CHEST Online Supplement

BAL Transcriptomes Characterize Idiopathic Pulmonary Fibrosis Endotypes With Prognostic Impact

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e-Appendix 1.

Supplementary Methods

Patient cohort

We used gene expression and clinical data included in the GSE70867 dataset. The dataset consists of gene expression data retrieved from bronchoalveolar lavage samples of 176 IPF cases and 20 controls. All IPF cases were diagnosed in a multidisciplinary discussion. BAL sampling was performed before initiation of antifibrotic or immunosuppressive treatment (for cases diagnosed before the antifibrotics era). Bronchoalveolar lavage sampling was performed in 3 centres: Freiburg, Siena and Leuven. All control samples were retrieved from Freiburg. Clinical data, included in the online GSE70867 dataset, were age and sex for controls and age, sex, GAP index, death and time to death (or end of follow-up) for IPF cases.

Gene expression data and clustering

After downloading this publicly available gene expression dataset from the GEO database (GSE70867), batch effects associated with the cohort were diagnosed and were removed using the Combat functionality[48] **e-Figure 1)**. Of note, gene expression differences associated with the BAL sampling centre were checked and proved to be negligible.

DDR Tree is a dimension reduction technique specifically designed for gene expression data sets to maximally preserve the intrinsic structure of the data[49]. First, a reverse graph embedding is applied to determine the intrinsic graph structure of the original high dimension dataset. Afterwards, dimension reduction is performed preserving distances of the datapoints in the resulting low dimension space.

Based on the coordinates of the resulting low dimension space (i.e. 3 dimensions), distances between datapoints were calculated using the Euclidean metric and clustering was performed using the complete linkage method. As the goal of the study was to explore the variability of the data and assess whether clustering could be meaningful, the number of clusters chosen as the maximum number of clusters possible, with a minimum of 10 samples per cluster.

For every cluster, differential gene expression versus controls was calculated using linear mixed models (for every gene separately) including gene expression data as the observed variable, age, gender and cluster as fixed effects and the centre in which the sample was performed as random effect. The latter was included to minimize the effect of small differences in processing between the 3 centres and to minimize the effect of imbalances between study populations. The estimate of the fixed effect 'cluster' was used as fold change and the false discovery rate (FDR)-corrected p-value of this fixed effect as p-value for significance. Overview of the number of differentially expressed genes were visualised with Euler diagrams (using the eulerr R package[50]).

Association with clinical variables and outcome

Continuous variables were presented as mean ± standard deviation. Categorical variables were presented as counts and percentages. Differences between IPF cases and controls were calculated using Student's T tests and fisher exact tests, for continuous and categorical variables, respectively. Differences between clusters regarding to clinical variables were calculated using Anova tests for continuous variables and fisher exact tests for categorical variables. Clustering was associated with clinical outcome using cox proportional hazards models and presented with Kaplan Meier curves.

Functional enrichment

In order to evaluate the functional annotations of the clusters, gene ontology enrichment was performed using 'generally applicable gene set enrichment analysis' (GAGE[51]). To obtain a broad overview of the functional enrichments of each cluster, we analysed differential expression of gene ontologies between each cluster and all other clusters. Per cluster, a graph was constructed using Cytoscape, with differentially expressed gene ontologies as nodes and the degree of overlapping genes as edge.

In a second phase, to assess direction of differential expression of these pathways, GAGE was used to determine differential expression of gene ontologies for each cluster compared to controls. Expression of gene ontologies associated with the pathways observed in the Cytoscape graphs were visualised using density plots.

Moreover, we performed cellular subtype deconvolution using xCell, which is based on several single cell dataset-based gene signatures, using a spill-over compensation technique to reduce associations of closely related cell types, which was validated using cytometry immunophenotyping and in-silico simulations.

Analysis of transcription factors regulating the expression of survival-associated genes

In order to evaluate whether distinct gene expression signatures would directly impact on survival, we assessed the expression of 1381 genes, shown to be associated with survival in the initial Prasse study[21]. We evaluated the expression of these genes in each cluster vs all other IPF samples. We evaluated whether these endotype-specific survival-associated gene sets were modulated by distinct motifs and/or transcription factors using iRegulon and the Rcistarget package[52].

Endotype validation in 3 independent validation cohorts

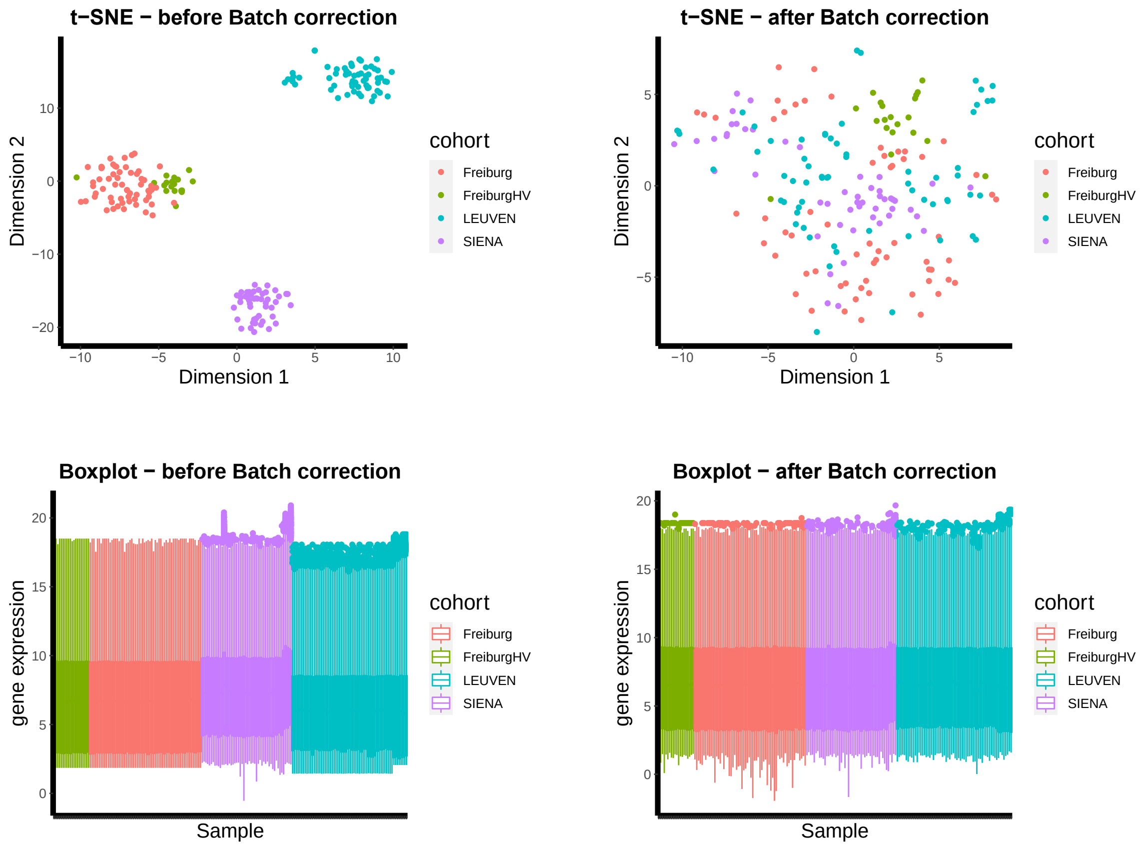
To validate the existence of these endotypes, gene expression of the 250 most differentially expressed genes was determined in 3 independent gene expression datasets retrieved from IPF blood samples, i.e. GSE28221[57] (n=75), GSE93606[58] (n=57) and GSE132607[59] (n=74). Gene expression was visualised using heatmaps which allowed the identification of these endotypes by hierarchical clustering. Survival differences between cases with and without an endotype-specific transcriptome in these cohorts were analysed using multivariable cox proportional hazards models, correcting for age and gender. **Supplementary Results**

Analysis of transcription factors regulating the expression of survival-associated genes

The original Prasse study derived 1582 genes associated with survival (988 associated with worse survival, 594 with better survival). From the original genes associated with worse survival, 100 were upregulated in both IPF5 and IPF6, 601 genes only in IPF5 and 76 genes only in IPF6. From the original genes associated with better survival, 93 genes were downregulated in both IPF5 and IPF6, 181 only in IPF5 and 90 in IPF6. The analysis of transcriptional regulation in IPF5 is elaborated in the main text. We evaluated the regulation of these sets of cluster-specific survival-associated genes. In IPF6, upregulated genes associated with worse survival showed a very different set of enriched transcription factors, including SNAI1-3, sirtuin 6 (SiRT6) and T-box transcription factor 2 and 3 (TBX2 & TBX3), whereof the latter showed very high expression in IPF6 but not in IPF5. Downregulated genes associated with better survival were regulated by another set of transcription factors including PKNOX1 and SETDB1 and both downregulated in IPF6 but not in IPF5 (e-Figure **4**).

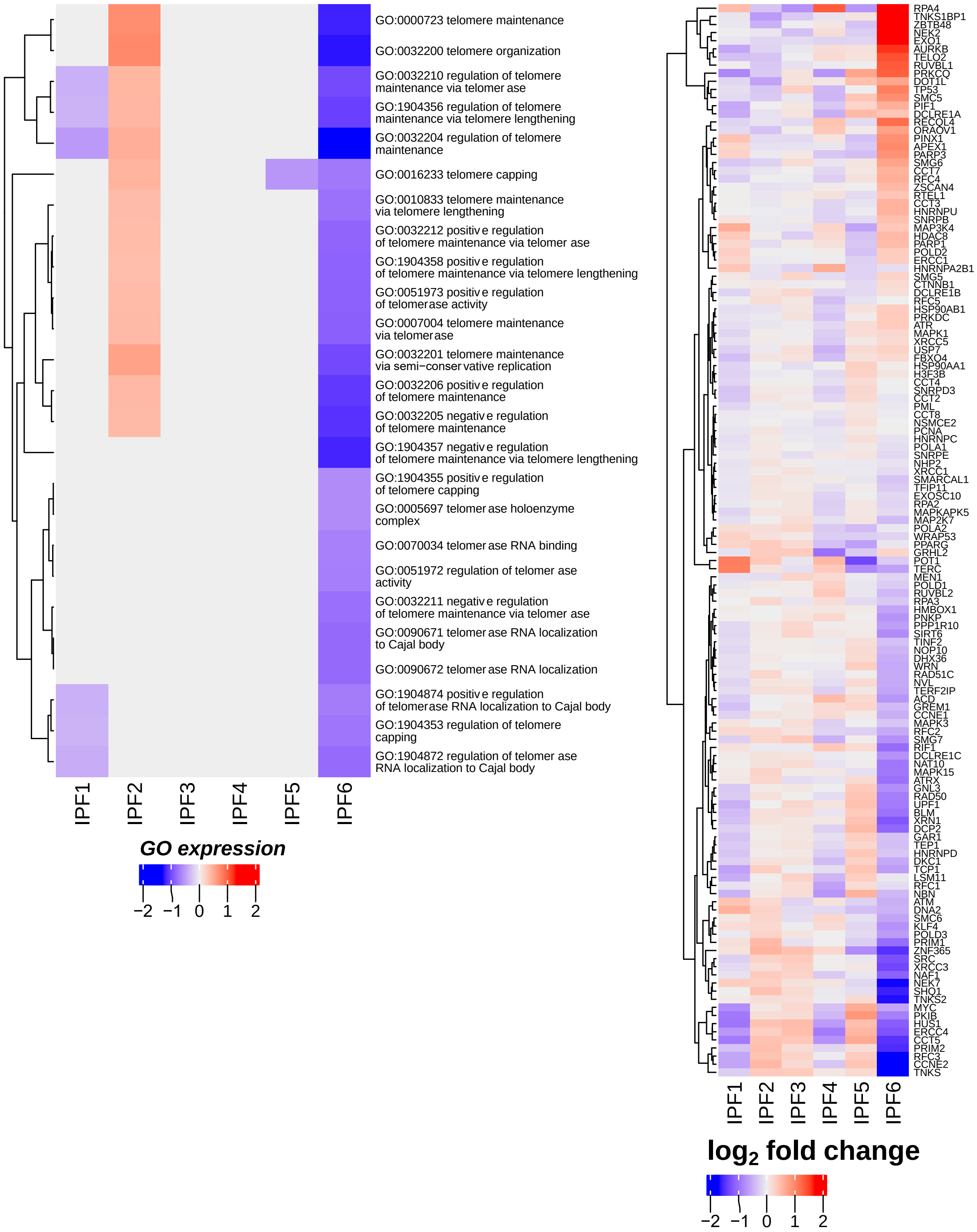
Validation of endotype existence and its impact on survival

We also validated the existence of the IPF6 endotype in the 3 independent datasets mentioned in the main text. Based on the gene expression of the 250 top differentially expressed genes for IPF5 and IPF6 (compared to all other IPF cases), 51 (24.8%) and 21 (10.2%) cases in the validation cohort showed an IPF5 and IPF6 transcriptome signature, respectively (**e-Figure 5A**). IPF6 endotype did not confer worse outcome (HR 0.44, p=0.11), shown in **e-Figure 5B**.

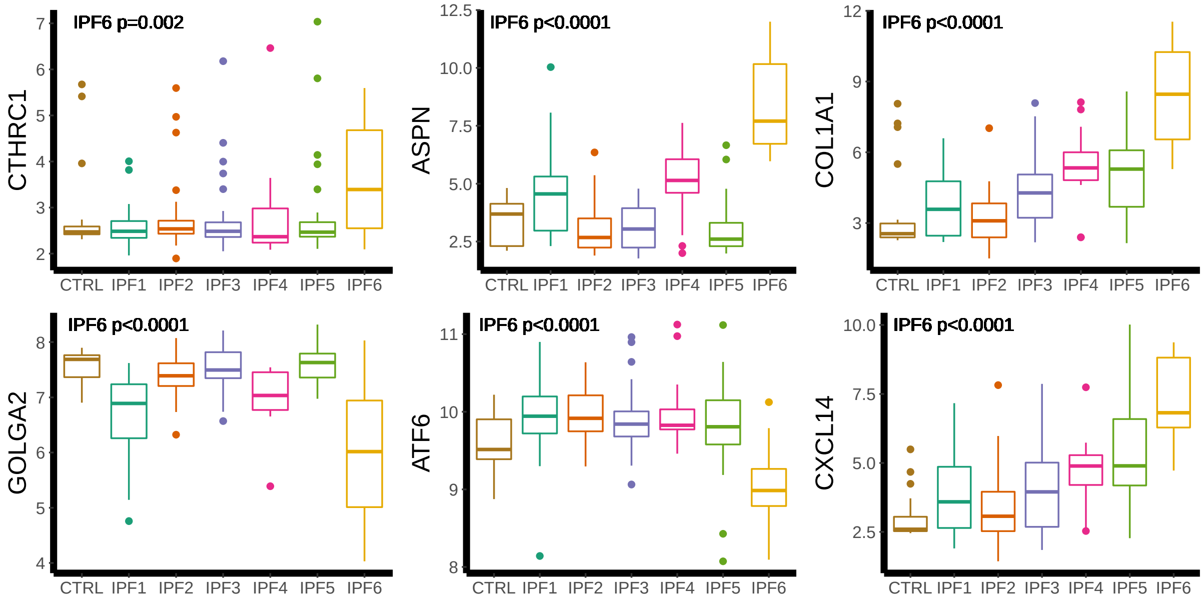


e-Figure 1. Batch effect removal using ComBat

Left: t-SNE plot and gene expression boxplot before batch effect removal. Right: t-SNE plot and gene expression boxplot after Batch effect removal. The Freiburg cohort was split into controls (healthy volunteers, "FreiburgHV") and IPF cases ("Freiburg").

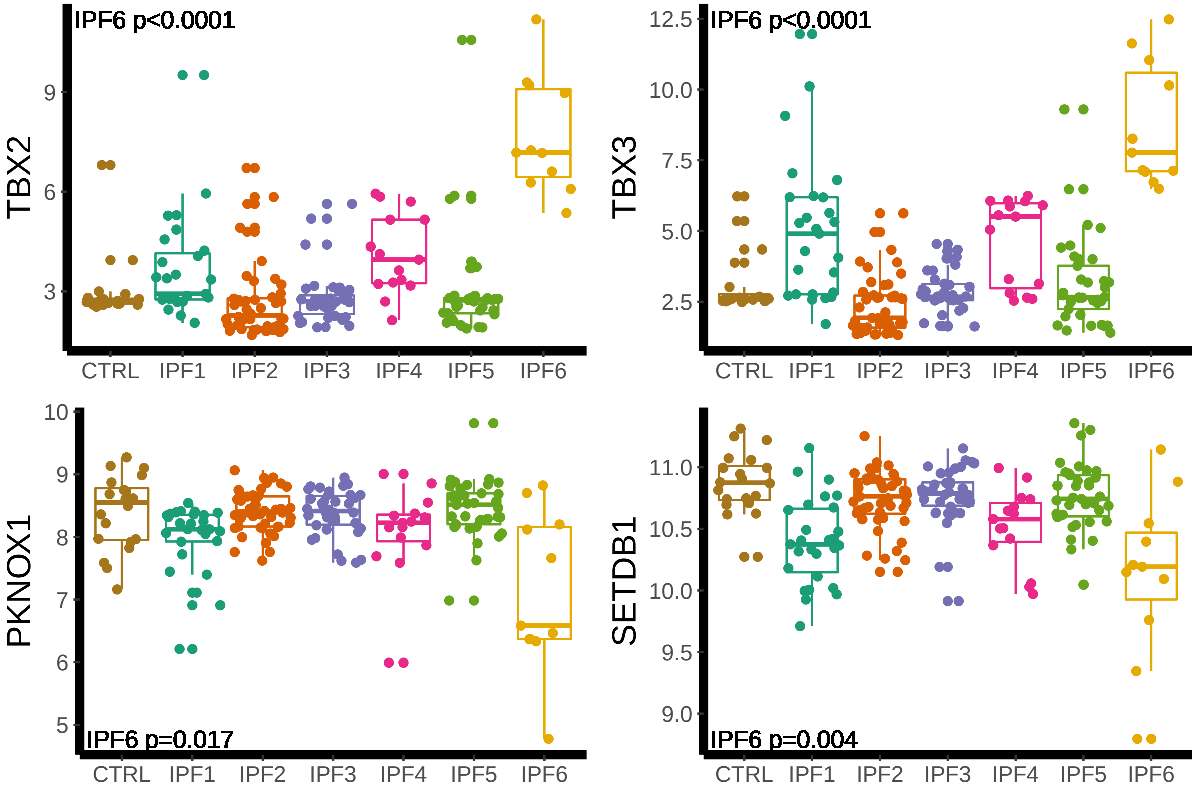


e-Figure 2: differential expression of Gene ontologies and genes related to telomere functions



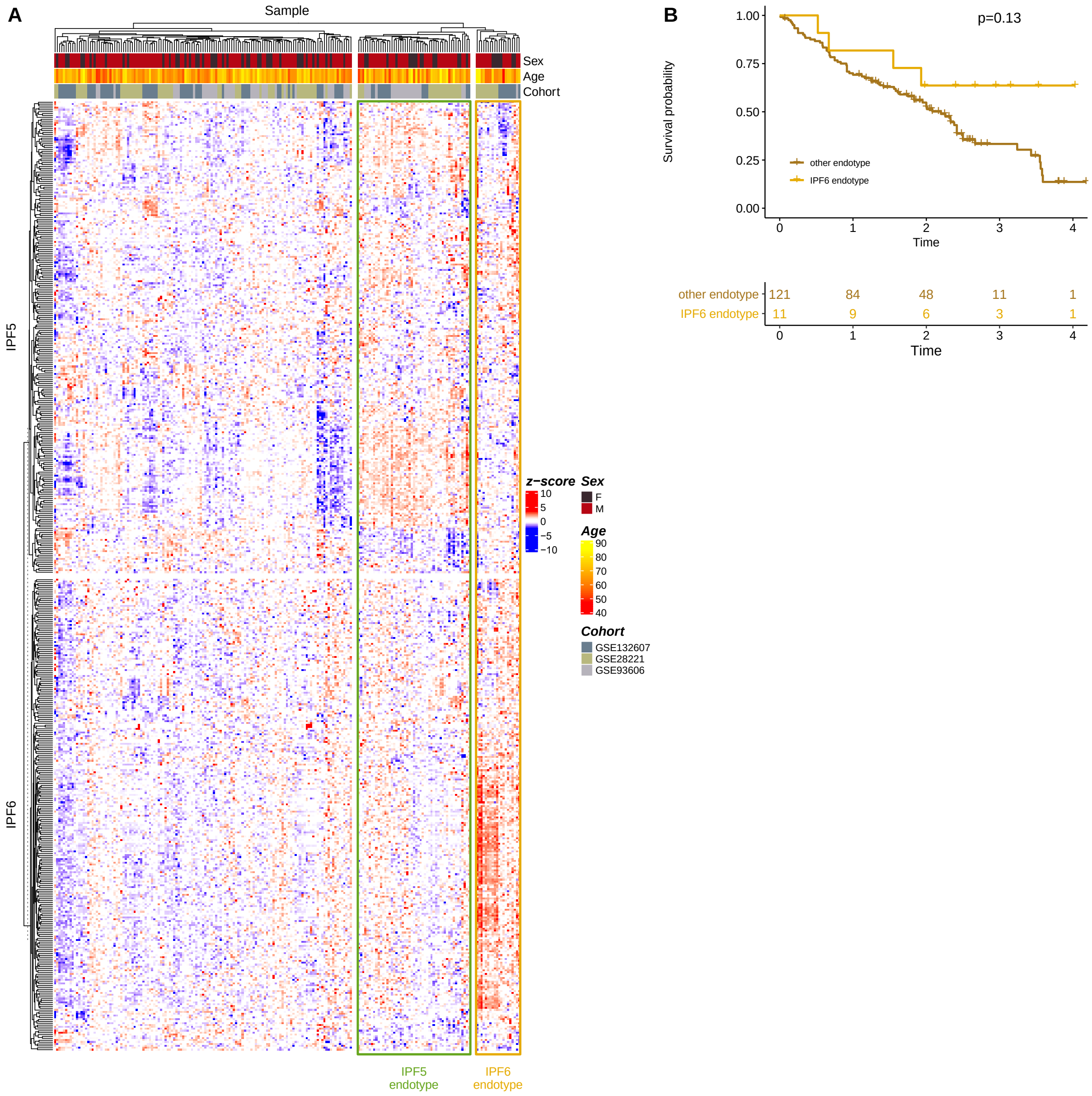
e-Figure 3 Gene expression of marker genes associated with enriched functions of IPF6.

A. Gene expression of several marker genes for myofibroblast functions (CTHRC1, ASPN and COL1A1) and cell homeostasis function (Golgi: GOLGA2, unfolded protein response: ATF6, developmental pathways (Hedgehog): CXCL14). P-values are determined vs all other IPF samples. B. cell subtype deconvolution using xCell based on bulk transcriptome datasets.



e-Figure 4. Gene expression of transcription factors regulating endotype-specific survival genes in IPF6

P-values are determined vs controls. Y-axis represents normalised expression.



e-Figure 5. IPF endotype validation in separate blood gene expression datasets

(A) Heatmap showing gene expression of most differentially expressed genes for IPF5 and IPF6 in 3 independent gene expression dataset based on blood RNA of IPF cases. (B) Cases with a IPF5-like gene expression in the validation cohorts show worse survival compared to other cases. (C) Survival of cases with a IPF6-like gene expression in the validation cohorts did not show different survival compared to other cases.

e-Table 1A. IPF5 genelist

gene	log2FC_vsotherIPF	p_vsotherIPF	log2FC_vsCTRL	p_vsCTRL
PRSS23	2.271429084	2.54054E-16	1.883992497	0.000213
TLR2	1.155916842	4.8831E-15	1.623453471	1.82E-08
NKX2-1	1.846051725	5.3956E-15	2.539199876	1.98E-06
RASSF2	1.521615122	7.5518E-15	1.894159655	1.95E-06
AMPD3	2.038471146	2.73532E-14	2.003699501	2.47E-07
CYR61	2.300547331	4.41077E-14	3.343624086	3.11E-08
PTPRN2	1.996786999	4.41077E-14	1.258251655	0.005398
SGPP2	1.66893515	8.17121E-14	1.916745585	4.51E-05
PXN	1.837181491	1.0439E-13	1.875300932	0.000254
DAZAP2	0.518336715	1.06123E-13	0.410277126	0.001423
SLCO4A1	1.80384868	1.0742E-13	2.064278597	1.16E-05
EFR3B	1.668586622	1.33713E-13	2.079044309	3.58E-08
ACPP	1.469399285	3.6045E-13	2.265997547	1.54E-09
CEACAM6	2.732327298	3.9498E-13	3.754655765	5.39E-09
MAL2	2.408853634	5.15643E-13	2.491442013	9.52E-05
NFKBIA	0.84293266	6.2131E-13	0.839472328	0.000109
TMEM154	1.856926778	6.24301E-13	1.942567035	6.23E-06
CHST15	2.471263033	7.80328E-13	3.159375922	7.43E-07
C9ORF152	1.625392704	1.40449E-12	1.877585985	0.000467
CTTN	1.966336387	1.4282E-12	1.347049194	0.000947
DENND3	0.81187425	1.66564E-12	0.933153077	3.99E-05
TMEM30B	1.697215835	1.66564E-12	1.421871902	0.00873
XYLT1	1.558771981	1.66564E-12	1.704167541	2.02E-06
CXCR4	1.335987567	1.8233E-12	1.655557832	0.0006
PRKCB	1.454453278	1.97703E-12	1.709409569	6.94E-06
PLIN5	1.899367018	2.00137E-12	2.026131426	0.000146
CHST2	1.854475798	2.09323E-12	2.257252353	3.78E-07
MARCKS	1.48816818	2.4839E-12	2.139775597	9.59E-07
TMEM71	1.25000433	3.31251E-12	1.721695108	5.54E-05
LCP2	0.684416833	3.41339E-12	0.619686968	0.000343
SERPINB9	1.912506576	3.75566E-12	1.794086263	1.56E-05
MERTK	2.214589329	4.238E-12	3.638899666	8.64E-11
S1PR3	1.737280325	4.27957E-12	2.846604279	4.2E-08
KCNK1	1.588862674	4.87806E-12	1.574343294	0.000446
FYB1	0.973084451	5.76402E-12	0.456345574	0.15854
LAMA3	1.835820667	5.76402E-12	2.699229155	3.65E-06
RFLNB	1.823972413	7.81132E-12	1.471373102	0.003023
DGKD	0.964626333	7.98264E-12	0.886936931	6.25E-05

MXD1	1.14440994	7.98264E-12	1.523626649	5.51E-06
SH3KBP1	0.831649636	7.98264E-12	0.517476754	0.027564
SLC7A11	1.863724738	7.98264E-12	1.808725863	0.000233
SLC25A37	1.607242457	8.75068E-12	1.720848053	0.000138
ARHGAP45	1.088261464	8.8743E-12	0.673721729	0.086144
KCNJ2	1.261541855	8.99159E-12	1.750581862	1.05E-09
LILRB2	0.82231994	8.99159E-12	0.69206316	0.002317
LBR	0.732630998	9.68019E-12	0.851304885	0.000121
FNBP1L	1.685160006	1.03508E-11	1.508186343	0.001012
HIF1A	1.2609953	1.03508E-11	1.477201571	3.25E-06
FAM49B	0.614705231	1.23368E-11	0.704651028	1.72E-05
FAM198B	1.506136145	1.27993E-11	2.452740215	3.58E-08
ST8SIA4	1.722895748	1.28026E-11	1.88039842	0.000103
ADAM8	1.511827175	1.48712E-11	1.81737684	8.18E-05
AP1S2	0.856439364	1.48712E-11	1.032889395	0.000146
MET	2.102047013	1.48712E-11	2.953468883	8.94E-07
LIMCH1	1.541408124	1.95112E-11	1.158315329	0.016421
PERP	1.780253567	1.95112E-11	0.917176526	0.028763
PRR5L	1.613797854	2.07984E-11	1.452155743	2.36E-05
SH2D3A	1.284254475	2.09423E-11	0.364795174	0.305908
WWC1	1.452721794	2.09423E-11	1.438814256	0.000915
CLDN18	2.125978725	2.11152E-11	2.989381726	7.72E-07
P2RY2	1.382961851	2.16001E-11	2.467974363	7.29E-10
PLA2G7	1.746795933	2.26833E-11	3.333787351	8.39E-11
CCL8	2.393795084	2.27709E-11	1.996223378	0.003187
SAT1	0.599388556	2.30418E-11	0.491248049	0.012365
PRDM1	1.579019043	2.6974E-11	0.976958103	0.027574
NINJ1	1.038131423	3.24361E-11	0.971058733	0.004286
ADGRF5	1.813217462	4.06179E-11	2.115418001	0.013951
MUC21	1.652961341	4.073E-11	2.546769586	1.46E-06
PRDM8	1.806704721	4.19149E-11	1.520466504	0.001058
SUSD6	0.55160448	4.39181E-11	0.32929428	0.016461
EPCAM	2.151017906	4.76147E-11	2.474096983	9.88E-05
KRT23	2.093993166	6.02625E-11	2.2527745	0.000113
LHFPL6	1.463012808	6.1226E-11	1.889494784	3.22E-07
MYLIP	1.017690976	6.33858E-11	0.663065936	0.012398
BASP1	1.262084476	6.55401E-11	1.837915524	9.53E-07
GALNT3	1.619358599	6.81897E-11	1.362236222	0.002317
CNKSR1	1.468210695	6.96875E-11	1.146393233	0.005558
GPD1	-1.416840343	6.96875E-11	-1.448700736	0.003966

RIPOR2	1.571663228	7.11704E-11	1.612779021	0.000148
ASPRV1	1.78589048	7.42516E-11	1.366278283	0.002227
CHD3	1.193374425	7.42516E-11	0.502263324	0.101605
SLC36A1	0.957262139	8.40401E-11	1.608494305	2.33E-07
SELL	1.829399139	8.60418E-11	1.63250636	0.000628
TESC	1.453269856	8.72861E-11	1.6412014	0.000636
KITLG	1.417697885	9.7026E-11	1.453707465	0.001048
SOD2	1.015909911	9.89841E-11	1.025575415	0.003149
ATL1	-1.003686679	1.0303E-10	-1.10725743	0.003085
CSF3R	1.173048884	1.12336E-10	1.220101166	0.002994
FHL1	-1.070822525	1.12336E-10	-0.998373109	7.51E-05
ADM	1.797564852	1.29593E-10	2.889102229	6.8E-07
ST6GAL1	1.120435185	1.45343E-10	0.74808936	0.035606
GLCCI1	1.449230382	1.65585E-10	0.66984659	0.065217
MTSS1	1.674176417	1.71018E-10	2.226410255	2.95E-06
LAPTM4B	1.446524425	1.86165E-10	1.943209795	5.56E-07
RAB25	1.499057683	1.96961E-10	1.811549384	0.000189
RAB37	1.422664904	2.31557E-10	0.902203975	0.04165
OXCT1	1.45388324	2.7814E-10	1.30395955	4.7E-05
ENO2	1.466974048	2.84122E-10	0.786522506	0.086215
TACC2	1.418742006	2.84277E-10	0.895260839	0.127172
LRRC70	1.368044269	2.88132E-10	1.465812747	0.00039
MMP24	1.472979085	2.94062E-10	1.699181103	0.000325
STEAP4	1.94631803	3.09317E-10	3.217596008	5.28E-08
SLC44A1	1.049554519	3.21399E-10	1.736750362	3.58E-08
HAMP	1.80989683	3.2211E-10	2.341730188	2.37E-05
TJP2	-0.895330278	3.79602E-10	-0.497449591	0.038276
CD93	1.477776389	3.81032E-10	1.783916265	7.23E-07
WDR26	0.540152073	3.81032E-10	0.460821561	0.001188
ABLIM1	1.66394437	3.94484E-10	0.666237267	0.154115
ANXA3	1.492747869	4.48753E-10	1.517153312	0.000179
CMTM8	1.348061251	4.48753E-10	0.922944637	0.019703
RHOH	1.142438631	4.48753E-10	0.856932895	0.017701
TAGAP	0.826487642	4.70589E-10	0.562677804	0.055858
ADGRG1	1.643318166	5.20321E-10	1.915757978	0.000168
VGF	1.066213912	5.20321E-10	1.238160035	0.000122
RNF145	0.908183065	5.96064E-10	0.748807605	0.001222
PLIN4	1.35387597	6.27684E-10	1.487501431	0.000371
F2RL1	1.734856732	6.49815E-10	2.816383208	1.39E-06
PPIF	0.686553806	6.62652E-10	0.778393154	0.001241

TMC5	1.830701774	6.67798E-10	1.132752578	0.039704
RASA3	0.744756357	6.7138E-10	0.420478346	0.099333
CCL3	1.554183286	6.8199E-10	2.025145799	2.43E-05
PHLDA3	-0.963403193	7.00868E-10	-1.185297669	0.002931
FOXQ1	1.636719603	7.27756E-10	1.969890203	0.007621
SGK1	0.835227093	7.40696E-10	1.111819339	3.74E-05
HOMER3	0.907547723	7.82516E-10	1.843753485	1.61E-10
GRAMD4	0.808653378	8.24664E-10	0.702262771	0.000779
SLC2A1	1.340894933	8.3711E-10	1.202814848	0.000379
INPP5A	1.152955076	8.79614E-10	1.53119826	7.23E-07
PAK1	0.533632553	8.97418E-10	0.772079875	6.27E-06
GALM	0.839881901	9.41877E-10	0.663550362	0.009427
GPR132	1.264597066	9.41877E-10	1.378564035	0.000405
SULF2	1.302397386	9.41877E-10	1.88577321	6.86E-05
OLIG1	2.023952872	9.54304E-10	3.398422686	1.64E-08
GYPC	-0.640594797	9.91473E-10	-0.751725092	0.001295
CMTM4	1.31132884	1.07291E-09	1.149212235	0.004467
SPNS2	1.105807511	1.07291E-09	1.409993996	2.52E-06
AREG	1.850066935	1.09099E-09	2.510387218	1.15E-07
RGL1	1.573742001	1.13571E-09	2.889567334	7.29E-10
CAT	-0.663609613	1.17197E-09	-0.842391483	0.000118
PLD6	1.314805653	1.22542E-09	1.095685866	1.21E-05
PTPN7	1.394655568	1.22542E-09	1.226131504	0.002724
IGFBP7	0.932490592	1.23265E-09	1.468546837	1.38E-05
CGN	1.822540151	1.26275E-09	1.017261764	0.087178
PTPRF	2.08676091	1.27186E-09	1.203553903	0.024678
EIF4E3	1.39922693	1.31587E-09	1.261330607	0.000521
FOLR3	-1.738122195	1.46951E-09	-2.307705336	9.38E-06
CD24	1.565466873	1.48572E-09	1.946998342	0.000196
MYO1D	1.600799223	1.49657E-09	1.640471869	6.07E-05
SELENBP1	1.981952054	1.50625E-09	1.236819347	0.037943
SCGB3A2	1.288779438	1.55791E-09	2.043734832	4.8E-05
ADGRF1	1.75908427	1.59454E-09	1.528659868	0.025742
ALDH1A3	1.476978984	1.77009E-09	1.388305437	0.003526
HIP1R	1.610897884	1.77009E-09	0.79278674	0.07229
ARHGAP9	0.647210931	1.77506E-09	0.277591254	0.358676
VMO1	-1.147660821	1.84065E-09	-1.679597716	0.00031
JAK3	1.447149997	1.87603E-09	0.703589005	0.222141
MRVI1	2.018674024	1.8763E-09	3.032214235	7.69E-08
PLEKHO1	0.740743008	1.8763E-09	0.563048954	0.023205

SLAMF7	1.681621484	2.14062E-09	0.968379238	0.08161
SLC24A3	1.475359097	2.19302E-09	2.153583683	2.49E-06
ID1	1.696582451	2.20026E-09	2.042547328	8.4E-05
LINC00626	-0.990414244	2.25383E-09	-0.942187546	0.002527
MAK	1.261506345	2.31815E-09	0.790318661	0.030173
TCF7L2	-1.167735181	2.38645E-09	-0.837275629	0.008824
ARF6	0.739708147	2.73883E-09	0.495214639	0.008267
RUNX3	0.879330669	2.73883E-09	0.359705156	0.345106
SLC26A11	1.066874056	2.73883E-09	0.745489157	0.011636
CNEP1R1	0.54548148	2.75233E-09	0.359988519	0.015105
HNRNPD	0.391214176	2.81191E-09	0.218278209	0.10258
TC2N	1.488752321	2.81191E-09	0.059924487	0.943974
NUP62	0.431681282	2.97343E-09	0.327400172	0.011228
SLC39A14	1.225113818	3.01183E-09	0.939217517	0.000524
ST6GALNAC1	1.608747122	3.01183E-09	0.557597179	0.406744
SCEL	1.459252798	3.06567E-09	2.11120269	0.000154
ADGRA3	1.202116142	3.13737E-09	1.193282381	0.009636
PROK2	2.454773188	3.13737E-09	1.944499283	0.002471
SLC1A1	0.925490093	3.13737E-09	0.728627024	0.089936
C9ORF47	1.407443641	3.28992E-09	1.804745706	6.97E-05
ARL4C	1.343102687	3.37131E-09	0.846398798	0.056727
HTRA1	1.811598592	3.50095E-09	3.581534	4.66E-09
MIAT	2.085735242	3.63111E-09	0.225173072	0.796965
TP53BP2	0.902266993	3.63223E-09	0.651497347	3.74E-05
TMEM121B	1.307639581	3.7418E-09	1.878417143	2.46E-07
SMAD3	1.826017716	3.74518E-09	0.829062207	0.155447
FAHD2CP	-0.511709986	3.93052E-09	-0.573397596	0.000253
CDH1	2.002527523	3.99474E-09	1.006920904	0.148651
YPEL4	-1.352923978	4.0545E-09	-0.387828439	0.357309
GHRL	1.247972917	4.07722E-09	1.373406407	0.000112
HS3ST3B1	1.743374541	4.07722E-09	1.639810214	0.000338
SLC7A5	1.636543586	4.07722E-09	1.287979539	0.000158
TRAF5	1.128728285	4.07722E-09	0.81896696	0.023674
RHOBTB3	1.235539562	4.1618E-09	1.424659255	5.04E-05
BMP6	1.384787229	4.17815E-09	1.965672359	1.79E-05
C1ORF116	1.468237596	4.17815E-09	2.116133478	8.94E-06
SMIM3	1.028545744	4.17815E-09	1.60441287	1.49E-06
OCIAD2	0.901599075	4.187E-09	0.408549252	0.22548
AJUBA	0.963934903	4.37367E-09	1.112802182	0.003767
DSP	1.726794209	4.48741E-09	0.501363703	0.437632

EEPD1	1.121565071	4.48741E-09	1.666707058	0.005946
RGS2	1.330947646	4.48741E-09	2.121155679	6E-06
TNFRSF10C	1.238031868	4.48741E-09	1.339310317	0.002735
NPL	0.924863059	4.6007E-09	0.97651345	0.000869
PPID	0.614552322	4.6007E-09	0.233782007	0.0795
EFNB1	-0.659293485	5.24191E-09	-0.5385239	0.049129
KDM7A	1.244666326	5.28923E-09	0.65654297	0.032426
KLHL5	1.185357571	5.3237E-09	0.988585069	0.000208
VSIG1	1.217829266	5.3237E-09	1.508830623	0.00079
CARD19	0.558119494	5.89428E-09	0.87736508	6.44E-06
IRAK2	1.683428828	5.90781E-09	1.114661865	0.003906
RELB	0.880568071	5.90781E-09	0.713472871	0.028121
RGL4	1.896738972	5.90781E-09	2.009745785	0.000642
PKP3	1.783374323	5.92751E-09	1.898272559	0.000534
S100A13	-0.826953976	5.92751E-09	-0.850444207	0.015952
TBC1D14	0.514982696	6.05794E-09	0.382805207	0.028802
MYCNOS	-1.325967037	6.19036E-09	-0.503060479	0.263478
TPST1	2.253045833	6.19036E-09	4.252373188	1.61E-10
TSPAN5	1.593534393	6.19036E-09	0.95833327	0.049991
PDE4B	0.884904316	6.23031E-09	0.780726959	0.011636
CLIC6	1.699115804	6.24602E-09	0.973669405	0.122779
KANK1	1.675670382	7.16851E-09	2.640247644	3.11E-07
CDK6	1.379314337	7.21216E-09	0.937531835	0.012406
IFNAR2	0.701310213	7.21216E-09	0.598723178	0.030802
OSBPL7	1.063142017	7.21216E-09	0.87166341	0.002999
SLC25A23	1.479129138	7.34212E-09	1.474258089	0.000429
SNCA	0.997976943	7.85133E-09	1.721863703	4.14E-06
GGA2	-0.592822588	7.86929E-09	-0.79025029	0.000681
FAM20A	1.356993661	8.17328E-09	1.916502493	1.35E-06
MPP6	1.020584995	8.17328E-09	1.402884234	2.9E-05
TPP1	-1.076793492	8.39153E-09	-0.510470302	0.25061
CLDN4	2.018327824	8.57219E-09	1.839337003	0.005238
FCAR	1.61372039	8.57219E-09	1.656691109	0.001766
MPP1	0.487260744	8.68227E-09	0.511496733	0.002262
DPEP3	-1.347722177	8.70925E-09	-0.585248046	0.152571
REC8	0.936091467	8.71688E-09	0.168078448	0.548715
TSHZ3	1.364051931	8.77668E-09	1.43300123	4.09E-06
AL121899.1	1.937475269	8.8433E-09	1.373386471	0.017307
CXCL17	2.044302655	8.90304E-09	1.246143153	0.055858
SGTB	0.940957882	9.13199E-09	0.99404643	0.00178

SEC14L1	0.698328962	9.14938E-09	0.903206475	0.000123
AL365203.2	1.464813033	9.33136E-09	0.409116487	0.352138
TRERF1	1.132415591	9.33136E-09	1.173065918	0.003784
DLG3	1.56392322	9.63995E-09	0.409637354	0.388872
SOD3	1.917395139	9.65966E-09	3.788794057	1.09E-09
ATP13A3	0.791616725	9.77475E-09	0.94096314	0.00079
S100A12	2.304662814	1.05967E-08	4.309204668	3.58E-08
COG3	0.860713944	1.08742E-08	0.372659073	0.036729
CTSL	0.785864961	1.13496E-08	0.821113543	0.015446
ADAMDEC1	1.368128368	1.15019E-08	1.047560202	0.08341
AP002008.2	-1.022292902	1.17494E-08	-0.26942819	0.503312
KIAA1551	0.7876675	1.18377E-08	0.395721879	0.267903

e-Table 1B. IPF6 genelist

gene	log2FC_vsotherIPF	p_vsotherIPF	log2FC_vsCTRL	p_vsCTRL
TNNI3K	3.309055	2.19E-42	2.195866	0.003706558
LINC01634	3.754876	3.46E-33	3.074595	0.001915418
FAM74A1	4.827657	5.1E-33	4.746859	3.78105E-09
AC137056.2	5.261797	4.29E-32	4.807171	2.74329E-05
DMP1	4.459153	1.43E-31	4.084708	3.63591E-08
AF067845.2	4.488181	2.99E-31	4.368217	1.14322E-06
OR4C13	3.0583	5.71E-30	2.732278	9.97308E-08
WNT8B	4.054472	7.43E-30	4.960717	2.49701E-06
OR6C6	2.728572	1.18E-29	2.538955	2.26958E-06
F9	4.305366	1.21E-29	4.541746	3.92386E-07
COL5A3	4.807838	8.85E-29	9.040208	7.27185E-11
CHRNB4	5.287316	1.83E-28	5.002354	1.95214E-07
SPEM2	4.538063	3.18E-28	4.61836	1.54759E-09
GNG3	4.881592	3.48E-28	4.901991	8.27501E-08
CDRT15	5.405081	5.61E-28	7.058584	0.002696734
OR4M1	4.857521	6.52E-28	5.605997	0.001303892
OR8B12	4.559598	8E-28	3.938363	7.51389E-05
TEX19	3.839366	8.65E-28	3.40329	0.006060828
OR13G1	4.388705	1.12E-27	5.716974	0.018544901
SLC24A5	6.352506	1.22E-27	8.105198	0.000515041
SHC3	3.207982	1.23E-27	5.052043	6.9509E-07
TNP1	5.788802	1.23E-27	8.091707	8.38005E-07
AC005176.1	3.715207	1.28E-27	3.641582	7.07622E-08
AC073188.5	4.060352	1.28E-27	3.968535	1.21399E-06
OR10A7	6.304946	1.28E-27	8.624804	0.001017198
GLYATL2	4.349545	1.48E-27	4.44266	6.79206E-08
PLA2G12B	5.78242	2.57E-27	5.432083	1.21749E-07
AC022784.6	5.524807	3.09E-27	8.789274	2.22699E-08
SORCS2	5.973615	3.09E-27	7.100803	0.007141834
OR1L1	5.068113	3.12E-27	9.313846	2.03471E-10
OR4S2	4.299681	3.12E-27	4.223462	1.81363E-07
SPDYA	4.869751	3.22E-27	4.860935	8.70145E-06
RNF180	5.850338	3.96E-27	9.510875	1.0241E-07
BSND	4.437584	4.15E-27	4.318167	2.54683E-06
ITIH3	5.291263	5.32E-27	5.483896	2.26294E-09
ADD2	6.239581	5.52E-27	9.833211	8.84769E-10
Z92544.1	5.876524	5.96E-27	5.632307	1.39392E-07
PDHA2	3.482258	6.94E-27	2.058576	0.121277391

KAAG1	3.62643	9.85E-27	5.867586	4.34255E-06
SLC12A3	4.698208	1.2E-26	3.994373	3.17766E-07
UST-AS1	3.797722	1.37E-26	5.113837	3.83859E-08
TRIM17	4.056187	1.47E-26	3.707387	4.24407E-07
FAM74A3	5.39815	1.54E-26	5.417668	5.25999E-09
CDH4	5.861094	1.76E-26	9.016127	0.000466854
FGF17	5.009488	2.12E-26	5.217181	1.1213E-09
OR52H1	2.414848	2.2E-26	2.579206	1.01333E-06
OR2A12	5.844014	2.57E-26	7.932956	4.33987E-05
INSC	5.246164	2.81E-26	7.275634	0.000836331
AC237221.2	4.733487	2.95E-26	5.177493	1.03227E-07
AMPD1	2.309743	4.38E-26	2.223143	1.71573E-07
LRRTM4	4.083497	4.38E-26	4.120739	2.02917E-09
SYT13	3.438089	4.45E-26	3.292234	1.87649E-06
PAPPA2	3.684027	5.91E-26	5.766621	0.000373886
DEFA11P	3.959025	7.89E-26	3.942363	5.48575E-06
KCNF1	4.526455	7.99E-26	4.478541	7.80102E-08
OR6S1	2.938434	7.99E-26	2.81382	1.21391E-05
MYH11	4.178099	8.07E-26	3.744223	0.000189598
TNN	6.447167	9.28E-26	8.854371	2.31625E-05
FMR1NB	4.812407	9.73E-26	5.115415	4.18753E-10
FAM71B	4.736256	1.1E-25	5.445687	0.000190291
ROS1	4.526442	1.17E-25	5.916418	3.08575E-05
AC062028.1	4.375694	1.24E-25	6.547016	2.94493E-05
LMOD3	3.701746	1.24E-25	3.485207	2.40606E-05
DDX4	3.435194	1.32E-25	6.519369	4.31861E-07
XAGE3	3.803881	1.32E-25	5.934458	1.94376E-07
C7ORF33	4.765964	1.54E-25	6.075515	0.061624568
AC010226.1	-2.43681	1.59E-25	-4.28102	1.12011E-06
GPM6A	2.737724	2E-25	2.975892	9.09634E-10
IL17B	4.402268	2.28E-25	5.027393	8.98195E-09
SOHLH1	5.123774	2.37E-25	6.658026	0.025594616
MFSD2B	5.772413	2.76E-25	5.373034	2.31836E-08
PCDHA13	3.444135	2.87E-25	3.080044	7.25253E-07
RBBP8NL	5.778809	3.69E-25	5.68895	8.27501E-08
PLA2G2F	5.493944	3.74E-25	8.170427	6.77737E-07
TMPPE	-2.31247	3.81E-25	-1.75944	3.73423E-05
OR2T4	3.980561	4.61E-25	3.671491	0.000308314
PNMA3	6.051716	4.68E-25	9.369736	4.50017E-07
ASB4	3.770733	4.72E-25	3.827434	4.13738E-08

PCDHA4	3.346388	5.44E-25	3.231354	3.88335E-08
ZCCHC12	4.024665	5.44E-25	4.2204	1.39557E-07
NID2	4.293139	5.66E-25	5.656029	0.003131091
TRIM40	5.150941	6.9E-25	4.991614	1.9787E-06
VWA5B2	4.767579	7.17E-25	5.01344	1.56812E-08
LINC00598	5.720817	7.98E-25	5.123054	1.22513E-07
CECR9	4.067329	8.16E-25	4.283028	2.20187E-07
CFAP99	3.496617	8.48E-25	3.399487	5.13524E-07
AC009501.1	3.950481	8.49E-25	4.237028	9.48333E-08
AC016924.1	5.035188	8.69E-25	9.20706	3.95388E-06
RNF227	5.469096	1.09E-24	5.793135	1.59176E-09
NRXN3	5.442192	1.12E-24	6.701633	0.001191169
TCF20	2.502178	1.12E-24	2.165074	2.82629E-08
LRRC4C	2.487945	1.27E-24	2.192854	0.001770909
OR4F6	2.881677	1.29E-24	2.821721	1.12187E-05
IL24	4.952453	1.29E-24	4.856997	3.63591E-08
MRGPRD	4.105758	1.34E-24	3.764158	0.00064491
KIF7	3.525428	1.35E-24	3.053125	2.7455E-06
KIF12	3.078851	1.48E-24	3.090366	4.82811E-06
MPPED2	5.2553	1.48E-24	5.302845	2.24813E-09
PDE3A	4.849614	1.66E-24	4.252027	7.80102E-08
CCNI2	4.970013	1.7E-24	3.504592	0.000316953
LSMEM2	5.658531	1.7E-24	8.832489	3.63591E-08
PDIA2	3.668504	1.92E-24	3.867773	6.81519E-07
AC093330.2	4.984044	2E-24	4.925356	4.60799E-10
MYO3B	3.381348	2E-24	3.179141	0.000310612
CEMP1	4.230197	2.26E-24	6.222864	0.000138961
CDKN2B	6.505937	2.37E-24	10.01968	1.2858E-08
EMID1	5.539719	2.37E-24	5.469249	1.55415E-09
SCAMP5	4.894847	2.48E-24	4.482607	1.78973E-07
SELENOV	4.927184	2.52E-24	4.984796	1.40251E-08
NBPF7	3.371469	2.62E-24	2.933216	5.30923E-05
XAGE2	6.091904	2.65E-24	9.986269	2.43629E-08
SPATA41	4.447894	3.21E-24	4.270349	7.28386E-07
BTNL9	4.827578	3.25E-24	4.773237	2.80667E-08
SDK1	6.210112	3.3E-24	8.55027	1.31747E-06
C3ORF85	5.390242	4.04E-24	4.727385	3.62171E-06
CYP39A1	4.797039	4.32E-24	4.787355	1.62346E-08
RALYL	5.733529	4.32E-24	5.627322	2.21477E-08
ANO7	5.677098	4.69E-24	4.867715	4.41523E-08

CD300LG	3.611178	4.73E-24	3.544759	1.61067E-06
DCDC1	5.479908	4.84E-24	5.149707	1.07739E-06
FTCD	5.353665	4.84E-24	4.589487	2.4201E-05
ITGB1BP2	4.732988	5.6E-24	4.378545	1.9476E-11
BX537318.2	2.668566	5.78E-24	2.671209	1.62346E-08
Z97634.1	5.239999	6.7E-24	4.843306	1.71825E-06
TBX4	3.56813	7.95E-24	7.02212	2.00289E-08
SPATA31E1	4.328491	8.57E-24	4.490691	9.26753E-08
MATN4	2.256815	8.77E-24	2.156963	4.46337E-05
OR10W1	5.541798	8.77E-24	5.633432	2.84872E-08
USP2	4.618551	8.94E-24	4.249781	2.18402E-06
HILS1	5.586975	1.01E-23	8.856831	1.60965E-07
LINC02171	3.325378	1.01E-23	6.345878	1.86585E-05
CSRNP3	5.085483	1.17E-23	4.977619	2.48141E-07
EXOC1	3.04842	1.26E-23	2.916171	7.4155E-08
HYALP1	5.168413	1.28E-23	4.972202	3.20558E-08
TNFRSF13B	4.04319	1.62E-23	5.641434	0.029210664
LINC00971	2.612994	1.8E-23	2.337352	0.000300891
OR56A5	6.062824	1.92E-23	9.735398	5.02118E-05
GCM2	6.866974	2.14E-23	8.442274	2.57341E-05
STS	4.614776	2.19E-23	3.118139	5.51407E-06
C2CD4B	5.2521	2.23E-23	4.943203	7.64772E-06
SELE	4.940159	2.27E-23	4.494022	2.69519E-07
GCNT4	4.622623	2.29E-23	8.598885	4.86504E-11
ZBTB48	2.738684	2.29E-23	1.999039	3.69568E-05
OR52E6	3.721695	2.62E-23	3.629616	8.50011E-06
HTR5A	4.242651	2.68E-23	4.216792	7.80102E-08
ALX1	6.465034	3.35E-23	9.938722	2.73062E-08
FGA	4.634556	3.56E-23	4.897747	9.21193E-08
MAP1B	5.271283	3.58E-23	6.656844	0.006741001
ZNF48	3.559277	4.41E-23	3.519169	4.63652E-06
MYL10	3.532575	4.96E-23	3.489844	3.10853E-08
OR6K6	3.966043	5.17E-23	4.317793	0.069249611
CALML6	4.585944	5.22E-23	4.640962	2.20187E-07
SLFNL1	3.523275	6.29E-23	3.128889	4.17695E-06
TOE1	3.021713	6.29E-23	2.477542	3.53637E-06
BBOX1	4.529758	6.35E-23	4.494148	8.36593E-08
NUTM1	4.382363	6.53E-23	7.46146	1.26887E-08
C19ORF71	5.516087	7.44E-23	5.368758	3.22716E-07
LAMB4	3.625147	7.44E-23	3.29287	1.85629E-06

RLN3	4.097714	7.44E-23	4.357897	3.77653E-08
CCDC189	-2.32311	7.81E-23	-2.74874	2.72383E-06
C22ORF23	4.81736	8.83E-23	4.744797	2.00104E-07
OR4C6	5.55388	9.56E-23	8.267545	0.000114318
MAGEB4	4.52977	1.04E-22	4.618874	9.49093E-08
OR5J2	5.75724	1.06E-22	9.202586	4.29266E-07
SLC5A5	3.988342	1.11E-22	3.459674	2.00104E-07
NTSR2	3.787244	1.11E-22	3.665672	1.68955E-05
LCN8	3.333459	1.16E-22	3.238319	0.000382788
TNR	4.306581	1.16E-22	4.6607	8.98195E-09
KLHL22	3.64878	1.26E-22	3.223207	6.02741E-06
SCG2	4.96154	1.29E-22	5.348755	4.03935E-07
LACTB2-AS1	3.481737	1.35E-22	3.595701	9.27726E-08
LINC01743	4.252543	1.57E-22	6.539719	9.09033E-08
LCE3E	4.729466	1.65E-22	4.65783	1.81363E-07
BARHL2	6.596443	1.68E-22	7.761448	0.011452592
LDB2	5.247172	1.74E-22	4.606907	3.74861E-07
ANKRD33B	5.112393	1.8E-22	7.605416	0.000180149
DRD4	3.165614	1.83E-22	2.38418	0.000106685
HGC6.3	2.586275	1.83E-22	2.262589	2.23131E-05
CLTC	5.625877	1.88E-22	5.65389	2.03471E-10
RNF113B	4.780895	1.94E-22	4.372588	1.11536E-07
LINC01973	6.192406	2.08E-22	6.551863	1.19935E-09
CNGB3	4.264815	2.24E-22	4.297444	1.67359E-08
KLK15	3.174821	2.44E-22	2.750889	0.000169574
C1QL1	4.267697	2.44E-22	6.401944	2.45074E-05
PDE6C	5.582122	2.46E-22	5.642657	3.21667E-08
SLCO1A2	3.235197	2.49E-22	7.085889	7.05598E-05
HIGD1B	3.219004	2.54E-22	3.307576	2.66005E-07
SV2B	4.742142	2.54E-22	4.957732	0.022041797
MBP	2.298723	2.59E-22	2.223262	6.26472E-09
CRYBB3	3.749109	2.63E-22	4.033579	2.24813E-09
SPACA5	5.115985	2.64E-22	5.016354	1.47757E-08
HOXD10	3.010447	2.7E-22	3.092165	7.51366E-09
OR2D3	4.501495	2.7E-22	6.975869	7.65402E-05
COL4A1	4.382664	2.74E-22	4.290525	2.50044E-07
SLC6A13	4.704843	2.97E-22	6.827042	0.001637769
ODAM	5.317124	3.07E-22	6.842158	2.00916E-05
MSH4	3.42858	3.09E-22	3.512265	1.41988E-07
MPPED1	5.639335	3.26E-22	8.179837	5.7957E-07

FZD9	4.34636	3.38E-22	4.620432	9.0357E-07
MMP11	4.142391	3.38E-22	4.307944	6.26472E-09
AC020658.3	3.59907	3.72E-22	3.541569	6.70464E-07
OR1F1	4.65432	3.72E-22	8.568967	1.68784E-08
SYT12	4.589036	3.79E-22	6.957909	1.93226E-06
KLK12	4.395881	3.87E-22	4.399147	1.07635E-05
SPON1	2.867066	3.87E-22	2.600879	0.000189598
SPDYE10P	5.652196	4.66E-22	4.832247	8.96769E-05
CATIP	4.120839	4.71E-22	3.73857	9.4689E-07
NGFR	4.253235	4.98E-22	4.240549	2.15139E-06
KBTBD12	2.588397	5.38E-22	2.714808	2.46542E-06
ARID3C	4.685453	5.4E-22	4.224641	5.74034E-06
PRPF40B	4.88326	5.52E-22	3.839745	8.02752E-06
SYNJ2	4.0003	6.56E-22	4.397552	3.77232E-08
KLK13	2.751315	6.59E-22	4.604931	0.000171854
NACAD	4.454435	6.72E-22	4.75357	1.30046E-08
GIF	2.236739	6.73E-22	2.355965	0.000192554
FAM196B	5.095278	6.74E-22	4.763916	3.44774E-05
PRKG1	4.075267	6.74E-22	3.774128	8.91407E-07
TEX44	4.148377	7.13E-22	4.196909	7.33057E-07
STEAP2	4.690012	7.4E-22	6.039026	2.03471E-10
MXRA8	5.626762	8.94E-22	7.893579	0.000371049
FAM19A4	2.513692	9.26E-22	2.146218	0.01567814
SF3B2	3.195258	9.43E-22	4.81532	3.71534E-05
TMEM262	5.432639	1E-21	8.078686	1.34027E-06
FAM182B	3.735411	1.01E-21	7.632326	9.32362E-09
DHX9	2.447842	1.1E-21	1.995016	0.000164843
GABRG3	2.670492	1.17E-21	2.645917	9.17721E-09
KLK14	3.733415	1.17E-21	3.446244	0.000220804
TNNT2	5.635796	1.17E-21	7.799948	0.000189715
LCE3A	4.202039	1.23E-21	4.176049	3.8712E-06
CRB2	4.047783	1.25E-21	7.836363	6.25747E-08
TCTE3	4.563037	1.3E-21	4.991095	0.028521412
C1QL2	4.466361	1.32E-21	7.702334	1.22247E-06
AL592486.1	4.06271	1.37E-21	5.742533	0.00017781
OR7E13P	-2.68141	1.37E-21	-2.43161	2.60656E-07
PHLDB3	3.988574	1.37E-21	3.398733	3.5085E-06
CCDC42	4.448991	1.39E-21	4.212491	2.60656E-07
OR52E4	4.914892	1.5E-21	4.086896	7.64772E-06
OR6X1	4.186322	1.5E-21	3.885308	1.04842E-06

NOP53-AS1	3.944027	1.5E-21	3.637742	7.667E-05
OR2AK2	3.223659	1.76E-21	7.639967	1.90589E-06
CCDC62	4.055868	1.8E-21	3.863257	3.17536E-08
MUC22	5.016502	1.94E-21	4.785027	2.79467E-06
CCDC185	2.85958	1.94E-21	2.83405	3.44752E-05
OR2A5	4.903388	1.95E-21	4.236738	1.63457E-07
TUBAL3	4.194628	2.04E-21	5.980369	0.002139024
TBX2	4.842344	2.32E-21	7.671264	1.05514E-07
GRXCR2	3.539469	2.33E-21	5.109928	0.001748903
WNT9A	2.754719	2.39E-21	3.00964	3.49668E-06
BEND7	5.144959	2.4E-21	5.454834	8.86968E-09
OR1J2	3.880935	2.46E-21	3.742323	2.77776E-05

e-Table 2. Gos

GO	p_value_overall	log2FC_IPF1vsCTRL	log2FC_IPF2vsCTRL	log2FC_IPF3vsCTRL	log2FC_IPF4vsCTRL	log2FC_IPF5vsCTRL	log2FC_IPF6vsCTRL
hsa04740 Olfactory transduction	3.6373E-33	3.27444985	1.03131523	0.53076294	2.57065175	-0.5546165	5.91201833
GO:0050906 detection of stimulus involved in sensory perception	3.6373E-33	2.96044574	0.81574636	0.27616392	2.35476237	-0.7450311	5.79748593
GO:0050907 detection of chemical stimulus involved in sensory perception	1.0955E-32	2.97887009	0.81435841	0.27961358	2.34698241	-0.7891476	5.71279375
GO:0050911 detection of chemical stimulus involved in sensory perception of smell	1.1509E-32	3.19742124	0.94819348	0.4691796	2.52652828	-0.5921539	5.98315788
GO:0004984 olfactory receptor activity	1.1509E-32	3.19742124	0.94819348	0.4691796	2.52652828	-0.5921539	5.98315788
GO:1903426 regulation of reactive oxygen species biosynthetic process	2.4131E-32	-0.8749586	-0.0552645	0.3057823	-0.103618	1.33197653	-0.5197552
GO:0007608 sensory perception of smell	3.102E-32	3.03447033	0.90991143	0.46742203	2.34712924	-0.6541062	5.75359332
GO:0009593 detection of chemical stimulus	9.0355E-32	2.90813132	0.78691981	0.28435711	2.28419234	-0.6230597	5.68666314
GO:0007606 sensory perception of chemical stimulus	3.8371E-31	2.81329944	0.80190226	0.27896977	2.18966697	-0.8274441	5.3709968
GO:1903409 reactive oxygen species biosynthetic process	1.6149E-29	-0.7927143	0.01267347	0.36582987	-0.0140985	1.42888621	-0.4643572
GO:0071260 cellular response to mechanical stimulus	1.3046E-28	-0.5991068	0.32893573	0.52242427	-0.0087694	1.04919553	-1.0986789
GO:2000377 regulation of reactive oxygen species metabolic process	8.1731E-28	-0.5746727	0.24170686	0.69689372	0.24232963	1.61920092	-0.2029549
GO:0044088 regulation of vacuole organization	1.459E-26	-0.5337487	-0.0205525	-0.0417547	-0.5547235	0.26592276	-1.4020176
GO:0051092 positive regulation of NF-kappaB transcription factor activity	2.4308E-26	-1.5137303	-0.6836103	-0.2348634	-1.0594069	0.6354895	-1.2822126
GO:0036473 cell death in response to oxidative stress	3.2655E-26	-0.7046779	0.26945457	0.58935641	-0.1249699	1.25384239	-0.798477
GO:1903201 regulation of oxidative stress-induced cell death	4.452E-26	-0.7076158	0.18695554	0.49351362	-0.2477608	1.13569248	-0.7571581
GO:0042058 regulation of epidermal growth factor receptor signaling pathway	1.5056E-25	-1.1846222	-0.4773659	-0.2659388	-0.445264	0.2199432	-1.4231495
GO:0022408 negative regulation of cell-cell adhesion	1.5932E-25	-1.4468312	-0.9396959	-0.2979539	-0.5293467	0.73144153	0.0534864
GO:1902882 regulation of response to oxidative stress	6.9077E-25	-0.449169	0.30407676	0.6895123	-0.0400073	1.35587164	-0.5071365

GO:0005549 odorant binding	7.4435E-25	1.49120986	0.40962891	0.37683587	1.35592408	-0.0561853	3.1613402
GO:0045446 endothelial cell differentiation	1.2059E-24	-0.6223433	0.20756243	0.40920927	0.1244281	1.34348733	-0.4973147
GO:1901184 regulation of ERBB signaling pathway	1.4582E-24	-1.0736772	-0.3826056	-0.1598822	-0.2907696	0.38875867	-1.2164143
GO:0007173 epidermal growth factor receptor signaling pathway	1.4952E-24	-1.2918887	-0.565112	-0.2137964	-0.2526961	0.49120955	-1.1909331
GO:0003158 endothelium development	1.9649E-24	-0.5131796	0.29270765	0.57212127	0.277348	1.39339773	-0.3525455
GO:0042542 response to hydrogen peroxide	4.2818E-24	-0.6082812	0.16556316	0.33951187	0.25745555	1.12795654	-1.0002007
GO:0035092 sperm chromatin condensation	1.051E-23	1.1629541	0.14765052	0.1028935	0.78991588	-0.0988515	1.73042535
GO:0001933 negative regulation of protein phosphorylation	1.0595E-23	-0.4598052	0.18083533	0.64018592	0.51220986	1.44476806	-0.7026908
GO:0003407 neural retina development	1.2405E-23	1.05492234	-0.0580793	0.00237802	0.87086129	-0.1458348	1.59178867
GO:0031647 regulation of protein stability	1.5848E-23	-1.1981366	-0.1527519	-0.0894087	-0.6086797	0.3704941	-1.7507685
GO:0031996 thioesterase binding	2.0146E-23	-1.0388266	-0.3451841	-0.2101741	-0.438669	0.4099327	-0.6586629
GO:0009141 nucleoside triphosphate metabolic process	2.0904E-23	-0.026543	0.97521714	0.61320191	-0.0076228	0.46070954	-1.4940127
GO:0030016 myofibril	2.4639E-23	0.62802898	-0.093602	-0.0226488	0.55868681	0.04160497	1.99190505
GO:0005261 cation channel activity	3.0104E-23	1.33150113	0.43844379	0.23614224	1.08729843	-0.1590996	2.38360869
GO:1900407 regulation of cellular response to oxidative stress	3.0939E-23	-0.5015906	0.27892871	0.65618087	-0.0221099	1.3474228	-0.5273246
GO:0022839 ion gated channel activity	4.802E-23	1.16813229	0.22097028	0.04961128	0.87124958	-0.4485365	2.42296375
GO:2000379 positive regulation of reactive oxygen species metabolic process	7.988E-23	-0.5714367	0.0746464	0.44161409	0.1389514	1.36108861	-0.0932007
GO:0009144 purine nucleoside triphosphate metabolic process	8.3964E-23	0.04961772	0.9461697	0.56576091	0.00799179	0.35451317	-1.4397408
GO:0032637 interleukin-8 production	9.2263E-23	-0.5618486	0.2292727	0.36945505	-0.4262013	1.09002288	-0.4078369
GO:0060042 retina morphogenesis in camera-type eye	1.121E-22	0.96601705	-0.0834025	-0.0007016	0.81617494	0.00054742	1.53748769
GO:0099699 integral component of synaptic membrane	1.2365E-22	1.45876194	0.4464781	0.27923224	1.14372058	-0.0552766	2.59702201
GO:0030017 sarcomere	2.2862E-22	0.90557587	0.06273404	0.04556402	0.78514745	0.06644863	2.11275748
GO:0035579 specific granule membrane	3.1536E-22	-0.7063578	0.17390252	0.63509316	0.09037238	1.38600789	-1.356905
GO:0009205 purine ribonucleoside triphosphate metabolic process	3.3594E-22	0.04266906	0.91103288	0.52643416	-0.0010534	0.30286967	-1.4156386
GO:0042326 negative regulation of phosphorylation	3.8588E-22	-0.4196734	0.23050026	0.65853854	0.50666863	1.40691866	-0.7394691

GO:0002444 myeloid leukocyte mediated immunity	4.0971E-22	-1.1120592	0.39155767	0.83376209	0.15098695	2.15940507	-2.5239496
GO:0022836 gated channel activity	4.0971E-22	1.08697384	0.16970808	0.03006473	0.85717286	-0.4234791	2.37444377
GO:0051272 positive regulation of cellular component movement	4.4641E-22	-0.7370745	-0.0981887	0.54165394	0.4356933	1.92930818	0.20685845
GO:0030335 positive regulation of cell migration	4.5417E-22	-0.6728103	-0.0409013	0.60545078	0.56106224	1.96879355	0.18685293
GO:0043292 contractile fiber	5.1295E-22	0.58307377	-0.135431	-0.0242969	0.50525125	0.06454289	2.00951563
GO:0048194 Golgi vesicle budding	6.4611E-22	-0.6609296	0.0900514	0.06763283	-0.5639253	0.03700387	-1.8050349
GO:0042059 negative regulation of epidermal growth factor receptor signaling pathway	7.163E-22	-1.0111624	-0.1679311	-0.1415418	-0.4182376	0.28444465	-1.4782244
GO:0009199 ribonucleoside triphosphate metabolic process	9.1261E-22	0.04376168	0.9375473	0.58329385	0.02431032	0.36114374	-1.3967456
GO:0072593 reactive oxygen species metabolic process	1.048E-21	-0.3953914	0.38186408	0.75269813	0.52797227	1.96172566	-0.0206836
GO:0002446 neutrophil mediated immunity	1.0721E-21	-1.0778746	0.3461683	0.81210564	0.09392905	2.10597449	-2.5507299
GO:0004935 adrenergic receptor activity	1.0721E-21	0.96993771	-0.0194157	0.06073602	1.10392085	0.11017779	2.32183214
GO:2000147 positive regulation of cell motility	1.1159E-21	-0.6703032	-0.0710469	0.57370042	0.52610626	1.95548126	0.22876595
GO:0005865 striated muscle thin filament	1.1494E-21	0.3225155	-0.5778394	-0.5005958	0.02414047	-0.7085667	2.04636152
GO:0101003 ficolin-1-rich granule membrane	1.3454E-21	-1.0743463	-0.2858784	-0.1331629	-0.3505705	0.80247155	-1.3579024
GO:1901185 negative regulation of ERBB signaling pathway	1.515E-21	-0.8901875	-0.1272713	-0.0455217	-0.2604072	0.4669159	-1.1873442
GO:0021903 rostrocaudal neural tube patterning	1.5414E-21	0.80650333	0.03666737	-0.0550443	0.75239234	-0.0544649	1.31754971
GO:0005216 ion channel activity	1.5556E-21	1.02972596	0.09889636	0.03479262	0.93196762	-0.2843222	2.54186168
GO:0034599 cellular response to oxidative stress	1.7531E-21	-0.7303224	0.32578819	0.56749223	-0.1100642	1.06630594	-1.1762644
GO:0044449 contractile fiber part	1.8625E-21	0.81897351	-0.0282876	0.00011141	0.70151384	0.06050974	2.11588522
GO:0002726 positive regulation of T cell cytokine production	2.064E-21	-1.342569	-0.536378	-0.1752242	-0.9498224	0.7128181	-0.6215331
GO:0055002 striated muscle cell development	2.5158E-21	0.83422158	-0.1194343	0.07166295	0.70148684	0.20195719	1.97681064
GO:0022838 substrate-specific channel activity	3.0385E-21	1.13804969	0.22084546	0.16908164	1.02644841	-0.1946228	2.65488749
GO:0008631 intrinsic apoptotic signaling pathway in response to oxidative stress	3.0875E-21	-0.4088619	0.19941033	0.44021292	0.08854337	0.87880287	-0.6421392
GO:0030239 myofibril assembly	3.2642E-21	0.6932056	-0.1581597	-0.0393904	0.58807204	0.04180328	2.05650839
GO:0032482 Rab protein signal transduction	3.2851E-21	-1.240762	-0.4991299	-0.3897282	-0.7093475	0.17481615	-1.7600133

GO:0002275 myeloid cell activation involved in immune response	3.4787E-21	-1.113057	0.30432182	0.76369356	0.10020666	2.0460939	-2.4885474
GO:0040017 positive regulation of locomotion	3.4977E-21	-0.7030173	-0.0463725	0.55049359	0.41457146	1.88887163	0.15050321
GO:0015267 channel activity	3.6728E-21	1.17437273	0.23528167	0.22851498	1.06590504	-0.106882	2.7770274
GO:0022803 passive transmembrane transporter activity	3.7786E-21	1.17967946	0.2363128	0.22551315	1.07841163	-0.1068222	2.76860298
GO:0042119 neutrophil activation	4.0905E-21	-1.0407116	0.32754365	0.81121026	0.16564674	2.16610987	-2.4395564
GO:0036379 myofilament	4.4475E-21	0.25515772	-0.58412	-0.5097099	-0.0254663	-0.7006984	1.89070527
GO:1903579 negative regulation of ATP metabolic process	4.5015E-21	-0.1746559	0.46530609	0.63909738	0.08865767	0.79911042	-0.832735
GO:0035116 embryonic hindlimb morphogenesis	4.5015E-21	1.115378	0.129905	0.04173063	0.88221139	-0.1701152	1.31467208
GO:0042481 regulation of odontogenesis	4.5788E-21	0.77751416	-0.0657273	0.056731	1.0690056	0.02301951	1.5852261
GO:0009167 purine ribonucleoside monophosphate metabolic process	4.7935E-21	0.12821905	1.06208152	0.66126268	0.04276545	0.39648949	-1.2041135
GO:0009636 response to toxic substance	6.1705E-21	-0.0776345	0.50943128	0.89773029	0.92732828	1.92982915	0.37932346
GO:0043312 neutrophil degranulation	6.206E-21	-1.030629	0.32804743	0.76492248	0.11412218	2.06362564	-2.5946223
GO:0035136 forelimb morphogenesis	7.1007E-21	1.69929418	0.59068006	0.36547016	1.32579009	0.0906962	1.72475089
GO:0046677 response to antibiotic	7.1007E-21	-0.4076884	0.18399708	0.51433652	0.42342689	1.23175603	-0.1396374
GO:0035137 hindlimb morphogenesis	7.555E-21	1.27760583	0.25220115	0.11721382	0.89246512	-0.1304321	1.44705614
GO:0036230 granulocyte activation	7.555E-21	-1.0694854	0.27988384	0.77652687	0.11073307	2.13442226	-2.4555673
GO:0002283 neutrophil activation involved in immune response	7.555E-21	-1.0433373	0.31983247	0.77119532	0.10538637	2.0509745	-2.5333137
GO:0072657 protein localization to membrane	8.8597E-21	-1.335161	-0.2702954	-0.1838789	-0.4566604	0.50961393	-1.4092852
GO:0034614 cellular response to reactive oxygen species	8.9041E-21	-0.3677036	0.34972231	0.55368411	0.22145318	1.12218407	-0.7732064
GO:0046034 ATP metabolic process	9.4255E-21	0.16432116	1.06145422	0.70539445	0.10840541	0.43862409	-1.1862954
GO:0055001 muscle cell development	1.1165E-20	0.89820121	-0.0788384	0.14026888	0.76685604	0.29336209	2.02719604
GO:0032757 positive regulation of interleukin-8 production	1.1165E-20	-0.5371044	0.26372629	0.3158774	-0.3113481	0.90652832	-0.5568197
GO:0035115 embryonic forelimb morphogenesis	1.1526E-20	1.52759614	0.46980953	0.26486503	1.2167647	-0.0516112	1.59883316
GO:0043299 leukocyte degranulation	1.2456E-20	-0.9879777	0.41727336	0.83391472	0.22236893	2.13448614	-2.4645389
GO:0031400 negative regulation of protein modification process	1.2549E-20	-0.4058432	0.33620341	0.59880988	0.46959475	1.15737709	-1.3082248

GO:0101002 ficolin-1-rich granule	1.2577E-20	-0.7530963	0.35577427	0.47364554	0.06825903	1.25669995	-1.7748873
GO:0009161 ribonucleoside monophosphate metabolic process	1.4772E-20	0.11521969	1.11014415	0.73086617	0.04179027	0.46242539	-1.2459299
GO:0019866 organelle inner membrane	1.504E-20	0.18369871	1.72746782	1.03580767	0.31030739	0.82698651	-2.0004551
GO:0051098 regulation of binding	1.8304E-20	-1.2040534	-0.4098141	-0.1394137	-0.3451685	0.38390695	-1.1807067
GO:0006979 response to oxidative stress	1.9545E-20	-0.604749	0.33716521	0.55415732	0.13487313	1.25372251	-1.0078413
GO:2000058 regulation of ubiquitin-dependent protein catabolic process	2.0697E-20	-0.8621327	-0.0857728	-0.1187996	-0.671758	0.04996576	-1.7933368
GO:0002367 cytokine production involved in immune response	2.1717E-20	-1.0250887	-0.0196942	0.3034632	-0.202174	1.46578365	-0.5264424
GO:0006643 membrane lipid metabolic process	2.5301E-20	-0.2085571	0.53329921	0.5891687	0.05291189	0.63124462	-1.6335108
GO:0010256 endomembrane system organization	2.6694E-20	-1.3760029	-0.3124172	-0.2528149	-0.8482126	0.23064799	-2.3939033
GO:0070820 tertiary granule	2.6765E-20	-0.3749431	0.50183884	0.73726691	0.30640885	1.63638997	-1.4733244
GO:0002043 blood vessel endothelial cell proliferation involved in sprouting angiogenesis	3.4009E-20	0.59214858	-0.0731181	0.08320241	1.07424286	0.6491677	1.89264884
GO:0099240 intrinsic component of synaptic membrane	3.8491E-20	1.35296542	0.42113222	0.27617386	1.07073249	-0.0868154	2.43739345
GO:0032507 maintenance of protein location in cell	4.4537E-20	-0.6352787	0.05123232	0.00706157	-0.4157828	0.14378787	-1.4782827
GO:1902175 regulation of oxidative stress-induced intrinsic apoptotic signaling pathway	4.7997E-20	-0.3543143	0.13256448	0.3547281	-0.0119239	0.72011762	-0.55916
GO:0009126 purine nucleoside monophosphate metabolic process	4.946E-20	0.1527245	1.05993771	0.65459911	0.05681006	0.40001512	-1.1371191
GO:0071216 cellular response to biotic stimulus	5.61E-20	-0.9253439	-0.0380547	0.45347292	-0.0432362	1.41970035	-0.4486518
GO:0032677 regulation of interleukin-8 production	5.9251E-20	-0.4264552	0.30090412	0.3372122	-0.3917891	0.95629984	-0.50575
GO:1901338 catecholamine binding	5.9251E-20	0.77522919	-0.0761125	0.00692187	0.77486593	0.01487294	2.05076893
GO:0098936 intrinsic component of postsynaptic membrane	5.977E-20	1.22469355	0.30756221	0.23458345	0.96085059	-0.0581958	2.42891381
GO:0070821 tertiary granule membrane	8.5968E-20	-0.5232824	0.21884053	0.53066455	0.09200231	1.34187517	-1.0824757
GO:0090114 COPII-coated vesicle budding	8.7834E-20	-0.6005302	0.07672278	0.0704787	-0.5287344	0.08293848	-1.6111628
GO:0016925 protein sumoylation	9.5646E-20	-0.3819551	0.02484099	-0.1498361	-0.3851698	-0.1096903	-1.4730554
GO:0099055 integral component of postsynaptic membrane	9.7176E-20	1.21874085	0.29281989	0.22319159	0.94313465	-0.0533156	2.41534901

GO:0007338 single fertilization	1.2852E-19	1.33859881	0.45802043	0.38047702	0.88973406	-0.0171537	1.50821597
GO:0060491 regulation of cell projection assembly	1.4514E-19	-1.113879	-0.3249336	-0.0774243	-0.218848	0.38118264	-1.380183
GO:0018205 peptidyl-lysine modification	1.6135E-19	-1.1874084	-0.0922233	-0.2523318	-0.9781695	-0.1612907	-2.2988705
GO:2000060 positive regulation of ubiquitin-dependent protein catabolic process	1.6281E-19	-0.8044513	-0.1847758	-0.0796628	-0.566514	0.16679122	-1.3551559
GO:0022843 voltage-gated cation channel activity	1.6667E-19	1.51669259	0.60399766	0.33853615	1.07723202	-0.1269236	1.85120282
GO:0120032 regulation of plasma membrane bounded cell projection assembly	1.9757E-19	-1.0958567	-0.3133489	-0.0612724	-0.1914672	0.39590598	-1.3666919
GO:0043161 proteasome-mediated ubiquitin-dependent protein catabolic process	2.1826E-19	-1.0429576	0.14753335	0.06105712	-0.7911516	0.39608734	-2.4088245
GO:0050821 protein stabilization	2.2213E-19	-1.1522494	-0.2588618	-0.3369702	-0.7780947	0.11434988	-1.7671694
GO:0042581 specific granule	2.2213E-19	-0.788634	0.09920565	0.62950216	0.08318902	1.72234295	-1.5051651
GO:0072606 interleukin-8 secretion	2.984E-19	-0.3662309	0.20918899	0.53891235	0.27410455	1.3773989	0.20101587
GO:0017112 Rab guanyl-nucleotide exchange factor activity	3.1758E-19	-0.4880255	0.01880894	0.02109532	-0.524245	-0.0481789	-1.6663707
GO:0030049 muscle filament sliding	3.5174E-19	0.23653122	-0.4993708	-0.5608933	0.10368201	-0.5236338	1.62662018
GO:0033275 actin-myosin filament sliding	3.5174E-19	0.23653122	-0.4993708	-0.5608933	0.10368201	-0.5236338	1.62662018
GO:0010563 negative regulation of phosphorus metabolic process	3.721E-19	-0.4540733	0.18857663	0.60495593	0.45152596	1.31342498	-0.7438789
GO:0045936 negative regulation of phosphate metabolic process	3.8349E-19	-0.4496924	0.18966768	0.6084251	0.45262186	1.31729428	-0.7352245
GO:0002698 negative regulation of immune effector process	3.8512E-19	-1.3734216	-0.6556732	-0.3228936	-0.8673419	0.34328247	-1.2484212
GO:0006998 nuclear envelope organization	4.138E-19	-0.0959044	0.60989677	0.58377175	-0.0684456	0.58736216	-1.1402662
GO:2000117 negative regulation of cysteine-type endopeptidase activity	4.1412E-19	-0.3082876	0.36066339	0.56013262	0.48512554	1.42873568	-0.4315658
GO:1901222 regulation of NIK/NF-kappaB signaling	4.1412E-19	-1.1022255	-0.5466895	-0.0553914	-0.6387667	0.73142802	-0.7418822
hsa04120 Ubiquitin mediated proteolysis	5.1062E-19	-1.3942969	-0.2530119	-0.1901625	-0.9253124	0.04334139	-2.4382601
GO:0001818 negative regulation of cytokine production	5.6607E-19	-1.4855358	-0.3883073	-0.0716085	-0.5669094	0.97799872	-1.4056434
GO:0043393 regulation of protein binding	5.9563E-19	-1.1308446	-0.5633478	-0.0681672	-0.2629901	0.33326686	-0.7894242
GO:0022407 regulation of cell-cell adhesion	5.9563E-19	-2.216449	-1.4680914	-0.7065496	-1.0300326	0.96272559	-0.2889747

GO:0006903 vesicle targeting	6.4311E-19	-0.5912051	0.072761	0.01733269	-0.5572471	0.08297174	-1.7595064
GO:0005743 mitochondrial inner membrane	6.4311E-19	0.33323023	1.8588876	1.13869181	0.34797523	0.77292801	-1.9625983
GO:1903362 regulation of cellular protein catabolic process	6.5487E-19	-0.8594031	-0.0574513	0.03905992	-0.616529	0.23226304	-2.0305728
GO:0071219 cellular response to molecule of bacterial origin	6.8936E-19	-0.8746555	-0.072836	0.43319057	0.04392286	1.49563431	-0.2819505
GO:0016050 vesicle organization	6.9744E-19	-1.3943303	-0.4293502	-0.4041337	-1.0916535	-0.0282857	-2.3862837
GO:0042487 regulation of odontogenesis of dentin-containing tooth	7.0605E-19	0.44932897	-0.2140912	-0.069144	0.76547524	0.13756736	1.46362009
GO:0071625 vocalization behavior	7.2658E-19	0.49154397	-0.3361878	-0.054491	0.80040476	0.12470437	1.4936639
GO:0033674 positive regulation of kinase activity	7.2888E-19	-0.6396866	-0.1047251	0.33207581	-0.0364573	1.39055425	-0.1511876
GO:0019058 viral life cycle	7.7549E-19	-1.079988	-0.3464561	-0.0424177	-0.6151502	0.57291679	-2.0436552
GO:0071222 cellular response to lipopolysaccharide	9.1831E-19	-0.9637683	-0.1379568	0.32673757	0.01360569	1.39754534	-0.3018441