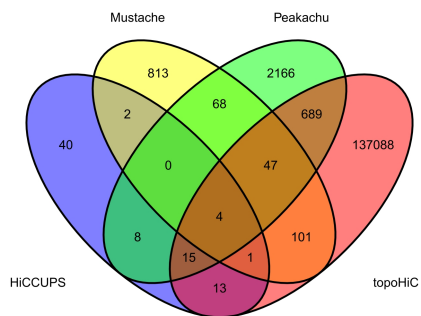
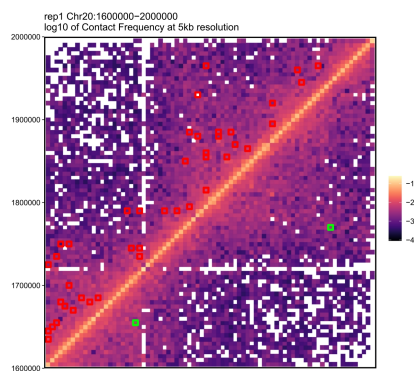
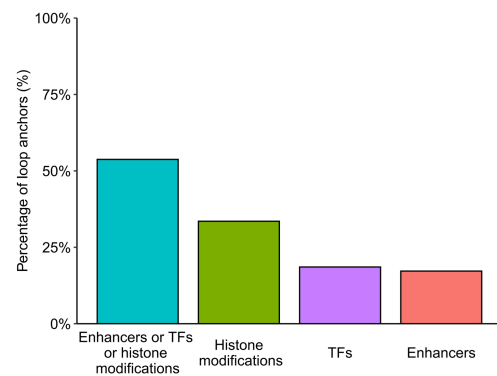
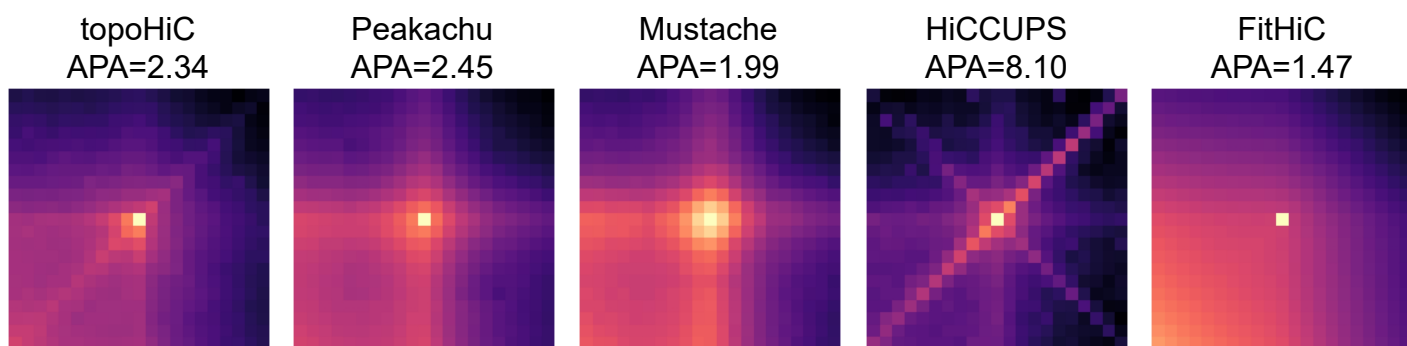
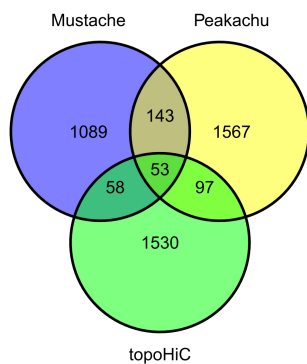
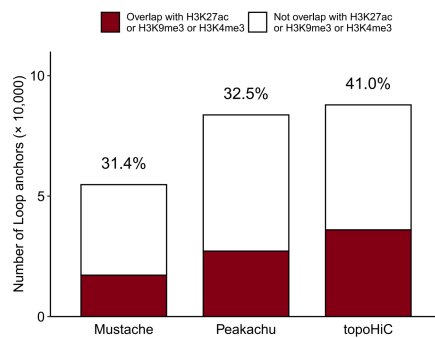
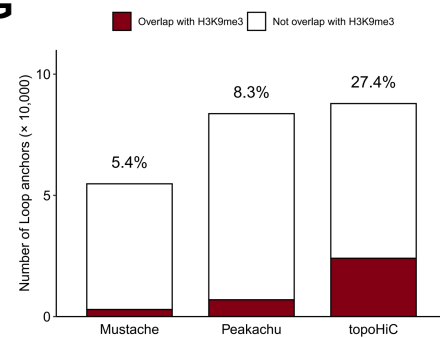
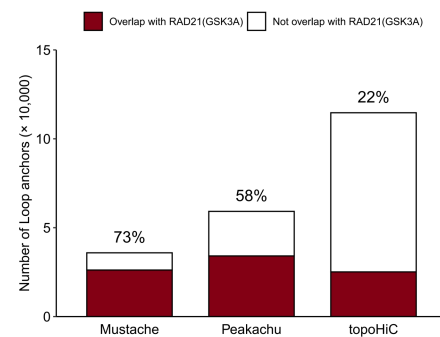
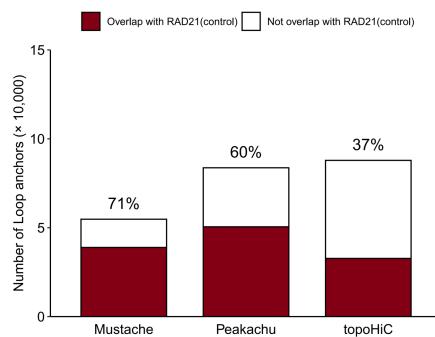
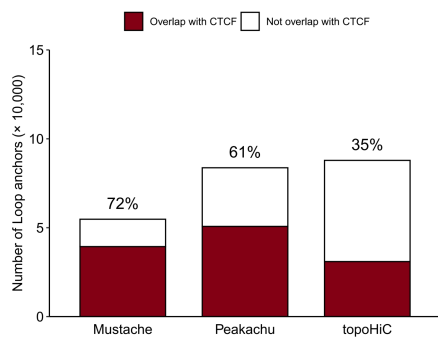


Supplementary Information

This file contains Supplementary Figure 1-7, Supplementary Table 1-48. Tables are separated into nine sections. Some tables could be used to reproduce some of the figures in our paper. A few tables are too big to put in this document and they are presented as separate files in Excel format.

A**B****C****D****E****F****G****H**

Supplementary Figure 1: Additional results of benchmarking topoHiC for calling loops.

(A) Venn diagrams that show the agreement of loops in chromosome 22 in ten biological replicates Dataset1 at 5kb resolution called by four loop callers.

(B) A side-by-side comparison of loops called by topoHiC (red) and Peakachu (green) at 5kb resolution in chromosome 20 biological replicate 1 Dataset1.

(C) The number of loop anchors called by topoHiC in Dataset1 at 5kb resolution that overlap with histone modifications or transcription factors or enhancers.

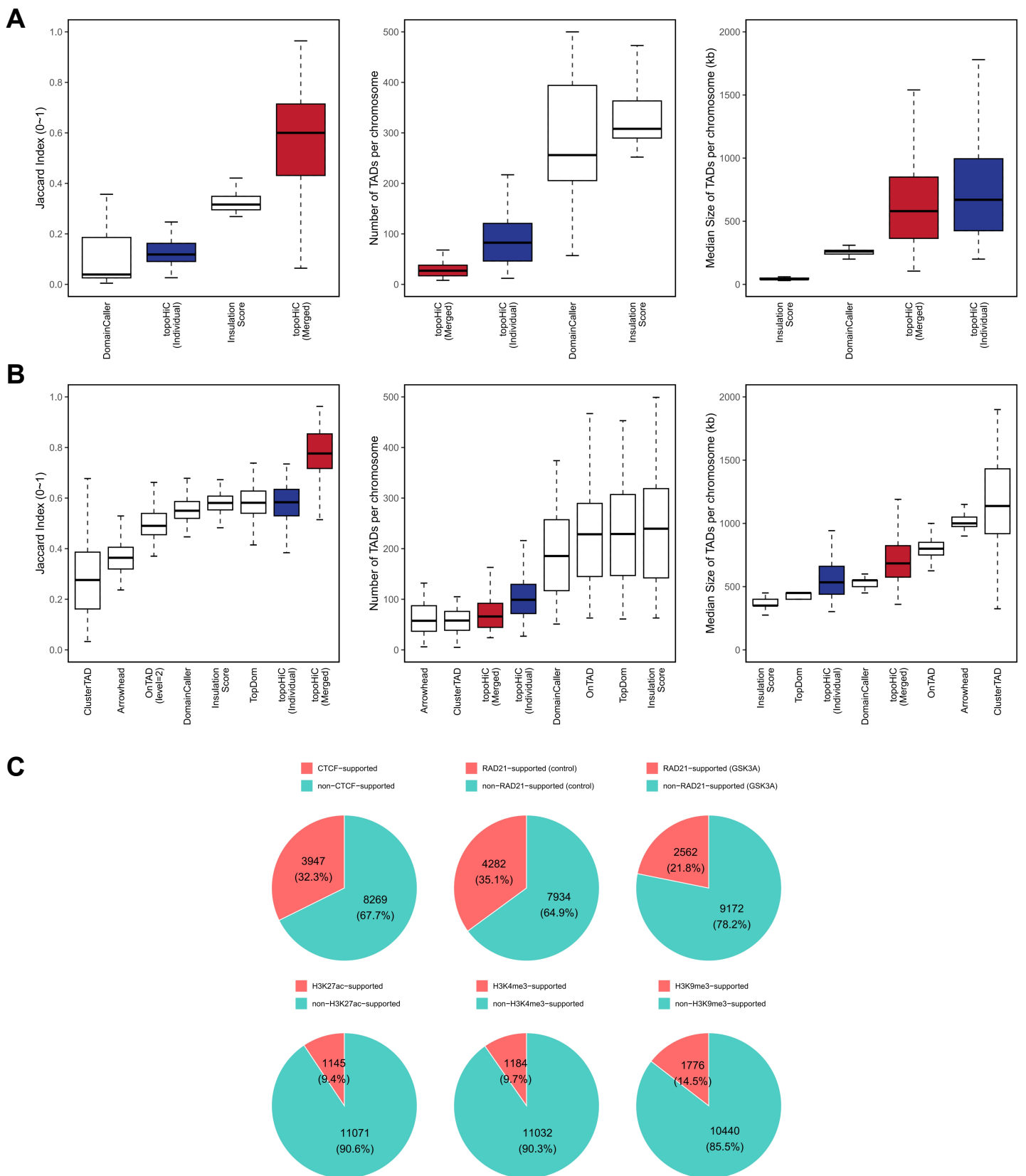
(D) Aggregate peak analysis of five different loop callers in biological replicate 1 in Dataset1 at 10kb resolution. APA scores are annotated at the top.

(E) Venn diagrams that show the agreement of loops in chromosome 22 in four samples in Dataset2 at 5kb resolution called by three loop callers.

(F) The number of loop anchors called by three loop callers in Dataset2 at 5kb resolution that overlap with H3K27ac or H3K9me3 or H3K4me3.

(G) Same as (F) but overlap with H3K9me3.

(H) Same as (F) but overlap with CTCF and RAD21.

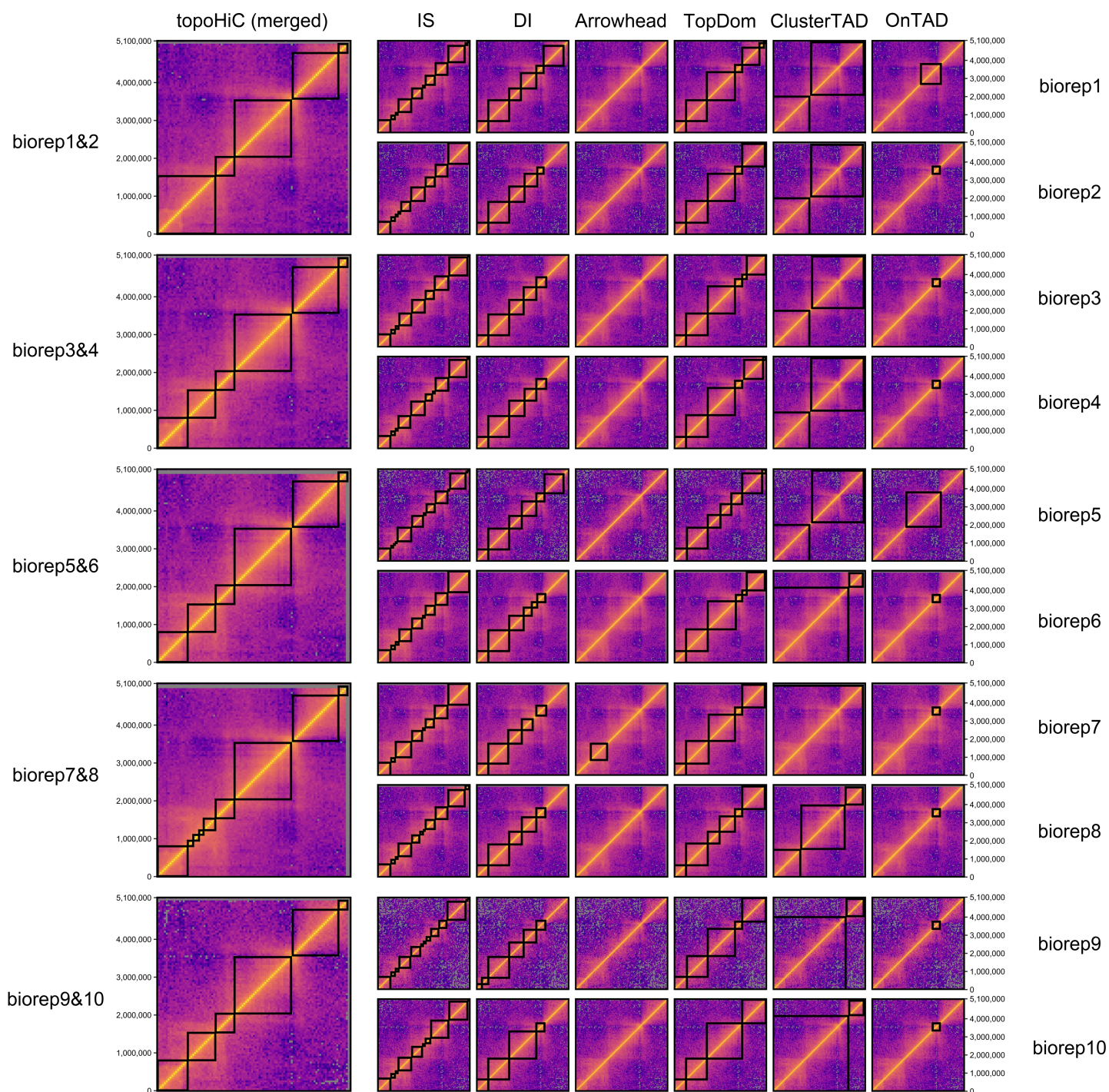


Supplementary Figure 2: Additional results of benchmarking topoHiC for calling TADs.

(A) Boxplots summarize the TADs called by four different TAD callers in biological replicates 1-5 in Dataset1 at 10kb resolution. The results from topoHiC were not coarsened.

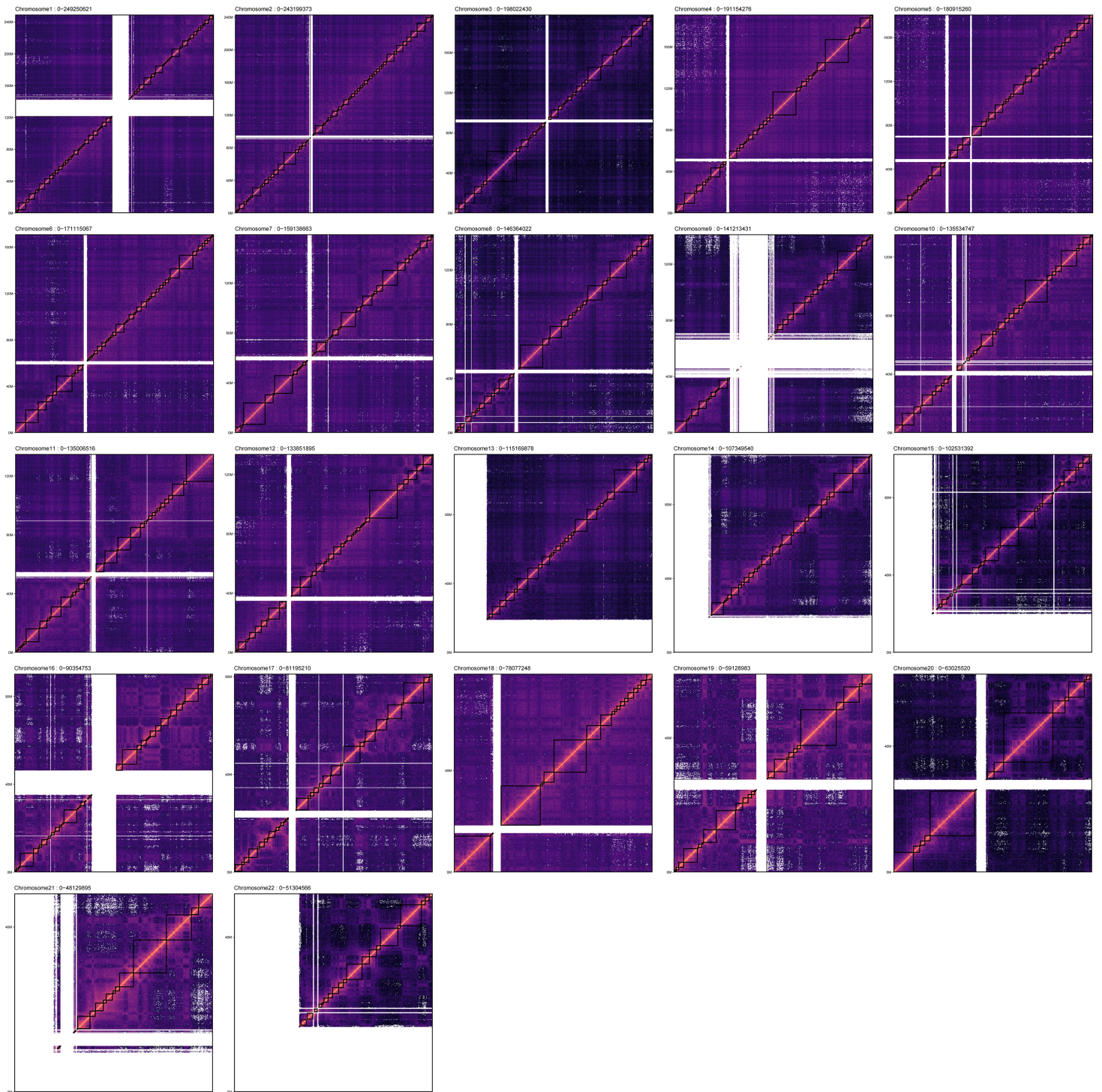
(B) Boxplots summarize the TADs called by seven different TAD callers in technical replicates in Dataset1. TopoHiC (individual and merged) is applied at 5kb resolution.

(C) The number of TAD boundaries called by topoHiC at 10kb resolution that overlap with peaks of CTCF, RAD21, H3K27ac, H3K4me3 and H3K9me3, referred to as supported boundaries, in Dataset2.



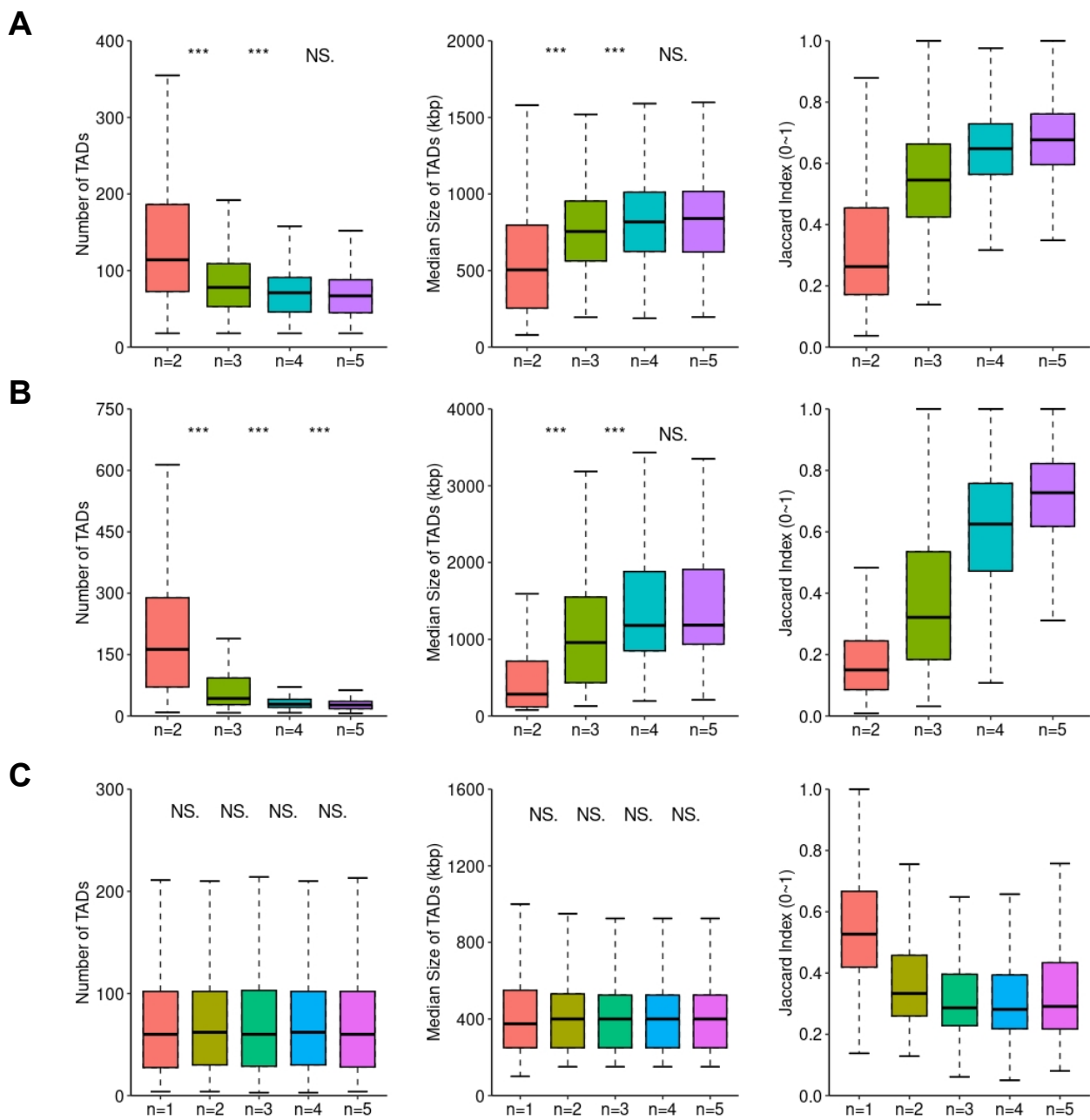
Supplementary Figure 3: Comparison of seven TAD callers in ten biological replicates.

This figure shows the TADs (annotated by black rectangles) called by seven TAD callers in a 5.1Mb region (chromosome 2, 0M-5.1M, ten biological replicates from Dataset1). Results of seven TAD callers are arranged in columns from left to right in the order of topoHiC (merged), Insulation Score (IS), DomainCaller (DI), Arrowhead, TopDom, ClusterTAD, OnTAD. Hi-C maps corresponding to 10 biological replicates are at 50kb resolution. TopoHiC (merged) calls TADs based on averaged loop scores, resulting in 45 sets of TADs. We take five of them as examples due to the limits of space. Notation biorepi&j indicates that these results are produced by averaging loop scores of biological replicates i and j. The corresponding Hi-C maps, that are at 50kb resolution, are generated by merging interaction frequencies



Supplementary Figure 4: TADs called by topoHiC through merged approach.

This figure shows TADs called by topoHiC on chromosome 1-22 through merged approach (merge biological replicate 1&2 in Dataset1). Hi-C maps at 50kb resolution are generated by merging interaction frequencies.



75 percentile of distances between points that are n genomic bins apart

Supplementary Figure 5: TADs called by topoHiC under different parameter settings.

(A) Number (left), median size (middle) and reproducibility (right) of TADs called by topoHiC at 5kb resolution. Results under four parameter settings (75 percentile of distances between points that are n genomic bins apart, $n=2, 3, 4, 5$) are displayed. Wilcox tests show significant differences of number and size of TADs between $n=2$ and $n=3$ as well as $n=3$ and $n=4$.

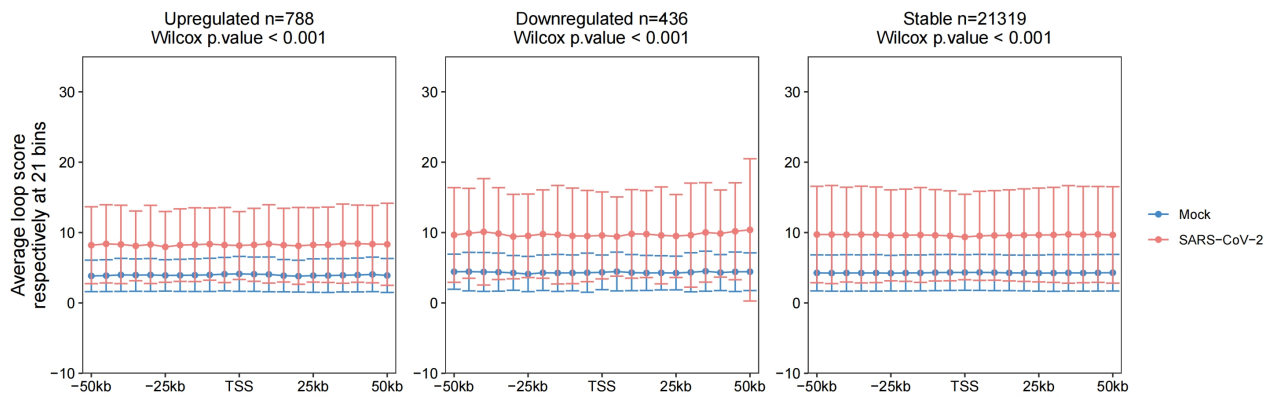
(B) Same as (A), but at 10kb resolution.

(C) Same as (A), but at 50kb resolution.

***: $p < 0.001$, ns: non-significant, $p > 0.05$.

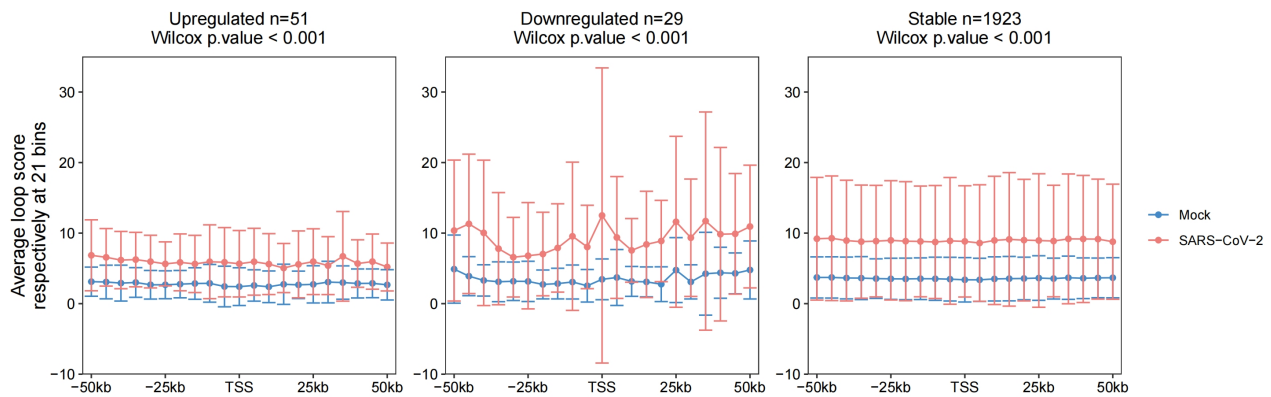
IGs n=22,543

Two genes were filtered out because they were at the end of chromosomes



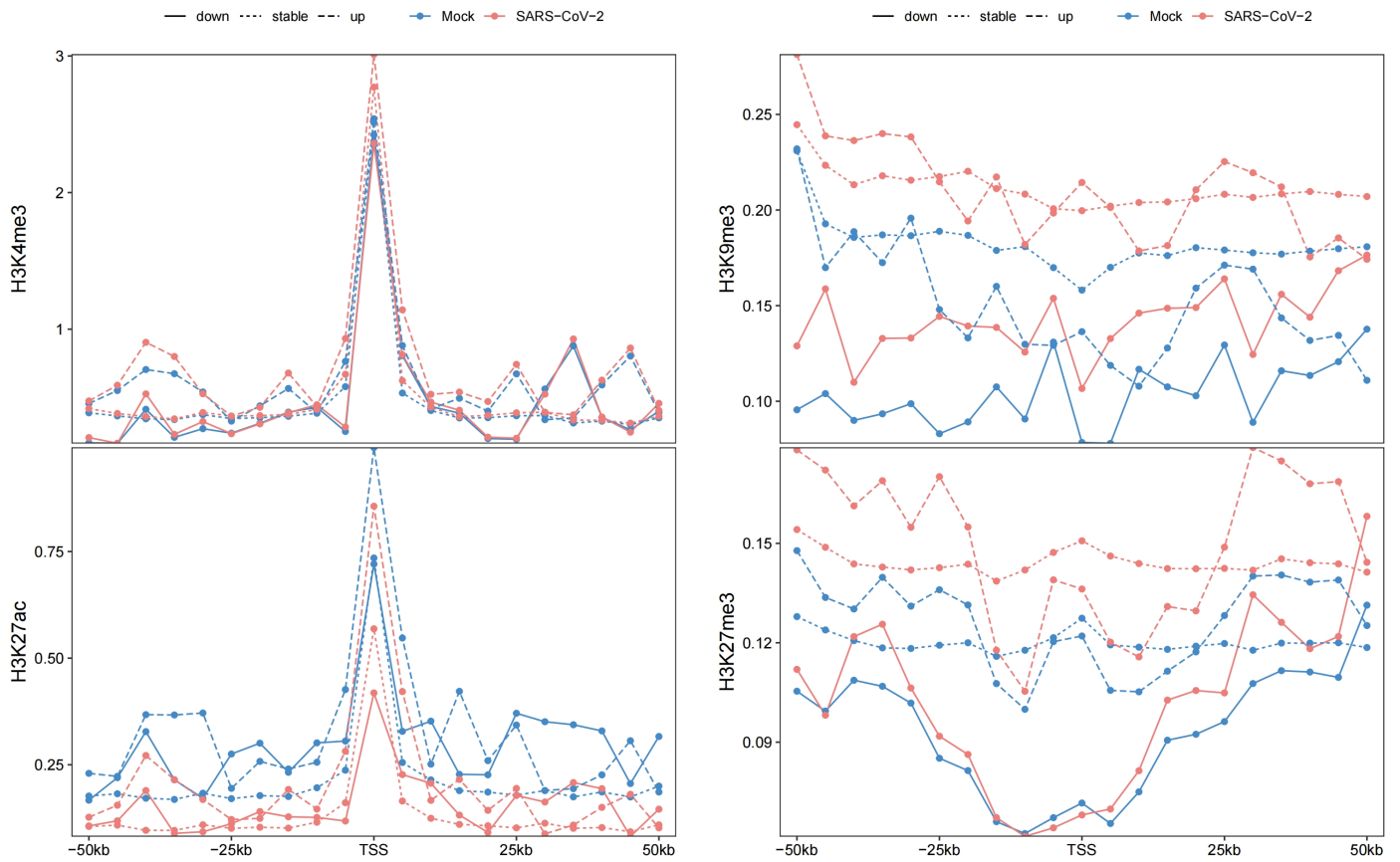
TGs n=2,003

19 genes were filtered out because they were at the end of chromosomes



Supplementary Figure 6: Alterations in chromatin loops impact gene expression.

Line plots with error bars ($\pm$ one standard deviation) show the relationships between LLS and the expression of inside genes (IGs) (top) and truncated genes (TGs) (bottom) in Mock and SARS. The x-axis represents the location of genomic bins relative to the bins that cover the TSS of genes. Each point in the line plot represents the averaged loop score at this relative location of all genes in a specific category in Mock or SARS. Wilcox tests were performed between averaged loop scores.



Supplementary Figure 7: Alterations in histone modifications impact gene expression.

Line plots show the relationships between histone modifications and the expression of truncated genes (TGs) in Mock and SARS. The x-axis represents the location of genomic bins relative to the bins that cover the TSS of genes. Each point in the line plot represents the averaged histone modification abundance at this relative location of all genes in a specific category in Mock or SARS. Different gene expression patterns (upregulated, downregulated, stable) are distinguished by line types.

Section1: The following **Supplementary Table 1-10** show the correlation between differential expression of genes and alterations in chromatin loops and TADs. Chisq-test was performed for each table, and p -value < 0.05 was considered as statistical significant. The following data could be used to reproduce Figure 4D and Figure 5B. They correspond to the third and the fourth subsections of Results in our paper, and they suggest the direct or indirect influence of chromatin loops and TADs on gene expression.

Supplementary Table 1: The distribution of DEGs among inside genes, truncated genes and outside genes (chisq-test p -value < 0.001).

	DEGs	non-DEGs	Total
Inside genes	1224	21321	22545
Truncated genes	80	1942	2022
Outside genes	37	1100	1137
Total	1341	24363	25704

Supplementary Table 2: The number of differentially or non-differentially expressed inside genes that reside in CDs or not (chisq-test p -value = 0.1540).

	DEGs	non-DEGs	Total
Reside in CDs	863	14609	15472
Reside in non-CDs	361	6712	7073
Total	1224	21321	22545

Supplementary Table 3: The number of differentially or non-differentially expressed inside genes that have differential LLS or not (chisq-test p -value = 0.0204).

	Differential LLS	Non-significant changes of LLS	Total
DEGs	1121	103	1224
non-DEGs	19899	1420	21319
Total	21020	1523	22543

Supplementary Table 4: The number of differential expressed inside genes that reside in CDs/non-CDs and have differential LLS or not (chisq-test p -value = 0.1204).

	Differential LLS	Non-significant changes of LLS	Total
Reside in CDs	338	23	361
Reside in non-CDs	783	80	863
Total	1121	103	1224

Supplementary Table 5: The number of differentially or non-differentially expressed truncated genes that adjacent to CDs/non-CDs (fisher test p -value = 0.0287).

	DEGs	non-DEGs	Total
Adjacent to CDs	77	1706	1783
Adjacent to non-CDs	3	217	220
Total	80	1923	2003

Supplementary Table 6: The number of differentially or non-differentially expressed truncated genes that have differential LLS or not (chisq-test p -value = 0.0124).

	Differential LLS	Non-significant changes of LLS	Total
DEGs	65	15	80
non-DEGs	1739	184	1923
Total	1804	199	2003

Supplementary Table 7: The number of differential expressed truncated genes that are adjacent to CDs/non-CDs and have differential LLS or not (chisq-test p -value = 0.7910).

	Differential LLS	Non-significant changes of LLS	Total
Adjacent to CDs	44	9	53
Adjacent to non-CDs	21	6	27
Total	65	15	80

Supplementary Table 8: The number of differentially or non-differentially expressed truncated genes whose nearby upstream TAD boundaries move forward or move backward or stay (chisq-test p -value = 0.0082).

	Forward	Backward	Stay	Total
DEGs	57	6	17	80
non-DEGs	1037	293	593	1923
Total	1094	299	610	2003

Supplementary Table 9: The number of differentially or non-differentially expressed truncated genes whose nearby downstream TAD boundaries move forward or move backward or stay (chisq-test p -value = 0.0110).

	Forward	Backward	Stay	Total
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DEGs	57	7	16	80
non-DEGs	1043	292	588	1923
Total	1100	299	604	2003

Supplementary Table 10: The number of differentially or non-differentially expressed truncated genes whose two nearby TAD boundaries both move forward or not (chisq-test p -value = 0.0020).

	Both forward	Not both forward	Total
DEGs	55	25	80
non-DEGs	971	952	1923
Total	1026	977	2003

Section2: The following **Supplementary Table 11-13** show the correlation between differential expression of genes and alterations in chromatin loops and TADs called by Insulation Score. Chisq-test was performed for each table, and p -value < 0.05 was considered as statistical significant. The following data suggest that the biological insights revealed by topoHiC cannot be fully revealed by Insulation Score.

Supplementary Table 11: The distribution of DEGs among inside genes, truncated genes and outside genes (chisq-test p -value = 0.6557).

	DEGs	non-DEGs	Total
Inside genes	911	16852	17763
Truncated genes	294	5513	5807
Outside genes	151	2588	2739
Total	1341	24363	25704

Supplementary Table 12: The number of differentially or non-differentially expressed inside genes that reside in CDs or not (chisq-test p -value = 0.4139).

	DEGs	non-DEGs	Total
Reside in CDs	775	14155	14930
Reside in non-CDs	136	2697	2833
Total	911	16852	17763

Supplementary Table 13: The number of differentially or non-differentially expressed truncated genes that adjacent to CDs/non-CDs (chisq-test p -value = 0.7129 for replicate1 and 0.6114 for replicate2).

Replicate1	DEGs	non-DEGs	Total
Adjacent to CDs	262	4864	5162
Adjacent to non-CDs	32	649	681
Replicate2	DEGs	non-DEGs	Total
Adjacent to CDs	265	4907	5172
Adjacent to non-CDs	29	606	635
Total	294	5513	5807

Section3: The following **Supplementary Table 14-15** show the number of CDs or non-CDs which were related to DEGs or non-DEGs. Chisq-test showed significant correlations. Combined with data in Section1, we conclude that while alterations in TADs do not invariably result in differential expression of genes, the occurrence of differential expression is typically contingent upon the alterations in TADs.

Supplementary Table 14: The number of CDs/non-CDs that cover differentially expressed inside genes or not (chisq-test p -value < 0.001).

	Cover at least one DEGs	Cover no DEGs	Total
CDs	471	2666	3,137
non-CDs	235	1777	2,012
Total	706	4443	5,149

Supplementary Table 15: The number of CDs/non-CDs in Mock and SARS that adjacent to differentially expressed truncated genes or not (chisq-test p -value < 0.001 both).

		Adjacent to DEGs	Not adjacent to DEGs	Total
Mock	CDs	61	3,076	3,137
	non-CDs	15	1,997	2,012
Total		76	5,073	5,149
SARS	CDs	65	2,424	2,489
	non-CDs	15	1,997	2,012
Total		80	4,421	4,501

Section4: The following **Supplementary Table 16-18** show the accession and some details of all the public datasets we used in our paper.

Supplementary Table 16: Hi-C data sources.

Accession	Library	Cell line	Notation	Replicate	Dataset	Intra-chromosomal contacts
GSE63525	GSM1551569	GM12878	rep1	biological replicate	Rao's data	226,966,076
GSE63525	GSM1551570	GM12878	rep2	biological replicate	Rao's data	110,314,873
GSE63525	GSM1551571	GM12878	rep3	biological replicate	Rao's data	200,397,427
GSE63525	GSM1551572	GM12878	rep4	biological replicate	Rao's data	194,876,534
GSE63525	GSM1551573	GM12878	rep5	biological replicate	Rao's data	65,546,147
GSE63525	GSM1551574	GM12878	rep6	biological replicate	Rao's data	193,724,418
GSE63525	GSM1551575	GM12878	rep7	biological replicate	Rao's data	197,665,750
GSE63525	GSM1551576	GM12878	rep8	biological replicate	Rao's data	197,509,933
GSE63525	GSM1551577	GM12878	rep9	biological replicate	Rao's data	42,976,132
GSE63525	GSM1551578	GM12878	rep10	biological replicate	Rao's data	87,663,490
GSE63525	GSM1551555	GM12878	tech1	technical replicate	Rao's data	102,022,209
GSE63525	GSM1551556	GM12878	tech2	technical replicate	Rao's data	192,990,609
GSE63525	GSM1551557	GM12878	tech3	technical replicate	Rao's data	99,786,882
GSE63525	GSM1551558	GM12878	tech4	technical replicate	Rao's data	117,206,139
GSE199607	GSM6926930	HCT-116	control1	biological replicate	Park's data	313,238
GSE199607	GSM6926931	HCT-116	control2	biological replicate	Park's data	592,418,750
GSE199607	GSM6926932	HCT-116	gsk3a1	biological replicate	Park's data	330,263
GSE199607	GSM6926933	HCT-116	gsk3a2	biological replicate	Park's data	470,450,519
GSE1791	GSM5411173	A549-ACE2	mock1	biological replicate	Wang's data	271,969,628

84						
GSE1791 84	GSM5411174	A549-ACE2	mock2	biological replicate	Wang's data	305,804,460
GSE1791 84	GSM5411175	A549-ACE2	sars1	biological replicate	Wang's data	185,678,975
GSE1791 84	GSM5411176	A549-ACE2	sars2	biological replicate	Wang's data	246,150,472

Supplementary Table 17: ChIP-seq data sources.

Accession	Cell Line	Target	Remark
ENCFF349LKU	HCT-116	H3K27ac	Control
ENCFF834RWR	HCT-116	H3K4me3	Control
ENCFF832IOO	HCT-116	H3K9me3	Control
GSM6926917,GSM6926920,GS M6926923	HCT-116	CTCF	Control
GSM6926916,GSM6926919	HCT-116	RAD21	Control
GSM6926924,GSM6926926,GS M6926928	HCT-116	RAD21	GSK3A group
ENCFF795URC	GM12878	H3K4me3	Control
ENCFF816AHV	GM12878	H3K27ac	Control
ENCFF682WIQ	GM12878	H3K9me3	Control
ENCFF052MHA	GM12878	H3K9ac	Control
ENCFF233NNT	GM12878	H3K36me3	Control
ENCFF247VUO	GM12878	H3K27me3	Control
ENCFF308WNH	GM12878	H4K20me1	Control
ENCFF357HZM	GM12878	H3K79me2	Control
ENCFF584NAD	GM12878	H2AFZ	Control
ENCFF921LKB	GM12878	H3K4me1	Control
ENCFF983SMS	GM12878	H3K4me2	Control
ENCFF967ACD	GM12878	YY1	Control
ENCFF686FLD	GM12878	SMC3	Control
ENCFF710VEH	GM12878	CTCF	Control
ENCFF002CPK	GM12878	RAD21	Control
GSM5411185	A549-ACE2	H3K27ac	Mock
GSM5411186	A549-ACE2	H3K27ac	SARS-CoV-2
GSM5411187	A549-ACE2	H3K4me3	Mock
GSM5411188	A549-ACE2	H3K4me3	SARS-CoV-2
GSM5411189	A549-ACE2	H3K27me3	Mock
GSM5411190	A549-ACE2	H3K27me3	SARS-CoV-2
GSM5411191	A549-ACE2	H3K9me3	Mock
GSM5411192	A549-ACE2	H3K9me3	SARS-CoV-2
GSM5411193	A549-ACE2	H3K27ac	Mock
GSM5411194	A549-ACE2	H3K27ac	SARS-CoV-2

GSM5411195	A549-ACE2	H3K27me3	Mock
GSM5411196	A549-ACE2	H3K27me3	SARS-CoV-2
GSM5411201	A549-ACE2	H3K4me3	Mock
GSM5411202	A549-ACE2	H3K4me3	SARS-CoV-2
GSM5411203	A549-ACE2	H3K9me3	Mock
GSM5411204	A549-ACE2	H3K9me3	SARS-CoV-2

Supplementary Table 18: RNA-seq data source.

Accession	Cell Line
GSE179184	A549-ACE2

Section5: The following **Supplementary Table 19-21** show the number of loop anchors overlapped with known biological evidence called by topoHiC and other existing loop callers. The following data could be used to reproduce Figure 1E, Supplementary Figure 1C, 1F, 1G, 1H.

Supplementary Table 19: Loop anchors in chromosome 22 across ten biological replicates in Dataset1 at 5kb resolution overlapped with histone modifications, transcription factors and enhancers. Histone modifications include H3K4me3, H3K27ac, H3K9me3, H3K9ac, H3K36me3, H3K27me3, H4K20me1, H3K79me2, H2AFZ, H3K4me1 and H3K4me2. Transcription factors include CTCF, RAD21, SMC3 and YY1. Any loop anchors overlapped with one of the histone modifications or transcription factors will be considered as overlapped with histone modifications or transcription factors.

	FitHiC	HiCCUPS	Mustache	Peakachu	topoHiC
Overlapped with histone modifications	35955	78	1444	3472	30369
Overlapped with transcription factors	19853	92	1366	3019	16983
Overlapped with enhancers	15932	49	658	1547	13644
Not overlapped	21641	64	177	564	19287

Supplementary Table 20: Loop anchors in Dataset2 at 5kb resolution overlapped with histone modifications and transcription factors.

		topoHiC	Mustache	Peakachu
H3K27ac	Overlapped	9832	11340	16398
	Not overlapped	78037	43427	67307
H3K9me3	Overlapped	24065	2938	6944
	Not overlapped	63804	51829	76761
H3K4me3	Overlapped	10547	12614	17841
	Not overlapped	77322	42153	65864
Any one of the above three histone modifications	Overlapped	36015	17199	27181
	Not overlapped	51854	37568	56524
CTCF	Overlapped	30952	39376	50733
	Not overlapped	56917	15391	32972
RAD21 (Control)	Overlapped	32730	38888	50511
	Not overlapped	55139	15879	33194
RAD21	Overlapped	25132	26190	34126

(GSK3A)	Not overlapped	89519	9676	25062
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Supplementary Table 21: Loop anchors called by topoHiC in chromosome 1-22 across ten biological replicates in Dataset1 at 5kb resolution overlapped with histone modifications, transcription factors and enhancers. Histone modifications include H3K4me3, H3K27ac, H3K9me3, H3K9ac, H3K36me3, H3K27me3, H4K20me1, H3K79me2, H2AFZ, H3K4me1 and H3K4me2. Transcription factors include CTCF, RAD21, SMC3 and YY1. Any loop anchors overlapped with one of the histone modifications or transcription factors will be considered as overlapped with histone modifications or transcription factors.

	Overlapped	Not overlapped
Histone modifications	1645667	3262558
Transcription factors	910919	3997306
Enhancers	845244	4062981
Overlap or not overlap with any one of the above biological evidence	2638837	2269388

Section6: The following **Supplementary Table 22-27** show the number of supported boundaries called by topoHiC, DomainCaller, Insulation Score and TopDom in Dataset2. The following data could be used to reproduce Figure 3A.

Supplementary Table 22: CTCF-supported boundaries. IS, Insulation Score. DI, DomainCaller. Due to data availability, these calculation was performed in control group of Dataset2.

	CTCF-supported boundaries	non-CTCF-supported boundaries	Percentage
DI	2651	7656	25.70%
IS	2988.5	9151.5	24.60%
topoHiC	4484	7300	38.10%
TopDom	4266.5	9181.5	31.70%

Supplementary Table 23: RAD21-supported boundaries in control group of Dataset2. IS, Insulation Score. DI, DomainCaller.

	RAD21-supported boundaries	non-RAD21-supported boundaries	Percentage
DI	2721	7586	26.40%
IS	3164	8976	26.10%
topoHiC	4958	6826	42.10%
TopDom	4544	8904	33.80%

Supplementary Table 24: RAD21-supported boundaries in *GSK3A*-depleted group of Dataset2. IS, Insulation Score. DI, DomainCaller.

	RAD21-supported boundaries	non-RAD21-supported boundaries	Percentage
DI	1774	7618	18.90%
IS	2006	8741	18.70%
topoHiC	2961	11241	20.80%
TopDom	3315.5	8974.5	27.00%

Supplementary Table 25: H3K27ac-supported boundaries. IS, Insulation Score. DI, DomainCaller. Due to data availability, these calculation was performed in control group of Dataset2.

	H3K27ac-supported boundaries	non-H3K27ac-supported boundaries	Percentage
DI	885	9422	8.60%
IS	1158	10982	9.50%
topoHiC	1318	10466	11.20%
TopDom	1502.5	11945.5	11.20%

Supplementary Table 26: H3K4me3-supported boundaries. IS, Insulation Score. DI, DomainCaller. Due to data availability, these calculation was performed in control group of

Dataset2.

	H3K4me3-supported boundaries	non-H3K4me3-supported boundaries	Percentage
DI	916.5	9390.5	8.90%
IS	1200	10940	9.90%
topoHiC	1371	10413	11.60%
TopDom	1595	11853	11.90%

Supplementary Table 27: H3K9me3-supported boundaries. IS, Insulation Score. DI, DomainCaller. Due to data availability, these calculation was performed in control group of Dataset2.

	H3K9me3-supported boundaries	non-H3K9me3-supported boundaries	Percentage
DI	524.5	9782.5	5.10%
IS	1224.5	10915.5	10.10%
topoHiC	1646	10138	14.00%
TopDom	960	12488	7.10%

Section7: The following **Supplementary Table 28-29** show the averaged local loop scores (LLS) calculated by topoHiC at different sizes. The following data could be used to reproduce Supplementary Figure 6.

Supplementary Table 28: Averaged LLS of inside genes. LLS is a 21-dimension vector, which means the average of all LLS is also a 21-dimension vector. In “Genomic bin index”, “11” indicates the bin that contains the TSS of inside genes, and “1”-“10” are upstream bins, “12”-“21” are downstream bins.

See *Supplementary Tables.xlsx*

Supplementary Table 29: Averaged LLS of truncated genes. LLS is a 21-dimension vector, which means the average of all LLS is also a 21-dimension vector. In “Genomic bin index”, “11” indicates the bin that contains the TSS of truncated genes, and “1”-“10” are upstream bins, “12”-“21” are downstream bins.

See *Supplementary Tables.xlsx*

Section8: The following **Supplementary Table 30** shows the peak coverage of CTCF, RAD21 and histone modifications in Dataset1 and Dataset2.

Supplementary Table 30: Peak coverage in Dataset1 and Dataset2.

Target	Dataset	Treatment	Coverage
CTCF	1	None	0.29%
CTCF	2	None	2.08%
RAD21	1	None	0.30%
RAD21	2	None	2.33%
RAD21	2	<i>GSK3A</i> -depleted	2.01%
H3K4me3	1	None	1.60%
H3K4me3	2	None	1.76%
H3K9me3	1	None	0.18%
H3K9me3	2	None	2.48%
H3K27ac	1	None	2.22%
H3K27ac	2	None	2.04%

Section9: The following **Supplementary Table 31-37** show the number and median size of TADs called by different TAD callers in Dataset1, Dataset2 and Dataset3. The following data could be used to reproduce Figure 3B.

Supplementary Table 31: The number and median size of TADs called by seven TAD callers in biological replicates of Dataset1.

See *Supplementary Tables.xlsx*

Supplementary Table 32: The number and median size of TADs called by seven TAD callers in technical replicates of Dataset1.

See *Supplementary Tables.xlsx*

Supplementary Table 33: The number of TADs called by four TAD callers in Dataset2.

See *Supplementary Tables.xlsx*

Supplementary Table 34: The number of TADs called by topoHiC in Dataset3.

See *Supplementary Tables.xlsx*

Supplementary Table 35: The mean and standard deviation of TADs called by different TAD callers in Dataset2. Wilcox tests are performed between each experimental group and control group. P-values of these tests are listed in this table.

	Control		GSK3A-depleted	
	Mean	sd	Mean	sd
topoHiC (merged)	267.8	123.5	322.8	156.6
	<i>p.value</i> =0.26			
IS	276.9	138.6	245.3	120.1
	<i>p.value</i> =0.43			
DI	234.3	119.3	213.5	105.1
	<i>p.value</i> =0.53			
TopDom	305.6	151.6	279.3	135.8
	<i>p.value</i> =0.50			

Supplementary Table 36: The size of TADs called by different TAD callers in Dataset2. Wilcox tests are performed between each experimental group and control group. P-values < 0.001 in all the tests.

See *Supplementary Tables.xlsx*

Supplementary Table 37: The median number of TADs called by different TAD callers.

	Dataset1 Biological replicates	Dataset1 Technical replicates	Dataset2 Control group	Dataset2 GSK3A-depleted group	Dataset3 Mock	Dataset3 SARS
topoHiC (merged)	71	66	248	289	248	200
topoHiC	118	99	-	-	-	-

(individual)						
IS	242	240	271	243	-	-
DI	190	186	228	205	-	-
TopDom	232	229	301	276	-	-
Arrowhead	58	58	-	-	-	-
ClusterTAD	56	58	-	-	-	-
OnTAD	230	228	-	-	-	-

Supplementary Table 38: The size of TADs called by topoHiC and Insulation Score both at 5kb resolution in Dataset2.

See *Supplementary Tables.xlsx*

Section10: The following **Supplementary Table 39-44** show the results of six logistic regression models.

Supplementary Table 39: The results of the multiscale model.

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-1.2744	1.1021	-1.1563	0.2475
C/nC	2.0239	1.0741	1.8844	0.0595
sdΔLLS	-0.2213	0.0729	-3.0367	0.0024

Supplementary Table 40: The results of the domain model.

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-1.0986	0.8165	-1.3455	0.1785
C/nC	1.0389	0.8346	1.2448	0.2132

Supplementary Table 41: The results of the loop model.

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	0.5040	0.3095	1.6286	0.1034
sdΔLLS	-0.1934	0.0720	-2.6852	0.0072

Supplementary Table 42: The results of the full model.

See *Supplementary Tables.xlsx*

Supplementary Table 43: The results of the domain-histone model.

See *Supplementary Tables.xlsx*

Supplementary Table 44: The results of the loop-histone model.

See *Supplementary Tables.xlsx*

Section11: The following **Supplementary Table 45-46** show the results of aggregate peak analysis in Dataset1.

Supplementary Table 45: The results of the five loop callers at 5kb resolution.

	Sample	FitHiC	HiCCUPS	Mustache	Peakachu	topoHiC
P2LL	rep1	2.16	12.26	2.10	2.85	3.67
	rep2	4.48	31.42	2.36	3.47	4.28
	rep3	2.25	14.35	2.08	2.81	3.34
	rep4	2.30	12.29	2.09	2.84	3.38
	rep5	7.24	31.64	2.86	4.23	9.52
	rep6	2.91	27.09	2.09	3.00	2.88
	rep7	2.86	21.15	2.03	2.99	2.82
	rep8	2.60	12.70	2.20	3.04	2.61
	rep9	9.69	100.57	1.52	4.12	10.55
	rep10	4.63	27.61	1.97	3.40	6.70
ZScoreLL	rep1	34.86	24.56	52.15	61.94	60.18
	rep2	105.15	24.00	33.54	64.41	75.98
	rep3	35.57	35.24	43.02	57.21	46.51
	rep4	37.00	31.51	61.83	51.93	48.61
	rep5	154.43	25.96	13.89	58.17	221.96
	rep6	69.91	47.60	56.21	66.03	42.80
	rep7	68.46	31.50	52.89	74.50	41.29
	rep8	52.54	25.72	57.03	72.82	33.09
	rep9	295.82	52.48	0.49	43.05	261.81
	rep10	120.93	18.24	11.36	57.19	144.76

Supplementary Table 46: The results of the five loop callers at 10kb resolution.

	Sample	FitHiC	HiCCUPS	Mustache	Peakachu	topoHiC
P2LL	rep1	1.47	8.10	1.99	2.45	2.34
	rep2	2.38	14.61	1.99	2.79	1.95
	rep3	1.46	8.67	1.89	2.34	2.32
	rep4	1.49	8.59	1.91	2.38	2.30
	rep5	3.52	20.19	2.51	3.51	3.67
	rep6	1.69	12.31	1.87	2.41	1.85
	rep7	1.68	10.79	1.82	2.41	1.82
	rep8	1.61	7.19	1.96	2.50	1.99
	rep9	4.24	37.28	2.35	3.36	4.83
	rep10	2.41	18.16	1.88	2.72	2.39
ZScoreLL	rep1	9.19	31.20	25.92	32.07	26.15
	rep2	32.26	18.12	25.66	40.72	18.60
	rep3	8.36	34.12	19.93	27.63	23.38
	rep4	9.11	28.65	21.00	29.20	22.37

	rep5	64.52	32.76	33.56	52.21	55.54
	rep6	16.27	38.01	28.93	42.64	22.32
	rep7	16.04	26.58	29.01	41.03	20.86
	rep8	12.64	44.81	24.18	34.28	23.08
	rep9	78.37	17.60	16.63	48.73	74.82
	rep10	34.28	21.26	19.85	39.35	26.47

Section12: The following **Supplementary Table 47-48** show the agreement of loops in Dataset1 called by five different loop callers. Supplementary Table 47 could be used to reproduce Figure 1B. Supplementary Table 48 could be used to reproduce Figure 1C.

Supplementary Table 47: The results at 5kb resolution.

	Shared with at least one other method	Method-specific
HiCCUPS	2787	22
Mustache	27511	6112
Peakachu	116998	22541
FitHiC	1933300	23959167
topoHiC	1837130	20656220

Supplementary Table 48: The results at 10kb resolution.

	Shared with at least one other method	Method-specific
HiCCUPS	10238	82
Mustache	62554	8067
Peakachu	150884	11886
FitHiC	1001389	33699120
topoHiC	837765	2083527