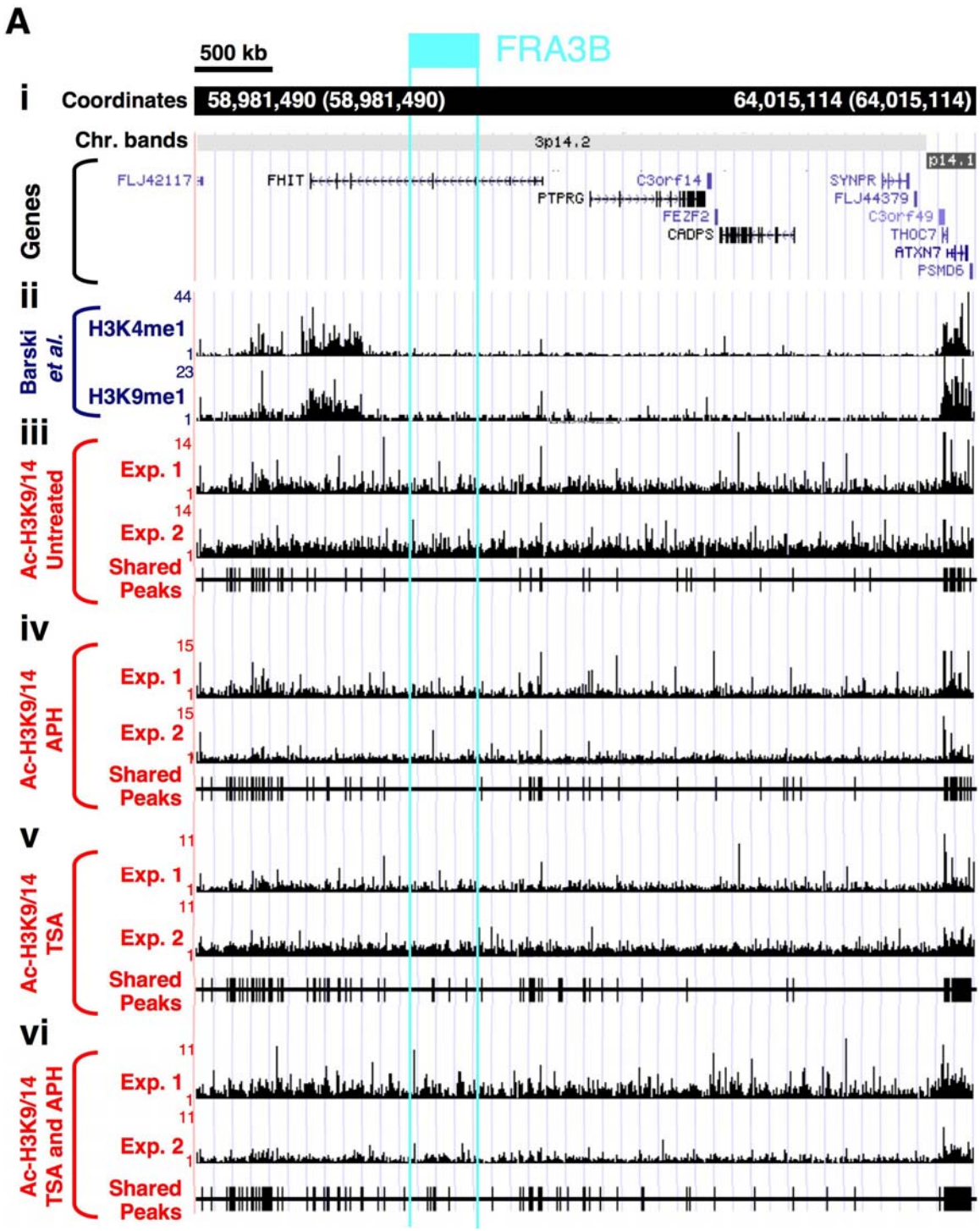
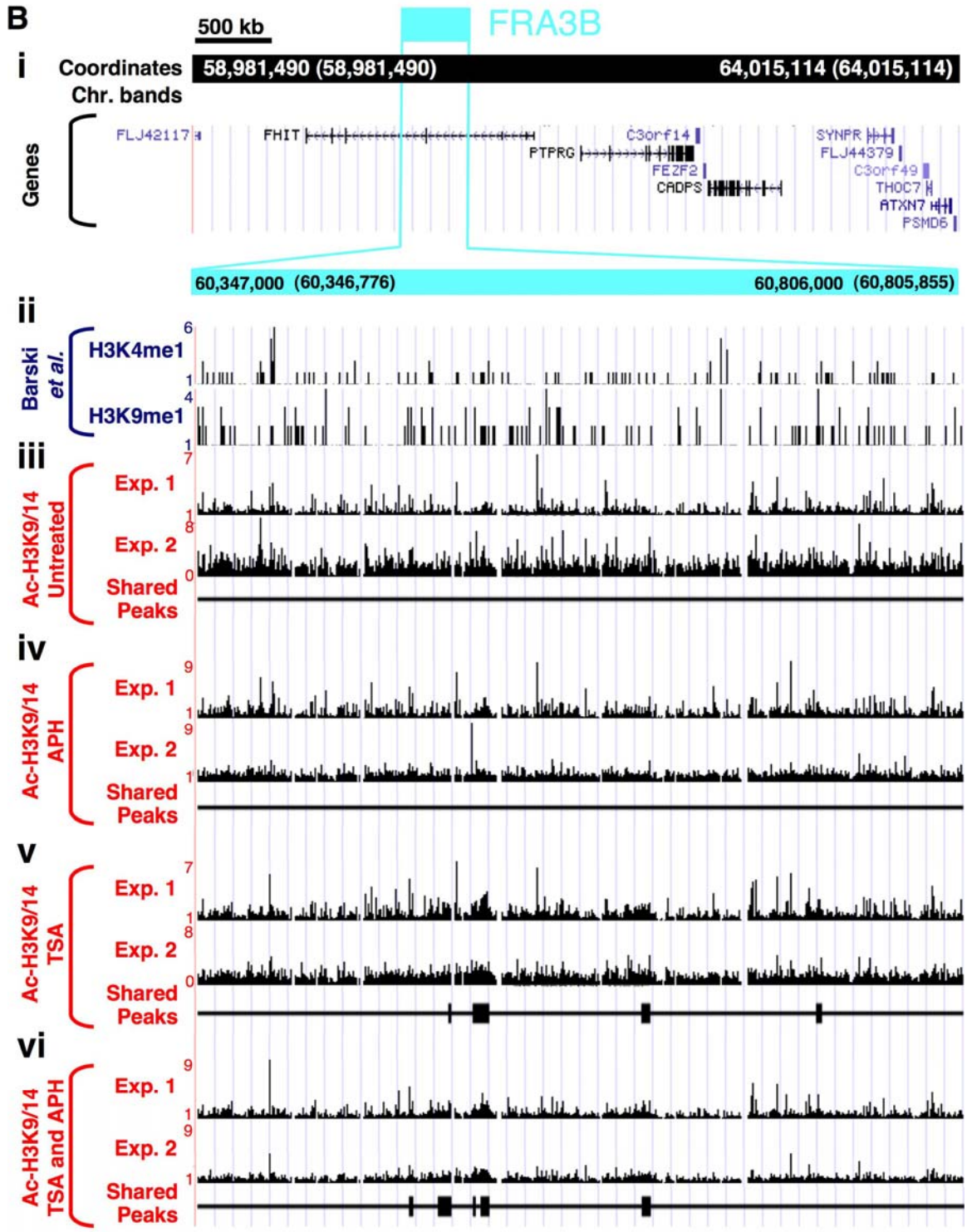
Supplementary Material
Figure S1

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THOC7
ATXN7
PSMD6
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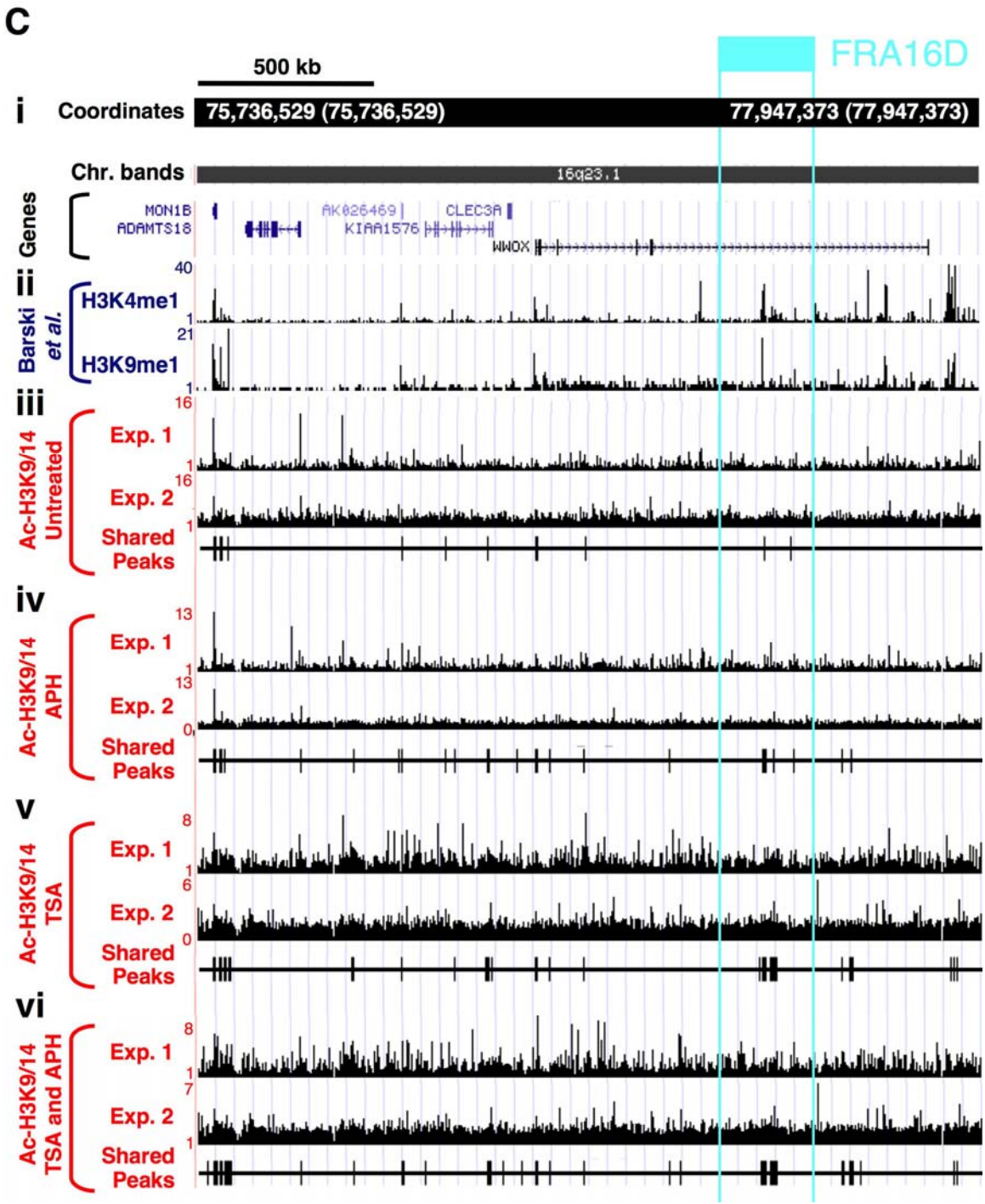
60,806,000 (60,805,855)
ii
Barski et al.
H3K4me1
H3K9me1
iii
Ac-H3K9/14 Untreated
Exp. 1
Exp. 2
Shared Peaks
iv
Ac-H3K9/14 APH
Exp. 1
Exp. 2
Shared Peaks
v
Ac-H3K9/14 TSA
Exp. 1
Exp. 2
Shared Peaks
vi
Ac-H3K9/14 TSA and APH
Exp. 1
Exp. 2
Shared Peaks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AK026469
KIAA1576
CLEC3A
WWOX
ii
Barski et al.
H3K4me1
H3K9me1
iii
Ac-H3K9/14 Untreated
Exp. 1
Exp. 2
Shared Peaks
iv
Ac-H3K9/14 APH
Exp. 1
Exp. 2
Shared Peaks
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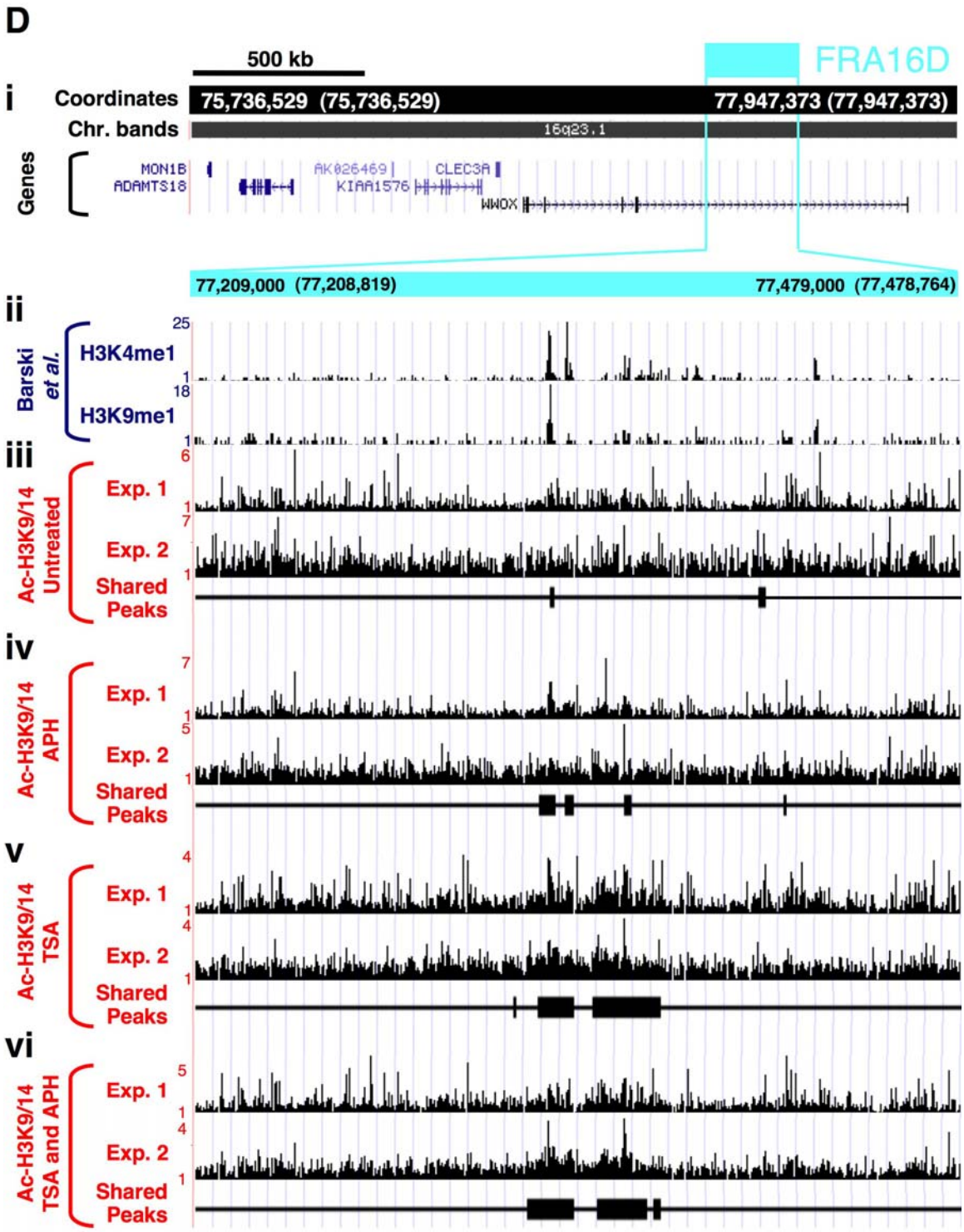
Exp. 1
Exp. 2
Shared Peaks
vi
Ac-H3K9/14 TSA and APH
Exp. 1
Exp. 2
Shared Peaks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Barski et al.
H3K4me1
H3K9me1
iii
Ac-H3K9/14 Untreated
Exp. 1
Exp. 2
Shared Peaks
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Ac-H3K9/14 APH
Exp. 1
Exp. 2
Shared Peaks
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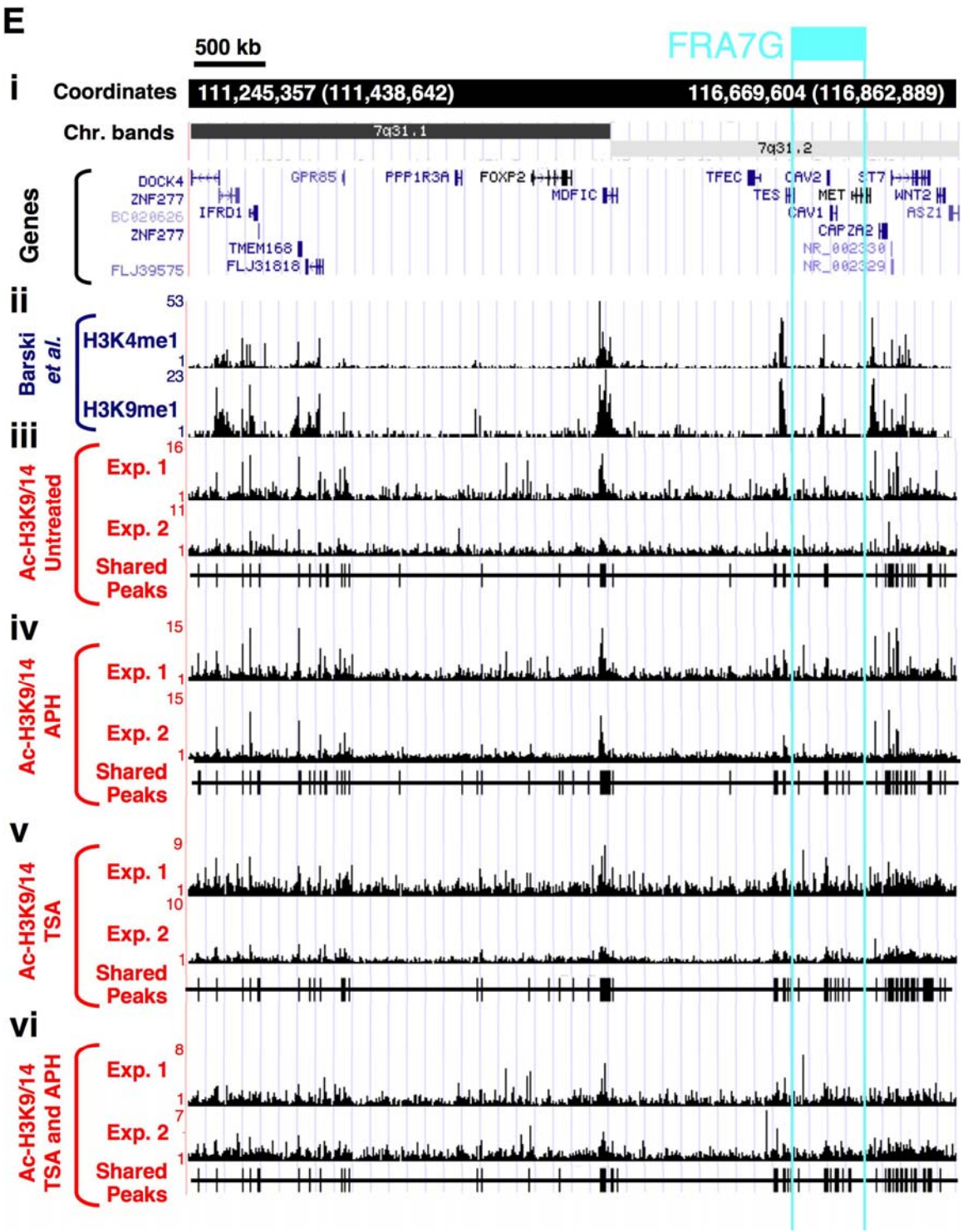
Exp. 1
Exp. 2
Shared Peaks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TMEM168
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FOXP2
MDFIC
TFEC
TES
CAV2
CAV1
ST7
MET
WNT2
ASZ1
CAPZA2
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NR_002329
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Barski et al.
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H3K9me1
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23
1
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Exp. 1
Exp. 2
Shared Peaks
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11
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Exp. 1
Exp. 2
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1
15
1
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Ac-H3K9/14 TSA
Exp. 1
Exp. 2
Shared Peaks
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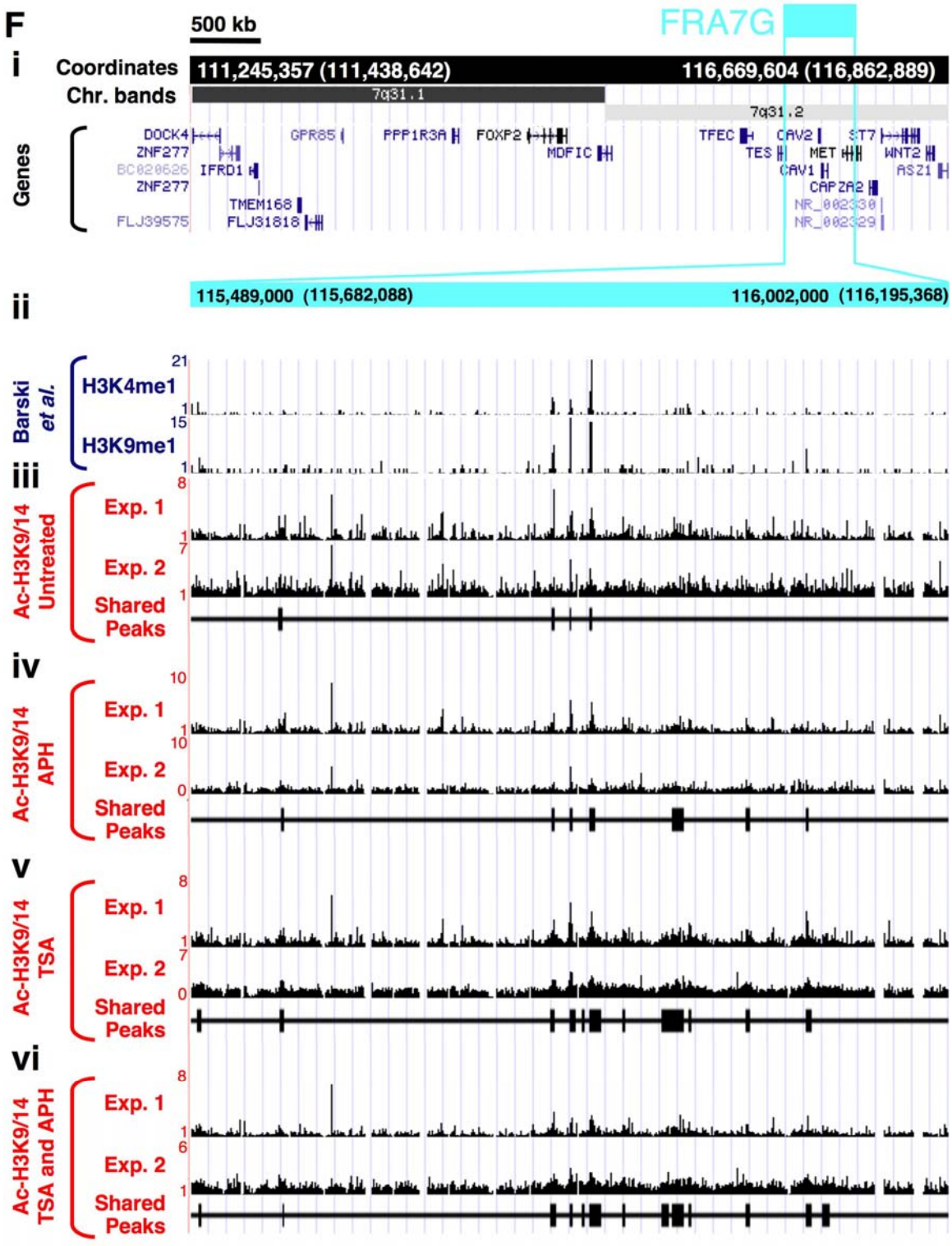
1
10
1
vi
Ac-H3K9/14 TSA and APH
Exp. 1
Exp. 2
Shared Peaks
8
1
7
1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DOCK4
ZNF277
BC020626
IFRD1
ZNF277
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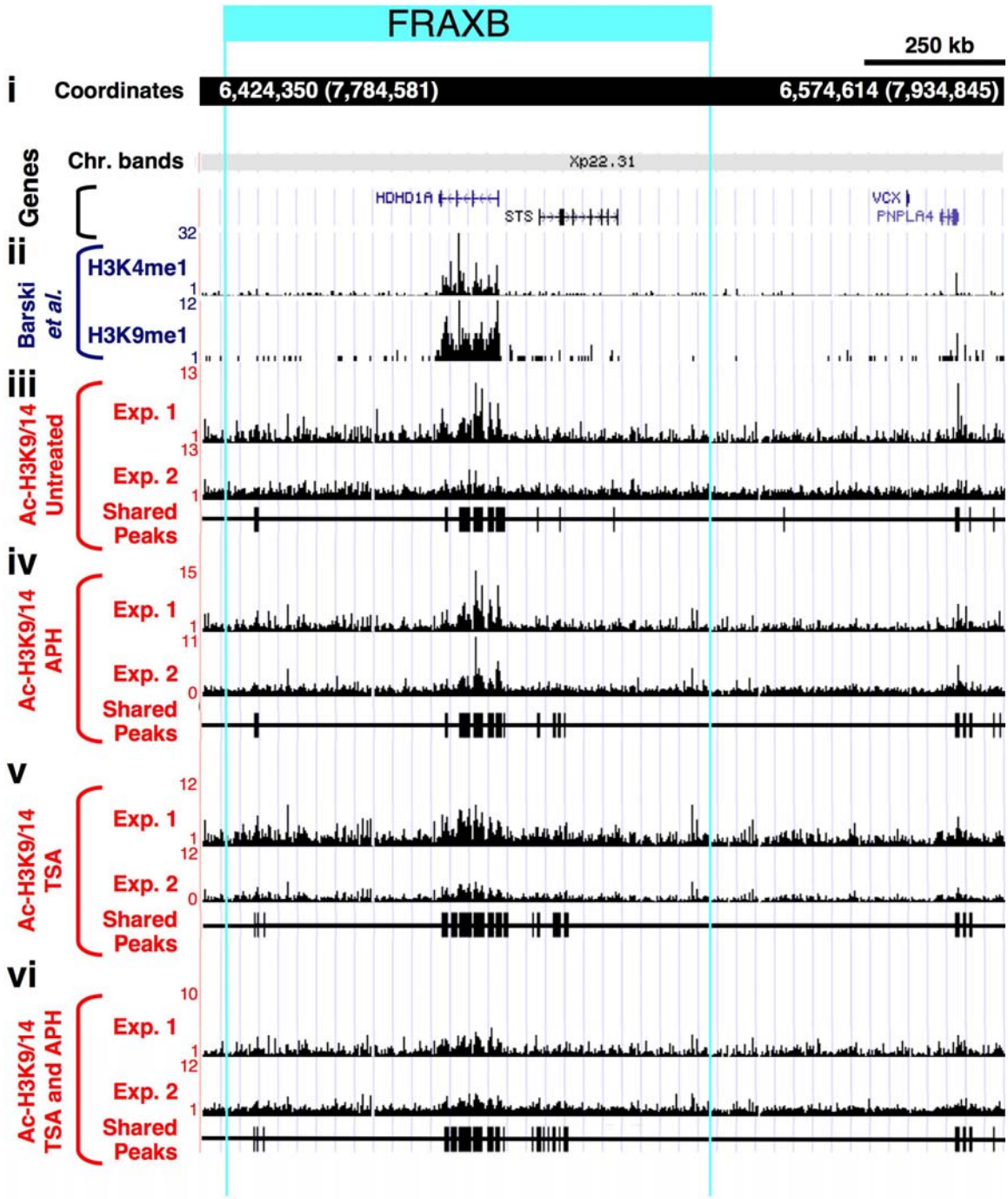
Barski et al.
H3K4me1
H3K9me1
iii
Ac-H3K9/14 Untreated
Exp. 1
Exp. 2
Shared Peaks
iv
Ac-H3K9/14 APH
Exp. 1
Exp. 2
Shared Peaks
v
Ac-H3K9/14 TSA
Exp. 1
Exp. 2
Shared Peaks
vi
Ac-H3K9/14 TSA and APH
Exp. 1
Exp. 2
Shared Peaks

G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Xp22.31
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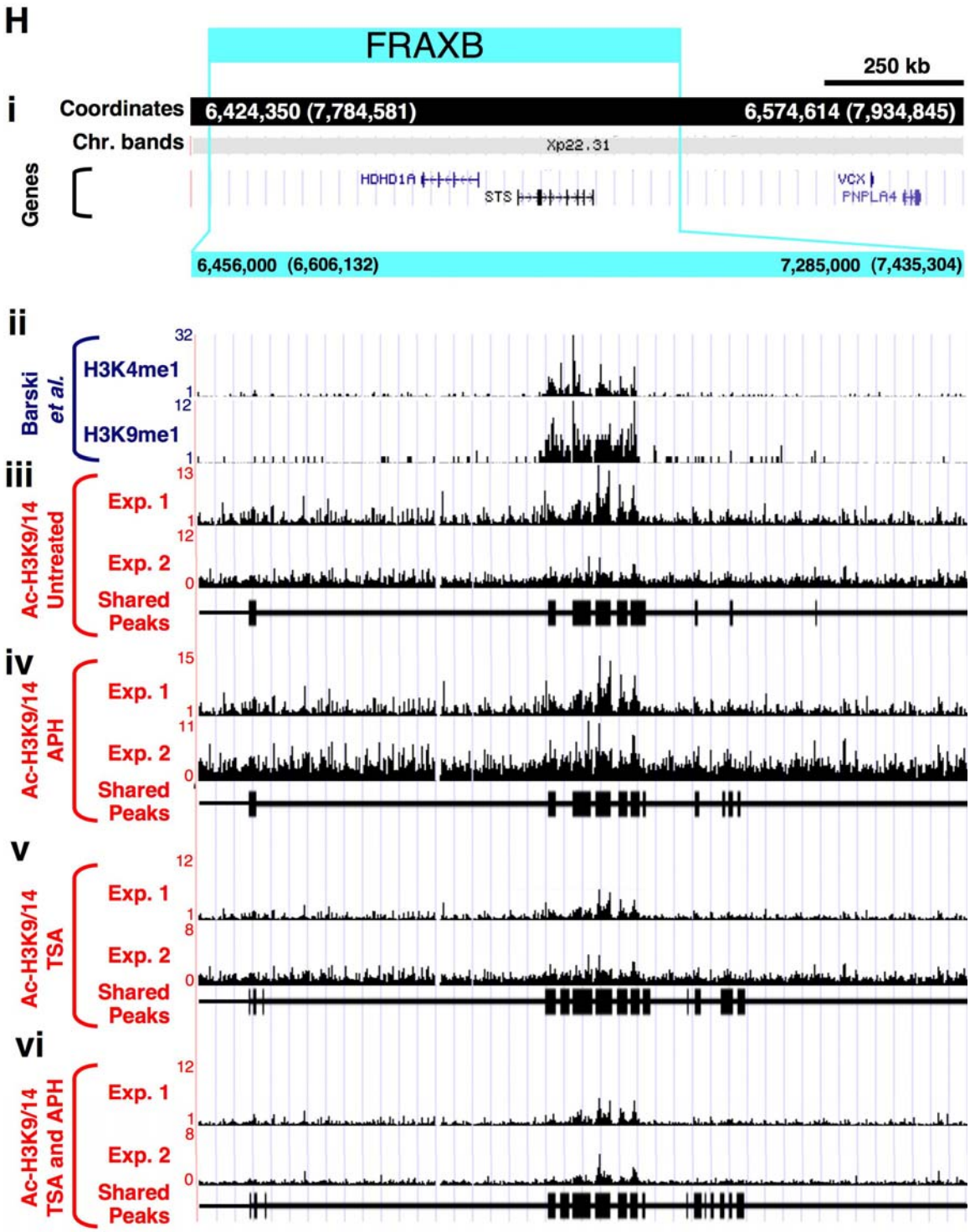
Genes
HDHD1A
STS
VCX
PNPLA4
Barski et al.
H3K4me1
H3K9me1
iii
Ac-H3K9/14 Untreated
Exp. 1
Exp. 2
Shared Peaks
iv
Ac-H3K9/14 APH
Exp. 1
Exp. 2
Shared Peaks
v
Ac-H3K9/14 TSA
Exp. 1
Exp. 2
Shared Peaks
vi
Ac-H3K9/14 TSA and APH
Exp. 1
Exp. 2
Shared Peaks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Chr. bands
Xp22.31
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STS
VCX
PNPLA4
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7,285,000 (7,435,304)
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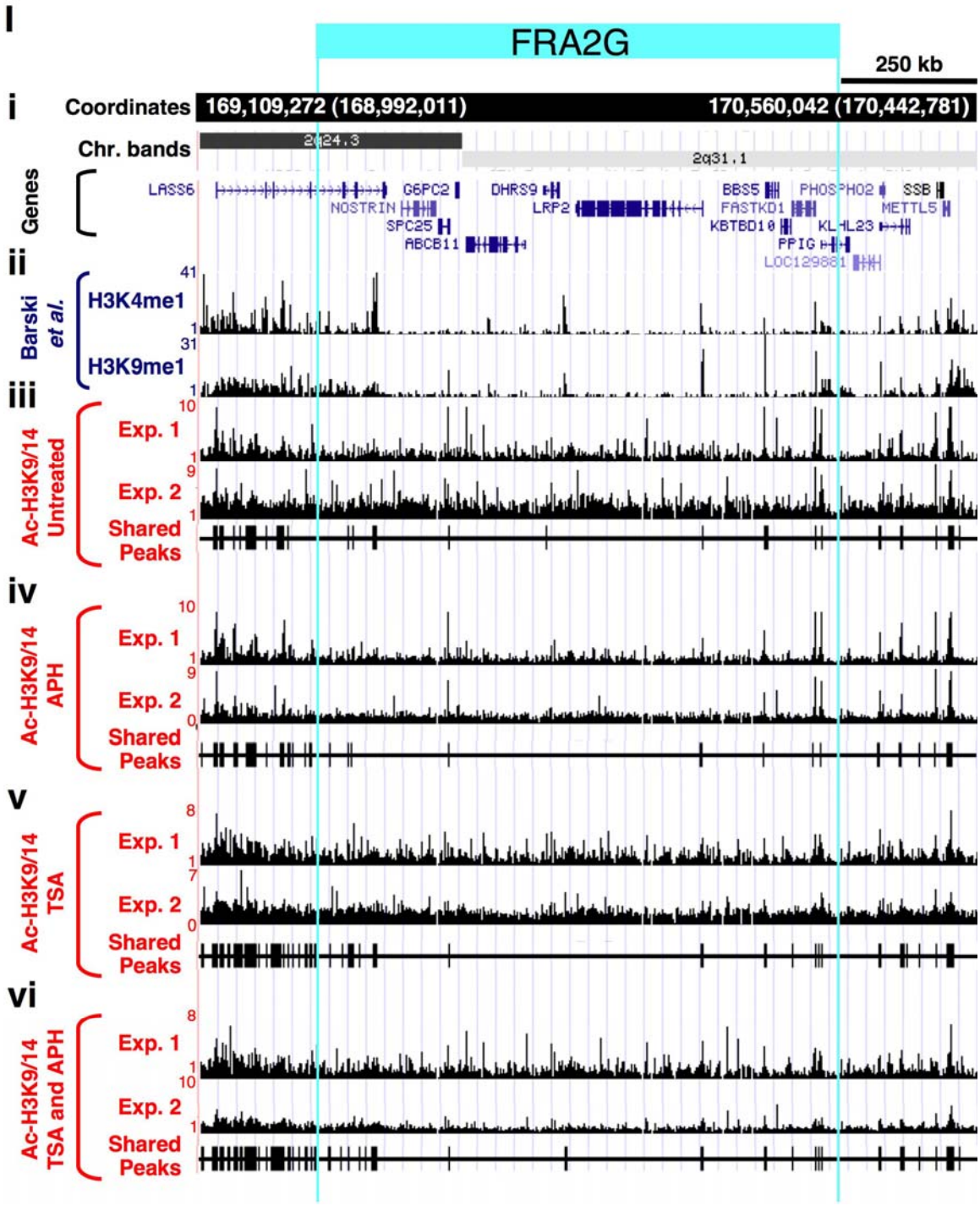
Barski et al.
H3K4me1
H3K9me1
iii
Ac-H3K9/14 Untreated
Exp. 1
Exp. 2
Shared Peaks
iv
Ac-H3K9/14 APH
Exp. 1
Exp. 2
Shared Peaks
v
Ac-H3K9/14 TSA
Exp. 1
Exp. 2
Shared Peaks
vi
Ac-H3K9/14 TSA and APH
Exp. 1
Exp. 2
Shared Peaks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G6PC2
NOSTRIN
SPC25
ABCB11
DHRS9
LRP2
BBS5
PHOSPHO2
SSB
FASTKD1
METTL5
KBTBD10
KL-HL23
PPIG
LOC129881
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Barski et al.
H3K4me1
H3K9me1
41
1
31
1
iii
Ac-H3K9/14 Untreated
Exp. 1
Exp. 2
Shared Peaks
10
1
9
1
iv
Ac-H3K9/14 APH
Exp. 1
Exp. 2
Shared Peaks
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9
0
v
Ac-H3K9/14 TSA
Exp. 1
Exp. 2
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Ac-H3K9/14 TSA and APH
Exp. 1
Exp. 2
Shared Peaks
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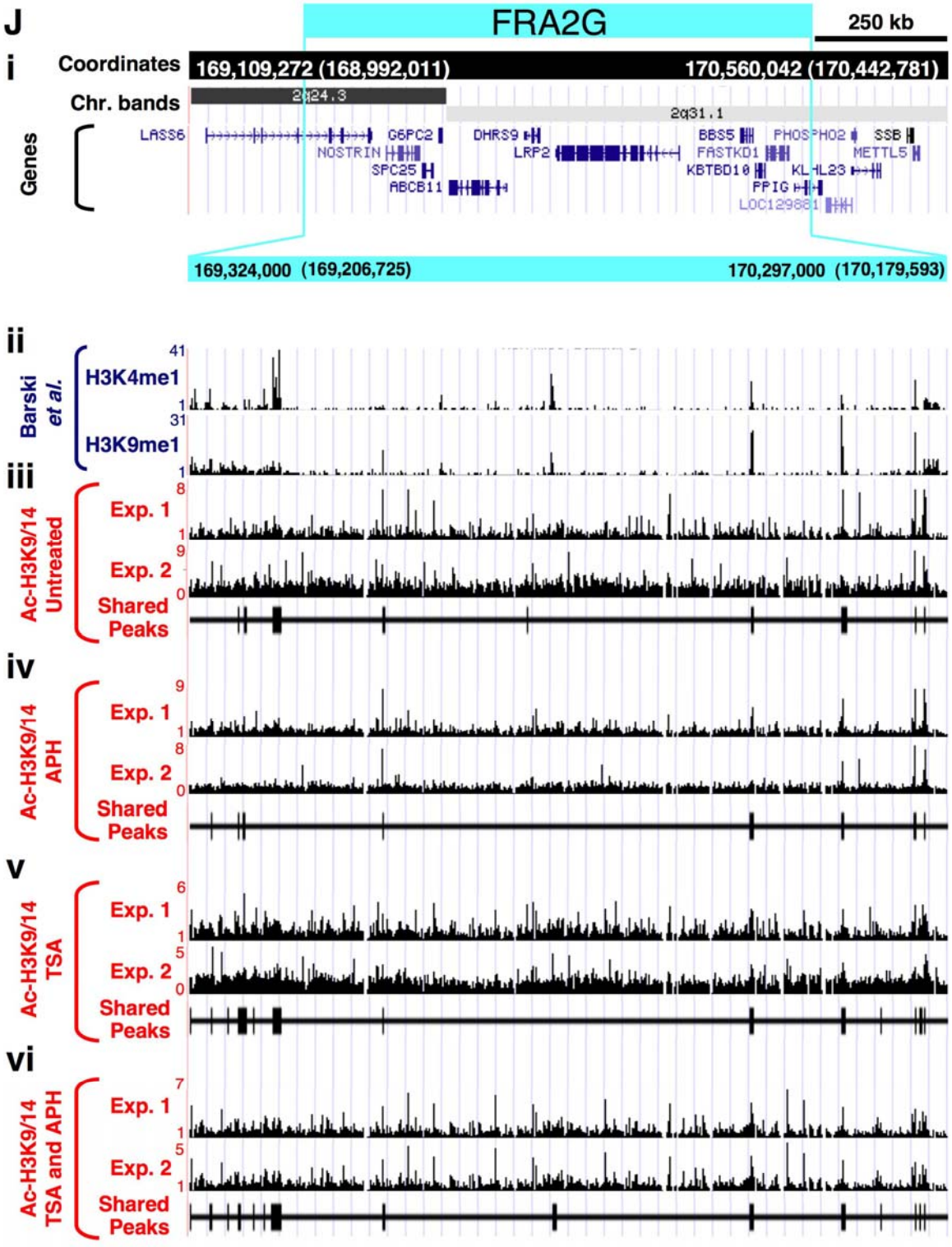
1
10
1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Genes
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DHRS9
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LRP2
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KBTBD10
KLHL23
ABCB11
PPIG
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Barski et al.
H3K4me1
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H3K9me1
31
1
iii
Ac-H3K9/14 Untreated
Exp. 1
8
1
Exp. 2
9
0
Shared Peaks
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Ac-H3K9/14 APH
Exp. 1
9
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Exp. 2
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0
Shared Peaks
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Ac-H3K9/14 TSA
Exp. 1
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Ac-H3K9/14 TSA and APH
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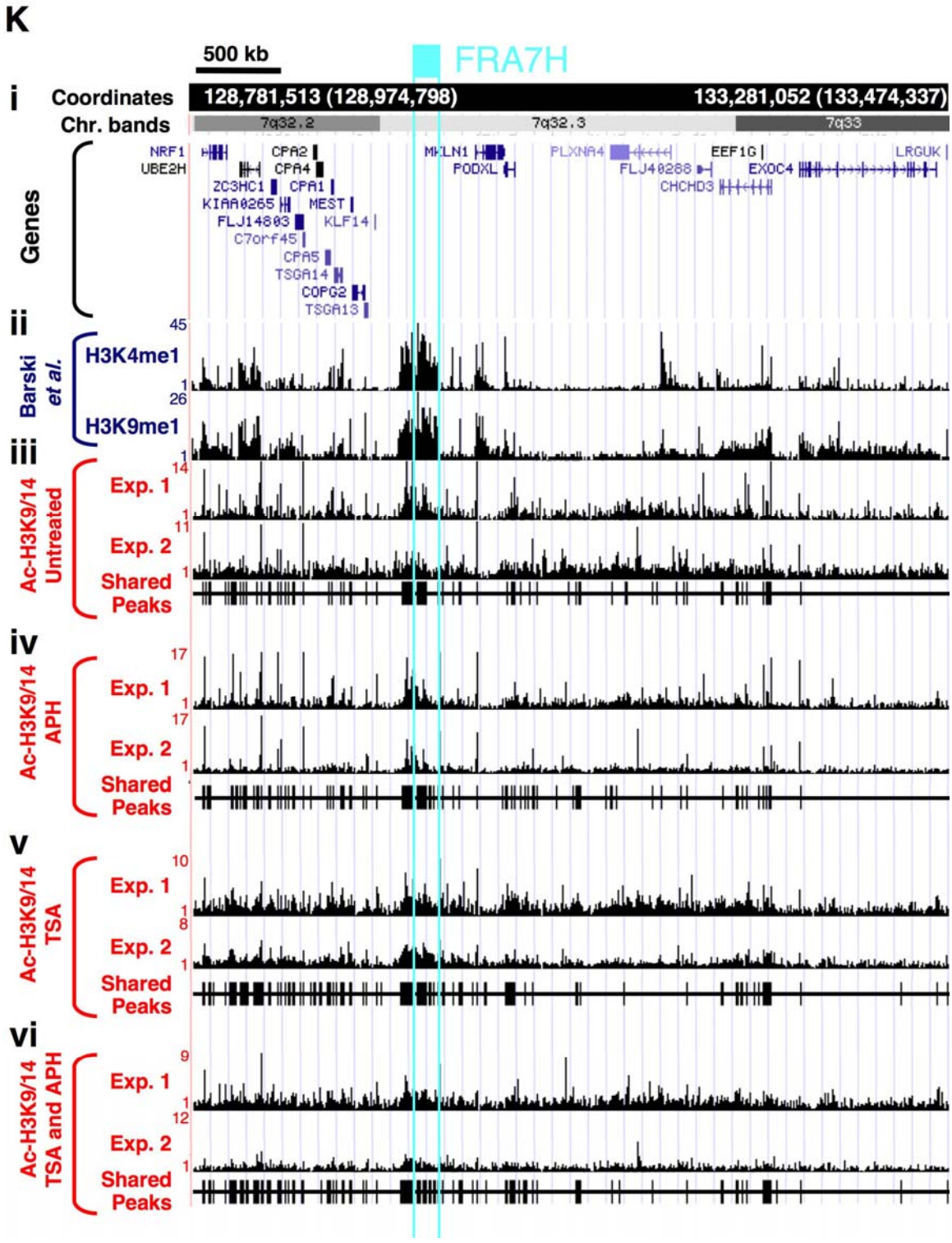
Exp. 2
5
1
Shared Peaks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7q33
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CPA4
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CPA1
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MEST
FLJ14803
KLF14
C7orf45
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COPG2
TSGA13
MKLN1
PODXL
PLXNA4
FLJ40288
CHCHD3
EEF1G
EXOC4
LRGUK
ii
Barski et al.
H3K4me1
H3K9me1
iii
Ac-H3K9/14 Untreated
Exp. 1
Exp. 2
Shared Peaks
iv
Ac-H3K9/14 APH
Exp. 1
Exp. 2
Shared Peaks
v
Ac-H3K9/14 TSA
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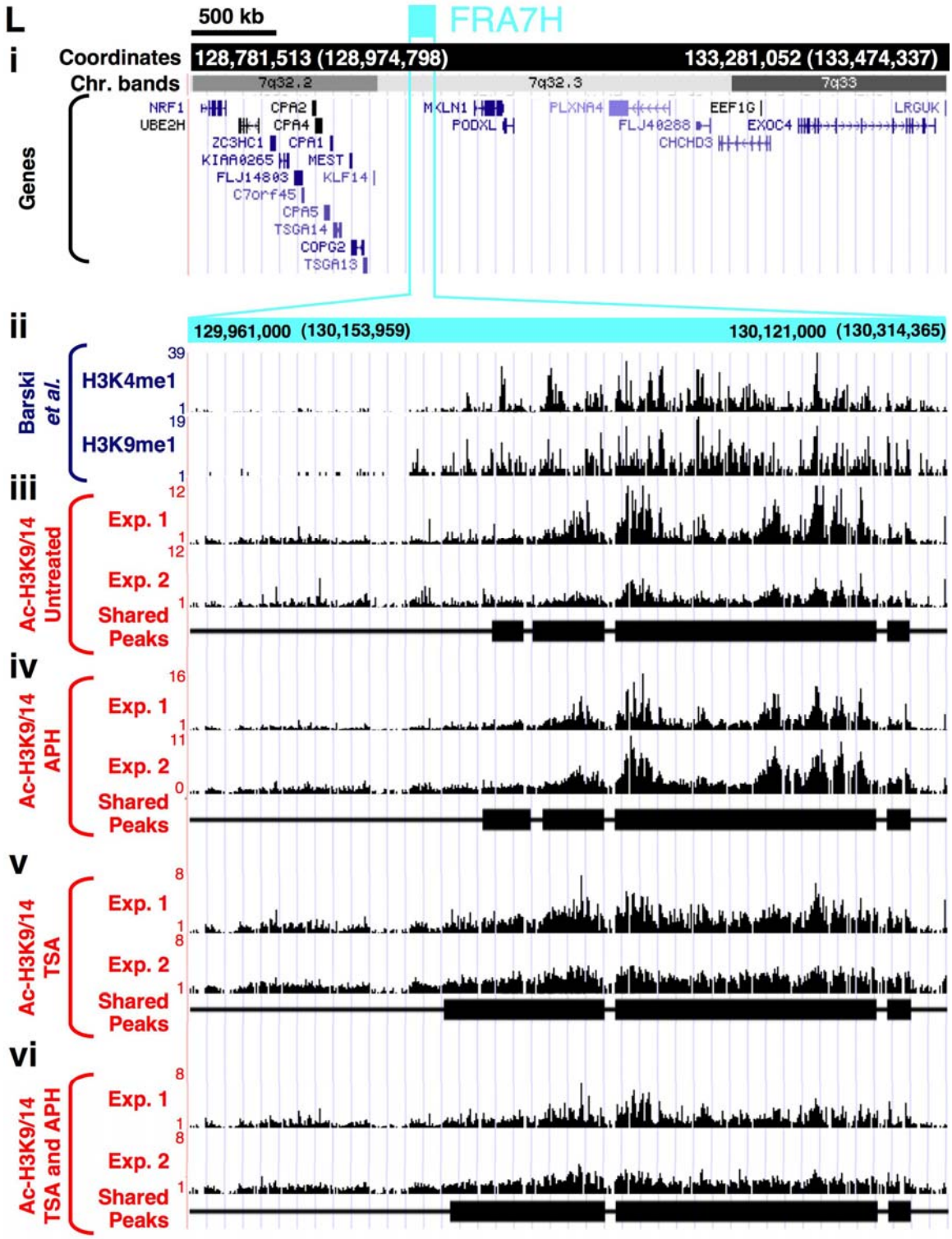
Exp. 2
Shared Peaks
vi
Ac-H3K9/14 TSA and APH
Exp. 1
Exp. 2
Shared Peaks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FRA7H
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133,281,052 (133,474,337)
Chr. bands
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7q32.3
7q33
Genes
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UBE2H
CPA2
CPA4
ZC3HC1
CPA1
KIAA0265
MEST
FLJ14803
KLF14
C7orf45
CPA5
TSGA14
COPG2
TSGA13
MKLN1
PODXL
PLXNA4
FLJ40288
CHCHD3
EEF1G
EXOC4
LRGUK
ii
129,961,000 (130,153,959)
130,121,000 (130,314,365)
Barski et al.
H3K4me1
H3K9me1
iii
Ac-H3K9/14 Untreated
Exp. 1
Exp. 2
Shared Peaks
iv
Ac-H3K9/14 APH
Exp. 1
Exp. 2
Shared Peaks
v
Ac-H3K9/14 TSA
Exp. 1
Exp. 2
Shared Peaks
vi
Ac-H3K9/14 TSA and APH
Exp. 1
Exp. 2
Shared Peaks

Figure S1. Summary of the results of the analysis of chromatin structure.

Panels A, C, E, G, I, and K illustrate regions represented on the microarray for each CFS examined, including its CFS and NCFS sequences; panels B, D, F, H, J, and L illustrate a zoomed-in view of the CFS sequences. For each region present on the microarray, the following information and mapping results are displayed: (*i*) The position of the CFS within the arrayed region is represented by the light blue box on top of each figure. The chromosome coordinates corresponding to the NCBI build 35 and 36 (in parentheses), and the chromosome bands are shown in the top two panels. The location of the annotated genes is represented below with genes from the Protein Databank in black, reviewed by RefSeq or SwissProt in dark blue, other RefSeq transcripts in medium blue, and non-RefSeq transcript in light blue. (*ii*) Screenshot from the UCSC genome browser showing ChIP-Seq data with antibody for H3K4me1 (1). (*iii-vi*) Screenshot from the UCSC genome browser showing ChIP-on-chip data for the lymphoblastoid cell line, 11365, using anti-Ac-H3K9/14 antibody. ChIP-on-chip data are displayed as the linear ratio of ChIP-on-chip sample fluorescence to input DNA fluorescence. The location of the mapped acetylated chromatin domains shared between two independent ChIP experiments is represented by vertical bars under the ChIP-on-chip data.

Figure S2

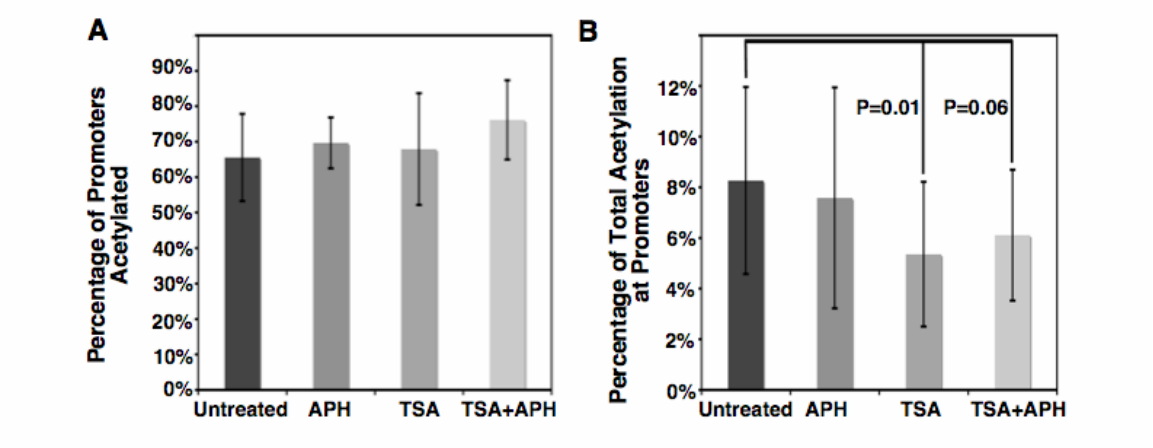
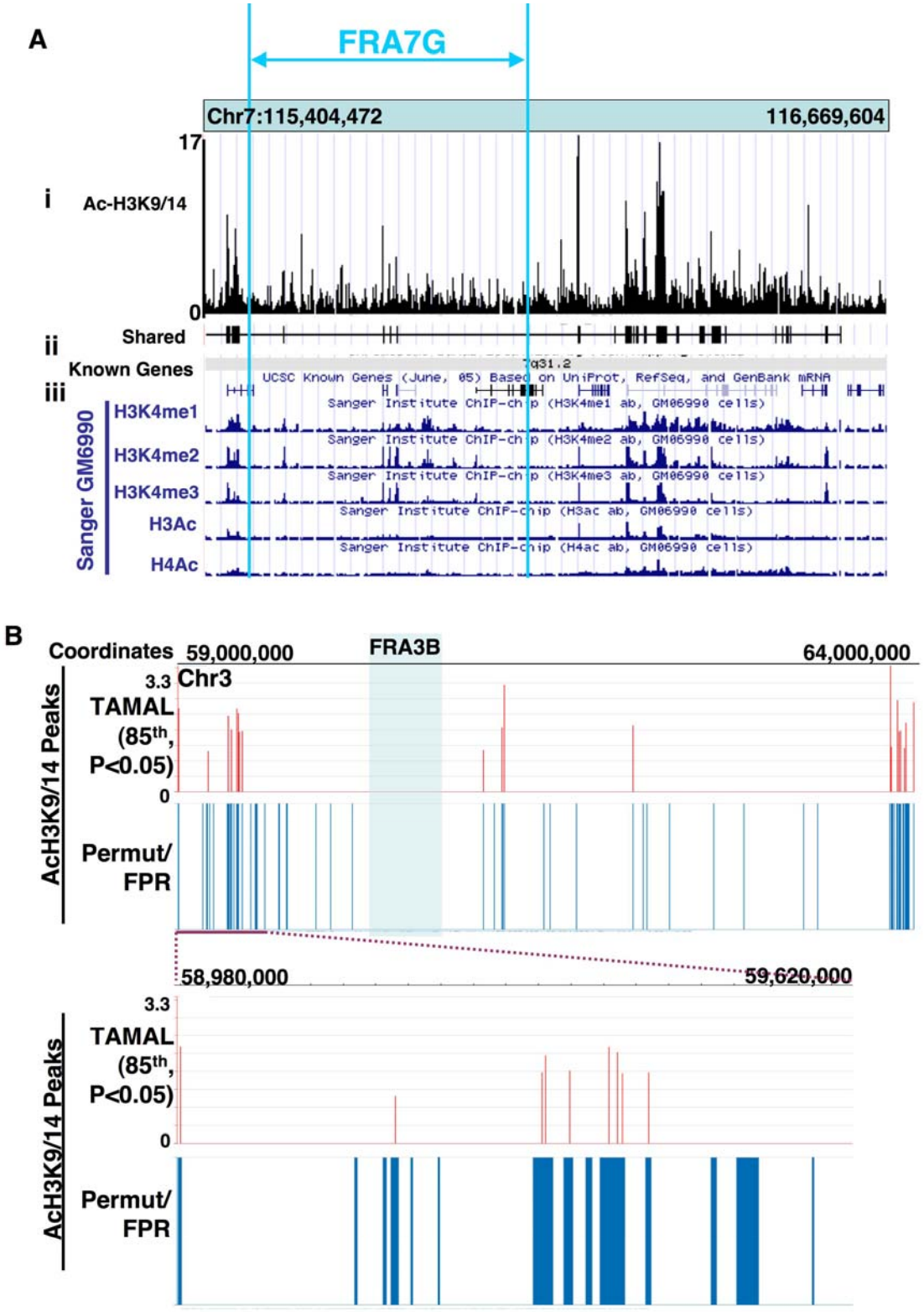


Figure S2: The majority of the Ac-H3K9/14-enriched sequences are not promoter sequences. *(A)* Promoter acetylation status of genes within common fragile site regions examined in this study. *(B)* Percentage of total acetylated regions represented by promoters. Statistical analysis was performed using the paired two-tailed student t-test assuming equal variance.

Figure S3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FRA7G
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17
i
Ac-H3K9/14
0
ii
Shared
Known Genes
iii
UCSC Known Genes (June, 05) Based on UniProt, RefSeq, and GenBank mRNA
Sanger GM6990
H3K4me1
H3K4me2
H3K4me3
H3Ac
H4Ac
Sanger Institute ChIP-chip (H3K4me1 ab, GM06990 cells)
Sanger Institute ChIP-chip (H3K4me2 ab, GM06990 cells)
Sanger Institute ChIP-chip (H3K4me3 ab, GM06990 cells)
Sanger Institute ChIP-chip (H3ac ab, GM06990 cells)
Sanger Institute ChIP-chip (H4ac ab, GM06990 cells)
B
Coordinates
59,000,000
FRA3B
64,000,000
Chr3
3.3
TAMAL (85th, P<0.05)
0
Permut/ FPR
AcH3K9/14 Peaks
58,980,000
59,620,000

C

Acetylation Coverage	Permut/FPR		TAMAL (85th, P<0.05)	
	CFS	NCFS	CFS	NCFS
FRA3B	0.30%	4.48%	0.00%	0.13%
FRA16D	1.87%	1.93%	0.00%	0.04%
FRA7G	1.62%	3.93%	0.03%	0.14%
FRAXB	8.47%	2.41%	0.63%	0.29%
FRA2G	2.35%	11.55%	0.07%	0.76%
FRA7H	40.50%	6.99%	1.10%	0.16%

Figure S3: Comparison between our acetylation mapping methods and data analysis using other methods. (*A*) Comparison between our acetylation mapping data and ENCODE project data for FRA7G sequences. (*i*) Screenshot from the UCSC genome browser showing ChIP-on-chip data for the lymphoblastoid cell line, 11365, using anti-Ac-H3K9/14 antibody. ChIP-on-chip data are displayed as the linear ratio of ChIP-on-chip sample fluorescence to input DNA fluorescence. The location of the mapped acetylated chromatin domains shared between two independent ChIP experiments is represented by vertical bars under the ChIP-on-chip data. (*ii*) The location of the annotated genes is represented below with genes from the Protein Databank in black, reviewed by RefSeq or SwissProt in dark blue, other RefSeq transcripts in medium blue, and non-RefSeq transcript in light blue. (*iii*) The location of the histone domains with active histone modifications mapped by the ENCODE project are illustrated below the acetylation data (2). (*B&C*) Comparison between our peak calling method (Permut/FPR) and TAMAL. (*B*) Screenshot from the NimbleScan browser showing the AcH3K9/14 peak of the Chr3 region identified either by TAMAL (85^{th} percentile, P<0.05) or our Permut/FPR method. The height of the peaks identified by TAMAL represents the average $\log_2$ ratio of the top four consecutive probes (3). The FRA3B locus is shaded in

blue. A zoomed-in section is shown underneath. (*C*) The acetylation coverage calculated using Permut/FPR and TAMAL.

Figure S4

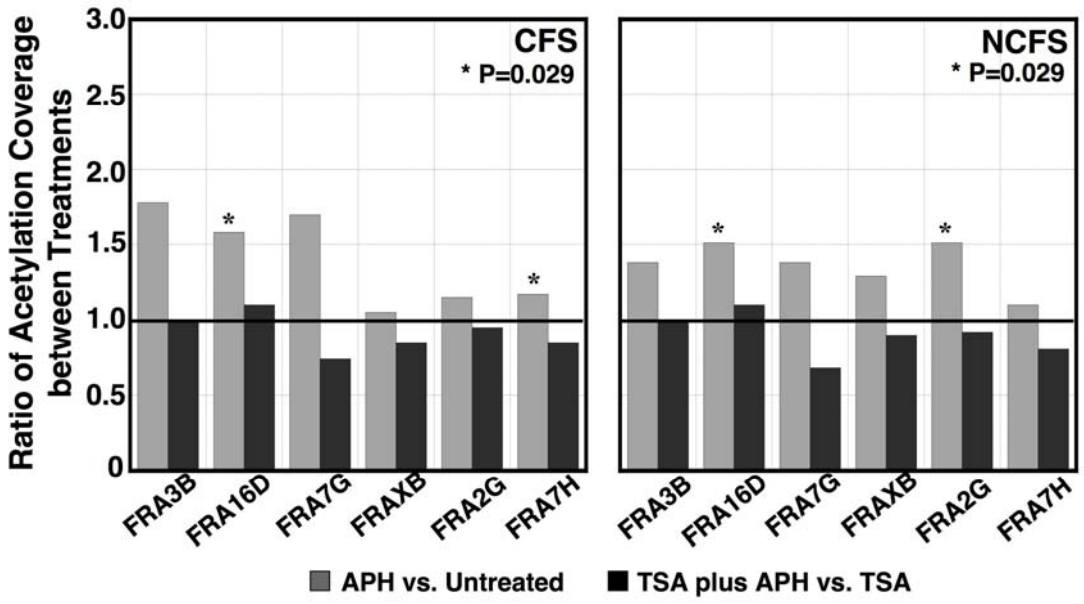

Figure S4: APH has relatively little effect on acetylation coverage at CFSs.

The graph illustrates the ratio of the acetylation coverage between treatments for the CFSs (left panel) and their flanking NCFSs (right panel) (*, P=0.029).

Figure S5

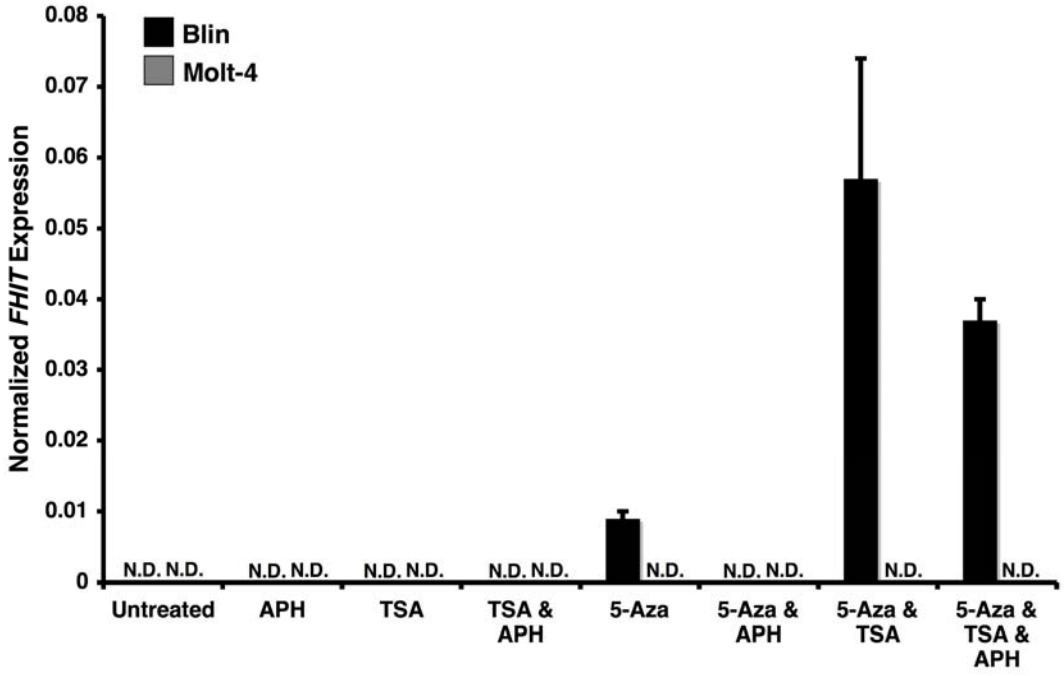

Figure S5: *FHIT* expression in Blin and Molt-4 cells. Total RNA was extracted from Blin and Molt-4 cells following various treatments and reverse transcribed. Real time RT-PCR was performed to assess the expression level of the *FHIT* gene, which was normalized to the expression level of *GAPDH*. N.D.=non-detected.

Figure S6

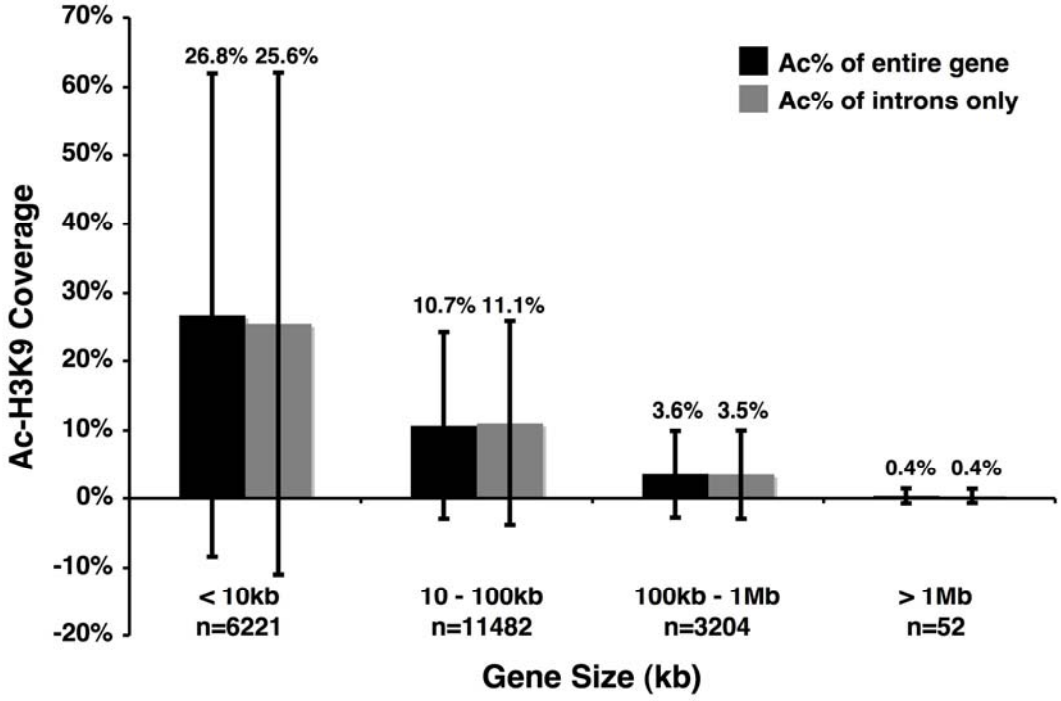

Figure S6: Comparison of the percentage of acetylation of genes (Ac%) grouped according to their size (<10kb, 10-100kb, 100kb-1Mb, >1Mb). Ac% of each gene (black bar, from transcription start to end), or Ac% of introns only for each gene (gray bar) was calculated based on the ChIP-Seq data generated by the ENCODE project (http://genome.ucsc.edu/cgi-bin/hgTrackUi?db=hg18&g=wgEncodeBroadChipSeq, track: wgEncodeBroadChipSeqPeaksGm12878H3k9ac) and averaged according to size. The average Ac% for each gene group is listed above the bars; the total number of genes within each gene group is listed below the bars, error bars represent standard deviation of each group. Note that due to the differences between the array platforms, the Ac% values illustrated in this graph cannot be compared directly to the Ac% values generated by our ChIP-on-chip experiments.

Table S1: Chromosomal regions covered on the microarray platform and coordinates of the CFS boundaries.

Region	Chromo-some	Category	Start (bp)*	Stop (bp)*	Size (bp)	Reference
FRA2G	2	Arrayed region	169,109,272	170,560,042	1,450,770	Limongi et al.[4]
		CFS region	169,324,000	170,297,000	973,000	
FRA3B	3	Arrayed region	58,981,490	64,015,114	5,033,624	Rassool et al.[5]
		CFS region	60,347,000	60,806,000	459,000	
FRA7G	7	Arrayed region	111,245,357	116,669,604	5,424,247	Huang et al.[6]
		CFS region	115,489,000	116,002,000	513,000	
FRA7H	7	Arrayed region	128,781,513	133,281,052	4,499,539	Mishmar et al.[7]
		CFS region	129,961,000	130,121,000	160,000	
FRA16D	16	Arrayed region	75,736,529	77,947,373	2,210,844	Mangelsdorf et al.[8]
		CFS region	77,209,000	77,479,000	270,000	
FRAXB	X	Arrayed region	6,424,350	7,784,581	1,360,231	Arlt et al.[9]
		CFS region	6,456,000	7,285,000	829,000	
TUBA1	2	Hyperacetylated region	219,939,053	219,945,878	6,825	N.A.
HET405	9	Hypoacetylated region	1,161,346	1,161,683	337	N.A.

* The chromosome coordinates are derived from the human genome sequence (NCBI, Build 35). N.A., not available.

Table S2: Summary of the Ac-H3 K9/14 Mapping Results.

		FRA3B		FRA16D		FRA7G		FRAXB		FRA2G		FRA7H	
		CFS	NCFS	CFS	NCFS	CFS	NCFS	CFS	NCFS	CFS	NCFS	CFS	NCFS
Untreated Acetylation Coverage	Exp1	0.28% ± 0.01	5.53% ± 0.09	2.06% ± 0.35	2.13% ± 0.16	2.34% ± 0.10	5.06% ± 0.08	9.83% ± 0.67	2.75% ± 0.21	3.26% ± 0.08	13.98% ± 0.04	42.82% ± 0.92	8.44% ± 0.11
	Exp2	0.32% ± 0.18	3.44% ± 0.01	1.68% ± 0.24	1.73% ± 0.05	0.90% ± 0.41	2.79% ± 0.13	7.11% ± 0.52	2.07% ± 0.25	1.44% ± 0.21	9.12% ± 0.51	38.18% ± 2.88	5.55% ± 0.35
	Conservation:												
	Exp1	100%	52%	33%	54%	50%	61%	100%	67%	75%	86%	63%	52%
	Exp2	0%	68%	100%	58%	100%	98%	82%	100%	64%	100%	80%	72%
APH Acetylation Coverage	Exp1	0.76% ± 0.16	7.13% ± 0.14	3.53% ± 0.38	3.44% ± 0.37	3.34% ± 0.18	5.14% ± 0.06	9.30% ± 0.59	2.81% ± 0.35	3.67% ± 0.17	19.98% ± 1.10	46.22% ± 1.08	8.44% ± 0.08
	Exp2	0.30% ± 0.25	5.22% ± 0.10	2.44% ± 0.04	2.34% ± 0.09	2.10% ± 0.23	5.64% ± 0.08	8.50% ± 0.54	3.36% ± 0.06	1.70% ± 0.21	15.14% ± 0.18	48.80% ± 0.59	6.90% ± 0.17
	Conservation:												
	Exp1	0%	74%	60%	58%	88%	84%	100%	0%	75%	100%	78%	66%
	Exp2	0%	90%	50%	67%	100%	91%	100%	85.7%	88%	100%	100%	85%
TSA Acetylation coverage	Exp 1	3.92% ± 0.36	7.08% ± 0.25	9.88% ± 1.65	4.50% ± 0.03	8.24% ± 0.50	5.18% ± 0.02	10.48% ± 0.28	2.74% ± 0.63	5.46% ± 0.25	20.35% ± 0.71	43.52% ± 5.10	10.26% ± 0.23
	Exp 2	2.98% ± 0.53	7.28% ± 0.08	9.61% ± 1.61	3.76% ± 1.12	8.79% ± 0.07	6.88% ± 0.06	12.64% ± 0.74	3.20% ± 0.09	4.32% ± 0.11	26.56% ± 0.03	56.87% ± 2.69	10.65% ± 0.06
	Conservation:												
	Exp 1	46%	60%	40%	34%	87%	75%	78%	67%	48%	87%	67%	68%
	Exp 2	71%	78%	43%	47%	100%	89%	80%	100%	71%	92%	100%	79%
TSA&APH Acetylation coverage	Exp 1	2.59% ± 1.09	5.68% ± 0.13	6.64% ± 1.37	3.54% ± 0.24	6.76% ± 0.07	2.96% ± 0.18	8.58% ± 0.18	2.62% ± 0.08	3.82% ± 0.40	15.62% ± 1.32	31.24% ± 3.04	7.63% ± 0.07
	Exp 2	4.22% ± 0.55	8.70% ± 0.15	14.09% ± 0.20	5.56% ± 0.13	5.84% ± 0.78	5.30% ± 0.23	10.97% ± 0.48	2.80% ± 0.04	5.42% ± 0.20	27.67% ± 0.51	53.90% ± 1.43	9.24% ± 0.52
	Conservation:												
	Exp 1	40%	56%	54%	52%	59%	66%	70%	67%	57%	90%	80%	66%
	Exp 2	100%	89%	57%	72%	100%	82%	91%	100%	77%	89%	100%	79%

The acetylation coverage corresponds to the sum of the width of all of the acetylated chromatin domains within that region divided by the total size of the region. It is displayed as the average of the acetylation coverage of both data

sets (FWD1 and 2) for experiments 1 and 2. The percentage of conserved acetylated regions between two experiments is given in the last row of each treatment.

Table S3: TSA treatment decreases fragile site expression.

Breaks per 25 cells	Subject 1			Subject 2			Subject 3		
	TSA	APH/Caf	TSA/APH /Caf	TSA	APH/Caf	TSA/APH /Caf	TSA	APH/Caf	TSA/APH /Caf
Total	1	219	44	2	767	25	6	298	94
FRA1D (1p22)	0	1	2	0	11	1	0	3	2
FRA1I (1q44)	0	9	2	0	20	0	0	6	1
FRA2C (2p24.2)	0	4	2	0	15	0	0	8	0
FRA2E (2p13)	0	0	0	0	13	1	0	1	1
FRA2F (2q21.3)	0	5	0	0	14	0	1	2	2
FRA2G (2q31)	0	1	0	0	4	0	0	3	2
FRA2H (2q32.1)	0	8	0	0	17	1	0	7	0
FRA2I (2q33)	0	1	0	0	8	0	0	0	0
FRA2J (2q37.3)	0	1	0	0	12	0	0	7	0
FRA3B (3p14.2)	0	18	4	0	33	3	0	26	6
FRA4A (4p16.1)	0	5	0	0	11	0	0	5	1
FRA4C (4q31.1)	0	5	0	0	19	0	0	4	2
FRA5D (5q15)	0	2	1	0	10	0	1	4	0
FRA6B (6p25.1)	0	1	0	0	13	0	0	4	0
FRA6E (6q26)	0	7	1	0	4	0	0	2	1
FRA7G (7q31.2)	0	11	0	0	14	0	0	6	1
FRA7H (7q32.3)	0	5	1	0	8	0	0	5	0
FRA8B (8q22.1)	0	2	1	0	20	0	0	7	0
FRA9E (9q32)	0	1	0	0	13	0	0	4	1
FRA11D (11p14.2)	0	4	0	0	15	0	0	0	3
FRA12B (12q21.3)	0	2	0	0	11	0	0	3	1
FRA12E (12q24.1)	0	3	0	0	12	0	0	0	0
FRA13A (13q13.2)	0	1	0	0	12	0	0	6	0
FRA14C (14q24.1)	0	5	1	0	12	0	0	6	0
FRA16D (16q23.2)	1	17	3	0	17	0	0	9	3
FRAXB (Xp22.3)	0	5	3	0	32	2	0	14	4
FRAXC (Xq22.1)	0	5	1	0	11	1	0	4	1

Fragile site breaks were scored in 25 trypsin-Giemsa banded metaphase cells from PHA-stimulated peripheral blood lymphocytes for each treatment as described in Figure 3. The table illustrates the breakage observed in the subset of CFSs that are expressed at the higher levels; CFSs in red are also displayed in Table 2.

Table S4: Primer sets used in bisulfite sequencing.

Primer Name	Forward Primer (Chromosome Coordinates)	Reverse Primer (Chromosome Coordinates)	Length (bp)	Annealing Temp. (°C)	$[Mg^{2+}]$ (mM)
Ex1-B2	GGAGGTAAGTTTAAGTG (61211983)	CTACACCCCCAAAACCAA (61211705)	279	55	2.5
Ex3-B1	GGGTGATATTAGTTGTTT (61002982)	TCTCTTTCTCTCCCTTCC (61002765)	218	50	3.75
Ex5-B2	GTGGGAGGGAGATGGATT (60497502)	ACTTCAACTATAAAAACATAT (60797752)	151	55	3.75
Ex6-B2	GAGAGTTTAGGTTTTGGT (59975025)	TATTTTTCCACCACTATC (59974807)	219	55	3.75
Ex8-B2	GAGAGTATTATTGTTAAG (59883253)	TCCATTTCAAACCATATC (59883007)	247	50	3.75
Ex9-B1	GGAGATTAGAGGAGGAAA (59713050)	CATCCCCATTCTAAAAAT (59712909)	142	55	3.75

The forward and reverse primers were modified from the original sequences to amplify bisulfite-treated DNA. The chromosome coordinates are derived from the human genome sequence (NCBI, Build 35).

Table S5: Genomic locations of Southern blot probes.

Probes	Coordinates (NCBI, Build 35)	Length (bp)
A	60,371,618-60,372,609	992
B	60,572,342-60,573,268	927
C	60,597,236-60,598,120	885
D	60,762,244-60,763,204	961
E	59,866,738-59,867,746	1005
F	60,126,108-60,127,081	974
G	61,033,477-61,034,475	999
H	61,261,209-61,262,169	961

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