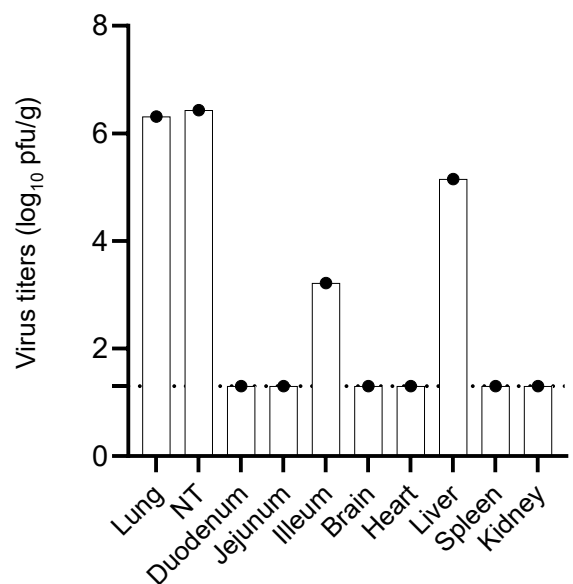


Supplementary Table 1. Summary of available samples used in this study

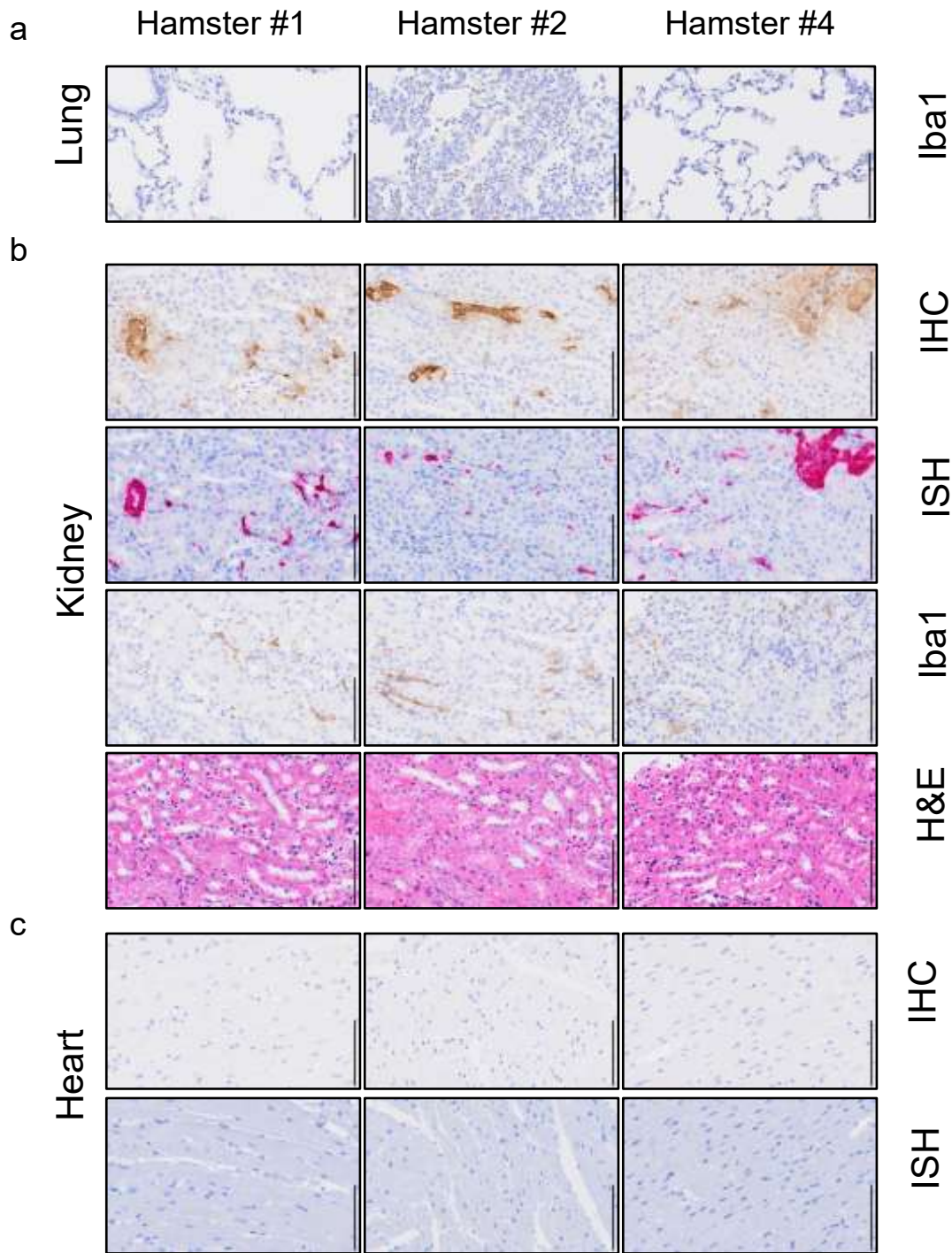
Hamster	Days oral swabs collected	Tissues (day 100)	Notes
Hamster #1	Days 39, 53, 64, 77, 97	Lung, duodenum, jejunum, ileum	
Hamster #2	Days 39, 53, 64, 77, 97	Lung, duodenum, jejunum, ileum	
Hamster #3	Days 39, 53, 64, 77	Lung, duodenum, jejunum, ileum (day 92 after infection)	No day 97 oral swab
Hamster #4	Days 39, 53, 64, 97	Lung, duodenum, jejunum, ileum	No day 77 oral swab

Supplementary Table 2. Number of iSNVs per open reading frame (ORF) for all hamsters (relative to the inoculum)

ORF	Non-synonymous	Synonymous	Total iSNVs
E	22	0	22
M	23	8	31
N	18	18	36
ORF10	28	31	59
ORF3a	33	10	43
ORF6	4	3	7
ORF7a	13	5	18
ORF8	10	2	12
Spike	126	48	174
Orf1ab	460	193	653
Overall	737	318	1055

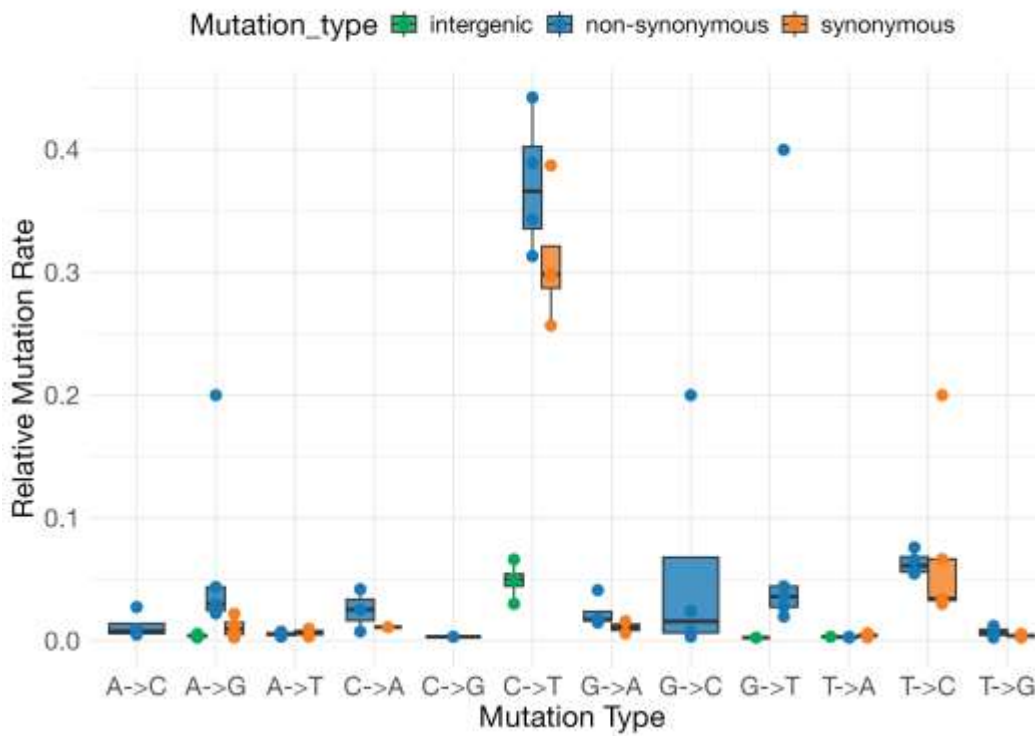


Supplementary Figure 1. Virus titers in different tissues of *IL2rg* KO hamster #3 that succumbed to its infection on day 92. Virus titers were determined by plaque assay with Vero E6 TMPRSS2-ACE2 cells. The lower limit of detection is indicated by the horizontal dashed line. All data are from one experiment. NT, nasal turbinate.

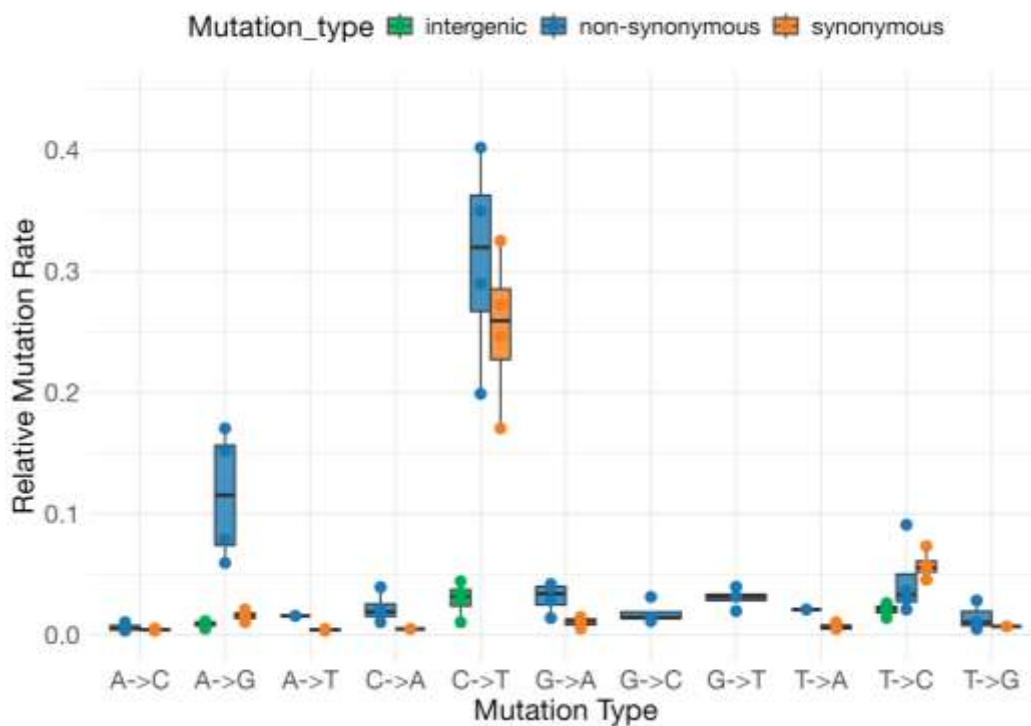


Supplementary Figure 2. Histopathological findings in *IL2rg* KO hamsters inoculated with XBB.1.16. a Kidney and **b** heart tissues were collected at 100 days after inoculation from hamsters #1, #2, and #4. Representative images of the tissues at high magnification are shown for: immunohistochemistry (IHC) with a rabbit monoclonal antibody that detects SARS-CoV-2 nucleocapsid; *in situ* hybridization (ISH) targeting the nucleocapsid gene of SARS-CoV-2; immunohistochemistry with a rabbit polyclonal antibody that detects the macrophage marker Iba1; and hematoxylin and eosin (H&E) staining. Scale bars, 100 μ m.

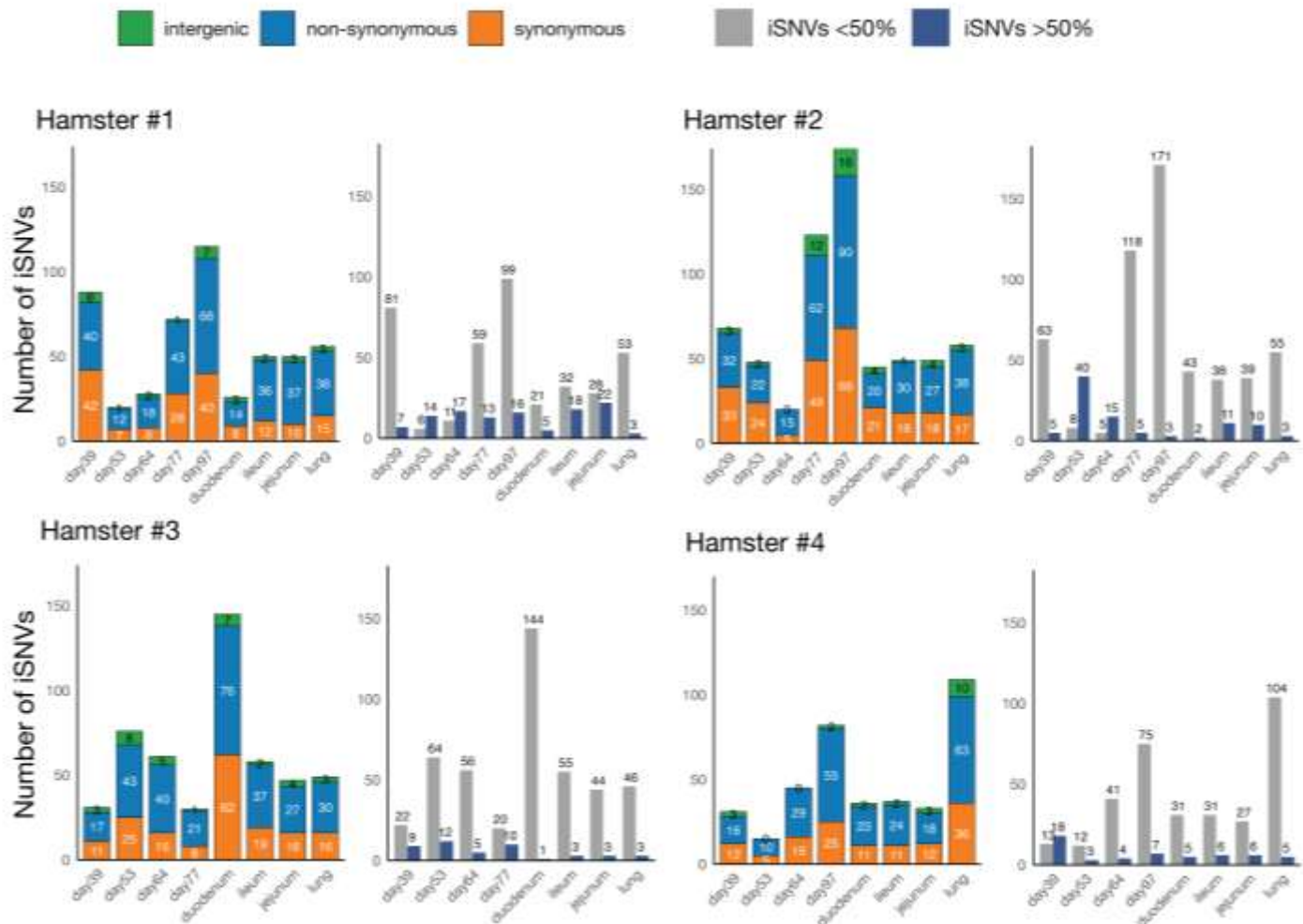
Oral Swabs



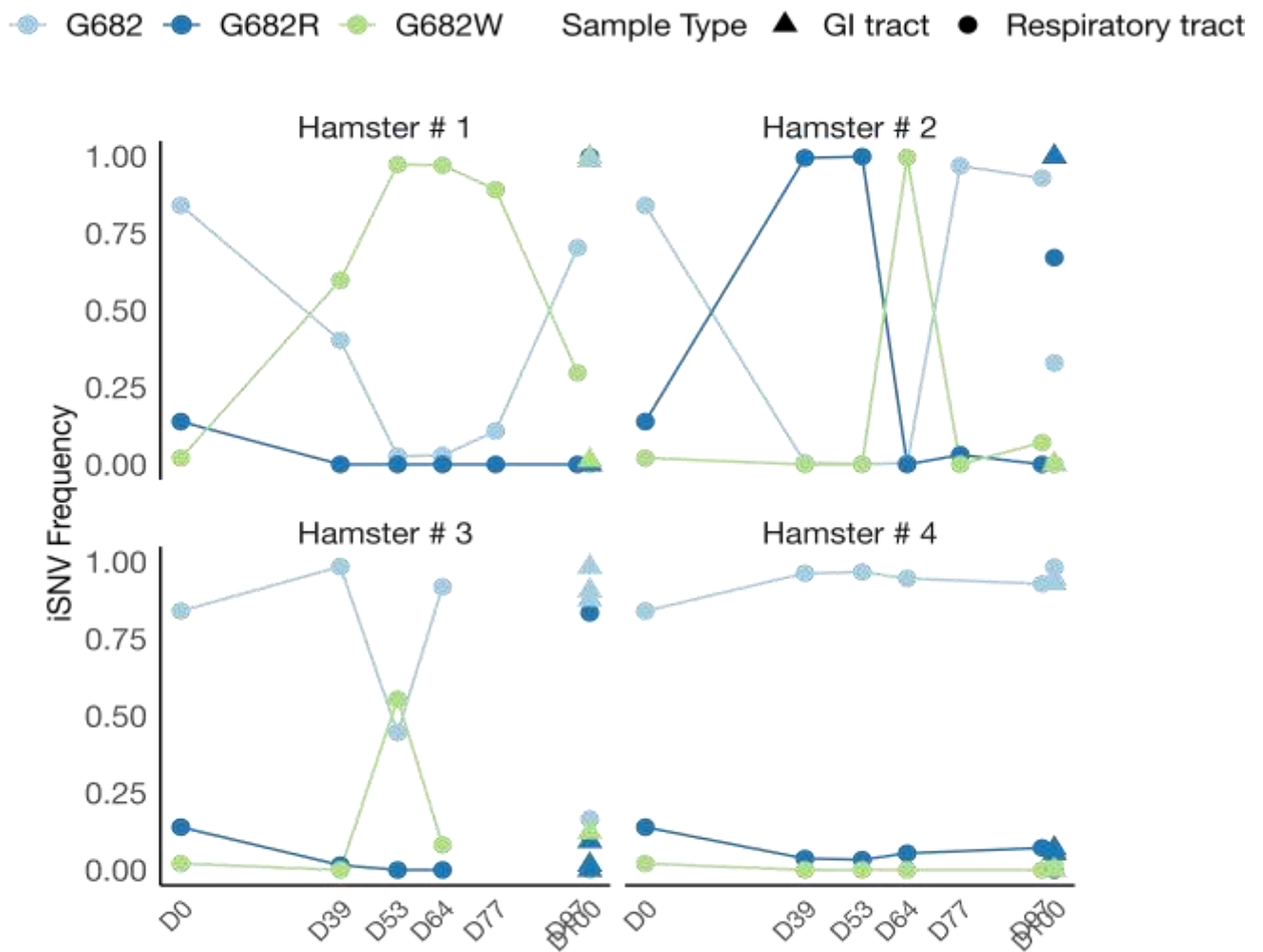
Tissue samples



Supplementary Figure 3. Box-and-whisker plots show the relative mutation rate across the SARS-CoV-2 genome-stratified variant type between hamster oral swab samples and tissue samples. Individual dots represent individual hamsters.



Supplementary Figure 4. iSNV summary for each hamster. Each color represents different types of iSNVs, as indicated. Subconsensus mutations are labeled gray, whereas consensus mutations are labeled dark blue.



Supplementary Figure 5. Fluctuating dynamics of Spike 682 in each hamster during persistent infection. Samples from oral swabs throughout infection and lung tissues are labeled as “respiratory tract” (circles), whereas samples from the duodenum, ileum, and jejunum tissues are labeled as “GI tract” (triangles).

Supplementary Data 1. Source data behind Figures 1a-1c and 3a-3c.

Supplementary Data 2. A complete list of amino acid changes at a frequency of $\geq 3\%$ from each sample type, hamster, and timepoint which was used to aid in the generation of Figures 4-6.