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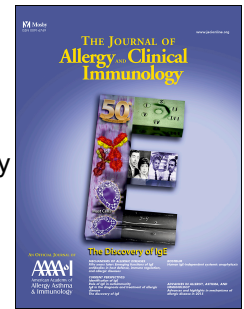
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Transcriptional determinants of individualized inflammatory responses at anatomically separate sites

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Competing financial interests

The authors have declared that no conflict of interest exists.

Author Contributions

L.C.T. and J.E.G. conceived and designed the study. J.E.G., A.A., J.H.K., J.J.V., and J.T.E. contributed to sample collection and phenotyping. Y.L., M.K.S., X.X., M.A.B., S.G. contributed to the *in vitro* or *in vivo* RNA-seq or qrt-PCR experiments. L.C.T. and J.Y. conducted the statistical analysis of the study. L.C.T. and K.R. conducted the Bioinformatics analysis. J.E.G., J.J.V., J.T.E., J.M.K., S.G., L.C.T. and J.H.K. contributed to the clinical and biological inferences for the experimental results.

Capsule Summary

We demonstrate how genes with individualized expression pattern have skin-specificity, are targets for cis-regulatory elements, and can explain transcriptional variation across individuals to a higher degree than psoriasis susceptibility loci. We also showed that IE genes can modulate cytokine responses in keratinocytes.

Key words

inflammatory diseases; RNA-seq; transcriptome; anatomically separate sites; bioinformatics; genomics; psoriasis

To the Editor:

A notable feature of many inflammatory conditions is the wide variation in treatment responses to targeted therapeutics. Intriguingly, anatomically separate lesions often subside at similar rate in responders, while in non-responders the lack of clinical improvement is consistent at most if not all sites of inflammation. The identification and characterization of processes that shape the individualized inflammatory response can lead to novel approaches to treat chronic inflammatory conditions in a personalized manner. To address this we used psoriasis as a model disease given the accessibility to tissue samples and our previous work in this field^{1,2}. Psoriasis is a chronic inflammatory skin condition, characterized by excessive growth of epidermal layer. While different transcriptomic studies have been performed, differences between anatomically separate sites of inflamed skin and the associations with synchronized responses within individuals have not yet been well-studied.

RNA-seq profiling of anatomically separate sites was done from five psoriatic patients (four plaque sites and one non-inflamed skin from each patient) (**Fig 1a; Fig E1; Table E1**). Using hierarchical clustering (**Fig 1a**), we showed that while the inflamed versus normal skin samples were readily distinguishable, transcriptomes from inflamed skin from same individuals clustered together regardless of the anatomic site. We then computed, for each gene, the ratios of between- (V_b) versus within- (V_w) individual (BWI) variance (i.e. the ANOVA F -statistics: V_b/V_w) with respect to: *i*) gene expressions in inflamed sites and *ii*) fold change (**FC**) between inflamed vs. normal skin samples (**Fig E2**). There were 397 genes with significant (False Discovery Rate, $FDR \leq 0.01$) F -statistics for gene expression in inflamed skin and 5,240 significant genes for **FC**, and these two gene sets were significantly enriched with each other ($p < 3 \times 10^{-34}$). For the 190

genes with significant F -statistics in both **FC** and absolute expression in inflamed skin, we defined them as genes exhibiting individualized expression (IE) pattern. There was no association ($p>0.05$) between the degree of differential expression in psoriatic skin and the individualized expression pattern³.

Significant enrichment for IE genes ($p<1\times 10^{-7}$) was found among cis-eQTL analysis identified from >190 skin samples in the GTEx project⁴, indicating the inter-individual variations of the IE genes can be driven by the cis-acting elements. Using independent RNA-seq samples of psoriatic skin², we devised a bootstrap sampling approach to compare the variance explained by genes from a) 63 psoriasis-associated loci⁵; b) IE genes; and c) randomly selected genes. As expected randomly selected genes did not explain the variation of transcriptomes across individuals (median $r^2=1.7\%$). In stark contrast, IE genes explained transcriptional variation to a higher degree than genes from psoriasis-associated loci (42% vs. 28%; $p<2\times 10^{-16}$) (**Fig 1b**). Notably, only one (i.e. *RUNX3*) of the IE genes overlap with genes from the psoriasis loci, indicating that IE contribution to the transcriptome variability is independent of genes from currently known disease susceptibility regions, which mainly contribute to the regulatory differences in psoriatic and unaffected individuals⁵. Furthermore, we demonstrate, using GTEx data², that IE genes demonstrate high degree of skin-specificity ($p<5\times 10^{-22}$; **Fig E3**).

Higher proportion of differential expression in lincRNAs was observed (13%; **Fig 1c**) compared to the proportion of lincRNA for skin-expressing transcripts (9%; **Fig E4**). We also replicated recent findings^{2, 6} that lincRNAs display higher between-individual expression variability (**Fig 1d**) than protein-coding genes ($V_b^{lincRNA} > V_b^{protein}$). Interestingly, lincRNAs

constituted the lowest proportion of genes illustrating IE patterns in inflamed psoriatic skin (4%, **Fig 1c**) and in terms of the **FC** difference (7%; **Fig E4**). In fact, lincRNAs displayed significantly ($p < 1 \times 10^{-16}$) higher coefficient of variation for both between- and within- individual variabilities, and the contrast was much greater for within- individual variability (**Fig 1d**).

Next, *in silico* analysis and *in vitro* experiments were performed in keratinocytes to address the biological implications of IE genes. Functional enrichment analysis of IE genes demonstrated enrichment in biological processes including translation regulation and immunological functions (e.g. phagocytosis and cytokine production) (**Table E2**). We then studied IE genes under different cytokine stimulations (i.e. IL-17A, IFN- γ , IFN- α , TNF- α , and IL-17A+TNF- α). Surprisingly, IE genes were enriched (FDR ≤ 0.1) among genes dysregulated by TNF- α and IFN- γ stimulations (**Fig 2a; Table E3**). We conducted shRNA experiments on three candidate IE genes showing prominent individualized pattern (**Table E3**): *i*) *LYN*: associated with autoimmunity⁷; *ii*) *JAG2*: associated with notch signaling and treatment response to anti-TNF agents in psoriasis⁸; and *iii*) *IFNGR1*: the receptor for the IFN- γ cytokine. The effect of each IE gene knock-down under different cytokine stimulations (**Fig E5**) was assessed on the expression of several genes associated with psoriasis or keratinocyte proliferation (*DEFB4*, *S100A7*) or cytokine responses (*IL1B*, *CXCL8*, *CCL20*, *IL36G*⁹). Notably, many of these target genes (i.e. *CCL20*, *IL36G*, and *S100A7*) were significantly dys-regulated upon cytokine stimulation when IE genes were knocked-down (**Figure 2b**), suggesting regulatory effect of IE genes on cytokine responses in keratinocytes. Future study should investigate the effect of IE gene knock-down on response of other cytokines that play important roles in psoriasis pathogenesis, including IL-22¹⁰, which can induce keratinocyte proliferation.

134
135 Lastly, we illustrated that drug targets of psoriasis exhibited higher between-to-within
136 individual variance than non-targets ($p < 2 \times 10^{-3}$). Among the targets, four genes consistently
137 harbor IE patterns in both FC and expression in inflamed skin: *RBP1*, *CAT*, *RPS6*, and *CYP1A1*.
138 These are known targets for acitretin, anthralin, cholecalciferol, and methoxsalen, respectively,
139 drugs that are thought to have primarily skin-directed mechanism of action. These results
140 indicate that IE genes can have translational implications regarding therapeutic responses.

141
142 In conclusion, our data provides a novel approach for the study of inflammatory
143 conditions, and facilitates identification of factors that influence biological, inflammatory, and
144 therapeutic responses. To our knowledge, this is the first transcriptomic study to compare intra-
145 individual and inter-individual variability from inflamed tissue from anatomically separate
146 regions. This study illustrates that inflammation is more homogenous transcriptionally in the
147 same individual than similar appearing inflammatory lesions among different individuals, and
148 that genetic variation of a limited number of genes contributes to this transcriptional
149 homogeneity to a greater extent than disease associated susceptibility variants. The identification
150 of genes showing individualized expression patterns may provide novel insights into the
151 mechanism that modify and shape inflammatory responses, lead to important insights for
152 different treatment outcomes, and ultimately advance personalized medicine.

153 154 **Supplementary**

155 Supplementary Figures, and Supplementary Table are in the Supplementary Material. The RNA-
156 seq data used in this study is available in Gene Expression Omnibus (GEO):

157 <http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE83645>

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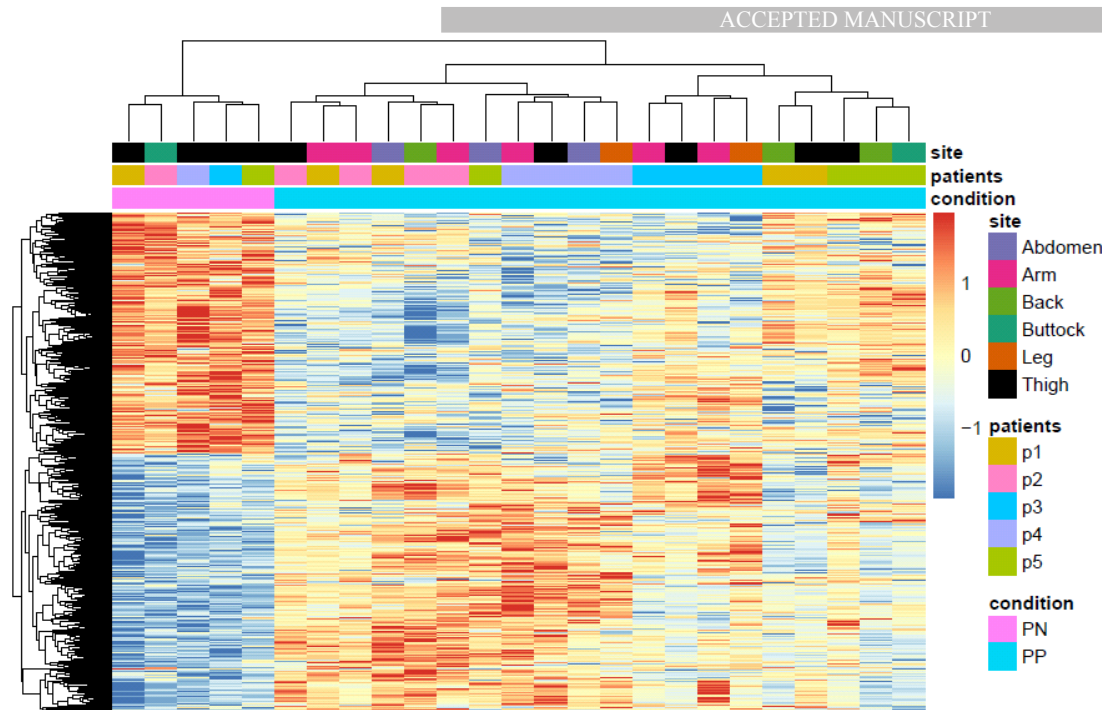
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Figure Legends

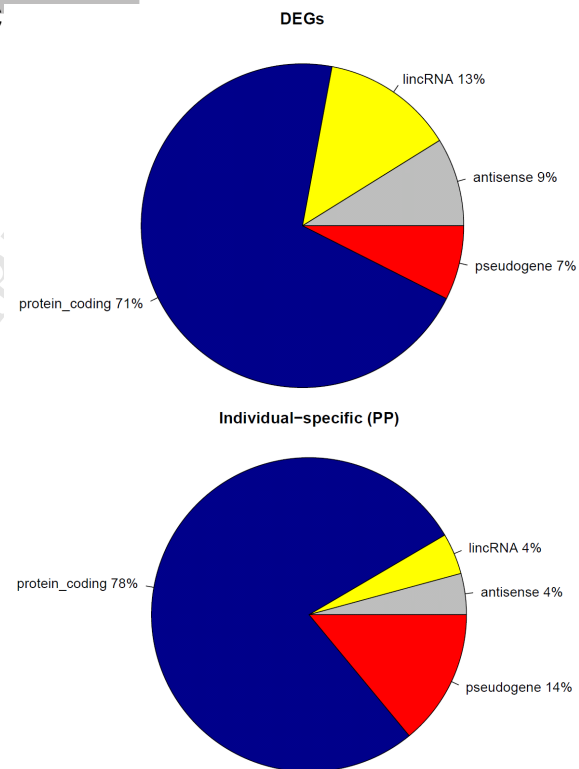
Fig 1. Transcriptomic properties for anatomically separate sites. *a)* heatmap showing the expression patterns of genes versus biopsy site. *b)* variance explained by *i)* associated loci (AG); *ii)* IE genes (IEG); *iii)* randomly selected genes (Random); and *iv)* AG+IEG (combined) using 92 independent psoriatic skin RNA-seq samples. *c)* Compositions among differential expressed genes (top) and genes with individualized lesional skin expression (bottom) computed using the 25 RNA-seq samples. *d)* Coefficients of variation for gene expressions in the 20 psoriatic skin samples for between (left) and within (right) individual.

Fig 2. IE genes participate in cytokine-induced response in keratinocytes. *a)* Heatmap showing the responses (fold change in logarithmic) for the IE genes under different cytokine-induced experiments: IFN γ (50ng/ml); IFN κ (50ng/ml); IFN α (50ng/ml); IL17 (20ng/ml); IL17 (20ng/ml)+TNF (10ng/ml); TNF (10ng/ml); *b-d)* The effect of IE genes on downstream targets under different cytokine stimulations. Color represents whether the IE gene would repress (blue) or induce (red) the cytokine stimulation during knock-down. **False Discovery Rate (FDR) $\leq$ 0.1; *p-value $\leq$ 0.05

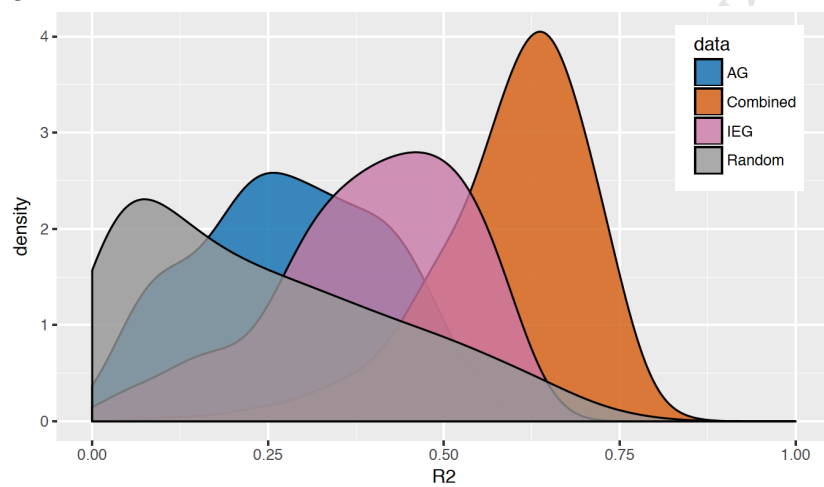
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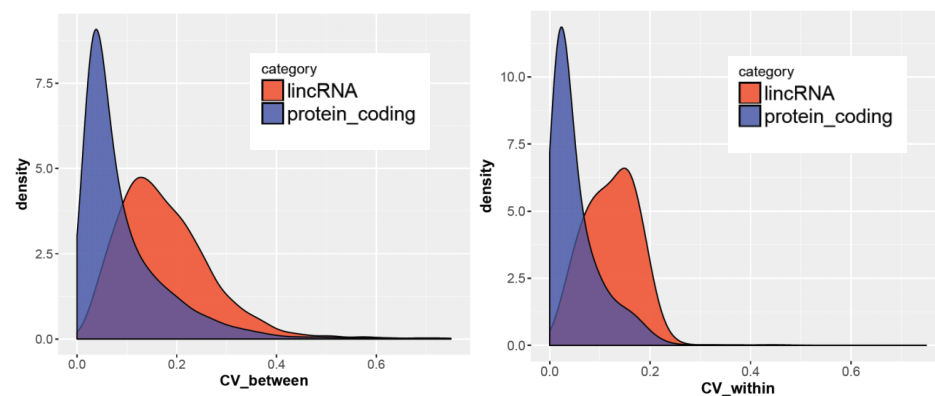
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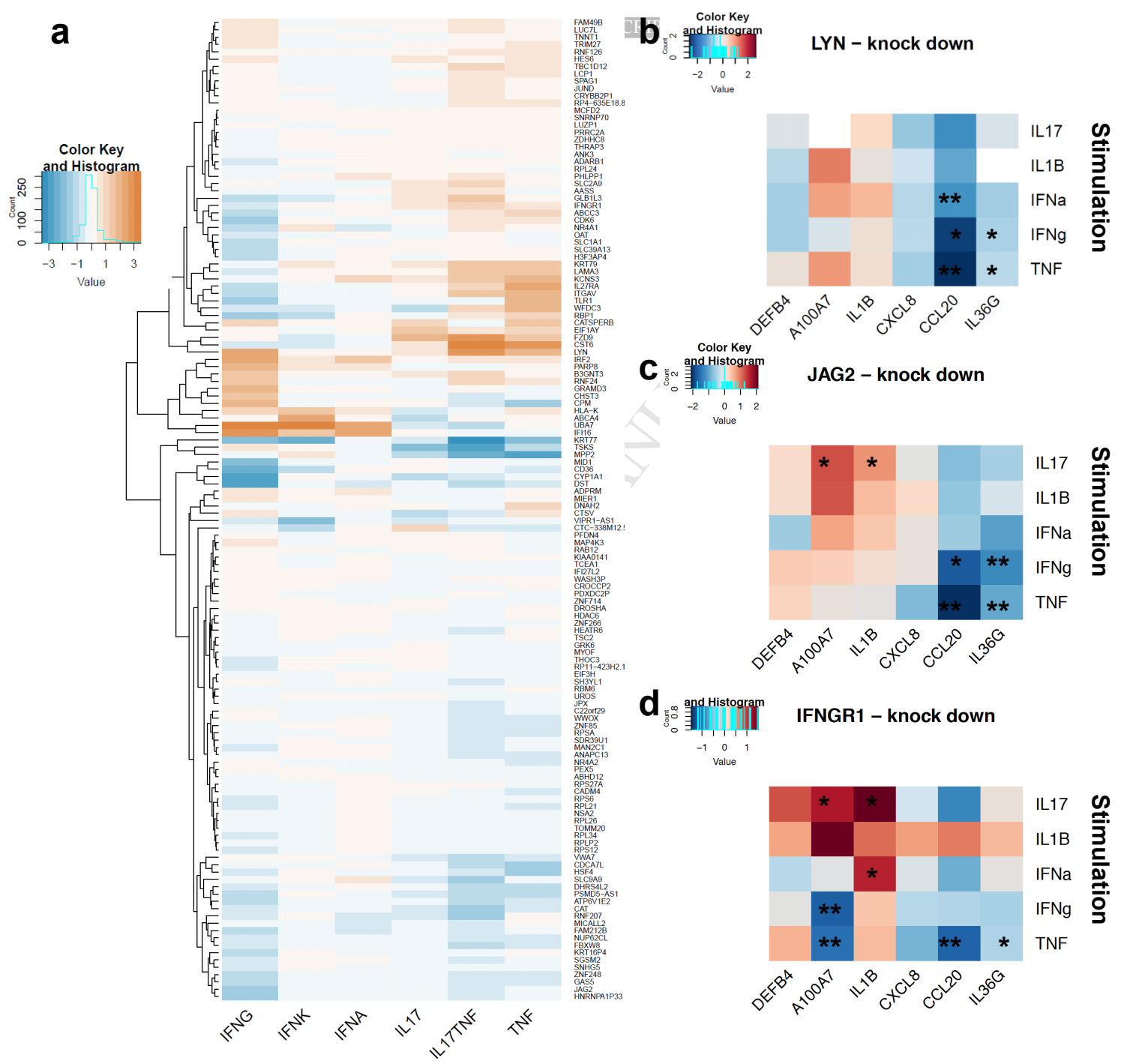


b



d





Supplementary materials

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The authors have declared that no conflict of interest exists.

Materials and Methods

Gene expression profiling for psoriasis patients

All five subjects involved in this study provided written informed consent under a protocol adherent to the Helsinki Guidelines and approved by the Institutional Review Board of the University of Michigan Medical School. All patients had discontinued all topical treatments at least 2 weeks prior to biopsy, and were off all systemic treatments and UV treatment for at least 4 weeks or 4 times the half-life of systemic drug, whichever is longer. After local anaesthesia, five 6mm punch biopsies were obtained from each subject (4 lesional psoriatic and 1 uninvolved skin). Tissue was snap frozen in liquid nitrogen and stored at -80C until processing. Samples were pulverized and RNA isolated using RNeasy plus mini kit (Qiagen #74136). All samples had RIN>8. Together we performed a total of 25 RNA-seq experiments. Libraries for RNA-seq were generated from polyadenylated skin punch biopsy RNA and sequenced at six libraries per lane on the Illumina Genome Analyzer IIX, using single end sequence with 50 bp in read length.

We used Tophat2 ¹ to align RNA-seq reads to the human genome, using annotations of GENCODE as gene model ². HTSeq was used to quantify gene expression levels ³; normalization and differential expression analysis were performed by DESeq2 ⁴. To ensure robustness in the downstream analysis, we only investigated genes with on average ≥ 1 read/sample, and we further used Cook's distance to filter out outlier expression data ⁴. We detected expression of 25,313 genes in our dataset, and differential expression analysis ⁴ identified 2,358 genes dysregulated in the psoriatic skin (≥ 2 fold change, False Discovery Rate, FDR ≤ 0.1).

Individualized expressed genes

In our ANOVA analysis, we computed the F -statistic to quantify the differential expression variability of between- versus within- individuals for each gene. To compare with what we would observe by chance, we permuted the sample labeling (individual and biopsy sites) and re-computed the F -statistics (**Fig 1b**). We applied the Welch correction⁵ for ANOVA implemented in R to correct for heteroscedasticity to identify genes that show individualized expression patterns. We compared the two F -statistic distributions to the null distributions obtained by permuting samples' labelings (**Fig E2**). The F values from the experiments were in general higher than those obtained from permutation, and this contrast was more significant for **FC** (**Fig E2b**) than expression in inflamed skin (**Fig E2a**).

To examine the associations between the degree of differential expression (between *PP* and *PN* samples) per individual and the individualized expression patterns, we first correlated the Welch's p -values against the Differential expression p -values, and did not identify significant correlation ($p\text{-value} > 0.05$). We then evaluated whether the genes showing individualized expression patterns in *PP* or *PP/PN* fold change levels are enriched with differentially expressed genes (i.e. $FDR \leq 0.1$ and $|\log_2 FC| \geq 1$) using hypergeometric test, and also did not observe significant results. The above results suggest that the differential expression between *PP* and *PN* samples does not confound with the identified individualized expression pattern.

We compared the variance in transcriptome explained using the first principal component of gene expression for each sample as surrogate. We used the 92 independent psoriatic skin RNA-seq samples from our previous cohort⁶; the RPKM values were

variance stabilized and then standardized across samples before the principal component analysis, and the first principal component is able to capture >90% of variation. We compared the variances in transcriptome explained by using correlation coefficient (R^2) for the three gene sets: psoriasis-associated loci, IE genes, and randomly selected genes. We identified genes from the 63 psoriasis-associated loci from our recent study, and for fair comparison we devised a bootstrapping approach to sample the same number of 63 genes from each gene set to estimate the variance explained. The samplings were conducted 10,000 times to approximate the expected variance explained under the selected number of genes. To study the skin specificity index⁷ in terms of expression levels, we processed the GTEx RNA-seq data, which consists of transcriptomic data from over 50 different tissues⁸.

In this study, we identified over 2,000 skin-expressing lincRNAs (9% of all genes identified in the dataset; Supplementary Figure 4a). Therefore, we speculated that the within-individual expression variability of lincRNAs would be greater than that for protein-coding genes ($V_w^{lincRNA} \gg V_w^{protein}$). To evaluate this, we compared the coefficients of variation (CofV), a standardized measure of dispersion, for expression in inflamed skin between these two gene categories.

Functional Characterization

We obtained functional gene annotations from different databases, including the Gene Ontology⁹, KEGG¹⁰, and Biocarta¹¹, and conducted enrichment analysis using hypergeometric distribution. Enriched functions were identified using $FDR \leq 0.1$ criteria,

and only functions annotating with at least three genes with individualized expression patterns were reported in the **Table E2**.

The protocol for the cytokine stimulation experiments (i.e. IL-17A, IFN- γ , IFN- α , TNF- α , and IL-17A+TNF- α) for keratinocytes was described previously ⁷. Briefly, we prepared normal human epidermal keratinocytes from adult skin and grew them to post-confluence. We then introduced different cytokines for stimulation for 24 hours. Total RNA was isolated using RNeasy Mini Plus kit (Qiagen # 74136) and RNA quality and quantity were assessed using an Agilent Bioanalyzer. Libraries for high throughput sequencing were prepared using the Illumina mRNA-Seq kit according to the manufacturer's description (Illumina) and libraries were sequenced on the Illumina Genome Analyzer IIX. The RNA-seq results were processed as described above. Significant cytokine-induced genes are differentially expressed between the cytokine versus control conditions with $FDR \leq 0.1$ and $|\log_2(FC)| > 0.585$.

For associating the IE patterns with drug targets, we identified gene targets for current psoriasis drugs from different public databases ¹²⁻¹⁴, and retrieved 220 skin-expressed targets for 15 different drugs.

Keratinocyte culture, cytokine stimulations, RNA interference and gene expression analyses.

Normal human keratinocytes were established from healthy adults, as previously described¹⁵, and grown in medium 154 CF (Thermo Fisher #M154CF500) with human keratinocyte growth supplement (Thermo Fisher #S0015). Small interfering RNA was introduced by means of electroporation with the Lonza 4D-Nucleofector (Lonza),

according to the manufacturer's instructions. Cytokine stimulations were performed, as previously reported¹⁶: IFN γ (50ng/ml); IFN κ (50ng/ml); IFN α (50ng/ml); IL17 (20ng/ml); IL17 (20ng/ml)+TNF (10ng/ml); TNF (10ng/ml). Three replicates were used for each condition. We then performed IE gene knock-down to assess their effect on mRNA expression of several genes up-regulated in psoriasis and involved in keratinocyte proliferation (*DEFB4*, *S100A7*) or cytokine responses (*IL1B*, *CXCL8*, *CCL20*, *IL36G*¹⁷), under different cytokine stimulations (i.e. *IL17*, *IL1B*, *IFN α* , *IFN γ* , *TNF*). We performed mock-transfected experiments by using scrambled siRNA as negative control. siRNA was purchased from ThermoFisher Scientific. Three replications for each condition (knock-down/mock-transfected in each of the stimulated/non-stimulated conditions) were conducted. We used the Student's t-test to evaluate if the si-RNA knock-down would have effect on the cytokine stimulation when comparing with the effect of the no-knock-down control condition. The Benjamini's False Discover Rate (FDR) approach was used as multiple testing procedure. Quantitative RT-PCR was performed on a 7900HT Fast Real-time PCR system (Applied Biosystems) with TaqMan Universal PCR Master Mix (Thermo Fisher #4304437).

Supplementary Figure legends

Fig E1. Principal component analysis results for the RNA-seq samples stratified by disease status (a) and sites (b). PN and PP conditions represent uninvolved and psoriatic skin.

Fig E2. *F*-statistics for *PP* expression (top) and *PP/PN* fold change (bottom).

Fig E3. Densities for skin specificity index for IE and non-IE genes in unexposed (top) and exposed (bottom) skin samples from the GTeX project.

Fig E4. Pie charts showing the gene compositions. a) all genes identified in the RNA-seq cohort; b) genes that are differentially expressed; c) genes with individualized *PP* expression; d) genes showing individualized *PP/PN* fold change.

Fig E5. Relative expression (in Fold change) of *Lyn* (a), *JAG2* (b), and *IFNGR1* (c) under siRNA knockdown when comparing against scrambled siRNA knockdown. All knockdown experiments are significant ($p < 0.05$). The experiments were conducted from 6 repeated experiments of *Lyn* knockdown, 6 for *JAG2* knockdown, and 3 for *IFNGR1*

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Table E1. Features of each RNA-seq sample used in the study. “Skin” refers to whether the biopsy was from psoriatic (PP) or “uninvolved” (PN) skin.

Sample	Skin	Patient	Site	Number of reads	Number of mapped reads	% of mapped reads
Sample_21634	PP	p1	Arm	32,423,713	31,309,235	96.56%
Sample_21635	PP	p1	Abdomen	36,973,542	35,983,124	97.32%
Sample_21636	PP	p1	Back	39,529,482	38,543,605	97.51%
Sample_21637	PP	p1	Thigh	43,705,010	42,651,131	97.59%
Sample_21638	PN	p1	Thigh	39,843,098	38,871,425	97.56%
Sample_21639	PP	p2	Back	36,065,023	35,086,650	97.29%
Sample_21640	PP	p2	Thigh	35,502,420	34,573,010	97.38%
Sample_21641	PP	p2	Arm	39,823,065	38,679,471	97.13%
Sample_21642	PP	p2	Arm	36,379,605	35,372,784	97.23%
Sample_21643	PN	p2	Buttock	30,925,135	30,185,091	97.61%
Sample_21644	PP	p3	Arm	43,441,836	42,328,732	97.44%
Sample_21645	PP	p3	Arm	36,325,593	35,523,557	97.79%
Sample_21646	PP	p3	Thigh	42,986,145	41,987,881	97.68%
Sample_21647	PP	p3	Leg	42,949,064	41,910,006	97.58%
Sample_21648	PN	p3	Thigh	38,050,757	37,092,970	97.48%
Sample_21649	PP	p4	Arm	46,475,829	45,249,713	97.36%
Sample_21650	PP	p4	Abdomen	34,132,698	33,173,908	97.19%
Sample_21651	PP	p4	Thigh	36,220,836	35,290,323	97.43%
Sample_21652	PP	p4	Leg	39,688,350	38,647,690	97.38%
Sample_21653	PN	p4	Thigh	41,537,851	40,597,290	97.74%
Sample_21654	PP	p5	Abdomen	49,635,013	48,373,354	97.46%
Sample_21655	PP	p5	Back	43,334,795	42,212,637	97.41%
Sample_21656	PP	p5	Buttock	47,599,866	46,419,965	97.52%
Sample_21657	PP	p5	Thigh	47,651,921	46,426,053	97.43%
Sample_21658	PN	p5	Thigh	33,122,448	32,297,262	97.51%

Table E2. Functional enrichment results for the genes showing individualized expression pattern.

Functions	p	FDR	Obs	Obs/Ex p	Genes
VIRAL_TRANSCRIPTION	4.13E-08	3.72E-05	9	11.60	RPL21;RPL24;RPL26;RPL34;RPLP2;RPS12;RPS27A;RPS6;RPSA
TRANSLATIONAL_TERMINATION	4.59E-08	3.72E-05	9	11.46	RPL21;RPL24;RPL26;RPL34;RPLP2;RPS12;RPS27A;RPS6;RPSA
FORMATION_OF_A_POOL_OF_FREE_40S_SUBUNIT	8.44E-08	3.72E-05	9	10.70	RPSA;RPL21;RPL24;RPL26;RPL34;RPLP2;RPS6;RPS12;EIF3H
CYTOSOLIC_RIBOSOME	9.30E-08	3.72E-05	9	10.58	RPL21;RPL24;RPL26;RPL34;RPLP2;RPS12;RPS27A;RPS6;RPSA
VIRAL_GENOME_EXPRESSION	1.02E-07	3.72E-05	9	10.46	RPL21;RPL24;RPL26;RPL34;RPLP2;RPS12;RPS27A;RPS6;RPSA
L13A_MEDIATED_TRANSLATIONAL_SILENCING_OF_CERULOPLASMIN_EXPRESSION	1.78E-07	4.93E-05	9	9.82	RPSA;RPL21;RPL24;RPL26;RPL34;RPLP2;RPS6;RPS12;EIF3H
GTP_HYDROLYSIS_AND_JOINING_OF_THE_60S_RIBOSOMAL_SUBUNIT	2.12E-07	4.93E-05	9	9.63	RPSA;RPL21;RPL24;RPL26;RPL34;RPLP2;RPS6;RPS12;EIF3H
CELLULAR_PROTEIN_COMPLEX_DISASSEMBLY	2.31E-07	4.93E-05	9	9.53	RPL21;RPL24;RPL26;RPL34;RPLP2;RPS12;RPS27A;RPS6;RPSA
TRANSLATIONAL_ELONGATION	2.51E-07	4.93E-05	9	9.44	RPL21;RPL24;RPL26;RPL34;RPLP2;RPS12;RPS27A;RPS6;RPSA
INFLUENZA_VIRAL_RNA_TRANSCRIPTION_AND_REPLICATION	3.46E-07	4.93E-05	8	10.97	RPSA;RPL21;RPL24;RPL26;RPL34;RPLP2;RPS6;RPS12
SYNTHESIS_OF_NASCENT_POLYPEPTIDE_CONTAINING_SIGNAL_SEQUENCE	3.46E-07	4.93E-05	8	10.97	RPSA;RPL21;RPL24;RPL26;RPL34;RPLP2;RPS6;RPS12
SYNTHESIS_OF_PB1_F2	3.46E-07	4.93E-05	8	10.97	RPSA;RPL21;RPL24;RPL26;RPL34;RPLP2;RPS6;RPS12
VIRAL_MRNA_TRANSLATION	3.46E-07	4.93E-05	8	10.97	RPSA;RPL21;RPL24;RPL26;RPL34;RPLP2;RPS6;RPS12
VIRAL_PROTEIN_SYNTHESIS	3.46E-07	4.93E-05	8	10.97	RPSA;RPL21;RPL24;RPL26;RPL34;RPLP2;RPS6;RPS12
COTRANSLATIONAL_PROTEIN_TARGETING_TO_MEMBRANE	3.50E-07	4.93E-05	9	9.08	RPL21;RPL24;RPL26;RPL34;RPLP2;RPS12;RPS27A;RPS6;RPSA
SRP_DEPENDENT_COTRANSLATIONAL_PROTEIN_TARGETING_TO_MEMBRANE	3.50E-07	4.93E-05	9	9.08	RPL21;RPL24;RPL26;RPL34;RPLP2;RPS12;RPS27A;RPS6;RPSA
EUKARYOTIC_TRANSLATION_INITIATION	3.50E-07	4.93E-05	9	9.08	RPSA;RPL21;RPL24;RPL26;RPL34;RPLP2;RPS6;RPS12;EIF3H
PROTEIN_TARGETING_TO_ER	3.80E-07	4.93E-05	9	9.00	RPL21;RPL24;RPL26;RPL34;RPLP2;RPS12;RPS27A;RPS6;RPSA
ESTABLISHMENT_OF_PROTEIN_LOCALIZATION_TO_ENDOPLASMIC_RETICULUM	4.12E-07	4.93E-05	9	8.91	RPL21;RPL24;RPL26;RPL34;RPLP2;RPS12;RPS27A;RPS6;RPSA

CAP_DEPENDENT_TRANSLATION_INITIATION	4.12E-07	4.93E-05	9	8.91	RPSA;RPL21;RPL24;RPL26;RPL34;RPLP2;RPS6;RPS12;EIF3H
EUKARYOTIC_TRANSLATION_TERMINATION	4.22E-07	4.93E-05	8	10.70	RPSA;RPL21;RPL24;RPL26;RPL34;RPLP2;RPS6;RPS12
NONSENSE_MEDIATED_DECAY_INDEPENDENT_OF_THE_EXON_JUNCTION_COMPLEX	4.22E-07	4.93E-05	8	10.70	RPSA;RPL21;RPL24;RPL26;RPL34;RPLP2;RPS6;RPS12
PEPTIDE_CHAIN_ELONGATION	4.22E-07	4.93E-05	8	10.70	RPSA;RPL21;RPL24;RPL26;RPL34;RPLP2;RPS6;RPS12
INFLUENZA_LIFE_CYCLE	4.65E-07	5.25E-05	8	10.56	RPSA;RPL21;RPL24;RPL26;RPL34;RPLP2;RPS6;RPS12
EUKARYOTIC_TRANSLATION_ELONGATION	5.63E-07	5.94E-05	8	10.31	RPSA;RPL21;RPL24;RPL26;RPL34;RPLP2;RPS6;RPS12
INFLUENZA_INFECTION	6.77E-07	6.92E-05	8	10.07	RPSA;RPL21;RPL24;RPL26;RPL34;RPLP2;RPS6;RPS12
NUCLEAR_TRANSCRIBED_MRNA_CATABOLIC_PROCESS_NONSENSE_MEDIATED_DECAY	8.15E-07	8.08E-05	9	8.23	RPL21;RPL24;RPL26;RPL34;RPLP2;RPS12;RPS27A;RPS6;RPSA
SMG6_CLEAVES_MRNA_WITH_PREMATURE_TERMINATION_CODON	8.86E-07	8.52E-05	8	9.72	RPSA;RPL21;RPL24;RPL26;RPL34;RPLP2;RPS6;RPS12
VIRAL_INFECTIONOUS_CYCLE	1.01E-06	9.44E-05	9	8.02	RPL21;RPL24;RPL26;RPL34;RPLP2;RPS12;RPS27A;RPS6;RPSA
PROTEIN_LOCALIZATION_TO_ENDOPLASMIC_RETICULUM	1.08E-06	9.62E-05	9	7.96	RPL21;RPL24;RPL26;RPL34;RPLP2;RPS12;RPS27A;RPS6;RPSA
NONSENSE_MEDIATED_DECAY	1.15E-06	9.62E-05	8	9.40	RPSA;RPL21;RPL24;RPL26;RPL34;RPLP2;RPS6;RPS12
NONSENSE_MEDIATED_DECAY_ENHANCED_BY_THE_EXON_JUNCTION_COMPLEX	1.15E-06	9.62E-05	8	9.40	RPSA;RPL21;RPL24;RPL26;RPL34;RPLP2;RPS6;RPS12
PHOSPHORYLATED_UPF1_RECRUITS_SMG5_SMG7_SMG6_AND_PP2A	1.15E-06	9.62E-05	8	9.40	RPSA;RPL21;RPL24;RPL26;RPL34;RPLP2;RPS6;RPS12
RIBOSOMAL_SUBUNIT	2.40E-06	1.82E-04	9	7.24	RPL21;RPL24;RPL26;RPL34;RPLP2;RPS12;RPS27A;RPS6;RPSA
STRUCTURAL_CONSTITUENT_OF_RIBOSOME	6.84E-06	4.86E-04	9	6.38	RPL21;RPL24;RPL26;RPL34;RPLP2;RPS12;RPS27A;RPS6;RPSA
METABOLISM_OF_MRNA	5.17E-05	3.19E-03	8	5.63	RPSA;RPL21;RPL24;RPL26;RPL34;RPLP2;RPS6;RPS12
NEGATIVE_REGULATION_OF_IMMUNE_RESPONSE	5.37E-05	3.25E-03	5	10.70	ADCYAP1;IFI16;IL27RA;LYN;TRIM27
CYTOSOLIC_LARGE_RIBOSOMAL_SUBUNIT	5.92E-05	3.52E-03	5	10.49	RPL21;RPL24;RPL26;RPL34;RPLP2
METABOLISM_OF_RNA	1.24E-04	6.97E-03	8	4.98	RPSA;RPL21;RPL24;RPL26;RPL34;RPLP2;RPS6;RPS12
CYTOSOLIC_SMALL_RIBOSOMAL_SUBUNIT	1.81E-04	9.39E-03	4	11.89	RPS12;RPS27A;RPS6;RPSA
LARGE_RIBOSOMAL_SUBUNIT	3.53E-04	1.70E-02	5	7.23	RPL21;RPL24;RPL26;RPL34;RPLP2
FORMATION_OF_THE_TERNARY_COMPLEX_AND_SUBSEQUENTLY_THE_43S_COMPLEX	4.35E-04	1.92E-02	4	9.51	RPSA;RPS6;RPS12;EIF3H

SINGLE_ORGANISM_TRANSPORT	4.98E-04	2.14E-02	36	1.71	ABCA4;ABCC3;ADCYAP1;ANK3;ATP6V1E2;CD36;DST;HDAC6;IGLC3;IGLC7;IPCEF1;ITGAV;KCNS3;LYN;PEX5;RAB12;RPL21;RPL24;RPL26;RPL34;RPLP2;RPS12;RPS27A;RPS6;RPSA;SLC1A1;SLC2A9;SLC39A13;SLC6A1;SLC9A9;TOMM20;TRIM27;TRPM1;TSC2;TULP1;WASH3P
TRANSLATION_INITIATION_COMPLEX_FORMATION	5.16E-04	2.16E-02	4	9.10	RPSA;RPS6;RPS12;EIF3H
RIBOSOMAL_SCANNING_AND_START_CODON_RECOGNITION	5.59E-04	2.31E-02	4	8.91	RPSA;RPS6;RPS12;EIF3H
RESPONSE_TO_TOXIC_SUBSTANCE	6.53E-04	2.67E-02	6	5.13	CYP1A1;HDAC6;LYN;NR4A2;SLC6A1;UROS
ACTIVATION_OF_THE_MRNA_UPON_BINDING_OF_THE_CAP_BINDING_COMPLEX_AND{EIFS__AND_SUBSEQUENT_BINDING_TO_43S	8.19E-04	3.25E-02	4	8.07	RPSA;RPS6;RPS12;EIF3H
POSITIVE_REGULATION_OF_PHAGOCYTOSIS	8.31E-04	3.25E-02	3	12.84	CD36;ITGAV;TULP1
PHAGOCYTOSIS	8.36E-04	3.25E-02	6	4.90	CD36;IGLC3;IGLC7;ITGAV;LYN;TULP1
SMALL_RIBOSOMAL_SUBUNIT	1.31E-03	4.66E-02	4	7.13	RPS12;RPS27A;RPS6;RPSA
TRANSPORT	1.61E-03	5.28E-02	41	1.54	ABCA4;ABCC3;ADCYAP1;ANK3;ATP6V1E2;CD36;DST;HDAC6;IGLC3;IGLC7;IPCEF1;ITGAV;KCNS3;LYN;MCFD2;MICALL2;NUP62CL;PEX5;RAB12;RPL21;RPL24;RPL26;RPL34;RPLP2;RPS12;RPS27A;RPS6;RPSA;SLC1A1;SLC2A9;SLC39A13;SLC46A2;SLC6A1;SLC9A9;THOC3;TOMM20;TRIM27;TRPM1;TSC2;TULP1;WASH3P
PRIMARY_ACTIVE_TRANSMEMBRANE_TRANSPORTER_ACTIVITY	1.75E-03	5.60E-02	5	5.09	ABCA4;ABCC3;ATP6V1E2;DST;TOMM20
P_P_BOND_HYDROLYSIS_DRIVEN_TRANSMEMBRANE_TRANSPORTER_ACTIVITY	1.75E-03	5.60E-02	5	5.09	ABCA4;ABCC3;ATP6V1E2;DST;TOMM20
REGULATION_OF_PHAGOCYTOSIS	1.90E-03	5.87E-02	3	9.72	CD36;ITGAV;TULP1
RESPONSE_TO_EXTRACELLULAR_STIMULUS	1.98E-03	6.04E-02	8	3.28	ADCYAP1;CAT;CYP1A1;HDAC6;IFI16;LYN;NR4A2;RBP1
ESTABLISHMENT_OF_LOCALIZATION	2.22E-03	6.48E-02	41	1.52	ABCA4;ABCC3;ADCYAP1;ANK3;ATP6V1E2;CD36;DST;HDAC6;IGLC3;IGLC7;IPCEF1;ITGAV;KCNS3;LYN;MCFD2;MICALL2;NUP62CL;PEX5;RAB12;RPL21;RPL24;RPL26;RPL34;RPLP2;RPS12;RPS27A;RPS6;RPSA;SLC1A1;SLC2A9;SLC39A13;SLC46A2;SLC6A1;SLC9A9;THOC3;TOMM20;TRIM27;TRPM1;TSC2;TULP1;WASH3P

RRNA_METABOLIC_PROCESS	2.24E-03	6.48E-02	5	4.82	DROSHA;NSA2;RPL26;RPS6;RPSA
REGULATION_OF_CYTOKINE_PRODUCTION	3.67E-03	8.35E-02	9	2.75	ADCYAP1;CD36;IFI16;IL27RA;LYN;RPS27A;TLR1;TRIM27;UBA7
ECM_RECEPTOR_INTERACTION	3.80E-03	8.35E-02	4	5.35	COL11A2;ITGAV;LAMA3;CD36
RAB_GTPASE_ACTIVATOR_ACTIVITY	4.38E-03	8.35E-02	3	7.29	SGSM1;SGSM2;TBC1D12
CYTOPLASMIC_MICROTUBULE	5.61E-03	9.39E-02	3	6.69	GRAMD3;HDAC6;MID1

ACCEPTED MANUSCRIPT

Table E3. The statistics for the cytokine induction experiments for the IE genes that are expressed in keratinocytes.

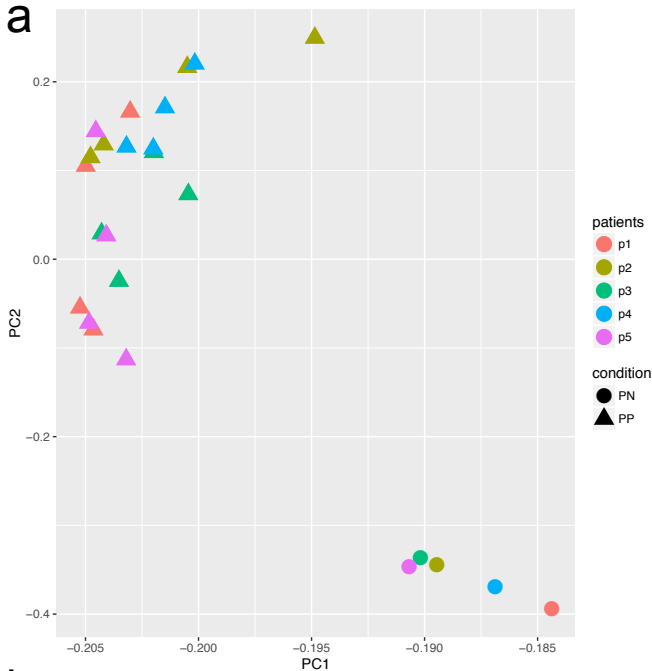
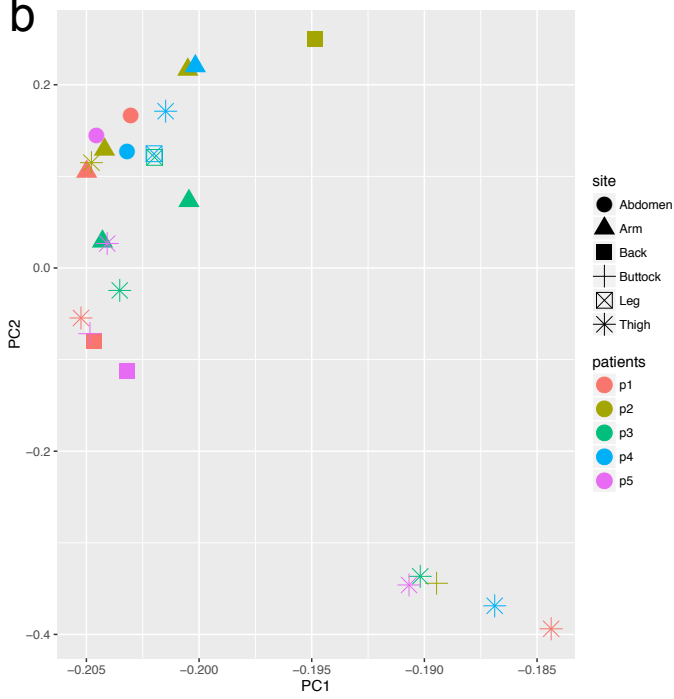
	CTL_IL17			CTL_TNF			CTL_IL17TNF			No_vs_IFNg			No_vs_IFNa			Unstim_vs_IFNk		
	log2FC	pvalue	padj	log2FC	pvalue	padj	log2FC	pvalue	padj	log2FC	pvalue	FDR	log2FC	pvalue	FDR	log2FC	pvalue	padj
AASS	0.66	1.65E-02	3.98E-01	-0.07	7.91E-01	9.73E-01	0.70	3.65E-02	1.68E-01	-0.04	8.64E-01	9.11E-01	0.06	3.45E-01	6.05E-01	-0.29	5.97E-04	8.44E-03
ABCA4	-1.06	2.59E-01	1.00E+00	0.16	7.77E-01	9.72E-01	0.18	7.46E-01	9.38E-01	0.39	4.77E-01	6.04E-01	0.21	1.18E-01	2.96E-01	2.59	2.41E-01	6.51E-01
ABCC3	-0.07	6.58E-01	1.00E+00	1.10	7.82E-09	2.98E-07	0.75	5.79E-03	4.17E-02	-1.20	6.85E-23	4.54E-22	0.05	3.36E-01	5.94E-01	-0.21	4.11E-03	4.14E-02
ABHD12	-0.16	2.75E-01	1.00E+00	-0.41	1.44E-02	9.33E-02	-0.09	7.58E-01	9.42E-01	-0.13	1.27E-02	2.62E-02	0.08	8.12E-02	2.24E-01	0.06	3.75E-01	7.84E-01
ADARB1	0.20	1.49E-01	1.00E+00	0.21	1.48E-01	4.88E-01	0.12	5.61E-01	8.57E-01	-0.45	6.88E-19	4.01E-18	0.07	2.30E-01	4.69E-01	0.03	6.13E-01	9.07E-01
ADPRM	-0.03	8.92E-01	1.00E+00	0.22	4.11E-01	8.19E-01	-0.10	7.54E-01	9.41E-01	0.77	3.17E-16	1.66E-15	0.57	1.92E-07	2.09E-06	0.17	1.80E-01	5.68E-01
ANAPC13	-0.13	3.86E-01	1.00E+00	-0.55	7.39E-04	8.41E-03	-0.71	1.57E-03	1.49E-02	-0.43	2.47E-16	1.30E-15	0.14	2.62E-03	1.31E-02	0.02	7.24E-01	9.41E-01
ANK3	0.28	6.63E-02	8.55E-01	0.27	1.40E-01	4.72E-01	-0.01	9.90E-01	9.98E-01	-0.12	2.14E-01	3.22E-01	0.11	1.72E-01	3.87E-01	-0.27	1.30E-03	1.61E-02
ATP6V1E2	-0.35	1.90E-01	1.00E+00	-0.59	4.71E-02	2.27E-01	-1.18	1.51E-03	1.44E-02	-1.24	5.38E-21	3.37E-20	-0.10	3.78E-01	6.38E-01	-0.28	2.32E-02	1.57E-01
B3GNT3	0.44	8.46E-02	9.55E-01	0.31	2.53E-01	6.54E-01	1.02	1.05E-03	1.07E-02	1.35	2.40E-08	8.55E-08	0.03	6.02E-01	8.14E-01	0.12	1.26E-01	4.71E-01
C22orf29	-0.33	1.88E-02	4.31E-01	-0.34	2.23E-02	1.31E-01	-0.73	4.50E-04	5.38E-03	0.11	1.02E-02	2.14E-02	-0.21	5.56E-07	5.72E-06	-0.13	2.70E-02	1.75E-01
CADM4	0.07	6.68E-01	1.00E+00	-0.50	8.80E-03	6.36E-02	0.00	9.92E-01	9.99E-01	-0.12	1.17E-01	1.93E-01	0.16	1.42E-01	3.39E-01	-0.24	4.92E-02	2.65E-01
CAT	-0.66	2.79E-05	3.05E-03	-0.67	7.50E-05	1.19E-03	-1.56	6.79E-06	1.50E-04	-0.81	1.02E-23	7.00E-23	-0.03	5.62E-01	7.87E-01	-0.26	3.01E-06	7.73E-05
CATSPERB	1.28	5.44E-01	1.00E+00	1.36	4.21E-01	8.26E-01	-0.15	6.77E-01	9.11E-01	1.07	6.35E-02	1.14E-01	0.05	7.87E-01	9.13E-01	0.12	9.04E-01	9.85E-01
CD36	0.37	7.93E-02	9.33E-01	-0.85	1.54E-03	1.55E-02	-0.16	6.50E-01	8.99E-01	-2.18	6.73E-17	3.62E-16	0.19	2.43E-01	4.85E-01	-0.93	2.98E-01	7.18E-01
CDCA7L	-0.07	7.54E-01	1.00E+00	-1.44	1.72E-06	4.14E-05	-0.89	4.47E-03	3.39E-02	-0.35	1.55E-04	4.07E-04	0.01	8.12E-01	9.24E-01	-0.08	2.03E-01	6.02E-01
CDK6	0.20	2.10E-01	1.00E+00	0.79	1.77E-07	5.18E-06	0.58	6.85E-03	4.73E-02	-1.38	1.04E-188	5.02E-187	-0.35	1.36E-18	3.51E-17	0.00	9.74E-01	9.96E-01
CHST3	-0.11	4.53E-01	1.00E+00	-0.31	4.96E-02	2.35E-01	-0.72	5.69E-04	6.52E-03	1.51	5.27E-227	3.08E-225	-0.21	2.82E-05	2.20E-04	-0.06	3.21E-01	7.42E-01
CPM	0.11	5.39E-01	1.00E+00	-1.50	1.62E-11	9.61E-10	-0.62	9.85E-02	3.36E-01	1.74	4.20E-136	1.46E-134	0.12	5.45E-01	7.77E-01	-0.08	7.64E-01	9.52E-01
CROCCP2	-0.14	6.94E-01	1.00E+00	0.22	5.44E-01	9.00E-01	-0.15	7.19E-01	9.28E-01	0.17	7.53E-02	1.32E-01	-0.31	1.43E-02	5.59E-02	0.13	2.94E-01	7.15E-01
CRYBB2P1	-0.02	9.60E-01	1.00E+00	0.23	5.25E-01	8.91E-01	0.60	1.36E-01	4.12E-01	0.11	4.65E-01	5.92E-01	-0.10	3.52E-01	6.11E-01	-0.09	5.01E-01	8.60E-01
CST6	0.77	1.20E-01	1.00E+00	2.67	4.57E-03	3.78E-02	3.15	1.38E-02	8.11E-02	-0.47	8.12E-04	1.97E-03	-0.24	2.69E-01	5.18E-01	-0.52	5.43E-01	8.80E-01
CTC-338M12.5	0.96	7.06E-01	1.00E+00	-0.57	8.51E-01	9.82E-01	-0.44	8.27E-01	9.64E-01	-0.43	5.07E-01	6.30E-01	0.05	8.22E-01	9.27E-01	-0.99	2.43E-01	6.53E-01
CTSV	-1.14	1.12E-17	1.01E-14	0.49	2.46E-03	2.28E-02	-0.80	6.82E-03	4.71E-02	0.82	1.45E-32	1.25E-31	0.00	9.71E-01	9.92E-01	-0.17	7.55E-03	6.73E-02
CYP1A1	-1.06	1.19E-01	1.00E+00	-0.42	1.46E-01	4.84E-01	-0.62	1.25E-01	3.94E-01	-2.92	1.44E-50	1.84E-49	-0.08	5.46E-01	7.78E-01	0.09	6.26E-01	9.12E-01
DHRS4L2	-0.36	2.60E-02	5.24E-01	-1.11	1.51E-06	3.66E-05	-1.13	2.22E-06	5.55E-05	-0.77	6.83E-12	2.96E-11	0.06	6.29E-01	8.32E-01	-0.13	1.34E-01	4.87E-01
DNAH2	0.13	9.92E-01	1.00E+00	1.03	4.91E-01	8.71E-01	-0.38	8.34E-01	9.65E-01	-0.02	9.73E-01	9.85E-01	0.41	4.65E-02	1.46E-01	-0.11	7.33E-01	9.44E-01
DROSHA	0.16	3.06E-01	1.00E+00	0.01	9.77E-01	9.99E-01	-0.26	2.71E-01	6.20E-01	0.09	9.43E-02	1.61E-01	0.39	2.21E-18	5.66E-17	0.12	3.87E-02	2.24E-01
DST	-0.04	7.60E-01	1.00E+00	-0.43	8.57E-04	9.46E-03	-1.00	8.81E-06	1.88E-04	-2.89	0.00E+00	0.00E+00	-0.85	3.94E-22	1.16E-20	-0.13	2.61E-02	1.70E-01

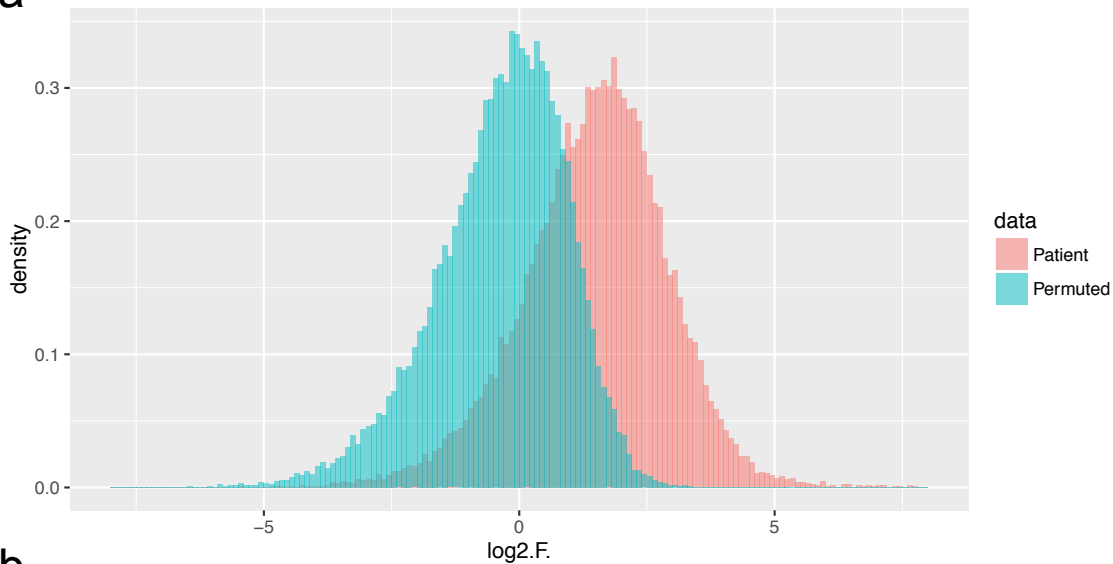
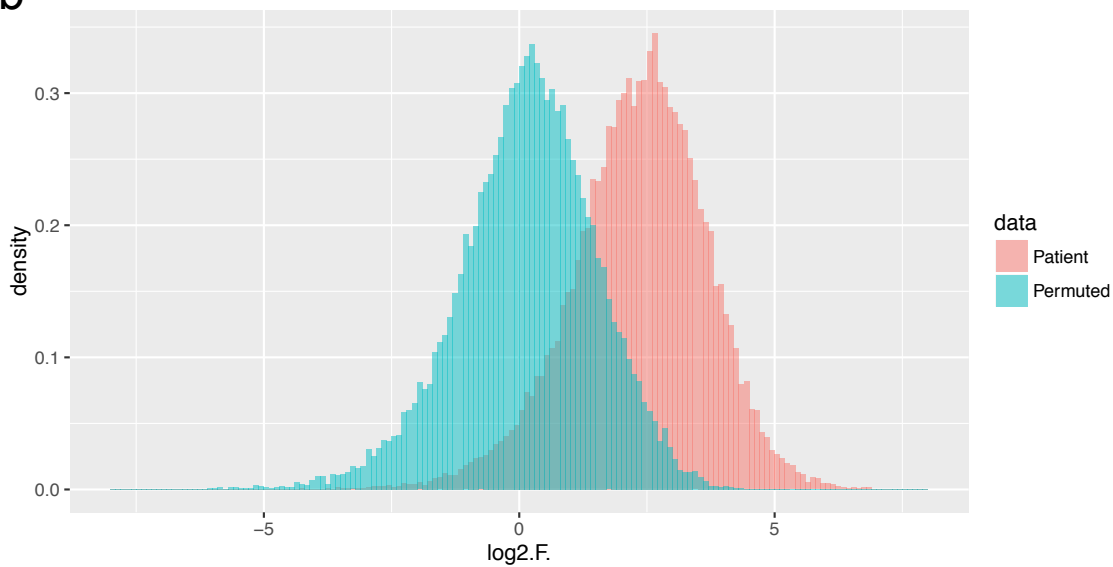
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EIF3H	-0.15	2.46E-01	1.00E+00	-0.40	5.76E-03	4.54E-02	-0.31	1.09E-01	3.60E-01	-0.02	5.89E-01	7.04E-01	0.10	4.00E-03	1.89E-02	-0.12	4.13E-03	4.15E-02
FAM212B	-0.10	6.16E-01	1.00E+00	-0.40	5.85E-02	2.65E-01	-0.81	4.41E-03	3.37E-02	-0.95	1.11E-29	8.88E-29	-0.56	2.99E-11	4.89E-10	-0.34	2.79E-04	4.47E-03
FAM49B	0.16	3.10E-01	1.00E+00	0.32	5.10E-02	2.40E-01	0.48	3.73E-02	1.70E-01	0.64	7.40E-29	5.81E-28	0.11	6.10E-03	2.72E-02	-0.11	2.14E-02	1.48E-01
FBXW8	-0.21	3.30E-01	1.00E+00	-0.49	3.01E-02	1.63E-01	-1.05	9.49E-04	9.92E-03	-0.63	6.23E-14	2.98E-13	-0.12	9.69E-02	2.55E-01	-0.02	8.31E-01	9.70E-01
FZD9	1.80	2.40E-01	1.00E+00	1.66	1.86E-01	5.54E-01	2.89	1.52E-02	8.75E-02	0.24	5.17E-01	6.39E-01	-0.37	8.43E-02	2.30E-01	-0.84	3.18E-01	7.39E-01
GAS5	-0.28	3.01E-02	5.74E-01	-0.53	5.86E-04	6.88E-03	-0.44	3.31E-02	1.56E-01	-1.24	8.77E-134	2.97E-132	-0.23	3.58E-05	2.75E-04	-0.22	1.72E-04	2.93E-03
GLB1L3	0.78	1.92E-02	4.36E-01	0.13	7.39E-01	9.67E-01	1.58	7.97E-04	8.61E-03	-0.97	8.51E-09	3.11E-08	-0.31	1.08E-01	2.77E-01	-0.70	4.48E-01	8.31E-01
GRAMD3	-0.36	1.16E-02	3.18E-01	-0.16	3.00E-01	7.14E-01	0.04	8.50E-01	9.69E-01	2.02	0.00E+00	0.00E+00	0.08	1.33E-01	3.23E-01	0.19	2.56E-03	2.82E-02
GRK6	0.00	9.82E-01	1.00E+00	-0.21	2.12E-01	5.96E-01	-0.05	8.30E-01	9.64E-01	-0.29	4.24E-07	1.38E-06	-0.10	1.47E-02	5.70E-02	-0.05	4.34E-01	8.23E-01
H3F3AP4	-0.02	9.18E-01	1.00E+00	0.04	8.27E-01	9.78E-01	0.18	4.26E-01	7.78E-01	-1.09	2.04E-05	5.82E-05	0.04	7.35E-01	8.90E-01	-0.13	1.14E-02	9.27E-02
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HEATR6	0.00	9.92E-01	1.00E+00	0.09	6.31E-01	9.36E-01	-0.61	1.88E-02	1.02E-01	-0.43	4.27E-12	1.87E-11	0.12	2.88E-02	9.92E-02	0.05	4.90E-01	8.55E-01
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HLA-K	-0.47	1.69E-01	1.00E+00	0.47	1.19E-01	4.26E-01	0.00	9.91E-01	9.98E-01	1.05	3.31E-05	9.29E-05	0.79	3.27E-04	2.06E-03	1.53	2.13E-11	1.07E-09
HNRNPA1P33	-0.19	2.66E-01	1.00E+00	-0.35	6.29E-02	2.78E-01	-0.64	7.90E-03	5.28E-02	-1.58	8.19E-67	1.37E-65	-0.27	9.67E-07	9.62E-06	-0.18	3.37E-02	2.04E-01
HSF4	-0.31	5.80E-01	1.00E+00	-1.48	1.50E-01	4.92E-01	-0.69	3.84E-01	7.42E-01	-0.67	2.73E-02	5.30E-02	-0.07	7.39E-01	8.93E-01	0.34	3.00E-01	7.20E-01
IFI16	0.11	4.31E-01	1.00E+00	-0.42	5.89E-03	4.62E-02	-0.31	2.01E-01	5.24E-01	2.61	0.00E+00	0.00E+00	2.33	0.00E+00	0.00E+00	1.46	5.82E-171	1.90E-168
IFI27L2	-0.30	4.04E-02	6.78E-01	-0.11	4.47E-01	8.44E-01	-0.15	4.77E-01	8.09E-01	0.29	6.46E-05	1.76E-04	0.20	1.46E-04	9.90E-04	0.10	1.10E-01	4.39E-01
IFNGR1	0.46	6.14E-04	3.64E-02	0.64	4.86E-06	1.06E-04	1.12	1.33E-08	5.35E-07	-0.83	3.97E-69	6.82E-68	0.06	2.02E-01	4.31E-01	0.02	8.00E-01	9.62E-01
IL27RA	0.04	8.69E-01	1.00E+00	2.44	5.43E-17	6.19E-15	1.18	6.57E-04	7.33E-03	-1.12	4.12E-05	1.15E-04	-0.05	5.77E-01	7.97E-01	-0.10	3.27E-01	7.46E-01
IRF2	0.08	6.15E-01	1.00E+00	0.82	1.41E-06	3.45E-05	0.52	1.51E-02	8.67E-02	2.42	0.00E+00	0.00E+00	1.57	7.36E-217	1.07E-214	0.51	6.30E-14	3.88E-12
ITGAV	0.22	1.88E-01	1.00E+00	1.90	8.42E-32	3.31E-29	1.34	6.76E-09	2.89E-07	-1.27	6.02E-95	1.40E-93	-0.02	6.57E-01	8.48E-01	-0.34	1.87E-10	8.70E-09
JAG2	-0.32	6.44E-02	8.47E-01	-0.16	2.84E-01	6.95E-01	-0.56	1.41E-02	8.24E-02	-1.47	6.65E-99	1.62E-97	-0.42	3.80E-11	6.17E-10	-0.25	9.85E-05	1.80E-03
JPX	-0.17	4.02E-01	1.00E+00	-0.14	5.01E-01	8.77E-01	-0.45	6.92E-02	2.66E-01	-0.29	1.61E-03	3.76E-03	-0.10	2.14E-01	4.47E-01	-0.20	4.12E-02	2.35E-01
JUND	0.10	7.69E-01	1.00E+00	0.24	1.96E-01	5.70E-01	0.53	3.25E-02	1.54E-01	0.02	7.35E-01	8.20E-01	-0.43	1.39E-10	2.15E-09	0.03	6.93E-01	9.34E-01
KCNS3	0.46	2.07E-01	1.00E+00	1.96	1.84E-10	9.43E-09	1.43	1.29E-04	1.88E-03	-0.04	8.03E-01	8.73E-01	1.24	1.28E-70	8.71E-69	0.17	5.09E-02	2.72E-01
KIAA0141	-0.12	4.72E-01	1.00E+00	0.05	7.92E-01	9.74E-01	0.01	9.74E-01	9.95E-01	0.32	3.84E-08	1.35E-07	0.02	7.06E-01	8.76E-01	-0.07	3.06E-01	7.26E-01
KRT16P4	-0.25	7.35E-02	8.96E-01	0.28	7.94E-02	3.26E-01	-0.18	4.50E-01	7.93E-01	-1.09	8.71E-03	1.85E-02	-0.31	1.56E-01	3.60E-01	0.03	6.86E-01	9.32E-01
KRT77	-0.60	1.70E-04	1.36E-02	-1.97	3.91E-22	7.43E-20	-3.47	8.85E-22	2.03E-19	-1.98	6.91E-54	9.34E-53	-0.03	8.41E-01	9.35E-01	-2.39	5.89E-02	3.00E-01
KRT79	0.51	2.72E-03	1.15E-01	1.32	3.26E-03	2.89E-02	1.62	2.75E-06	6.69E-05	-0.19	4.06E-02	7.60E-02	0.10	6.33E-01	8.35E-01	0.53	5.10E-04	7.37E-03
LAMA3	0.10	4.93E-01	1.00E+00	1.59	5.51E-24	1.19E-21	1.33	7.17E-09	3.03E-07	-0.72	5.09E-34	4.53E-33	0.12	2.56E-02	9.01E-02	0.19	1.53E-06	4.15E-05
LCP1	-0.11	7.37E-01	1.00E+00	0.50	2.60E-01	6.64E-01	0.82	1.18E-01	3.79E-01	0.40	2.46E-01	3.62E-01	-0.04	6.78E-01	8.60E-01	-0.26	2.96E-02	1.87E-01
LUC7L	0.04	8.32E-01	1.00E+00	0.23	2.38E-01	6.32E-01	0.54	2.98E-02	1.44E-01	0.44	1.27E-11	5.44E-11	-0.02	6.67E-01	8.55E-01	0.06	4.86E-01	8.52E-01

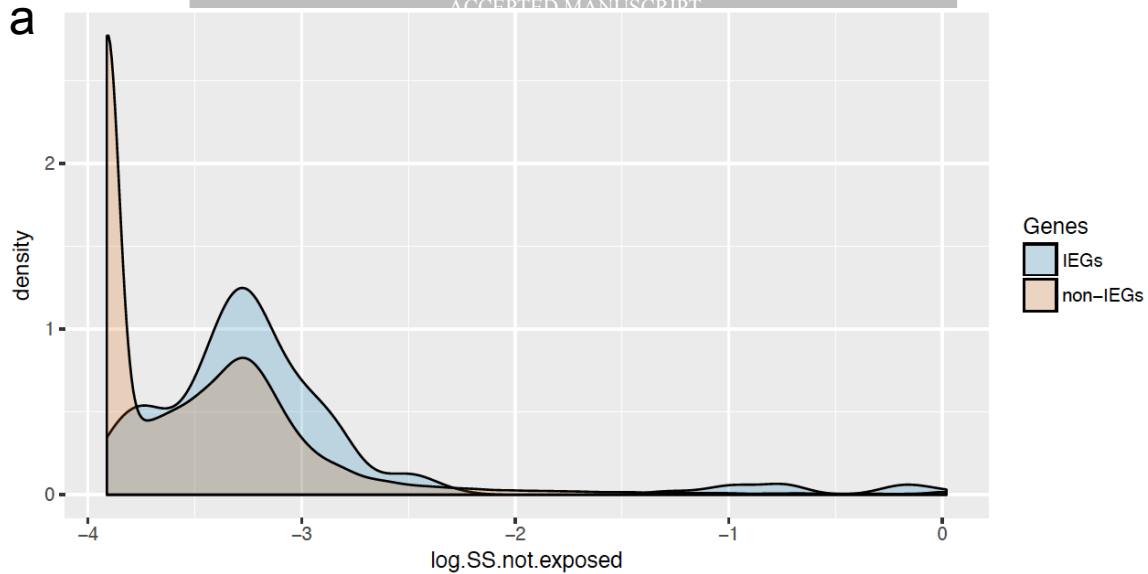
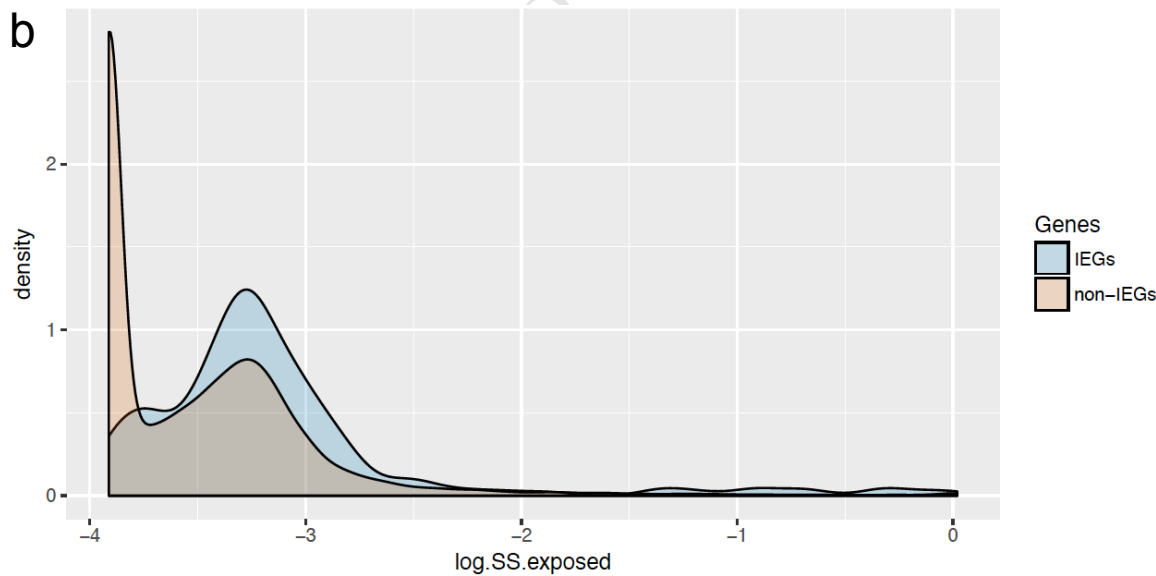
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LYN	0.77	3.20E-05	3.40E-03	1.87	1.93E-25	5.01E-23	2.68	1.20E-35	5.62E-33	2.18	0.00E+00	0.00E+00	0.27	7.70E-08	8.85E-07	0.16	3.56E-02	2.11E-01
MAN2C1	-0.20	2.37E-01	1.00E+00	-0.41	2.84E-02	1.56E-01	-0.67	4.13E-03	3.21E-02	-0.44	1.05E-08	3.82E-08	0.10	8.64E-02	2.35E-01	0.02	8.06E-01	9.63E-01
MAP4K3	0.02	8.95E-01	1.00E+00	-0.11	5.16E-01	8.85E-01	0.02	9.36E-01	9.88E-01	0.51	1.94E-19	1.15E-18	0.02	6.58E-01	8.49E-01	-0.15	2.16E-02	1.49E-01
MCFD2	0.11	4.46E-01	1.00E+00	0.05	7.59E-01	9.69E-01	0.35	9.05E-02	3.17E-01	0.08	9.45E-03	1.99E-02	0.08	7.67E-03	3.31E-02	0.07	1.47E-01	5.11E-01
MICALL2	-0.06	7.55E-01	1.00E+00	0.06	7.29E-01	9.65E-01	-0.76	6.59E-03	4.58E-02	-0.12	1.12E-01	1.87E-01	-0.55	2.48E-08	3.04E-07	-0.08	6.81E-01	9.31E-01
MID1	0.30	8.51E-02	9.55E-01	-0.39	5.50E-02	2.54E-01	-0.12	6.47E-01	8.97E-01	-2.05	3.74E-145	1.36E-143	-0.32	4.54E-09	6.02E-08	-0.21	8.88E-03	7.67E-02
MIER1	-0.07	6.58E-01	1.00E+00	0.01	9.63E-01	9.97E-01	-0.16	4.35E-01	7.84E-01	0.81	7.46E-82	1.49E-80	0.26	6.45E-10	9.36E-09	0.05	3.86E-01	7.93E-01
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MYOF	0.05	6.63E-01	1.00E+00	-0.21	1.27E-01	4.42E-01	-0.26	2.24E-01	5.57E-01	-0.42	1.29E-35	1.20E-34	0.12	1.23E-01	3.06E-01	0.00	9.21E-01	9.88E-01
NR4A1	-0.33	5.66E-01	1.00E+00	0.11	8.10E-01	9.77E-01	0.44	3.87E-01	7.45E-01	-0.89	1.25E-06	3.94E-06	-0.58	5.28E-03	2.41E-02	0.51	8.99E-02	3.89E-01
NR4A2	-0.04	9.21E-01	1.00E+00	-0.75	2.88E-01	6.99E-01	-0.02	9.75E-01	9.95E-01	0.04	8.71E-01	9.16E-01	-0.03	8.92E-01	9.60E-01	-0.06	8.58E-01	9.76E-01
NSA2	-0.04	8.12E-01	1.00E+00	-0.34	4.95E-02	2.35E-01	-0.11	5.95E-01	8.73E-01	-0.27	1.31E-07	4.45E-07	0.02	7.43E-01	8.95E-01	-0.19	3.48E-04	5.34E-03
NUP62CL	-0.27	7.01E-01	1.00E+00	-0.44	5.11E-01	8.82E-01	-0.69	3.69E-01	7.28E-01	-0.58	7.31E-02	1.29E-01	-0.26	5.80E-02	1.73E-01	-0.14	3.67E-01	7.78E-01
OAT	-0.03	8.41E-01	1.00E+00	-0.18	2.08E-01	5.90E-01	0.41	7.83E-02	2.88E-01	-0.82	5.58E-69	9.55E-68	0.00	9.45E-01	9.82E-01	-0.15	7.04E-04	9.69E-03
PARP8	-0.12	5.79E-01	1.00E+00	0.41	3.81E-02	1.94E-01	-0.10	7.04E-01	9.22E-01	1.81	6.00E-128	1.92E-126	0.87	2.99E-55	1.69E-53	0.45	1.30E-09	5.50E-08
PDXDC2P	-0.08	7.02E-01	1.00E+00	-0.04	8.49E-01	9.81E-01	0.00	9.98E-01	1.00E+00	0.02	9.57E-01	9.74E-01	-0.31	1.53E-01	3.56E-01	-0.13	2.83E-01	7.02E-01
PEX5	-0.02	8.98E-01	1.00E+00	-0.38	2.68E-02	1.50E-01	-0.09	6.79E-01	9.11E-01	0.04	4.40E-01	5.68E-01	-0.02	6.75E-01	8.59E-01	0.10	1.24E-01	4.69E-01
PFDN4	0.02	9.04E-01	1.00E+00	-0.05	7.97E-01	9.74E-01	0.22	3.75E-01	7.34E-01	0.32	2.94E-03	6.65E-03	0.13	2.27E-02	8.13E-02	-0.01	8.96E-01	9.83E-01
PHLPP1	0.14	4.32E-01	1.00E+00	0.11	5.44E-01	9.00E-01	0.56	2.35E-02	1.21E-01	-0.18	3.52E-03	7.89E-03	0.52	4.95E-24	1.54E-22	0.29	3.00E-05	6.26E-04
PRRC2A	0.21	1.03E-01	1.00E+00	0.12	3.81E-01	7.93E-01	0.15	4.36E-01	7.84E-01	-0.09	5.41E-03	1.18E-02	-0.02	7.48E-01	8.97E-01	0.08	1.85E-01	5.75E-01
PSMD5-AS1	-0.60	1.01E-02	2.89E-01	-0.91	4.54E-04	5.54E-03	-1.29	1.40E-04	2.02E-03	-0.95	4.51E-19	2.64E-18	0.00	9.89E-01	9.97E-01	0.20	1.16E-01	4.51E-01
RAB12	0.06	6.85E-01	1.00E+00	-0.11	5.15E-01	8.84E-01	0.00	9.89E-01	9.98E-01	0.33	2.52E-11	1.07E-10	-0.01	7.78E-01	9.09E-01	0.00	9.84E-01	9.98E-01
RBM6	-0.08	6.12E-01	1.00E+00	0.09	5.94E-01	9.22E-01	-0.33	1.91E-01	5.08E-01	-0.03	5.85E-01	7.01E-01	-0.05	5.06E-01	7.47E-01	-0.09	2.15E-01	6.18E-01
RBP1	-0.28	8.88E-02	9.68E-01	1.01	5.09E-08	1.65E-06	0.74	8.42E-03	5.54E-02	-1.40	4.69E-42	5.06E-41	0.18	3.64E-01	6.24E-01	-1.13	1.07E-01	4.32E-01
RNF126	0.22	2.04E-01	1.00E+00	0.48	3.81E-03	3.28E-02	0.61	8.36E-03	5.52E-02	0.31	1.00E-06	3.18E-06	0.06	1.23E-01	3.05E-01	0.15	4.17E-02	2.37E-01
RNF207	-0.57	4.42E-01	1.00E+00	0.10	8.48E-01	9.81E-01	-1.35	8.55E-02	3.05E-01	-0.68	7.81E-02	1.37E-01	-0.44	2.08E-02	7.58E-02	0.33	3.63E-01	7.74E-01
RNF24	-0.03	8.70E-01	1.00E+00	0.60	2.50E-03	2.31E-02	0.90	5.58E-04	6.42E-03	1.64	2.73E-186	1.28E-184	-0.08	2.36E-01	4.76E-01	-0.08	3.75E-01	7.84E-01
RP11-423H2.1	0.01	9.36E-01	1.00E+00	-0.21	1.74E-01	5.36E-01	-0.15	4.63E-01	8.01E-01	-0.47	1.81E-03	4.22E-03	0.00	9.73E-01	9.92E-01	0.03	5.28E-01	8.71E-01
RP4-635E18.8	-0.26	8.29E-01	1.00E+00	0.76	6.58E-01	9.47E-01	0.50	8.09E-01	9.58E-01	0.22	5.67E-01	6.85E-01	-0.07	7.28E-01	8.87E-01	0.27	6.86E-01	9.32E-01
RPL21	-0.05	6.81E-01	1.00E+00	-0.48	4.31E-04	5.31E-03	-0.23	2.16E-01	5.46E-01	-0.63	1.06E-66	1.76E-65	0.08	3.31E-02	1.11E-01	-0.28	6.70E-12	3.50E-10
RPL24	0.02	8.85E-01	1.00E+00	-0.02	8.70E-01	9.86E-01	0.20	3.26E-01	6.84E-01	-0.40	8.42E-34	7.47E-33	0.14	7.74E-04	4.47E-03	-0.11	3.16E-02	1.95E-01
RPL26	-0.02	9.08E-01	1.00E+00	-0.40	8.00E-03	5.90E-02	-0.20	3.33E-01	6.92E-01	-0.34	6.73E-16	3.48E-15	0.10	5.11E-02	1.57E-01	-0.14	4.29E-03	4.28E-02
RPL34	-0.04	7.54E-01	1.00E+00	-0.31	2.95E-02	1.61E-01	-0.14	4.68E-01	8.04E-01	-0.57	2.16E-50	2.75E-49	0.12	8.03E-03	3.44E-02	-0.13	2.52E-03	2.79E-02

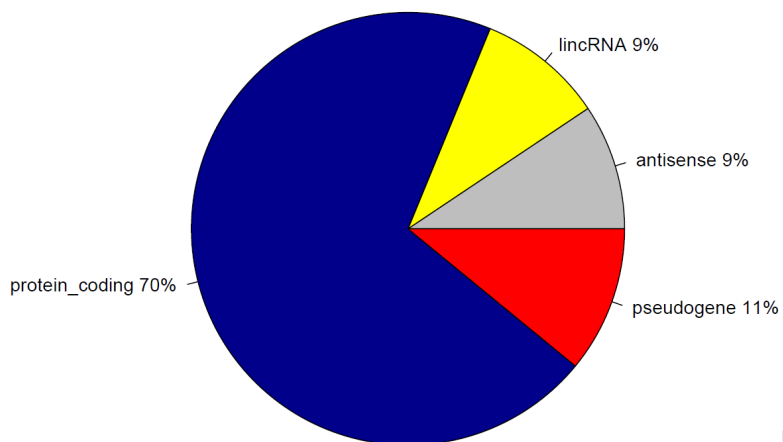
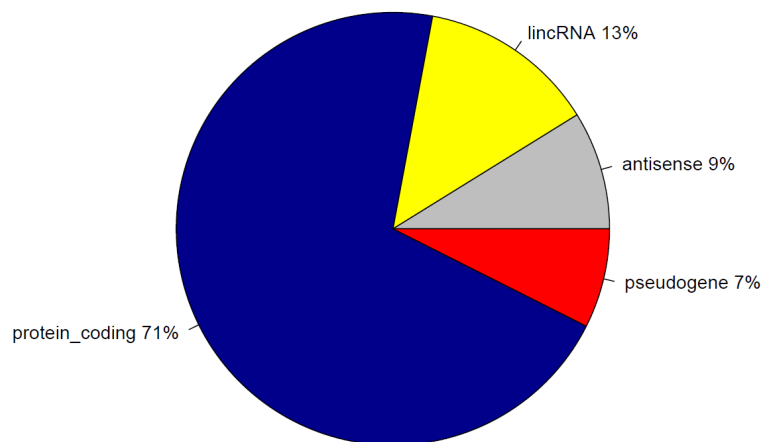
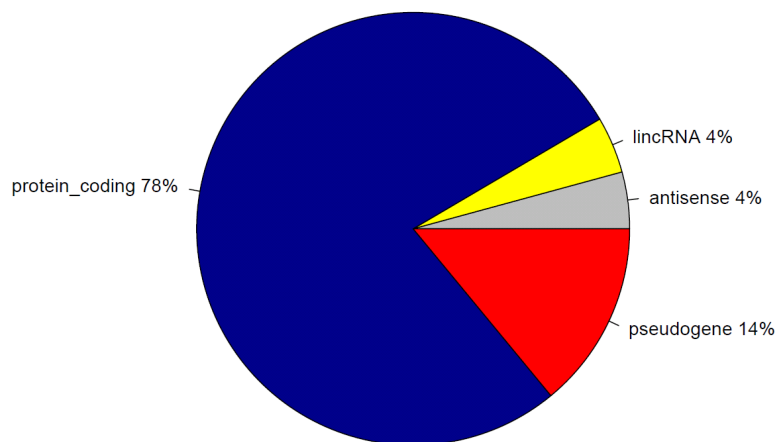
RPLP2	-0.15	2.64E-01	1.00E+00	-0.27	5.58E-02	2.56E-01	-0.11	5.72E-01	8.63E-01	-0.39	3.76E-28	2.89E-27	0.10	2.09E-02	7.60E-02	-0.04	4.69E-01	8.43E-01
RPS12	-0.11	3.84E-01	1.00E+00	-0.43	2.27E-03	2.14E-02	-0.12	5.23E-01	8.37E-01	-0.44	8.80E-43	9.65E-42	0.16	1.39E-04	9.48E-04	-0.11	5.25E-03	5.05E-02
RPS27A	0.05	6.77E-01	1.00E+00	-0.22	1.06E-01	3.94E-01	0.04	8.40E-01	9.67E-01	-0.20	1.64E-10	6.63E-10	0.10	1.07E-02	4.36E-02	-0.26	1.58E-10	7.44E-09
RPS6	-0.04	7.46E-01	1.00E+00	-0.43	2.98E-03	2.69E-02	-0.23	2.36E-01	5.74E-01	-0.62	1.65E-97	3.95E-96	0.08	3.40E-02	1.13E-01	-0.34	1.91E-19	1.51E-17
RPSA	-0.15	2.11E-01	1.00E+00	-0.68	1.26E-06	3.14E-05	-0.47	1.15E-02	7.02E-02	-0.34	3.12E-20	1.90E-19	0.16	2.88E-04	1.84E-03	-0.20	4.98E-05	9.85E-04
SDR39U1	-0.19	6.05E-01	1.00E+00	-0.42	3.01E-01	7.15E-01	-0.46	2.82E-01	6.34E-01	-0.32	5.15E-02	9.41E-02	-0.03	7.61E-01	9.03E-01	0.07	7.08E-01	9.37E-01
SGSM2	-0.29	8.66E-02	9.59E-01	-0.30	8.26E-02	3.34E-01	-0.55	1.82E-02	9.99E-02	-0.78	2.27E-20	1.39E-19	0.02	7.70E-01	9.06E-01	0.15	1.36E-01	4.91E-01
SH3YL1	-0.22	1.39E-01	1.00E+00	-0.36	3.25E-02	1.73E-01	-0.45	4.56E-02	1.98E-01	0.05	4.44E-01	5.72E-01	0.10	1.78E-02	6.67E-02	-0.11	5.70E-02	2.94E-01
SLC1A1	0.10	8.92E-01	1.00E+00	-0.10	8.68E-01	9.86E-01	0.18	6.85E-01	9.14E-01	-1.27	2.97E-02	5.73E-02	-0.06	6.61E-01	8.51E-01	0.03	9.78E-01	9.97E-01
SLC2A9	0.52	9.04E-03	2.69E-01	0.19	3.47E-01	7.63E-01	1.03	1.53E-04	2.17E-03	0.33	7.43E-05	2.01E-04	-0.03	5.00E-01	7.43E-01	-0.07	2.46E-01	6.57E-01
SLC39A13	0.13	3.56E-01	1.00E+00	0.18	2.38E-01	6.32E-01	0.18	3.80E-01	7.38E-01	-0.94	1.87E-59	2.75E-58	0.02	5.62E-01	7.88E-01	-0.02	8.09E-01	9.64E-01
SLC9A9	-0.47	1.49E-02	3.74E-01	-0.17	5.34E-01	8.94E-01	-1.48	1.54E-06	4.06E-05	-0.36	5.47E-02	9.93E-02	0.66	2.34E-05	1.85E-04	0.30	5.95E-02	3.03E-01
SNHG5	-0.26	6.29E-02	8.41E-01	-0.40	1.66E-02	1.04E-01	-0.31	2.07E-01	5.32E-01	-0.84	8.43E-35	7.67E-34	-0.27	3.47E-05	2.66E-04	0.04	5.85E-01	8.97E-01
SNRNP70	0.20	2.09E-01	1.00E+00	0.03	8.39E-01	9.80E-01	0.35	1.13E-01	3.69E-01	0.00	9.24E-01	9.53E-01	0.10	1.77E-02	6.64E-02	0.04	4.10E-01	8.09E-01
SPAG1	0.20	2.46E-01	1.00E+00	0.14	4.32E-01	8.35E-01	0.63	7.56E-03	5.10E-02	0.25	1.96E-04	5.10E-04	-0.28	6.20E-06	5.42E-05	-0.03	7.10E-01	9.38E-01
TBC1D12	0.21	2.74E-01	1.00E+00	0.73	1.43E-04	2.07E-03	0.90	2.03E-04	2.74E-03	0.19	9.11E-03	1.92E-02	-0.18	2.01E-02	7.37E-02	-0.17	9.43E-02	4.00E-01
TCEA1	-0.04	7.81E-01	1.00E+00	-0.04	7.51E-01	9.69E-01	-0.10	6.15E-01	8.83E-01	0.12	7.14E-04	1.75E-03	0.00	9.63E-01	9.88E-01	-0.09	6.11E-02	3.07E-01
THOC3	0.04	7.64E-01	1.00E+00	-0.15	3.21E-01	7.35E-01	-0.12	5.49E-01	8.50E-01	-0.58	2.37E-06	7.34E-06	0.10	1.15E-01	2.90E-01	0.07	1.55E-01	5.25E-01
THRAP3	0.10	4.66E-01	1.00E+00	0.19	1.85E-01	5.53E-01	0.21	3.02E-01	6.57E-01	-0.20	7.21E-07	2.32E-06	0.13	8.14E-03	3.48E-02	0.03	5.56E-01	8.85E-01
TLR1	-0.04	8.62E-01	1.00E+00	1.95	2.43E-12	1.61E-10	-0.06	9.64E-01	9.93E-01	-1.51	1.09E-03	2.61E-03	-0.05	8.10E-01	9.22E-01	-0.05	9.22E-01	9.88E-01
TNNT1	-0.03	8.14E-01	1.00E+00	0.37	1.36E-02	8.95E-02	0.30	1.53E-01	4.43E-01	0.54	4.79E-33	4.16E-32	0.14	4.82E-04	2.91E-03	-0.02	7.54E-01	9.49E-01
TOMM20	-0.01	9.40E-01	1.00E+00	-0.31	3.47E-02	1.81E-01	-0.18	3.77E-01	7.35E-01	-0.41	6.81E-38	6.70E-37	0.01	7.46E-01	8.96E-01	-0.14	5.85E-03	5.52E-02
TRIM27	0.04	7.81E-01	1.00E+00	0.46	5.31E-03	4.26E-02	0.15	4.84E-01	8.13E-01	0.53	6.95E-35	6.35E-34	-0.02	6.06E-01	8.16E-01	-0.06	2.72E-01	6.89E-01
TSC2	-0.05	7.06E-01	1.00E+00	0.03	8.23E-01	9.78E-01	-0.03	9.00E-01	9.81E-01	-0.28	5.87E-08	2.04E-07	-0.01	8.47E-01	9.38E-01	0.02	7.39E-01	9.45E-01
TSKS	-1.94	2.11E-02	4.61E-01	-1.19	1.62E-01	5.15E-01	-2.98	1.12E-03	1.13E-02	0.50	4.39E-01	5.67E-01	-0.25	1.94E-01	4.20E-01	0.19	3.82E-01	7.89E-01
UBA7	-0.76	3.64E-04	2.44E-02	0.09	6.87E-01	9.55E-01	-1.18	5.16E-04	6.02E-03	3.12	3.62E-81	7.19E-80	2.30	2.67E-106	2.49E-104	3.08	1.85E-210	8.42E-208
UROS	0.00	9.94E-01	1.00E+00	-0.21	2.29E-01	6.21E-01	-0.28	1.99E-01	5.19E-01	-0.08	2.39E-01	3.53E-01	0.02	6.02E-01	8.14E-01	0.00	9.71E-01	9.96E-01
VIPRI-AS1	-0.69	4.28E-01	1.00E+00	-0.12	9.82E-01	9.99E-01	-0.09	9.05E-01	9.81E-01	-0.58	3.10E-01	4.35E-01	-0.07	6.42E-01	8.40E-01	-1.91	4.23E-01	8.17E-01
VWA7	-0.55	1.32E-01	1.00E+00	-0.86	3.58E-02	1.86E-01	-1.21	9.93E-03	6.29E-02	0.12	5.72E-01	6.90E-01	-0.35	1.10E-01	2.82E-01	0.31	4.94E-01	8.56E-01
WASH3P	-0.15	4.91E-01	1.00E+00	0.22	3.39E-01	7.56E-01	0.03	9.29E-01	9.87E-01	0.24	2.20E-01	3.30E-01	0.01	9.77E-01	9.94E-01	0.12	3.05E-01	7.25E-01
WFDC3	-1.05	3.97E-01	1.00E+00	2.03	2.82E-03	2.57E-02	0.99	2.40E-01	5.80E-01	-0.44	4.80E-01	6.07E-01	-0.10	6.37E-01	8.36E-01	-0.74	3.49E-01	7.63E-01
WVOX	-0.25	3.48E-01	1.00E+00	-0.79	6.89E-03	5.24E-02	-0.73	2.53E-02	1.28E-01	0.08	6.59E-01	7.58E-01	0.06	6.87E-01	8.66E-01	-0.29	1.20E-01	4.60E-01
ZDHHC8	0.07	6.89E-01	1.00E+00	0.09	6.02E-01	9.26E-01	0.10	6.52E-01	9.00E-01	-0.15	1.13E-02	2.35E-02	0.02	7.76E-01	9.08E-01	0.12	1.04E-01	4.23E-01
ZNF248	-0.04	9.13E-01	1.00E+00	-0.53	1.41E-01	4.74E-01	-0.44	2.73E-01	6.22E-01	-1.11	5.97E-13	2.72E-12	-0.41	5.44E-04	3.25E-03	-0.17	2.21E-01	6.25E-01

ZNF266	-0.21	2.99E-01	1.00E+00	-0.11	6.18E-01	9.32E-01	-0.23	3.78E-01	7.36E-01	-0.17	6.73E-02	1.20E-01	0.03	6.50E-01	8.44E-01	0.25	5.70E-03	5.40E-02
ZNF714	0.13	7.07E-01	1.00E+00	-0.28	4.76E-01	8.64E-01	-0.15	7.43E-01	9.36E-01	0.39	2.33E-02	4.60E-02	-0.38	7.78E-02	2.18E-01	0.08	7.91E-01	9.59E-01
ZNF85	-0.06	8.57E-01	1.00E+00	-0.59	5.28E-02	2.47E-01	-0.74	2.68E-02	1.34E-01	-0.10	6.38E-01	7.41E-01	0.08	3.70E-01	6.31E-01	0.17	1.37E-01	4.94E-01

a**b**

a**b**

a**b**

a**All Genes****b****DEGs****c****Individual-specific (PP)****d****Individual-specific (FC)**