

Transcriptomic signatures associated with regional cortical thickness changes in Parkinson's disease

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1 Supplementary Methods

1.1 Transcriptomic data

To filter and map probes to genes in the AHBA dataset, the data was concatenated across the six donors. We removed 10,521 probes with missing Entrez IDs, and 6,068 probes with low presence as they were expressed above the background in <1% of samples (PA-call containing presence/absence flag) (Hawrylycz *et al.*, 2015). The remaining 44,072 probes were mapped to 20,017 genes with unique Entrez IDs using the *collapseRows*-function in R-package WGCNA v1.64.1 (Langfelder and Horvath, 2008) as follows: i) if there is one probe, that one probe is chosen, ii) if there are two probes, the one with maximum variance across all samples is chosen (method="maxRowVariance"), iii) if there are more than two probes, the probe with the highest connectivity (summed adjacency) is chosen (connectivityBasedCollapsing=TRUE).

1.2 Partial least squares regression

As any linear regression method, PLS tries to find a relationship across *n* samples:

$$Y = XB + B_0 \tag{1}$$

, where data matrix *Y* ($n \times p$) with *p* response variables is predicted by data matrix *X* ($n \times m$) with *m* predictor variables, *B* ($m \times p$) is a matrix of regression coefficients, and *B*₀ ($n \times p$) is a background term. Variables from both datasets *X* and *Y* are projected to latent variables such that they are maximally correlated:

$$X = TP^T + E \tag{2}$$

$$Y = UQ^T + F \tag{3}$$

, where *T* And *U* $(n \times c)$ are projections of *X* and projections of *Y*, respectively, for *c* components. *P* $(m \times c)$ and *Q* $(p \times c)$ are loading matrices, and *E* and *F* are the error terms. The scores for the latent variables *T* and *U* are optimized for maximal covariance between *X* and *Y*:

$$U = TB + H \tag{4}$$

, where B ($m \times p$) is a matrix of correlation coefficients, and H ($n \times p$) is the error term. Once the PLS model is calculated, the coefficients B can be used to predict Y directly from X as in Equation 1, by using all m variables in X and all p variables in Y and their projections to T and U, respectively. The estimation of each PLS component is determined iteratively, by successfully deflating E and F, where projections of X to the latent variables in T are represented by W($m \times c$). Since W is calculated from deflated matrices, it cannot be used to represent weights that relate back to the original predictor matrix X. Instead, the weights can be represented by:

$$R = W(P^T W)^{-1} \tag{5}$$

, where R ($m \times c$) relates back to the original matrix such that:

$$T = XR \tag{6}$$

, and R can be used to rank the predictor variables according to their contribution to T. Depending on the number of selected components, the regression coefficients B are calculated by:

$$B = RQ^T \tag{7}$$

Based on the calculation of B in Equation 7, we can also use Q to assess the contribution of each response variable to the latent components in U.

2 Supplementary Figures



Supplementary Figure 1 Score distribution for nine clinical domains of Parkinson's disease. Scores are available for 82-123 patients.



Supplementary Figure 2 Root mean squared error of prediction (RMSEP) given the number of PLS components.



APC:Cdc20 mediated degradation of cell cycle proteins prior to satisfation of the cell cycle checkpoint

Supplementary Figure 3 Pathway enrichment of genes ranked by their weights to PLS *component-1* of PLS *model-1*. Enrichment was done using GSEA and Reactome pathways (BH-corrected P < 0.05). Node size indicates the number of genes in the pathway and node color shows the unadjusted *P*-values. Edge thickness indicates the number of overlapping genes between two pathways. This dense graph shows that the enriched pathways are highly related to each other. For visualization purpose, this graph only shows the top 30 (out of 90) enriched pathways. A list of all enriched pathways is given in Supplementary Table 5.



Supplementary Figure 4 Expression of all significant enriched pathways in cortical regions. Expression is based on the mean expression of genes in the pathways. Gene expression was Z-scored across regions. Regions are sorted based on the *t*-statistics of Δ CT between Parkinson's disease patients and controls; positive scores are indicative of cortical atrophy. The pathways are sorted based on the average PLS regression coefficients of genes involved in the pathway. BH-corrected *P*-values for all significantly enriched pathways are in Supplementary Table 5. * = APC:Cdc20 mediated degradation of cell cycle proteins prior to satisfation of the cell cycle checkpoint. ** = APC/C:Cdh1 mediated degradation of Cdc20 and other APC/C:Cdh1 targeted proteins in late mitosis/early G1.



Supplementary Figure 5 Explained variance in (A) predictor and (B) response variables of PLS *model-2*.



Supplementary Figure 6 Top 30 significantly enriched pathways based on the PLS gene weights for *component-1* of *model-2* (BH-corrected P < 0.05). Node size indicates the number of genes in the pathway, node color shows the unadjusted *P*-values, and edge thickness indicates the number of overlapping genes between two pathways. A list of all enriched pathways is given in Supplementary Table 6.



Supplementary Figure 7 Top 30 significantly enriched pathways based on the PLS gene weights for *component-2* of *model-2* (BH-corrected P < 0.05). Node size indicates the number of genes in the pathway, node color shows the unadjusted *P*-values, and edge thickness indicates the number of overlapping genes between two pathways. A list of all enriched pathways is given in Supplementary Table 7.





Supplementary Figure 8 Expression of all significant enriched pathways in cortical regions in PLS *model-2* for *component-1*. Expression is based on the mean expression of genes in the pathways. Gene expression was Z-scored across regions. Regions are sorted based on the *t*-statistics of Δ CT between Parkinson's disease patients and controls; positive scores are indicative of cortical atrophy. The pathways are sorted based on the average PLS regression coefficients of genes involved in the pathway. BH-corrected *P*-values for all significantly enriched pathways are in Supplementary Table 6. * = Activation of the mRNA upon binding of the cap–binding complex and eIFs, and subsequent binding to 43S, ** = Activated PKN1 stimulates transcription of AR (androgen receptor) regulated genes KLK2 and KLK3. *** = Recruitment and ATM–mediated phosphorylation of repair and signaling proteins at DNA double strand breaks. **** = Respiratory electron transport, ATP synthesis by chemiosmotic coupling, and heat production by uncoupling proteins.







Supplementary Figure 9 Expression of all significant enriched pathways in cortical regions in PLS *model-2* for *component-2*. Expression is based on the mean expression of genes in the pathways. Gene expression was Z-scored across regions. Regions are sorted based on the *t*-statistics of Δ CT between Parkinson's disease patients and controls; positive scores are indicative of cortical atrophy. The pathways are sorted based on the average PLS regression coefficients of genes involved in the pathway. BH-corrected *P*-values for all significantly enriched pathways are in Supplementary Table 7. * = Respiratory electron transport, ATP synthesis by chemiosmotic coupling, and heat production by uncoupling proteins. ** = APC:Cdc20 mediated degradation of cell cycle proteins prior to satisfation of the cell cycle checkpoint. *** = APC/C:Cdh1 mediated degradation of Cdc20 and other APC/C:Cdh1 targeted proteins in late mitosis/early G1. **** = Activated PKN1 stimulates transcription of AR (androgen receptor) regulated genes KLK2 and KLK3.

3 Supplementary Tables

Supplementary Table 1 Effect of gender and age in imaging cohorts of Parkinson's disease patients and healthy controls. *P*-values are based on *t*-tests.

	Patients	Controls	
Ν	149	369	p-Value
Men/women (% men)	98/51 (65.7)	178/192 (48.1)	0.001
Age, year, mean (SD)	64.8 (7.2)	65.7 (6.7)	0.234

Supplementary Table 2 All 68 cortical regions from both hemispheres with cortical thickness differences (Δ CT) in age-matched controls compared to Parkinson's disease patients. Regions are sorted based on the BH-corrected *P* and "lh" and "rh" indicates the left or right hemisphere, respectively. PD = Parkinson's disease.

Region ID	Region name	<i>t</i> -score	ΔCT	Mean CT	Mean CT	BH-corrected P
				control	PD	
10	lh_lateraloccipital	4.29	0.05	2.03	1.97	1.66e-03
58	rh_parsopercularis	-3.98	-0.07	2.41	2.48	2.98e-03
51	rh_lateraloccipital	3.70	0.05	2.07	2.03	5.88e-03
17	lh_parsopercularis	-3.26	-0.05	2.42	2.48	2.00e-02
67	rh_rostralmiddlefrontal	-3.21	-0.05	2.26	2.31	2.00e-02
2	lh_caudalanteriorcingulate	3.12	0.09	2.84	2.75	2.25e-02
73	rh_temporalpole	-3.07	-0.10	3.41	3.51	2.25e-02
70	rh_superiortemporal	-2.96	-0.05	2.60	2.65	2.84e-02
50	rh_isthmuscingulate	2.89	0.06	2.29	2.24	3.14e-02
61	rh_pericalcarine	2.77	0.03	1.39	1.36	4.09e-02
48	rh_inferiorparietal	2.66	0.04	2.34	2.30	5.13e-02
53	rh_lingual	2.61	0.03	1.80	1.77	5.53e-02
7	lh_inferiorparietal	2.54	0.04	2.31	2.27	5.53e-02
15	lh_parahippocampal	2.52	0.08	2.51	2.42	5.53e-02
26	lh_rostralmiddlefrontal	-2.53	-0.04	2.27	2.31	5.53e-02
5	lh_entorhinal	-2.47	-0.09	3.11	3.20	5.85e-02
9	lh_isthmuscingulate	2.46	0.05	2.32	2.28	5.85e-02
46	rh_entorhinal	-2.32	-0.08	3.27	3.36	7.87e-02
19	lh_parstriangularis	-2.27	-0.04	2.30	2.34	8.12e-02
22	lh_posteriorcingulate	2.29	0.04	2.45	2.40	8.12e-02
56	rh_parahippocampal	1.94	0.06	2.48	2.43	1.74e-01
62	rh_postcentral	-1.91	-0.03	1.88	1.91	1.76e-01
32	lh_temporalpole	-1.81	-0.06	3.32	3.38	2.10e-01
64	rh_precentral	-1.79	-0.03	2.37	2.40	2.10e-01
63	rh_posteriorcingulate	1.53	0.03	2.45	2.42	3.47e-01
20	lh_pericalcarine	1.49	0.01	1.36	1.35	3.51e-01
21	lh_postcentral	-1.48	-0.02	1.92	1.95	3.51e-01
29	lh_superiortemporal	-1.35	-0.02	2.59	2.61	4.32e-01
1	lh_bankssts	-1.31	-0.02	2.30	2.32	4.33e-01
44	rh_caudalmiddlefrontal	-1.31	-0.02	2.43	2.46	4.33e-01
30	lh_supramarginal	1.25	0.02	2.43	2.41	4.53e-01
74	rh_transversetemporal	1.25	0.03	2.15	2.12	4.53e-01
42	rh_bankssts	-1.21	-0.02	2.40	2.42	4.57e-01
57	rh_paracentral	1.22	0.03	2.23	2.20	4.57e-01
3	lh_caudalmiddlefrontal	-1.06	-0.02	2.46	2.48	5.37e-01

11	lh_lateralorbitofrontal	-1.06	-0.02	2.56	2.58	5.37e-01
75	rh_insula	-1.08	-0.02	2.86	2.88	5.37e-01
25	lh_rostralanteriorcingulate	0.98	0.02	2.87	2.84	5.62e-01
43	rh_caudalanteriorcingulate	0.97	0.03	2.69	2.67	5.62e-01
52	rh_lateralorbitofrontal	1.00	0.02	2.53	2.51	5.62e-01
71	rh_supramarginal	0.92	0.02	2.43	2.41	5.92e-01
23	lh_precentral	-0.88	-0.02	2.40	2.42	6.12e-01
13	lh_medialorbitofrontal	-0.83	-0.01	2.38	2.39	6.40e-01
12	lh_lingual	0.78	0.01	1.75	1.74	6.47e-01
34	lh_insula	-0.78	-0.02	2.89	2.91	6.47e-01
59	rh_parsorbitalis	0.80	0.02	2.57	2.55	6.47e-01
18	lh_parsorbitalis	-0.71	-0.02	2.54	2.56	6.88e-01
72	rh_frontalpole	-0.48	-0.02	2.68	2.70	8.94e-01
65	rh_precuneus	0.46	0.01	2.19	2.18	9.01e-01
14	lh_middletemporal	0.43	0.01	2.75	2.74	9.06e-01
28	lh_superiorparietal	-0.41	-0.01	2.01	2.02	9.06e-01
27	lh_superiorfrontal	-0.36	-0.01	2.66	2.67	9.27e-01
66	rh_rostralanteriorcingulate	0.36	0.01	2.87	2.86	9.27e-01
4	lh_cuneus	0.28	0.00	1.61	1.61	9.30e-01
6	lh_fusiform	-0.26	0.00	2.47	2.48	9.30e-01
49	rh_inferiortemporal	-0.27	0.00	2.65	2.66	9.30e-01
54	rh_medialorbitofrontal	0.33	0.01	2.47	2.46	9.30e-01
69	rh_superiorparietal	-0.30	0.00	1.99	2.00	9.30e-01
55	rh_middletemporal	-0.20	0.00	2.76	2.76	9.69e-01
8	lh_inferiortemporal	-0.17	0.00	2.66	2.66	9.70e-01
16	lh_paracentral	-0.14	0.00	2.21	2.21	9.70e-01
24	lh_precuneus	0.06	0.00	2.16	2.16	9.70e-01
31	lh_frontalpole	-0.08	0.00	2.74	2.74	9.70e-01
45	rh_cuneus	0.06	0.00	1.62	1.62	9.70e-01
47	rh_fusiform	0.08	0.00	2.47	2.46	9.70e-01
60	rh_parstriangularis	-0.10	0.00	2.32	2.33	9.70e-01
68	rh_superiorfrontal	-0.06	0.00	2.66	2.66	9.70e-01
33	lh_transversetemporal	-0.04	0.00	2.09	2.09	9.71e-01

Supplementary Table 3 Cortical thickness differences (Δ CT) of the left hemisphere compared to the right in Parkinson's disease patients. Regions are sorted based on the BH-corrected *P*.

Region ID	Region name	<i>t</i> -score	ΔCT	Mean CT	Mean CT	BH-corrected P
				left hemisphere	right hemisphere	
1	lh_bankssts	4.52	0.10	2.42	2.32	3.02e-04
5	lh_entorhinal	3.60	0.15	3.36	3.20	1.25e-02
32	lh_temporalpole	3.43	0.12	3.51	3.38	2.24e-02
13	lh_medialorbitofrontal	3.40	0.07	2.46	2.39	2.35e-02
10	lh_lateraloccipital	3.31	0.05	2.03	1.97	3.10e-02
11	lh_lateralorbitofrontal	-3.21	-0.06	2.51	2.58	4.21e-02
2	lh_caudalanteriorcingulate	-2.65	-0.09	2.67	2.75	2.35e-01
3	lh_caudalmiddlefrontal	-0.86	-0.02	2.46	2.48	1.00e+00
4	lh_cuneus	0.68	0.01	1.62	1.61	1.00e+00
6	lh_fusiform	-0.79	-0.02	2.46	2.48	1.00e+00
7	lh_inferiorparietal	1.42	0.03	2.30	2.27	1.00e+00
8	lh_inferiortemporal	-0.09	0.00	2.66	2.66	1.00e+00
9	lh_isthmuscingulate	-1.80	-0.04	2.24	2.28	1.00e+00
12	lh_lingual	1.49	0.02	1.77	1.74	1.00e+00
14	lh_middletemporal	1.13	0.02	2.76	2.74	1.00e+00
15	lh_parahippocampal	0.03	0.00	2.43	2.42	1.00e+00
16	lh_paracentral	-0.28	-0.01	2.20	2.21	1.00e+00
17	lh_parsopercularis	0.31	0.01	2.48	2.48	1.00e+00
18	lh_parsorbitalis	-0.39	-0.01	2.55	2.56	1.00e+00

19	lh_parstriangularis	-0.86	-0.02	2.33	2.34	1.00e+00
20	lh_pericalcarine	1.17	0.01	1.36	1.35	1.00e+00
21	lh_postcentral	-1.79	-0.03	1.91	1.95	1.00e+00
22	lh_posteriorcingulate	0.88	0.02	2.42	2.40	1.00e+00
23	lh_precentral	-0.76	-0.02	2.40	2.42	1.00e+00
24	lh_precuneus	0.86	0.02	2.18	2.16	1.00e+00
25	lh_rostralanteriorcingulate	0.65	0.02	2.86	2.84	1.00e+00
26	lh_rostralmiddlefrontal	-0.01	0.00	2.31	2.31	1.00e+00
27	lh_superiorfrontal	-0.42	-0.01	2.66	2.67	1.00e+00
28	lh_superiorparietal	-1.01	-0.02	2.00	2.02	1.00e+00
29	lh_superiortemporal	1.93	0.04	2.65	2.61	1.00e+00
30	lh_supramarginal	0.27	0.01	2.41	2.41	1.00e+00
31	lh_frontalpole	-1.04	-0.04	2.70	2.74	1.00e+00
33	lh_transversetemporal	0.92	0.03	2.12	2.09	1.00e+00
34	lh_insula	-1.21	-0.03	2.88	2.91	1.00e+00

Supplementary Table 4 Number of AHBA samples in ROIs from FreeSurfer. All samples and segmented cortical regions are from the left hemisphere only.

Region	Name	Donor	Donor	Donor	Donor	Donor	Donor	Total
ID		861	10021	12876	14380	15496	15697	
1	bankssts	6	3	4	3	3	3	22
2	caudalanteriorcingulate	1	0	7	5	6	4	23
3	caudalmiddlefrontal	8	6	3	4	4	5	30
4	cuneus	2	2	2	6	5	4	21
5	entorhinal	5	2	3	5	2	8	25
6	fusiform	10	10	8	18	16	16	78
7	inferiorparietal	7	11	8	6	6	10	48
8	inferiortemporal	19	5	13	17	14	11	79
9	isthmuscingulate	0	4	3	5	6	3	21
10	lateraloccipital	3	9	0	12	8	10	42
11	lateralorbitofrontal	6	4	5	7	6	8	36
12	lingual	5	6	9	10	7	6	43
13	medialorbitofrontal	3	7	9	10	10	6	45
14	middletemporal	15	6	6	12	9	9	57
15	parahippocampal	7	2	3	5	5	3	25
16	paracentral	3	6	2	3	4	5	23
17	parsopercularis	5	1	0	3	6	5	20
18	parsorbitalis	0	0	2	6	6	2	16
19	parstriangularis	5	5	2	5	2	2	21
20	pericalcarine	1	2	1	0	5	6	15
21	postcentral	10	8	8	10	6	7	49
22	posteriorcingulate	7	6	6	10	4	7	40
23	precentral	16	9	10	12	8	10	65
24	precuneus	5	3	11	9	11	7	46
25	rostralanteriorcingulate	1	6	3	4	1	2	17
26	rostralmiddlefrontal	7	10	6	9	10	10	52
27	superiorfrontal	23	14	11	11	17	16	92
28	superiorparietal	8	8	11	13	9	12	61
29	superiortemporal	13	5	12	18	14	18	80
30	supramarginal	6	3	3	10	5	5	32
31	frontalpole	0	5	0	0	0	0	5
32	temporalpole	2	0	1	3	0	4	10
33	transversetemporal	2	2	1	1	1	0	7
34	insula	9	5	5	7	6	6	38

Supplementary Table 5 Pathway enrichment of genes ranked by their weight for PLS *model-1* and *component-1*.

Class C3 (Metabotopic jubanate/pheromore receptors) 191e.03 5.55.e02 Signaling by cytosolic FCRPI fusion matants 2.01e.03 5.35.e02 Signaling by cytosolic FCRPI fusion matants 2.02e.03 5.35.e02 CPCEC faultway 2.03e.03 5.35.e02 APC:CAC20 mediated degradation of cell cycle proteins prior to satisfation of the cell cycle checkpoint 2.03e.03 5.35.e02 APC:CAC20 mediated degradation of mitotic proteins 2.05e.03 5.35.e02 Callular response to bypoxia 2.05e.03 5.35.e02 Activation of APC/C CaC20 mediated degradation of mitotic proteins 2.05e.03 5.35.e02 Signaling by NOTCH4 2.05e.03 5.35.e02 Signaling by NOTCH4 2.05e.03 5.35.e02 Signaling by NOTCH4 2.05e.03 5.35.e02 Mitochondrial translation congution 2.05e.03 5.35.e02 Signaling by NOTCH4 2.06e.03 5.35.e02 Mitochondrial translation indicion 2.06e.03 5.35.e02 Signaling by NOTCH4 2.06e.03 5.35.e02 Mitochondrial translation indicion 2.06e.03 5.35.e02 Sign	Pathway	P-value	BH-corrected <i>P</i> -value
SUMONPLAINON of chromatin organization proteins 198-08 3.53-02 Synain by Cycoloic FGFR I fusion mutants 2.00e-03 3.53-02 PCCCCC pathway 2.02e-03 3.53-02 PCCCCC and incidiand degradation of cell cycle proteins prior to satisfation of the cell cycle checkpoint 2.03e-03 3.53-02 ABC transporter disorders 2.05e-03 3.53e-02 ABC Cac2/D modiated degradation of mitotic proteins 2.05e-03 3.53e-02 ACCCCCA2D modiated degradation of mitotic proteins 2.05e-03 3.53e-02 Regulation of mRNA stability by proteins that bind AU-rich elements 2.05e-03 3.53e-02 Signaling by NOTCH4 2.05e-03 3.53e-02 Downstream signaling events of B Cell Receptor (BCR) 2.05e-03 3.53e-02 Reputation of APCC activators between G1/S and carly anaphase 2.06e-03 3.53e-02 Reputation of APCC activators between G1/S and carly anaphase 2.06e-03 3.53e-02 Mitochondrial translation entimation 2.06e-03 3.53e-02 Mitochondrial translation of Cell cycle proteins 2.06e-03 3.53e-02 CDE-mediated degradation of Cell cycle proteins 2.06e-03 3.53e-02	Class C/3 (Metabotropic glutamate/pheromone receptors)	1.91e-03	3.53e-02
Signaling by cytosolic FCRPI fusion mutants 2.04e-03 3.53e-02 CPC/CE gathway 2.02e-03 3.53e-02 APCCAdc20 mediated degradation of cell cycle proteins prior to satisfation of the cell cycle checkpoint 2.03e-03 3.53e-02 ABC transporter disorders 2.05e-03 3.53e-02 Cellular response to hyposia 2.05e-03 3.53e-02 Activation of APC-Cadc20 mediated degradation of mitotic proteins 2.05e-03 3.53e-02 Signaling by NOTCH4 2.05e-03 3.53e-02 Signaling by NOTCH4 2.05e-03 3.53e-02 Downstream signaling events of B Cell Receptor (BCR) 2.05e-03 3.53e-02 Replacion of MRNA stability by NOTCH4 2.05e-03 3.53e-02 Mitochondrial translation terproteins 2.06e-03 3.53e-02 Regulation of MRNA stability by Note (BCR) 2.06e-03 3.53e-02 Mitochondrial translation termination 2.06e-03 3.53e-02 Mitochondrial translation termination 2.06e-03 3.53e-02 Mitochondrial translation termination 2.06e-03 3.53e-02 Mitochondrial translation of Cell cycetoreceins 2.06e-03 3.	SUMOylation of chromatin organization proteins	1.93e-03	3.53e-02
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The role of GTSE1 in G2/M progression after G2 checkpoint2.08e-033.53e-02Regulation of Apoptosis2.09e-033.53e-02Autodegradation of the E3 ubiquitin ligase COP12.09e-033.53e-02Regulation of RAS by GAPs2.10e-033.53e-02G1/S DNA Damage Checkpoints2.10e-033.53e-02Activation of NF-kappaB in B cells2.10e-033.53e-02ACtivation of NF-kappaB in B cells2.10e-033.53e-02APC/C:Cdc20 mediated degradation of Securin2.10e-033.53e-02Assembly of the pre-replicative complex2.10e-033.53e-02Vif-mediated degradation of APOBEC3G2.10e-033.53e-02FBXL7 down-regulates AURKA during mitotic entry and in early mitosis2.10e-033.53e-02Negative regulation of NOTCH4 signaling2.10e-033.53e-02Cross-presentation of soluble exogenous antigens (endosomes)2.11e-033.53e-02SCF-beta-TrCP mediated degradation of Emi12.11e-033.53e-02Regulation of activated PAK-2p34 by proteasome mediated degradation2.11e-033.53e-02AUF1 (hnRNP D0) binds and destabilizes mRNA2.11e-033.53e-02Degradation of AXIN2.11e-033.53e-02Hh mutants that don't undergo autocatalytic processing are degraded by ERAD2.11e-033.53e-02	p53-Independent G1/S DNA damage checkpoint	2.08e-03	3.53e-02
Regulation of Apoptosis2.09e-033.53e-02Autodegradation of the E3 ubiquitin ligase COP12.09e-033.53e-02Regulation of RAS by GAPs2.10e-033.53e-02G1/S DNA Damage Checkpoints2.10e-033.53e-02Activation of NF-kappaB in B cells2.10e-033.53e-02APC/C:Cdc20 mediated degradation of Securin2.10e-033.53e-02Assembly of the pre-replicative complex2.10e-033.53e-02Vif-mediated degradation of APOBEC3G2.10e-033.53e-02FBXL7 down-regulates AURKA during mitotic entry and in early mitosis2.10e-033.53e-02Negative regulation of NOTCH4 signaling2.10e-033.53e-02Cross-presentation of soluble exogenous antigens (endosomes)2.11e-033.53e-02SCF-beta-TrCP mediated degradation of Emi12.11e-033.53e-02Regulation of AXIN2.11e-033.53e-02Hh mutants that don't undergo autocatalytic processing are degraded by ERAD2.11e-033.53e-02	The role of GTSE1 in G2/M progression after G2 checkpoint	2.08e-03	3.53e-02
Autodegradation of the E3 ubiquitin ligase COP12.09e-033.53e-02Regulation of RAS by GAPs2.10e-033.53e-02G1/S DNA Damage Checkpoints2.10e-033.53e-02Activation of NF-kappaB in B cells2.10e-033.53e-02AppC/C: Cdc20 mediated degradation of Securin2.10e-033.53e-02Assembly of the pre-replicative complex2.10e-033.53e-02Vif-mediated degradation of APOBEC3G2.10e-033.53e-02FBXL7 down-regulates AURKA during mitotic entry and in early mitosis2.10e-033.53e-02Negative regulation of NOTCH4 signaling2.10e-033.53e-02Cross-presentation of soluble exogenous antigens (endosomes)2.11e-033.53e-02SCF-beta-TrCP mediated degradation of Emi12.11e-033.53e-02Regulation of activated PAK-2p34 by proteasome mediated degradation2.11e-033.53e-02AUF1 (hnRNP D0) binds and destabilizes mRNA2.11e-033.53e-02Degradation of AXIN2.11e-033.53e-02Hh mutants that don't undergo autocatalytic processing are degraded by ERAD2.11e-033.53e-02	Regulation of Apoptosis	2.09e-03	3.53e-02
Regulation of RAS by GAPs2.10e-033.53e-02G1/S DNA Damage Checkpoints2.10e-033.53e-02Activation of NF-kappaB in B cells2.10e-033.53e-02APC/C:Cdc20 mediated degradation of Securin2.10e-033.53e-02Assembly of the pre-replicative complex2.10e-033.53e-02Vif-mediated degradation of APOBEC3G2.10e-033.53e-02FBXL7 down-regulates AURKA during mitotic entry and in early mitosis2.10e-033.53e-02Negative regulation of NOTCH4 signaling2.10e-033.53e-02Cross-presentation of soluble exogenous antigens (endosomes)2.11e-033.53e-02SCF-beta-TrCP mediated degradation of Emi12.11e-033.53e-02Regulation of activated PAK-2p34 by proteasome mediated degradation2.11e-033.53e-02AUF1 (hnRNP D0) binds and destabilizes mRNA2.11e-033.53e-02Degradation of AXIN2.11e-033.53e-02Hh mutants that don't undergo autocatalytic processing are degraded by ERAD2.11e-033.53e-02	Autodegradation of the E3 ubiquitin ligase COP1	2.09e-03	3.53e-02
G1/S DNA Damage Checkpoints2.10e-033.53e-02Activation of NF-kappaB in B cells2.10e-033.53e-02APC/C:Cdc20 mediated degradation of Securin2.10e-033.53e-02Assembly of the pre-replicative complex2.10e-033.53e-02Vif-mediated degradation of APOBEC3G2.10e-033.53e-02FBXL7 down-regulates AURKA during mitotic entry and in early mitosis2.10e-033.53e-02Negative regulation of NOTCH4 signaling2.10e-033.53e-02Cross-presentation of soluble exogenous antigens (endosomes)2.11e-033.53e-02SCF-beta-TrCP mediated degradation of Emi12.11e-033.53e-02Regulation of activated PAK-2p34 by proteasome mediated degradation2.11e-033.53e-02AUF1 (hnRNP D0) binds and destabilizes mRNA2.11e-033.53e-02Degradation of AXIN2.11e-033.53e-02Hh mutants that don't undergo autocatalytic processing are degraded by ERAD2.11e-033.53e-02	Regulation of RAS by GAPs	2.10e-03	3.53e-02
Activation of NF-kappaB in B cells2.10e-033.53e-02APC/C:Cdc20 mediated degradation of Securin2.10e-033.53e-02Assembly of the pre-replicative complex2.10e-033.53e-02Vif-mediated degradation of APOBEC3G2.10e-033.53e-02FBXL7 down-regulates AURKA during mitotic entry and in early mitosis2.10e-033.53e-02Negative regulation of NOTCH4 signaling2.10e-033.53e-02Cross-presentation of soluble exogenous antigens (endosomes)2.11e-033.53e-02SCF-beta-TrCP mediated degradation of Emi12.11e-033.53e-02Regulation of activated PAK-2p34 by proteasome mediated degradation2.11e-033.53e-02AUF1 (hnRNP D0) binds and destabilizes mRNA2.11e-033.53e-02Degradation of AXIN2.11e-033.53e-02Hh mutants that don't undergo autocatalytic processing are degraded by ERAD2.11e-033.53e-02	G1/S DNA Damage Checkpoints	2.10e-03	3.53e-02
APC/C:Cdc20 mediated degradation of Securin2.10e-033.53e-02Assembly of the pre-replicative complex2.10e-033.53e-02Vif-mediated degradation of APOBEC3G2.10e-033.53e-02FBXL7 down-regulates AURKA during mitotic entry and in early mitosis2.10e-033.53e-02Negative regulation of NOTCH4 signaling2.10e-033.53e-02Cross-presentation of soluble exogenous antigens (endosomes)2.11e-033.53e-02SCF-beta-TrCP mediated degradation of Emi12.11e-033.53e-02Regulation of activated PAK-2p34 by proteasome mediated degradation2.11e-033.53e-02AUF1 (hnRNP D0) binds and destabilizes mRNA2.11e-033.53e-02Degradation of AXIN2.11e-033.53e-02Hh mutants that don't undergo autocatalytic processing are degraded by ERAD2.11e-033.53e-02	Activation of NF-kappaB in B cells	2.10e-03	3.53e-02
Assembly of the pre-replicative complex2.10e-033.53e-02Vif-mediated degradation of APOBEC3G2.10e-033.53e-02FBXL7 down-regulates AURKA during mitotic entry and in early mitosis2.10e-033.53e-02Negative regulation of NOTCH4 signaling2.10e-033.53e-02Cross-presentation of soluble exogenous antigens (endosomes)2.11e-033.53e-02SCF-beta-TrCP mediated degradation of Emi12.11e-033.53e-02Regulation of activated PAK-2p34 by proteasome mediated degradation2.11e-033.53e-02AUF1 (hnRNP D0) binds and destabilizes mRNA2.11e-033.53e-02Degradation of AXIN2.11e-033.53e-02Hh mutants that don't undergo autocatalytic processing are degraded by ERAD2.11e-033.53e-02	APC/C:Cdc20 mediated degradation of Securin	2.10e-03	3.53e-02
Vif-mediated degradation of APOBEC3G2.10e-033.53e-02FBXL7 down-regulates AURKA during mitotic entry and in early mitosis2.10e-033.53e-02Negative regulation of NOTCH4 signaling2.10e-033.53e-02Cross-presentation of soluble exogenous antigens (endosomes)2.11e-033.53e-02SCF-beta-TrCP mediated degradation of Emi12.11e-033.53e-02Regulation of activated PAK-2p34 by proteasome mediated degradation2.11e-033.53e-02AUF1 (hnRNP D0) binds and destabilizes mRNA2.11e-033.53e-02Degradation of AXIN2.11e-033.53e-02Hh mutants that don't undergo autocatalytic processing are degraded by ERAD2.11e-033.53e-02	Assembly of the pre-replicative complex	2.10e-03	3.53e-02
FBXL7 down-regulates AURKA during mitotic entry and in early mitosis2.10e-033.53e-02Negative regulation of NOTCH4 signaling2.10e-033.53e-02Cross-presentation of soluble exogenous antigens (endosomes)2.11e-033.53e-02SCF-beta-TrCP mediated degradation of Emi12.11e-033.53e-02Regulation of activated PAK-2p34 by proteasome mediated degradation2.11e-033.53e-02AUF1 (hnRNP D0) binds and destabilizes mRNA2.11e-033.53e-02Degradation of AXIN2.11e-033.53e-02Hh mutants that don't undergo autocatalytic processing are degraded by ERAD2.11e-033.53e-02	Vif-mediated degradation of APOBEC3G	2.10e-03	3.53e-02
Negative regulation of NOTCH4 signaling2.10e-033.53e-02Cross-presentation of soluble exogenous antigens (endosomes)2.11e-033.53e-02SCF-beta-TrCP mediated degradation of Emil2.11e-033.53e-02Regulation of activated PAK-2p34 by proteasome mediated degradation2.11e-033.53e-02AUF1 (hnRNP D0) binds and destabilizes mRNA2.11e-033.53e-02Degradation of AXIN2.11e-033.53e-02Hh mutants that don't undergo autocatalytic processing are degraded by ERAD2.11e-033.53e-02	FBXL7 down-regulates AURKA during mitotic entry and in early mitosis	2.10e-03	3.53e-02
Cross-presentation of soluble exogenous antigens (endosomes)2.11e-033.53e-02SCF-beta-TrCP mediated degradation of Emi12.11e-033.53e-02Regulation of activated PAK-2p34 by proteasome mediated degradation2.11e-033.53e-02AUF1 (hnRNP D0) binds and destabilizes mRNA2.11e-033.53e-02Degradation of AXIN2.11e-033.53e-02Hh mutants that don't undergo autocatalytic processing are degraded by ERAD2.11e-033.53e-02	Negative regulation of NOTCH4 signaling	2.10e-03	3.53e-02
SCF-beta-TrCP mediated degradation of Emi12.11e-033.53e-02Regulation of activated PAK-2p34 by proteasome mediated degradation2.11e-033.53e-02AUF1 (hnRNP D0) binds and destabilizes mRNA2.11e-033.53e-02Degradation of AXIN2.11e-033.53e-02Hh mutants that don't undergo autocatalytic processing are degraded by ERAD2.11e-033.53e-02	Cross-presentation of soluble exogenous antigens (endosomes)	2.11e-03	3.53e-02
Regulation of activated PAK-2p34 by proteasome mediated degradation2.11e-033.53e-02AUF1 (hnRNP D0) binds and destabilizes mRNA2.11e-033.53e-02Degradation of AXIN2.11e-033.53e-02Hh mutants that don't undergo autocatalytic processing are degraded by ERAD2.11e-033.53e-02	SCF-beta-TrCP mediated degradation of Emil	2.11e-03	3.53e-02
AUF1 (hnRNP D0) binds and destabilizes mRNA2.11e-033.53e-02Degradation of AXIN2.11e-033.53e-02Hh mutants that don't undergo autocatalytic processing are degraded by ERAD2.11e-033.53e-02	Regulation of activated PAK-2p34 by proteasome mediated degradation	2.11e-03	3.53e-02
Degradation of AXIN2.11e-033.53e-02Hh mutants that don't undergo autocatalytic processing are degraded by ERAD2.11e-033.53e-02	AUF1 (hnRNP D0) binds and destabilizes mRNA	2.11e-03	3.53e-02
Hh mutants that don't undergo autocatalytic processing are degraded by ERAD 2.11e-03 3.53e-02	Degradation of AXIN	2.11e-03	3.53e-02
	Hh mutants that don't undergo autocatalytic processing are degraded by ERAD	2.11e-03	3.53e-02

Stabilization of p53	2.11e-03	3.53e-02
Regulation of RUNX3 expression and activity	2.11e-03	3.53e-02
Mitochondrial protein import	2.12e-03	3.53e-02
Oxygen-dependent proline hydroxylation of Hypoxia-inducible Factor Alpha	2.12e-03	3.53e-02
Hh mutants abrogate ligand secretion	2.13e-03	3.53e-02
NIK>noncanonical NF-kB signaling	2.13e-03	3.53e-02
p53-Dependent G1 DNA Damage Response	2.14e-03	3.53e-02
p53-Dependent G1/S DNA damage checkpoint	2.14e-03	3.53e-02
Hedgehog ligand biogenesis	2.14e-03	3.53e-02
Mitotic Metaphase and Anaphase	2.14e-03	3.53e-02
Mitotic G2-G2/M phases	2.14e-03	3.53e-02
Defective CFTR causes cystic fibrosis	2.14e-03	3.53e-02
Peptide ligand-binding receptors	2.15e-03	3.53e-02
Degradation of DVL	2.15e-03	3.53e-02
Separation of Sister Chromatids	2.17e-03	3.53e-02
Regulation of expression of SLITs and ROBOs	2.17e-03	3.53e-02
DNA Damage Recognition in GG-NER	2.18e-03	3.53e-02
Mitotic Anaphase	2.18e-03	3.53e-02
G2/M Checkpoints	2.18e-03	3.53e-02
SCF(Skp2)-mediated degradation of p27/p21	2.18e-03	3.53e-02
Autodegradation of Cdh1 by Cdh1:APC/C	2.18e-03	3.53e-02
Dectin-1 mediated noncanonical NF-kB signaling	2.18e-03	3.53e-02
Degradation of GLI1 by the proteasome	2.18e-03	3.53e-02
Degradation of GLI2 by the proteasome	2.18e-03	3.53e-02
GLI3 is processed to GLI3R by the proteasome	2.18e-03	3.53e-02
Protein localization	2.18e-03	3.53e-02
The citric acid (TCA) cycle and respiratory electron transport	2.18e-03	3.53e-02
Asymmetric localization of PCP proteins	2.18e-03	3.53e-02
Neddylation	2.19e-03	3.53e-02
Neutrophil degranulation	2.20e-03	3.53e-02
ER to Golgi Anterograde Transport	2.22e-03	3.53e-02
Asparagine N-linked glycosylation	2.22e-03	3.53e-02
Translation	2.24e-03	3.53e-02
Signaling by Interleukins	2.24e-03	3.53e-02
Class A/1 (Rhodopsin-like receptors)	2.28e-03	3.56e-02
Metabolism of amino acids and derivatives	2.33e-03	3.59e-02

Supplementary Table 6 Pathway enrichment of genes ranked by their weight for PLS *model-2* and *component-1*.

Pathway	<i>P</i> -value	BH-corrected <i>P</i> -value
Intra-Golgi and retrograde Golgi-to-ER traffic	1.24e-03	4.31e-02
The citric acid (TCA) cycle and respiratory electron transport	1.28e-03	4.31e-02
Protein localization	1.29e-03	4.31e-02
ER to Golgi Anterograde Transport	1.31e-03	4.31e-02
Golgi-to-ER retrograde transport	1.34e-03	4.31e-02
MHC class II antigen presentation	1.35e-03	4.31e-02
Potassium Channels	1.36e-03	4.31e-02
Respiratory electron transport, ATP synthesis by chemiosmotic coupling, and heat production by		
uncoupling proteins.	1.36e-03	4.31e-02
tRNA processing	1.36e-03	4.31e-02
Macroautophagy	1.37e-03	4.31e-02
Respiratory electron transport	1.37e-03	4.31e-02
Glucose metabolism	1.38e-03	4.31e-02
Unfolded Protein Response (UPR)	1.38e-03	4.31e-02
Mitochondrial translation	1.38e-03	4.31e-02
Mitochondrial biogenesis	1.38e-03	4.31e-02

Mitochondrial translation elongation	1.39e-03	4.31e-02
Mitochondrial translation initiation	1.39e-03	4.31e-02
Mitochondrial translation termination	1.39e-03	4.31e-02
Metabolism of polyamines	1.40e-03	4.31e-02
Glycolysis	1.42e-03	4.31e-02
Mitochondrial protein import	1.43e-03	4.31e-02
tRNA processing in the nucleus	1.46e-03	4.31e-02
Pyruvate metabolism and Citric Acid (TCA) cycle	1.48e-03	4.31e-02
Glycosphingolipid metabolism	1.50e-03	4.31e-02
Complex I biogenesis	1.50e-03	4.31e-02
tRNA Aminoacylation	1.50e-03	4.31e-02
tRNA modification in the nucleus and cytosol	1.52e-03	4.31e-02
Voltage gated Potassium channels	1.52e-03	4.31e-02
RNA Polymerase III Transcription Initiation	1.55e-03	4.31e-02
Uptake and actions of bacterial toxins	1.57e-03	4.31e-02
Cristae formation	1.62e-03	4.316-02
Cytosolic iron sulfur eluster essembly	1.63e-03	4.516-02
Vytosone non-suntui cluster asseniory Mitechondrial iron sulfur aluster biogenesis	1.000-03	4.516-02
Processing of SMDT1	1.000-03	4.316-02
Processing of SMD11 Pergulation of purpuste dehudrogenese (PDH) complex	1.70e-03	4.316-02
CDC6 association with the OPC origin complex	1.70e-03	4.316-02
Neuronal System	2 210 03	4.316-02
Asparagine N-linked glycosylation	2.21e-03	4.31e-02
Metallothioneins hind metals	2.200-03 2.40e-03	4.31e-02
Transport to the Golgi and subsequent modification	2.460 03 2.55e-03	4.31e-02
A tetrasaccharide linker sequence is required for GAG synthesis	2.55e-03	4.31e-02
RUNX2 regulates osteoblast differentiation	2.58e-03	4.31e-02
Sphingolipid metabolism	2.74e-03	4.31e-02
RUNX2 regulates bone development	2.75e-03	4.31e-02
COPI-mediated anterograde transport	2.75e-03	4.31e-02
Signaling by NOTCH3	2.94e-03	4.31e-02
Packaging Of Telomere Ends	2.94e-03	4.31e-02
Chemokine receptors bind chemokines	2.94e-03	4.31e-02
Interleukin-3, Interleukin-5 and GM-CSF signaling	2.94e-03	4.31e-02
Binding and Uptake of Ligands by Scavenger Receptors	2.97e-03	4.31e-02
Chondroitin sulfate/dermatan sulfate metabolism	2.99e-03	4.31e-02
Recognition and association of DNA glycosylase with site containing an affected pyrimidine	3.05e-03	4.31e-02
Cleavage of the damaged pyrimidine	3.05e-03	4.31e-02
Depyrimidination	3.05e-03	4.31e-02
Recognition and association of DNA glycosylase with site containing an affected purine	3.06e-03	4.31e-02
Cleavage of the damaged purine	3.06e-03	4.31e-02
Depurination	3.06e-03	4.31e-02
Formation of the ternary complex, and subsequently, the 43S complex	3.06e-03	4.31e-02
RNA Polymerase I Promoter Opening	3.13e-03	4.31e-02
Base-Excision Repair, AP Site Formation	3.13e-03	4.31e-02
Translation initiation complex formation	3.13e-03	4.31e-02
Ribosomal scanning and start codon recognition	3.13e-03	4.31e-02
DNA methylation	3.14e-03	4.31e-02
Activation of the mRNA upon binding of the cap-binding complex and eIFs, and subsequent binding to		
43S	3.14e-03	4.31e-02
Activated PKN1 stimulates transcription of AR (androgen receptor) regulated genes KLK2 and KLK3	3.25e-03	4.31e-02
SIRT1 negatively regulates rRNA expression	3.27e-03	4.31e-02
Citric acid cycle (TCA cycle)	3.29e-03	4.31e-02
Condensation of Prophase Chromosomes	3.31e-03	4.31e-02
DNA Damage/Telomere Stress Induced Senescence	3.37e-03	4.31e-02
Nonnomologous End-Joining (NHEJ)	5.5/e-03	4.31e-02
Netotic recombination	3.3/e-03	4.31e-02
KM1s metnylate histone arginines	5.5/e-03	4.31e-02
recommend with the second seco	3.3/e-03	4.51e-02
EKCCO (CSB) and EHM12 (G9a) positively regulate rKNA expression	3.3/e-03	4.31e-02

Recruitment and ATM-mediated phosphorylation of repair and signaling proteins at DNA double strand		
breaks	3.38e-03	4.31e-02
PRC2 methylates histones and DNA	3.38e-03	4.31e-02
Antigen processing: Ubiquitination & Proteasome degradation	3.41e-03	4.31e-02
Deposition of new CENPA-containing nucleosomes at the centromere	3.42e-03	4.31e-02
Nucleosome assembly	3.42e-03	4.31e-02
Meiotic synapsis	3.44e-03	4.31e-02
DNA Double Strand Break Response	3.45e-03	4.31e-02
Formation of the beta-catenin:TCF transactivating complex	3.46e-03	4.31e-02
B-WICH complex positively regulates rRNA expression	3.46e-03	4.31e-02
rRNA processing in the mitochondrion	3.48e-03	4.31e-02
RNA Polymerase I Promoter Escape	3.50e-03	4.31e-02
Base Excision Repair	3.53e-03	4.31e-02
Peptide chain elongation	3.53e-03	4.31e-02
Viral mRNA Translation	3.53e-03	4.31e-02
RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function	3.57e-03	4.31e-02
Neddylation	3.58e-03	4.31e-02
Nonsense Mediated Decay (NMD) independent of the Exon Junction Complex (EJC)	3.61e-03	4.31e-02
Eukaryotic Translation Elongation	3.62e-03	4.31e-02
Selenocysteine synthesis	3.62e-03	4.31e-02
Eukaryotic Translation Termination	3.62e-03	4.31e-02
Pre-NOTCH Transcription and Translation	3.66e-03	4.31e-02
Chromosome Maintenance	3.68e-03	4.31e-02
Negative epigenetic regulation of rRNA expression	3.68e-03	4.31e-02
Positive epigenetic regulation of rRNA expression	3.68e-03	4.31e-02
Interferon gamma signaling	3.69e-03	4.31e-02
RHO GTPases activate PKNs	3.69e-03	4.31e-02
HDACs deacetylate histones	3.69e-03	4.31e-02
GTP hydrolysis and joining of the 60S ribosomal subunit	3.69e-03	4.31e-02
SRP-dependent cotranslational protein targeting to membrane	3.69e-03	4.31e-02
Mitotic G2-G2/M phases	3.71e-03	4.31e-02
Formation of a pool of free 40S subunits	3.73e-03	4.31e-02
Amyloid fiber formation	3.75e-03	4.31e-02
L13a-mediated translational silencing of Ceruloplasmin expression	3.75e-03	4.31e-02
Meiosis	3.76e-03	4.31e-02
Pre-NOTCH Expression and Processing	3.79e-03	4.31e-02
Senescence-Associated Secretory Phenotype (SASP)	3.79e-03	4.31e-02
RNA Polymerase I Promoter Clearance	3.79e-03	4.31e-02
Nonsense-Mediated Decay (NMD)	3.79e-03	4.31e-02
Nonsense Mediated Decay (NMD) enhanced by the Exon Junction Complex (EJC)	3.79e-03	4.31e-02
RNA Polymerase I Transcription	3.82e-03	4.31e-02
Interleukin-4 and Interleukin-13 signaling	3.82e-03	4.31e-02
NoRC negatively regulates rRNA expression	3.83e-03	4.31e-02
Eukaryotic Translation Initiation	3.83e-03	4.31e-02
Cap-dependent Translation Initiation	3.83e-03	4.31e-02
Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell	3.86e-03	4.31e-02
Selenoamino acid metabolism	3.86e-03	4.31e-02
S Phase	3.87e-03	4.31e-02
Oxidative Stress Induced Senescence	3.88e-03	4.31e-02
Activation of anterior HOX genes in hindbrain development during early embryogenesis	3.88e-03	4.31e-02
Activation of HOX genes during differentiation	3.88e-03	4.31e-02
RUNX1 regulates transcription of genes involved in differentiation of HSCs	3.95e-03	4.33e-02
Cell surface interactions at the vascular wall	3.95e-03	4.33e-02
Influenza Viral RNA Transcription and Replication	4.05e-03	4.40e-02
Metabolism of nucleotides	4.13e-03	4.45e-02
Influenza Infection	4.18e-03	4.47e-02
HATs acetylate histones	4.24e-03	4.48e-02
Influenza Life Cycle	4.26e-03	4.48e-02
Regulation of expression of SLITs and ROBOs	4.31e-03	4.49e-02
Estrogen-dependent gene expression	4.33e-03	4.49e-02
Major pathway of rRNA processing in the nucleolus and cytosol	4.59e-03	4.72e-02

4.67e-03	4.78e-02
4.91e-03	4.91e-02
4.96e-03	4.91e-02
4.98e-03	4.91e-02
5.01e-03	4.91e-02
5.01e-03	4.91e-02
5.01e-03	4.91e-02
5.10e-03	4.96e-02
5.14e-03	4.96e-02
	4.67e-03 4.91e-03 4.96e-03 4.98e-03 5.01e-03 5.01e-03 5.01e-03 5.10e-03 5.10e-03 5.10e-03 5.14e-03

Supplementary Table 7 Pathway enrichment of genes ranked by their weight for PLS *model-2* and *component-2*.

Pathway	P-value	BH-	
		corrected	
		P-value	
Neutrophil degranulation	1.40e-03	1.67e-02	
Metabolism of amino acids and derivatives	1.44e-03	1.67e-02	
Asparagine N-linked glycosylation	1.45e-03	1.67e-02	
Translation	1.45e-03	1.67e-02	
Infectious disease	1.45e-03	1.67e-02	
HIV Infection	1.51e-03	1.67e-02	
Transport to the Golgi and subsequent modification	1.52e-03	1.67e-02	
Separation of Sister Chromatids	1.52e-03	1.67e-02	
Fatty acid metabolism	1.52e-03	1.67e-02	
Neddylation	1.52e-03	1.67e-02	
G2/M Transition	1.53e-03	1.67e-02	
Mitotic Anaphase	1.53e-03	1.67e-02	
Mitotic Metaphase and Anaphase	1.53e-03	1.67e-02	
Metabolism of vitamins and cofactors	1.53e-03	1.67e-02	
Mitotic G2-G2/M phases	1.53e-03	1.67e-02	
Regulation of expression of SLITs and ROBOs	1.54e-03	1.67e-02	
The citric acid (TCA) cycle and respiratory electron transport	1.54e-03	1.67e-02	
Intra-Golgi and retrograde Golgi-to-ER traffic	1.54e-03	1.67e-02	
ER to Golgi Anterograde Transport	1.55e-03	1.67e-02	
Protein localization	1.55e-03	1.67e-02	
Mitotic G1-G1/S phases	1.55e-03	1.67e-02	
C-type lectin receptors (CLRs)	1.56e-03	1.67e-02	
PTEN Regulation	1.56e-03	1.67e-02	
G1/S Transition	1.56e-03	1.67e-02	
S Phase	1.56e-03	1.67e-02	
Beta-catenin independent WNT signaling	1.56e-03	1.67e-02	
DNA Replication	1.56e-03	1.67e-02	
Signaling by Hedgehog	1.56e-03	1.67e-02	
Metabolism of nucleotides	1.57e-03	1.67e-02	
COPI-mediated anterograde transport	1.57e-03	1.67e-02	
Fc epsilon receptor (FCERI) signaling	1.57e-03	1.67e-02	
Antigen processing-Cross presentation	1.57e-03	1.67e-02	
Downstream TCR signaling	1.57e-03	1.67e-02	
Protein folding	1.57e-03	1.67e-02	
TCR signaling	1.58e-03	1.67e-02	
CLEC7A (Dectin-1) signaling	1.58e-03	1.67e-02	
UCH proteinases	1.58e-03	1.67e-02	
COPI-dependent Golgi-to-ER retrograde traffic	1.58e-03	1.67e-02	
Golgi-to-ER retrograde transport	1.58e-03	1.67e-02	
Mitochondrial translation	1.58e-03	1.67e-02	
Host Interactions of HIV factors	1.58e-03	1.67e-02	
Respiratory electron transport, ATP synthesis by chemiosmotic coupling, and heat production by	1.58e-03	1.67e-02	

uncoupling proteins.		
Synthesis of DNA	1.58e-03	1.67e-02
TNFR2 non-canonical NF-kB pathway	1.58e-03	1.67e-02
Cyclin A:Cdk2-associated events at S phase entry	1.59e-03	1.67e-02
Hedgehog 'on' state	1.59e-03	1.67e-02
DNA Replication Pre-Initiation	1.59e-03	1.67e-02
MHC class II antigen presentation	1.60e-03	1.67e-02
Metabolism of polyamines	1.60e-03	1.67e-02
Mitochondrial translation elongation	1.61e-03	1.67e-02
APC/C-mediated degradation of cell cycle proteins	1.61e-03	1.67e-02
Regulation of mitotic cell cycle	1.61e-03	1.67e-02
Switching of origins to a post-replicative state	1.61e-03	1.67e-02
Chaperonin-mediated protein folding	1.61e-03	1.67e-02
Mitochondrial translation initiation	1.61e-03	1.67e-02
Mitochondrial translation termination	1.61e-03	1.67e-02
Cyclin E associated events during G1/S transition	1.61e-03	1.67e-02
Downstream signaling events of B Cell Receptor (BCR)	1.61e-03	1.67e-02
ER-Phagosome pathway	1.61e-03	1.67e-02
Regulation of mRNA stability by proteins that bind AU-rich elements	1.61e-03	1.67e-02
Signaling by the B Cell Receptor (BCR)	1.61e-03	1.67e-02
Hedgehog 'off' state	1.62e-03	1.67e-02
Macroautophagy	1.62e-03	1.67e-02
Respiratory electron transport	1.62e-03	1.67e-02
Regulation of APC/C activators between G1/S and early anaphase	1.62e-03	1.67e-02
PCP/CE pathway	1.62e-03	1.67e-02
Regulation of PTEN stability and activity	1.62e-03	1.67e-02
Degradation of heta-catenin by the destruction complex	1.63e-03	1.07C-02
Signaling by NOTCH4	1.63e-03	1.67e-02
Orc1 removal from chromatin	1.63e-03	1.67e-02
Mitochondrial protein import	1.64e.03	1.670.02
Oxygen dependent proline hydroxylation of Hypoxia inducible Factor Alpha	1.640.03	1.670.02
Description of DAS by GADs	1.640-03	1.670.02
C1/S DNA Damage Checkpoints	1.640.03	1.670.02
Activation of NE kannaB in B calls	1.640.03	1.670.02
ACtivation of Nr-Kappad in Dicens	1.640.03	1.670.02
Assembly of the pro-replicative complex	1.642.03	1.670.02
ABC transporter disorders	1.640-03	1.670.02
ECEDI mediated NE hB activation	1.040-03	1.67.02
FCERT Inculated INF-KD activation	1.040-03	1.67.02
PNA medification in the mediane and extend	1.040-03	1.07e-02
rKNA modification in the nucleus and cytosol	1.65-03	1.67e-02
pos-Dependent GLUDNA Damage Response	1.65e-03	1.6/e-02
pos-Dependent GI/S DINA damage checkpoint	1.65e-03	1.6/e-02
APC:Cdc20 mediated degradation of cell cycle proteins prior to satisfation of the cell cycle checkpoint	1.65e-03	1.6/e-02
Hedgenog ligand biogenesis	1.65e-03	1.67e-02
Defective CFTR causes cystic fibrosis	1.65e-03	1.6/e-02
Regulation of RUNX2 expression and activity	1.65e-03	1.6/e-02
CDK-mediated phosphorylation and removal of Cdc6	1.66e-03	1.6/e-02
APC/C:Cdh1 mediated degradation of Cdc20 and other APC/C:Cdh1 targeted proteins in late mitosis/early		
GI	1.66e-03	1.67e-02
Cdc20:Phospho-APC/C mediated degradation of Cyclin A	1.66e-03	1.67e-02
Cellular response to hypoxia	1.66e-03	1.67e-02
APC/C:Cdc20 mediated degradation of mitotic proteins	1.66e-03	1.67e-02
The role of GTSE1 in G2/M progression after G2 checkpoint	1.66e-03	1.67e-02
SCF(Skp2)-mediated degradation of p27/p21	1.66e-03	1.67e-02
Autodegradation of Cdh1 by Cdh1:APC/C	1.66e-03	1.67e-02
Dectin-1 mediated noncanonical NF-kB signaling	1.66e-03	1.67e-02
Degradation of GLI1 by the proteasome	1.66e-03	1.67e-02
Degradation of GLI2 by the proteasome	1.66e-03	1.67e-02
GLI3 is processed to GLI3R by the proteasome	1.66e-03	1.67e-02
Asymmetric localization of PCP proteins	1.67e-03	1.67e-02
AUF1 (hnRNP D0) binds and destabilizes mRNA	1.67e-03	1.67e-02

Hh mutants that don't undergo autocatalytic processing are degraded by ERAD	1.67e-03	1.67e-02
CDT1 association with the CDC6:ORC:origin complex	1.67e-03	1.67e-02
Stabilization of p53	1.67e-03	1.67e-02
Iron uptake and transport	1.67e-03	1.67e-02
Pyruvate metabolism and Citric Acid (TCA) cycle	1.67e-03	1.67e-02
Hh mutants abrogate ligand secretion	1.68e-03	1.67e-02
NIK>noncanonical NF-kB signaling	1.68e-03	1.67e-02
Vif-mediated degradation of APOBEC3G	1.68e-03	1.67e-02
FBXL7 down-regulates AURKA during mitotic entry and in early mitosis	1.68e-03	1.67e-02
Negative regulation of NOTCH4 signaling	1.68e-03	1.67e-02
HSP90 chaperone cycle for steroid hormone receptors (SHR)	1.69e-03	1.67e-02
Regulation of Apoptosis	1.69e-03	1.67e-02
SCF-beta-TrCP mediated degradation of Emi1	1.69e-03	1.67e-02
Degradation of AXIN	1.69e-03	1.67e-02
Regulation of RUNX3 expression and activity	1.69e-03	1.67e-02
Autodegradation of the E3 ubiquitin ligase COP1	1.69e-03	1.67e-02
Complex I biogenesis	1.69e-03	1.67e-02
Cross-presentation of soluble exogenous antigens (endosomes)	1.69e-03	1.67e-02
Regulation of activated PAK-2p34 by proteasome mediated degradation	1.69e-03	1.67e-02
Degradation of DVL	1.69e-03	1.67e-02
Recycling pathway of L1	1.70e-03	1.67e-02
Ubiquitin-dependent degradation of Cyclin D	1.71e-03	1.67e-02
Vpu mediated degradation of CD4	1.71e-03	1.67e-02
Regulation of ornithine decarboxylase (ODC)	1.71e-03	1.67e-02
Ubiquitin Mediated Degradation of Phosphorylated Cdc25A	1.71e-03	1.67e-02
p53-Independent DNA Damage Response	1.71e-03	1.67e-02
p53-Independent G1/S DNA damage checkpoint	1.71e-03	1.67e-02
Gap junction trafficking and regulation	1.71e-03	1.67e-02
Gluconeogenesis	1.72e-03	1.67e-02
ROS and RNS production in phagocytes	1.72e-03	1.67e-02
COPI-independent Golgi-to-ER retrograde traffic	1.72e-03	1.67e-02
Gap junction trafficking	1.73e-03	1.67e-02
DNA Damage Recognition in GG-NER	1.74e-03	1.67e-02
Gap junction assembly	1.74e-03	1.67e-02
Carboxyterminal post-translational modifications of tubulin	1.76e-03	1.67e-02
Signaling by FGFR2 IIIa TM	1.76e-03	1.67e-02
RNA Pol II CTD phosphorylation and interaction with CE during HIV infection	1.77e-03	1.67e-02
RNA Pol II CTD phosphorylation and interaction with CE	1.77e-03	1.67e-02
Activation of AMPK downstream of NMDARs	1.77e-03	1.67e-02
Transferrin endocytosis and recycling	1.77e-03	1.67e-02
Cooperation of Prefoldin and TriC/CCT in actin and tubulin folding	1.77e-03	1.67e-02
RHO GTPases activate IQGAPs	1.77e-03	1.67e-02
Cristae formation	1.77e-03	1.67e-02
mRNA Capping	1.78e-03	1.67e-02
Prefoldin mediated transfer of substrate to CCT/TriC	1.78e-03	1.67e-02
Post-chaperonin tubulin folding pathway	1.80e-03	1.67e-02
Abortive elongation of HIV-1 transcript in the absence of Tat	1.81e-03	1.67e-02
Insulin receptor recycling	1.81e-03	1.67e-02
Nucleotide salvage	1.83e-03	1.67e-02
Formation of tubulin folding intermediates by CCT/TriC	1.83e-03	1.67e-02
Citric acid cycle (TCA cycle)	1.83e-03	1.67e-02
Microtubule-dependent trafficking of connexons from Golgi to the plasma membrane	1.86e-03	1.69e-02
Transport of connexons to the plasma membrane	1.88e-03	1.69e-02
Pregnenolone biosynthesis	1.91e-03	1.71e-02
mitochondrial fatty acid beta-oxidation of saturated fatty acids	1.96e-03	1.74e-02
Formation of Senescence-Associated Heterochromatin Foci (SAHF)	2.13e-03	1.89e-02
Regulation of MECP2 expression and activity	2.35e-03	2.07e-02
HDMs demethylate histones	2.43e-03	2.12e-02
Activated PKN1 stimulates transcription of AR (androgen receptor) regulated genes KLK2 and KLK3	2.49e-03	2.13e-02
Transcriptional Regulation by MECP2	2.49e-03	2.13e-02
SIRT1 negatively regulates rRNA expression	2.52e-03	2.13e-02

DNA methylation	2.52e-03	2.13e-02
Meiotic synapsis	2.54e-03	2.13e-02
PKMTs methylate histone lysines	2.54e-03	2.13e-02
DNA Damage/Telomere Stress Induced Senescence	2.56e-03	2.13e-02
SUMOylation of chromatin organization proteins	2.57e-03	2.13e-02
PRC2 methylates histones and DNA	2.57e-03	2.13e-02
Pre-NOTCH Expression and Processing	2.58e-03	2.13e-02
Formation of the beta-catenin: TCF transactivating complex	2.62e-03	2.14e-02
Pre-NOTCH Transcription and Translation	2.64e-03	2.14e-02
Gene Silencing by RNA	2.73e-03	2.20e-02
HATs acetylate histones	2.74e-03	2.20e-02
Mitotic Prophase	2.79e-03	2.22e-02
Estrogen-dependent gene expression	2.80e-03	2.22e-02
SUMOylation	2.86e-03	2.25e-02
Cellular Senescence	2.87e-03	2.25e-02
SUMO E3 ligases SUMOylate target proteins	2.90e-03	2.26e-02
Rab regulation of trafficking	3.16e-03	2.43e-02
L1CAM interactions	3.18e-03	2.43e-02
Resolution of Sister Chromatid Cohesion	3.19e-03	2.43e-02
Chromatin modifying enzymes	3.21e-03	2.43e-02
Chromatin organization	3.21e-03	2.43e-02
MAPK6/MAPK4 signaling	3.22e-03	2.43e-02
mRNA Splicing - Minor Pathway	3.37e-03	2.53e-02
Metabolism of steroid hormones	3.43e-03	2.56e-02
Formation of the Early Elongation Complex	3.52e-03	2.60e-02
Formation of the HIV-1 Early Elongation Complex	3.52e-03	2.60e-02
Cholesterol biosynthesis	3.55e-03	2.61e-02
Diseases associated with glycosylation precursor biosynthesis	3.59e-03	2.63e-02
Cytosolic tRNA aminoacylation	3.62e-03	2.64e-02
Metabolism of cofactors	3.70e-03	2.68e-02
Formation of ATP by chemiosmotic coupling	3.75e-03	2.70e-02
CDC6 association with the ORC:origin complex	3.81e-03	2.73e-02
Tight junction interactions	4.54e-03	3.23e-02
NOTCH1 Intracellular Domain Regulates Transcription	4.78e-03	3.39e-02
Metabolism of water-soluble vitamins and cofactors	4.82e-03	3.40e-02
trans-Golgi Network Vesicle Budding	4.97e-03	3.48e-02
RNA Polymerase I Promoter Opening	4.99e-03	3.48e-02
ERCC6 (CSB) and EHMT2 (G9a) positively regulate rRNA expression	5.04e-03	3.50e-02
RMTs methylate historie arginines	5.13e-03	3.55e-02
Mitochondrial Fatty Acid Beta-Oxidation	5.24e-03	3.60e-02
Assembly and cell surface presentation of NMDA receptors	5.26e-03	3.60e-02
Assembly of active LPL and LIPC lipase complexes	5.39e-03	3.66e-02
Oxidative Stress Induced Senescence	5.39e-03	3.66e-02
RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function	5.42e-03	3.66e-02
Epigenetic regulation of gene expression	5.48e-03	3.68e-02
Phenylalanine and tyrosine catabolism	5.87e-03	3.92e-02
Interleukin-1 signaling	6.28e-03	4.17e-02
Visual phototransduction	6.32e-03	4.17e-02
Mitochondrial biogenesis	6.33e-03	4.17e-02
Apoptosis induced DNA fragmentation	6.44e-03	4.20e-02
Regulation of IFNG signaling	6.44e-03	4.20e-02
COPII-mediated vesicle transport	6.53e-03	4.24e-02
Translocation of SLC2A4 (GLUT4) to the plasma membrane	6.58e-03	4.25e-02
Golgi Associated Vesicle Biogenesis	6.78e-03	4.36e-02
Notch-HLH transcription pathway	6.82e-03	4.36e-02
tRNA Aminoacylation	6.84e-03	4.36e-02
Detoxification of Reactive Oxygen Species	6.94e-03	4.41e-02
Packaging Of Telomere Ends	7.28e-03	4.60e-02
Platelet activation, signaling and aggregation	7.32e-03	4.60e-02
Metabolism of porphyrins	7.43e-03	4.66e-02
Mitotic Prometaphase	7.65e-03	4.76e-02
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SUMOylation of DNA damage response and repair proteins	7.69e-03	4.76e-02
Deposition of new CENPA-containing nucleosomes at the centromere	7.75e-03	4.76e-02
Nucleosome assembly	7.75e-03	4.76e-02
RHO GTPases Activate Formins	7.79e-03	4.76e-02
Interleukin-1 family signaling	7.81e-03	4.76e-02
Meiosis	8.09e-03	4.89e-02
RAB GEFs exchange GTP for GDP on RABs	8.09e-03	4.89e-02