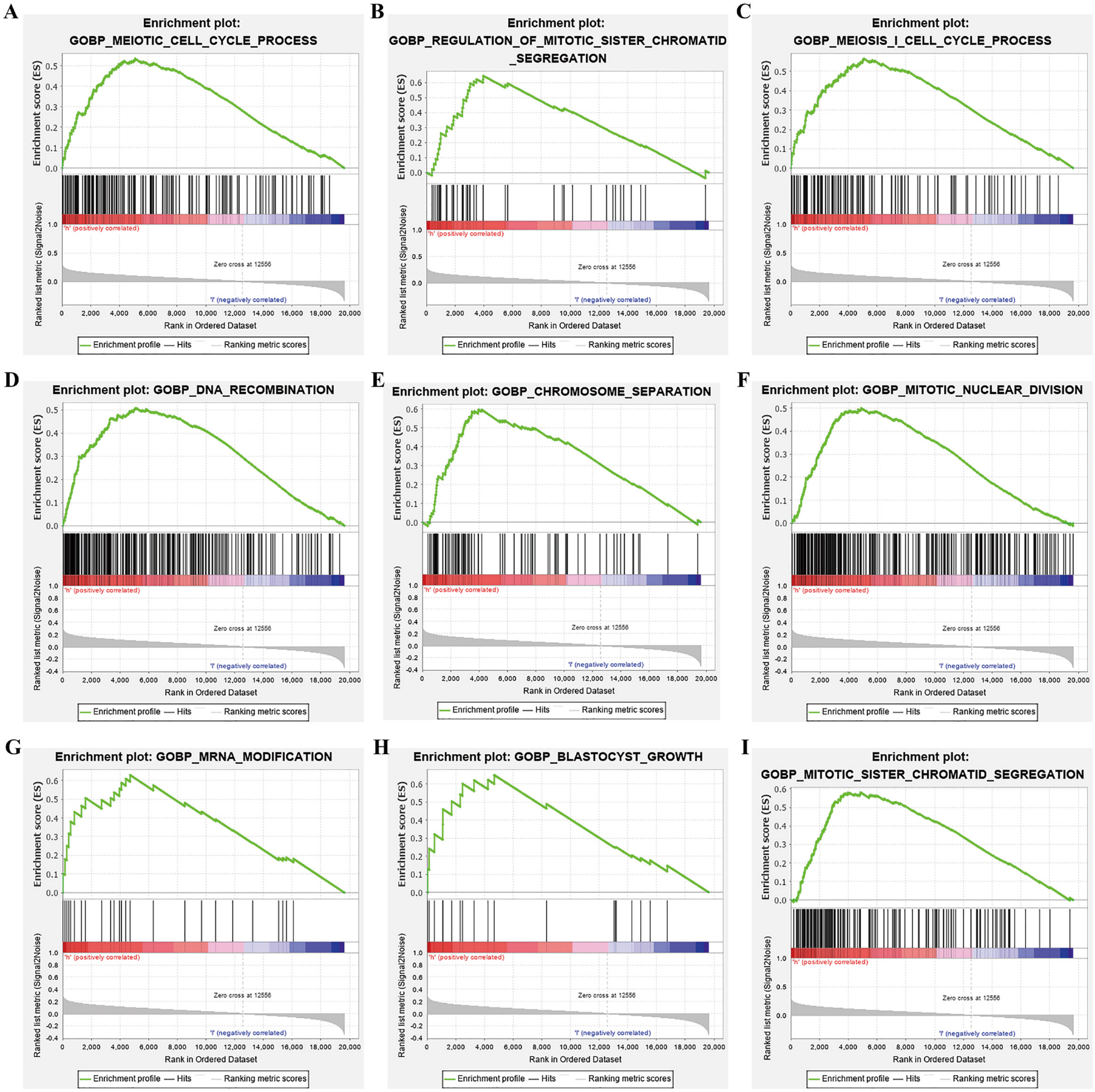

Figure S5 Possible involvement of TRIM6 in the biological functions of LAC via gene set enrichment analysis. TRIM6, tripartite motif containing 6; LAC, lung adenocarcinoma.

Table S1 Possible involvement of TRIM6 in the biological functions of LAC via gene set enrichment analysis

Type	Size	NES	NOM p
Protein polyubiquitination	328	2.0655742	0
Regulation of chromosome separation	69	2.0007765	0
Double strand break repair	248	1.989513	0.001949318
Chromosome separation	92	1.9889274	0.003816794
Recombinational repair	136	1.9847534	0
Positive regulation of defense response to virus by host	30	1.9818842	0
Meiotic cell cycle	242	1.9756027	0.001992032
Nuclear chromosome segregation	261	1.9673109	0.005882353
Chromosome segregation	323	1.9607008	0.005870841
Sister chromatid segregation	190	1.9484386	0.007858546
Meiosis I cell cycle process	121	1.9462405	0.002024292
Mitotic sister chromatid segregation	161	1.9437069	0.011627907
Replication fork processing	40	1.9385577	0.005882353
Metaphase anaphase transition of cell cycle	63	1.9362124	0.005836576
Telomere organization	146	1.936024	0
DNA recombination	277	1.9346648	0.007843138
DNA dependent DNA replication	157	1.932359	0.01171875
RNA methylation	80	1.9304466	0
Organelle fission	473	1.9303519	0.004016064
Meiotic cell cycle process	184	1.9299093	0.002028398
Regulation of mitotic sister chromatid segregation	44	1.9287176	0.007827789
Mitotic nuclear division	292	1.9174657	0.009689922
Meiotic chromosome segregation	85	1.9171549	0.00407332
Chromosome organization involved in meiotic cell cycle	64	1.9163623	0.002008032
Telomere maintenance via recombination	15	1.8963774	0
Regulation of chromosome segregation	84	1.8915232	0.007905139
Regulation of double strand break repair	84	1.8908021	0.003976143
DNA dependent DNA replication maintenance of fidelity	49	1.8879464	0.00996016
Regulation of defense response to virus	66	1.8852271	0
Regulation of telomere maintenance via telomere lengthening	60	1.8835573	0.002066116
DNA replication	279	1.8831266	0.01908397
Regulation of type I interferon mediated signaling pathway	34	1.8816944	0.004132231
SCF dependent proteasomal ubiquitin dependent protein catabolic process	92	1.8759762	0.00390625
Negative regulation of chromosome organization	88	1.8624744	0.00984252
Regulation of defense response to virus by host	40	1.8556365	0.002024292
Cellular response to ionizing radiation	64	1.8535588	0.002
Regulation of double strand break repair via nonhomologous end joining	28	1.851538	0.00203666
mRNA modification	25	1.8494092	0.003913894
Blastocyst growth	19	1.848844	0.004210526
Negative regulation of metaphase anaphase transition of cell cycle	41	1.8479091	0.019493178
Regulation of telomere maintenance	79	1.8467653	0.006160164
Regulation of transposition	26	1.8463326	0.004024145
Membrane disassembly	15	1.8456028	0.005976096
Mitotic recombination	24	1.840489	0.007889546
Postreplication repair	52	1.8396925	0.005859375
Sister chromatid cohesion	55	1.8393118	0
Negative regulation of nuclear division	54	1.8375087	0.01775148
Maintenance of protein location in nucleus	23	1.8354908	0.004246285
Oligosaccharide lipid intermediate biosynthetic process	21	1.8331665	0.001988072
Modulation by virus of host cellular process	18	1.8325902	0
Positive regulation of DNA replication	37	1.8324372	0.004032258
RNA modification	163	1.8277454	0.006122449
Homologous recombination	58	1.827212	0.008080808
DNA double strand break processing	25	1.824733	0.011881189
DNA geometric change	112	1.8239932	0.017578125
Cellular carbohydrate catabolic process	45	1.8213698	0
Homologous chromosome segregation	57	1.817825	0.006036217
Negative regulation of telomere maintenance via telomere lengthening	27	1.8165724	0.004016064
Regulation of mitotic nuclear division	109	1.815922	0.019762846
Protein modification by small protein removal	299	1.8151141	0
Interstrand cross link repair	56	1.8144042	0.00996016
Cellular response to virus	62	1.8094558	0
RNA 3 end processing	152	1.8071829	0.019607844
Positive regulation of telomere maintenance	51	1.8029904	0.008196721
Positive regulation of double strand break repair via nonhomologous end joining	16	1.8029343	0.00610998
Negative regulation of viral genome replication	50	1.793344	0.019305019
Regulation of viral genome replication	79	1.789701	0.009861933
mRNA methylation	16	1.788956	0.006060606
tRNA methylation	39	1.7867619	0.008196721
Nucleic acid phosphodiester bond hydrolysis	291	1.786635	0.005836576
Non recombinational repair	90	1.7844683	0.006048387
Regulation of stem cell differentiation	110	1.7821914	0.007827789
Response to ionizing radiation	139	1.7808094	0.004246285
Cell cycle g2 M phase transition	270	1.7789677	0.017441861
Positive regulation of double strand break repair	41	1.7763609	0.004056795
Telomere maintenance via telomere lengthening	79	1.7752088	0.010080645
Regulation of cell cycle g2 M phase transition	214	1.7729582	0.01764706
Transposition	31	1.772282	0.006024096
DNA replication independent nucleosome organization	38	1.771991	0.030360531
Positive regulation of chromosome separation	17	1.7672647	0.004008016
Polysaccharide catabolic process	27	1.7659845	0
Negative regulation of telomere maintenance	35	1.7628858	0.004065041
Cell cycle checkpoint	207	1.7625858	0.024291499
DNA dealkylation	34	1.7602825	0.008230452
Response to interferon beta	28	1.7585148	0.005940594
Nucleobase biosynthetic process	18	1.7528863	0.017892644
Regulation of protein polyubiquitination	23	1.7523298	0.00407332
snRNA processing	35	1.7519541	0.024856597
DNA synthesis involved in DNA repair	52	1.750701	0.011857707
Protein k48 linked ubiquitination	60	1.7494944	0.010526316
DNA conformation change	274	1.7472078	0.031434186
Nucleus organization	118	1.7452762	0.006355932
Translesion synthesis	42	1.7414287	0.01004016
Regulation of DNA recombination	93	1.7411702	0.016032064
Positive regulation of response to cytokine stimulus	56	1.7411567	0.010183299
Regulation of DNA dependent DNA replication	47	1.7345353	0.04892368
Protein k63 linked ubiquitination	56	1.7336906	0.006147541
Cytoskeleton dependent cytokinesis	85	1.7321087	0.012875536
Regulation of DNA replication	106	1.7296755	0.032128513
Histone phosphorylation	38	1.7291313	0.01629328
Glycosyl compound biosynthetic process	41	1.7280432	0.020283977
Regulation of DNA repair	127	1.7274215	0.015936255
Mitotic sister chromatid cohesion	26	1.7274014	0.008130081
Negative regulation of DNA repair	34	1.7263863	0.018036073
DNA strand elongation	26	1.7250932	0.015414258
Cytoplasmic pattern recognition receptor signaling pathway	71	1.7219815	0.00610998
Centromere complex assembly	40	1.7216959	0.03006012
Homologous chromosome pairing at meiosis	47	1.7216927	0.012121212
Mitotic cell cycle checkpoint	158	1.721513	0.033464566
Formation of extrachromosomal circular DNA	15	1.7201111	0.015748031
RNA dependent DNA biosynthetic process	69	1.7189876	0.01629328
Positive regulation of DNA templated transcription elongation	26	1.7167281	0.014112903
Mitotic cytokinesis	69	1.7158481	0.016666668
Negative regulation of telomere maintenance via telomerase	20	1.7155759	0.007889546
Cellular response to interferon beta	20	1.7134181	0.02366864
mRNA 3 end processing	99	1.7061754	0.03868472
Protein localization to chromosome	87	1.705618	0.033009708
Cytokinesis	158	1.703202	0.008602151
Nucleobase metabolic process	33	1.703117	0.022132797
fc epsilon receptor signaling pathway	111	1.7028207	0.016260162
Proteasomal protein catabolic process	474	1.7016457	0
Mismatch repair	33	1.7004143	0.028688524
Regulation of DNA templated transcription elongation	51	1.6986502	0.026422765
Positive regulation of organelle assembly	63	1.6985744	0.01026694
RNA polyadenylation	46	1.696868	0.029239766
Pyrimidine nucleobase metabolic process	16	1.6966265	0.021276595
Regulation of hematopoietic progenitor cell differentiation	89	1.6957196	0.015655577
Negative regulation of type i interferon production	44	1.6953702	0.018595042
Negative regulation of cell cycle g2 M phase transition	107	1.6935197	0.030947777
DNA unwinding involved in DNA replication	16	1.6928427	0.022
Pyrimidine containing compound biosynthetic process	38	1.6922145	0.02414487
Response to virus	345	1.6913255	0.008
Interleukin 1 mediated signaling pathway	100	1.6909347	0.02734375
DNA replication initiation	40	1.6889527	0.04347826
Cell cycle DNA replication	64	1.6882298	0.04733728
Macromolecule methylation	287	1.6861122	0.017928287
DNA methylation or demethylation	93	1.6852771	0.01
Mitotic spindle assembly	64	1.680707	0.042
DNA demethylation	28	1.6781073	0.016771488
Carbohydrate catabolic process	193	1.676927	0.00204499
Negative regulation of mitotic cell cycle	300	1.6752526	0.02357564
Regulation of mRNA catabolic process	210	1.6739118	0.020408163
ncRNA 3 end processing	49	1.6724991	0.029821074
Positive regulation of DNA repair	73	1.6717656	0.010162601
snRNA metabolic process	46	1.6713082	0.029296875
Regulation of nuclear division	134	1.6706567	0.043392505
Protein localization to kinetochore	19	1.6703609	0.036750484
Regulation of chromosome organization	265	1.670021	0.034
Centrosome duplication	71	1.6663222	0.027944112
Male meiotic nuclear division	46	1.6661023	0.010162601
Mitotic chromosome condensation	15	1.6654531	0.03868472
Negative regulation of cell cycle process	332	1.6620698	0.025641026
Regulation of mRNA 3 end processing	28	1.6617905	0.030303031
Toll like receptor 2 signaling pathway	17	1.6612055	0.040899795
Positive regulation of metaphase anaphase transition of cell cycle	15	1.6607779	0.01764706
Response to gamma radiation	51	1.6607736	0.014344262
Protein localization to cytoskeleton	58	1.6604872	0.018292682
Defense response to virus	254	1.6584971	0.014285714
Nucleoside metabolic process	102	1.6582175	0.0234375
tRNA modification	86	1.6577955	0.038539555
Positive regulation of telomere maintenance via telomere lengthening	36	1.6576422	0.026639344
Methylation	338	1.6567373	0.019723866
Chromosome localization	80	1.6555444	0.034
Regulation of transcription by RNA polymerase III	23	1.6554717	0.023076924
Pore complex assembly	20	1.6531744	0.031809144
Regulation of hematopoietic stem cell differentiation	74	1.6530024	0.034816246
g2 DNA damage checkpoint	35	1.6516953	0.03696498
Negative regulation of DNA dependent DNA replication	17	1.6509221	0.03846154
tRNA processing	124	1.6503595	0.03968254
Chromatin remodeling at centromere	31	1.6500474	0.0483559
snRNA transcription	75	1.646255	0.023904383
Microtubule organizing center organization	139	1.6456436	0.03258656
Regulation of signal transduction by p53 class mediator	175	1.6454203	0.03929273
Regulation of spindle assembly	25	1.6452734	0.018
Preassembly of gpi anchor in er membrane	17	1.6452149	0.022357723
Protein localization to chromosome centromeric region	25	1.6435722	0.04950495
Signal transduction by p53 class mediator	261	1.6434695	0.031007752
Pyrimidine containing compound catabolic process	39	1.6431837	0.020408163
Innate immune response activating signal transduction	117	1.6429831	0.027613413
Nuclear envelope organization	52	1.6416669	0.016460905
Regulation of response to DNA damage stimulus	216	1.6403896	0.016032064
Negative regulation of DNA recombination	33	1.6386507	0.031746034
Nuclear export	198	1.6379824	0.036
Nucleotide excision repair	107	1.636564	0.032193158
RNA localization	230	1.6360102	0.041420117
Type I interferon production	125	1.6354352	0.03629032
mRNA transport	148	1.6344478	0.04715128
Regulation of cell cycle phase transition	441	1.6341908	0.027131783
Spindle assembly	111	1.6336192	0.033864543
Positive regulation of peptidyl threonine phosphorylation	30	1.6331973	0.010526316
DNA integrity checkpoint	154	1.6325916	0.038854804
Glycosyl compound metabolic process	125	1.6321492	0.01775148
Telomere capping	40	1.6315233	0.01871102
Ribonucleoside metabolic process	70	1.6305566	0.027613413
Negative regulation of cell cycle phase transition	244	1.6303072	0.037181996
Regulation of viral life cycle	142	1.6290175	0.024340771
Nucleoside monophosphate metabolic process	72	1.6275378	0.025096525
Non canonical Wnt signaling pathway	153	1.626171	0.021113243
Regulation of mRNA metabolic process	334	1.6257578	0.03508772
Pyrimidine nucleoside biosynthetic process	16	1.6235046	0.03846154
mRNA cleavage	21	1.6228366	0.026915114
Entry of bacterium into host cell	15	1.6224107	0.049586777
Pyruvate metabolic process	149	1.6218556	0.014112903
RNA phosphodiester bond hydrolysis	151	1.6210061	0.02385686
Somatic diversification of immune receptors	72	1.6197379	0.029598309
Copper ion transport	16	1.6196064	0.016393442
Autophagosome organization	95	1.6186426	0.010660981
Positive regulation of leukocyte apoptotic process	26	1.6166025	0.01992032
NADH metabolic process	42	1.6161786	0.02970297
Regulation of double strand break repair via homologous recombination	46	1.6156191	0.046464648
Positive regulation of gene expression epigenetic	44	1.615551	0.030181086
Positive regulation of transcription initiation from RNA Polymerase II promoter	28	1.6155479	0.019607844
Nucleotide phosphorylation	131	1.61505	0.016064256
Centriole assembly	45	1.6147758	0.04637097
Spindle organization	178	1.6137023	0.04637097
Golgi organization	145	1.6119738	0.029288704
Stress granule assembly	23	1.6113374	0.03671706
Interferon beta production	50	1.6112705	0.030303031
Ribonucleoside monophosphate biosynthetic process	32	1.6110724	0.046511628
DNA templated transcription elongation	111	1.6100688	0.044265594
Regulation of DNA metabolic process	334	1.6090451	0.025896415
Lymphocyte homeostasis	56	1.6073787	0.040733196
Exit from mitosis	28	1.6067088	0.026209677
Ribonucleoside monophosphate metabolic process	54	1.6036354	0.02734375
Regulation of histone h3 k9 methylation	19	1.6015913	0.0392562
Viral genome replication	123	1.6010172	0.034068137
Protein k11 linked ubiquitination	29	1.6001047	0.02834008
Clathrin coat assembly	18	1.5998569	0.029469548
Base excision repair	39	1.5982872	0.036217302
ncRNA transcription	105	1.5977081	0.04133858
Activation of innate immune response	144	1.5942322	0.030487806
tRNA metabolic process	156	1.5940431	0.04950495
Protein localization to chromosome telomeric region	29	1.5926508	0.036960986
erad pathway	100	1.5913696	0.01775148
Nuclear transcribed mRNA catabolic process deadenylation dependent decay	76	1.5909041	0.030737706
Transcription by RNA polymerase I	60	1.5905643	0.047808766
Nucleotide sugar metabolic process	35	1.5892948	0.04233871
Membrane docking	180	1.5885885	0.016427105
Regulation of response to cytokine stimulus	170	1.5863873	0.022267206
Regulation of vacuole organization	47	1.5860375	0.019723866
Positive regulation of i kappab kinase NF kappab signaling	182	1.5859853	0.020408163
Purine nucleoside monophosphate metabolic process	41	1.5851974	0.03065134
Protein quality control for misfolded or incompletely synthesized proteins	28	1.5849327	0.04
Pyrimidine nucleoside metabolic process	36	1.5817347	0.04597701
Establishment of protein localization to telomere	18	1.5815899	0.04743083
rRNA methylation	25	1.580509	0.034764826
Protein localization to chromatin	25	1.5796822	0.04208417
Negative regulation of double strand break repair via homologous recombination	18	1.5793256	0.049407113
Dosage compensation	15	1.5769355	0.040511727
Regulation of sister chromatid cohesion	21	1.5737301	0.04140787
Regulation of biological process involved in symbiotic interaction	191	1.572002	0.028455285
Vesicle targeting	91	1.5716345	0.023605151
DNA modification	115	1.5715665	0.032128513
Nuclear transport	339	1.5706556	0.041257367
Regulation of cellular amide metabolic process	409	1.5695508	0.016194332
Protein monoubiquitination	64	1.5685945	0.041493777
Tumor necrosis factor mediated signaling pathway	169	1.5681828	0.041257367
Regulation of centrosome cycle	47	1.5681388	0.038617887
Nucleoside diphosphate metabolic process	154	1.5674165	0.014112903
rig i signaling pathway	25	1.5660802	0.032520324
Glutamine metabolic process	22	1.565387	0.046464648
Pyrimidine containing compound metabolic process	82	1.5637685	0.03168317
NAD metabolic process	50	1.5596288	0.034
Base conversion or substitution editing	20	1.5593028	0.042596348
Viral life cycle	339	1.5587832	0.016032064
Establishment of tissue polarity	123	1.5569111	0.033464566
Cytoplasmic pattern recognition receptor signaling pathway in response to virus	31	1.5560801	0.038306452
Positive regulation of response to DNA damage stimulus	106	1.5546569	0.030425964
Vacuole organization	170	1.5536447	0.006289308
Positive regulation of DNA metabolic process	197	1.553395	0.030181086
Guanosine containing compound metabolic process	39	1.5526001	0.016032064
Macroautophagy	306	1.5495206	0.01026694
Negative regulation of DNA metabolic process	109	1.5489824	0.046747968
Determination of adult lifespan	18	1.546193	0.04375
nik NF kappab signaling	167	1.5438156	0.043392505
Positive regulation of response to biotic stimulus	249	1.5433587	0.04897959
Regulation of spindle organization	39	1.540542	0.042769857
Regulation of exit from mitosis	16	1.5373284	0.048484847
Signal transduction in response to DNA damage	129	1.5361433	0.04715128
Viral RNA genome replication	33	1.5291849	0.034274194
Monosaccharide catabolic process	61	1.5286518	0.04761905
Post translational protein modification	358	1.5268416	0.007858546
Regulation of autophagosome assembly	38	1.5258355	0.038854804
DNA biosynthetic process	185	1.5239446	0.037848607
Regulation of translational initiation	80	1.5235577	0.038
Morphogenesis of a polarized epithelium	144	1.5226166	0.04296875
Regulation of carbohydrate catabolic process	88	1.5197762	0.04024145
Binding of sperm to zona pellucida	43	1.5171808	0.038986355
Protein localization to nucleus	273	1.5160446	0.016494846
Protein phosphopantetheinylation	329	1.5140212	0.008247423
Cellular response to gamma radiation	27	1.5138853	0.04660194
Positive regulation of translation	129	1.513046	0.042510122
Cellular response to heat	115	1.5113117	0.043209877
Pyridine containing compound metabolic process	41	1.5098954	0.023762377
Biological process involved in interaction with host	219	1.507992	0.018181818
Positive regulation of DNA templated transcription initiation	35	1.505726	0.047524754
Golgi vesicle transport	369	1.5033838	0.015250545
Regulation of organelle assembly	182	1.5015489	0.029787235
Tor signaling	116	1.5009478	0.023206752
DNA damage response signal transduction by p53 class mediator	105	1.4997541	0.034136545
Male meiosis I	23	1.4994725	0.033970278
Regulation of response to biotic stimulus	406	1.4925996	0.044989776
Nucleobase containing small molecule biosynthetic process	112	1.4857869	0.034136545
Protein import	193	1.4849188	0.03726708
Endomembrane system organization	468	1.476467	0.02783726
Regulation of tumor necrosis factor mediated signaling pathway	59	1.4691786	0.036659878
Endoplasmic reticulum organization	81	1.4663379	0.046709128
Response to heat	156	1.4625585	0.046558704
Phosphate ion transmembrane transport	15	1.461592	0.038229376
Maintenance of protein location in cell	64	1.4604704	0.031620555
Regulation of macroautophagy	158	1.4545101	0.029787235
Positive regulation of protein modification by small protein conjugation or removal	134	1.4407438	0.032258064
Establishment of organelle localization	425	1.4399235	0.03837953
Maintenance of protein localization in organelle	42	1.4307377	0.043912176
Regulation of autophagy	324	1.4213198	0.034408603
Female gamete generation	125	1.4089407	0.044989776
Negative regulation of oxidative stress induced cell death	40	1.4082843	0.045454547
Regulation of protein modification by small protein conjugation or removal	231	1.3988352	0.042168673
Maintenance of protein location	92	1.3823981	0.046938777
Cell death in response to oxidative stress	78	1.3608412	0.04595186
Regulation of proteasomal protein catabolic process	178	1.3602904	0.04809619

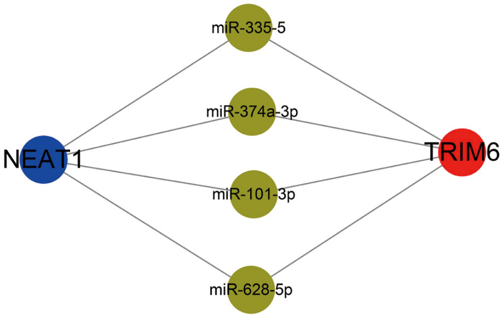

Figure S6 TRIM6 related-network.

https://dx.doi.org/10.21037/tcr-21-2181