	Coefficient	Std Error	T value	P value
(Intercept)	-166.3	22.40	-7.423	0
ENSG00000205927	-0.5728	0.2411	-2.376	0.01771
ENSG00000113389	3.550	0.6763	5.249	0
ENSG00000164047	1.194	0.2233	5.346	0
ENSG00000158497	-1.994	0.9674	-2.061	0.03955
ENSG00000061273	1.727	0.4345	3.976	0
ENSG00000167186	-2.563	0.9489	-2.701	0.007039
ENSG00000151012	1.983	0.4868	4.074	0
ENSG00000133687	-0.4661	0.1285	-3.627	0.0003017
ENSG00000134827	1.403	0.4792	2.928	0.003487
ENSG00000172292	-2.956	0.5767	-5.126	0
ENSG00000038219	5.337	0.6258	8.529	0
ENSG00000158488	-2.556	0.6875	-3.718	0.0002124
ENSG00000135373	2.603	0.8006	3.252	0.001186
ENSG00000204345	-0.8332	0.2993	-2.784	0.005477
ENSG00000062716	8.633	0.6668	12.95	0
ENSG00000050748	-4.712	0.9498	-4.961	0
ENSG00000164187	-2.656	0.5261	-5.047	0
ENSG00000124721	1.668	0.4876	3.421	0.0006495
ENSG00000108846	-0.6706	0.2472	-2.712	0.006796
ENSG00000118292	1.991	0.8279	2.405	0.01634
ENSG00000150051	-2.048	0.7065	-2.898	0.003836
ENSG00000149516	-1.692	0.3243	-5.219	0
ENSG00000120949	1.723	0.5864	2.938	0.003386
ENSG00000163162	4.798	0.7300	6.572	0
ENSG00000175793	3.463	0.8893	3.894	0.0001052
ENSG00000083290	2.315	0.8190	2.827	0.004799
ENSG00000092969	-1.899	0.7666	-2.477	0.01342

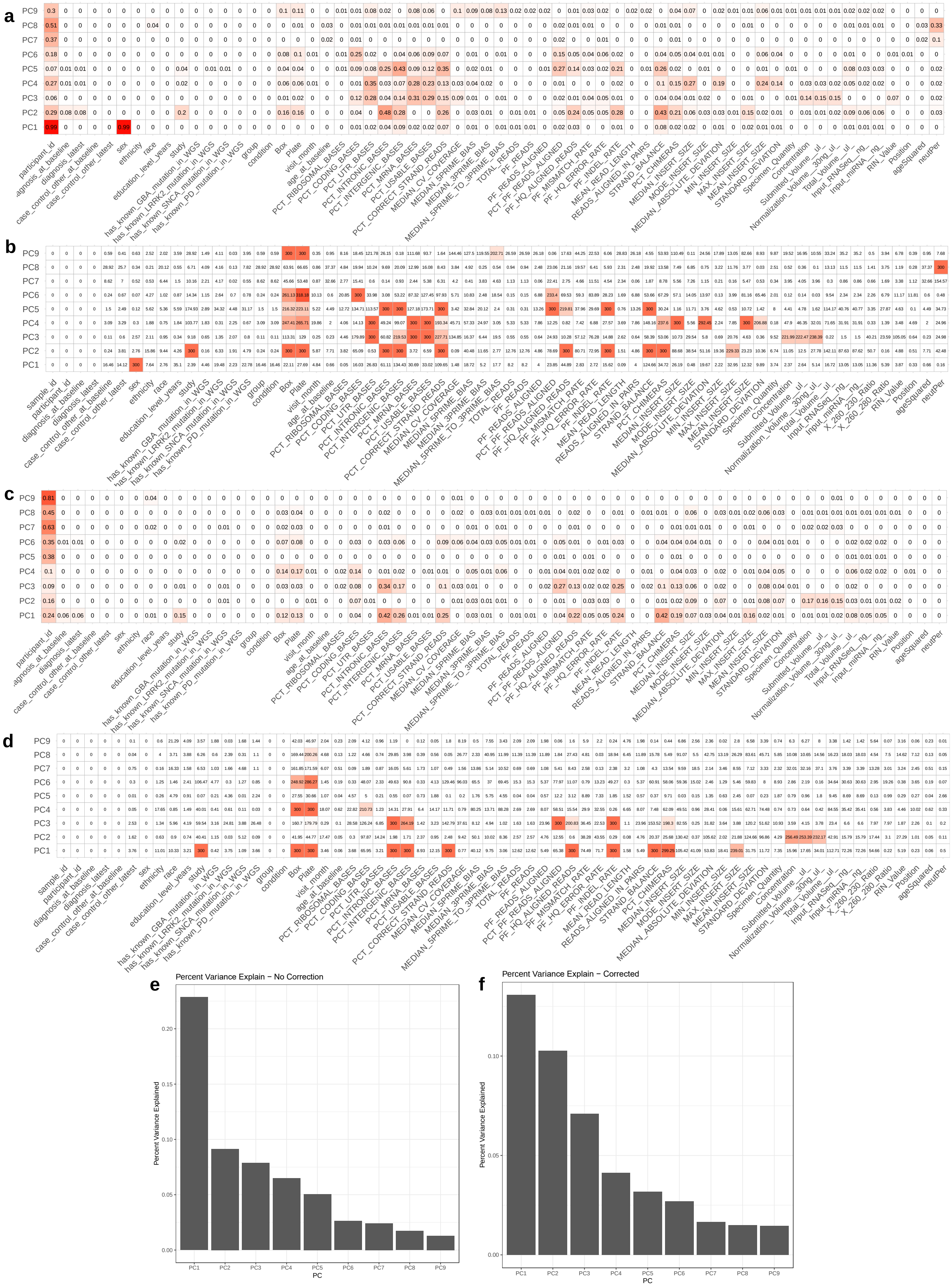
Supplemental Table 1 | Blood cell-based linear model genes and coefficient estimates.

	Coefficient	Std Error	T value	P value
(Intercept)	-157.6	6.996	-22.52	0
ENSG00000151948	2.138	0.7743	2.761	0.005869
ENSG00000153179	-2.558	0.8106	-3.156	0.001650
ENSG00000179299	1.688	0.4408	3.829	0.0001366
ENSG00000143226	-4.342	0.7855	-5.527	0
ENSG00000173110	1.362	0.4507	3.021	0.002583
ENSG00000196549	-2.219	0.4847	-4.579	0
ENSG00000062716	5.451	0.7661	7.115	0
ENSG00000146592	-1.169	0.4500	-2.598	0.009522
ENSG00000163162	6.500	1.043	6.234	0
ENSG00000102010	2.596	0.4706	5.521	0
ENSG00000181274	-2.015	0.5764	-3.495	0.0004975
ENSG00000138463	-2.471	0.6754	-3.659	0.00026661
ENSG00000148572	3.838	0.6504	5.902	0
ENSG00000197208	3.137	0.5838	5.373	0
ENSG00000128594	3.248	0.6099	5.326	0
ENSG00000070731	2.087	0.4887	4.271	0
ENSG00000165046	4.371	0.6230	7.016	0

Supplemental Table 2 | Mutual information feature selection-based linear model genes and coefficient estimates.

	Coefficient	Std Error	T value	P value
(Intercept)	-119.1	19.45	-6.124	0
ENSG00000205927	-0.5725	0.2368	-2.417	0.01583
ENSG00000113389	3.602	0.6545	5.502	0
ENSG00000164047	1.002	0.2224	4.507	0
ENSG00000167186	-3.047	0.9139	-3.335	0.0008862
ENSG00000151012	1.194	0.4800	2.488	0.01301
ENSG00000179299	1.429	0.3890	3.673	0.0002529
ENSG00000143226	-3.080	0.6326	-4.868	0
ENSG00000133687	-0.3179	0.1252	-2.539	0.01128
ENSG00000134827	1.067	0.4715	2.264	0.02381
ENSG00000172292	-1.330	0.5919	-2.248	0.02482
ENSG00000038219	3.638	0.7248	5.020	0
ENSG00000158488	-2.470	0.6610	-3.736	0.0001977
ENSG00000135373	2.594	0.7782	3.333	0.0008923
ENSG00000204345	-0.7559	0.2935	-2.576	0.0101458
ENSG00000196549	-1.345	0.4162	-3.232	0.001272
ENSG00000062716	6.168	0.7486	8.239	0
ENSG00000050748	-5.986	0.9333	-6.412	0
ENSG00000164187	-2.387	0.5955	-4.008	0
ENSG00000124721	1.213	0.4704	2.579	0.01005
ENSG00000108846	-0.5261	0.2389	-2.203	0.02785
ENSG00000150051	-2.078	0.6796	-3.058	0.002289
ENSG00000149516	-1.494	0.3243	-4.607	0
ENSG00000163162	4.403	0.9119	4.829	0
ENSG00000175793	3.267	0.8585	3.805	0.0001506
ENSG00000083290	3.250	0.7634	4.257	0
ENSG00000092969	-2.166	0.7468	-2.900	0.003810
ENSG00000148572	3.133	0.6347	4.937	0
ENSG00000197208	2.177	0.5319	4.092	0
ENSG00000128594	1.819	0.5224	3.483	0.0005188
ENSG00000070731	1.389	0.4644	2.992	0.002846
ENSG00000165046	1.571	0.5831	2.695	0.007159

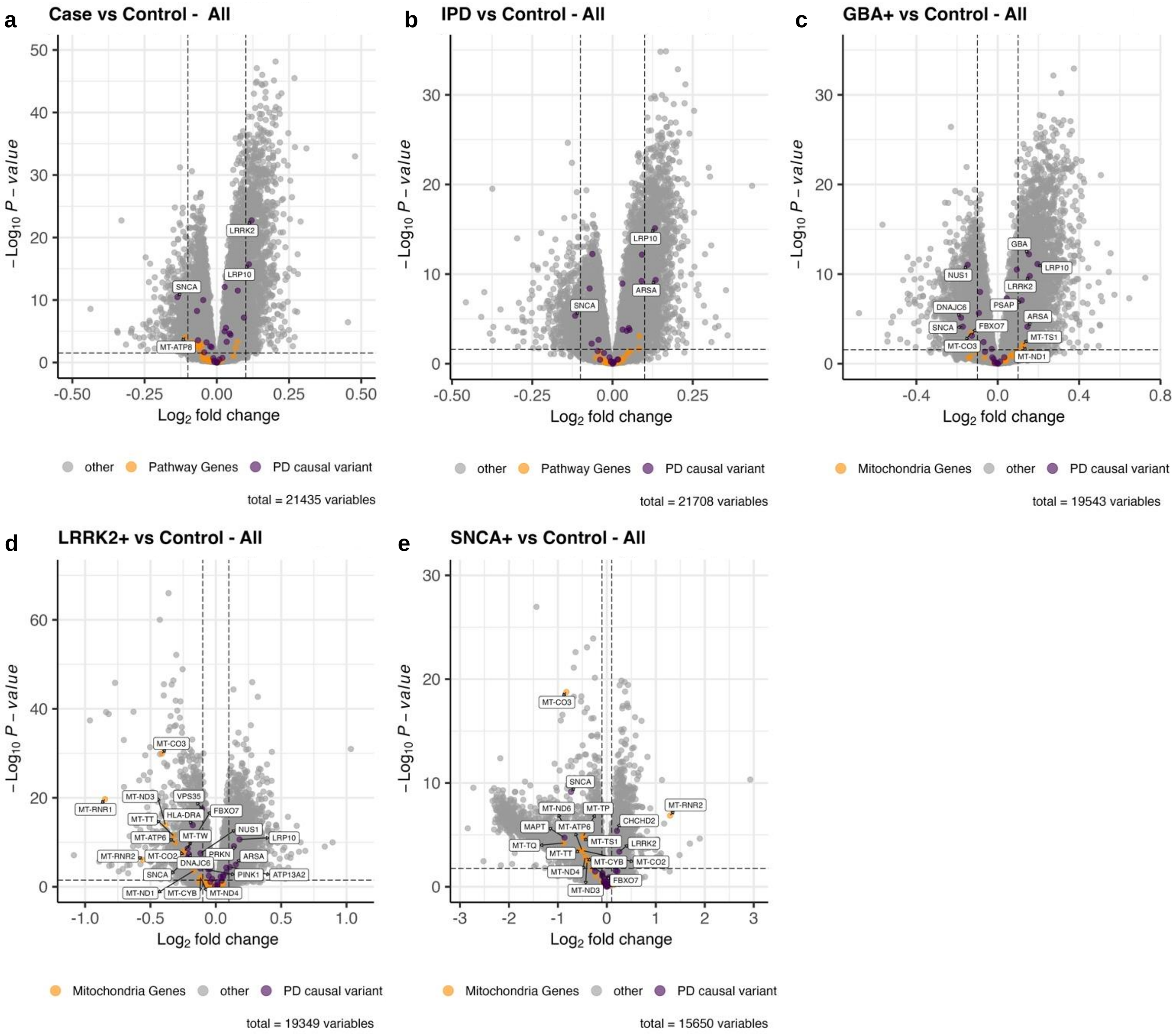
Supplemental Table 3 | Combined feature selection linear model genes and coefficient estimates.



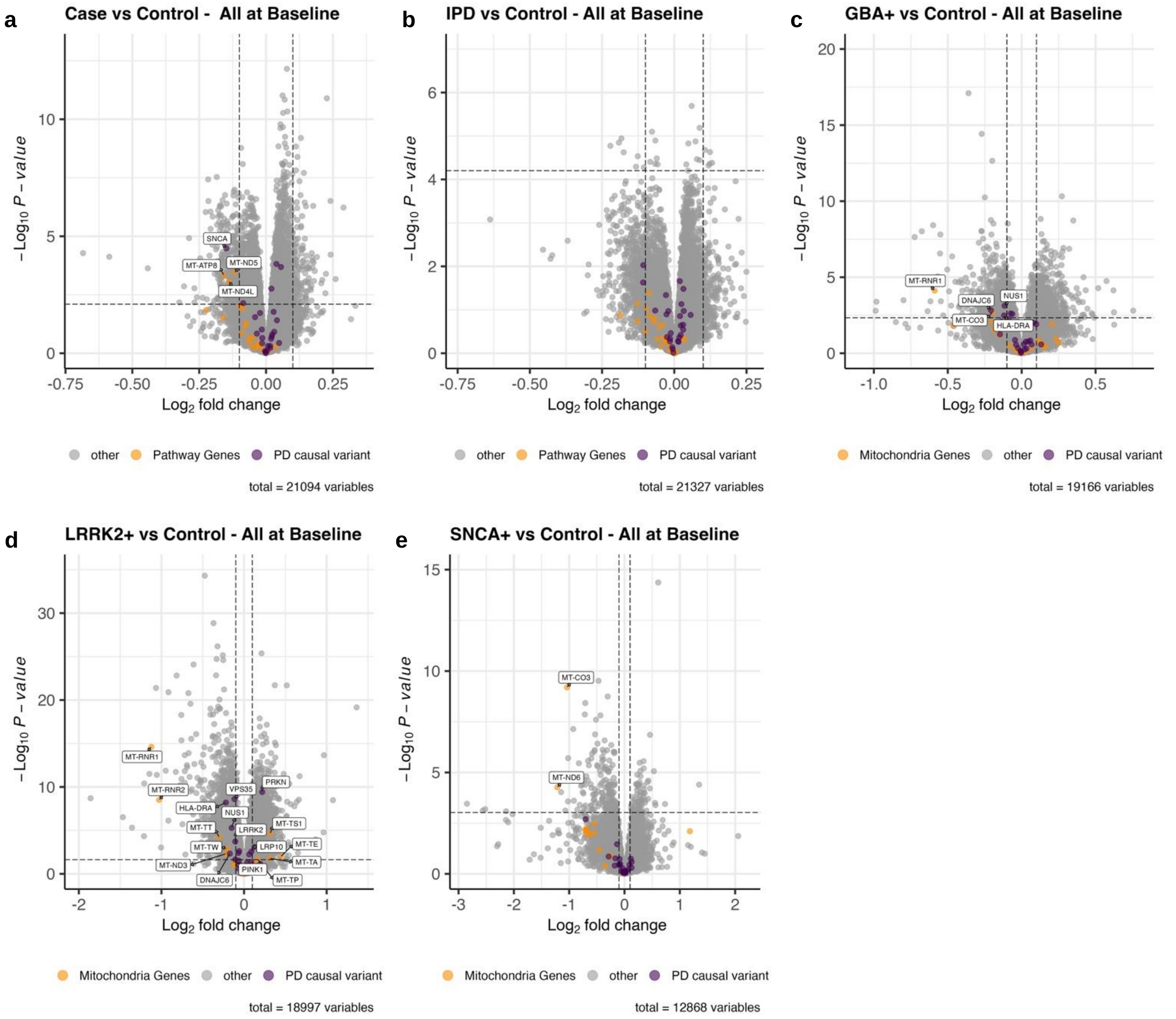
Supplemental Figure 1 | PCA analysis of whole blood transcriptomic variance. a,b,c,d, PCs were correlated to sample demographic, QC, and clinical data. Correlation with categorical values (such as participant_id, study, etc.) were calculated using the intraclass correlation coefficient. Continuous value correlations were calculated with spearman rho. Plots were created both without batch correction (**a**) with associated p-values (**b**) and with case, sex, predicted neutrophil percentage (neutPer), mrna base percentage, and age-squared correction (**c**) with associated p-values (**d**). All correlations are statistically significant. **e,f,** Plots of percent variance explained by each PC without correction (**e**) and with correction (**f**).

Design	Upregulated	Downregulated	Total	SNCA Adjusted P-value rank
~0 + case	1772	1000	2772	1458
~0 + case + sex	1523	765	2288	1320
~0 + case + sex + neutPer	184	441	625	31
~0 + case + sex + neutPer + plate	174	390	564	54
~0 + case + sex + neutPer + study	217	384	601	38
~0 + case + sex + neutPer + ageSquared	135	329	464	20
~0 + case + sex + neutPer + ageSquared + intronicBases	126	334	460	21
~0 + case + sex + neutPer + ageSquared + mrnaBases	110	357	467	18
~0 + case + sex + ageSquared + mrnaBases	1224	530	1754	973

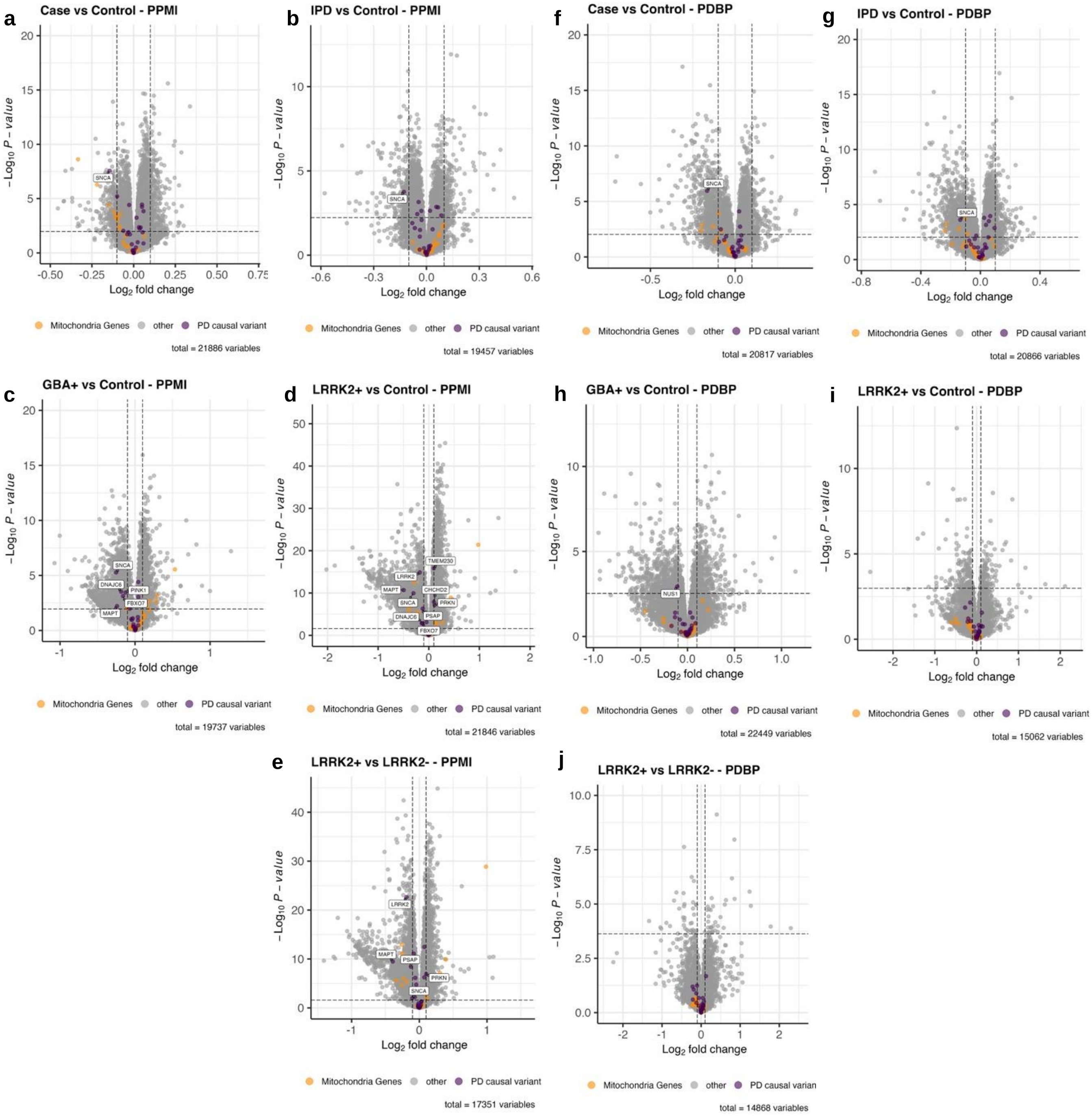
Supplemental Table 4 | Design testing for PD differential expression analysis. Testing was conducted with PD case vs all control samples. The design with the highest SNCA rank was used for all DE analyses in the study.



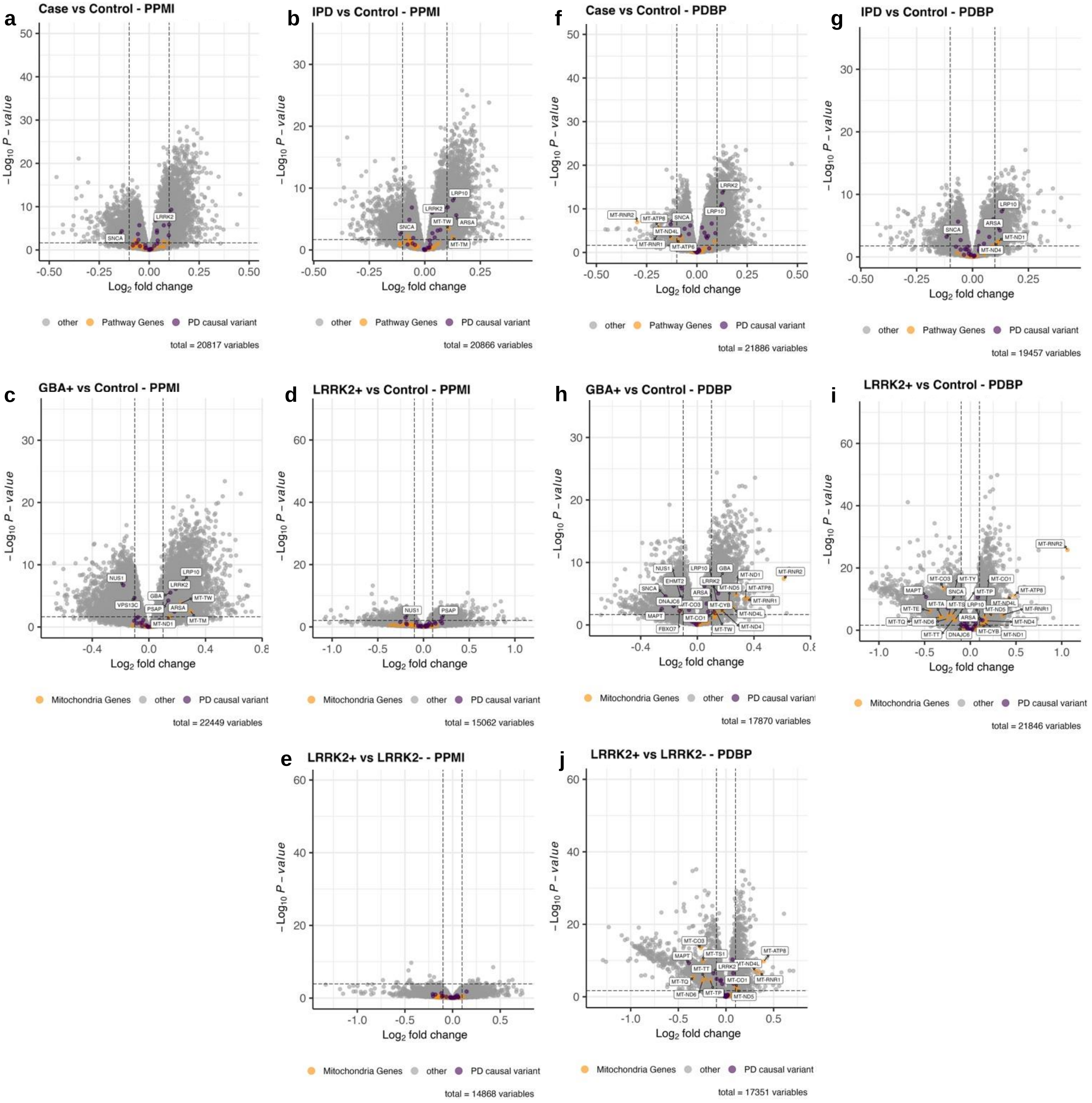
Supplemental Figure 2 | Differential expression analysis of PD case cohorts vs control without predicted neutrophil percentage correction. PD causal variants are colored purple, and mitochondrial genes are colored orange. Differentially expressed PD causal variants are additionally labeled by gene name. **a,** All PD cases were compared to all control samples based on the diagnosis at baseline. **b,** Idiopathic case samples with no SNCA+/LRRK2+/GBA+ mutation were compared to control samples with no PD-related mutations. **c,d,e,** Control samples with no PD-related mutations were compared to case samples with GBA+ (**c**), LRRK2+ (**d**), and SNCA+ (**e**) mutations.



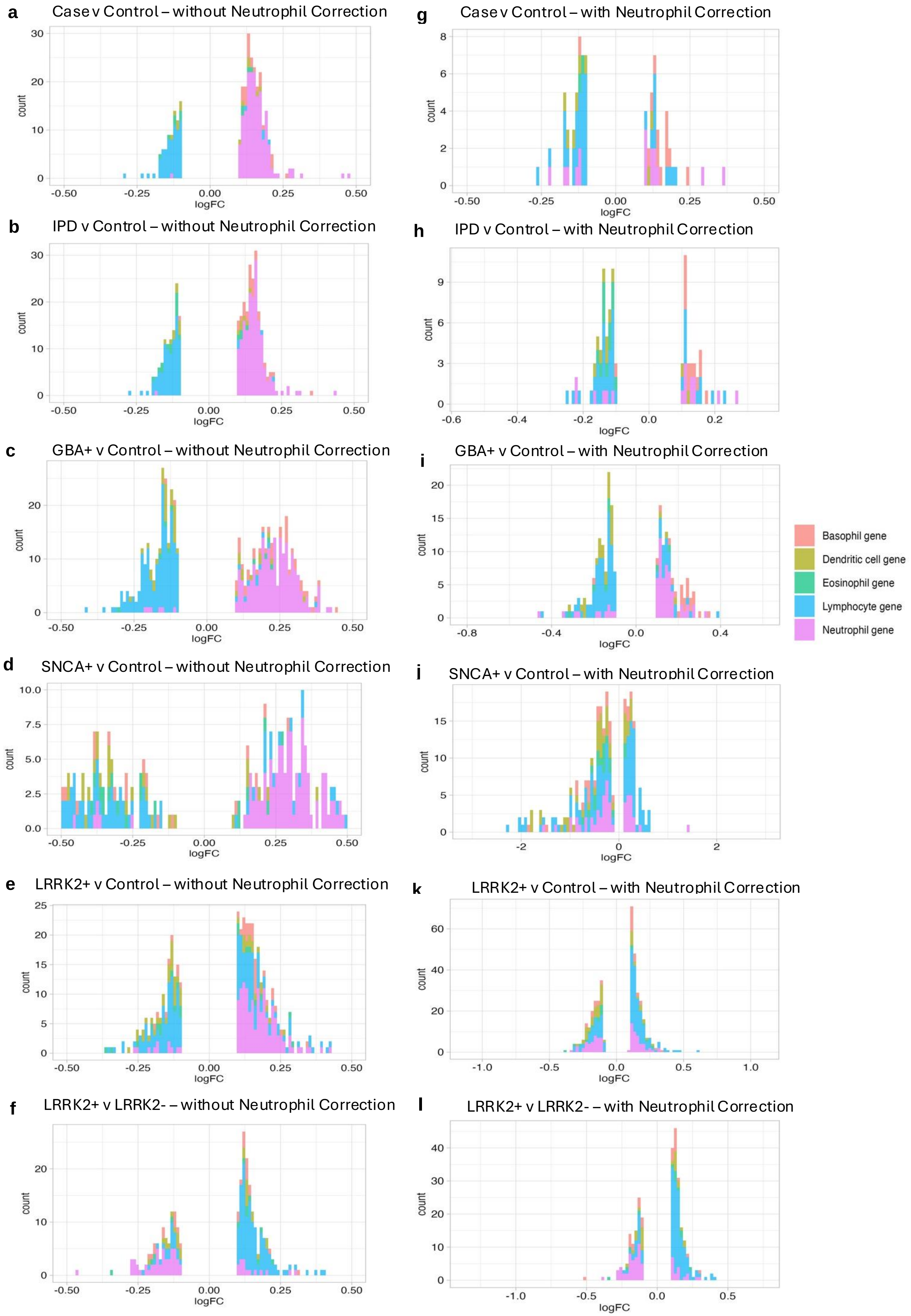
Supplemental Figure 3. Differential expression analysis of PD case cohorts vs control at baseline with predicted neutrophil percentage correction. All DE analyses were conducted with only baseline samples taken upon initial enrollment into either the PPMI or PDBP study. PD causal variants are colored purple, and mitochondrial genes are colored orange. Differentially expressed PD causal variants are additionally labeled by gene name. **a,** All PD cases were compared to all control samples based on the diagnosis at baseline. **b,** Idiopathic case samples with no SNCA+/LRRK2+/GBA+ mutation were compared to control samples with no PD-related mutations. **c,d,e,** Control samples with no PD-related mutations were compared to case samples with GBA+ (**c**), LRRK2+ (**d**), and SNCA+ (**e**) mutations.



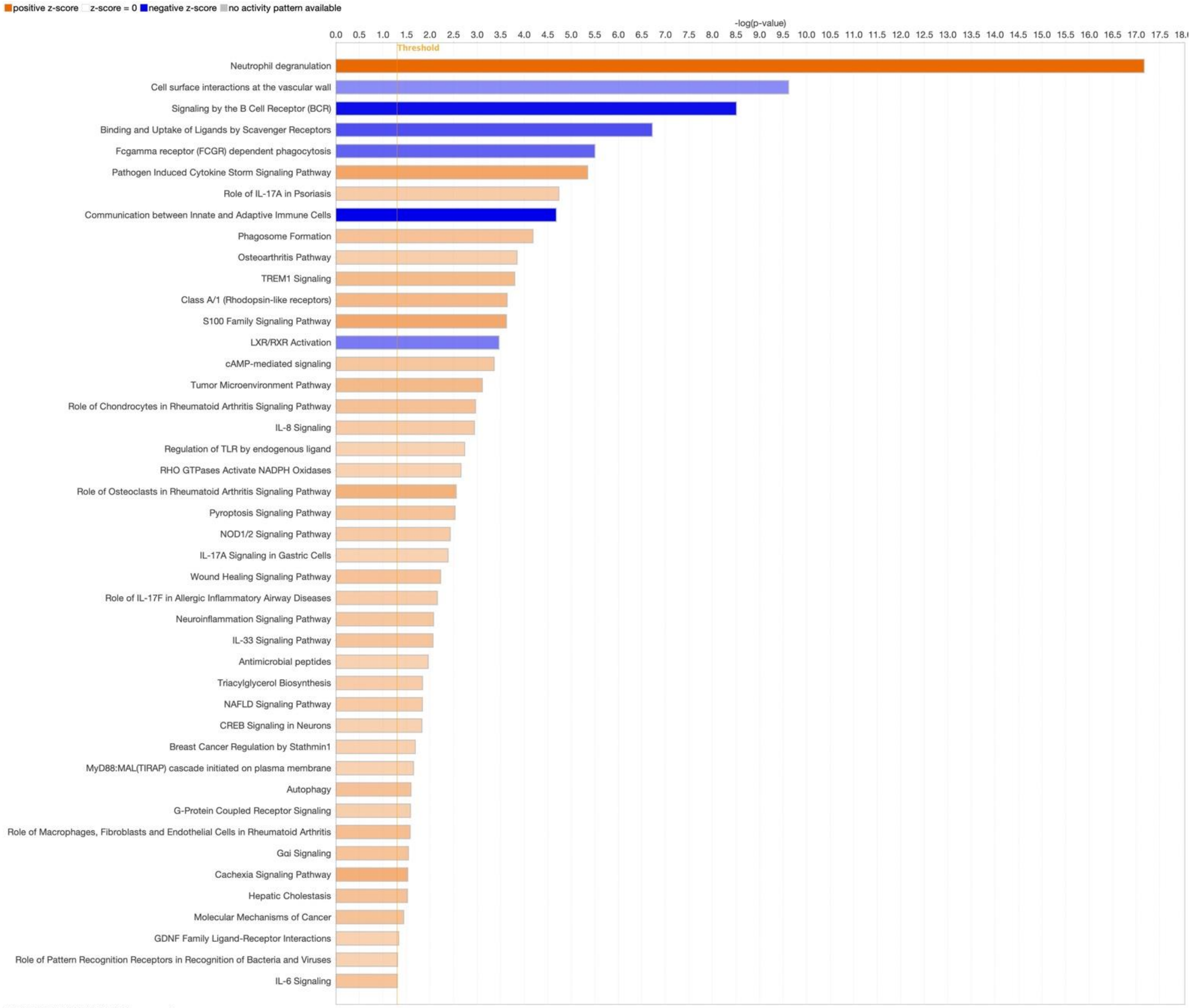
Supplemental Figure 4 | Differential expression analysis with predicted neutrophil percentage correction split by study. DE analyses were conducted with only PPMI samples. PD causal variants are colored purple, and mitochondrial genes are colored orange. Differentially expressed PD causal variants are additionally labeled by gene name. **a**, All PD cases were compared to all control samples based on the diagnosis at baseline. **b**, Idiopathic case samples with no SNCA+/LRRK2+/GBA+ mutation were compared to control samples with no PD-related mutations. **c,d,e,** Control samples with no PD-related mutations were compared to case samples with GBA+ (**c**) and LRRK2+ (**d**) mutations. LRRK2+ case vs LRRK2- case samples in PPMI were also compared (**e**). **f,g,h,i,j,** The same analyses were conducted, but this time with only PDBP sample. SNCA+ samples were only present in PPMI and were included in Figure 4.



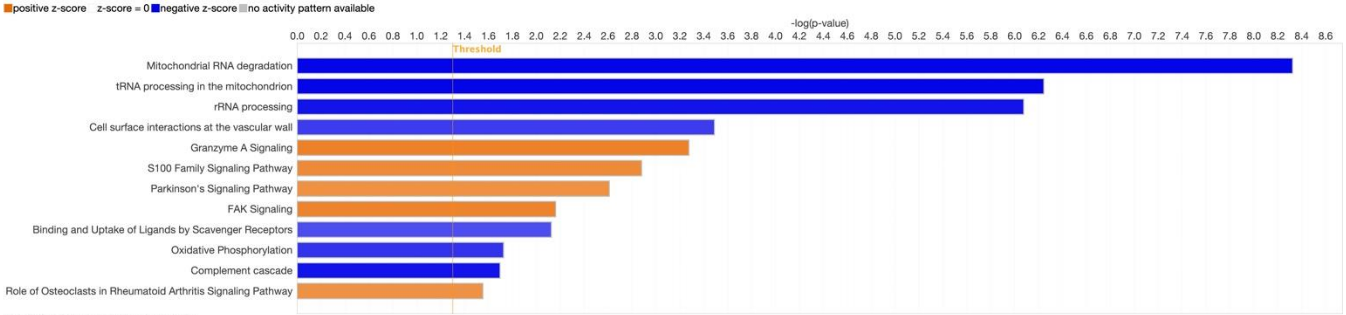
Supplemental Figure 5 | Differential expression analysis without predicted neutrophil percentage correction split by study. DE analyses were conducted with only PPMI samples but without including predicted neutrophil percentage in the covariate design. PD causal variants are colored purple, and mitochondrial genes are colored orange. Differentially expressed PD causal variants are additionally labeled by gene name. **a,** All PD cases were compared to all control samples based on the diagnosis at baseline. **b,** Idiopathic case samples with no SNCA+/LRRK2+/GBA+ mutation were compared to control samples with no PD-related mutations. **c,d,e,** Control samples with no PD-related mutations were compared to case samples with GBA+ (**c**) and LRRK2+ (**d**) mutations. LRRK2+ case vs LRRK2- case samples in PPMI were also compared (**e**). **f,g,h,i,j,** The same analyses were conducted, but this time with only PDBP sample. SNCA+ samples were only present in PPMI and were included in Supplemental Figure 2.



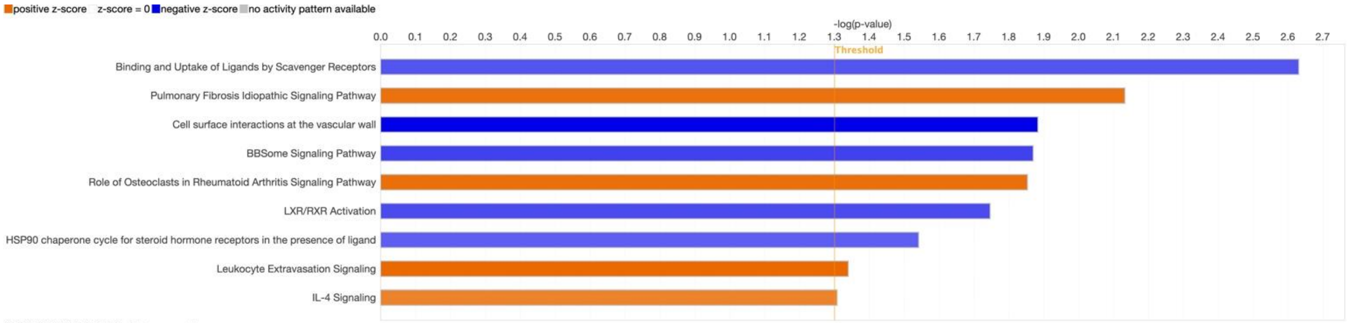
Supplemental Figure 6 | Bar plots of differential expressed blood cell-enriched genes by PD cohort vs control comparison. a,b,c,d,e,f, Blood cell-enriched genes that are differentially expressed in DE analyses without including predicted neutrophil percentage in covariate design. **g,h,i,j,k,l,** Blood cell-enriched genes that are differentially expressed in DE analyses with predicted neutrophil percentage in covariate design.



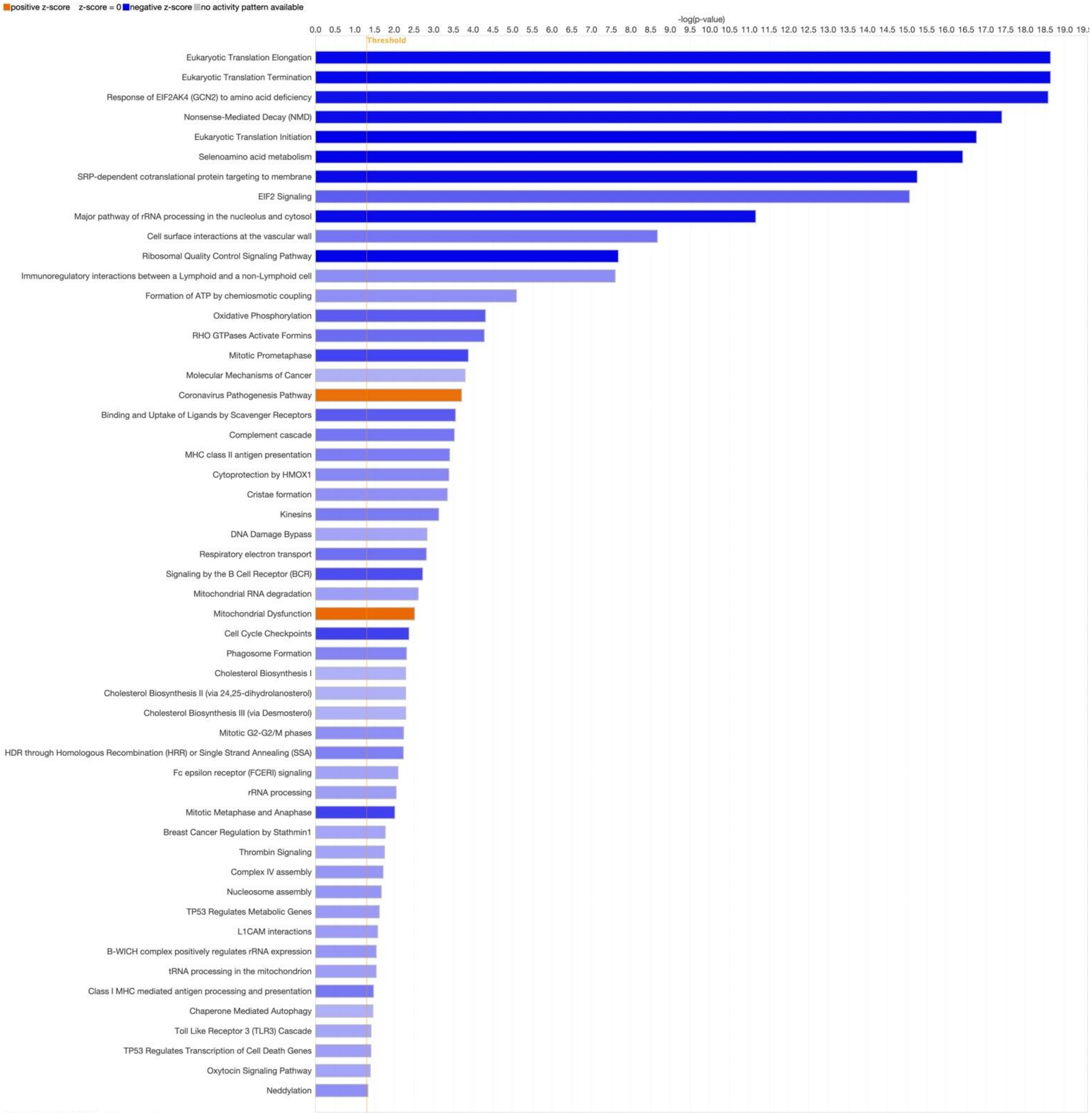
Supplemental Figure 7 | Differentially expressed pathways in PD case vs control in all samples without predicted neutrophil percentage correction.



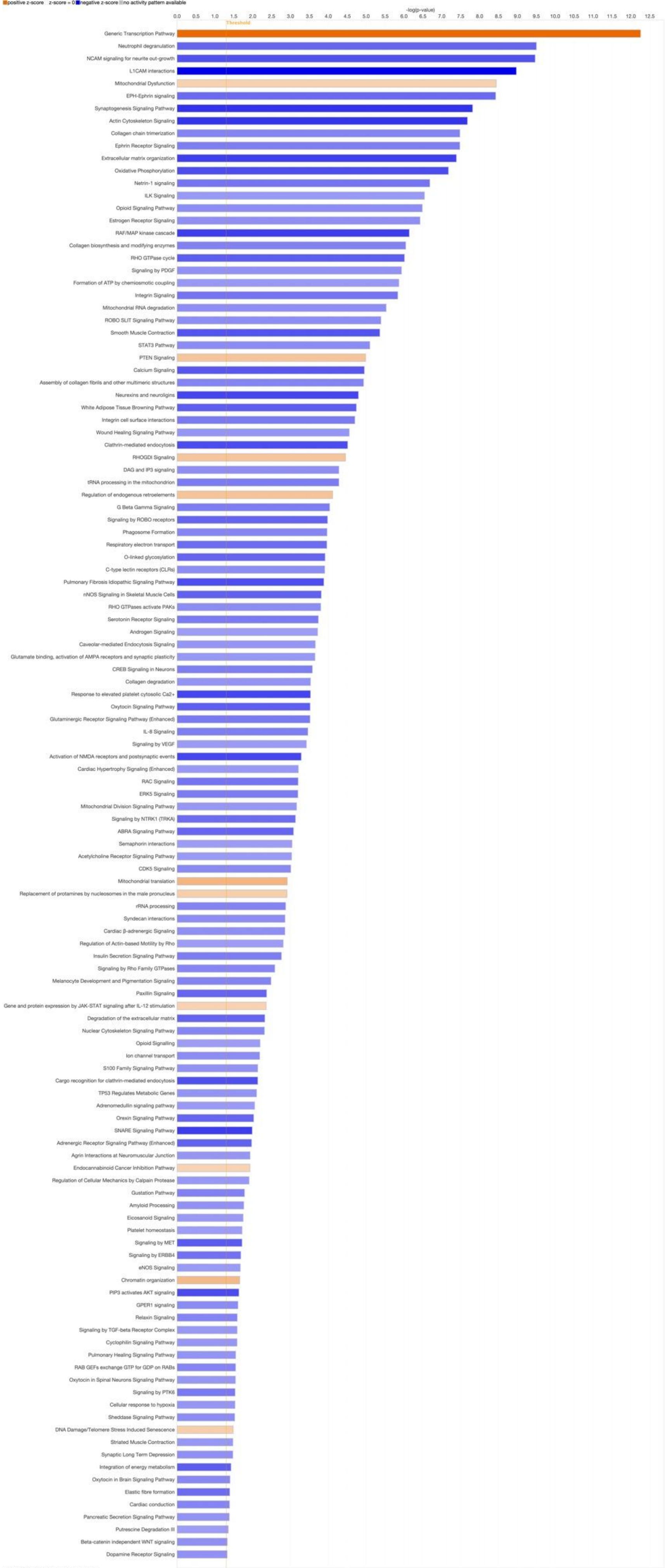
Supplemental Figure 8 | Differentially expressed pathways in PD case vs control in all samples with predicted neutrophil percentage correction.



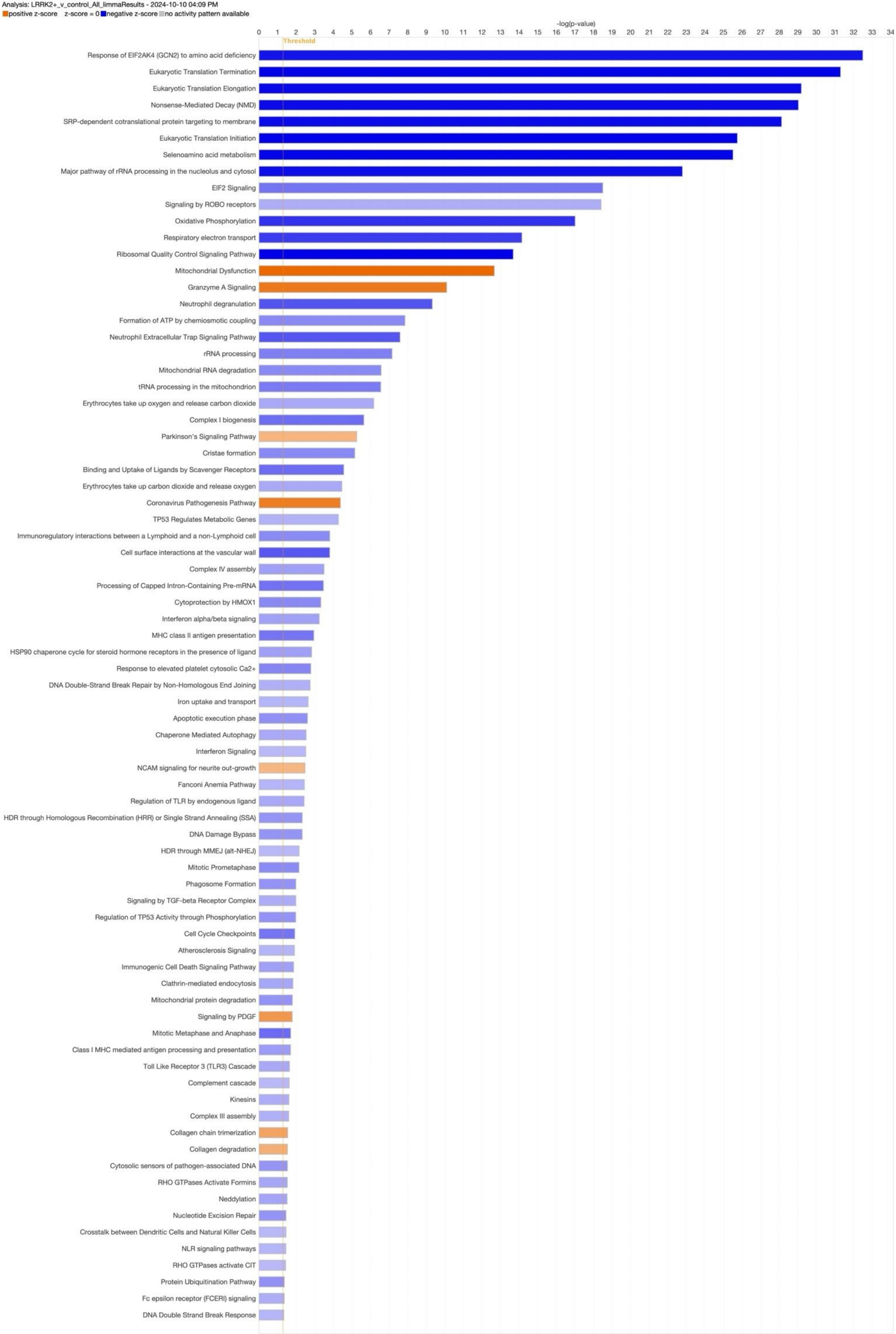
Supplemental Figure 9 | Differentially expressed pathways in IPD vs control in all samples with predicted neutrophil percentage correction.



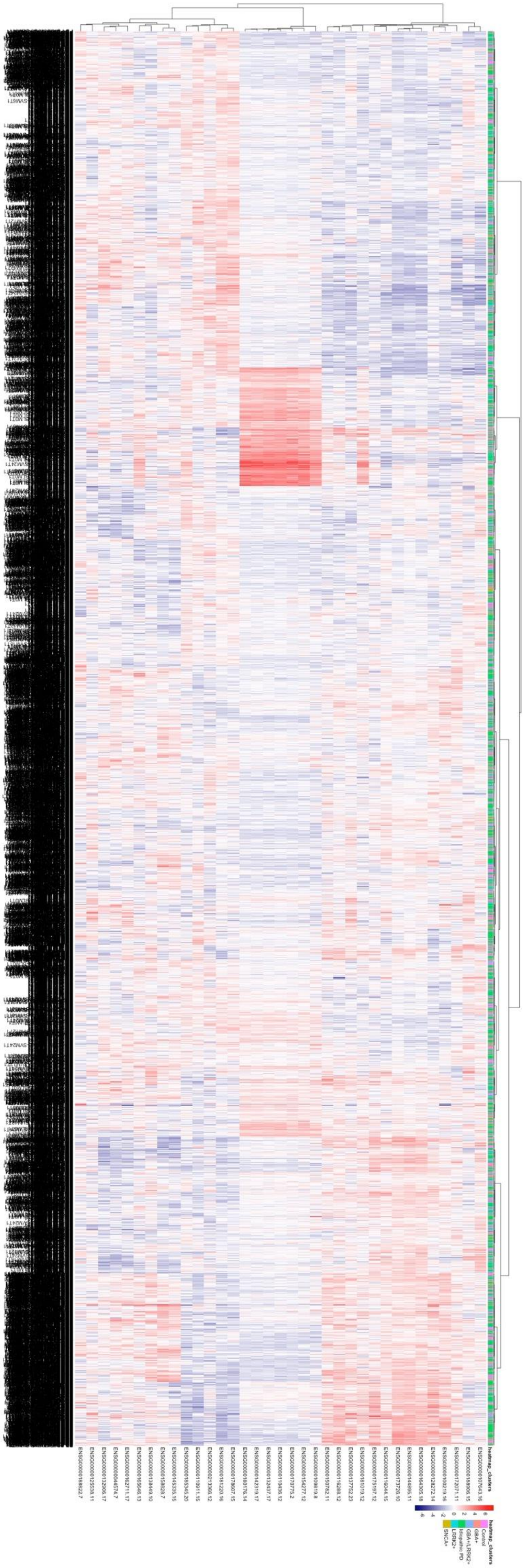
Supplemental Figure 10 | Differentially expressed pathways in GBA+ case vs control in all samples with predicted neutrophil percentage correction.



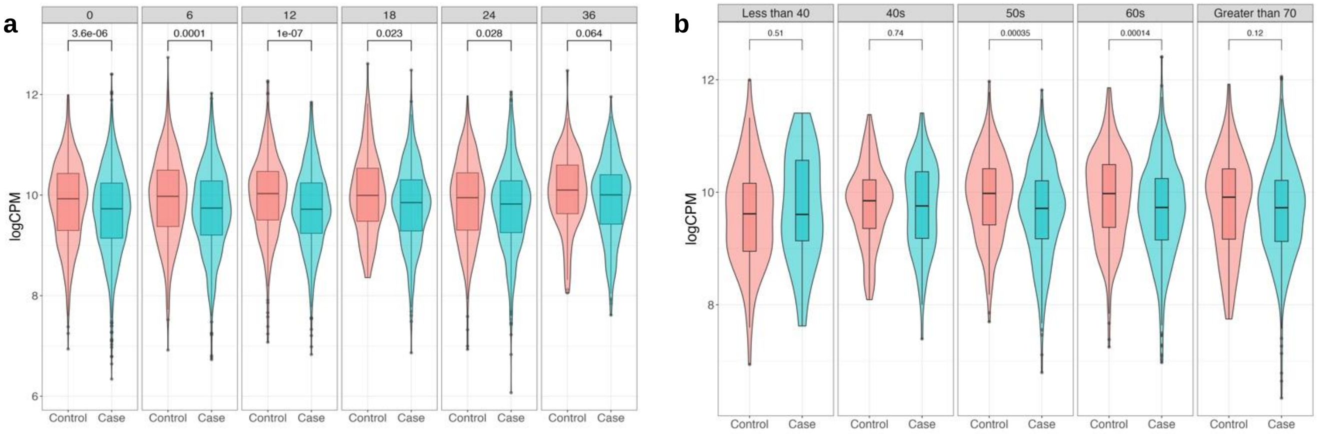
Supplemental Figure 11 | Differentially expressed pathways in SNCA+ case vs control in all samples with predicted neutrophil percentage correction.



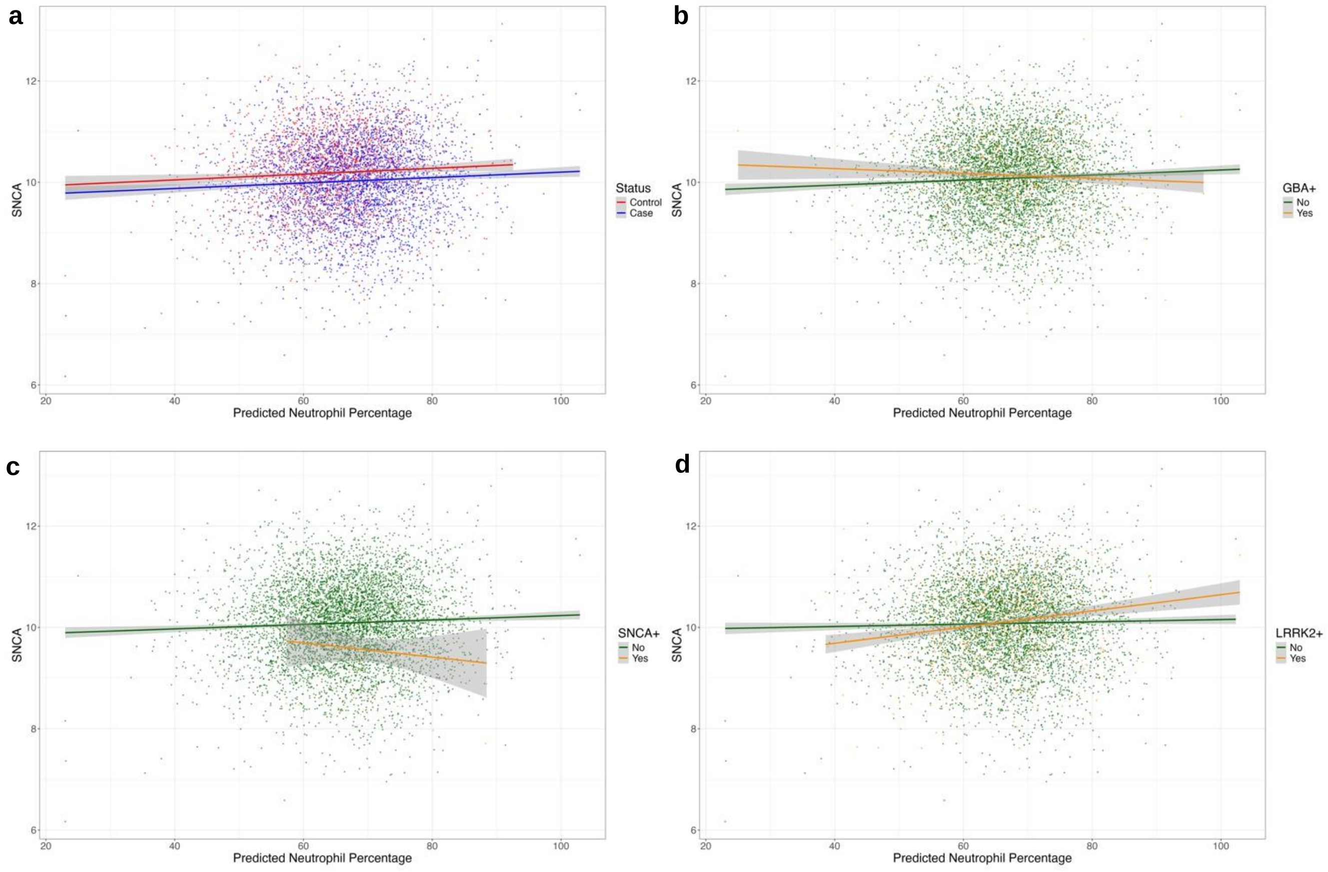
Supplemental Figure 12 | Differentially expressed pathways in LRRK2+ case vs control in all samples with predicted neutrophil percentage correction.



Supplemental Figure 13 | Hierarchical clustering of PPMI and PDBP samples by 'Parkinson's Signaling Pathway' genes.



Supplemental Figure 14 | SNCA expression plots by participant visit month and age at baseline sample. SNCA gene counts were log(CPM) normalized and corrected for predicted neutrophil percentage. **a,** Violin plots of SNCA expression stratified by visit month. **b,** Violin plots of SNCA expression stratified by age at enrollment into PPMI or PDBP. A two-tailed Wilcoxon test was applied to compare case and control expression.



Supplemental Figure 15 | SNCA expression by predicted neutrophil percentage. SNCA counts were log(CPM) normalized for plotting. **a**, SNCA expression by predicted neutrophil percentage, colored by disease status (PD case and control). **b**, SNCA expression by predicted neutrophil percentage in GBA+ and GBA- samples. **c**, SNCA expression by predicted neutrophil percentage in SNCA+ and SNCA- samples. **d**, SNCA expression by predicted neutrophil percentage in LRRK2+ and LRRK2- samples.