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Supplementary Materials for

SARS-CoV-2 within-host diversity and transmission

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§The full list of names and affiliations of COG-UK members is provided in the supplementary materials.

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This PDF file includes:

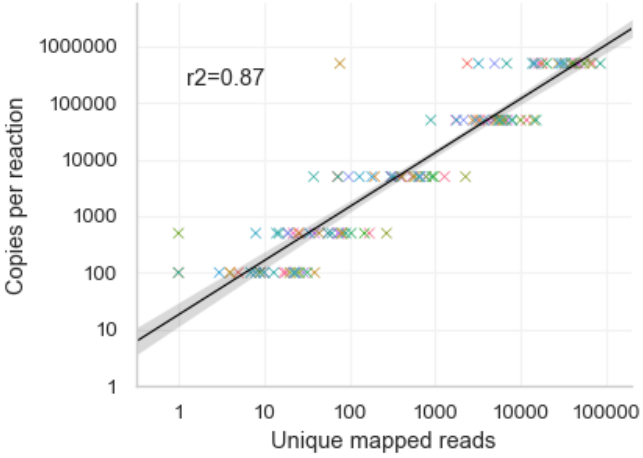
- Figs. S1 to S8
- Tables S1 to S5
- List of OVSG members
- List of COG-UK consortium names and affiliations

Other Supplementary Material for this manuscript includes the following:
(available at science.sciencemag.org/cgi/content/full/science.abg0821/DC1)

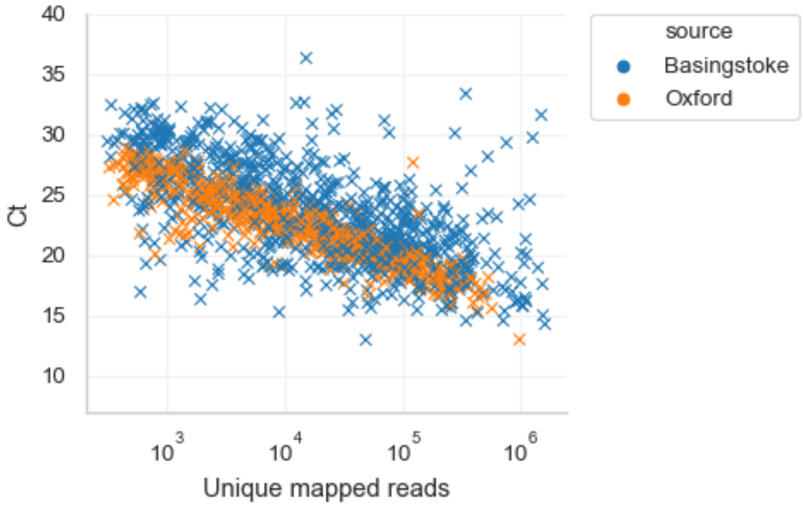
- MDAR Reproducibility Checklist (PDF)

Figures S1-S8

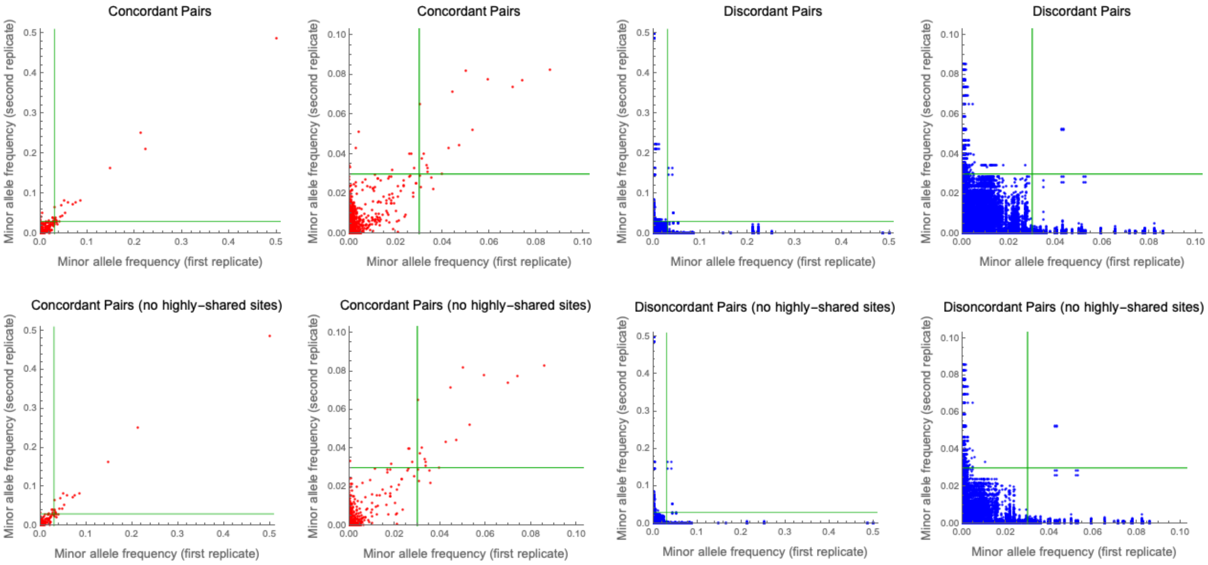
a



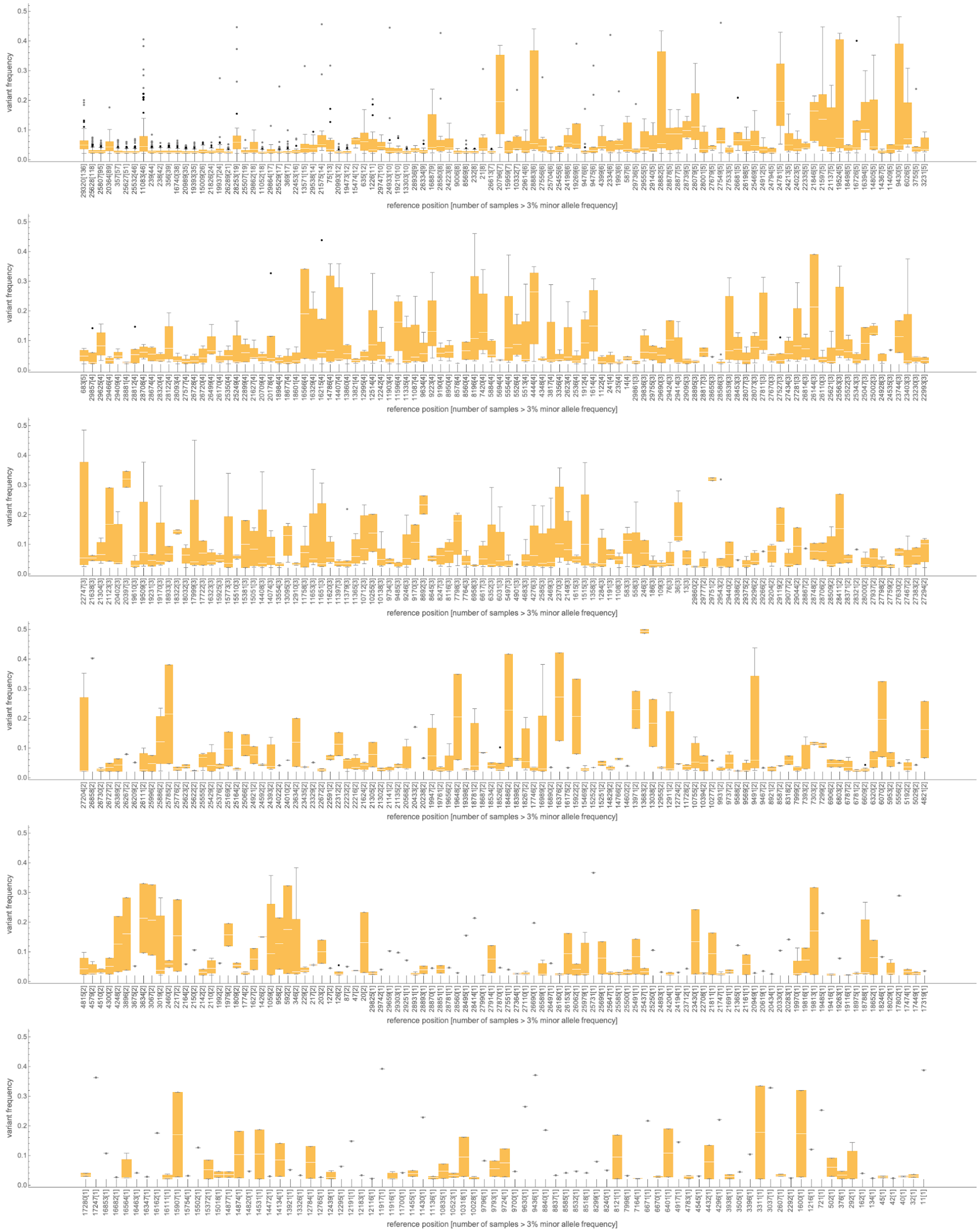
b



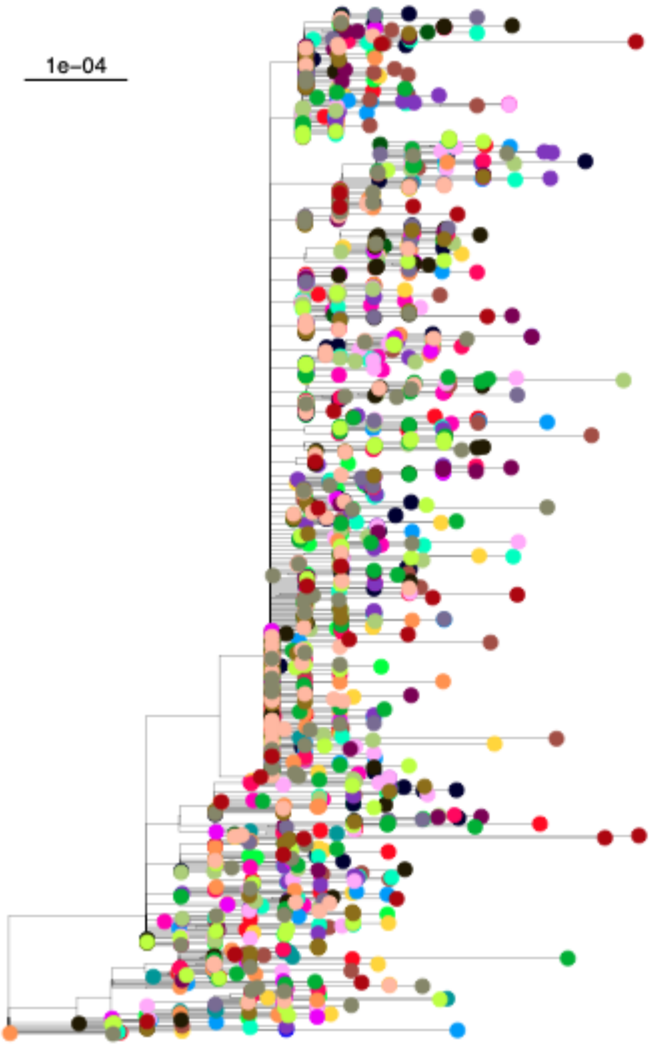
Supplementary Figure 1. (a) Correlation between number of SARS-CoV-2 unique reads and RNA copies/ml for within-batch standard curves for dilution series of positive control RNA. Colour indicates batch. Synthetic SARS-CoV-2 RNA (generated by in vitro transcription by Twist Bioscience) was serially diluted into Universal Human Reference RNA (UHRR) to a final concentration of SARS-CoV-2 RNA of 500,000, 50,000, 5,000, 500, 100 and 0 copies/reaction. Controls were processed and sequenced alongside each batch of samples (batches 3-27). Batches 1 and 2 were processed prior to controls being available and did not have a standard curve. (b) Correlation between nearest available cycle threshold (Ct) value for sequenced clinical samples, as reported by the collecting laboratory, and the number of unique mapped reads. Due to variation in qPCR methodology, Ct values varied substantially between laboratories and over time (*r2* = 0.43 Basingstoke, *r2*=0.81 Oxford, overall *r2*=0.50) Slightly lower Ct values were observed for Basingstoke samples for the same viral load (estimated from the standard curve), consistent with laboratory variation in Ct estimates.



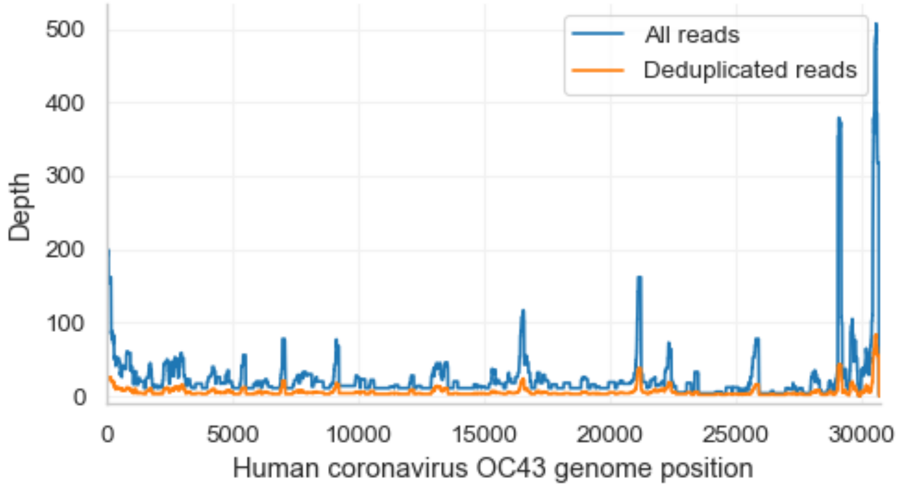
Supplementary Figure 2. Comparison of minor allele frequencies among replicate samples. Data is only included for the 27 replicate pairs where both replicates had more than 50,000 unique mapped reads, and for all sites where minor allele frequency (MAF) >=2% and depth >= 100 in at least one of the 54 replicates. For MAFs > 3%, and excluding highly-shared sites, MAFs are highly reproducible. Concordant pairs: The points represent the MAFs in each of the replicate pairs, for all 27 replicate pairs for all identified sites. If MAFs are reproducible, we expect a positive correlation. Discordant pairs: The points represent the MAFs for all pairwise permutations of replicates for all identified sites, excluding concordant replicates. Unless variants are present in multiple samples, the expectation is for points to be positioned along the axes. Top row includes all sites, whereas the bottom row exclude highly-shared sites (those observed at MAF >=3% in 20 or more samples across the entire dataset). The blue points in the upper-right quadrants represent site 28580, which is present in phylogenetically linked individuals, with two of these included in the 27 replicate pairs. The green line shows MAF 3%.



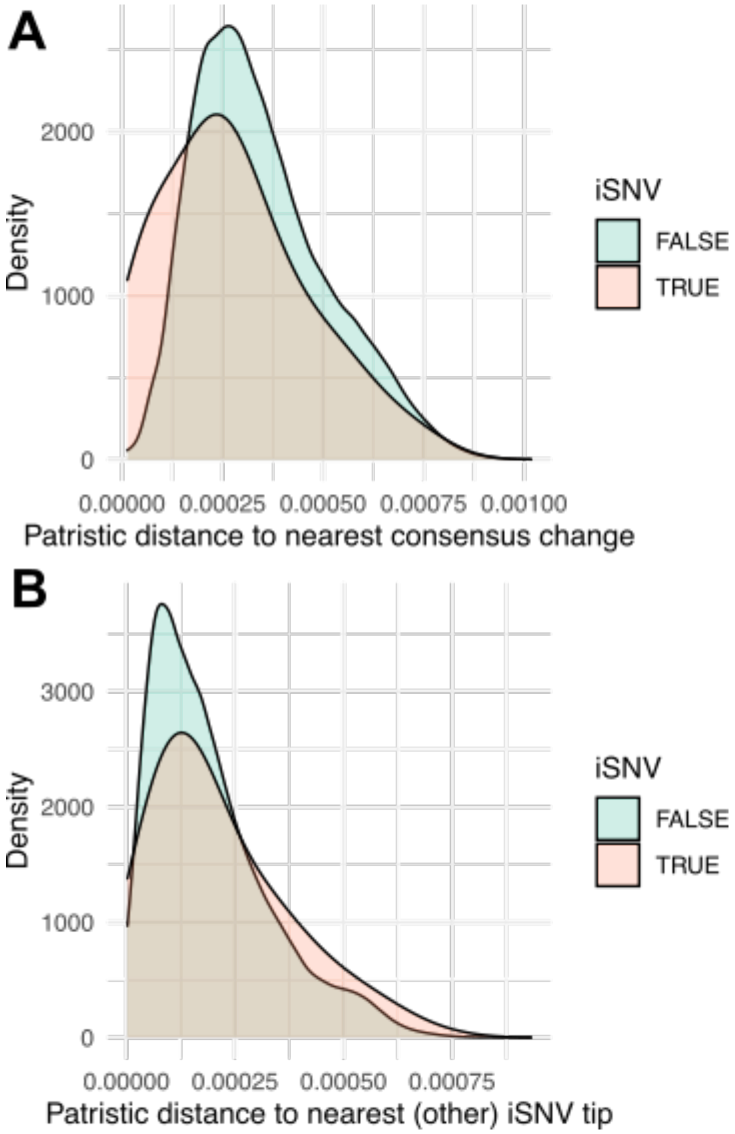
Supplementary Figure 3. Box-whisker plots showing distribution of variant frequencies. All sites variable at minor allele frequency (MAF) > 3% in at least one high-depth sample (>50,000 mapped reads) are included. All variants with MAF > 2% are plotted. The x-axis gives the nucleotide position, with the number of samples MAF > 3% in brackets. All sites are included except the poly A tail, and sites diverse in synthetic controls. The first 18 'highly-shared' sites are either ubiquitous, or only ever seen at low frequencies, suggesting these are non-genomic variants.



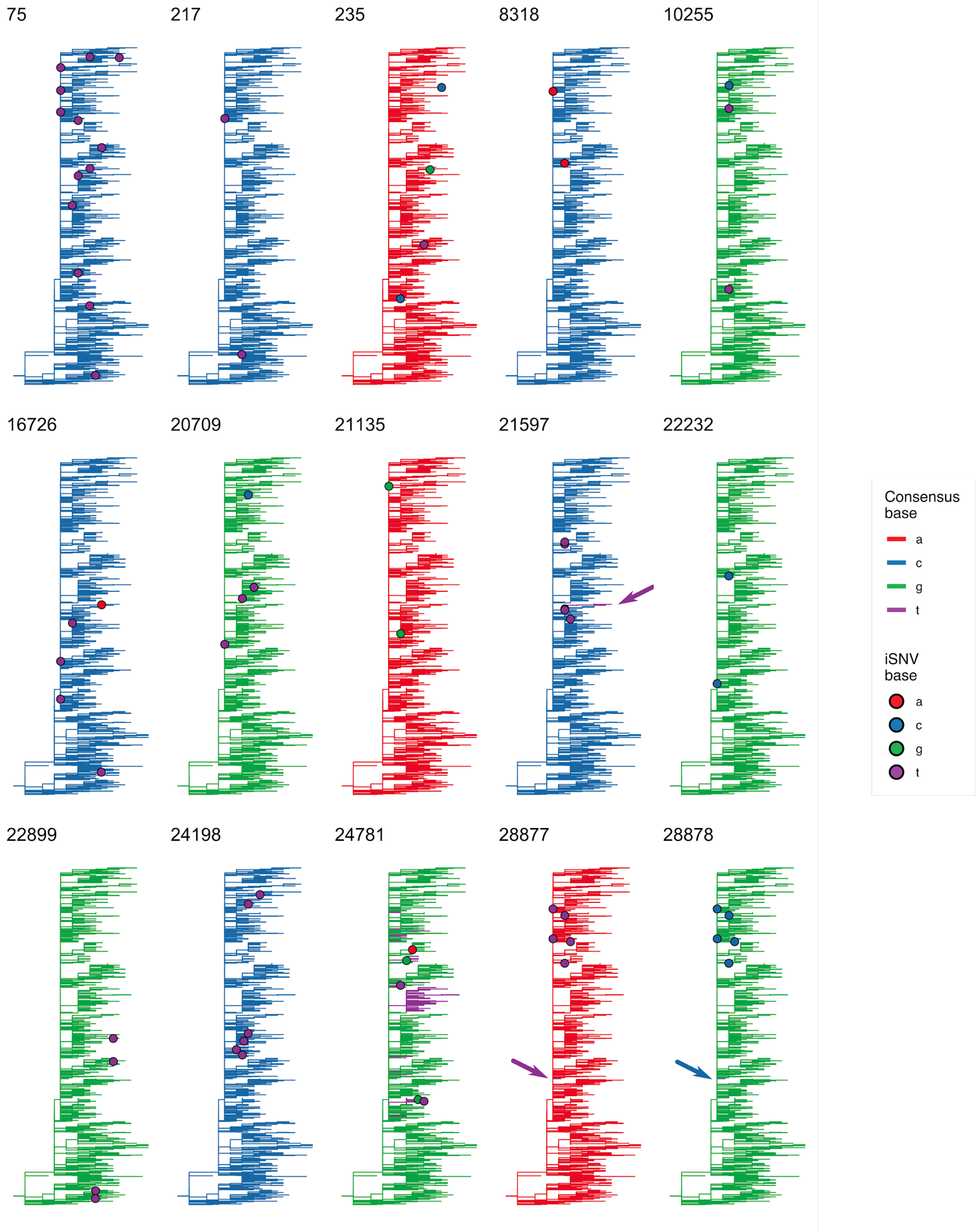
Supplemental Figure 4 - Consensus phylogeny of all 1390 Oxford and Basingstoke samples. Tips are coloured by sequencing batch.



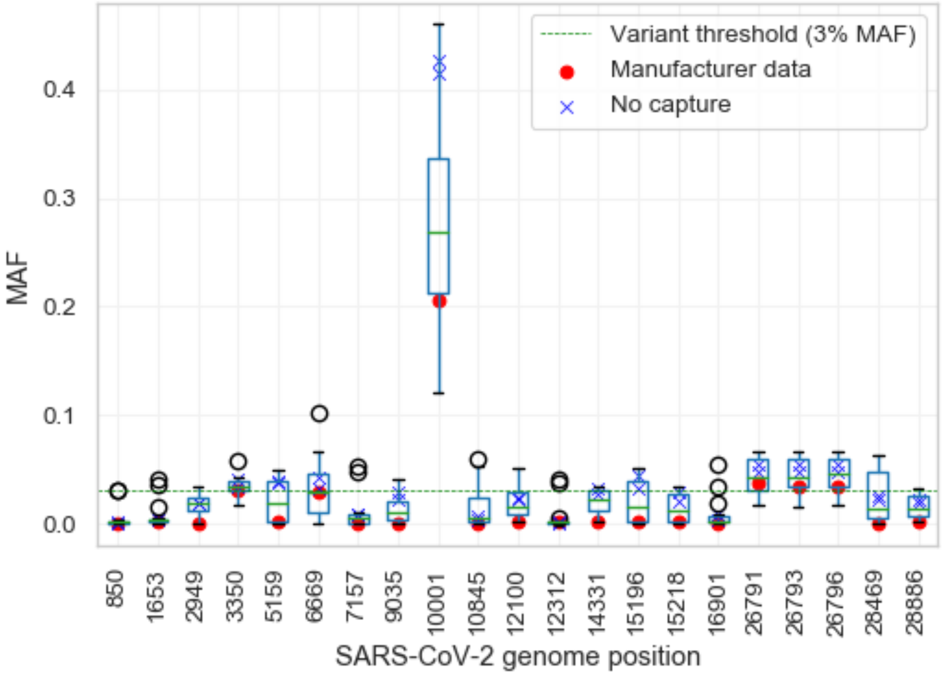
Supplementary Figure 5. Genome coverage for co-infecting human coronavirus OC43 in a SARS-CoV-2-positive sample, OXON-AEC3D. A single co-infection with a non-SARS-CoV-2 circulating coronavirus was detected among a subset of 111 samples analysed with both SARS-CoV-2-specific probes and the Castanet metagenomic respiratory probe panel. Shown in blue are positions of the 2953 proper read pairs mapping to the Castanet reference for OC43, with unique (deduplicated) read depth in orange.



Supplementary Figure 6 - A Across all iSNVs that reach consensus, kernel density plot of the patristic distances from iSNV tips (orange) and other tips (green) to the nearest consensus branch change of the nucleotides involved. **B** Across all iSNVs that do not reach consensus and occur at least twice, kernel density plot of the patristic distances from iSNV tips and other tips to the nearest iSNV tip (other than the tip itself).



Supplementary Figure 7 - The consensus phylogeny coloured by SNP and iSNV for sites mentioned in the main text. Where consensus changes are hard to see they are indicated with an appropriately coloured arrow. Sites 21597, 24781, 28877 and 28878 are the remaining positions where a statistically significant association of iSNV tips with branches with a consensus base change was identified (along with 20796 and 28580). For some of these, coloured arrows indicate the presence of branches with consensus SNPs where this is difficult to see. Sites 22899 and 24198 are Spike variants shown to exhibit reduced sensitivity to convalescent sera (44). The remaining 9 subfigures are for iSNVs which never reach consensus but show a $p<0.025$ for phylogenetic association of iSNV tips using the association index or the mean patristic distance between iSNV tips. While we lack the power to identify these once the Benjamini-Hochberg adjustment is applied, the patterns remain suggestive of transmission of iSNVs by eye.



Supplementary Figure 8. Within-sample diversity assessed in control RNA (Twist Bioscience). Within-sample diversity was assessed in RNA controls sequenced with each sequencing batch (0.5 mln copies per reaction). At all sites where at least 2 replicates had a minor variant with minimum 3% MAF (boxplot), diversity was compared against a set of NGS reads obtained from Twist Bioscience for the ancestral stock of the *in vitro* transcribed RNA used in this study (red circles). Six variants were consistently recovered from both the manufacturer data and the in-batch controls, at positions 3350, 6669, 10001, 26791, 26793, 26796. To check whether the remaining within-host variants arose during the SMARTer library prep or during probe capture, we additionally resequenced two replicates of the Twist RNA without capture (blue crosses), by diluting neat RNA 50:50 v/v in Universal Human Reference RNA (UHRR) and taking a proportion for sequencing, to yield approximately 50,000 copies of the Twist control RNA per sample. We generated SMARTer libraries from these replicates, and sequenced these alongside other samples in separate batches. The two capture-free replicates had the same range of intra-sample variants as were observed in our routinely sequenced controls, implying that any differences from the manufacturer data cannot be explained by probe capture and must be the result of the SMARTer library protocol and/or stochastic variation between our laboratory aliquot and the ancestral RNA stock sequenced by Twist.

Tables S1-S5

Table S1. Baseline characteristics of SARS-CoV-2 samples in our dataset collected by participating hospitals in Oxford and Basingstoke, UK, between 8 March and 10 June 2020. Total number of SARS-CoV-2 genomes includes replicate sequences from the same starting material (swab); number of samples corresponds to unique nasopharyngeal swabs. Participant age and sex excludes the 92 samples from anonymous participants in Oxford. Lineages were determined using Pangolin v2.1.7 (*1*) on 26 January 2021.

	Collecting laboratory	
	Oxford	**Basingstoke**
SARS-CoV-2 genomes, n(%)	552 (39.7)	838 (60.3)
Samples (swabs), n(%)	539 (41.0)	774 (58.9)
Participants, n(%)	539* (43.0)	727 (57.0)
Proportion female	0.60	0.61
Age, median	48	49
(min - max)	(0 - 98)	(0 - 100)
Sampling date, median	10-Apr-20	09-Apr-20
(min - max)	(16-Mar-2020 - 06-May-2020)	(06-Mar-2020 - 10-Jun-2020)
Ct value, median	22.2	23.2
(min - max)	(13.0 3 - 28.89)	(13.0 - 36.3)
SARS-CoV-2 lineage, n(%) - first sample per participant:		
B.1.1.119	216 (40.07)	261 (35.90)
B.1	73 (13.54)	84 (11.55)
B.1.1.194	1 (0.19)	142 (19.53)
B.1.1.1	38 (7.05)	22 (3.03)
B.1.1.220	3 (0.56)	33 (4.54)
B.1.1.175	20 (3.71)	15 (2.06)
B.40	11 (2.04)	22 (3.03)
B	15 (2.78)	12 (1.65)
B.1.1.10	4 (0.74)	20 (2.75)
B.39	2 (0.37)	21 (2.89)
B.1.1.114	15 (2.78)	2 (0.28)
B.1.1.257	15 (2.78)	1 (0.14)

B.1.1.51	1 (0.19)	14 (1.93)
B.1.13	4 (0.74)	10 (1.38)
B.1.1.289	13 (2.41)	0 (0.00)
B.28	8 (1.48)	4 (0.55)
B.1.391	9 (1.67)	3 (0.41)
B.1.1.217	7 (1.30)	5 (0.69)
B.1.1.269	4 (0.74)	6 (0.83)
B.3	4 (0.74)	5 (0.69)
B.1.1.237	7 (1.30)	0 (0.00)
B.1.321	7 (1.30)	0 (0.00)
B.1.1.270	7 (1.30)	0 (0.00)
B.1.1.104	0 (0.00)	7 (0.96)
B.1.1.164	2 (0.37)	4 (0.55)
B.1.231	6 (1.11)	0 (0.00)
B.1.1.261	5 (0.93)	0 (0.00)
B.1.1.304	5 (0.93)	0 (0.00)
B.1.1.64	4 (0.74)	1 (0.14)
B.1.249	3 (0.56)	0 (0.00)
B.1.379	3 (0.56)	0 (0.00)
B.1.93	2 (0.37)	1 (0.14)
B.1.1.277	0 (0.00)	3 (0.41)
B.1.1.123	2 (0.37)	1 (0.14)
B.31	0 (0.00)	3 (0.41)
B.1.1.90	2 (0.37)	1 (0.14)
B.29	0 (0.00)	2 (0.28)
B.1.147	2 (0.37)	0 (0.00)
B.1.104	2 (0.37)	0 (0.00)
B.1.91	0 (0.00)	2 (0.28)
B.54	2 (0.37)	0 (0.00)
B.1.1.10.2 (L.2)	0 (0.00)	2 (0.28)
B.1.1.273	2 (0.37)	0 (0.00)

B.1.1.208	1 (0.19)	1 (0.14)
B.1.1.49	0 (0.00)	1 (0.14)
B.1.1.211	0 (0.00)	1 (0.14)
B.47	0 (0.00)	1 (0.14)
B.45	1 (0.19)	0 (0.00)
B.35	0 (0.00)	1 (0.14)
B.1.1.106	1 (0.19)	0 (0.00)
B.1.1.127	0 (0.00)	1 (0.14)
B.1.1.166	1 (0.19)	0 (0.00)
B.1.1.180	0 (0.00)	1 (0.14)
B.23	1 (0.19)	0 (0.00)
B.1.98	1 (0.19)	0 (0.00)
B.1.1.183	0 (0.00)	1 (0.14)
B.1.1.216	0 (0.00)	1 (0.14)
B.1.1.71	0 (0.00)	1 (0.14)
B.1.1.256	1 (0.19)	0 (0.00)
B.1.1.264	0 (0.00)	1 (0.14)
B.1.229	1 (0.19)	0 (0.00)
B.1.222	1 (0.19)	0 (0.00)
B.1.199	0 (0.00)	1 (0.14)
B.1.182	0 (0.00)	1 (0.14)
B.1.153	0 (0.00)	1 (0.14)
B.1.1.292	0 (0.00)	1 (0.14)
B.1.1.31	1 (0.19)	0 (0.00)
B.1.1.4	1 (0.19)	0 (0.00)
B.1.1.89	0 (0.00)	1 (0.14)
B.1.1.8	1 (0.19)	0 (0.00)
A.1	0 (0.00)	1 (0.14)
A.2	1 (0.19)	0 (0.00)
A.2.2	0 (0.00)	1 (0.14)

* Includes 92 swabs from anonymous participants

Table S2. Sites masked due to sequenced diversity in Twist synthetic controls (112) or as "highly shared" sites with low-level within-host diversity in more than 20 samples (18). https://github.com/katrinalythgoe/COVIDdiversity (70).

Table S3. Identified within-host variable sites.
Sites with at least one minor allele at frequency >= 3% at depth of at least 100 reads, in a sample depth >=50,000 unique mapped reads. Throughout, "samples" refers to all sequencing runs, and therefore includes replicates in the totals. n_notPopConsensus refers to the number of samples in which the minor variant is not the population-level consensus (most common consensus allele); n_SNPs gives the number of SNPs on the tree; homoplasy is "TRUE" if a homoplasy exists on the tree; maf_median is the median minor allele frequency (MAF) for all samples with >2% MAF; maf_IQR is the inter-quartile range of minor allele frequencies for all samples with >2% MAF. https://github.com/katrinalythgoe/COVIDdiversity (70).

Table S4. Summary data for the household transmission analysis. Number of intra-host nucleotide variants sites (iSNVs) in source and recipient pairs (minor allele frequency >3%), and number of mapped reads. Stochastic sampling effects elevate the true number of iSNVs in low viral load samples (<50,000 mapped reads).

Direction inferred from collection dates (at least 7 days difference)

Household number	iSNVs (source)	iSNVs (recipient)	Mapped reads (source)	Mapped reads (recipient)
1	28	58	[10000,1e+05)	[100,1000)
3	45	0	[100,1000)	[10000,1e+05)
4	6	4	[100,1000)	[1000,10000)
8	0	3	[1e+06,1e+07)	[1e+05,1e+06)
9	1	37	[1e+05,1e+06)	[10000,1e+05)
13	3	2	[1e+05,1e+06)	[10000,1e+05)
14	2	43	[10000,1e+05)	[100,1000)

No direction inferred

Household number	iSNVs (patient 1)	iSNVs (patient 2)	Mapped reads (patient 1)	Mapped reads (patient 2)
2	2	4	[1e+05,1e+06)	[1e+05,1e+06)
5	31	35	[1000,10000)	[10000,1e+05)
6	3	0	[1e+06,1e+07)	[1e+06,1e+07)
7	34	2	[1000,10000)	[100,1000)
10	0	5	[10000,1e+05)	[100,1000)
11	19	6	[10000,1e+05)	[10000,1e+05)
12	1	1	[10000,1e+05)	[1e+05,1e+06)
16	1	4	[1e+05,1e+06)	[10000,1e+05)

Table S5. iSNVs and dn/ds by gene and over the whole genome, counting each variant only once regardless of frequency. All genome positions are relative to the Wuhan-Hu-1 reference sequence. iSNVs at the 18 “highly shared” sites and those identified from the synthetic controls are excluded, as are those in the poly-A tail (positions 29865-29903). Note that due to gene overlap and non-coding intergenic regions, the total number of iSNVs (781) cannot be obtained as the sum of any column in this table, even if the rows for nonstructural proteins in ORF1ab are excluded. * nsp12 overlaps the boundary between ORF1a and ORF1b. ** Intergenic regions are excluded from this row.

Gene	Start	End	Length	Unique iSNVs			Alternative $\mathrm{d}n/\mathrm{d}s$ (95% CI)
				Total	NS	S	
5’UTR	1	265	265	40	-	-	-
ORF1a	266	13483	13218	205	125	80	0.44 (0.33, 0.58)
nsp1	266	805	540	12	5	7	0.22 (0.06, 0.68)
nsp2	806	2719	1914	36	21	15	0.4 (0.21, 0.79)
nsp3	2720	8554	5835	74	46	28	0.45 (0.29, 0.74)
nsp4	8555	10054	1500	35	21	14	0.43 (0.22, 0.87)
nsp5A	10055	10972	918	10	9	1	2.55 (0.48, 46.97)
nsp6	10973	11842	870	17	10	7	0.39 (0.15, 1.09)
nsp7	11843	12091	249	3	1	2	0.14 (0.01, 1.48)
nsp8	12092	12685	594	7	4	3	0.36 (0.08, 1.83)
nsp9	12686	13024	339	7	4	3	0.41 (0.09, 2.08)
nsp10	13025	13441	417	4	4	0	∞ (0.46, ∞)
nsp12*	13442	16236	2795	42	23	19	0.32 (0.17, 0.59)
ORF1b	13468	21555	8088	127	73	54	0.37 (0.26, 0.52)
nsp13	16237	18039	1803	25	14	11	0.37 (0.17, 0.85)
nsp14	18040	19620	1581	30	16	14	0.3 (0.15, 0.63)
nsp15	19621	20658	1038	17	12	5	0.65 (0.24, 2.04)
nsp16	20659	21552	894	13	8	5	0.43 (0.14, 1.43)
S	21563	25384	3822	56	37	19	0.55 (0.32, 0.98)
ORF3a	25393	26220	828	33	28	5	1.6 (0.68, 4.72)
E	26245	26472	228	3	2	1	0.68 (0.07, 14.66)
M	26523	27191	669	11	7	4	0.54 (0.16, 2.05)
ORF6	27202	27387	186	5	4	1	0.97 (0.14, 18.97)
ORF7a	27394	27759	366	12	10	2	1.47 (0.39, 9.58)
ORF7b	27756	27887	132	4	4	0	∞ (0.41, ∞)
ORF8	27894	28259	366	11	7	4	0.47 (0.14, 1.78)
N	28274	29533	1260	50	33	17	0.58 (0.33, 1.06)
ORF10	29558	29674	117	3	2	1	0.53 (0.05, 11.28)
3’UTR	29675	29903	229	26	-	-	-
All coding regions**	266	29674	29256	519	331	188	0.49 (0.41, 0.59)
Full genome	1	29903	22903	781	-	-	-

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