

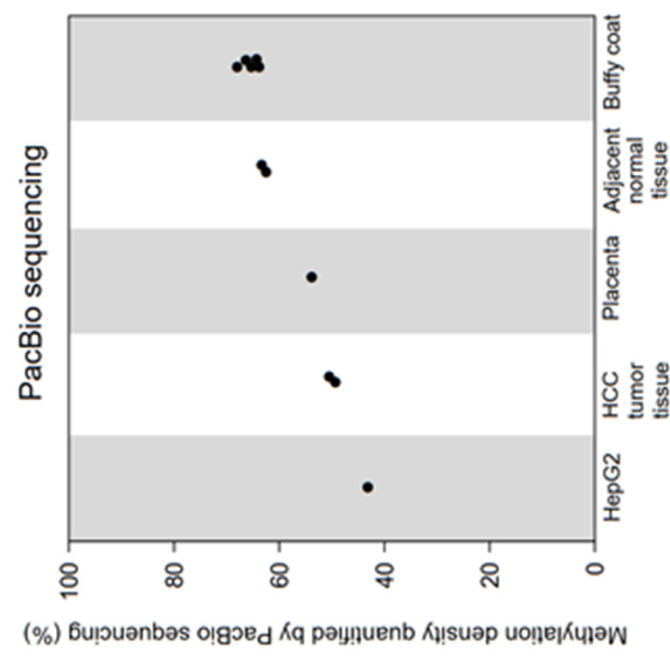


FIG. 62B

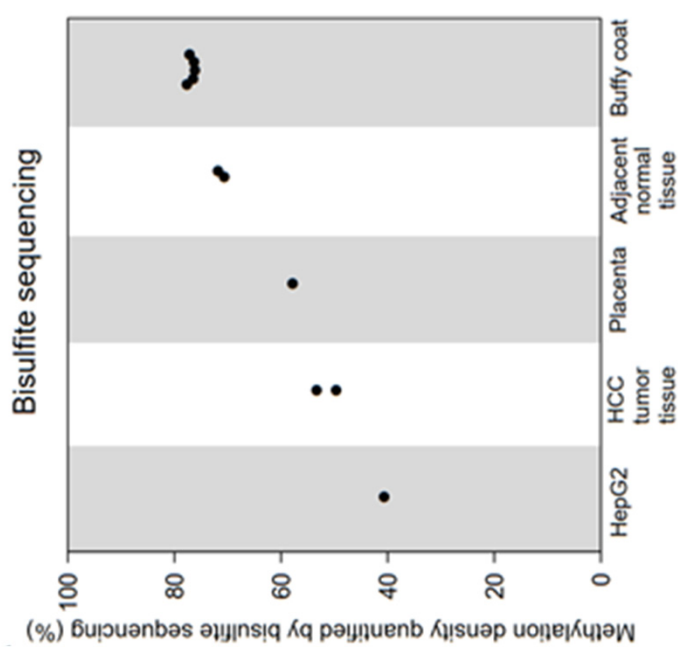


FIG. 62A

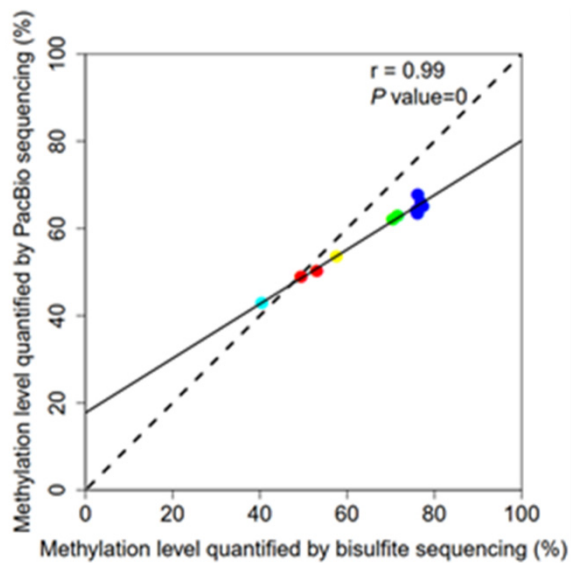


FIG. 63A

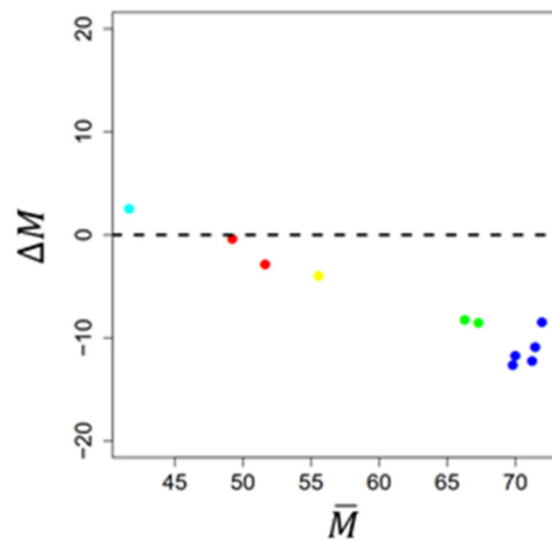


FIG. 63B

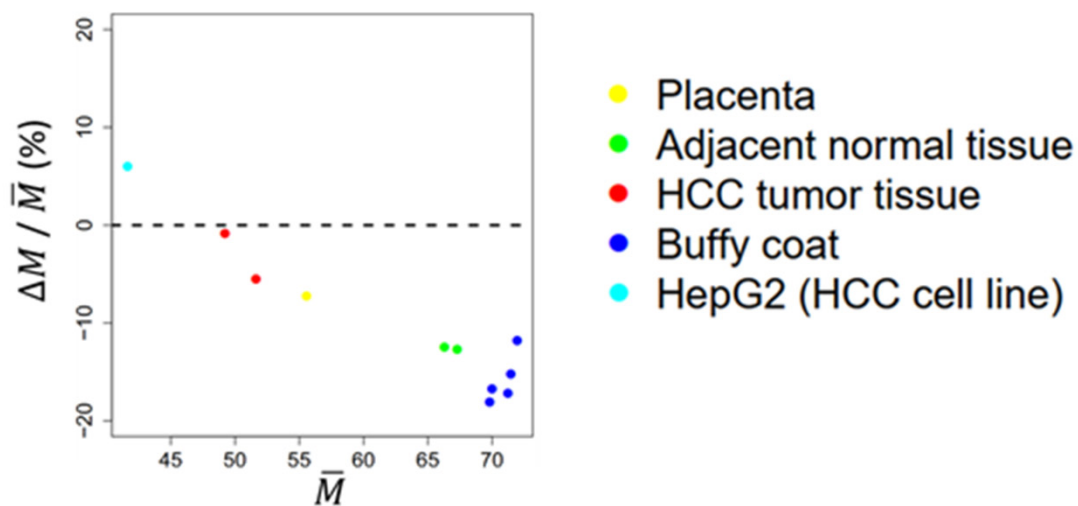


FIG. 63C

F2 (Buffy coat)

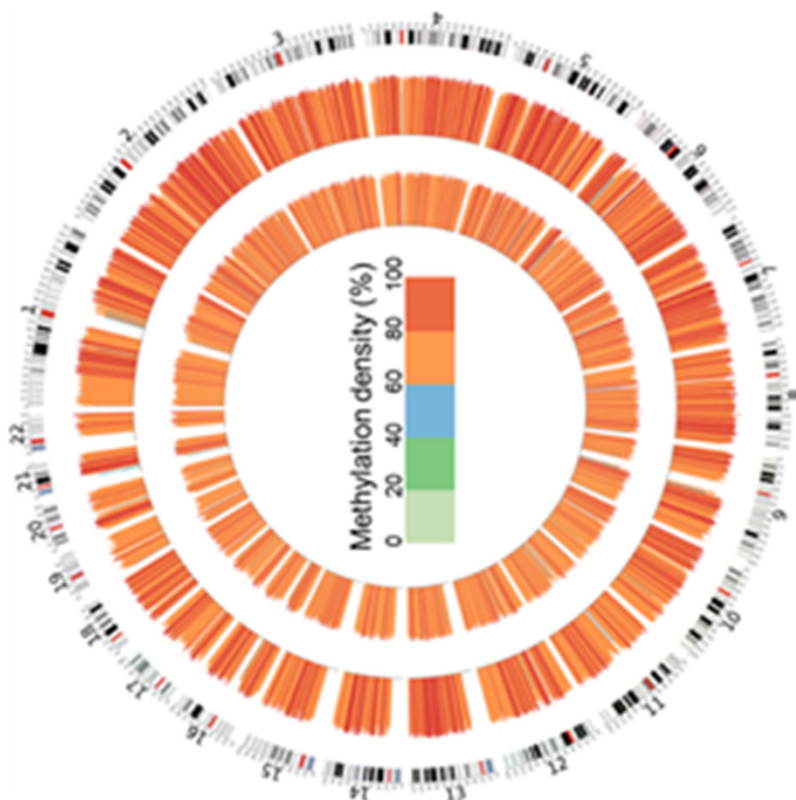


FIG. 64B

HepG2 (HCC cell line)

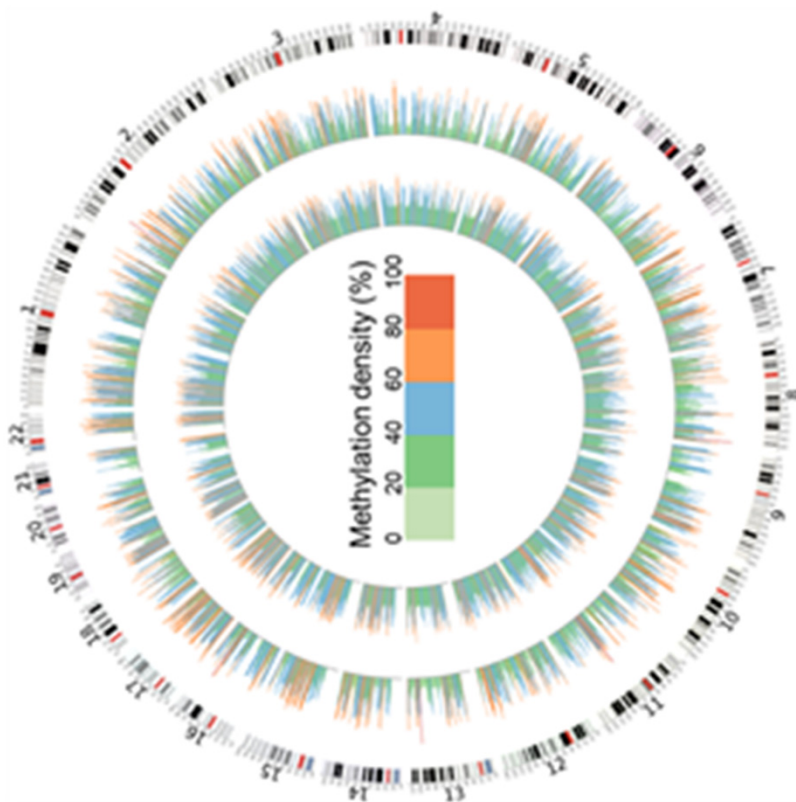


FIG. 64A

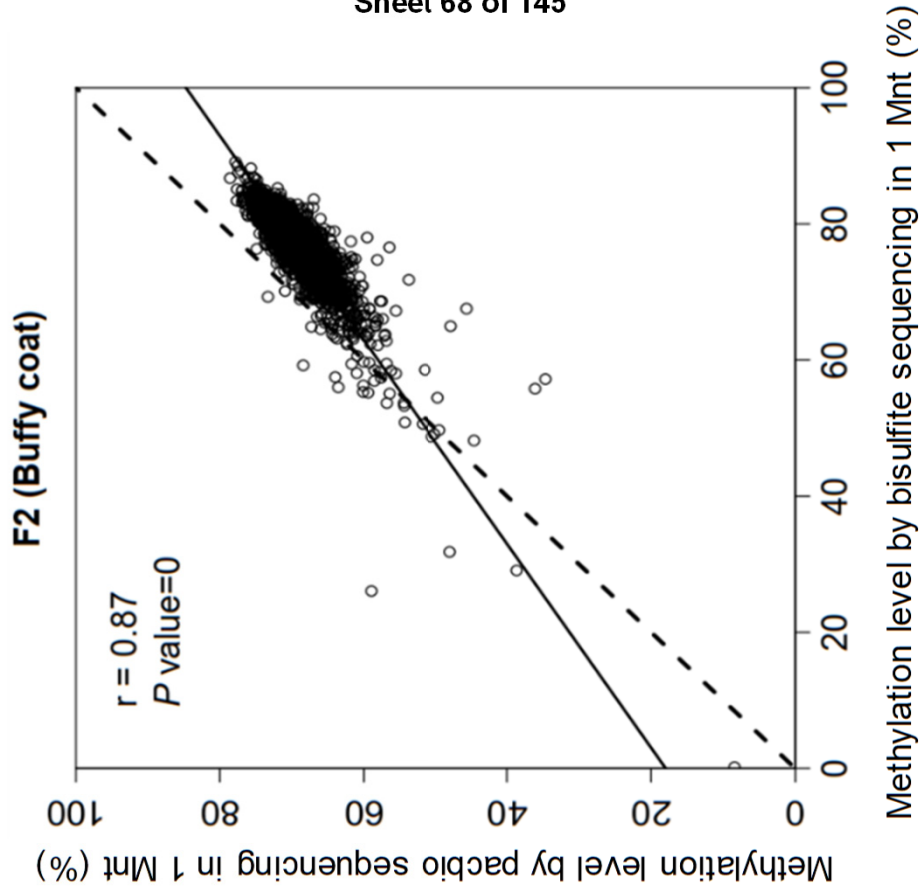


FIG. 65B

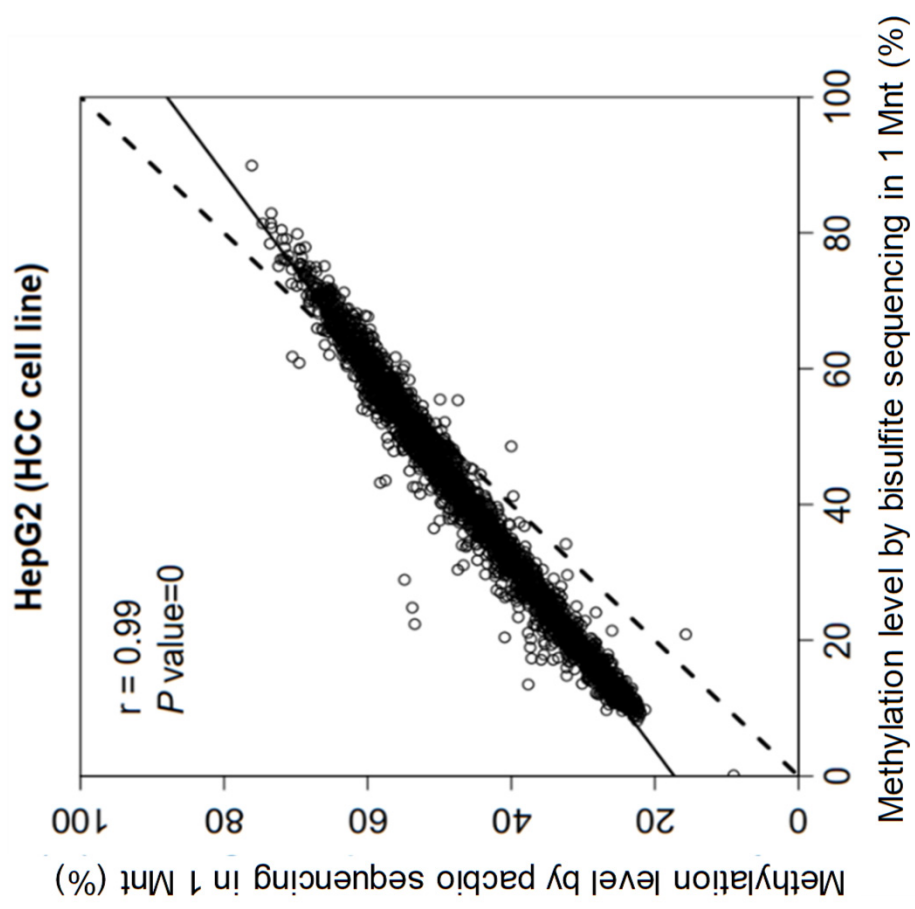


FIG. 65A

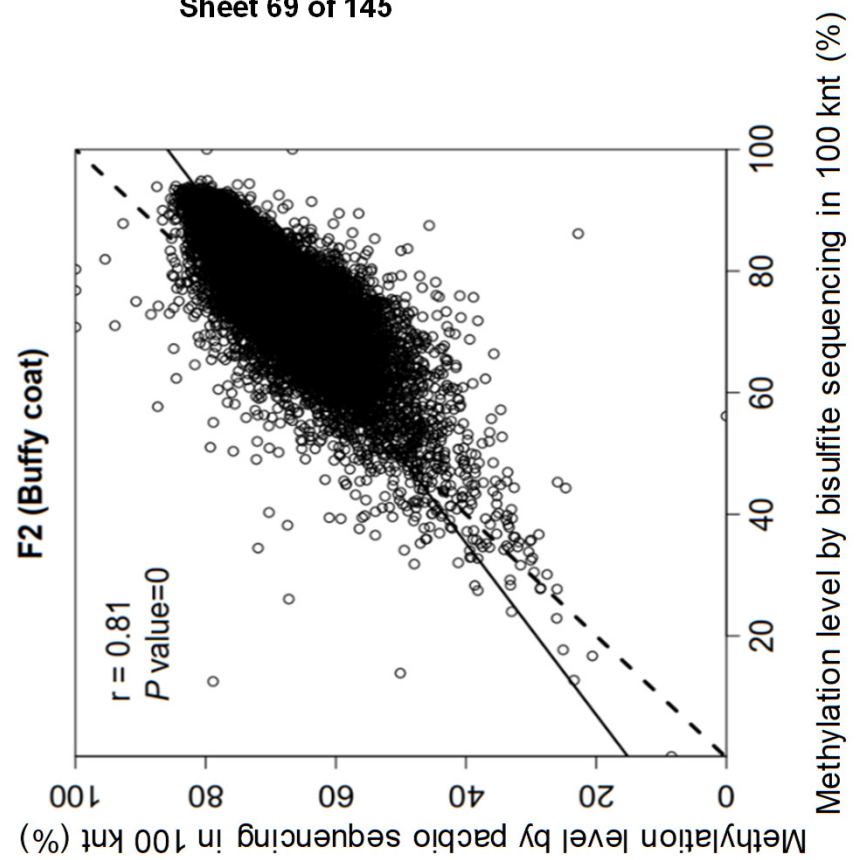


FIG. 66A

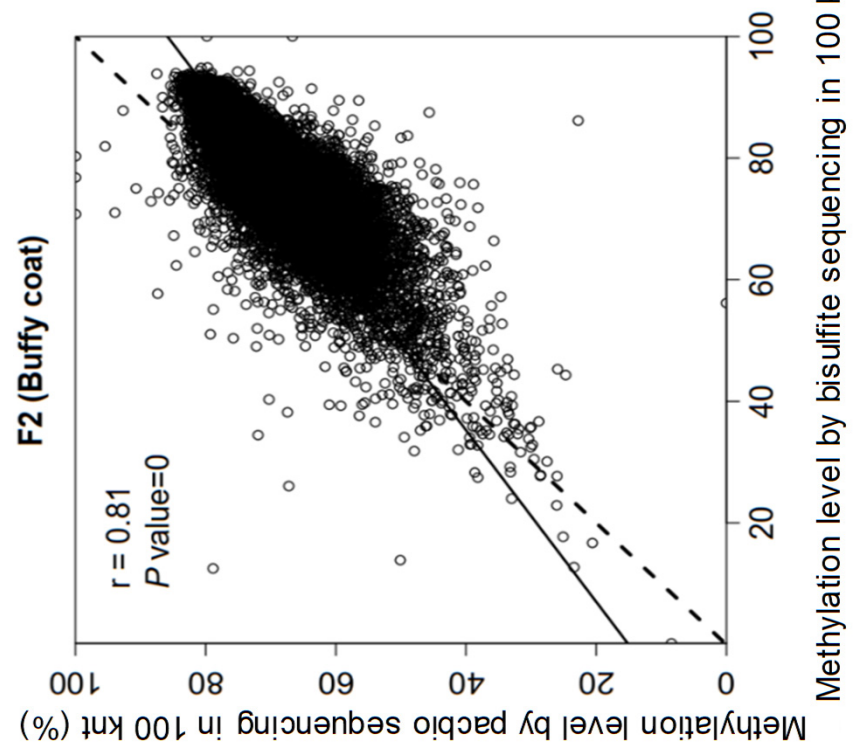


FIG. 66B

TBR3033N (Adjacent normal tissue)

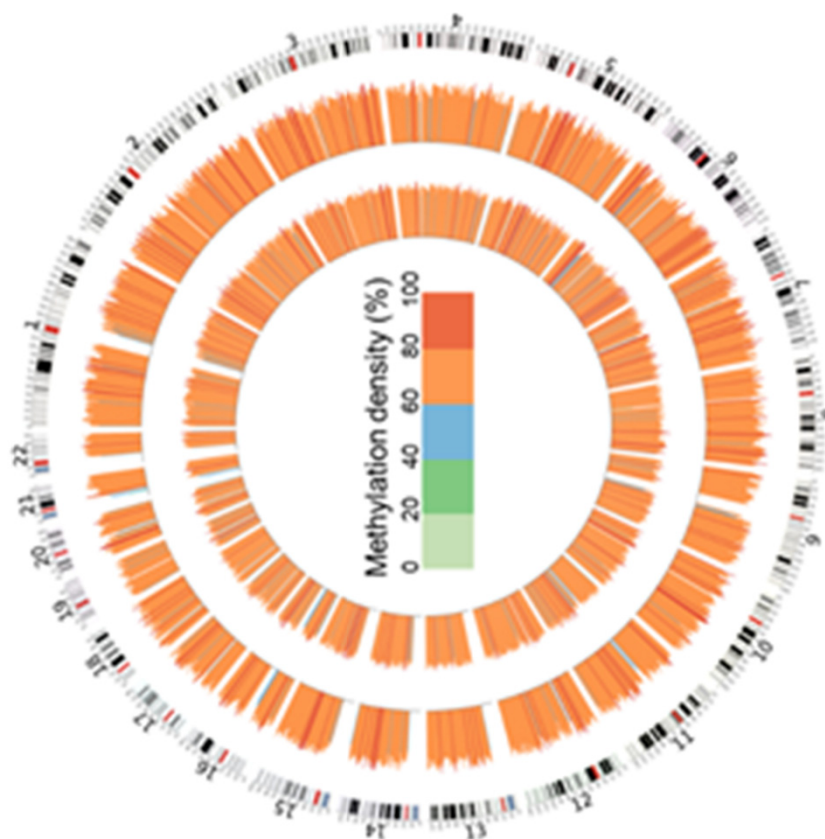


FIG. 67B

TBR3033T (HCC tumor)

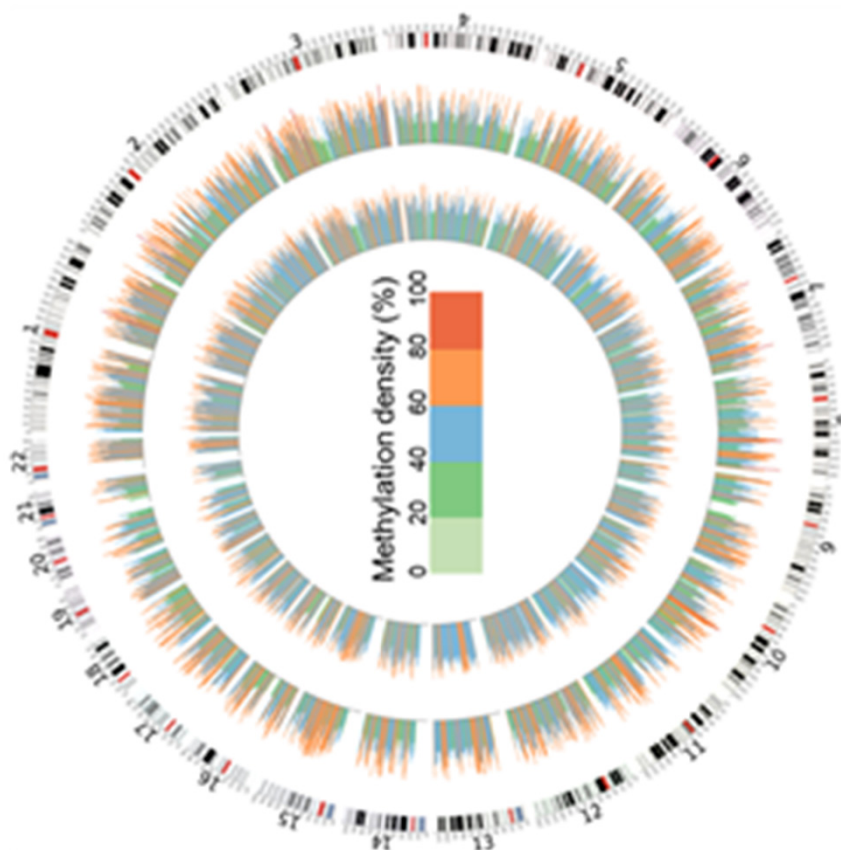


FIG. 67A

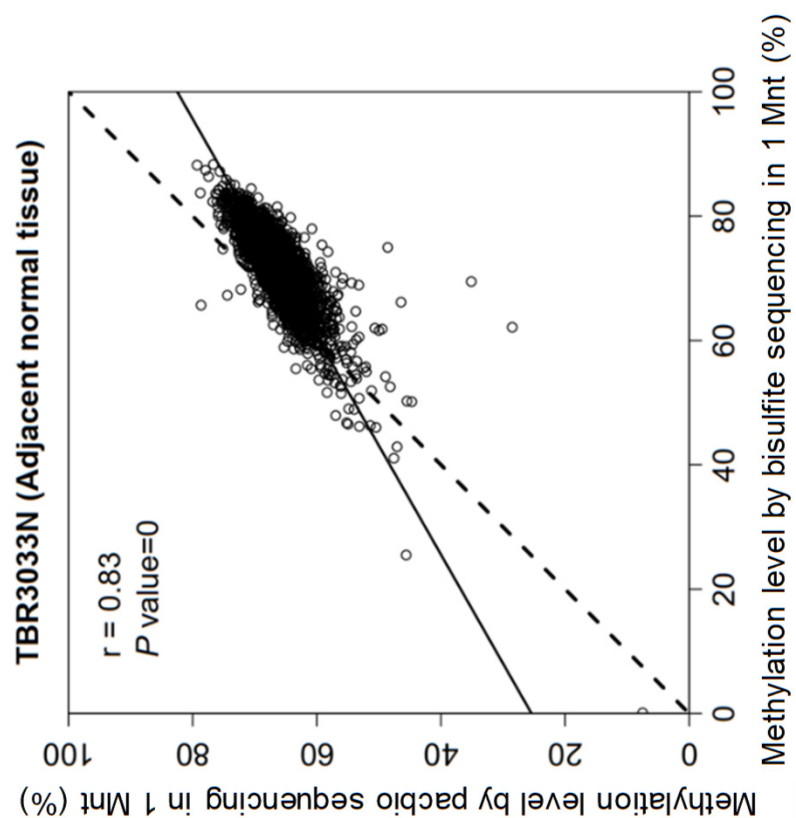


FIG. 68B

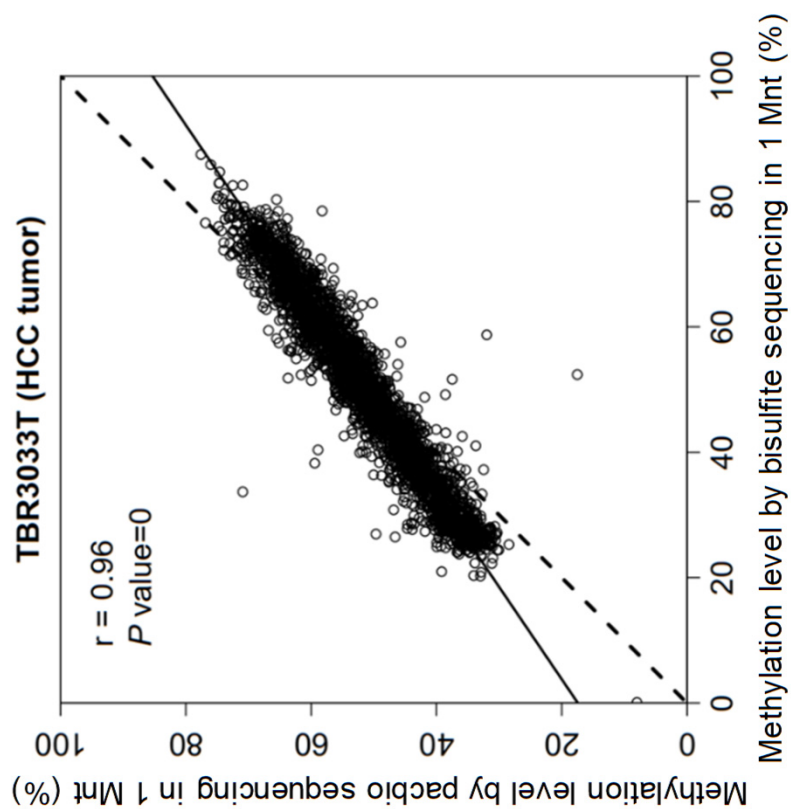


FIG. 68A

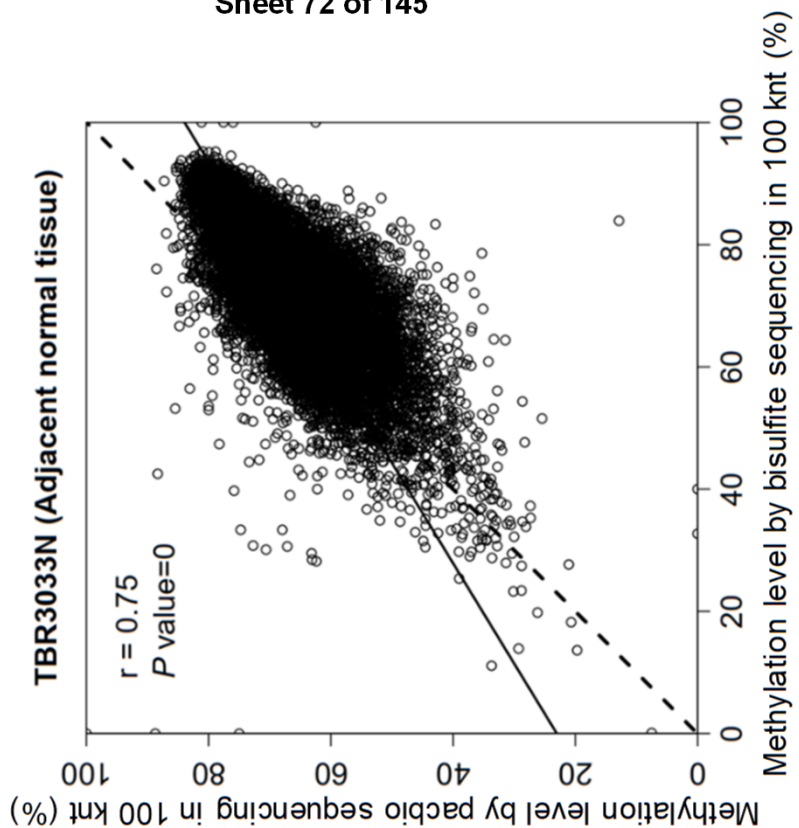


FIG. 69B

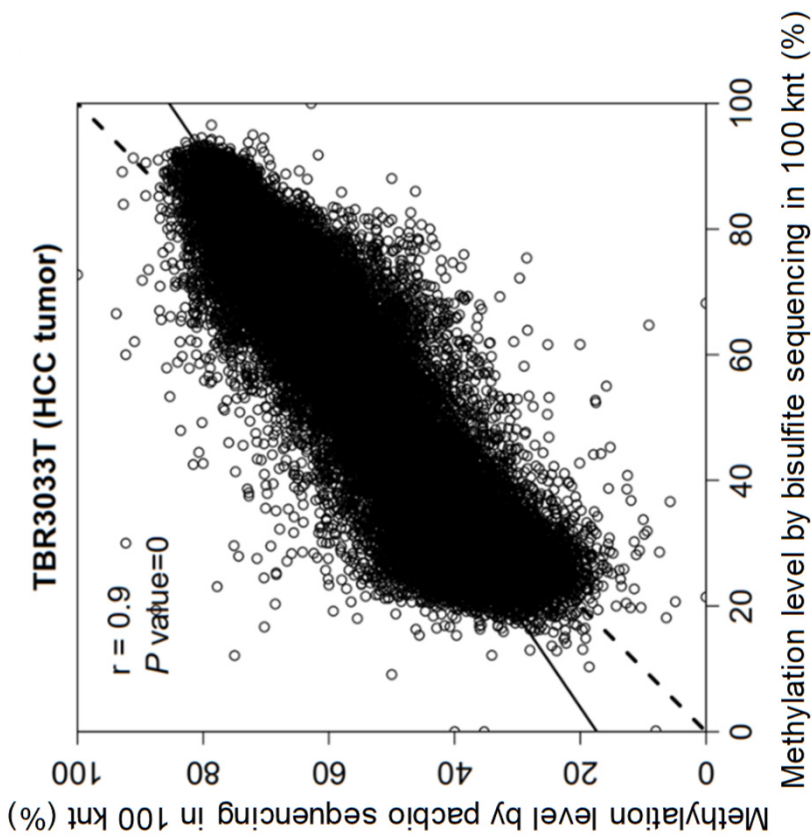


FIG. 69A

TBR3032N (Adjacent normal tissue)

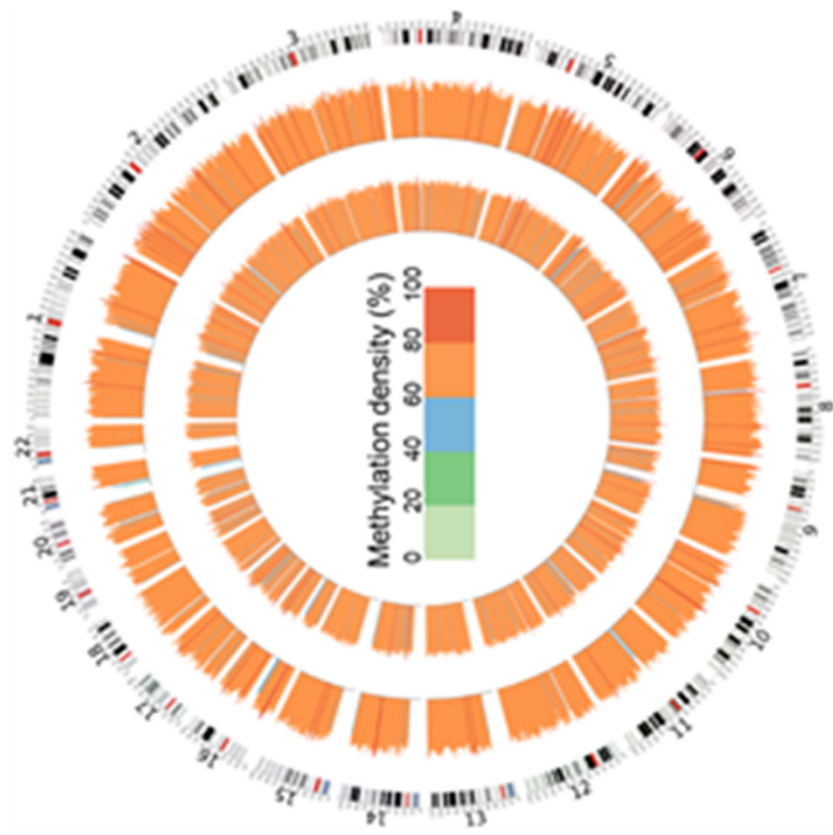


FIG. 70B

TBR3032T (HCC tumor)

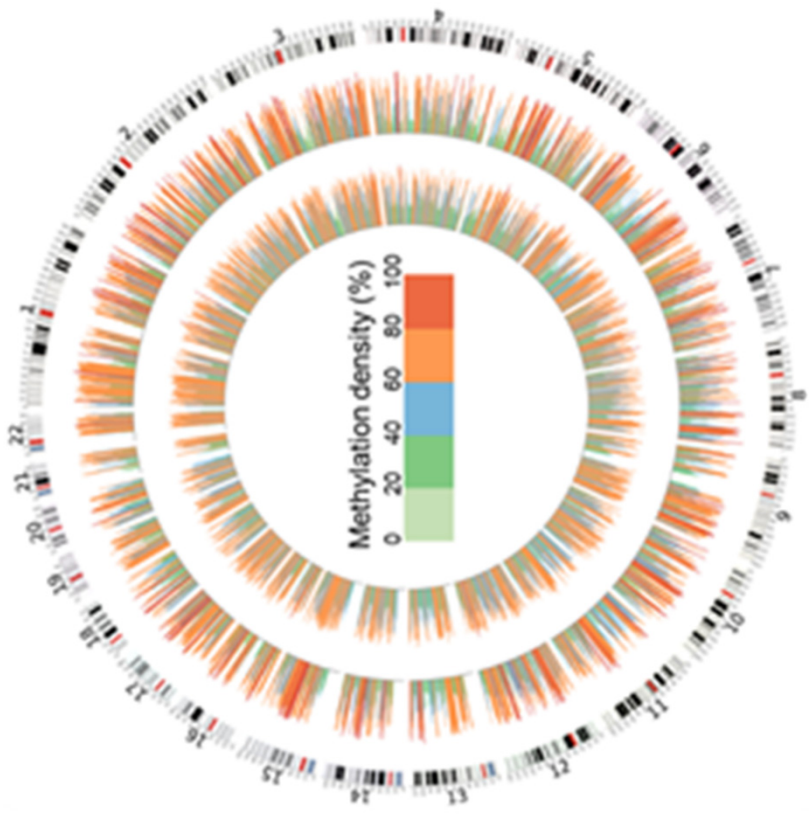


FIG. 70A

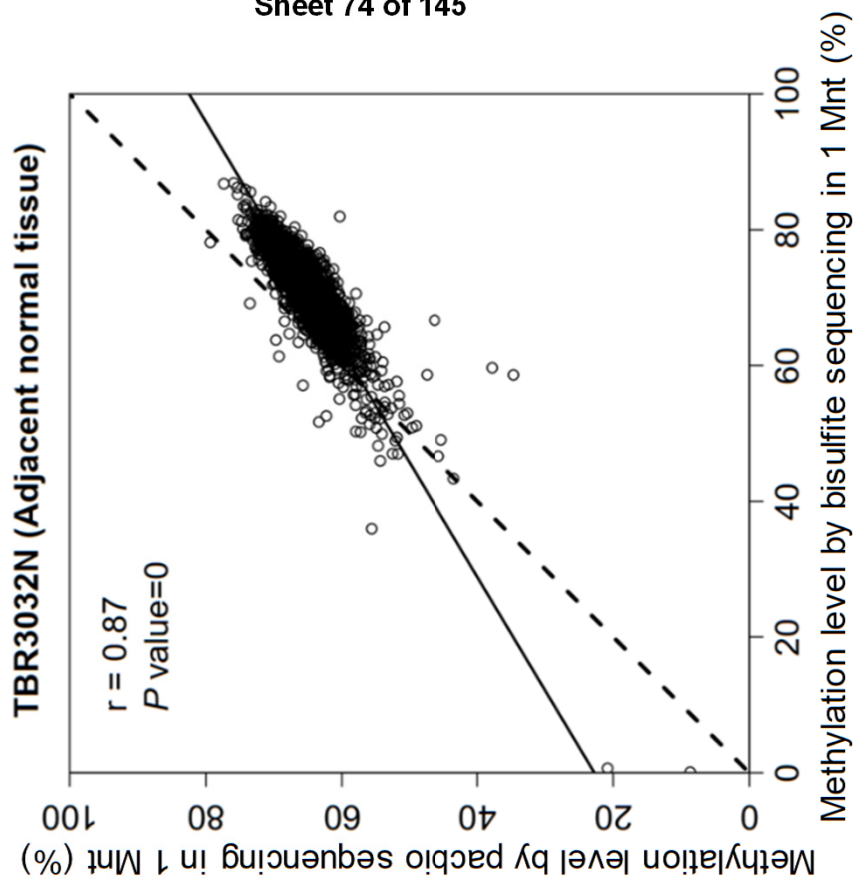


FIG. 71B

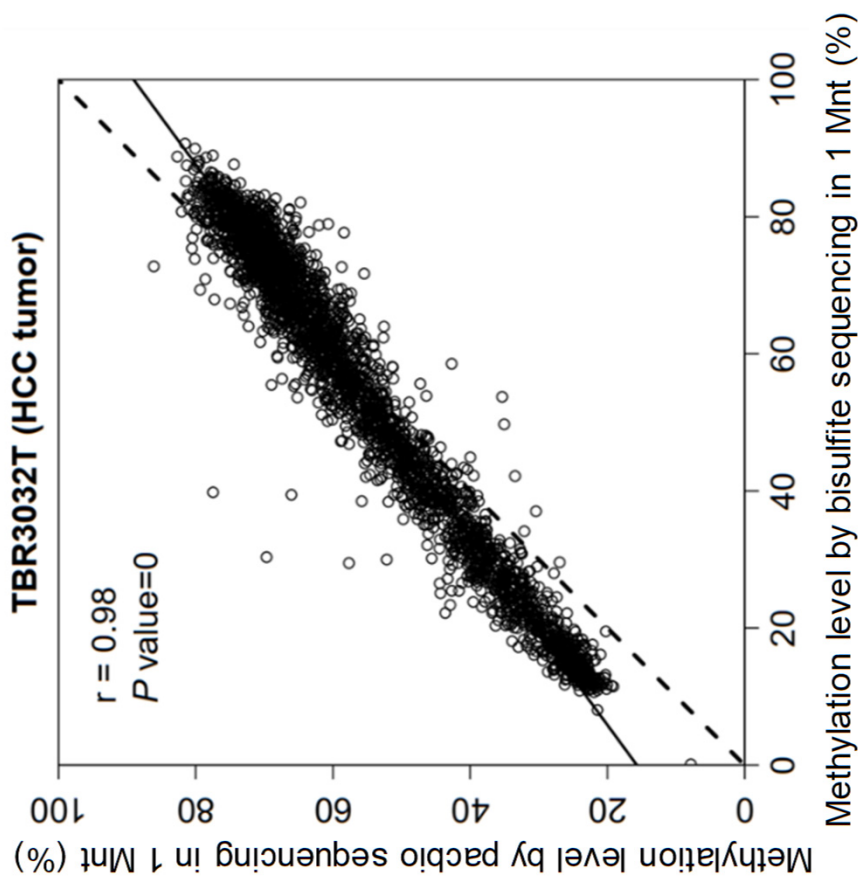


FIG. 71A

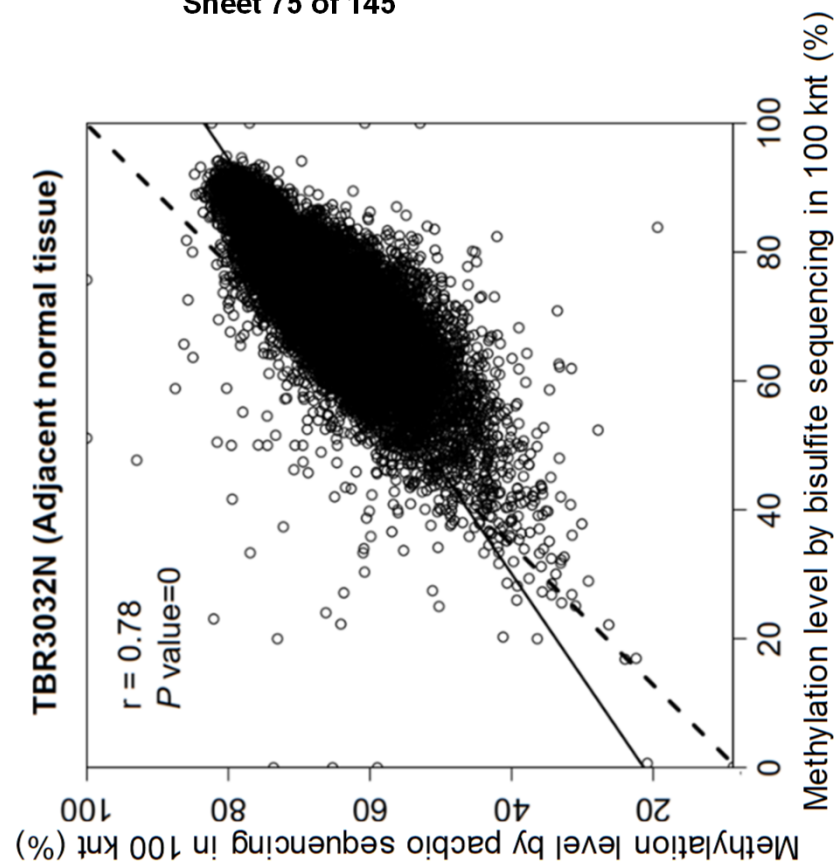


FIG. 72A

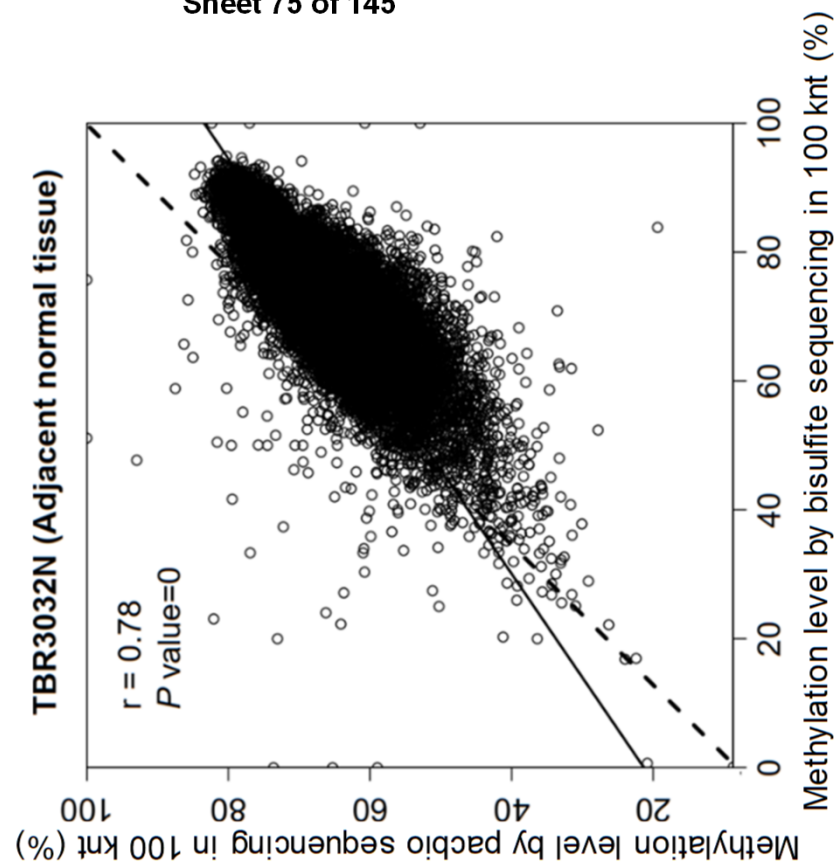


FIG. 72B

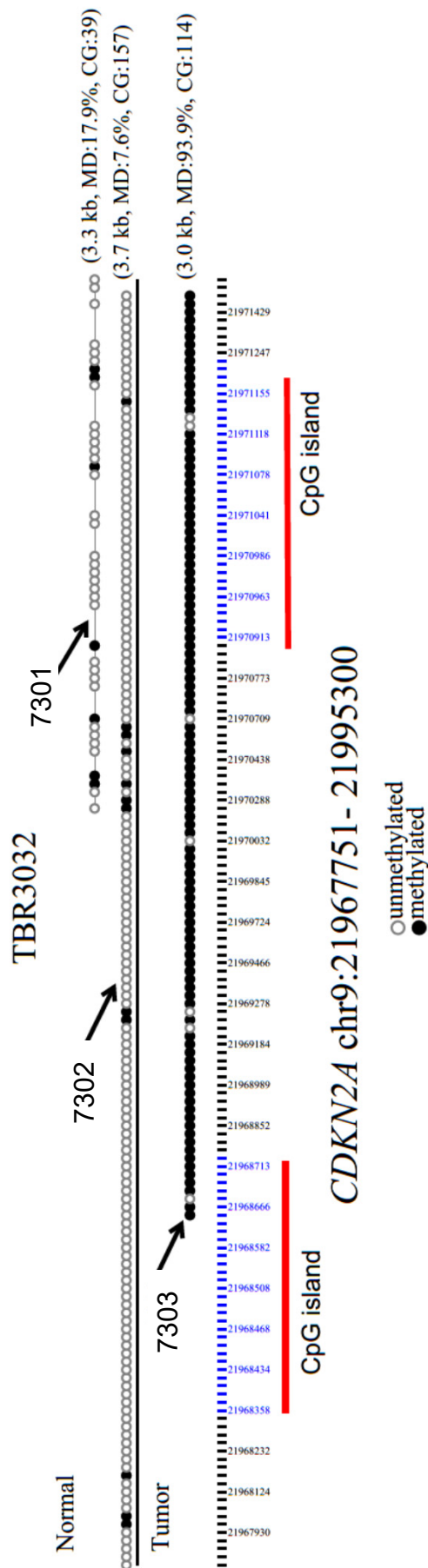


FIG. 73

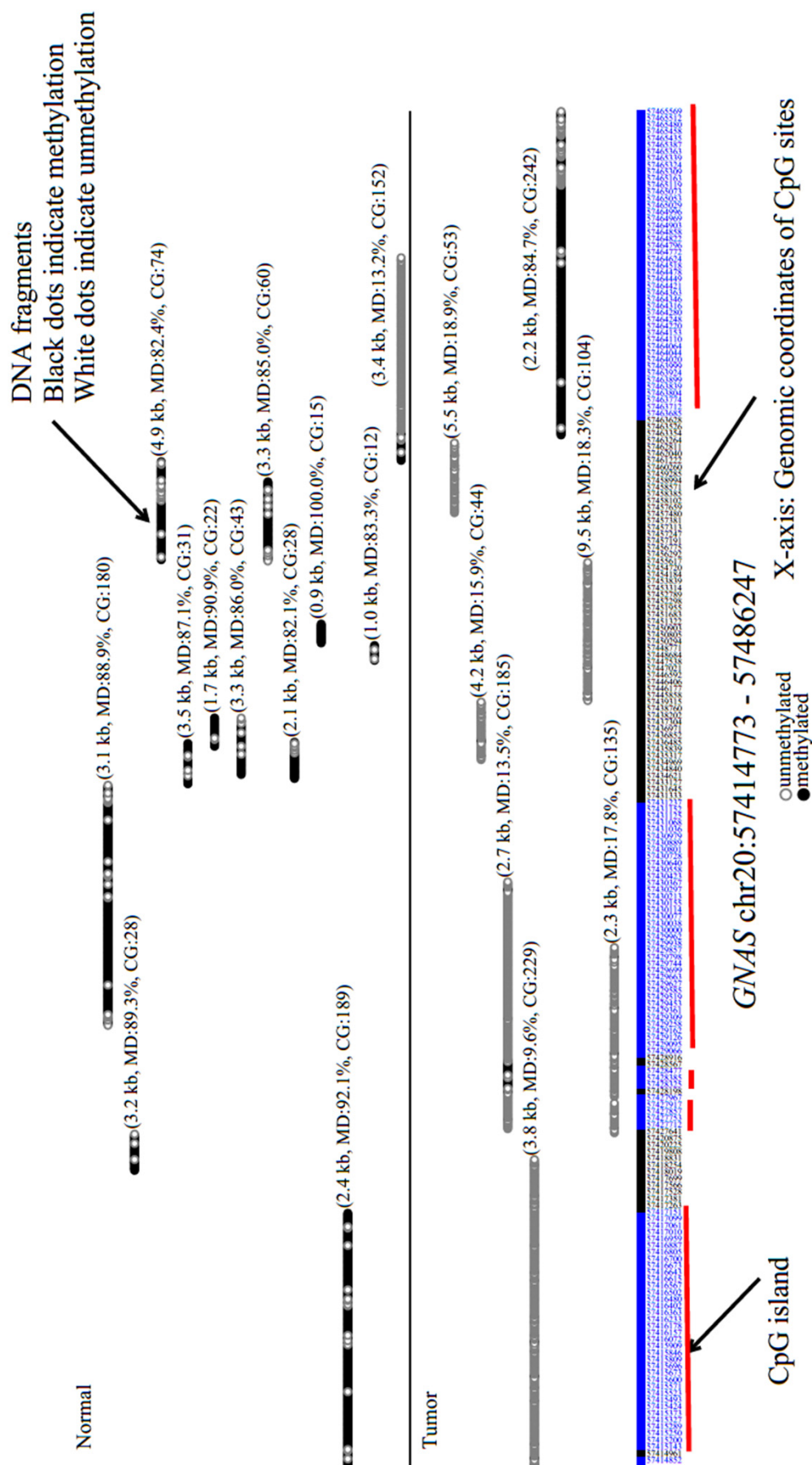


FIG. 74A

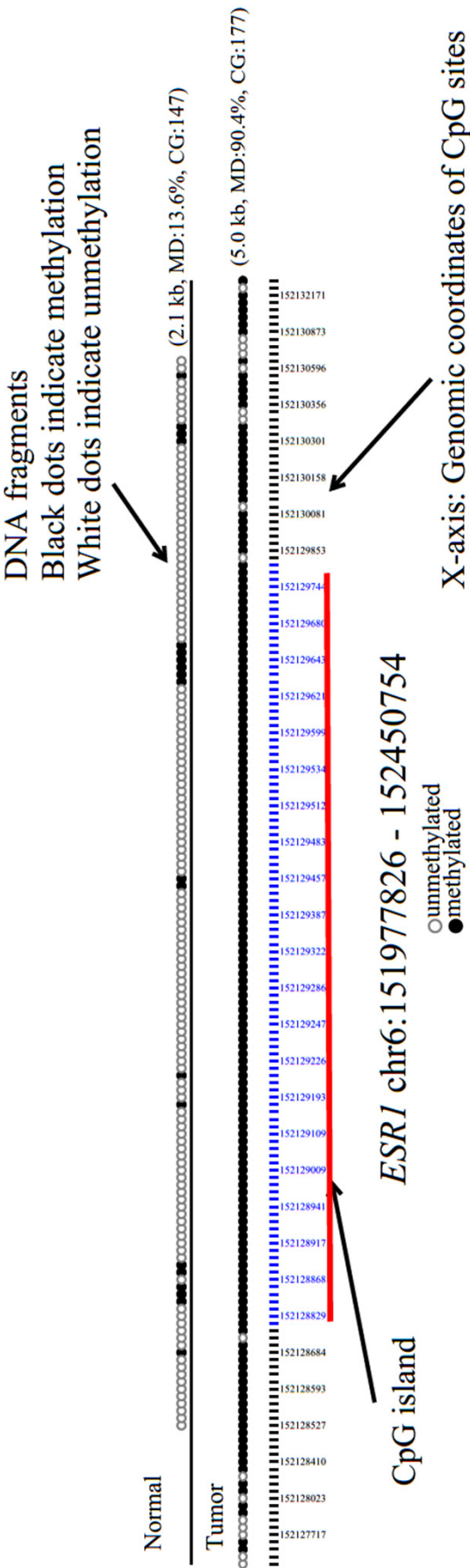


FIG. 74B

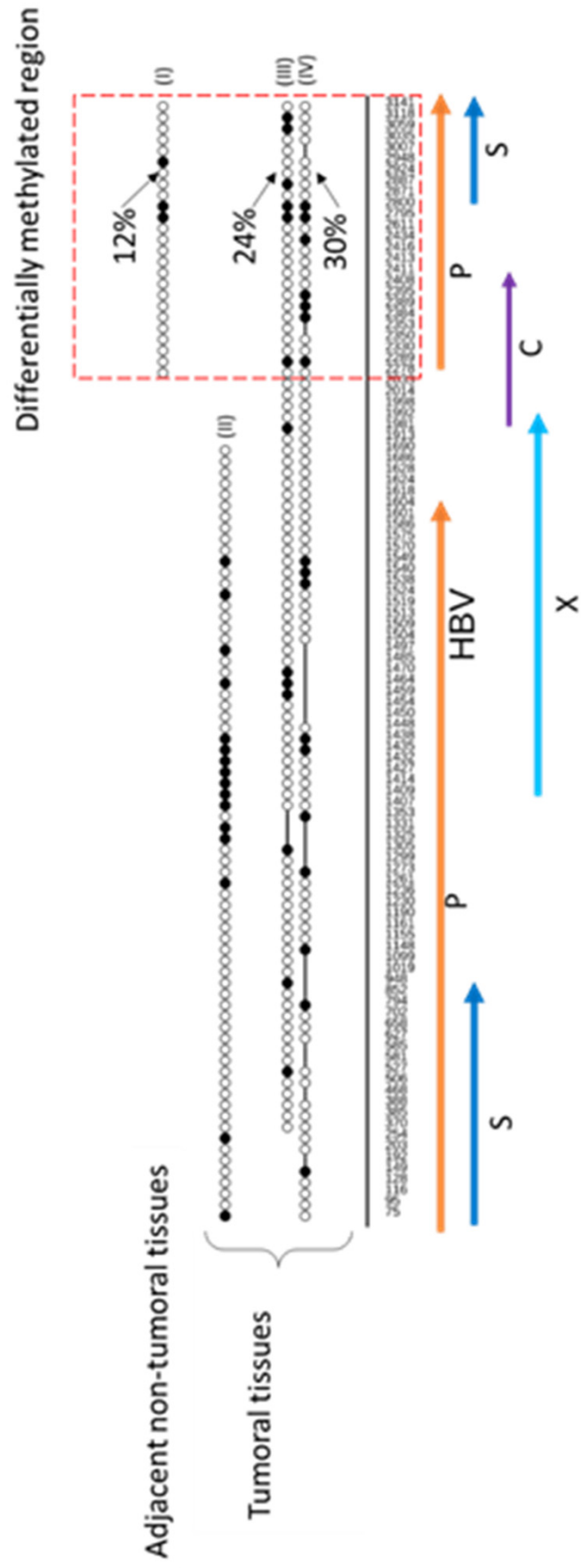
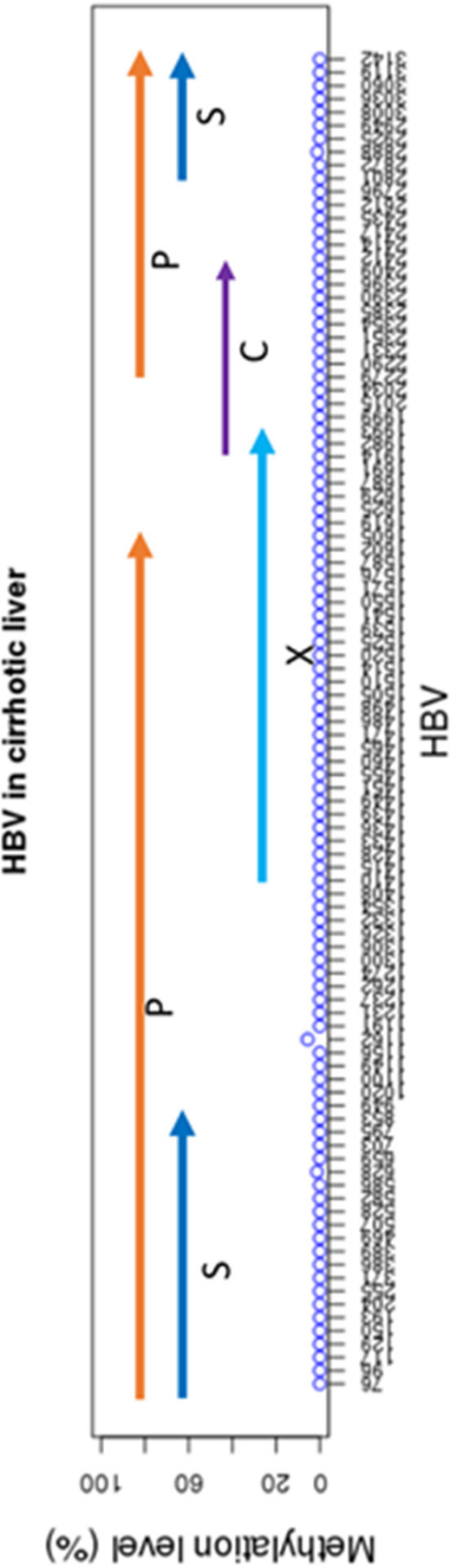
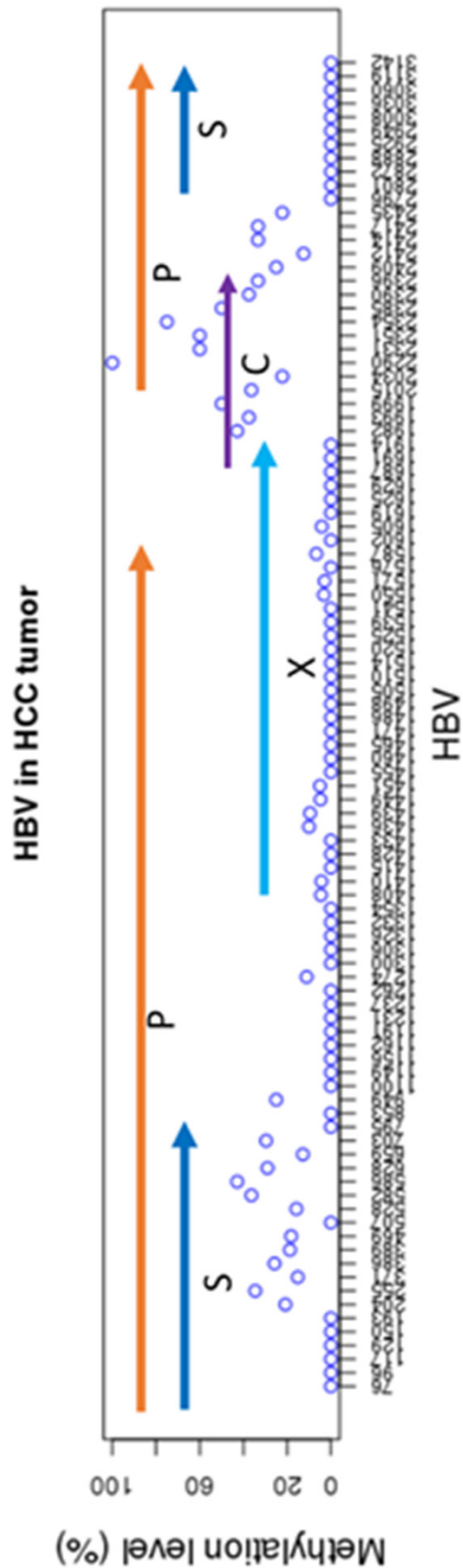


FIG. 75



HBV in 4 cirrhotic liver tissues: a median of 25 X depth
FIG. 767A



HBV in 15 HCC tumor tissues: a median of 14 X depth
FIG. 76B

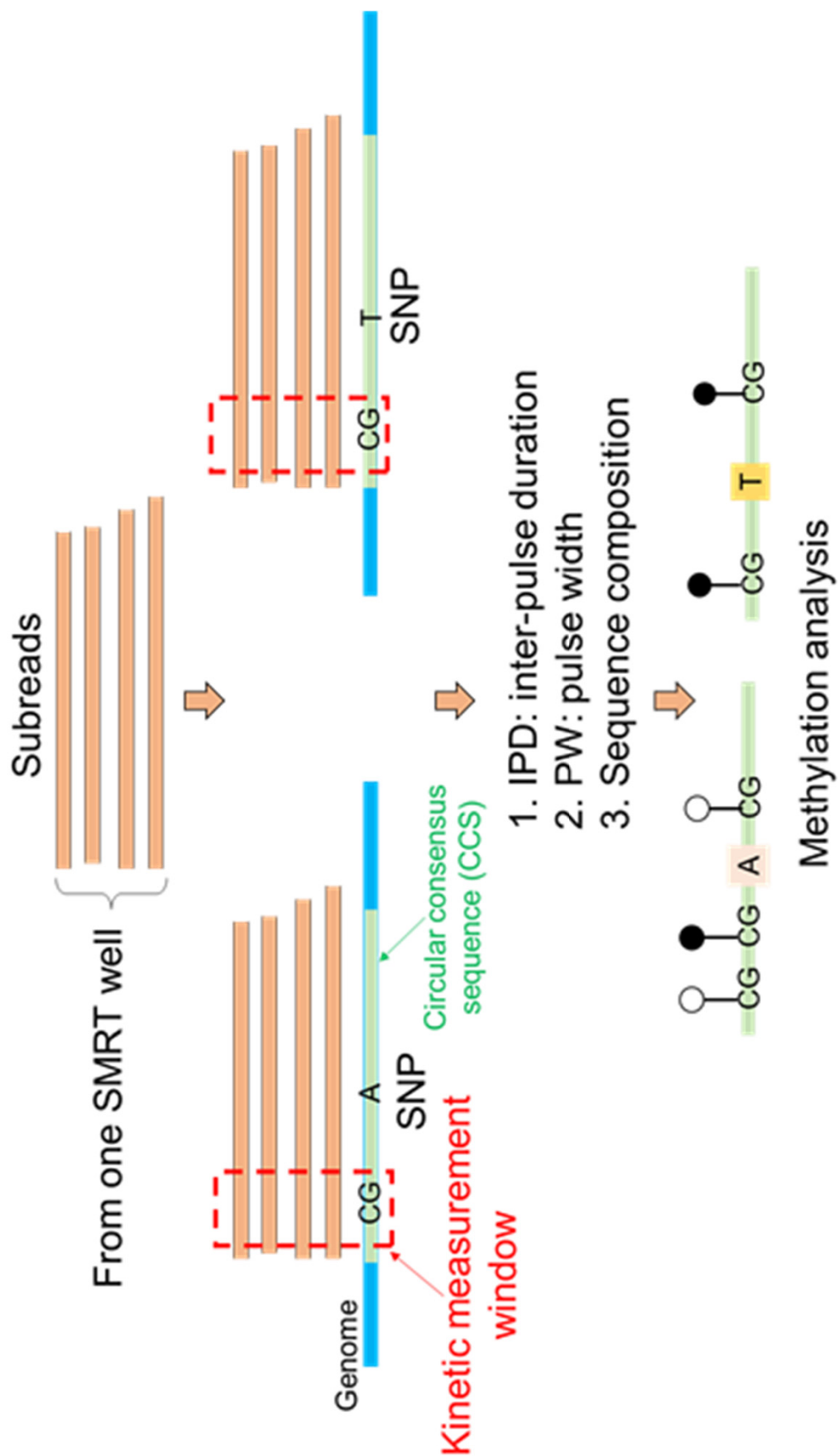


FIG. 77

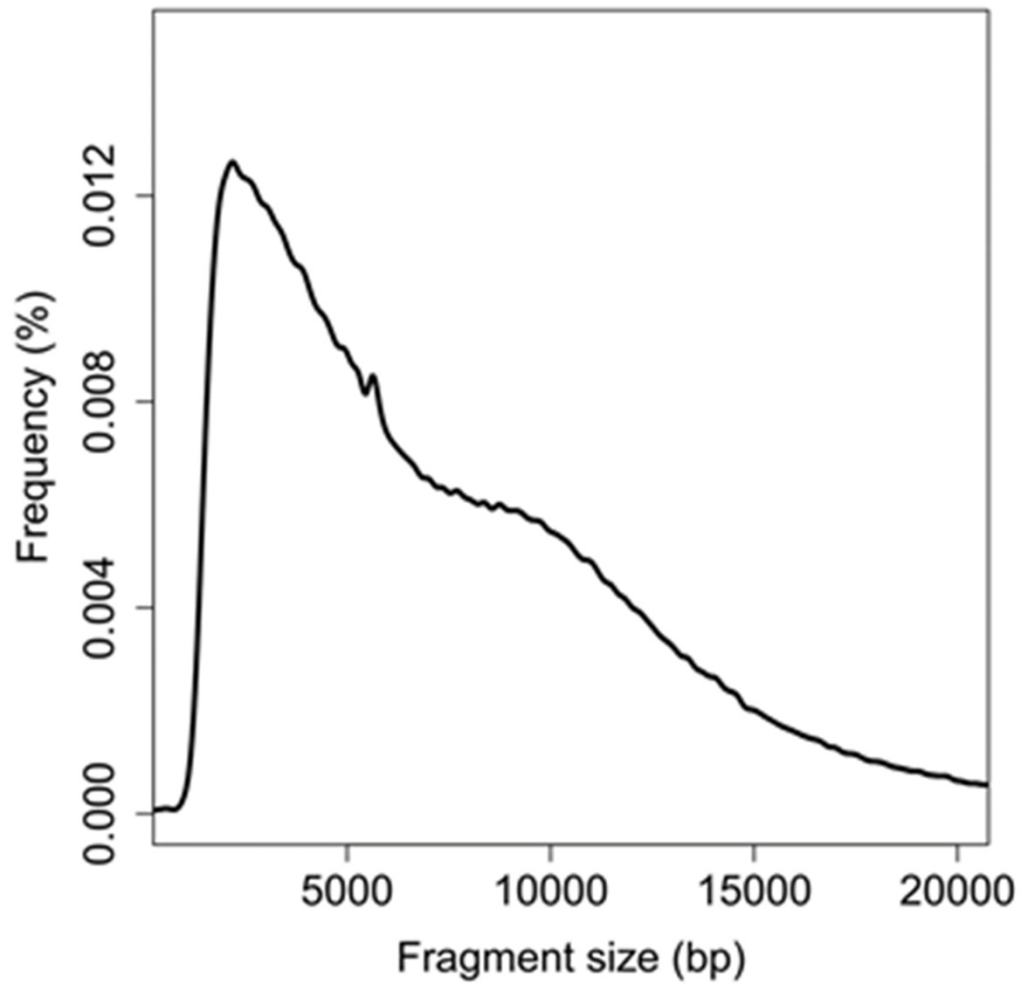


FIG. 78

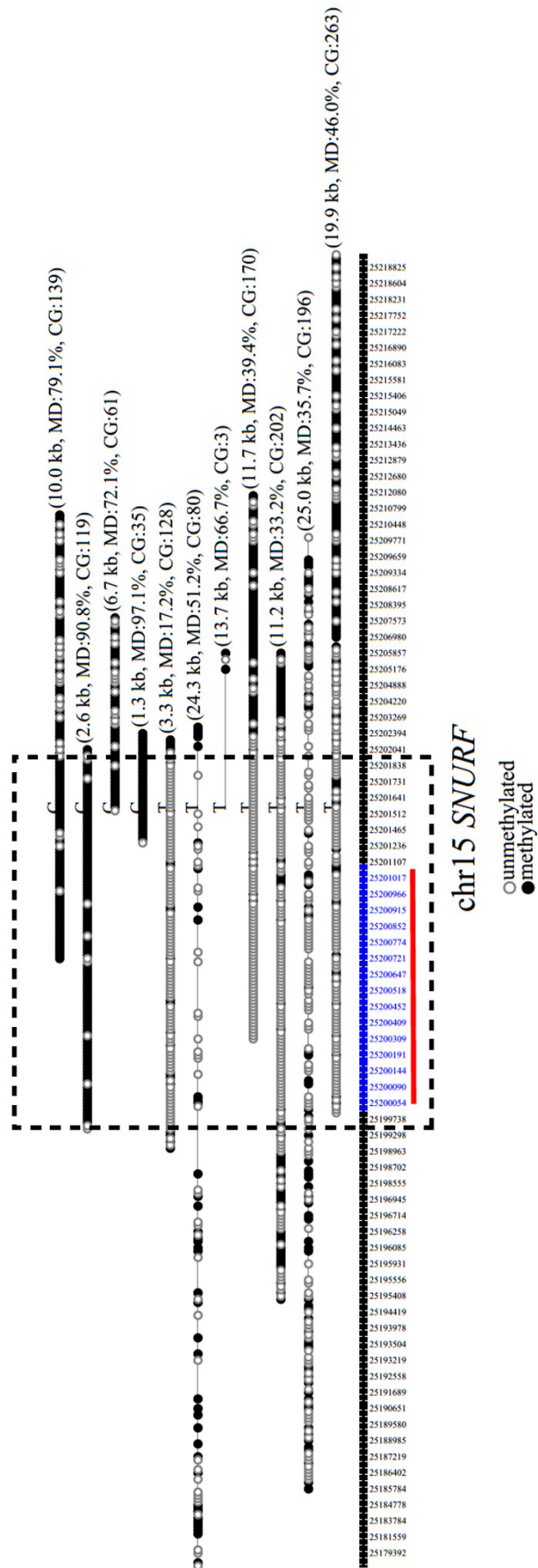


FIG. 79A

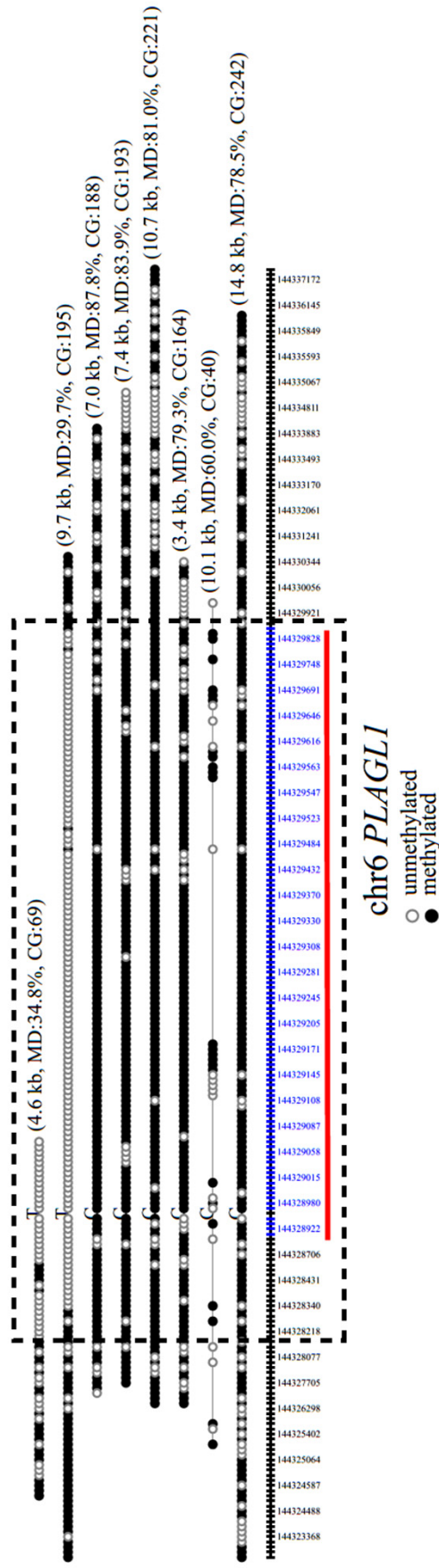


FIG. 79B

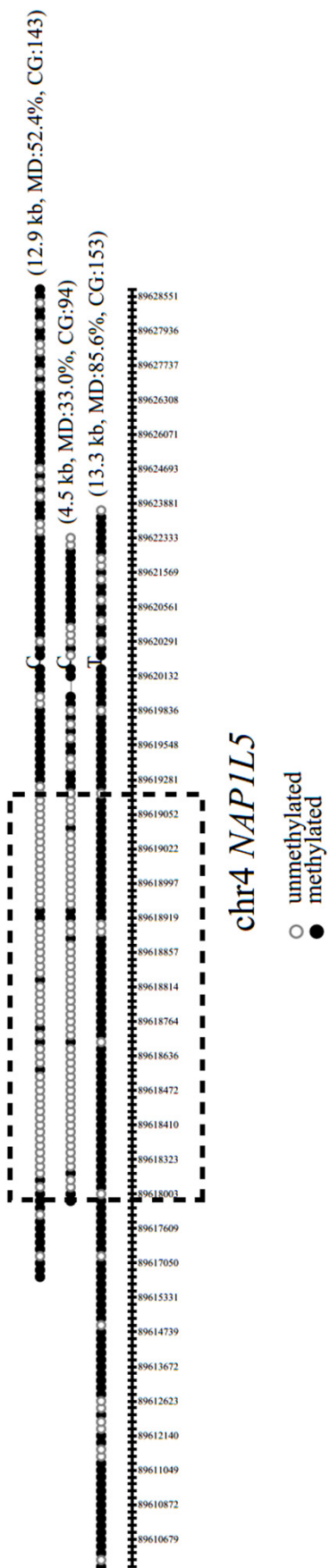


FIG. 79C

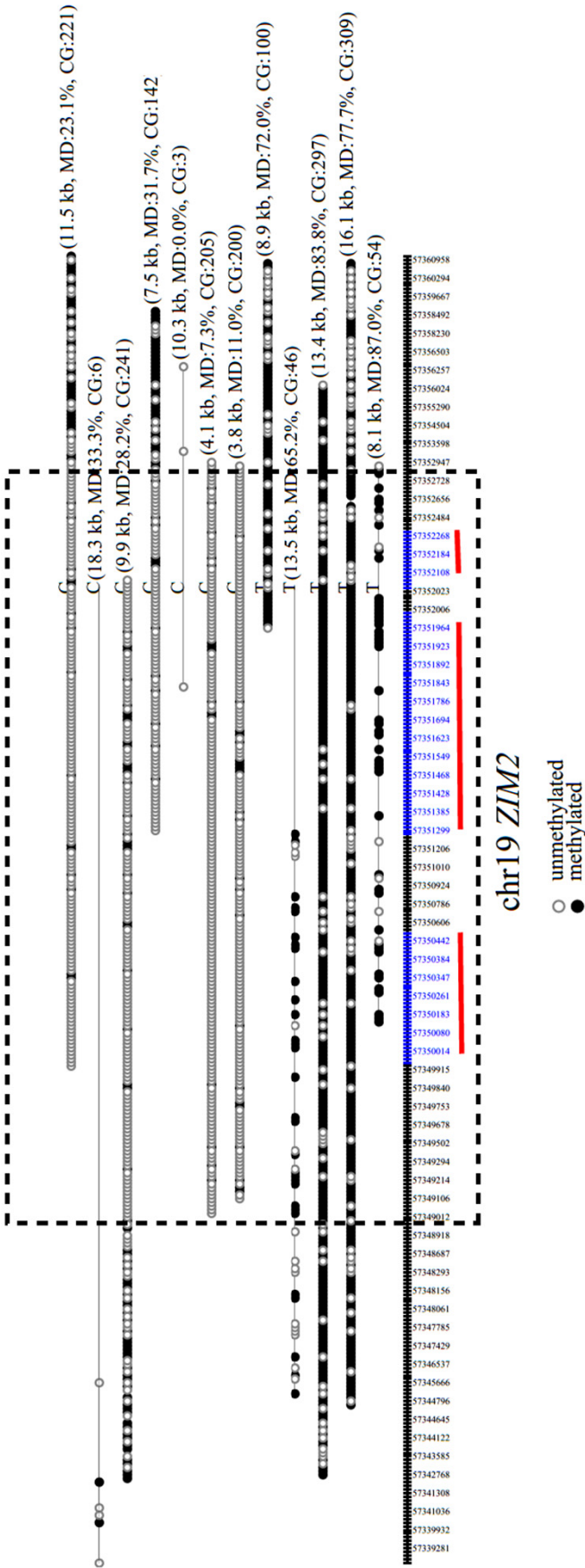


FIG. 79D

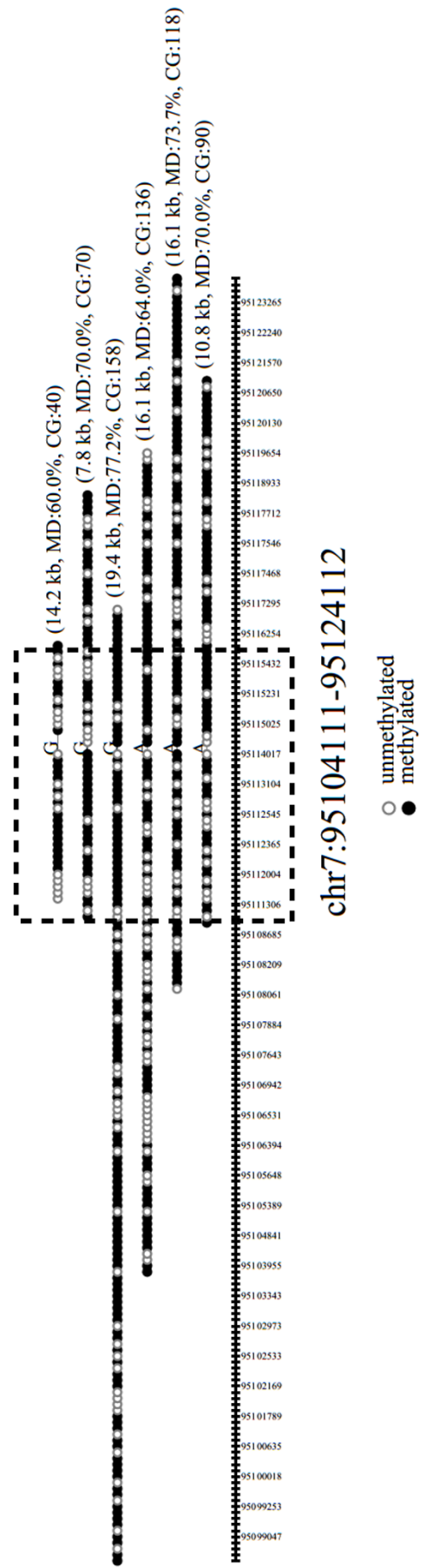


FIG. 80A

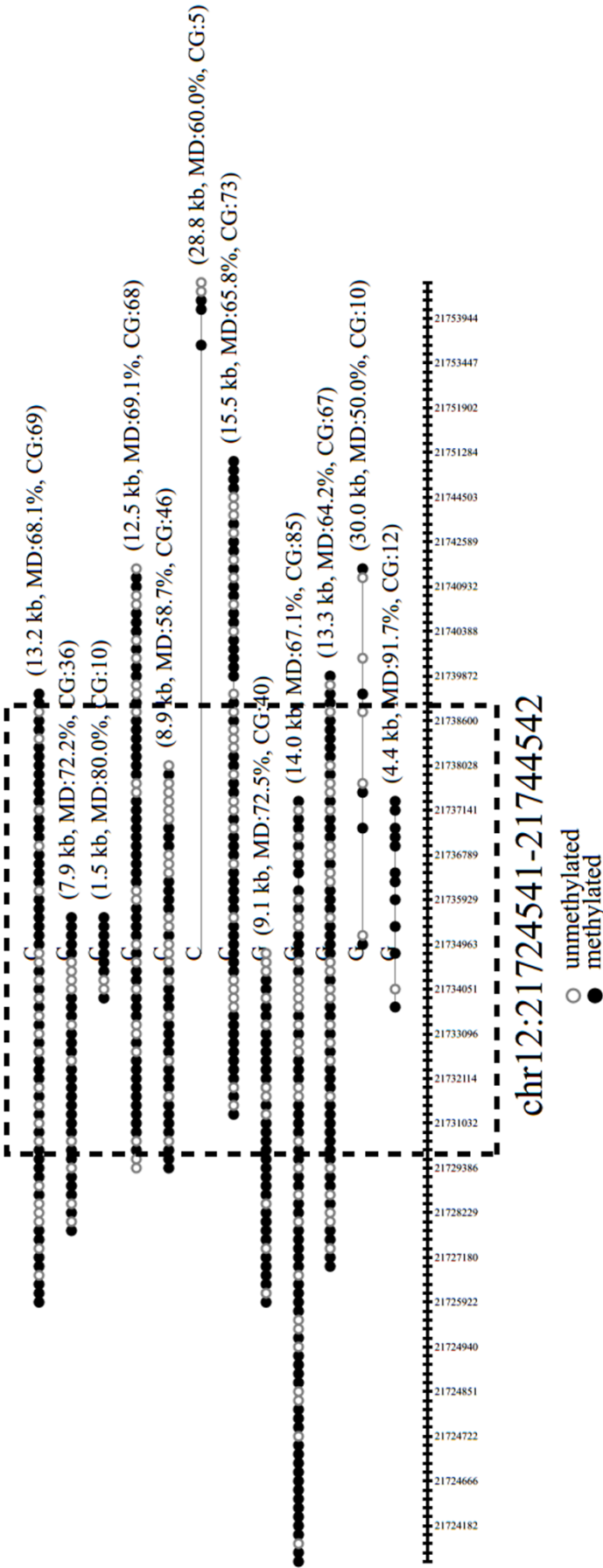


FIG. 80B

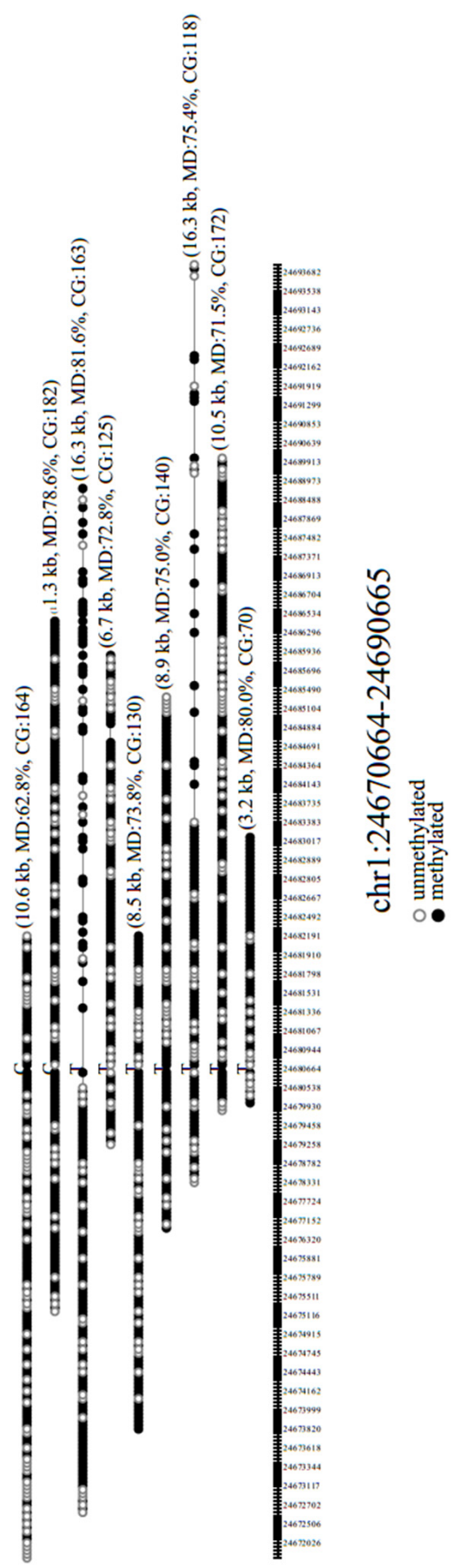


FIG. 80C



	Gene	Allele 1	Allele 2	Methylation level (%)	
				Allele 1	Allele 2
Imprinted genes	<i>SNURF</i>	T	C	15.73	89.37
	<i>PLAGL1</i>	T	C	7.56	89.41
	<i>NAP1L5</i>	C	T	12.5	91.07
	<i>ZIM2</i>	C	T	13	84.64
Randomly selected regions	Region 01	G	A	71.79	69.17
	Region 02	T	G	63.22	65.22
	Region 03	C	T	73.33	74.9
	Region 04	C	T	10.83	8.51

FIG. 81



FIG. 82



FIG. 83

Sequel Sequencing Kit 3.0

Training dataset

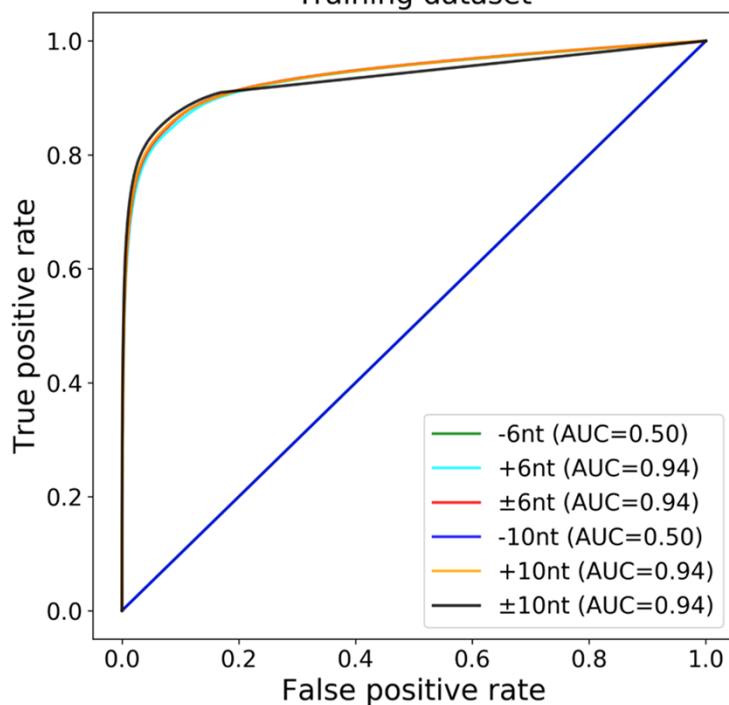


FIG. 84A

Sequel II Sequencing Kit 1.0

Training dataset

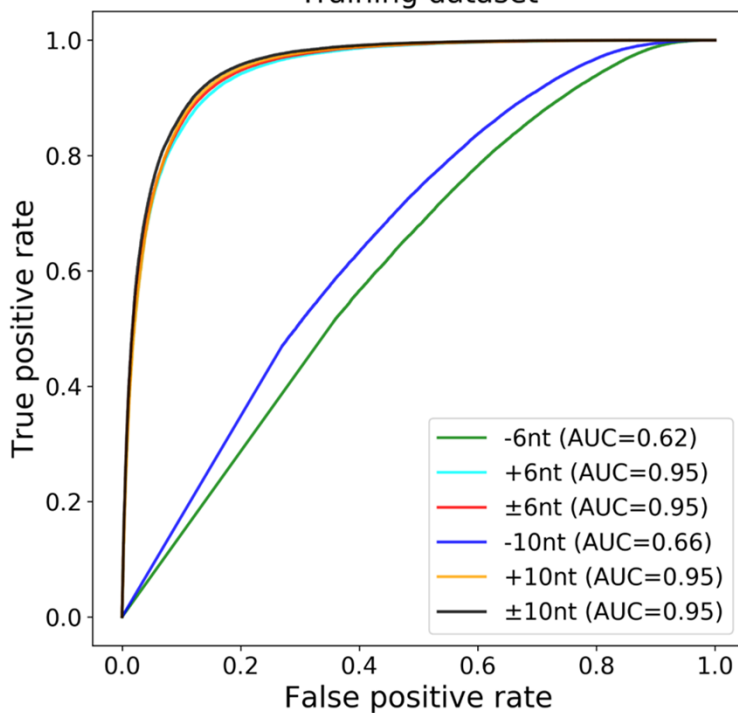


FIG. 84B

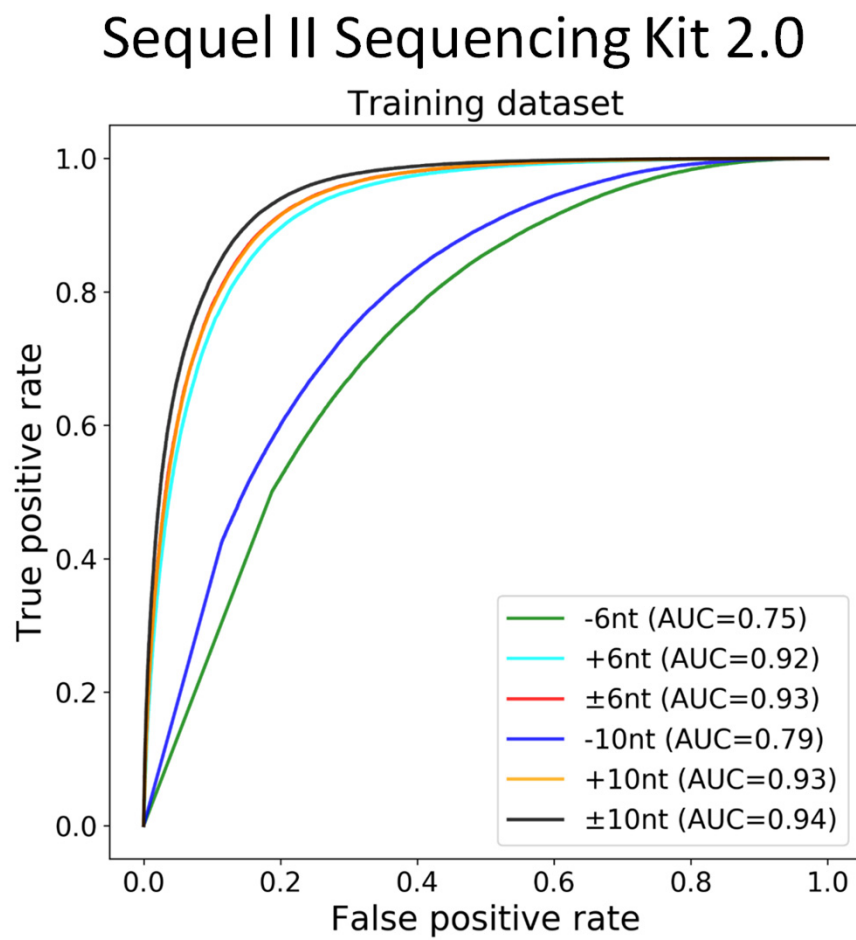


FIG. 84C

Sequel Sequencing Kit 3.0

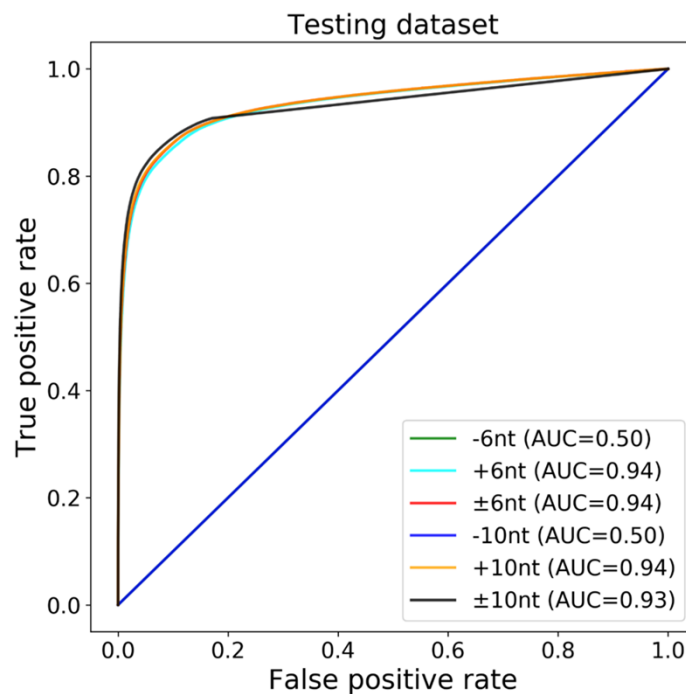


FIG. 85A

Sequel II Sequencing Kit 1.0

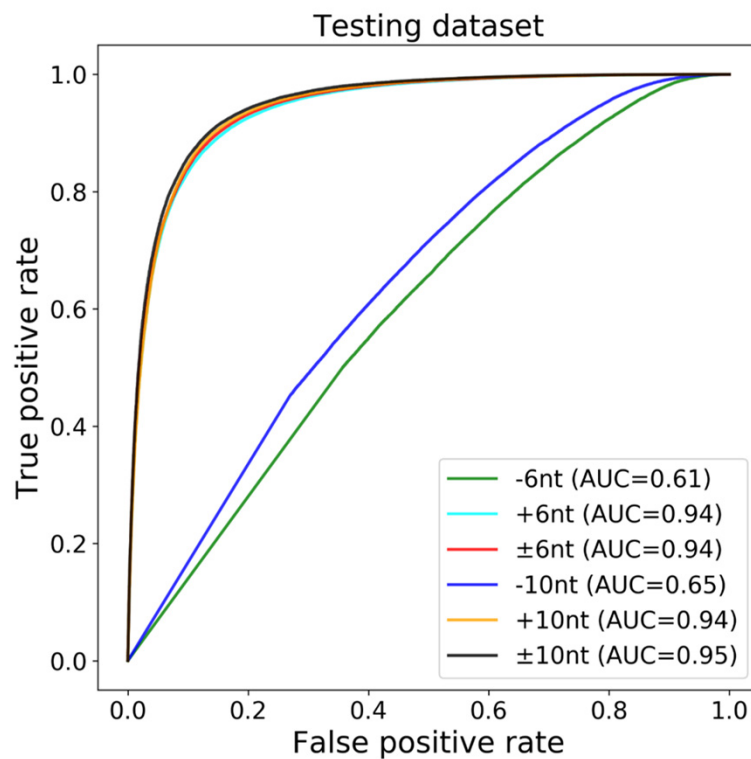


FIG. 85B

Sequel II Sequencing Kit 2.0

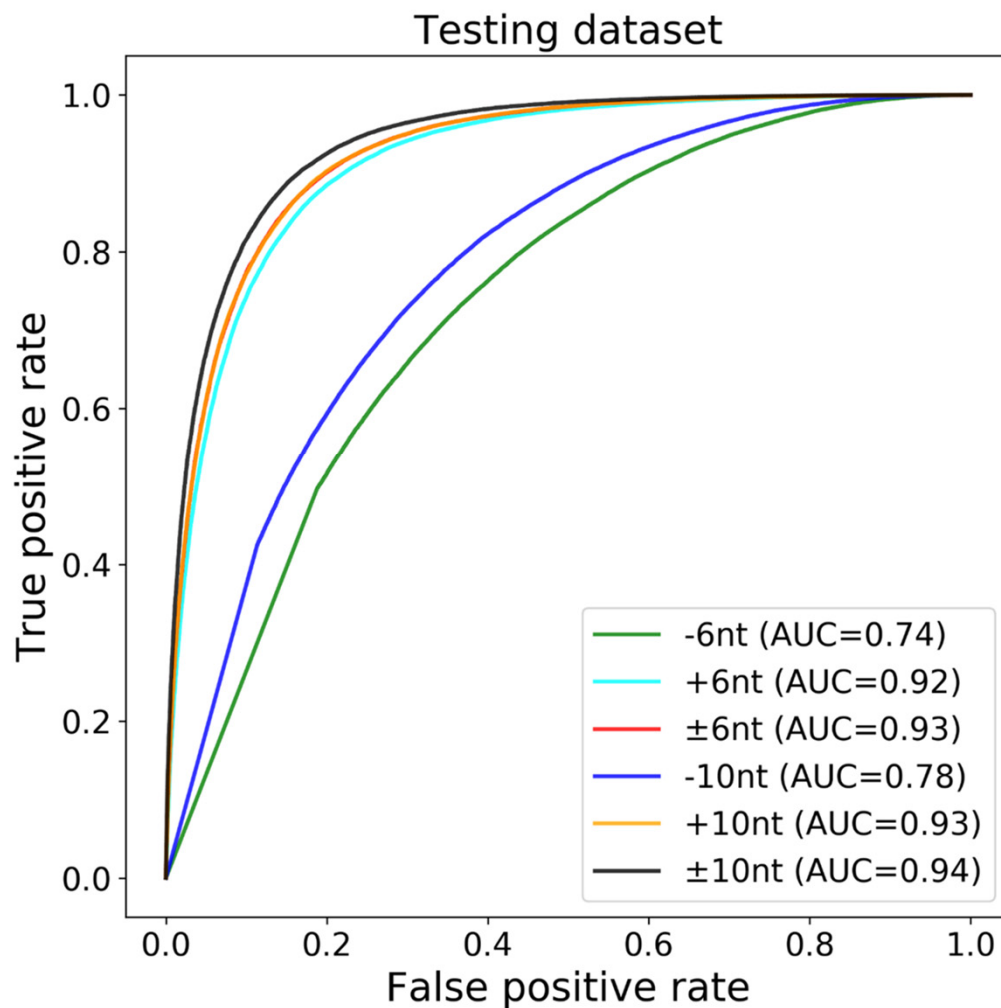


FIG. 85C

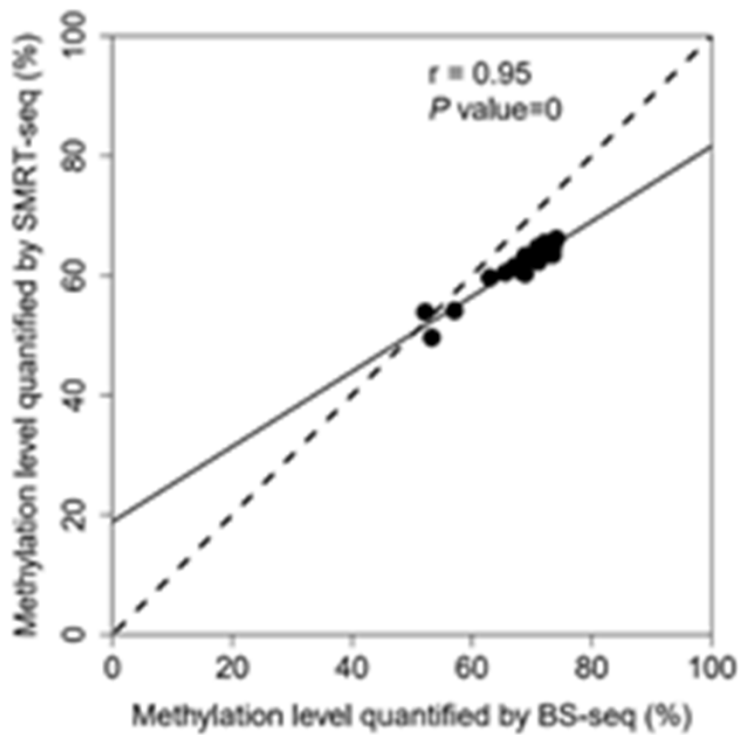


FIG. 86A

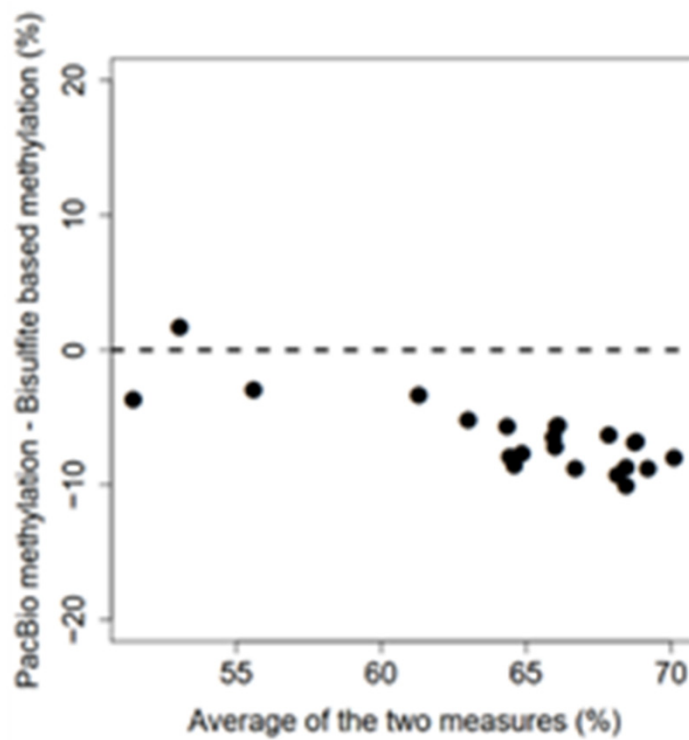


FIG. 86B

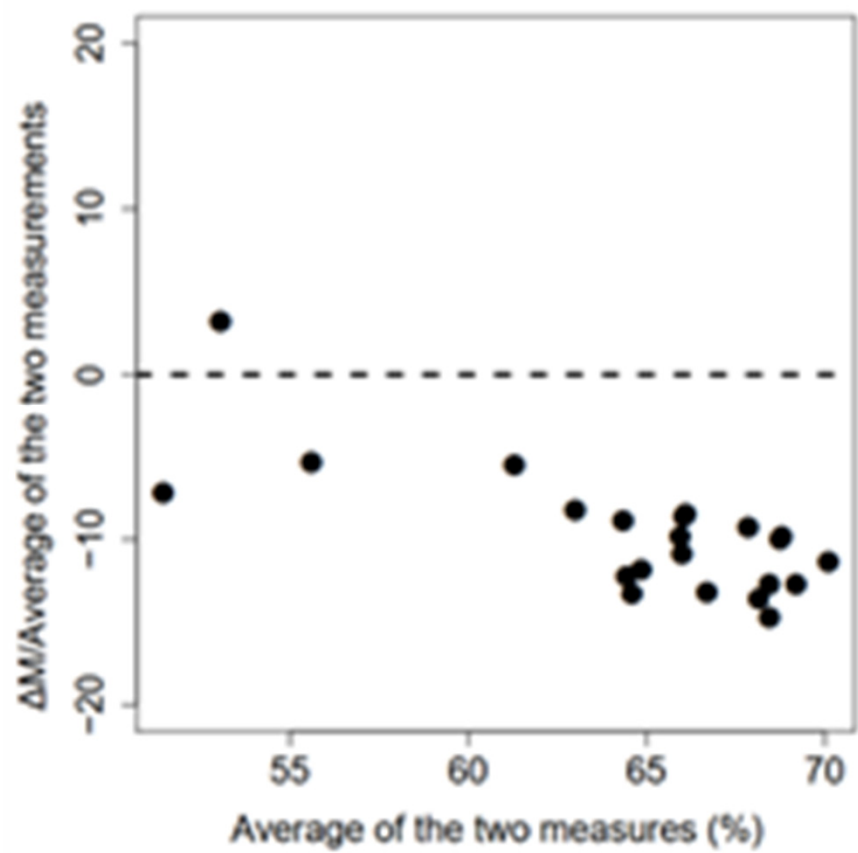


FIG. 86C

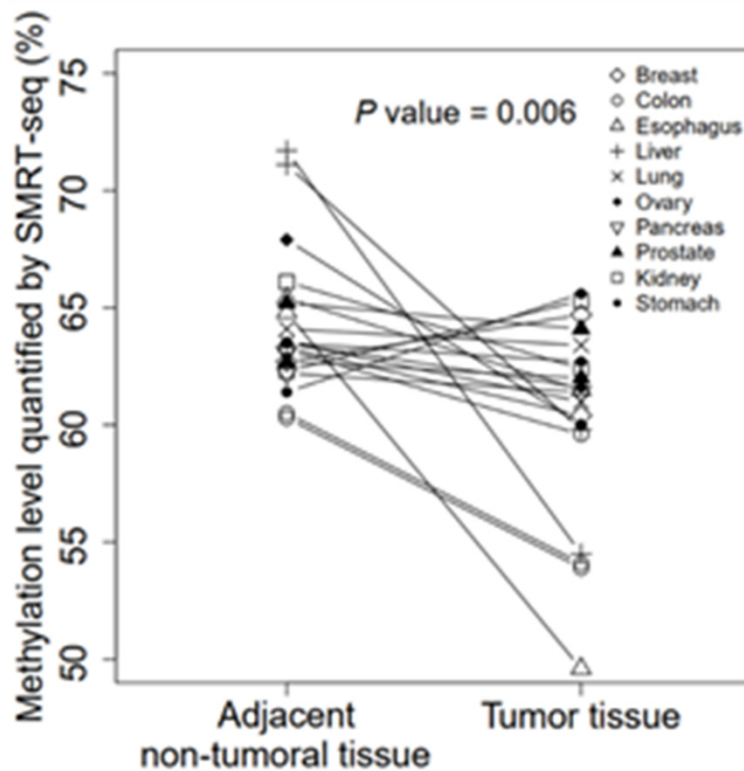


FIG. 87A

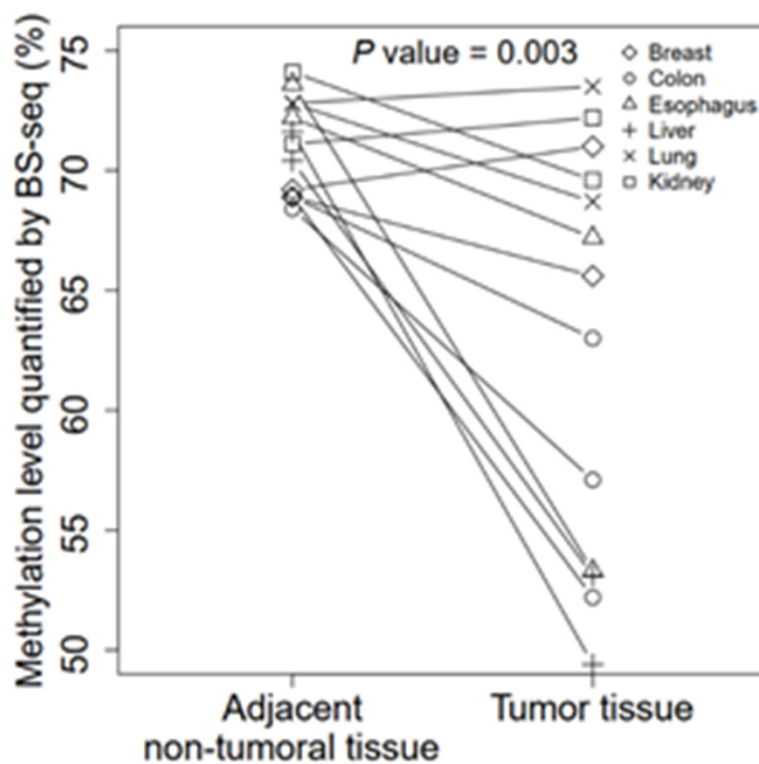


FIG. 87B

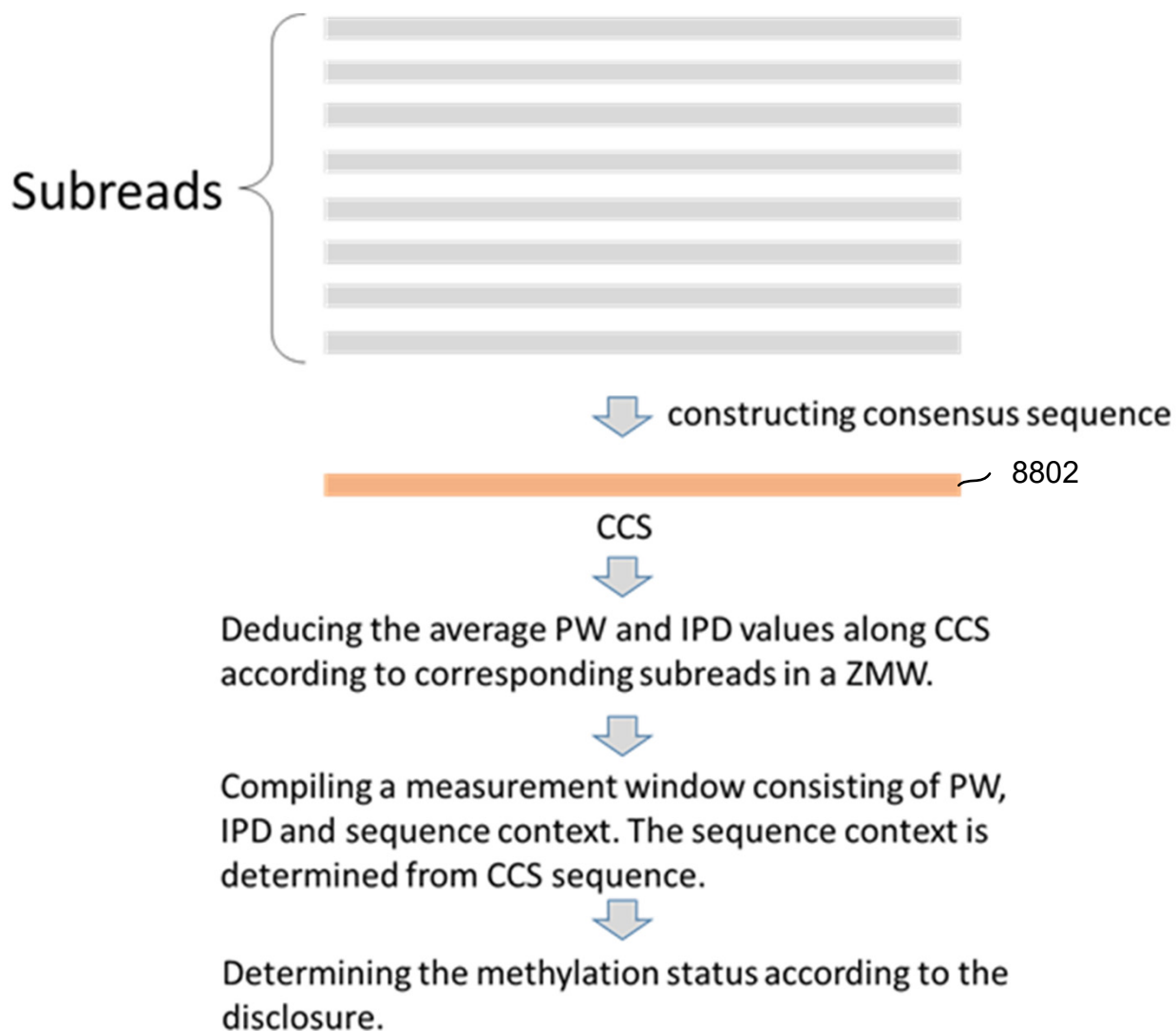


FIG. 88

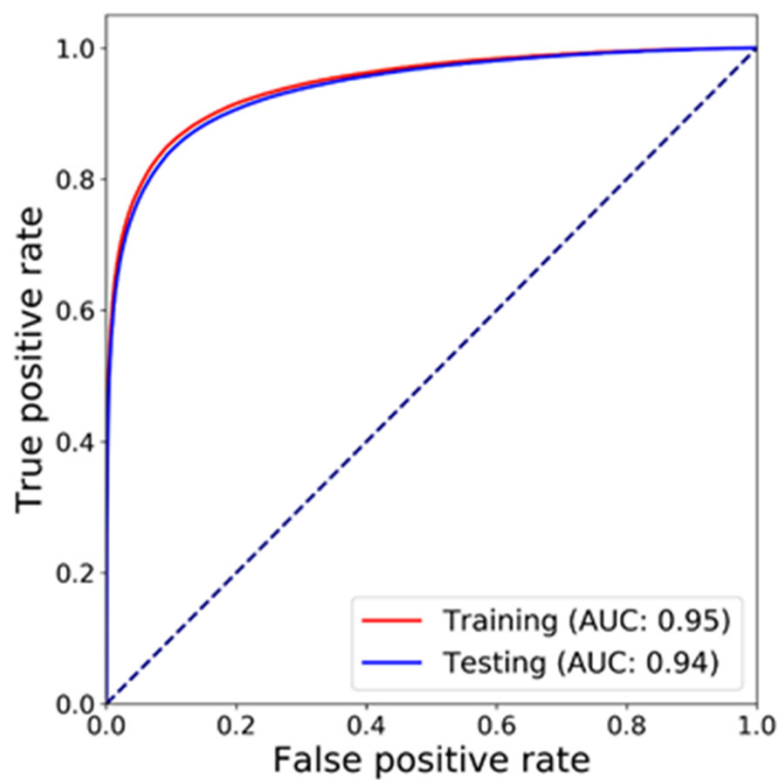


FIG. 89

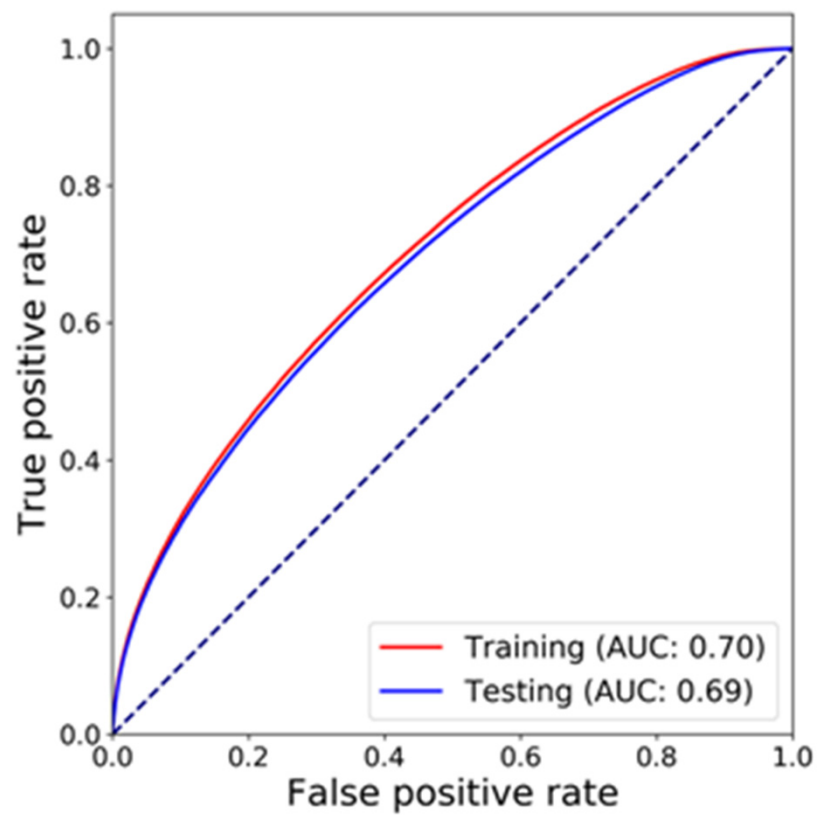


FIG. 90

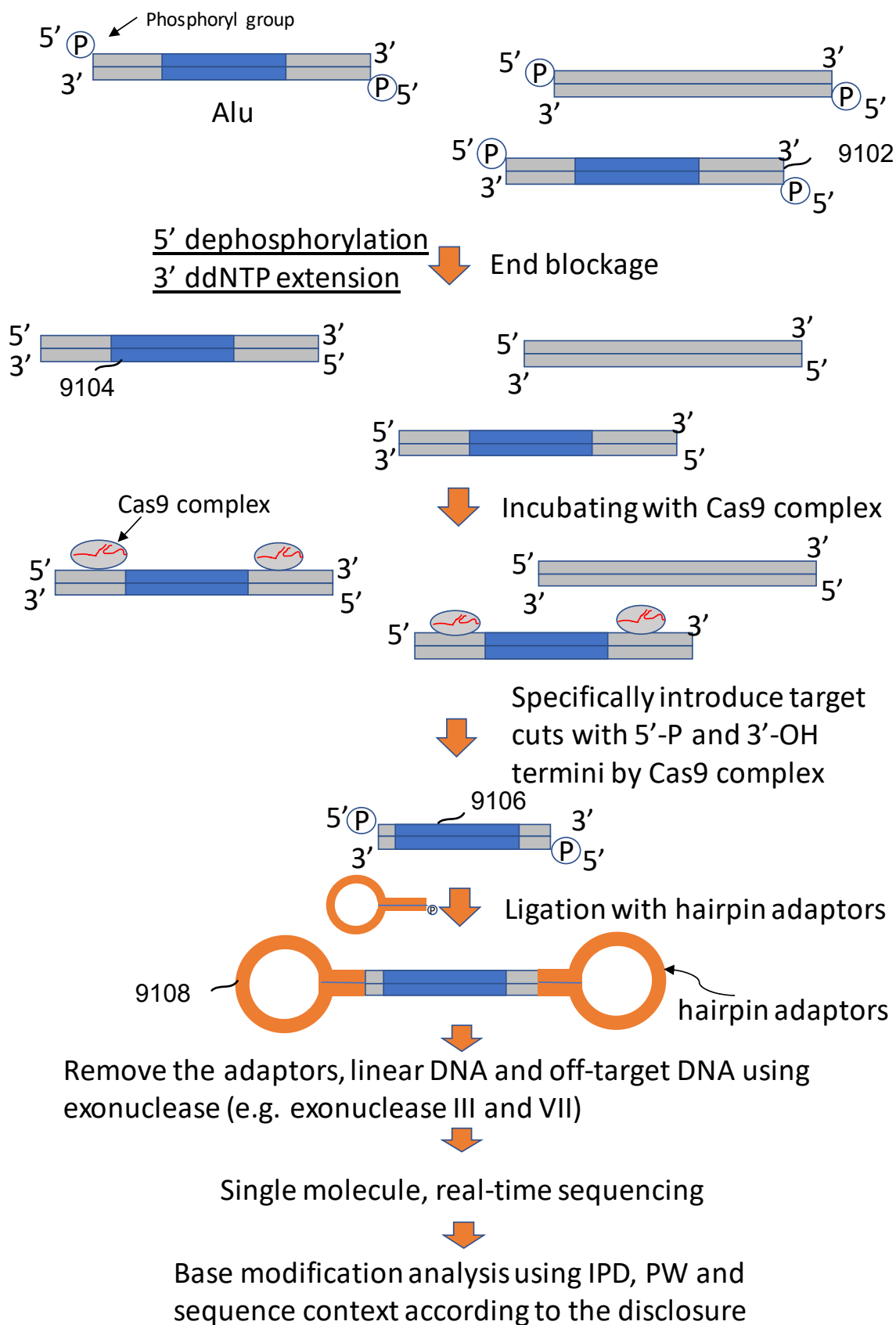


FIG. 91

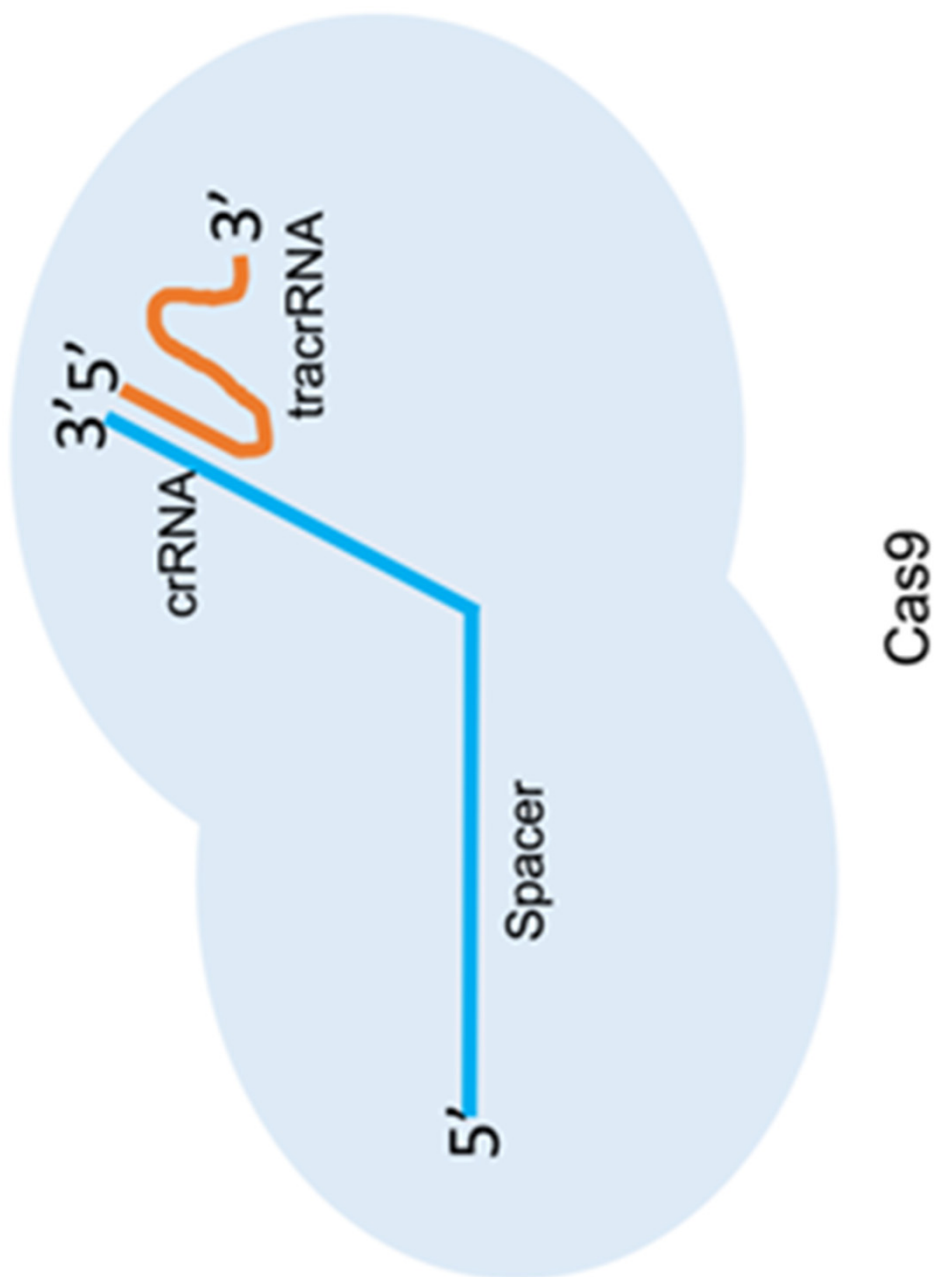


FIG. 92

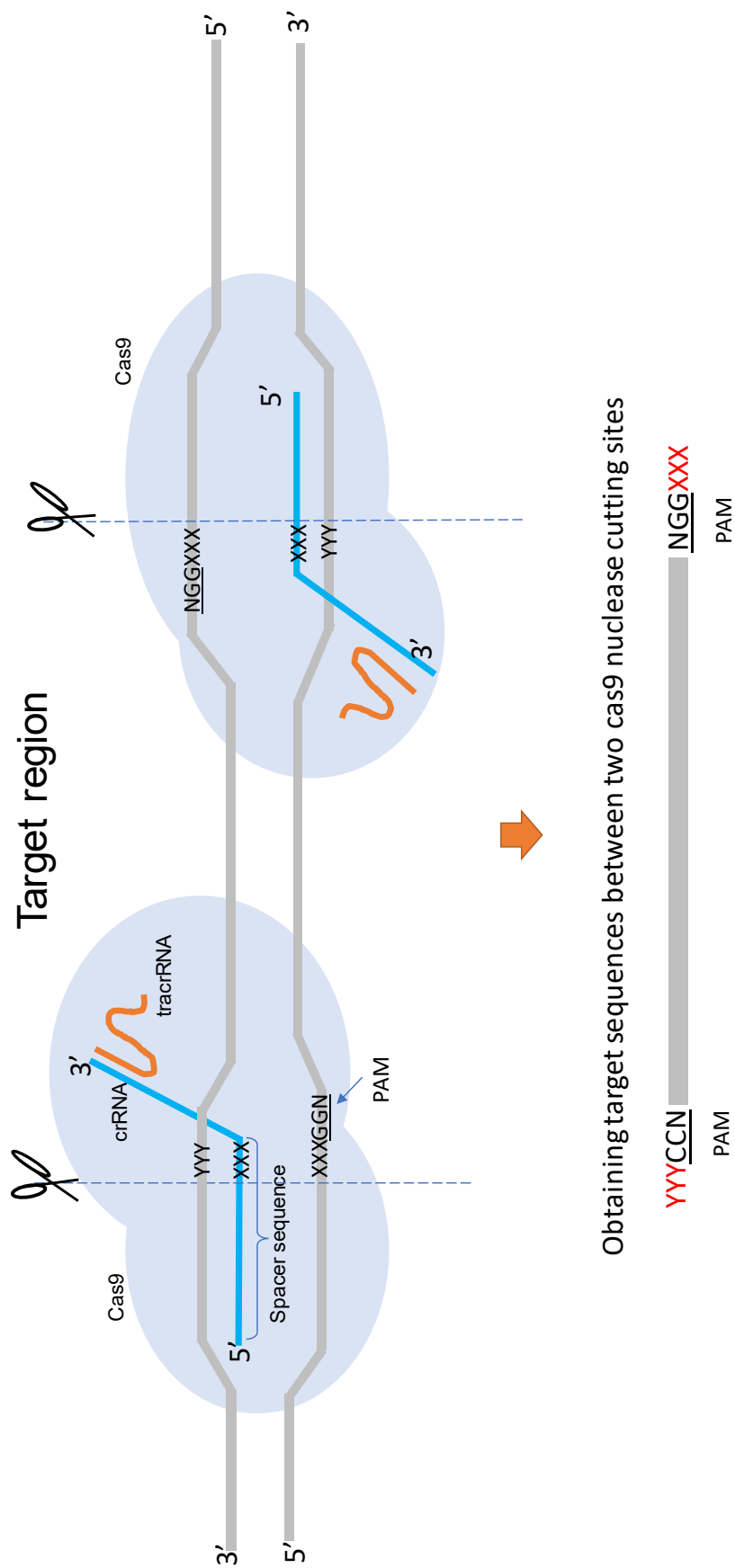


FIG. 93

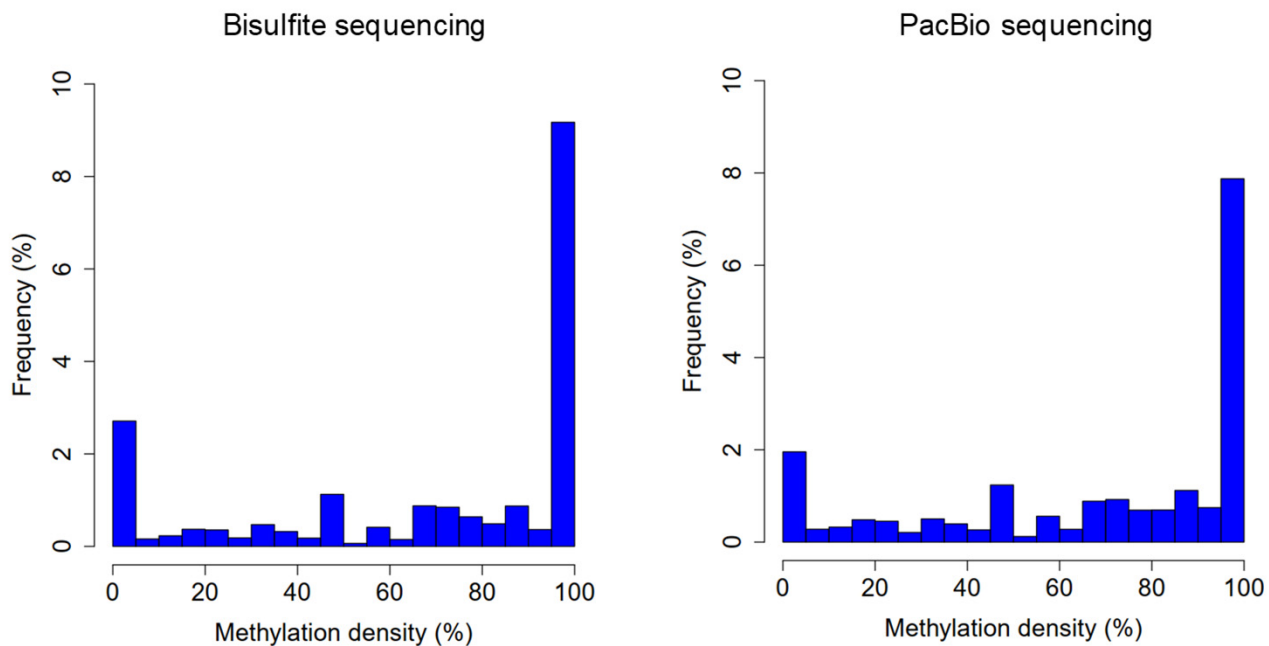


FIG. 94

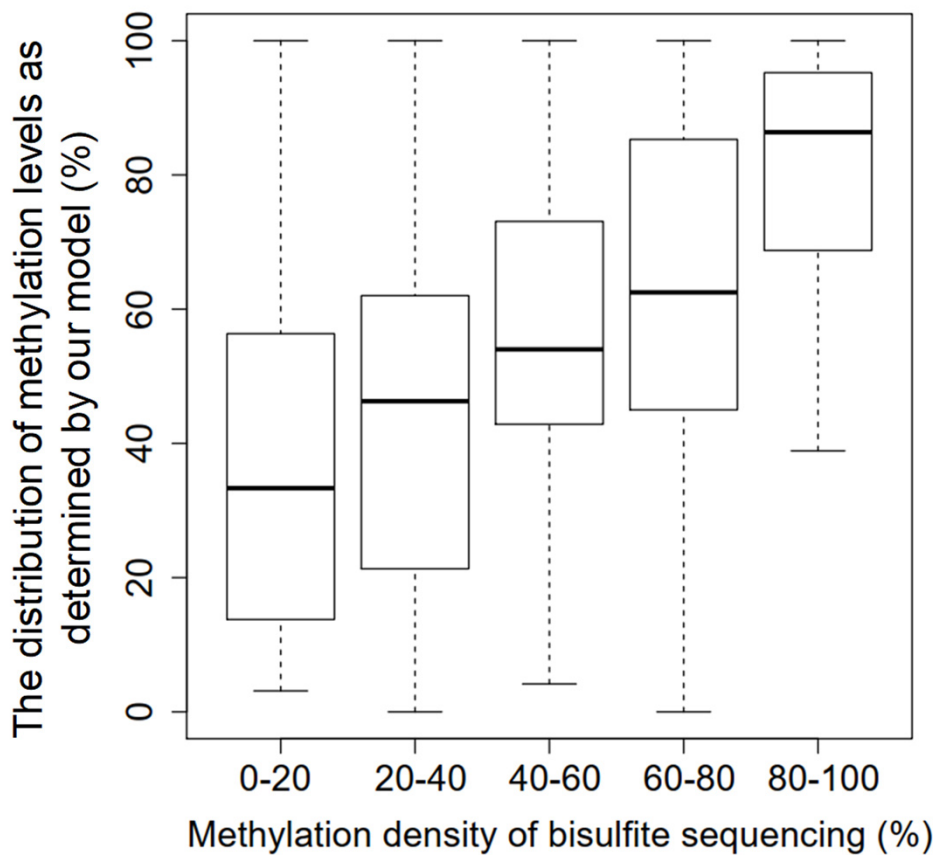


FIG. 95

Tissues	Methylation level of Alu (%)
Buffy coat	89.54
Liver	88.18
Colon	89.56
Lung	91.52
Small intestine	86.56
Adrenal gland	89.07
Adipose	91.44
Pancreas	85.82
Brain	91.79
HCC	76.74
Placenta	73.04

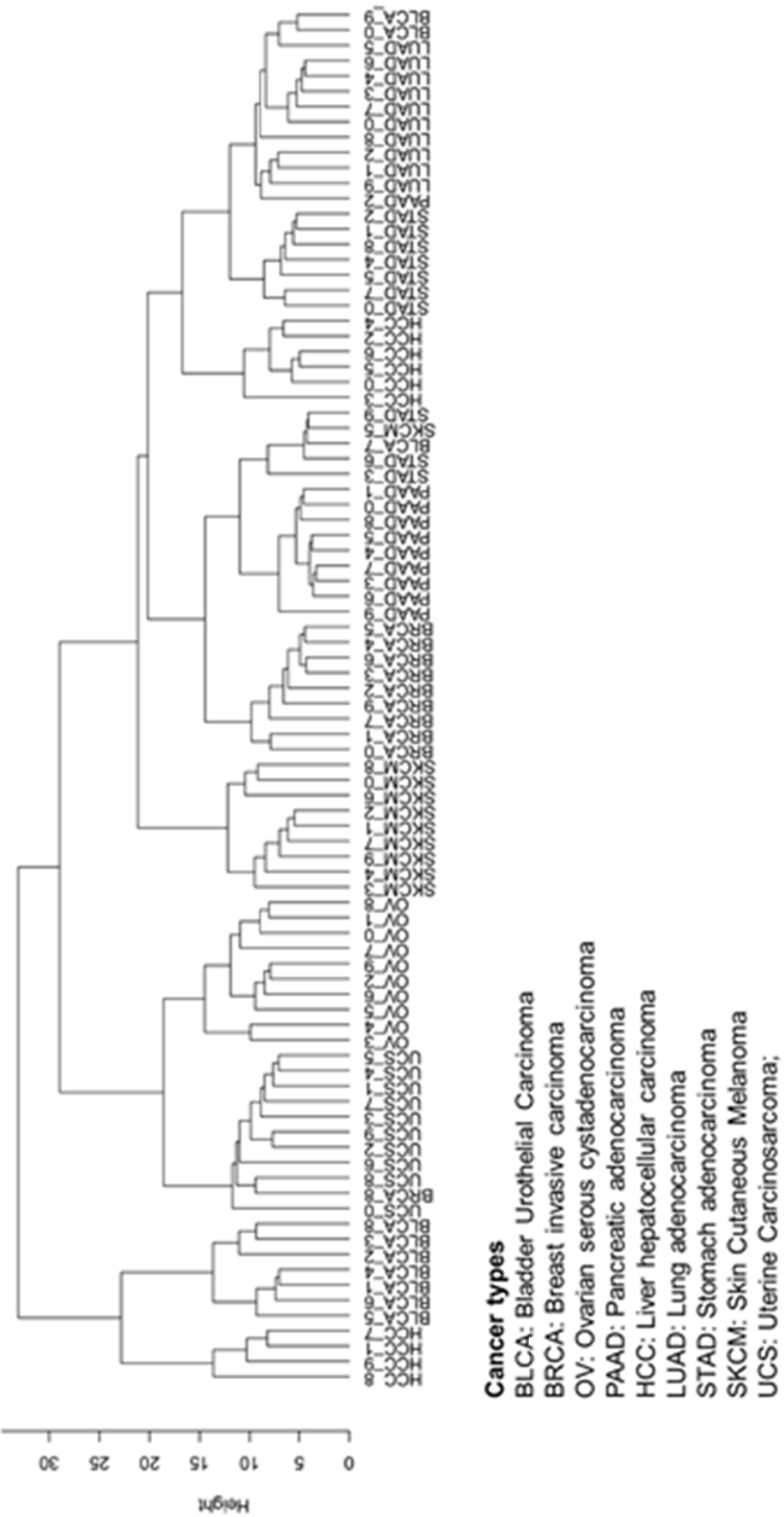


FIG. 97

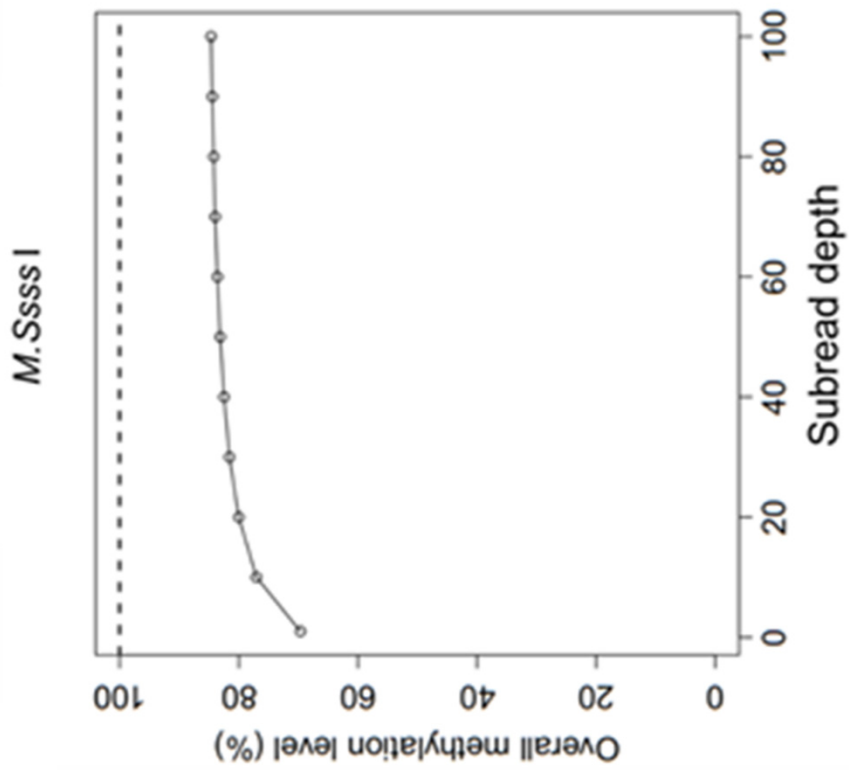


FIG. 98B

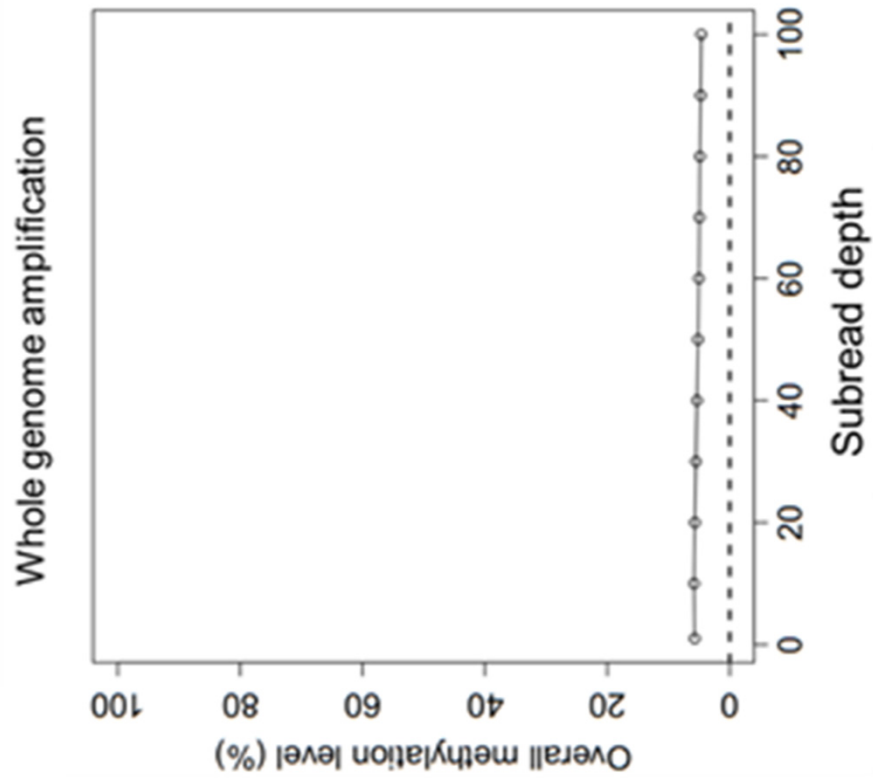


FIG. 98A

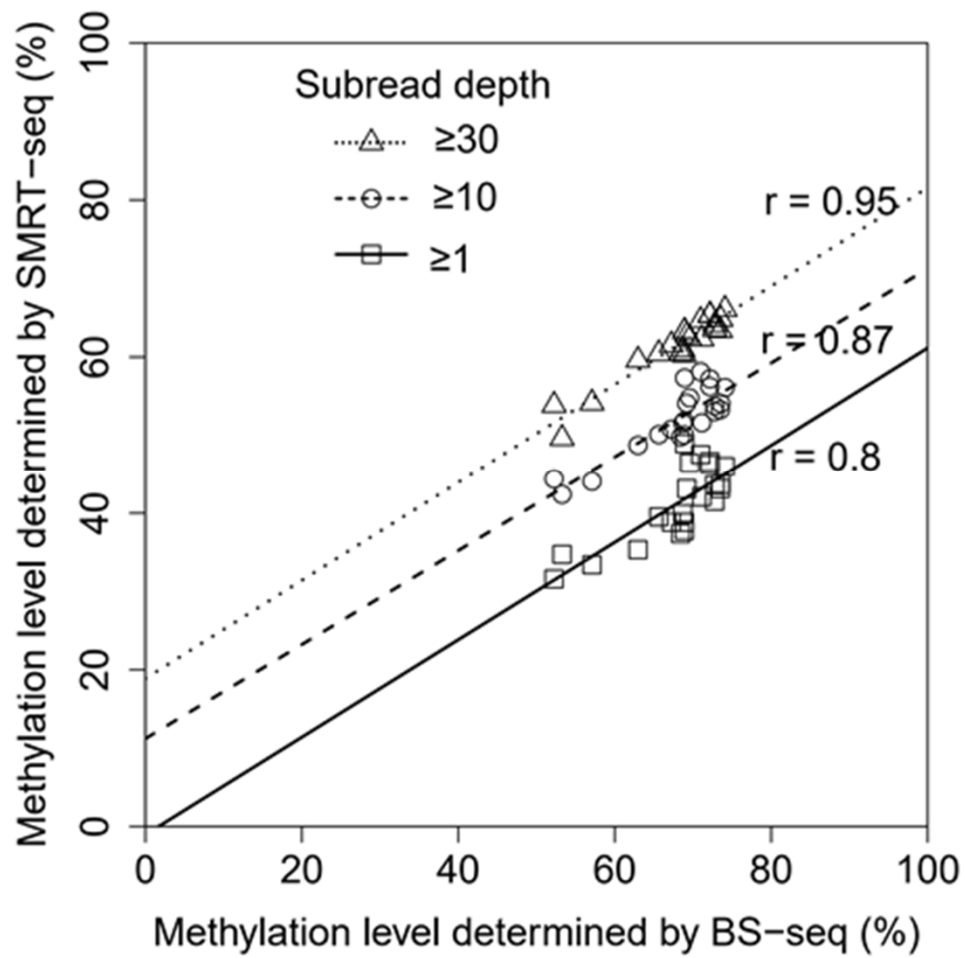


FIG. 99

Subread depth cutoffs $\geq$	Pearson's r (SMRT-seq vs BS-seq)	No. of CpG sites
1	0.797	25,606,068 (23,949,832-27,008,582)
10	0.873	21,668,418 (18,263,886-23,515,147)
20	0.933	14,276,212 (10,526,406-16,736,887)
30	0.952	6,736,890 (4,255,452-10,449,814)
40	0.948	3,420,790 (2,232,511-5,792,825)
50	0.941	1,684,871 (1,278,475-3,055,876)
60	0.929	911,961 (707,295-1,581,313)
70	0.917	532,422 (350,001-866,045)
80	0.907	284,375 (177,698-534,540)
90	0.906	150,974 (98,000-333,933)
100	0.875	89,788 (58,552-182,861)

FIG. 100

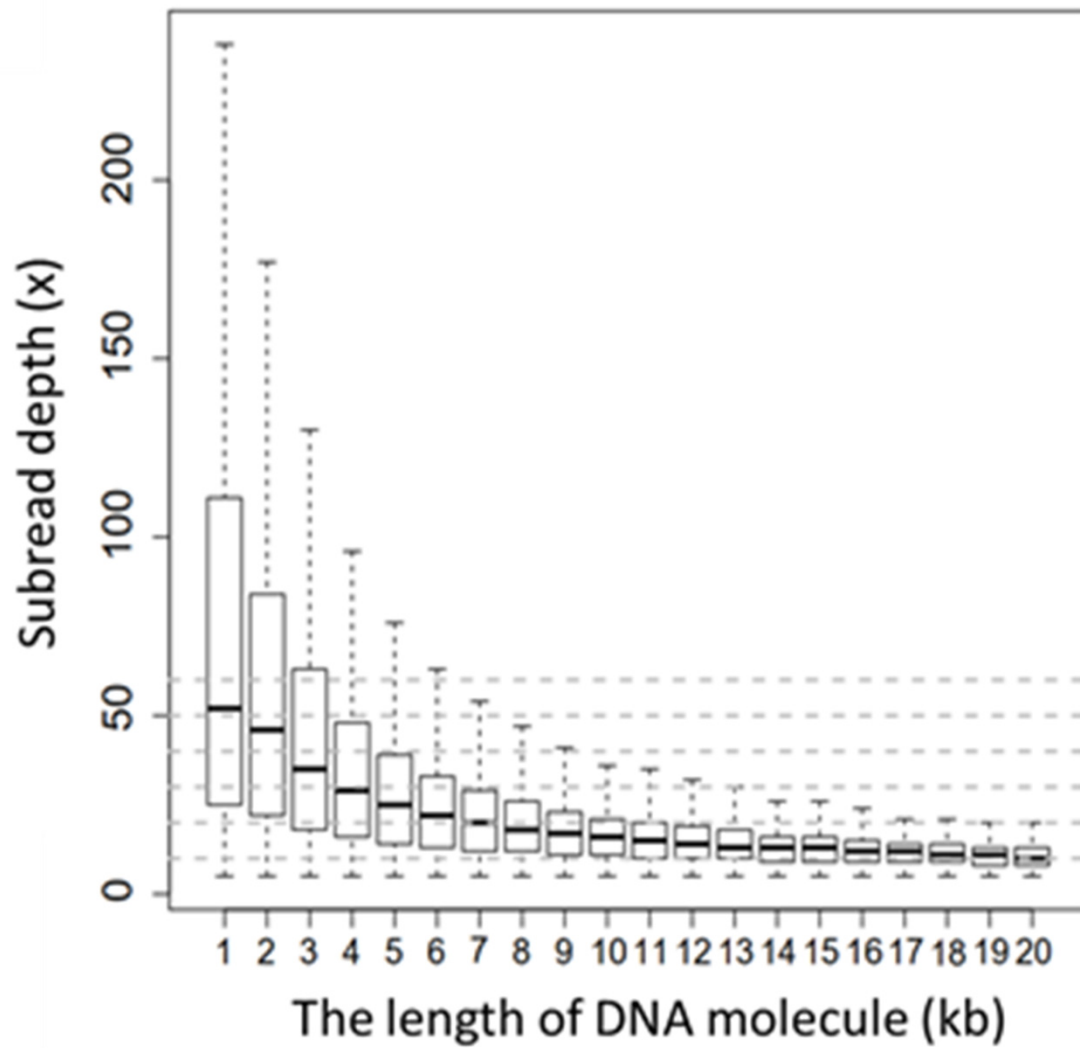


FIG. 101

1020

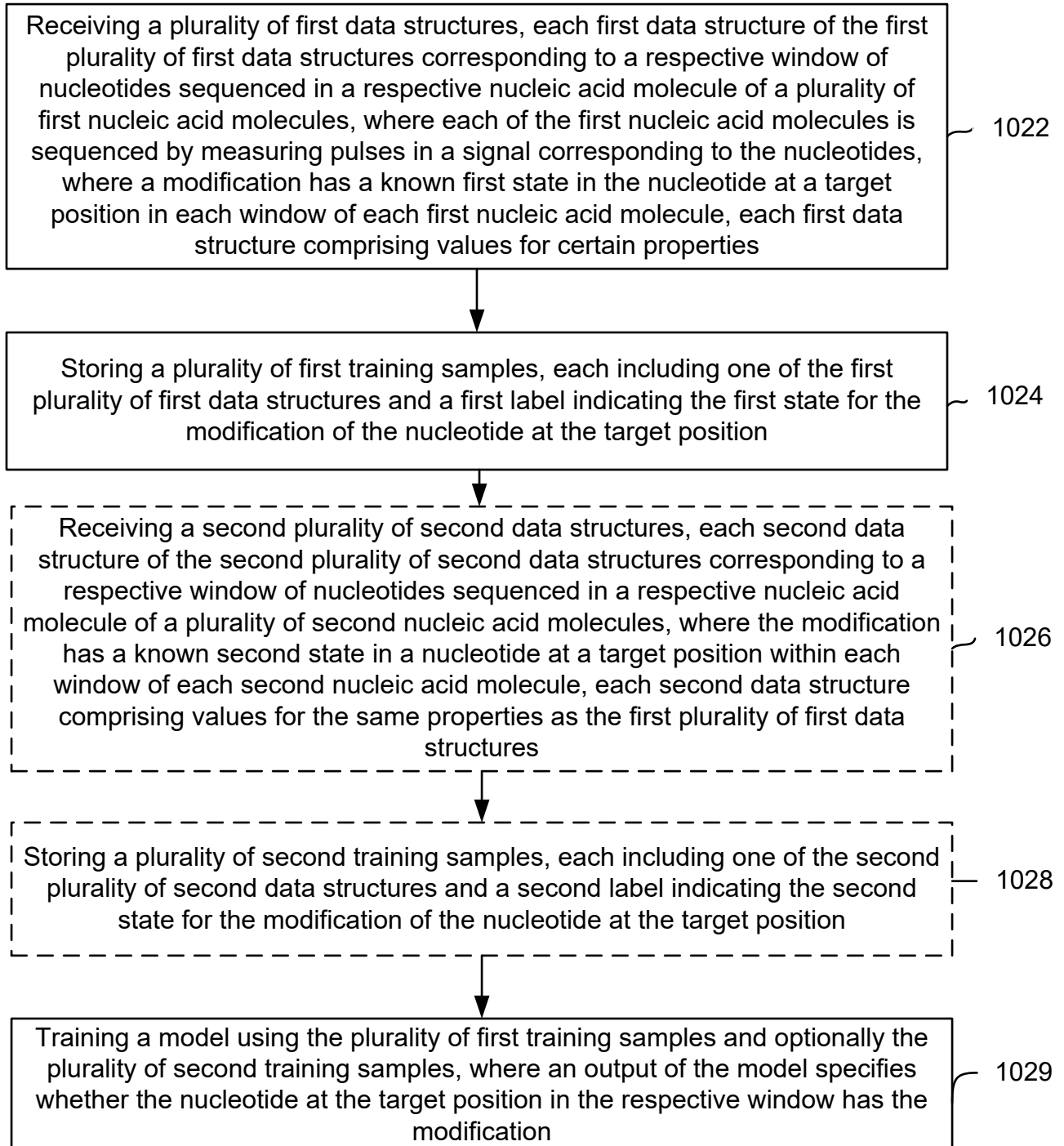


FIG. 102

1030

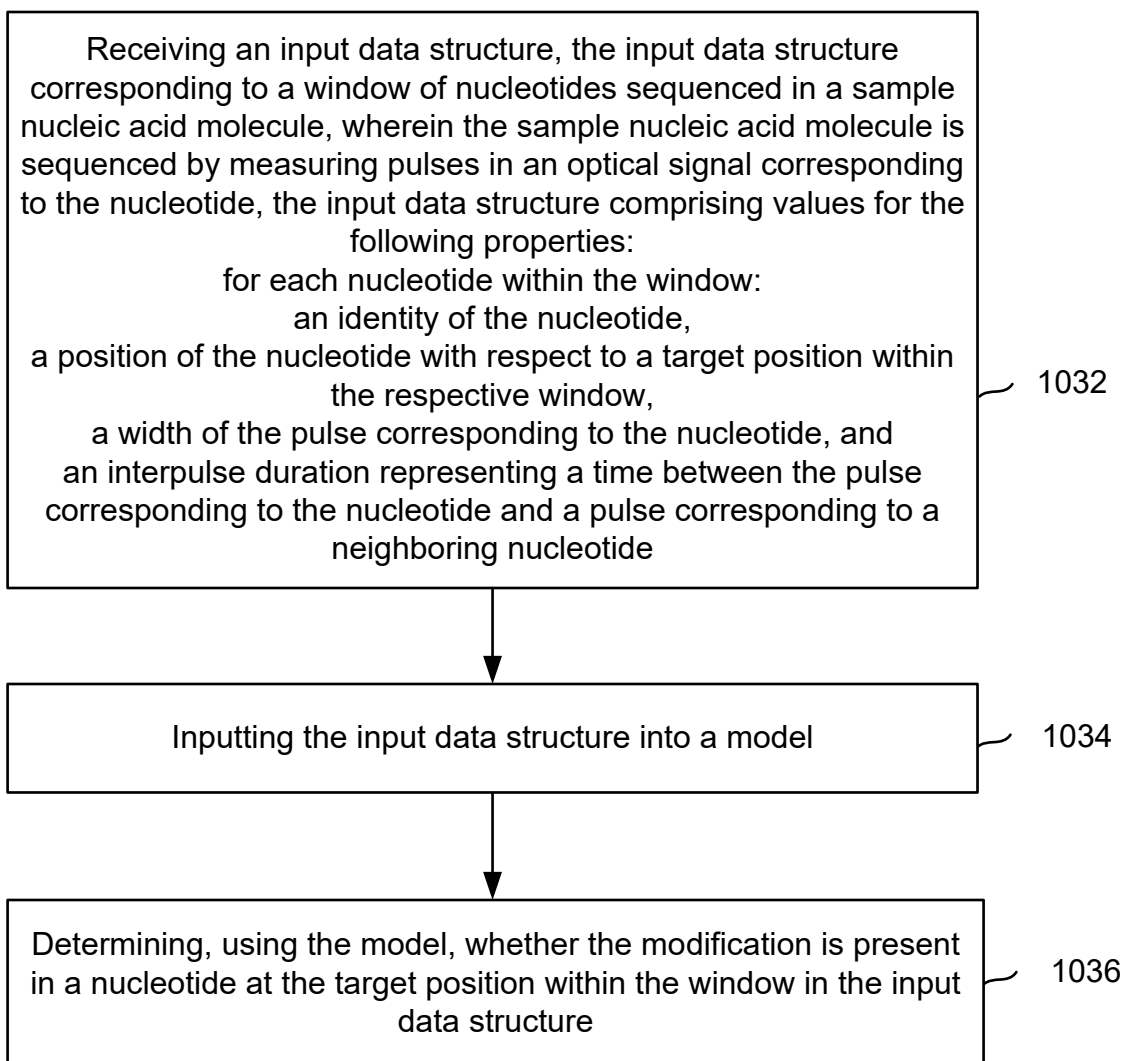
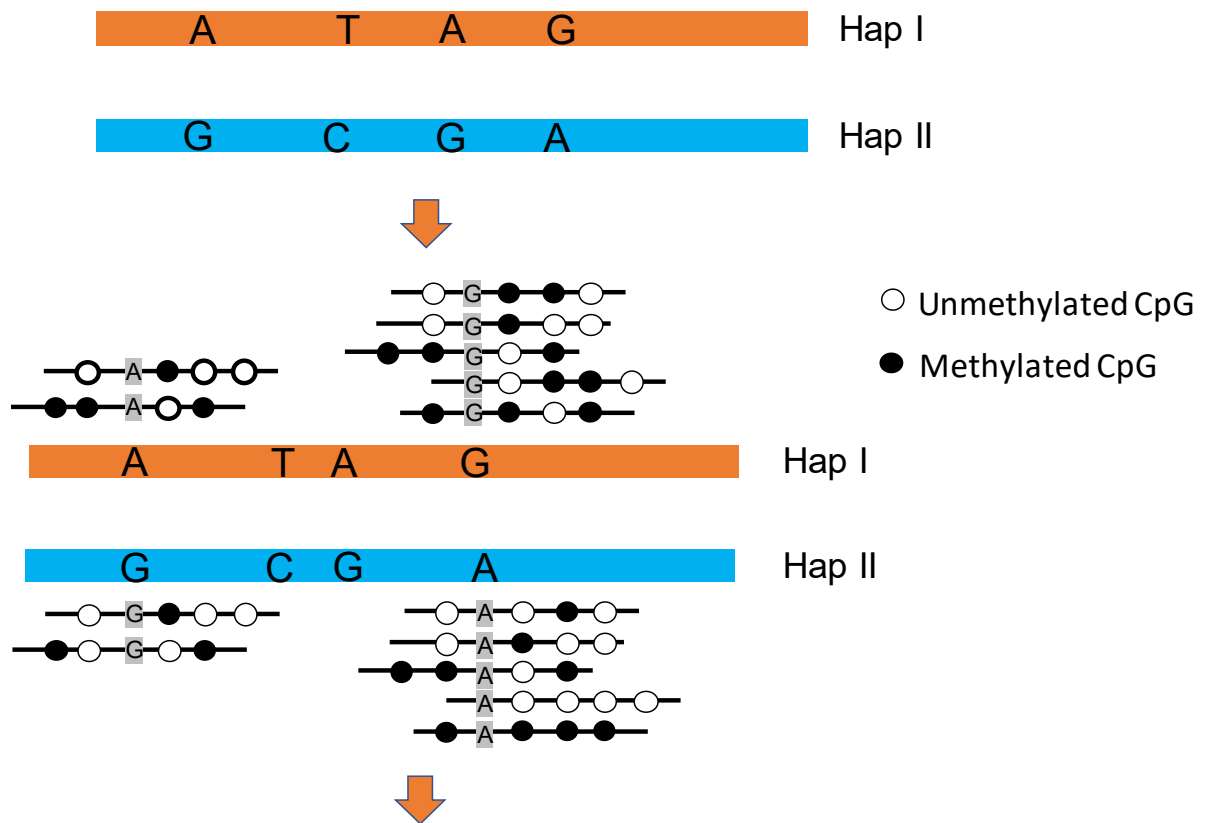


FIG. 103



Relative haplotype-based methylation imbalance index

e.g. Methylation level of Hap I – Methylation level of Hap II

FIG. 104

Sheet 116 of 145

Chr	start	end	Length	Haplotype block id	PacBio sequencing			
					Methylation level in adjacent non- tumoral tissue		Methylation level in tumor tissue	
					Hap I	Hap II	Hap I	Hap II
chr1	56312395	56347696	35301	hap1927	68.2	67.4	60.3	23.5
chr1	194413819	194424806	10987	hap5953	52.8	49.5	48.8	9.3
chr1	220674478	220699011	24533	hap6863	63.0	64.5	50.4	17.3
chr10	113088792	113124248	35456	hap11838	62.7	63.4	38.1	5.7
chr11	5482746	5498801	16055	hap12904	70.3	75.0	16.3	51.7
chr11	42819351	42852772	33421	hap14385	54.6	54.9	65.3	17.8
chr11	57983961	58051078	67117	hap14930	67.3	66.4	58.2	18.6
chr11	60174708	60204209	29501	hap14990	58.4	59.8	49.6	10.8
chr12	128079419	128114656	35237	hap22249	60.0	58.3	12.1	45.2
chr15	20480575	20533464	52889	hap29631	64.7	69.1	27.7	59.3
chr15	94902853	94946231	43378	hap32161	74.1	74.5	74.9	15.8
chr15	96526684	96549225	22541	hap32221	70.8	68.8	28.9	64.4
chr16	31595372	31613277	17905	hap33499	55.9	59.3	46.3	14.4
chr16	80151778	80182097	30319	hap34821	71.1	71.0	11.5	51.8
chr16	82519715	82554191	34476	hap34920	71.3	66.5	47.4	13.0
chr17	21668593	21685572	16979	hap36049	50.3	47.8	67.4	19.6
chr17	44999177	45012087	12910	hap36640	47.1	45.2	81.6	35.1
chr17	69911623	69926625	15002	hap37435	67.3	63.0	37.8	5.2
chr18	11441122	11458521	17399	hap38335	65.5	66.8	65.9	22.4
chr18	23405569	23423387	17818	hap38673	66.3	61.7	3.3	48.1
chr18	68887284	68925031	37747	hap40390	63.0	61.0	22.0	53.4
chr18	69487809	69505470	17661	hap40414	74.5	74.1	33.3	72.2
chr2	41480394	41514135	33741	hap43972	54.0	54.0	14.9	77.8
chr2	114171214	114182880	11666	hap46226	72.4	68.8	79.7	16.7
chr2	123762541	123797629	35088	hap46589	66.7	68.1	24.0	54.5
chr2	125236882	125241950	5068	hap46673	58.9	59.2	10.7	46.4
chr2	130016110	130040331	24221	hap46835	54.6	50.8	5.6	41.6
chr2	137757638	137783716	26078	hap47090	61.8	61.4	13.5	69.2
chr2	144128597	144160845	32248	hap47343	65.8	66.6	9.3	50.3
chr20	15736792	15753459	16667	hap51505	78.9	74.3	45.8	77.3
chr20	26167979	26177235	9256	hap51868	55.0	52.2	38.5	68.6
chr20	44255808	44264190	8382	hap52246	57.4	56.1	9.7	50.6
chr20	59518410	59559273	40863	hap52761	61.0	62.4	30.0	72.8
chr21	21402034	21424129	22095	hap53197	63.5	67.3	25.0	75.5
chr21	24750027	24768793	18766	hap53333	68.2	64.6	3.4	38.9
chr21	26666833	26701575	34742	hap53418	62.1	66.5	47.6	16.7
chr3	2364024	2387896	23872	hap55539	67.4	67.8	54.9	10.9
chr3	21036965	21049451	12486	hap56223	54.8	51.4	53.1	21.1
chr3	56011690	56046642	34952	hap57346	64.2	61.2	71.2	22.6

FIG. 105A

chr3	73330942	73371216	40274	hap57939	60.9	62.9	9.4	42.9
chr3	106372440	106401301	28861	hap59077	67.8	67.9	13.8	53.2
chr3	107772994	107807482	34488	hap59122	69.6	73.5	30.4	66.4
chr3	116742501	116776747	34246	hap59493	64.3	69.1	14.1	51.6
chr3	171076306	171100102	23796	hap61495	68.0	66.0	80.6	48.8
chr3	193058272	193080344	22072	hap62231	65.5	64.7	54.6	20.0
chr4	30411613	30432317	20704	hap63589	59.3	60.6	53.4	14.6
chr4	31304718	31338193	33475	hap63633	60.2	60.0	7.2	55.0
chr4	92003467	92030505	27038	hap65794	65.3	65.1	54.1	21.7
chr4	155224697	155250915	26218	hap68104	60.5	57.5	57.3	25.0
chr5	2281802	2299281	17479	hap69632	71.5	66.9	69.9	6.6
chr5	4624948	4664704	39756	hap69739	62.8	61.0	14.0	52.0
chr5	89593236	89606080	12844	hap72628	76.6	74.0	20.3	78.4
chr5	119214026	119233058	19032	hap73698	62.8	61.2	57.6	13.1
chr5	119940397	119972658	32261	hap73720	59.1	54.7	53.8	12.2
chr5	132859668	132877415	17747	hap74150	62.5	66.6	59.5	28.3
chr6	26914610	26936918	22308	hap76887	41.9	40.9	71.9	32.6
chr6	66879106	66957243	78137	hap78266	61.6	59.6	25.4	62.0
chr6	77349083	77377529	28446	hap78674	64.5	66.4	27.0	62.9
chr6	159738794	159751033	12239	hap81616	79.6	79.0	21.2	59.8
chr7	26585255	26641907	56652	hap83161	66.2	64.7	49.4	13.3
chr7	48214640	48248036	33396	hap84003	76.0	76.7	78.0	32.3
chr7	88558182	88575482	17300	hap85335	63.8	59.6	63.8	22.9
chr7	96588562	96607580	19018	hap85620	60.4	63.1	19.7	50.0
chr7	122942180	122956897	14717	hap86454	42.3	39.0	19.2	50.0
chr7	132321970	132344802	22832	hap86807	61.4	60.7	52.5	11.5
chr7	153296219	153302441	6222	hap87487	48.7	53.7	64.4	19.3
chr7	156356247	156371897	15650	hap87631	74.9	71.6	87.5	56.6
chr7	159091986	159119486	27500	hap87738	54.0	49.1	52.0	13.2
chr8	51530582	51550889	20307	hap89477	66.4	65.7	68.0	19.9
chr8	63513932	63537543	23611	hap89942	62.0	63.3	11.6	48.4
chr8	72373321	72398122	24801	hap90226	58.0	54.9	71.6	32.0
chr8	94100451	94141855	41404	hap90991	65.2	65.7	36.2	68.7
chr8	109300499	109326404	25905	hap91510	63.6	67.7	29.5	65.8

FIG. 105B

Chr	start	end	Length	Haplotype block id	PacBio sequencing			
					Methylation level in adjacent non- tumoral tissue		Methylation level in tumor tissue	
					Hap I	Hap II	Hap I	Hap II
chr9	27803548	27888202	84654	hap58508	64.2	60.9	20.6	75.4
chr6	242149	386636	144487	hap47880	62.3	63.3	77.4	32.2
chr5	28219159	28302858	83699	hap44666	59.3	58.0	16.8	58.2
chr5	18119943	18153743	33800	hap44475	61.6	65.0	53.2	21.7
chr7	24906307	25046195	139888	hap52069	69.3	68.7	44.0	76.2
chr15	27689897	27752573	62676	hap18337	65.9	61.9	64.8	20.5
chr12	42183870	42212433	28563	hap12045	63.5	68.4	19.4	51.2
chr21	9825597	9935752	110155	hap34175	54.3	53.5	60.9	29.1
chr2	118813055	118893366	80311	hap30060	62.6	62.3	77.0	38.6
chr6	90307702	90344869	37167	hap49779	69.1	66.4	84.7	53.9
chr7	107932914	108049376	116462	hap53838	67.2	62.9	43.8	76.4
chr7	137039327	137160933	121606	hap54447	59.5	60.9	22.9	72.0
chr17	21193754	21254930	61176	hap22633	59.2	54.3	69.7	31.6
chr12	11473697	11644714	171017	hap11451	62.8	66.4	35.5	75.9
chr5	129212299	129353349	141050	hap46632	50.9	54.5	45.5	14.0
chr11	93910738	94028887	118149	hap10288	67.6	63.6	36.6	74.2
chr3	131707434	132003636	296202	hap38642	57.8	55.9	17.9	60.2
chr3	43024004	43161785	137781	hap36769	69.1	66.5	46.1	80.2
chr3	190403156	190606658	203502	hap39947	60.9	61.6	36.9	72.7
chr15	40218970	40279780	60810	hap18606	53.4	57.5	79.1	47.4

FIG. 106

Tissue types	No. of haplotype blocks showing methylation imbalance between two haplotypes in tumor tissues	No. of haplotype blocks showing methylation imbalance between two haplotypes in paired adjacent non-tumoral tissues
Colon	92	47
Breast	57	13
Kidney	68	18
Lung	31	21
Prostate	26	19
Stomach	2	0

FIG. 107A

Tissue types	No. of haplotype blocks showing methylation imbalance between two haplotypes in tumor tissues	Tumor Staging information (TNM) available
Breast	18	T2
	57	T3
Kidney	68	T3a
	0	T2

FIG. 107B

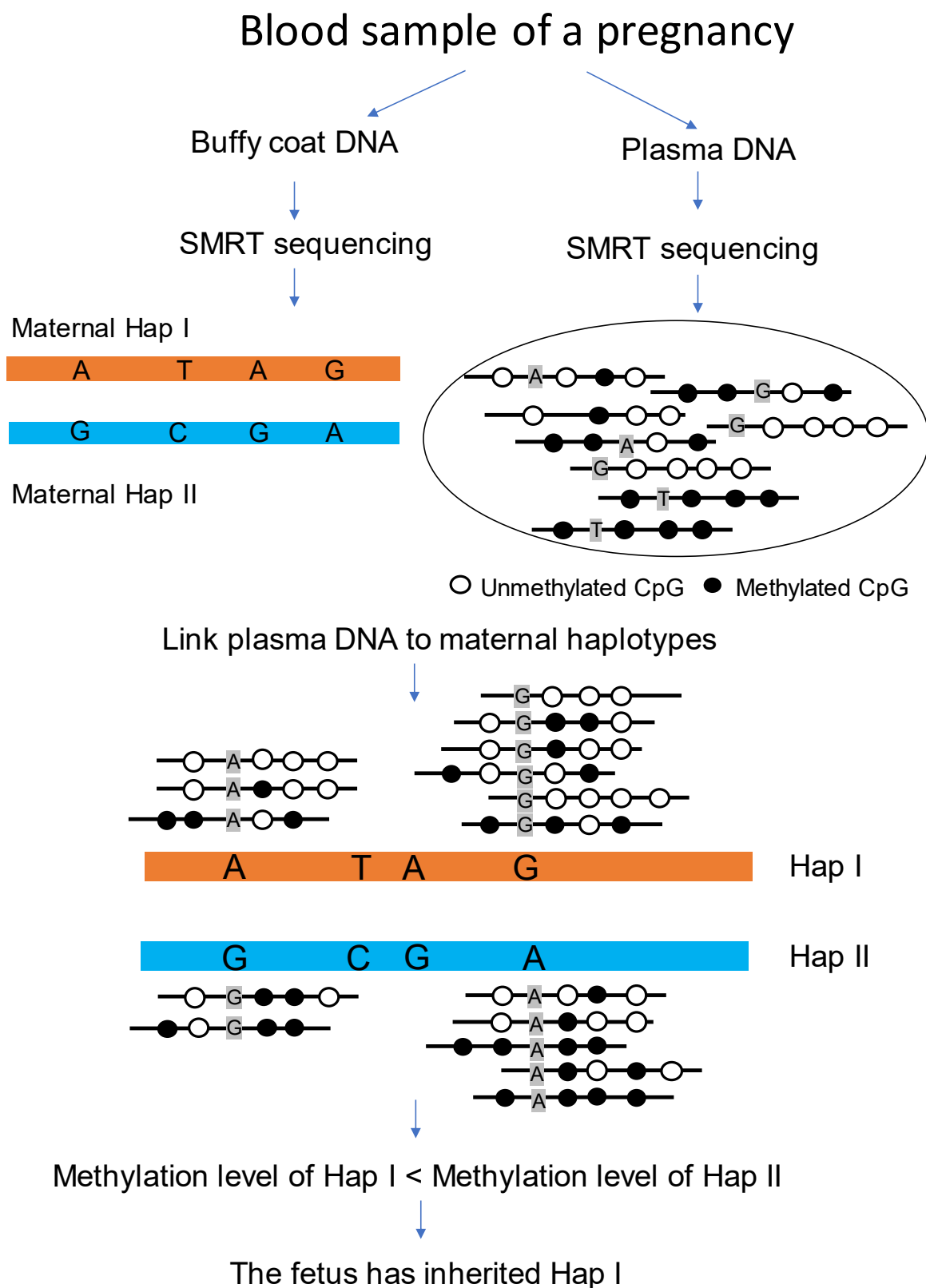


FIG. 108

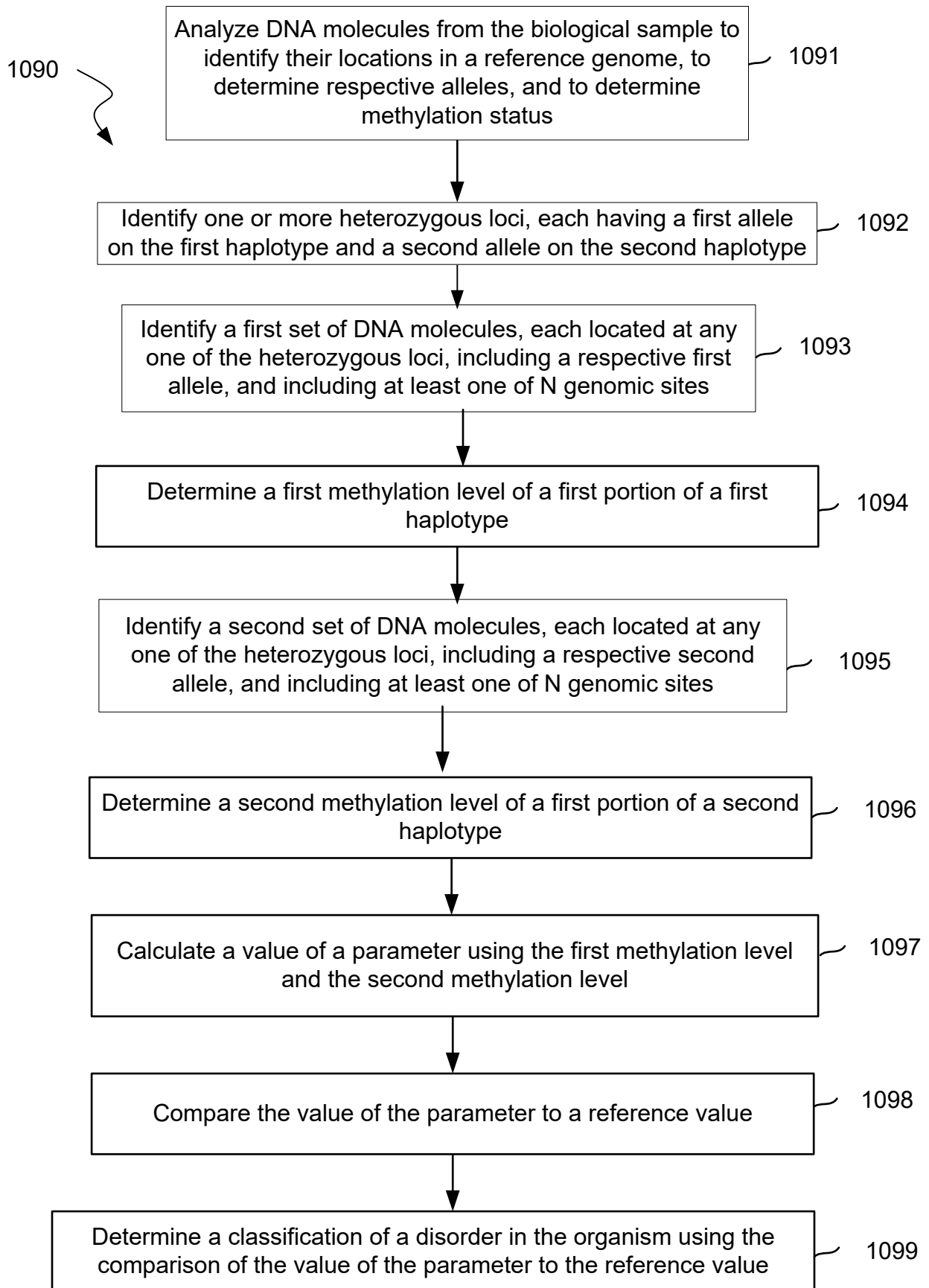


FIG. 109

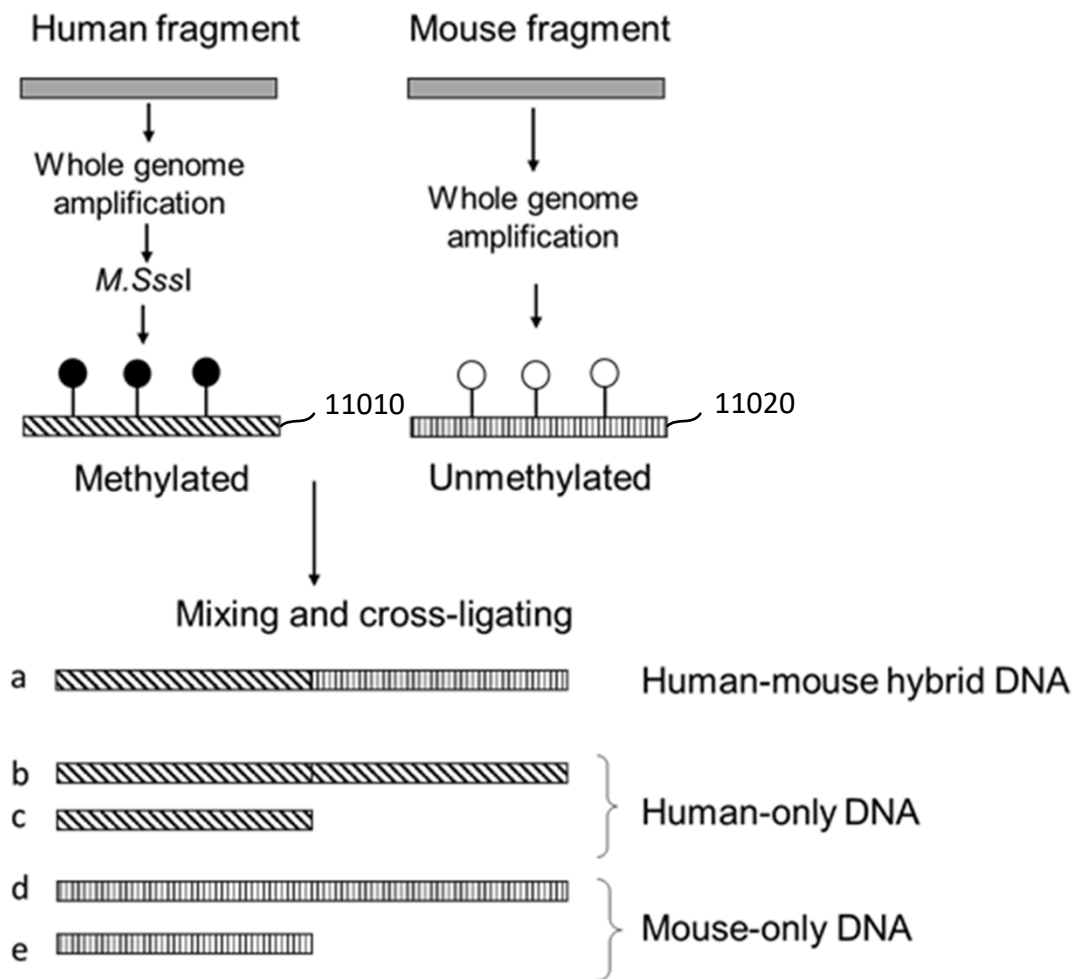


FIG. 110

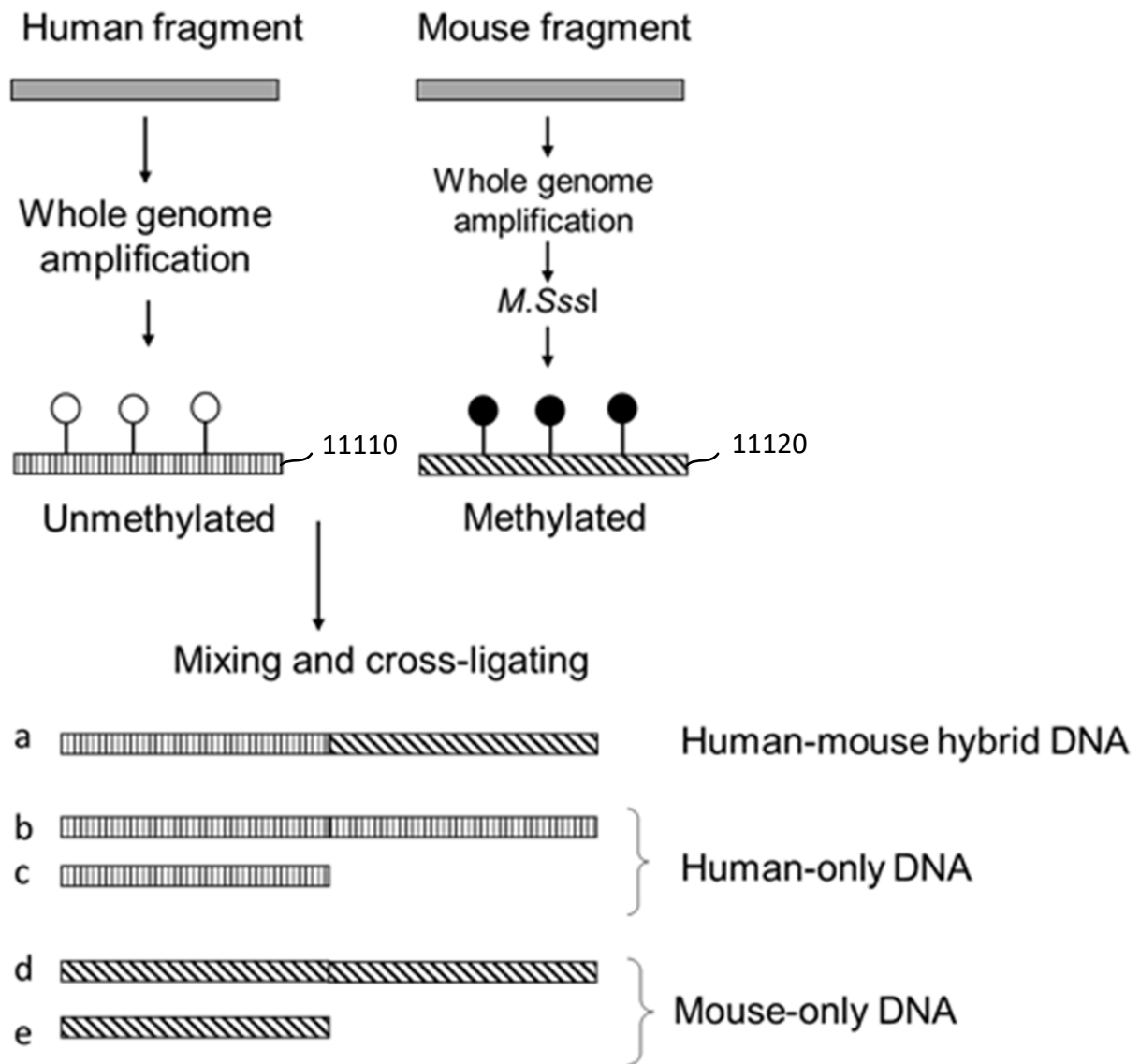


FIG. 111

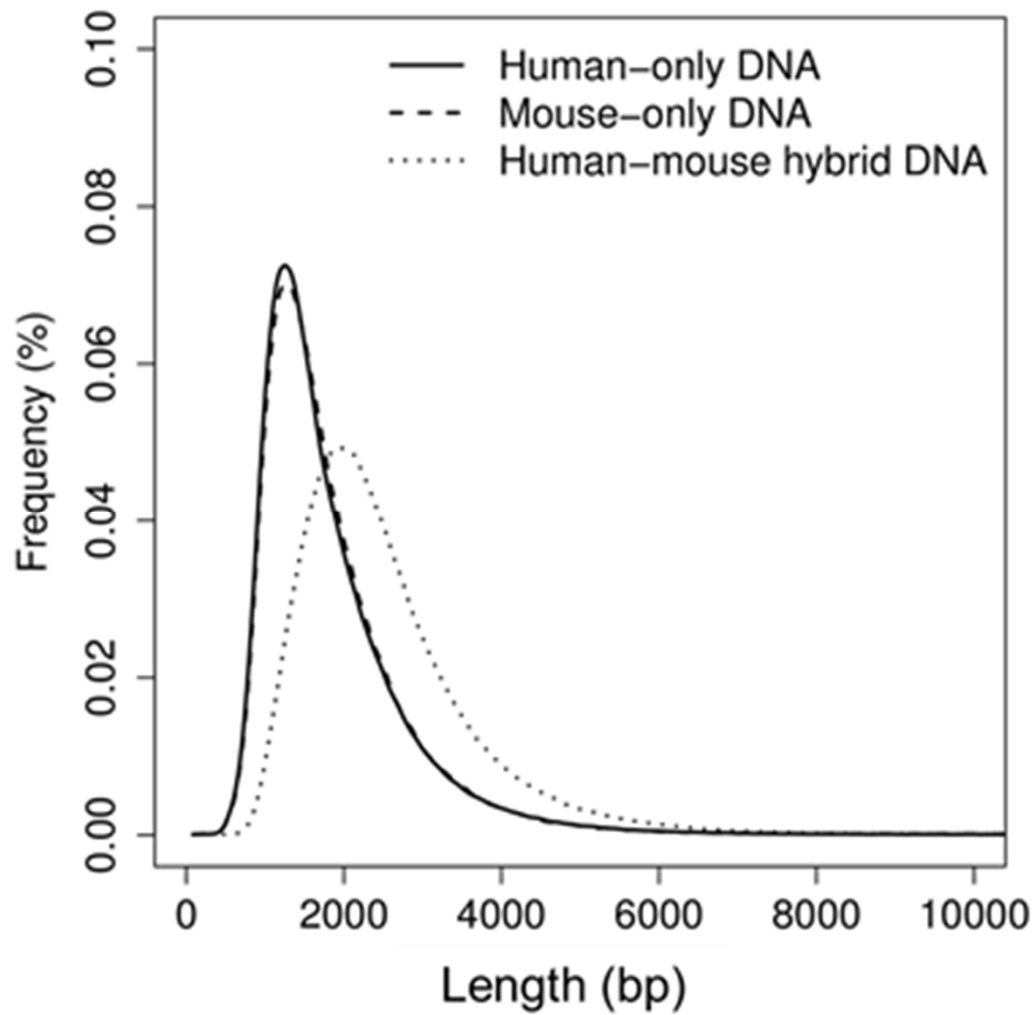


FIG. 112

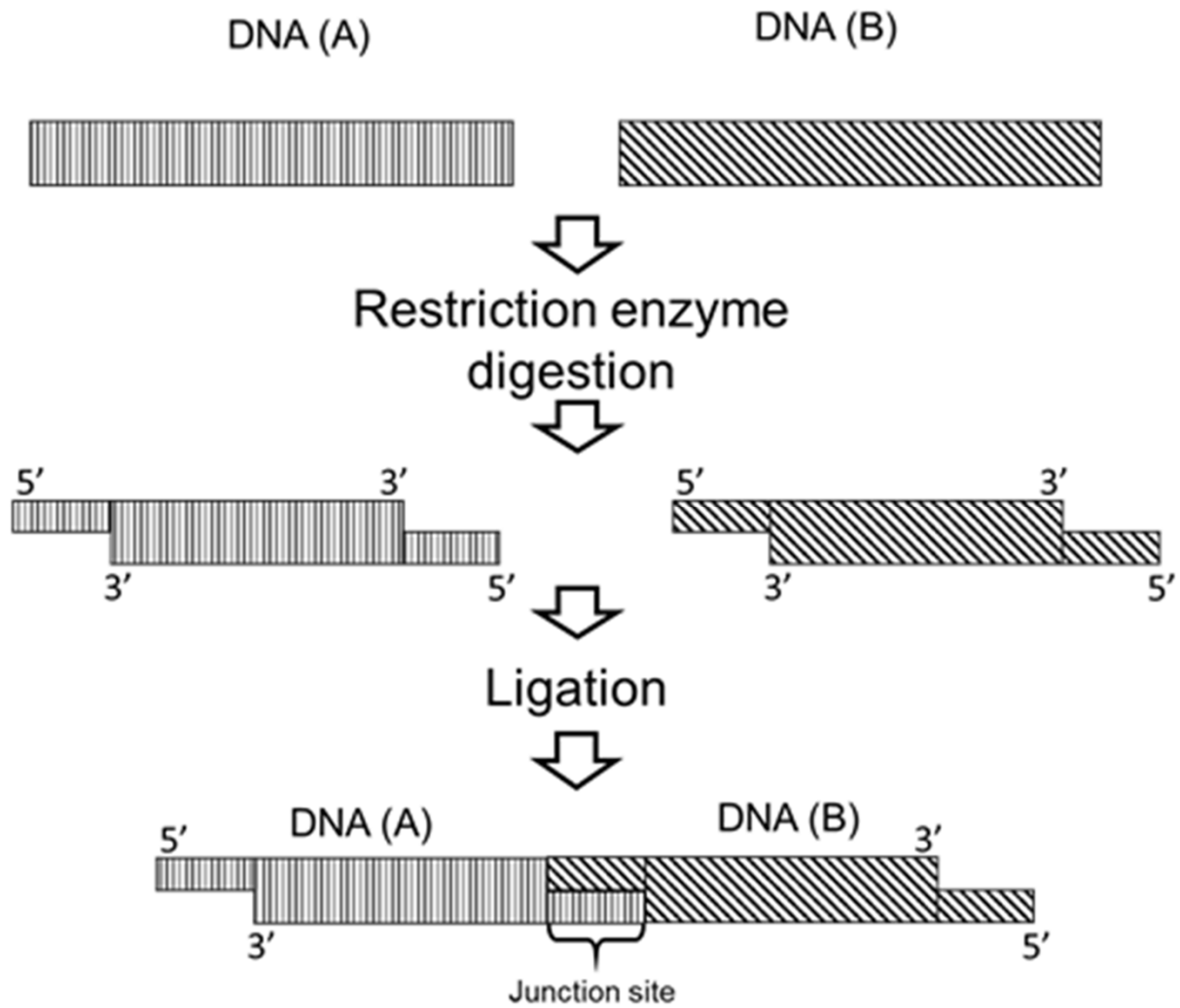


FIG. 113

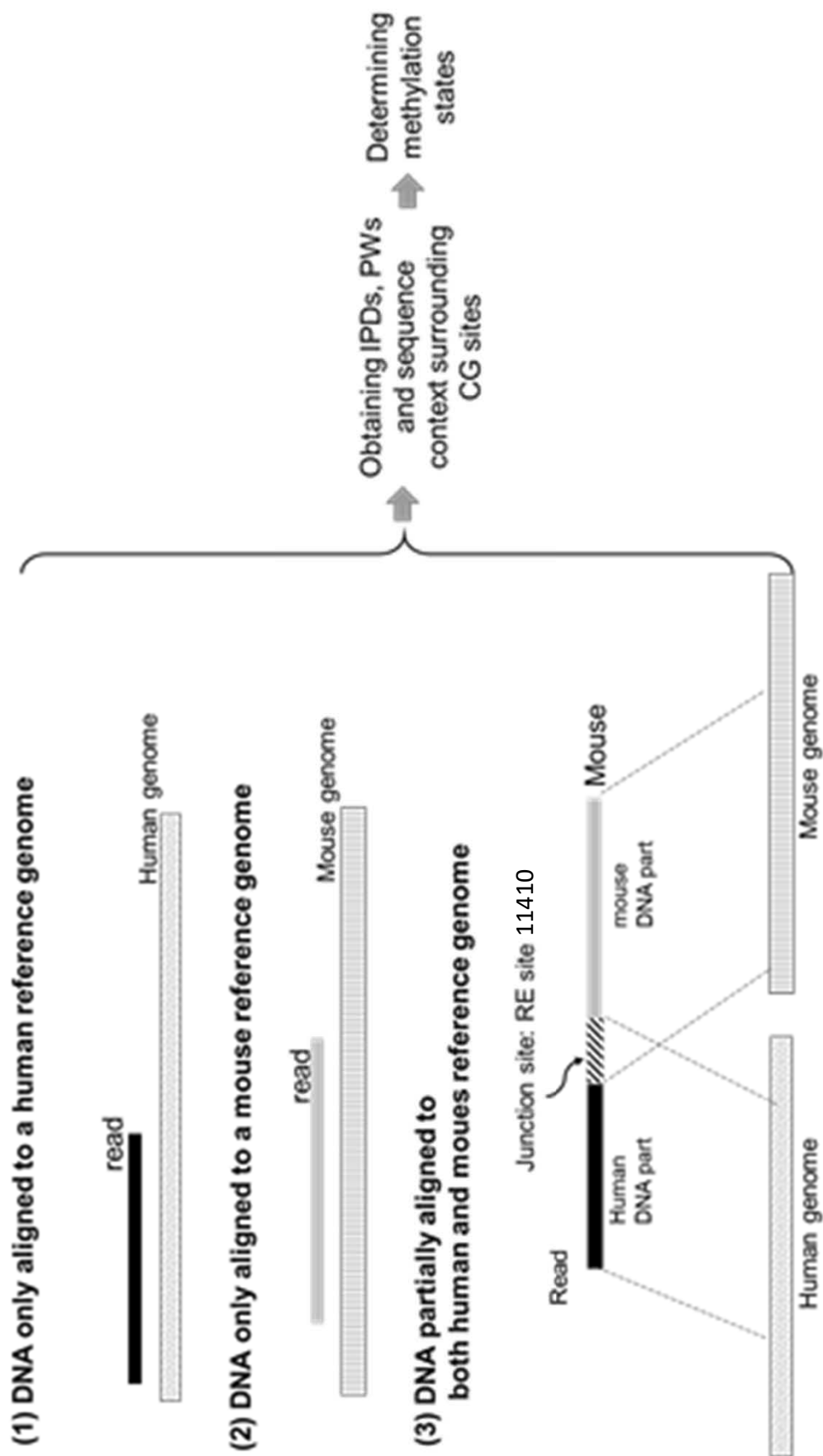


FIG. 114

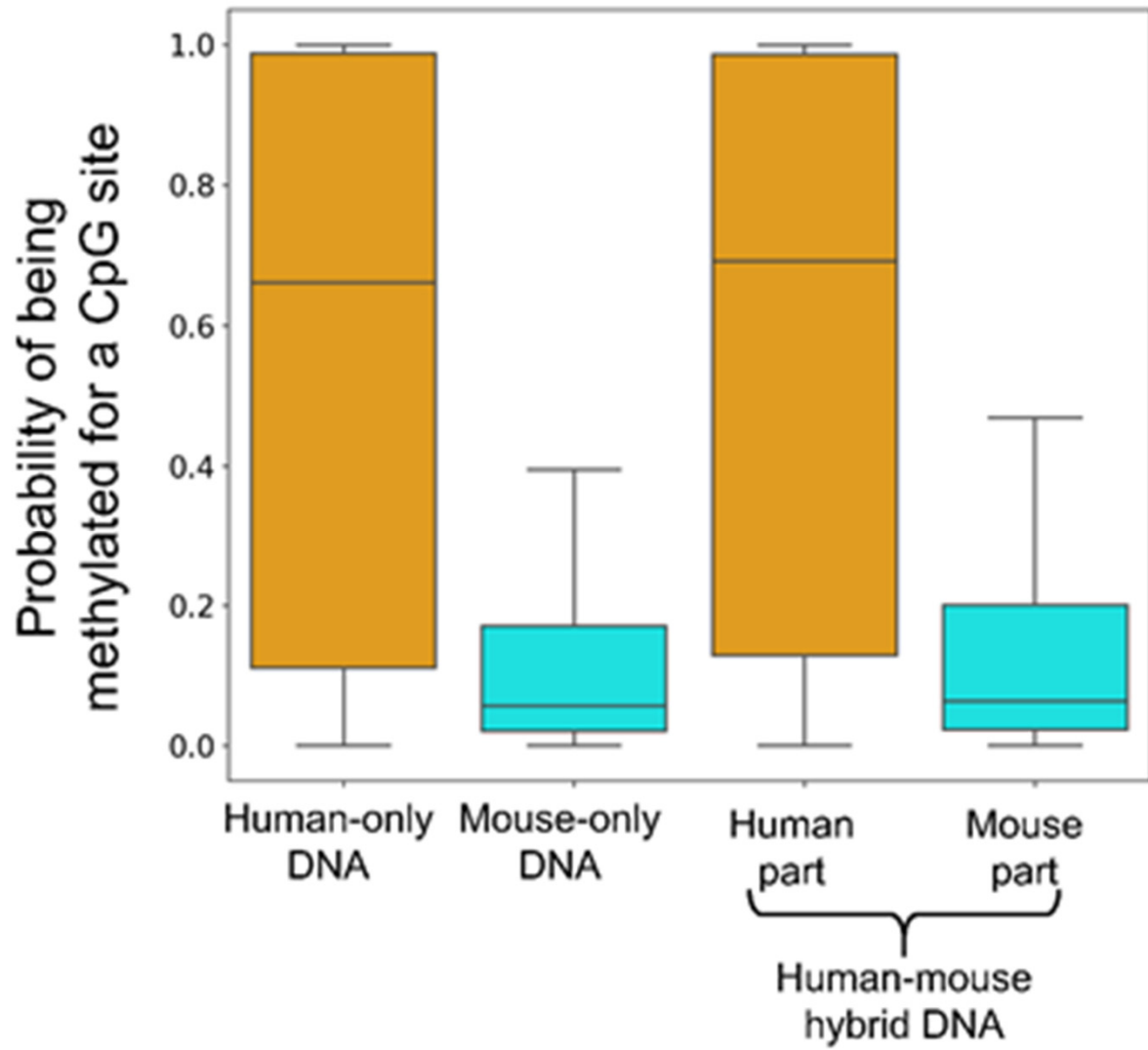


FIG. 115

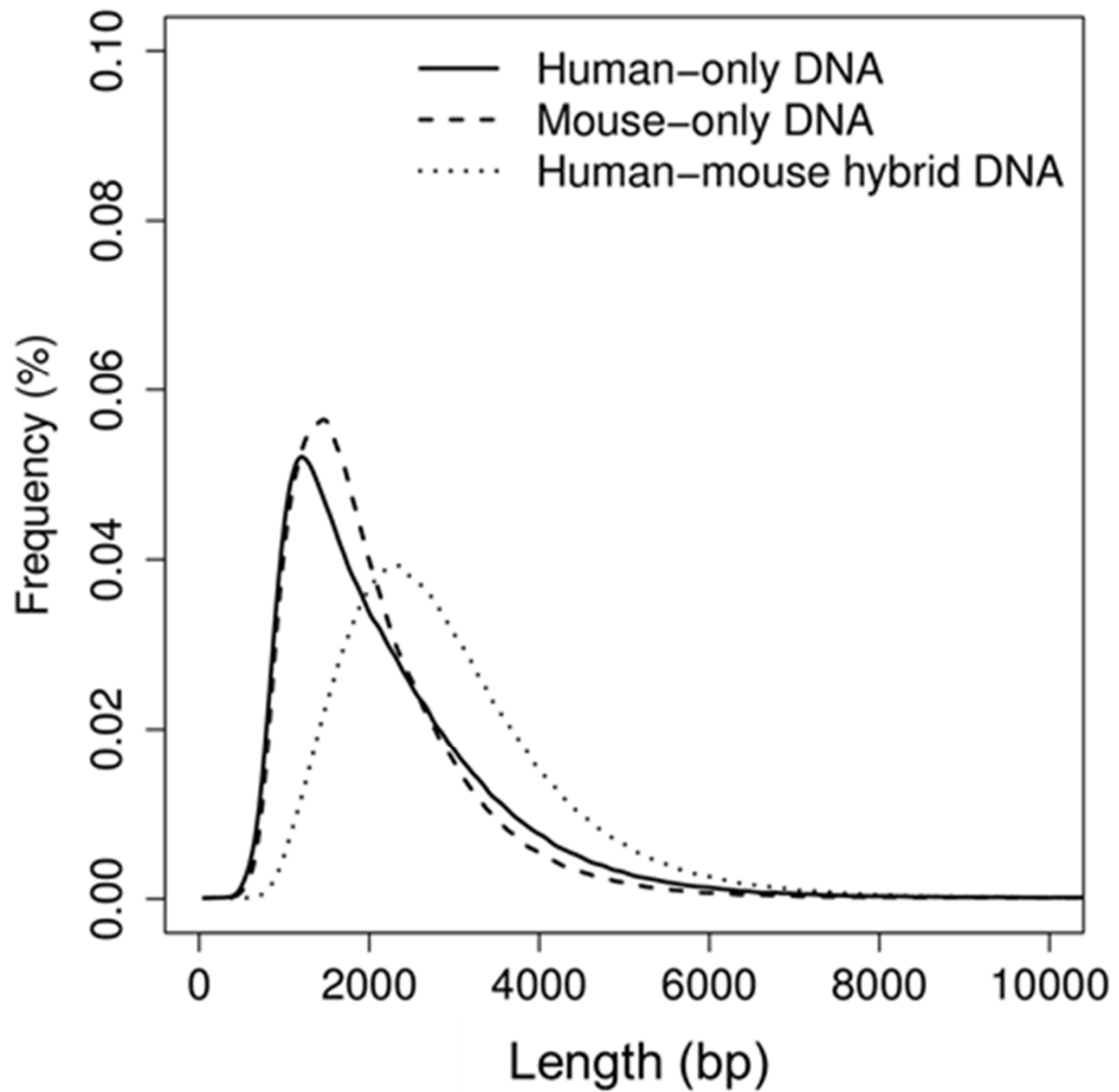


FIG. 116

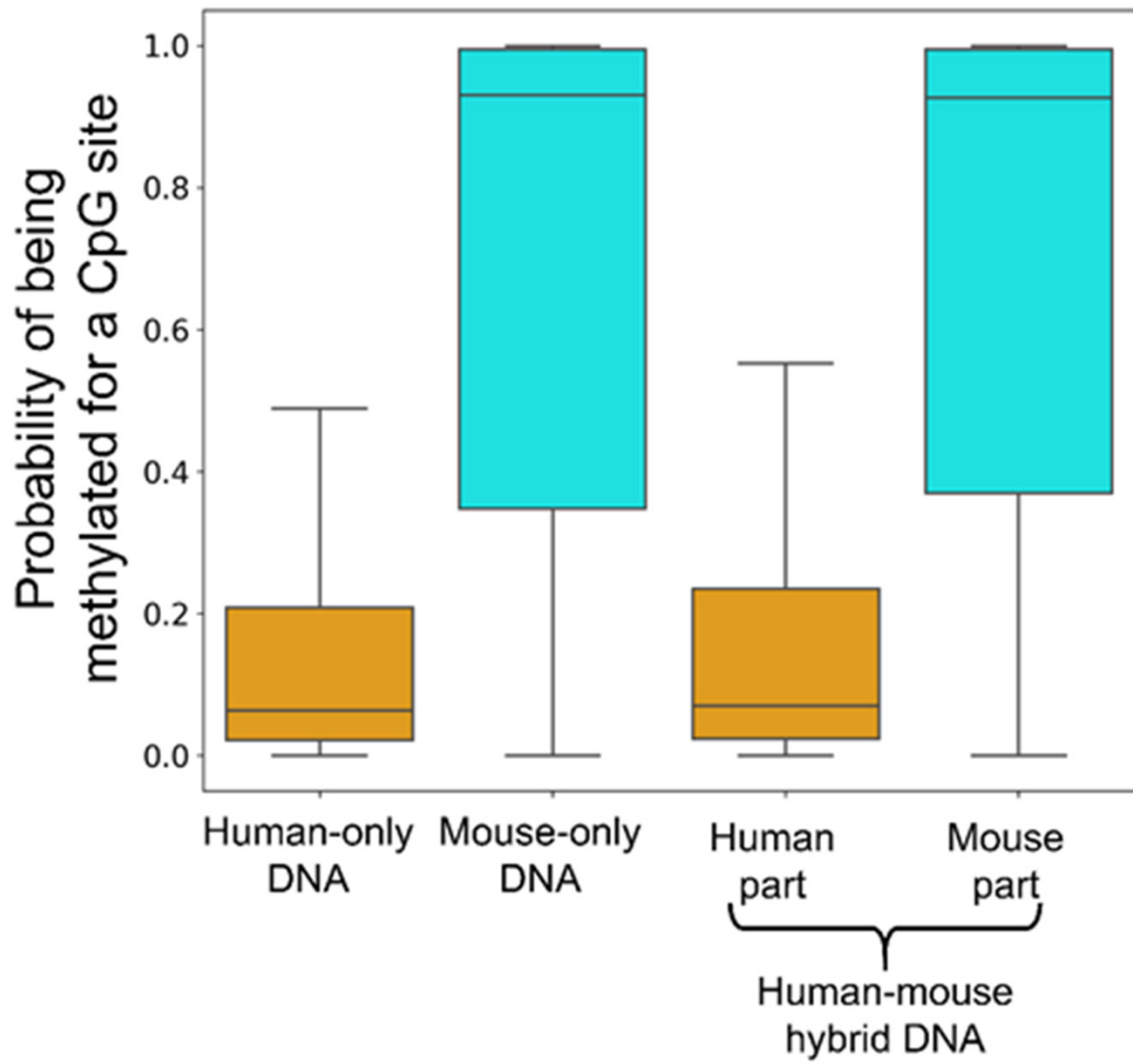


FIG. 117

	Bisulfite sequencing		PacBio sequencing	
	No. of CG sites	Methylation density (%)	No. of CG sites	Methylation density (%)
1) Human-only	2,230,407	41.4	16,226,014	56.0
2) Mouse-only	2,726,499	1.6	9,398,340	10.7
3) Human-mouse hybrid DNA	Human part	46.8	4,838,454	57.4
	Mouse part	2.3	4,385,046	12.1

FIG. 118

	Bisulfite sequencing		PacBio sequencing	
	No. of CG sites	Methylation density (%)	No. of CG sites	Methylation density (%)
1) Human-only	2,938,088	1.6	14,503,548	11.6
2) Mouse-only	1,513,971	62.4	11,348,555	71.5
3) Human-mouse hybrid DNA	Human part	1.8	5,824,379	13.1
	Mouse part	67.4	5,093,097	72.2

FIG. 119

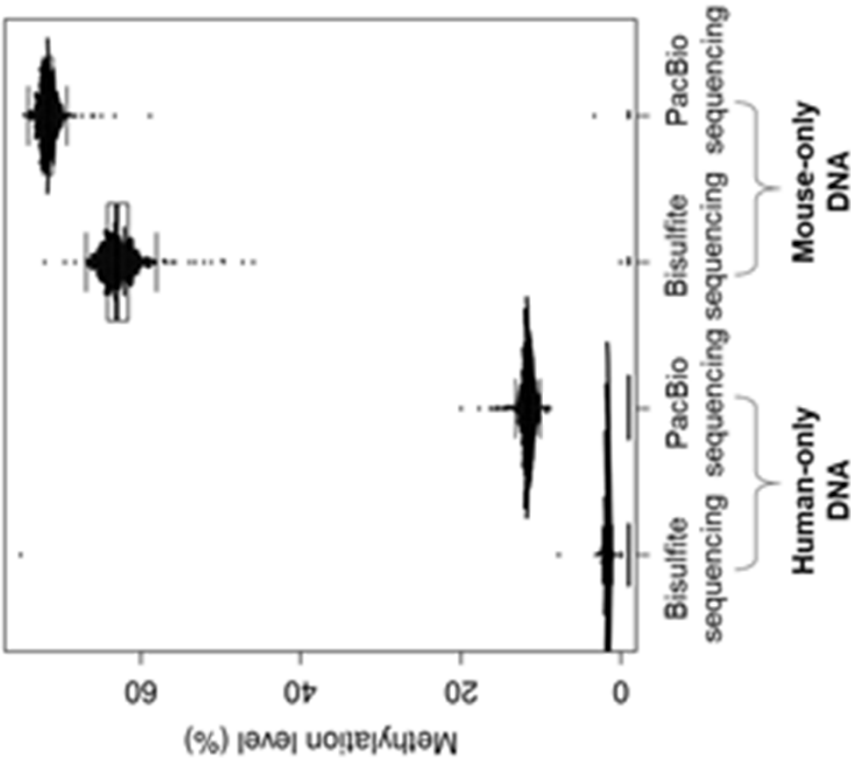


FIG. 120A

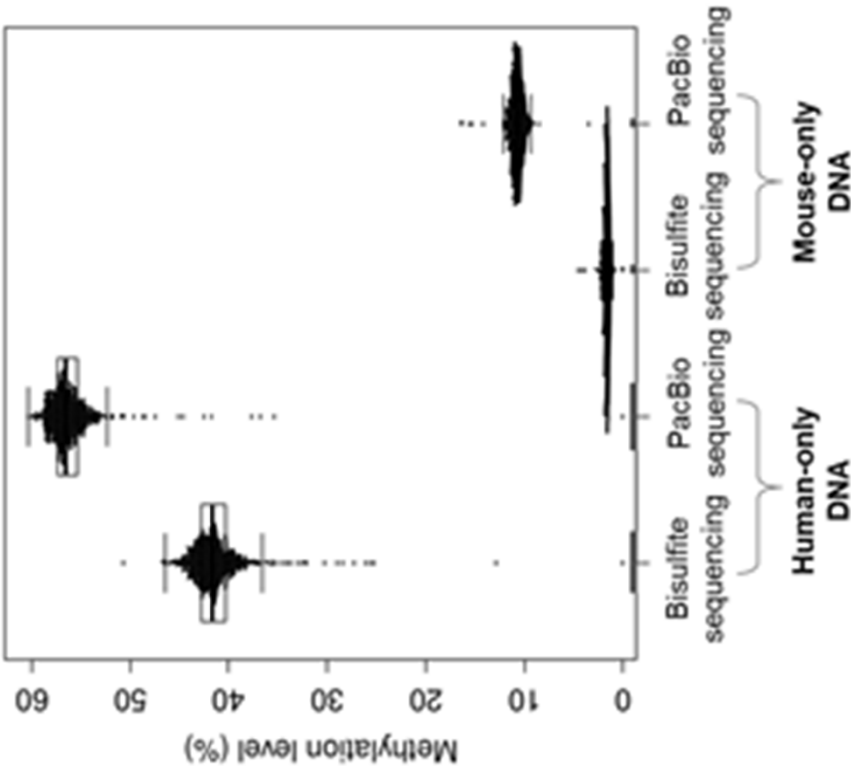


FIG. 120B

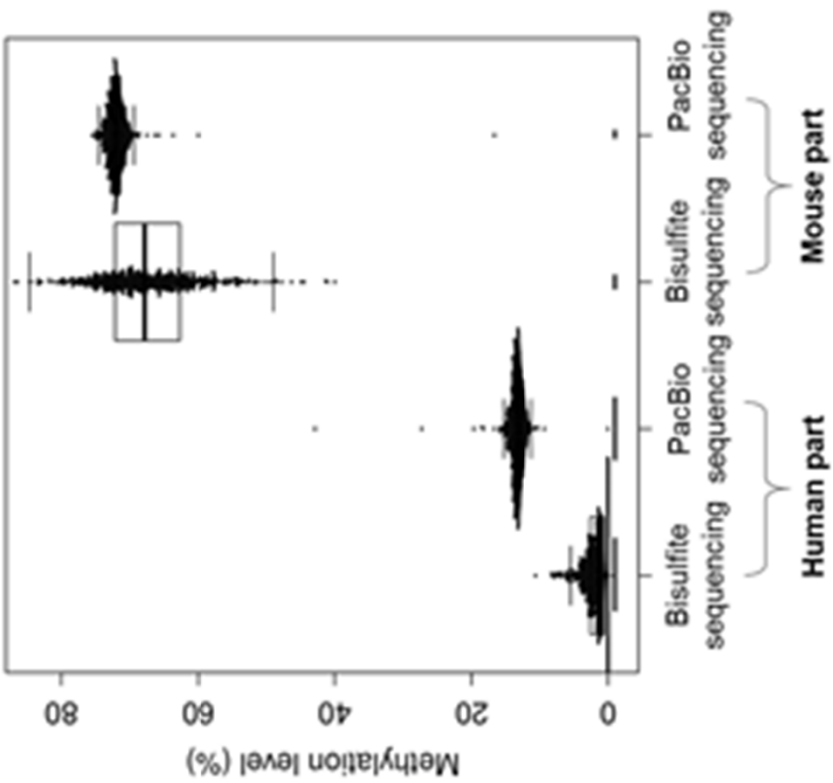


FIG. 121A

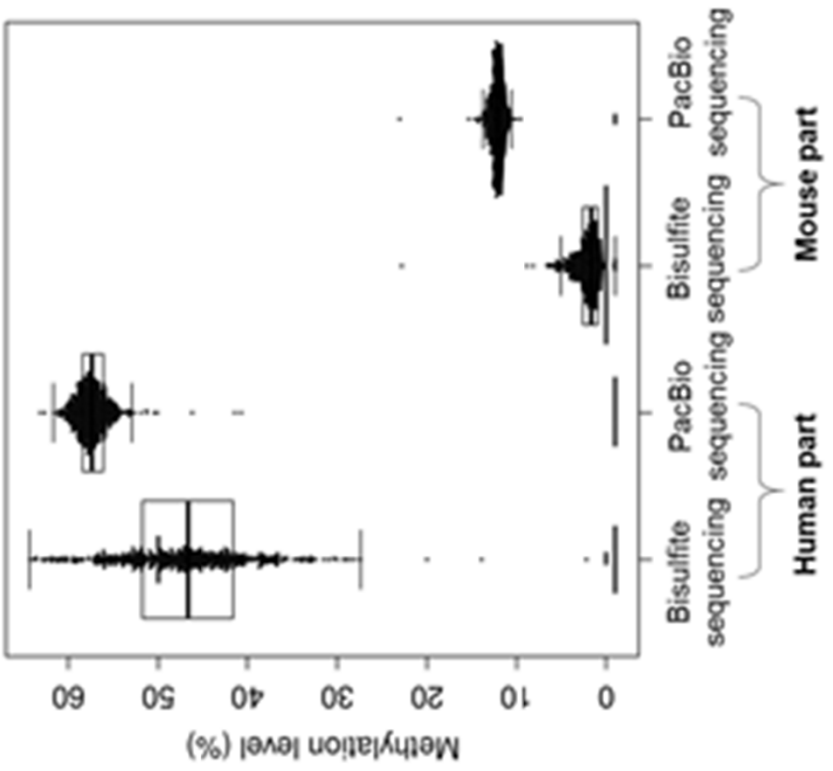


FIG. 121B

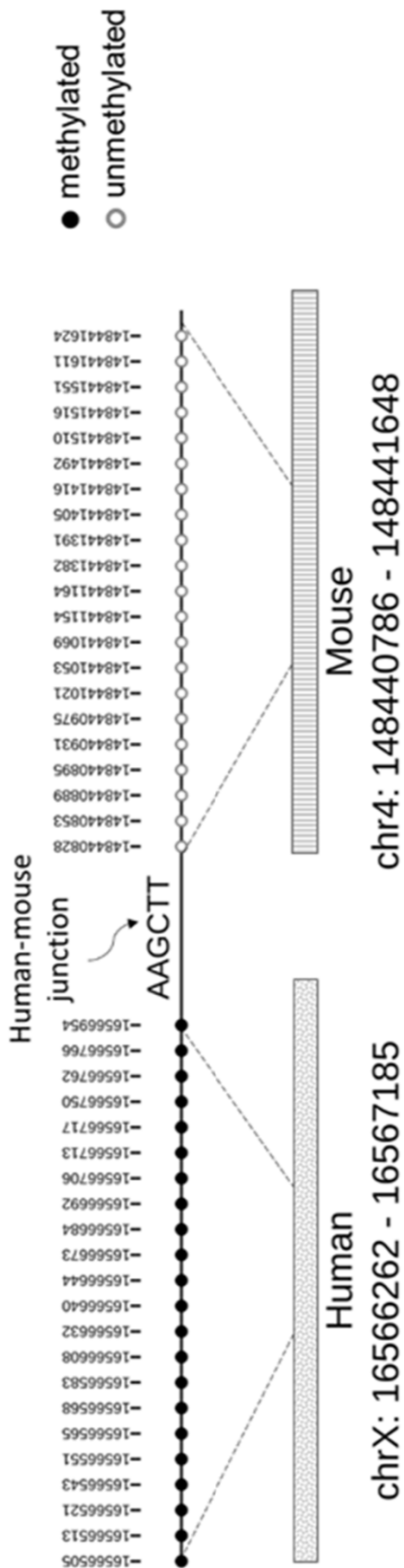


FIG. 122A

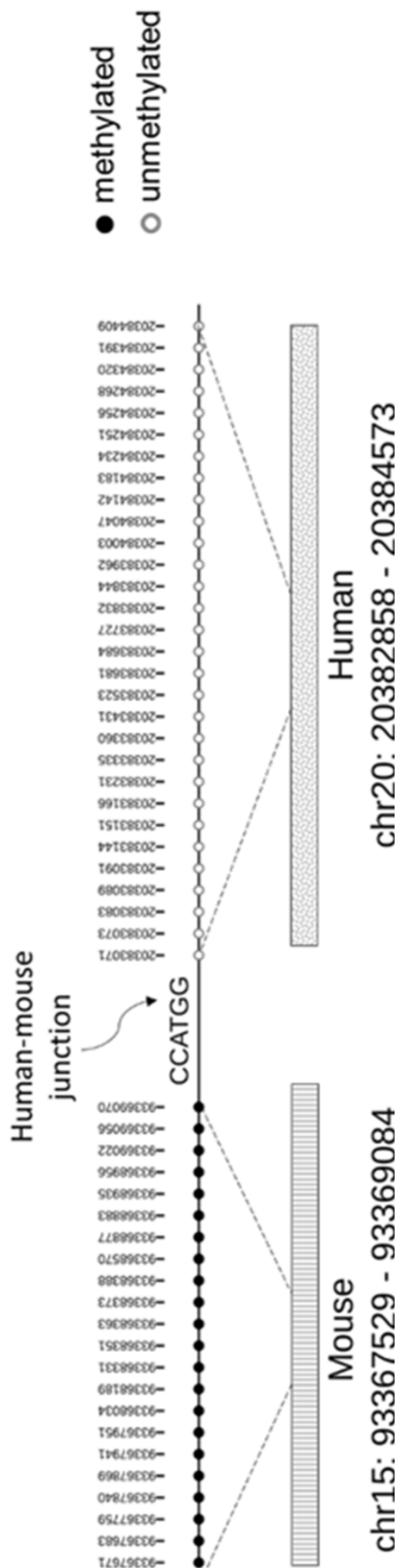


FIG. 122B

1230

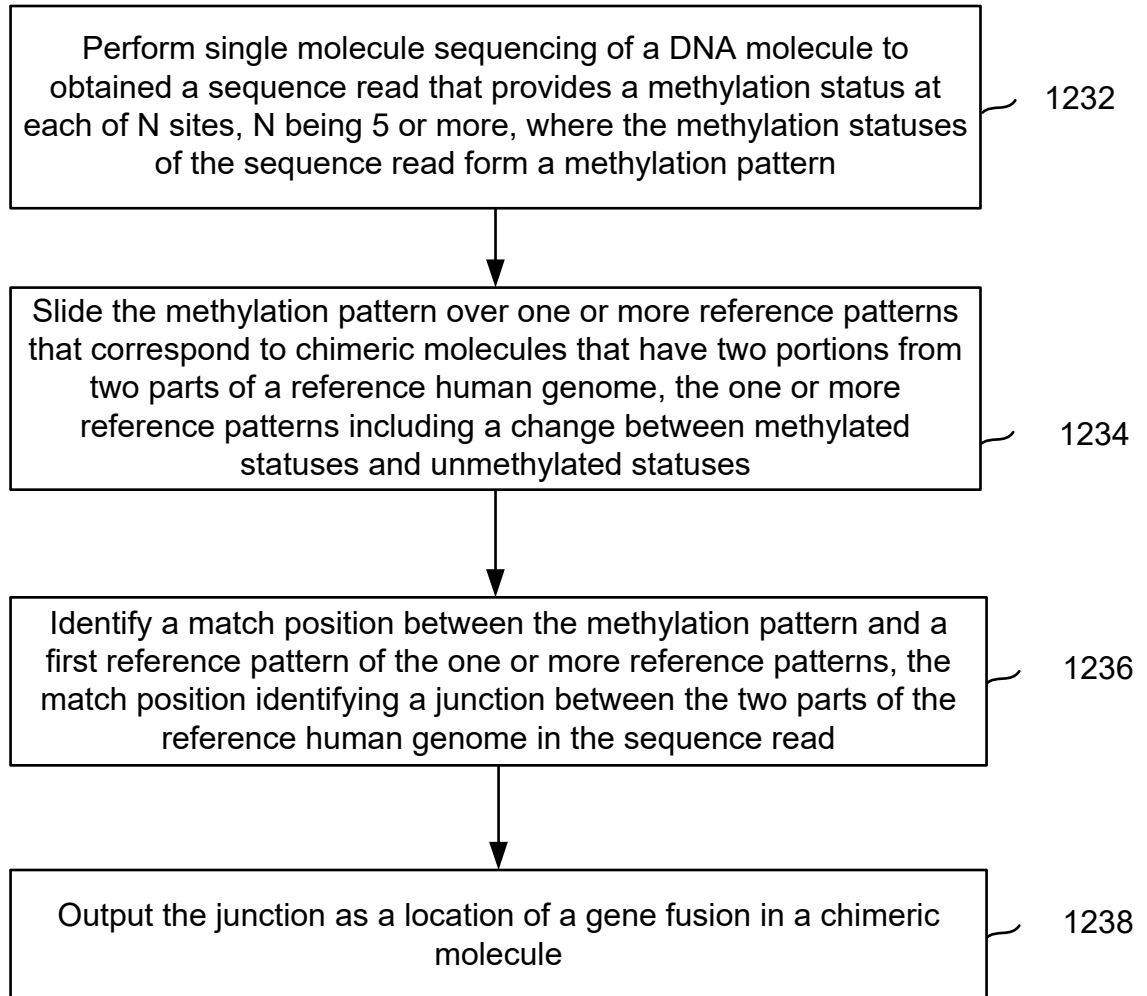


FIG. 123

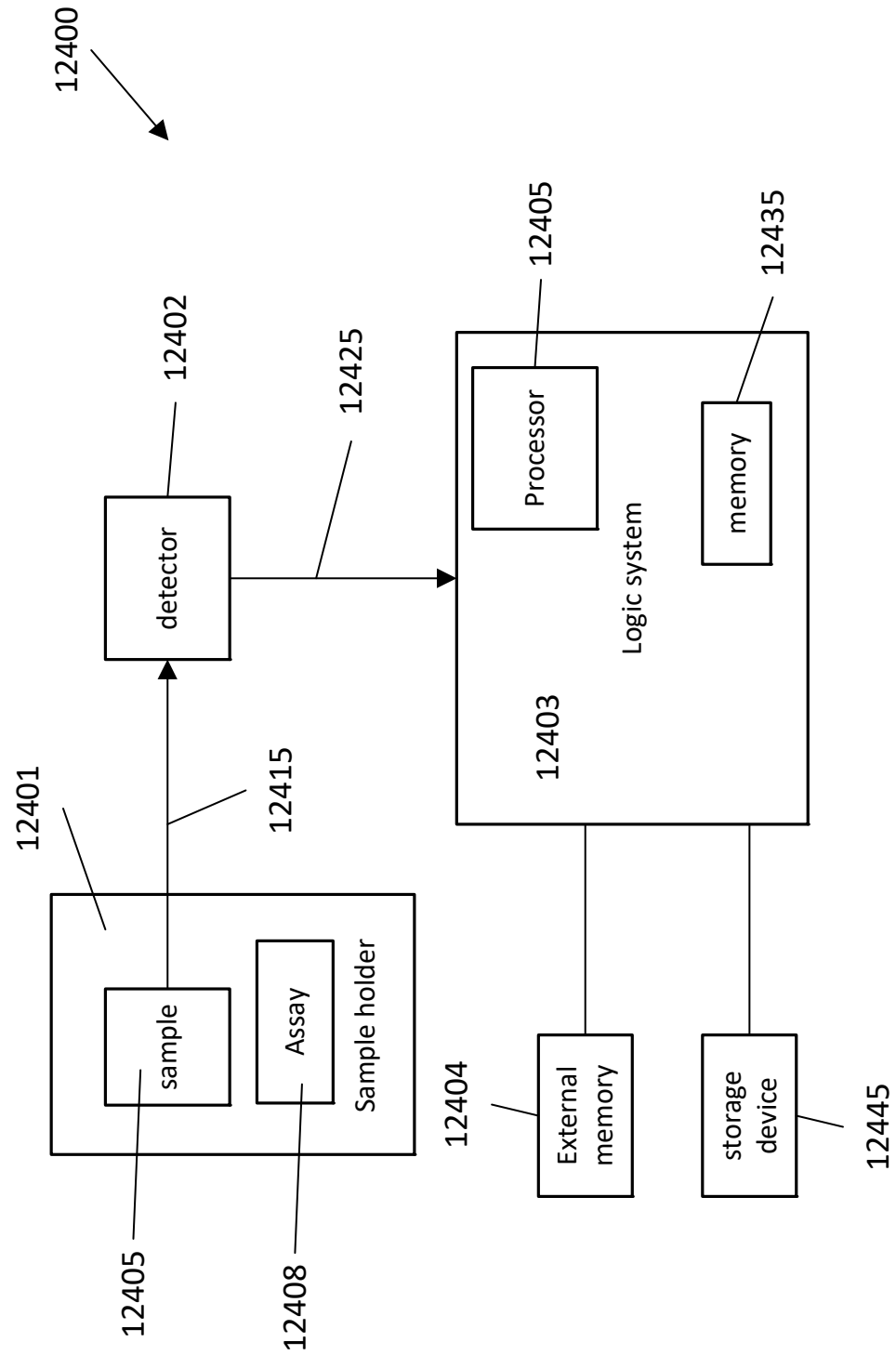


FIG. 124

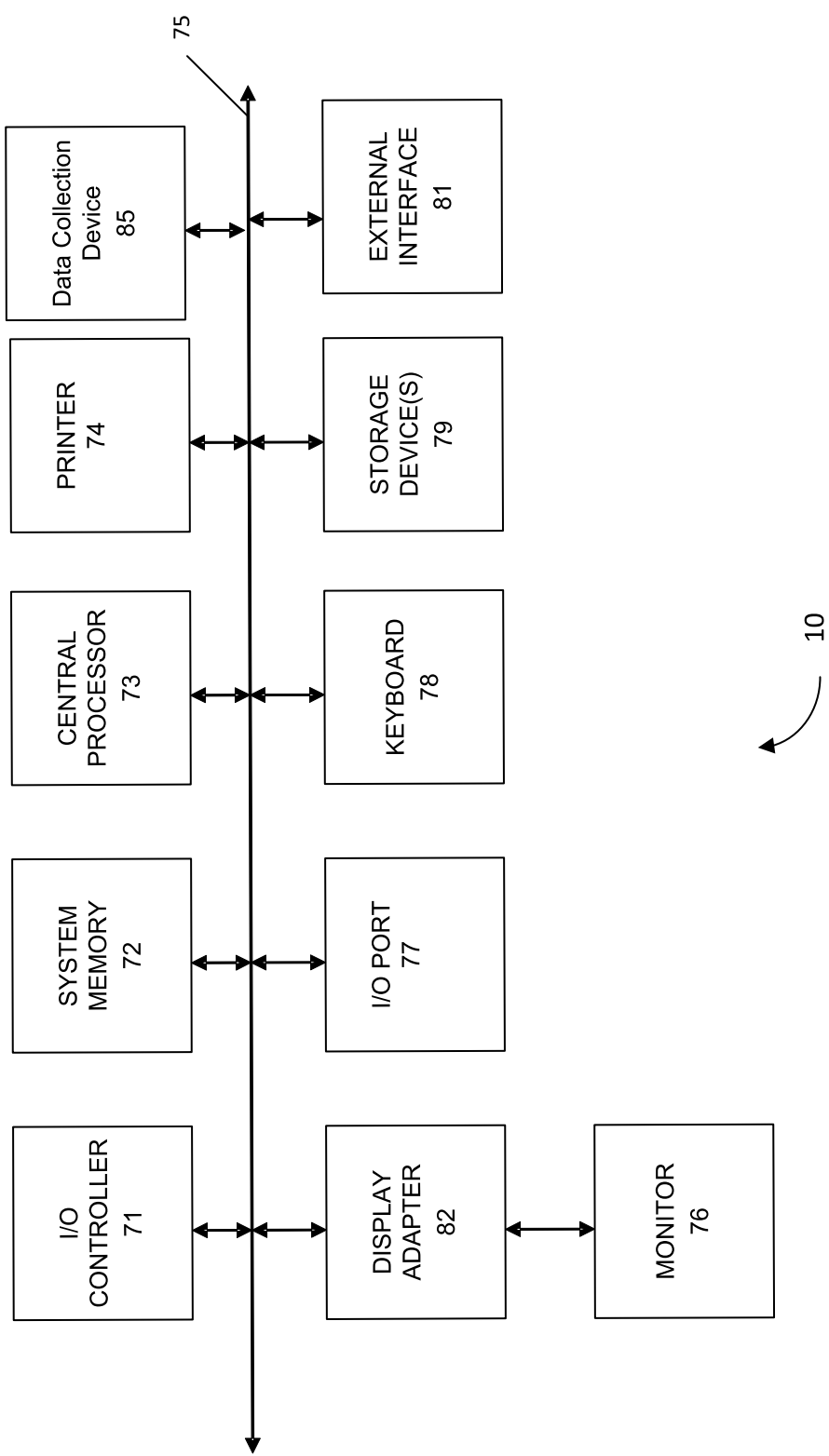


FIG. 125

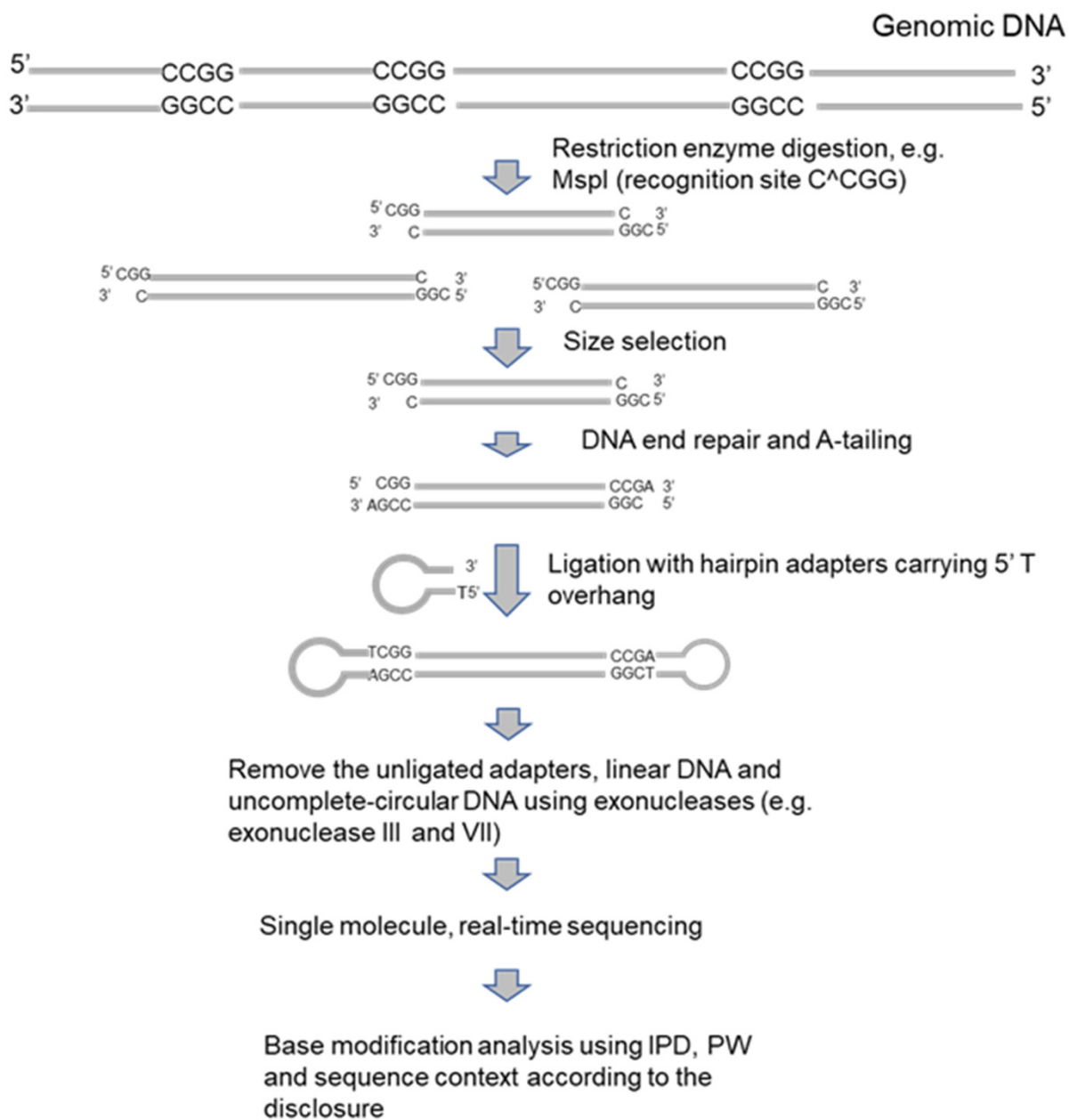


FIG. 126

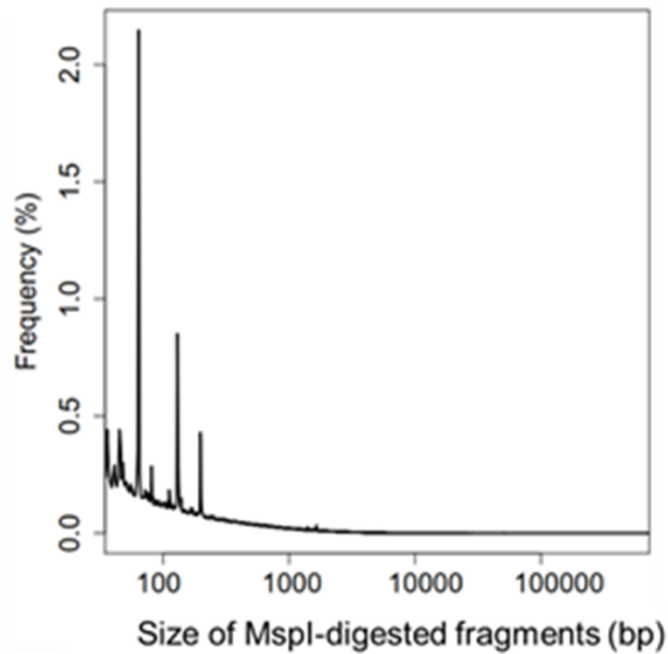


FIG. 127A

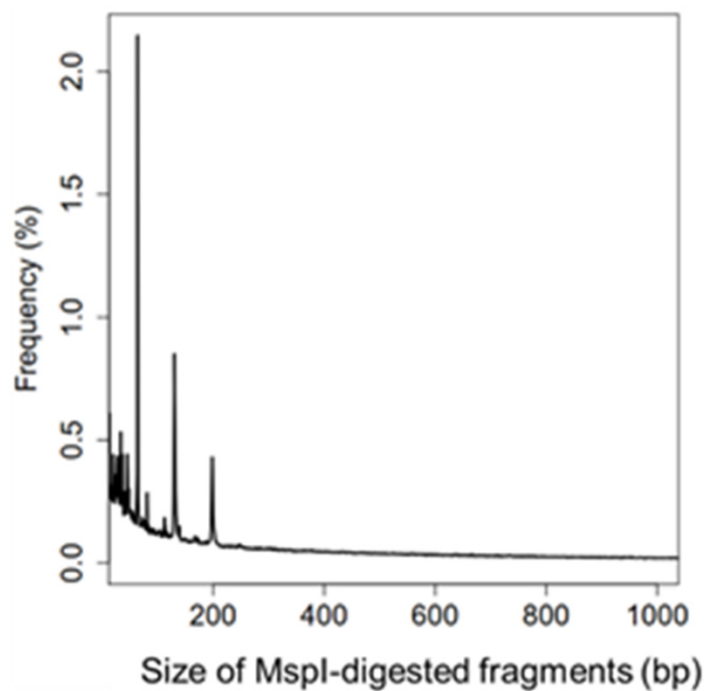


FIG. 127B

Size ranges (bp)	No. of molecules	Percentage of molecules within a size range relative to total fragments (%)	No. of molecules within a size range overlapping CpG islands	Percentage of molecules within a size range overlapping CpG islands (%)	No. of CpG sites being sequenced	No. of CpG sites falling within CpG islands	Percentage of CpG sites targeted by size selection and falling within CpG islands (%)
50-200	526,543	23.03	104,059	19.76	2,358,020	885,041	37.53
200-400	269,562	11.79	23,927	8.88	1,781,556	353,087	19.82
400-600	177,776	7.77	7,369	4.15	1,468,561	107,130	7.29
600-800	133,927	5.86	3,673	2.74	1,326,544	48,851	3.68
800-1000	104,976	4.59	2,168	2.07	1,193,233	25,821	2.16
1000-2000	311,596	13.63	4,596	1.47	4,610,504	58,288	1.26
2000-3000	149,468	6.54	1,771	1.18	3,036,951	25,106	0.83
3000-4000	86,760	3.79	809	0.93	2,165,171	10,785	0.50
5000-6000	36,931	1.62	266	0.72	1,242,712	3,412	0.27
6000-7000	25,027	1.09	202	0.81	947,874	3,354	0.35
7000-8000	17,597	0.77	86	0.49	736,830	791	0.11
8000-9000	12,658	0.55	76	0.60	583,680	993	0.17
9000-10000	9,184	0.40	48	0.52	461,935	591	0.13
10000-15000	20,790	0.91	97	0.47	1,255,731	2,003	0.16
15000-20000	5,111	0.22	16	0.31	414,400	163	0.04
20000-25000	1,441	0.06	6	0.42	147,731	34	0.02

FIG. 128

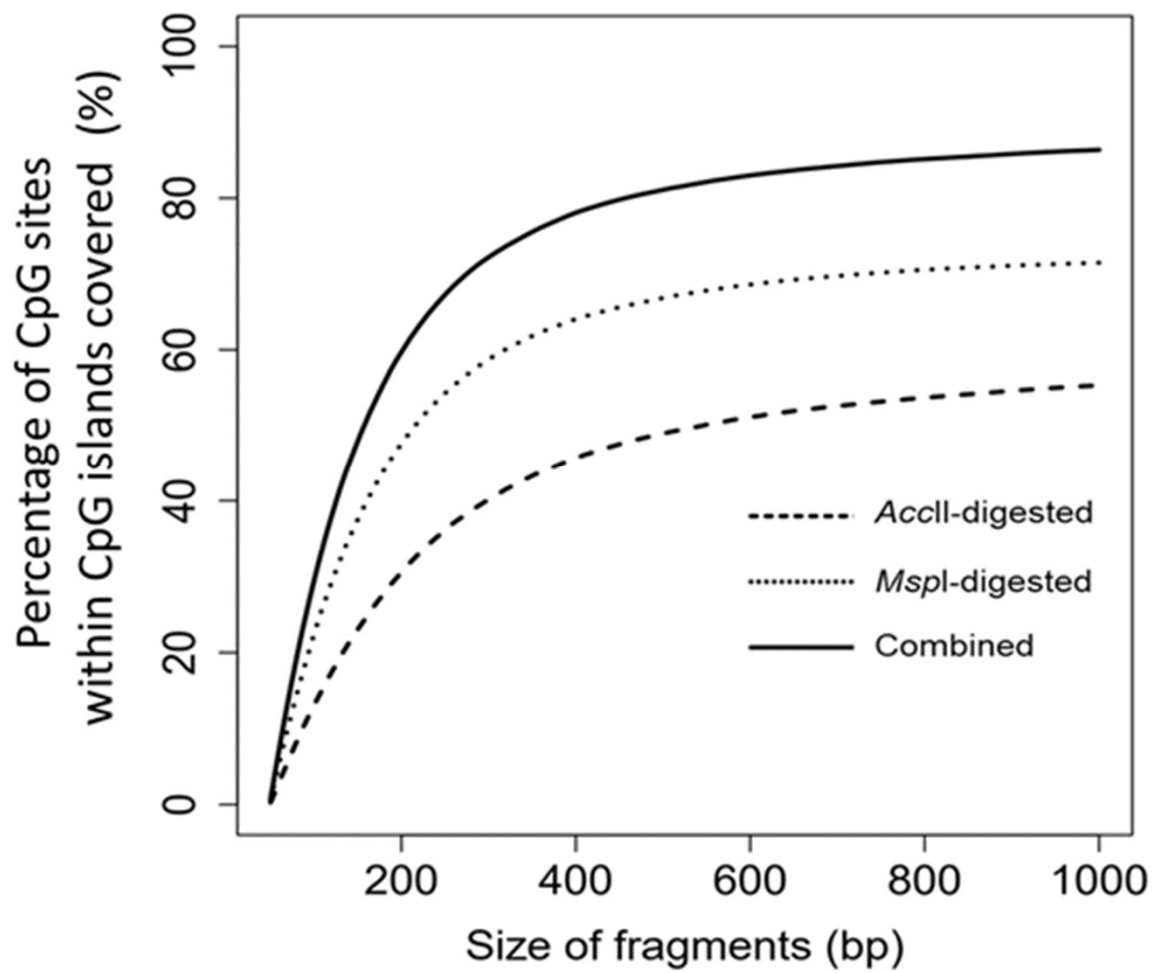


FIG. 129

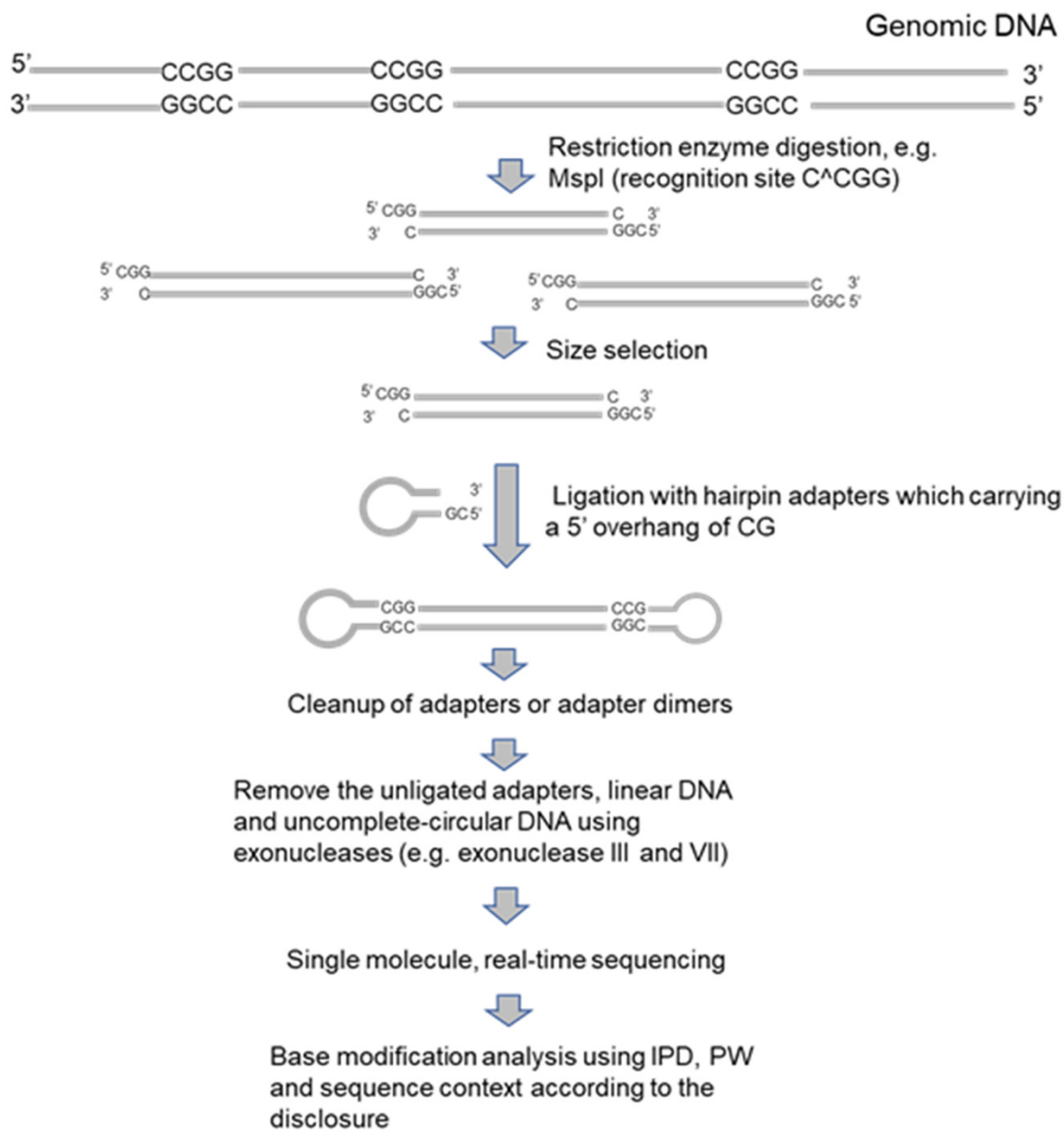


FIG. 130

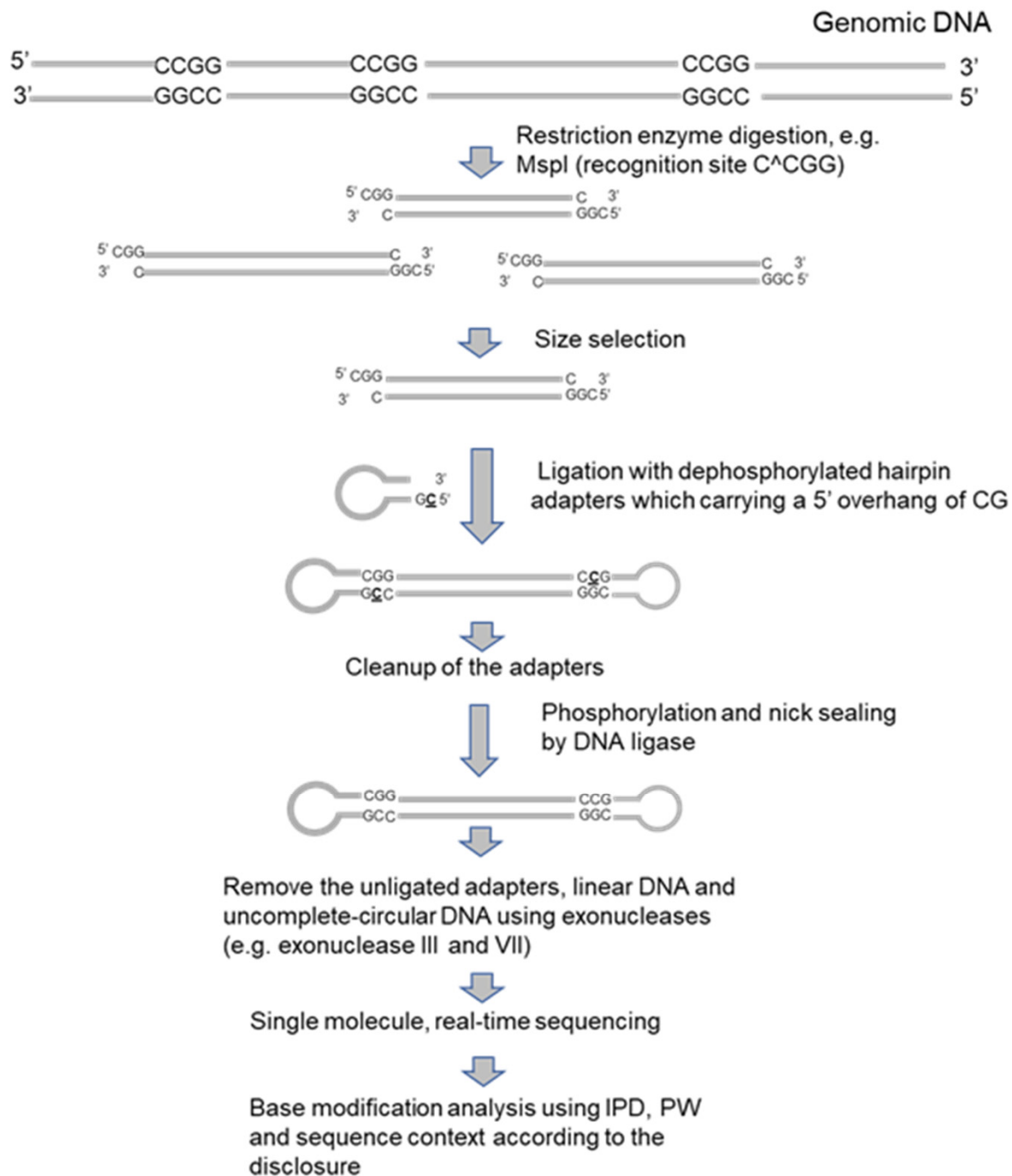


FIG. 131

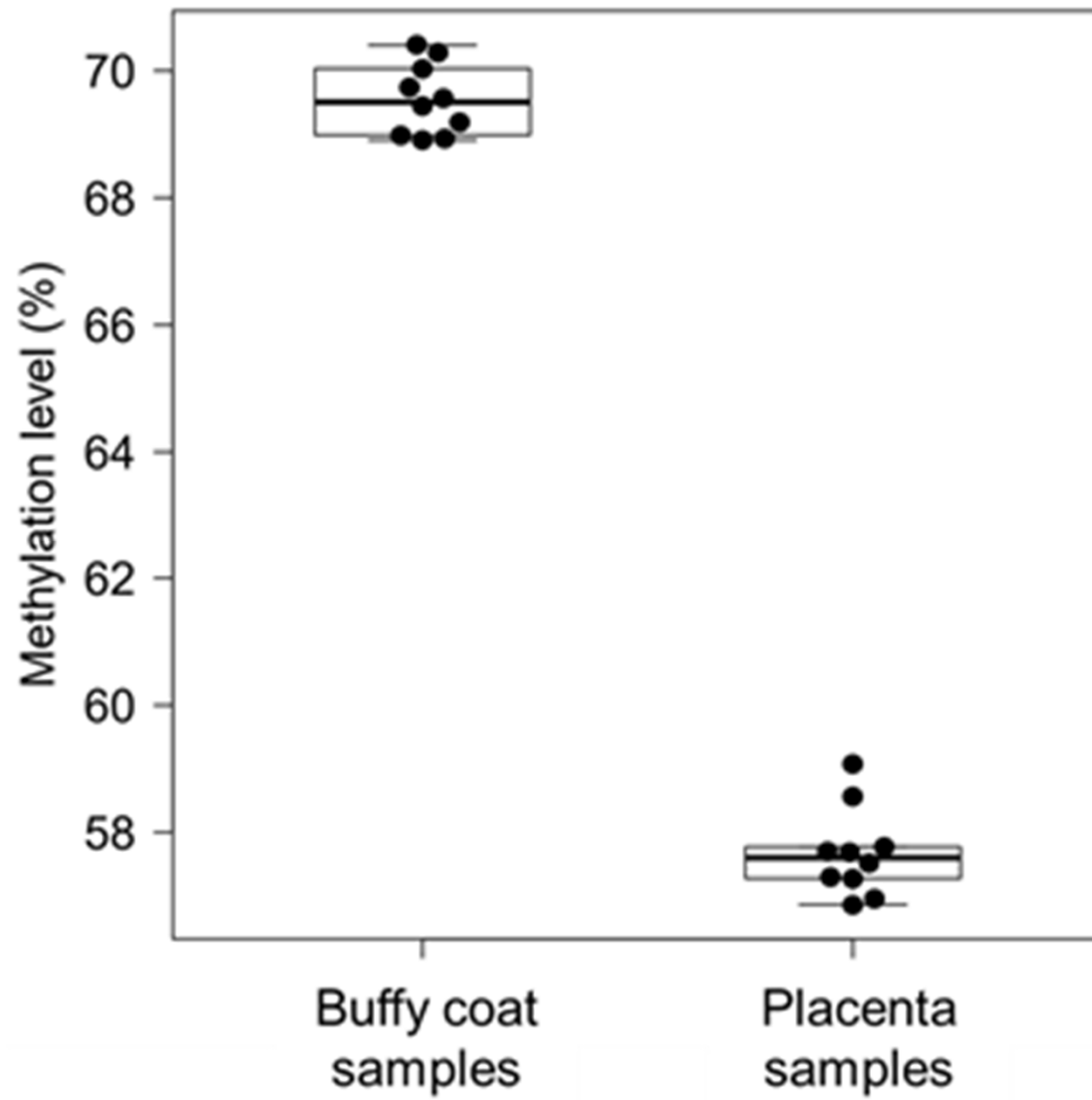


FIG. 132

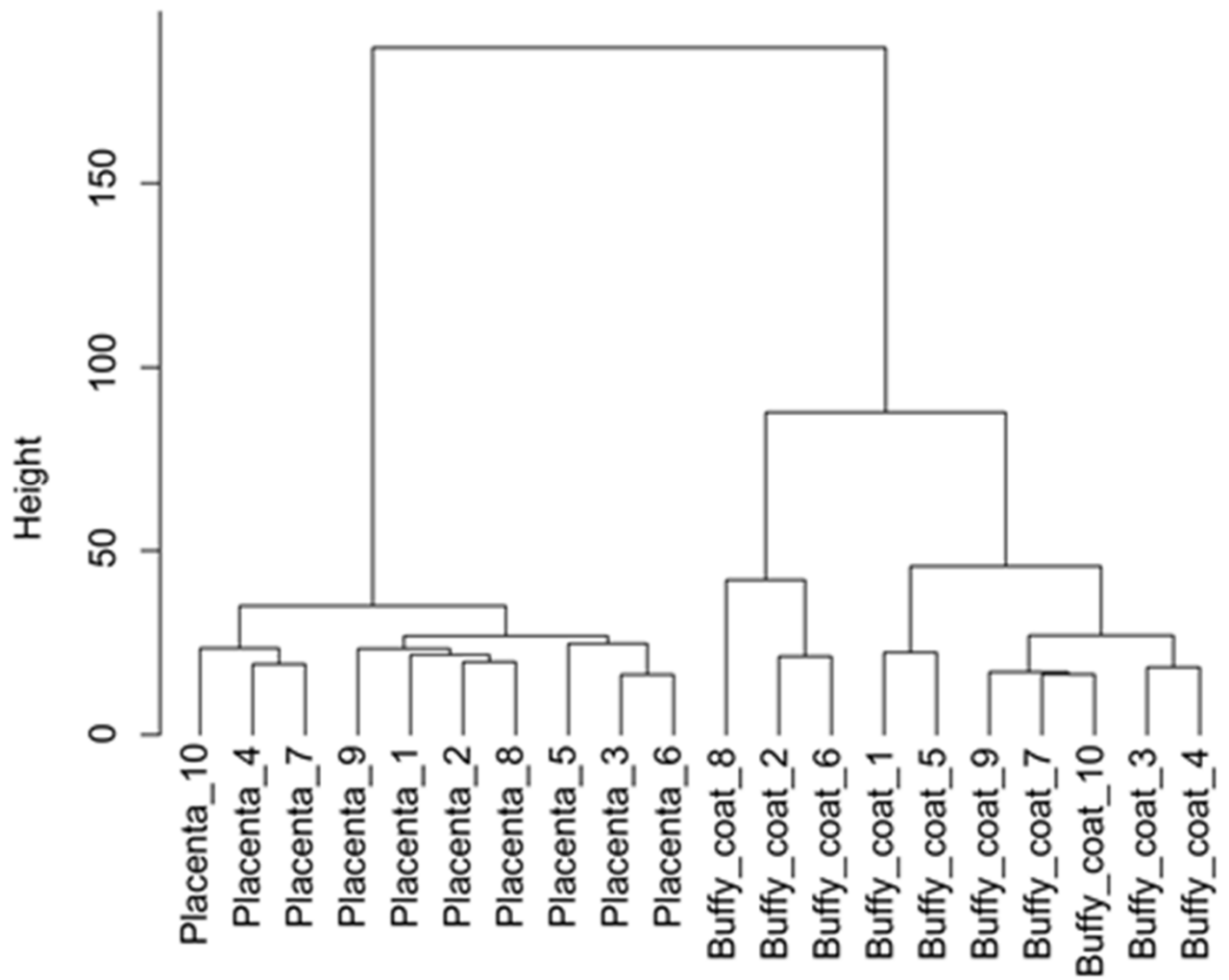


FIG. 133