SUPPLEMENTARY INFORMATION

Methylation patterns of the nasal epigenome of hospitalized SARS-CoV-2 positive patients reveals insight into molecular mechanisms of COVID-19

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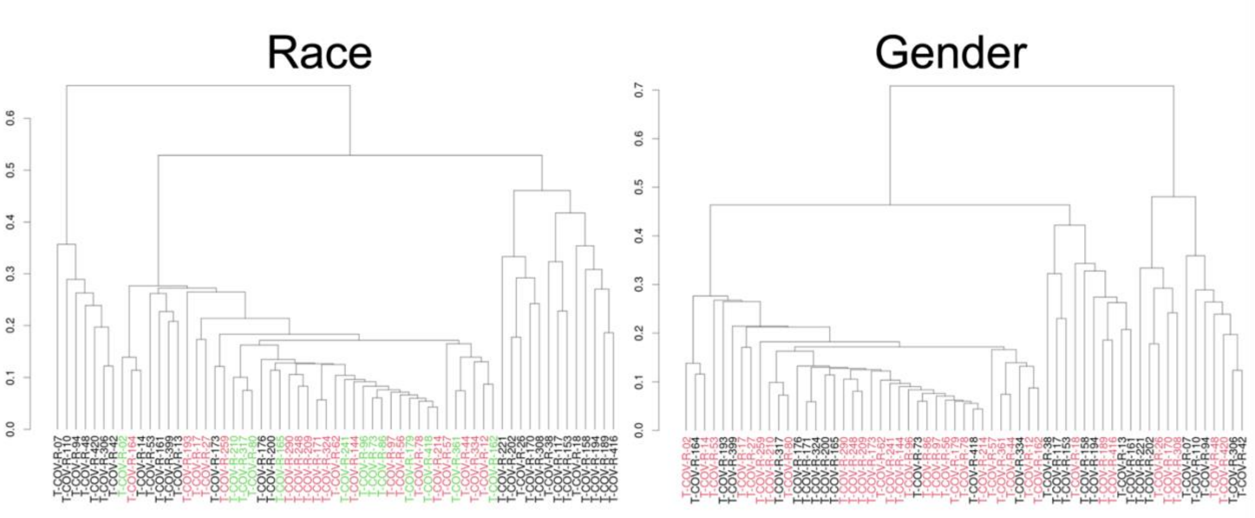
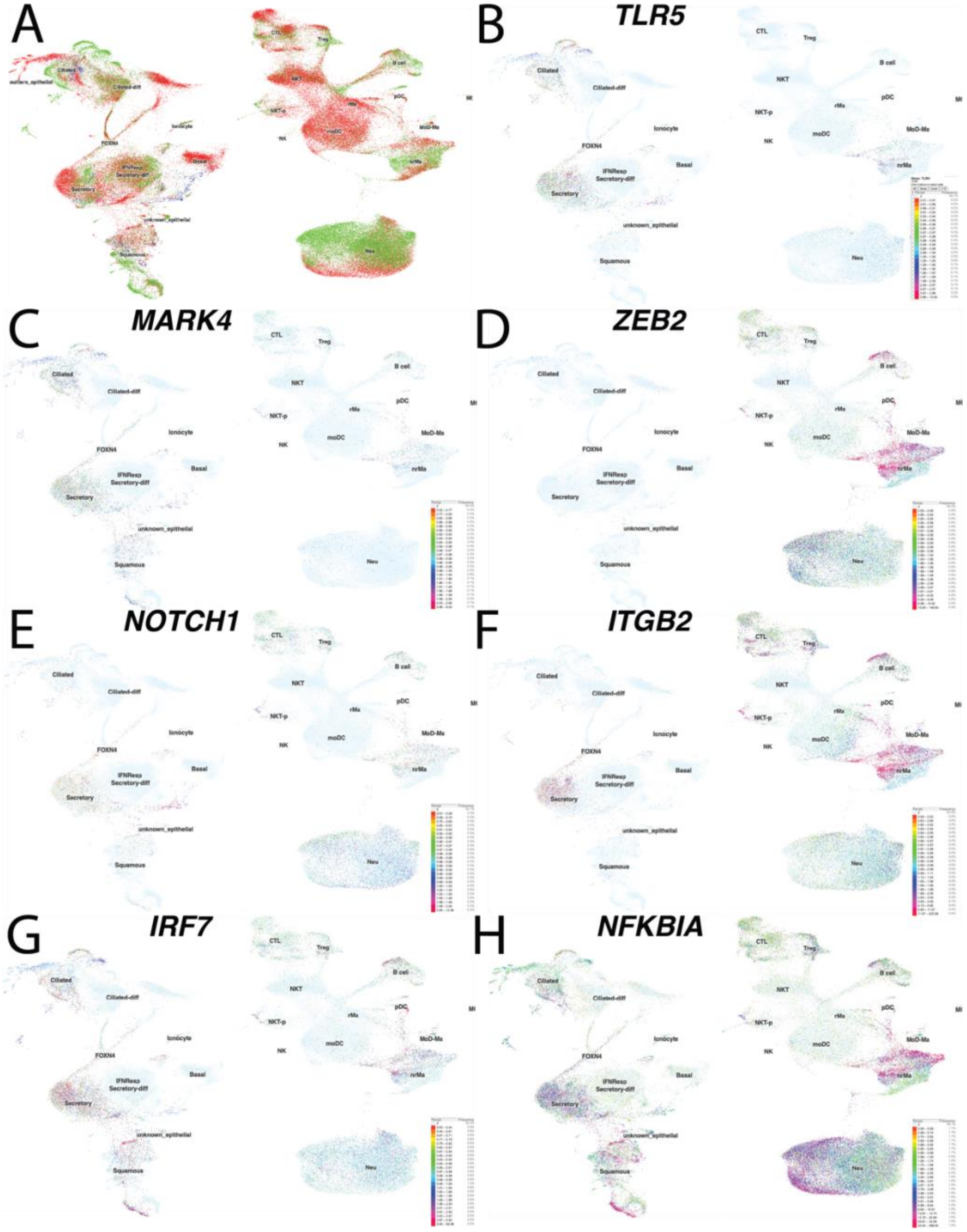
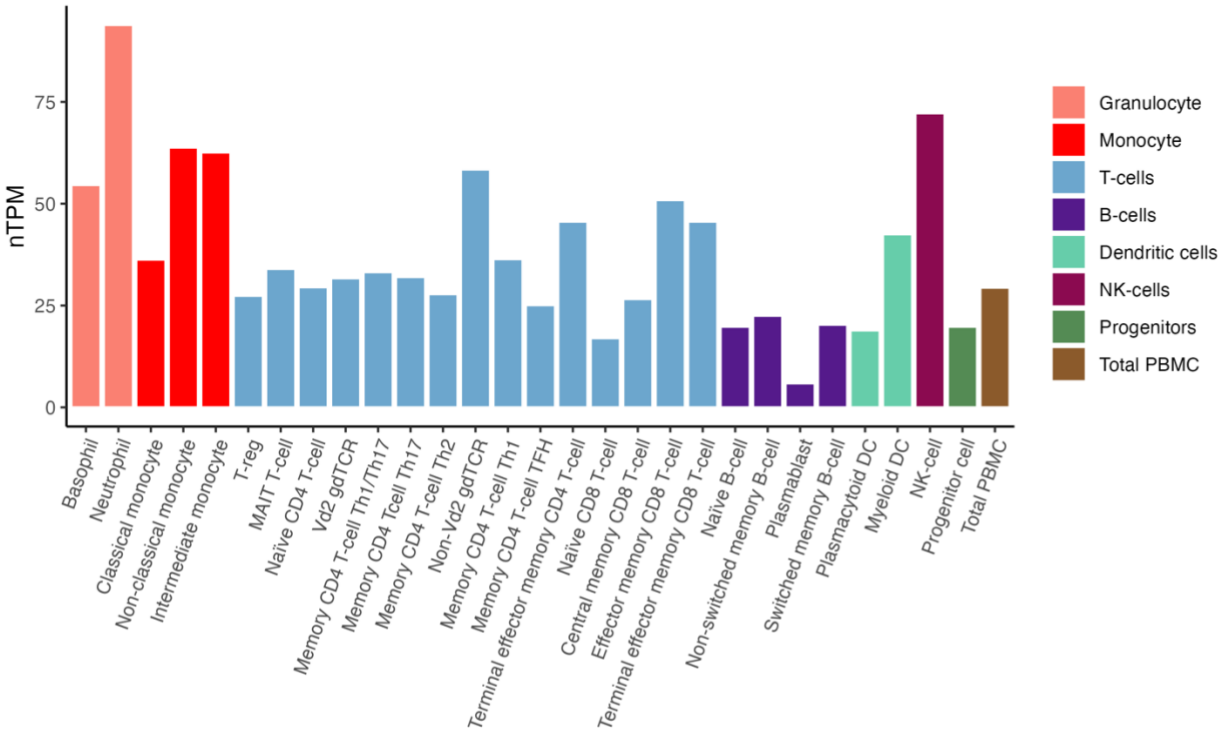


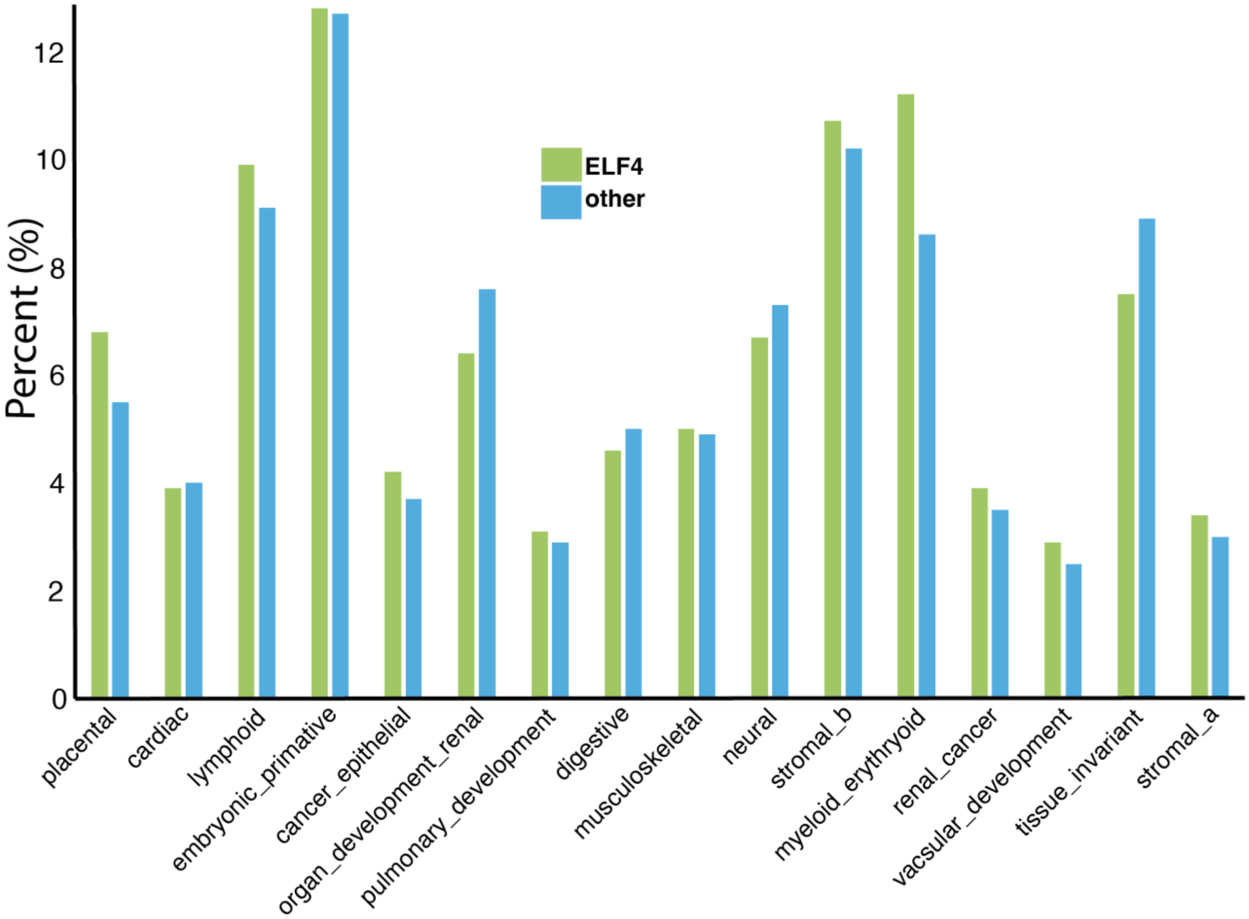
Supplemental Figure 1: Hierarchical clustering of COVID-19 positive individuals shows no clustering by race or gender. Hierarchical clustering was performed at the top 25th percentile most variable CpG methylation sites and showed no clustering structure by race (Black individuals = Black, Caucasian individuals = Green, Other races = Red), or gender (Female = Black, Male = Red).



Supplemental Figure 2: CTL = Cytotoxic T lymphocytes, MC = Mast cell, moDC = Monocyte-derived dendritic cell, MoD-Ma = Monocyte-derived macrophage, Neu = Neutrophil, NK = Natural killer cell, NKT = NK T cell, NKT-p = Proliferating NKT cell, nrMA = non-resident macrophage, pDC = Plasmacytoid dendritic cell, rMA = Resident macrophage, Treg = Regulatory T cell. UMAP demonstrating differential gene expression by disease severity and cell-type in the nasopharynx. **(A)** Clustering by COVID-19 severity, Blue = Control, Red= Mild/moderate disease, Green = Critical disease. Gene expression as determined by scRNA-seq of **(B)** *TLR5,* **(C)** *MARK4*, **(D)** *ZEB2*, **(E)** *NOTCH1*, **(F)** *ITGB2*, **(G)** *IRF7*, **(H)** *NFKBIA.* Figure generated using the dataset of Chua *et al.* and the UCSC Cell Browser (https://covid-airways.cells.ucsc.edu) [45,47].



Supplemental Figure 3: ***ELF4*** **expressed broadly across immune cell types.** Presented as normalized transcripts per million (y-axis). Granulocytes = pink, Monocytes = red, T-cells = blue, B-cells = purple, Dendritic cells = teal, NK cells = magenta, Progenitors = olive, Total PBMC = brown. Figure generated using dataset of Monaco *et al.* Image credit: Human Protein Atlas. Image available from: v23.proteinatlas.org/ENSG00000102034-ELF4/immune+cell



Supplemental Figure 4: **Distribution of *ELF4* transcription factor binding motifs across cell type-specific DHSs.** Among hypermethylated regions, a higher percentage of *ELF4* transcription factor binding motifs (blue) localize to myeloid specific DHSs as compared to hypermethylated DMRs that are not targets of the *ELF4* transcription factor (orange).

Supplemental Table 1: Percent UMR and LMR overlapping regulatory elements by cell type in COVID-19 positive (severe + mild) and negative individuals.

	Overlapping single or multiple cell types				**Overlapping single cell type only**			
Cell Type	**COVID-19 Status**		[a]**Fold Difference**	[b]***p***	**COVID-19 Status**		[a]**Fold Difference**	[b]***p***
	Positive (%)	Negative (%)			Positive (%)	Negative (%)		
Immune								
UMR	64	62	1.0	0.0054	8	4	1.9	0.069
LMR	46	25	1.9	$< 2.2 \times 10^{-16}$	31	8	4.1	0.0037
Lymphoid								
UMR	49	48	1.0	0.051	5	3	1.8	0.21
LMR	24	15	1.6	$< 2.2 \times 10^{-16}$	11	4	2.6	5.6×10^{-16}
Myeloid								
UMR	33	32	1.0	0.0015	3	1	2.5	0.26
LMR	28	12	2.4	$< 2.2 \times 10^{-16}$	20	3	6.3	$< 2.2 \times 10^{-16}$
Pulmonary								
UMR	15	17	0.91	7.0×10^{-5}	0.6	0.7	0.83	1.0
LMR	7	10	0.66	$< 2.2 \times 10^{-16}$	2	3	0.27	$< 2.2 \times 10^{-16}$
Epithelial								
UMR	13	17	0.76	$< 2.2 \times 10^{-16}$	0.6	3	0.18	0.032
LMR	8	19	0.43	$< 2.2 \times 10^{-16}$	3	11	0.22	$< 2.2 \times 10^{-16}$

[a] Fold difference between COVID-19 positive *vs* negative patients

[b] *p*-value reflects chi-square examining COVID-19 positive *vs* negative patients

Supplemental Table 2: Percent UMR and LMR overlapping regulatory elements by cell type in severe and mild COVID-19.

	Overlapping single or multiple cell types				**Overlapping single cell type only**			
Cell Type	**COVID-19 Status**		[a]**Fold Difference**	[b]***p***	**COVID-19 Status**		[a]**Fold Difference**	[b]***p***
	Severe (%)	Mild (%)			Severe (%)	Mild (%)		
Immune								
UMR	64	64	1.0	0.84	9	9	1.1	0.87
LMR	44	46	0.97	2.5×10^{-6}	28	31	0.90	9.3×10^{-8}
Lymphoid								
UMR	49	49	1.0	0.86	6	6	1.1	0.89
LMR	24	24	1.0	0.74	10	11	0.96	0.25
Myeloid								
UMR	34	33	1.0	0.55	3	3	1.0	1.0
LMR	26	28	0.94	1.8×10^{-9}	18	20	0.87	1.1×10^{-7}
Pulmonary								
UMR	15	15	1.0	0.89	0.3	0.3	0.95	1.0
LMR	7	7	0.99	0.59	1	2	0.93	0.50
Epithelial								
UMR	13	13	1.0	0.45	2	0.6	2.8	0.32
LMR	9	8	1.1	4.8×10^{-8}	4	3	1.4	5.1×10^{-6}

[a] Fold difference between severe *vs* mild COVID-19 patients

[b] *p*-value reflects chi-square examining severe *vs* mild COVID-19 patients

Supplemental Table 7: PI3k/Akt pathway associated DMRs. Methylation difference reflects percent difference in mean regional methylation between hospitalized versus non-hospitalized COVID-19 subjects.

Gene	**Chromosome**	**Start**	**Stop**	**Methylation difference (%)**	***q*-value**
AKT1	chr14	104796001	104796500	-18.38	2.22×10^{-22}
ISG15	chr1	1013751	1014250	-32.27	2.49×10^{-35}
ZEB2	chr2	144524251	144524750	-24.39	2.52×10^{-32}
SNAI1	chr20	49983251	49983750	-28.98	6.11×10^{-16}
TLR5	chr1	223133001	223133750	-15.09	1.22×10^{-16}
MARK4	chr19	45248251	45248750	-10.08	2.33×10^{-19}
NOTCH1	chr9	136549501	136550000	-20.24	2.23×10^{-16}
ITGB2	chr21	44923751	44924500	-22.09	1.08×10^{-33}
IRF7	chr11	615001	615500	-17.76	1.43×10^{-33}
NFKBIA	chr14	35402001	35402500	-15.80	1.02×10^{-16}