

**Table S1. Non-synonymous (Ns) mutations of SARS-CoV-2 recovered from NT and lungs from mice infected or infected:challenged with WA1, Alpha or Delta.** To be included in the table, Ns mutation were present at a frequency higher than 1% and at a minimum depth of 100 reads per nucleotide.

Ns mutation	No. obs.	Group	dpi/dpc	Tissue	Ns mutation frequency (%)
ORF1a:A3697V	2	Alpha	3	lung	24.44
ORF1a:G82_M85delinsV	4	WA1	3	lung	1.1 - 1.97
ORF1a:G82_M85delinsV	1	Alpha	3	lung	3.68
ORF1a:I222V	2	WA1	3	lung	1.04 - 1.78
ORF1a:M85del	1	WA1	1	lung	1.88
ORF1a:M85del	3	WA1	3	lung	1.04 - 1.99
ORF1a:T1731I	4	WA1	3	lung	2.13 - 5.11
ORF1b:D2175fs	1	Alpha	3	lung	3.16
ORF1b:D2175fs	1	Alpha	1	NT	4.26
ORF1b:L2497F	2	WA1	1	lung	2.1 - 2.26
ORF1b:L2497F	4	WA1	3	lung	2.06 - 2.59
ORF1b:L2497F	3	WA1	1	NT	4.24 - 7.01
ORF1b:L2497F	3	WA1	3	NT	1.3 - 16.26
ORF1b:L2497F	2	Delta	1	lung	30-34
ORF1b:L2497F	2	Delta	3	lung	43.00
ORF1b:L2497F	3	Delta	1	NT	16 - 34
ORF1b:L2497F	2	Delta	3	NT	27 - 32
ORF1b:K2395N	1	Delta	1	lung	10.98
ORF1b:K2395N	2	Delta	3	lung	5.91 - 8.45
ORF1b:K2395N	4	Delta	1	NT	9.68 - 12.5
ORF1b:K2395N	1	Delta	3	NT	8.52
S:N148K	2	WA1	1	lung	1.3 - 2.15
S:N148K	2	WA1	3	lung	1.16 - 1.25
S:N149K	2	WA1	1	lung	1.15 - 1.78
S:N149K	3	WA1	3	lung	1.57 - 1.89
S:N149K	2	WA1	1	NT	2.12 - 2.14
S:N149K	1	WA1	3	NT	1.18
S:N99delinsKLNY	2	WA1	1	lung	1.18 - 2.13
S:N99delinsKLNY	2	WA1	3	lung	1.07 - 1.42
S:N99delinsKLNY	2	WA1	1	NT	2.42 - 5.23
S:N99delinsKLNY	2	WA1	3	NT	7 - 8.03
S:D215_L216insKLRS	3	WA1	1	lung	7.39 - 11.22
S:D215_L216insKLRS	3	WA1	3	lung	6.87 - 8.84
S:D215_L216insKLRS	4	WA1	1	NT	5.17 - 11.46
S:D215_L216insKLRS	2	WA1	3	NT	10.07 - 15.03
S:D215N	2	WA1	1	lung	1.08 - 1.5
S:D215N	1	WA1	3	lung	1.44
S:D215H	3	WA1	1	lung	29.75 - 33.84
S:D215H	4	WA1	3	lung	33.75 - 46.74
S:D215H	4	WA1	1	NT	17.52 - 44.34
S:D215H	3	WA1	3	NT	17.31 - 38.3
S:E1072K	2	Delta	3	NT	1.89 - 2.37

S:E96A	1	WA1	1	lung	1.21
S:E96A	2	WA1	3	lung	1 - 1.01
S:V62G	2	WA1	1	lung	1.58 - 2.77
S:V62G	4	WA1	3	lung	1.58 - 2.17
S:V62G	2	WA1	1	NT	2.79 - 2.98
S:V62G	1	Delta	3	lung	4.39
ORF3a:A39S	1	Alpha	3	NT	2.48
ORF3a:E239D	1	Alpha	3	lung	1.02
ORF3a:E239D	1	Alpha	1	NT	1.94
ORF3a:E239D	1	Alpha	3	NT	3.47
ORF3a:H182Y	1	Alpha	1	NT	7.73
ORF3a:S165Y	1	Alpha	1	NT	1.61
ORF3a:T176I	1	Alpha	1	NT	1.92
M:I24R	1	Alpha	3	NT	2.29
M:T7I	3	WA1	1	lung	32.86 - 39.47
M:T7I	4	WA1	3	lung	41.24 - 47.04
M:T7I	4	WA1	1	NT	23.22 - 53.16
M:T7I	3	WA1	3	NT	28.36 - 43.36
M:Y179fs	1	Alpha	3	NT	1
ORF6:I33T	1	Alpha	3	NT	2.35
ORF7a:*122L	1	Alpha	1	lung	1.29
ORF8:Q23H	3	Delta	1	lung	1.44 - 1.88
ORF8:Q23H	4	Delta	3	lung	1.26 - 1.98
ORF8:Q23H	4	Delta	1	NT	1.42 - 3.59
ORF8:Q23H	4	Delta	3	NT	1.59 - 3.94
ORF8:S67F	1	Alpha	1	NT	1.4
N:R14C	1	Alpha	1	NT	1.43
N:P365L	1	Alpha	1	NT	3.57
N:S194T	1	WA1:Alpha	3	NT	98.02
ORF10:L37F	1	Alpha	1	NT	1.13

**Abbreviations:** nonsynonymous mutation (Ns), observations (obs.), days post-infection (dpi), days post-challenge (dpc)

**Table S2. Fold change of Log<sub>2</sub> values of selected RNA-Seq transcripts from lungs of infection or infection:challenge groups as compared to mock-inoculated on 1 dpi, 1 dpc, 3 dpi, or 3 dpc. All values shown have a Log<sub>2</sub> fold change  $\geq 1.5$  and a p value  $\leq 0.05$ .**

<i>Gene</i>	1 dpi			1 dpc			3 dpi			3 dpc		
	WA1	Alpha	Delta	WA1: WA1	WA1: Alpha	WA1: Delta	WA1	Alpha	Delta	WA1: WA1	WA1: Alpha	WA1: Delta
<i>AICDA</i>	-	-	-	3.38	2.94	4.75	-	-	-	3.86	3.66	3.72
<i>C3AR1</i>	-	-	-	-	-	-	4.15	2.91	2.67	-	-	-
<i>CCL2</i>	3.27	1.74	1.65	-	-	1.55	6.86	6.16	6.35	-	-	-
<i>CCL3</i>	1.80	-	-	-	1.54	-	3.02	3.06	2.86	-	-	-
<i>CD80</i>	-	-	-	-	-	-	2.00	1.58	1.45	-	-	-
<i>CD86</i>	-	-	-	-	-	-	1.58	1.69	1.37	-	-	-
<i>CD8A</i>	3.01	-	-	-	-	-	-	-	-	-	-	-
<i>CXCL10</i>	6.10	3.72	4.25	2.91	2.82	3.97	7.59	7.85	7.81	2.10	2.22	2.30
<i>CXCL11</i>	6.33	3.19	3.50	3.61	3.39	4.57	8.26	8.57	8.15	-	-	-
<i>DDX58</i>	-	-	-	-	-	-	2.16	2.12	1.98	-	-	-
<i>FCGR1</i>	2.06	2.03	2.00	-	-	-	4.27	3.74	3.70	-	-	-
<i>IDO1</i>	-	-	-	-	-	-	2.73	2.75	2.63	-	-	-
<i>IFIH1</i>	-	-	-	-	-	-	2.38	2.38	2.10	-	-	-
<i>IFNB1</i>	4.54	-	-	-	-	-	8.95	8.39	6.84	-	-	-
<i>IFNG</i>	-	-	-	-	-	1.68	2.06	2.63	2.17	-	-	-
<i>IL10</i>	-	-	-	-	3.10	3.11	3.07	2.85	2.03	-	-	-
<i>IL1RN</i>	-	-	-	-	-	-	2.89	2.93	2.58	-	-	-
<i>IL27</i>	-	-	-	-	-	-	2.59	2.89	2.51	-	-	-
<i>IL6</i>	3.41	-	-	-	-	-	5.65	5.80	5.57	-	-	-
<i>IRF7</i>	3.06	3.00	2.68	-	-	-	5.05	4.88	4.80	-	-	-
<i>JCHAIN</i>	-	-	-	4.35	4.40	4.21	-	-	-	3.78	3.92	3.93
<i>OAS2</i>	2.22	2.15	1.92	-	-	-	2.95	2.81	2.66	-	-	-
<i>OAS3</i>	2.26	2.36	2.01	-	-	-	4.14	4.05	3.74	-	-	-
<i>TLR2</i>	-	-	-	-	-	-	1.60	1.54	-	-	-	-
<i>TLR7</i>	-	-	-	-	-	-	1.66	-	-	-	-	-
<i>TNF</i>	-	-	-	-	-	1.56	2.54	2.66	2.47	-	-	-
<i>ZBP1</i>	2.92	2.75	2.56	-	-	-	4.13	3.91	3.84	-	-	-

**Abbreviations:** days post-infection (dpi), days post-challenge (dpc), dash (-) represent any fold change less than 1.5 and/or a P value  $<0.05$ .

**Table S3. Fold change of Log<sub>2</sub> values of selected RNA-Seq transcripts from nasal turbinates from infection or infection:challenge groups as compared to mock-inoculated on 1 dpi, 1 dpc, 3 dpi, or 3 dpc. All values shown have a Log<sub>2</sub> fold change  $\geq 1.5$  and a p value  $\leq 0.05$ .**

<i>Gene</i>	1 dpi			1 dpc			3 dpi			3 dpc		
	WA1	Alpha	Delta	WA1: WA1	WA1: Alpha	WA1: Delta	WA1	Alpha	Delta	WA1: WA1	WA1: Alpha	WA1: Delta
<i>C3AR1</i>	-	-	-	-	-	-	1.78	-	-	-	-	-
<i>CCL2</i>	3.94	3.22	3.49	-	-	2.86	4.29	-	-	-	-	-
<i>CCL22</i>	-	-	1.56	-	-	1.53	-	-	-	-	-	-
<i>CCL3</i>	3.34	2.83	2.89	-	-	-	1.98	-	-	-	-	-
<i>CCL5</i>	3.47	2.39	2.61	-	2.32	2.92	3.02	2.84	2.95	-	-	-
<i>CD80</i>	-	-	-	-	-	-	1.56	-	-	-	-	-
<i>CD8A</i>	2.16	2.16	2.03	2.92	3.04	3.58	2.87	2.51	2.55	2.40	3.15	3.47
<i>CXCL10</i>	7.83	7.20	7.09	-	5.39	6.01	5.60	3.33	3.85	-	-	-
<i>CXCL11</i>	7.39	6.55	6.44	-	5.66	6.16	4.01	-	-	-	-	-
<i>DDX58</i>	3.06	3.00	2.83	-	-	1.62	1.78	-	-	-	-	-
<i>FCGR1</i>	2.72	2.30	2.35	-	-	-	2.70	-	2.18	-	-	-
<i>IDO1</i>	-	-	-	-	-	5.69	6.27	-	-	-	-	-
<i>IFIH1</i>	3.45	3.30	3.03	-	1.57	1.95	2.03	1.66	2.06	-	-	-
<i>IFNB1</i>	7.87	8.24	7.27	-	-	-	7.12	-	-	-	-	-
<i>IFNG</i>	4.94	4.28	4.17	-	4.46	5.54	4.54	-	-	-	-	-
<i>IL15</i>	-	-	-	-	-	-	-	-	-	-	-	-
<i>IL27</i>	3.60	-	-	-	-	-	-	-	-	-	-	-
<i>IL6</i>	7.77	6.85	6.59	-	-	4.49	4.14	-	-	-	-	-
<i>IRF7</i>	4.72	4.60	4.38	-	2.96	3.44	4.01	4.16	4.60	-	-	-
<i>JCHAIN</i>	-	-	-	1.81	-	-	-	-	-	-	-	2.71
<i>NOS2</i>	2.10	-	-	-	-	-	-	-	-	-	-	-
<i>OAS2</i>	4.32	4.42	4.09	-	3.13	3.46	2.89	2.80	3.19	-	-	-
<i>OAS3</i>	4.75	4.76	4.51	-	3.47	3.86	3.77	3.10	3.72	-	-	-
<i>TLR2</i>	1.50	-	-	-	-	-	-	-	-	-	-	-
<i>TLR3</i>	2.74	2.62	2.44	-	-	-	-	-	-	-	-	-
<i>TLR7</i>	-	-	-	-	-	-	2.52	-	-	-	-	-
<i>TLR8</i>	-	-	-	-	-	-	2.29	-	-	-	-	-
<i>TNF</i>	2.57	-	-	-	-	-	-	-	-	-	-	-
<i>ISG15</i>	4.86	4.88	4.59	-	3.27	3.52	3.12	3.39	3.90	-	-	-
<i>ZBP1</i>	4.85	4.68	4.56	-	3.57	4.28	3.60	3.35	3.86	-	-	-

**Abbreviations:** days post-infection (dpi), days post-challenge (dpc), dash (-) represent any fold change less than 1.5 and/or a P value <0.05.

**Table S4. Neutralizing titers of the pre- and post-challenge sera of mice against WA1, Alpha, or Delta antigen.**

<b>Mouse ID</b>	<b>Challenge strain</b>	<b>Antigen</b>	<b>21 dpi</b>	<b>21 dpc</b>	<b>Fold change</b>
117	WA1	WA1	2213.8	5654.0	2.6
118	WA1	WA1	937.2	2432.7	2.6
119	WA1	WA1	2211.4	1527.4	0.7
120	WA1	WA1	1895.6	2931.0	1.5
153	Alpha	WA1	1042.7	1853.8	1.8
154	Alpha	WA1	655.1	2425.2	3.7
155	Alpha	WA1	904.2	1971.8	2.2
156	Alpha	WA1	1166.0	1531.3	1.3
141	Delta	WA1	1841.6	7272.8	3.9
142	Delta	WA1	1554.7	3758.9	2.4
143	Delta	WA1	3757.6	4213.8	1.1
144	Delta	WA1	2924.3	3106.6	1.1
117	WA1	Alpha	1224.0	4558.7	3.7
118	WA1	Alpha	931.2	1364.6	1.5
119	WA1	Alpha	1522.0	928.1	0.6
120	WA1	Alpha	1171.4	1631.9	1.4
153	Alpha	Alpha	831.2	1188.3	1.4
154	Alpha	Alpha	558.2	2992.2	5.4
155	Alpha	Alpha	669.3	2261.5	3.4
156	Alpha	Alpha	560.6	2215.7	4.0
141	Delta	Alpha	1074.9	1670.4	1.6
142	Delta	Alpha	1639.8	3935.4	2.4
143	Delta	Alpha	1089.6	1288.0	1.2
144	Delta	Alpha	1751.5	1444.8	0.8
117	WA1	Delta	246.1	2583.0	10.5
118	WA1	Delta	123.0	835.4	6.8
119	WA1	Delta	1711.0	457.2	0.3
120	WA1	Delta	1776.1	1446.4	0.8
153	Alpha	Delta	156.0	515.9	3.3
154	Alpha	Delta	139.4	1650.6	11.8
155	Alpha	Delta	130.1	234.9	1.8
156	Alpha	Delta	320.5	738.0	2.3
141	Delta	Delta	262.2	543.6	2.1
142	Delta	Delta	332.8	1528.0	4.6

143	Delta	Delta	228.2	733.0	3.2
144	Delta	Delta	428.6	380.2	0.9

**Abbreviations:** days post-infection (dpi), days post-challenge (dpc).