

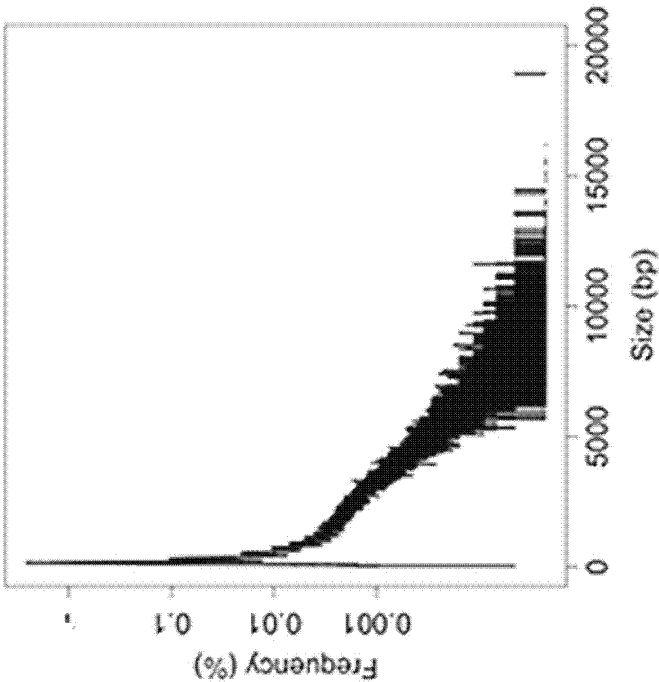


FIG. 1B

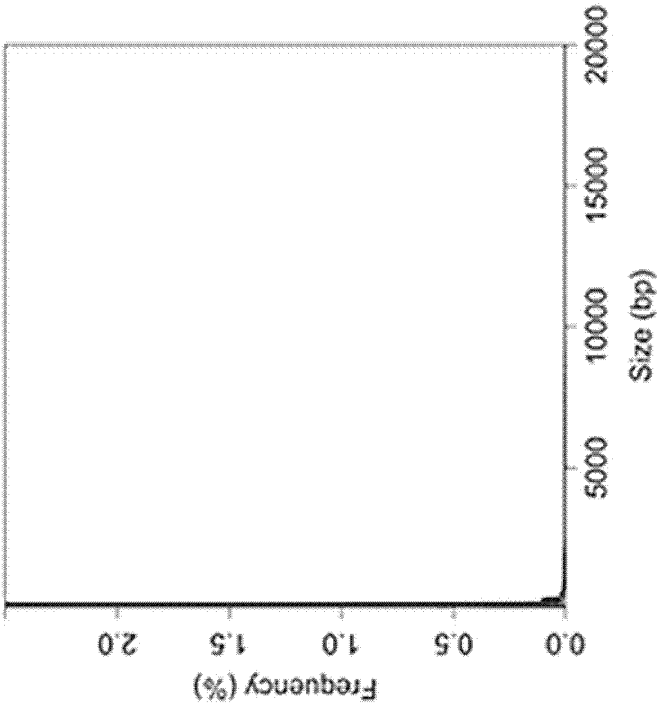


FIG. 1A

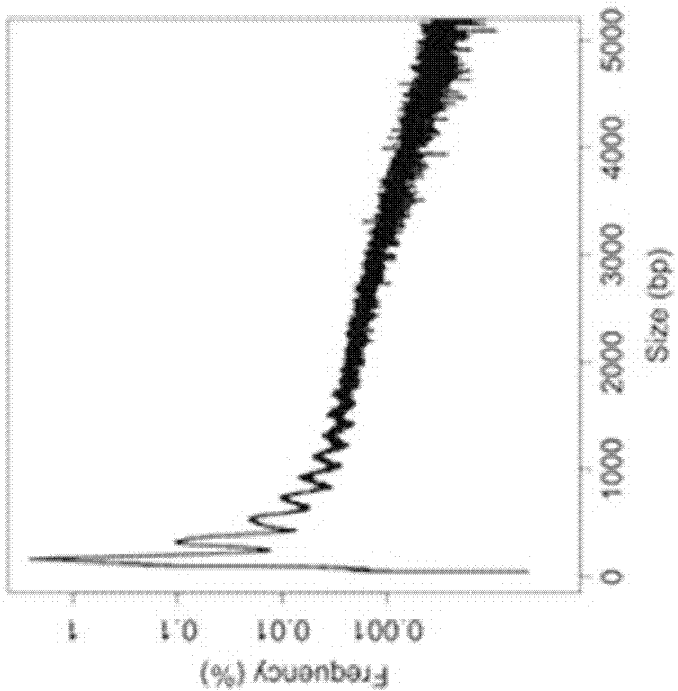


FIG. 2B

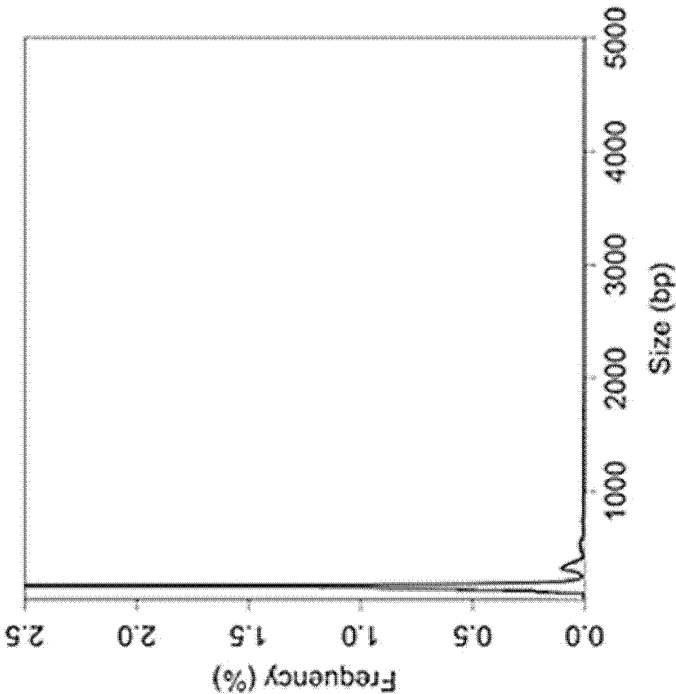


FIG. 2A

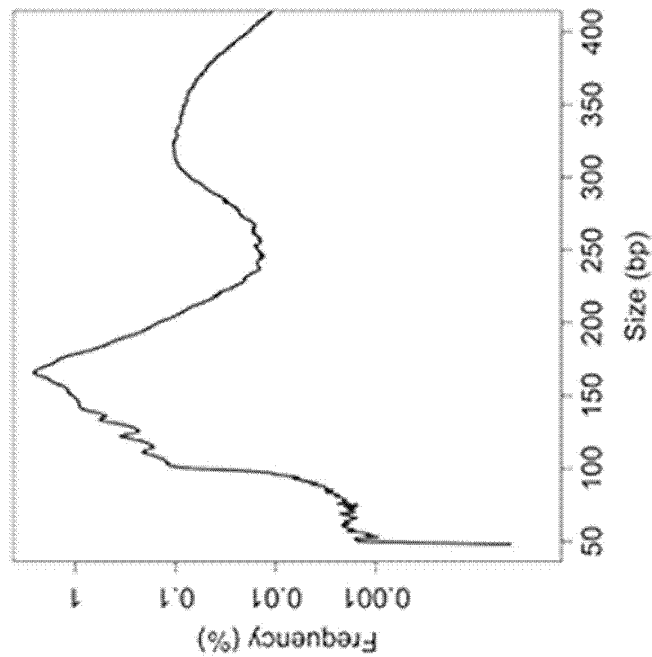


FIG. 3B

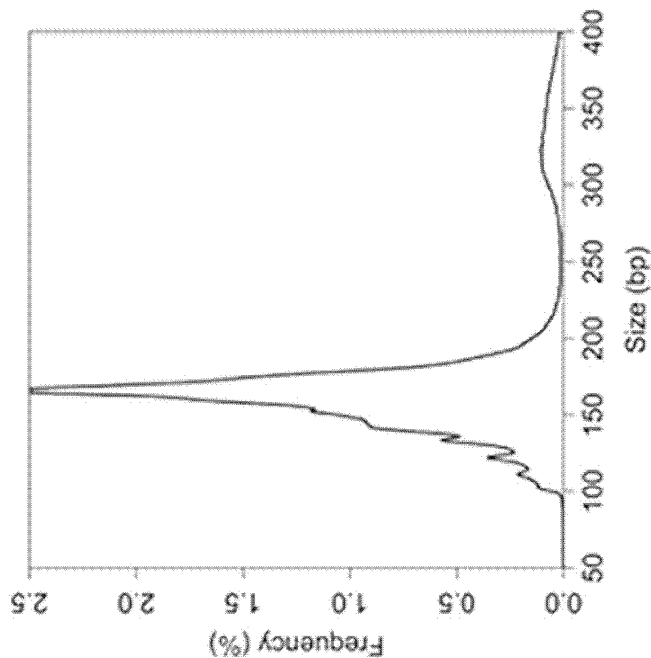


FIG. 3A

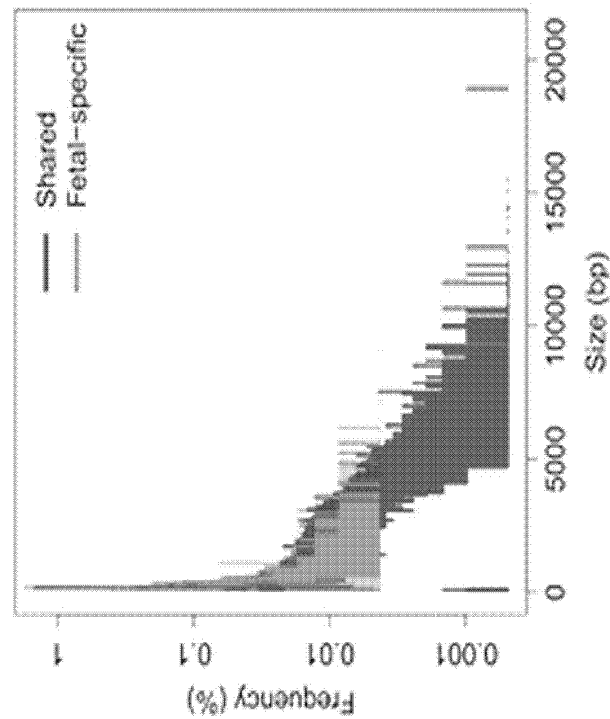


FIG. 4B

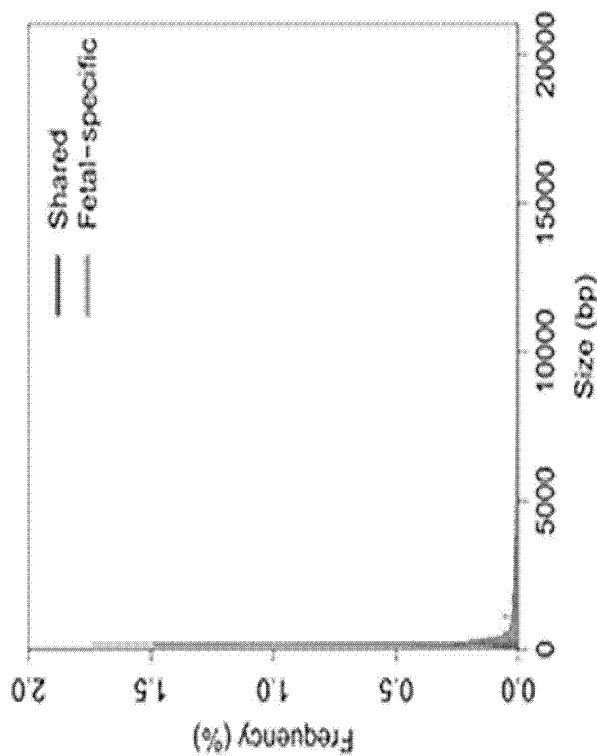


FIG. 4A

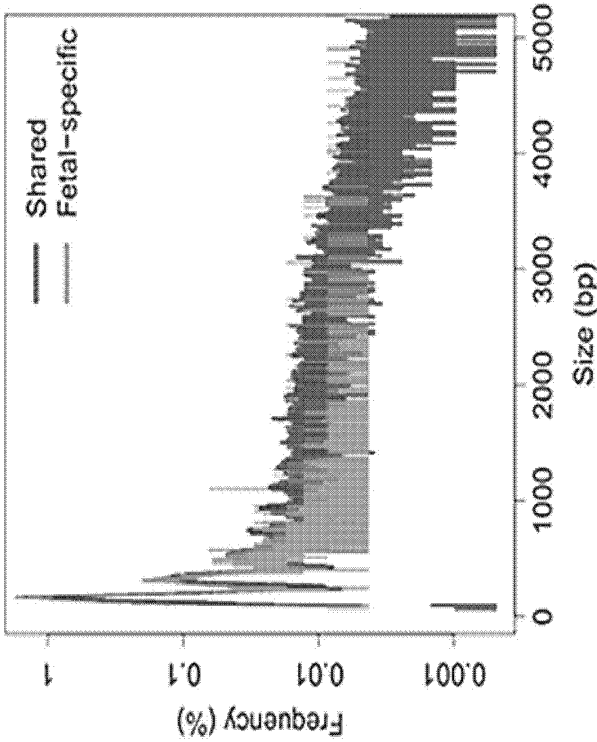


FIG. 5B

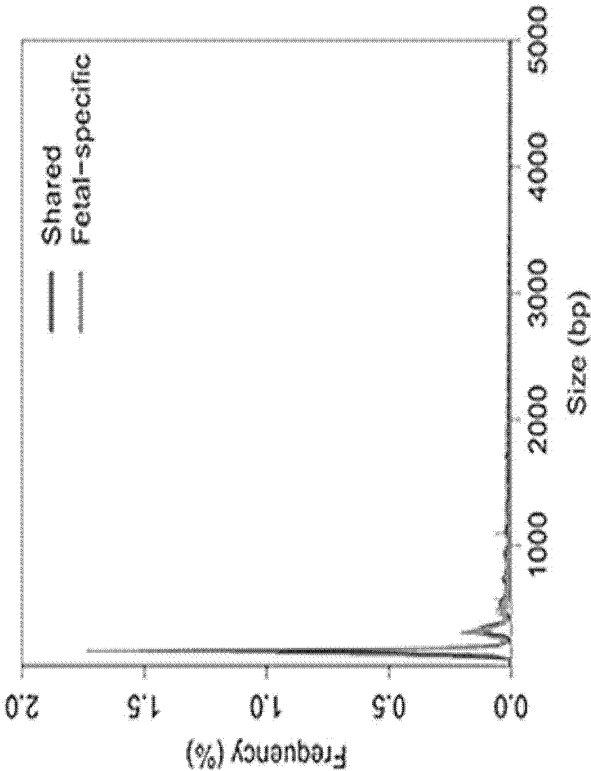


FIG. 5A

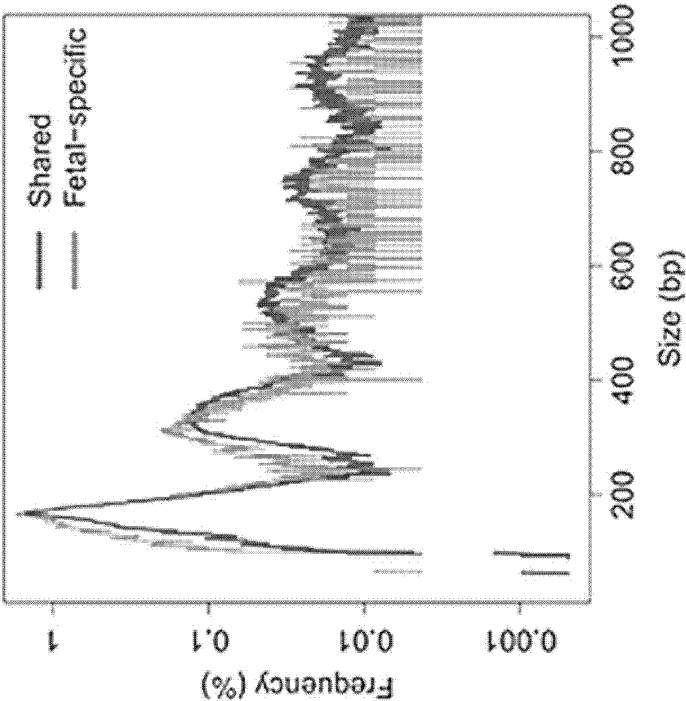


FIG. 6B

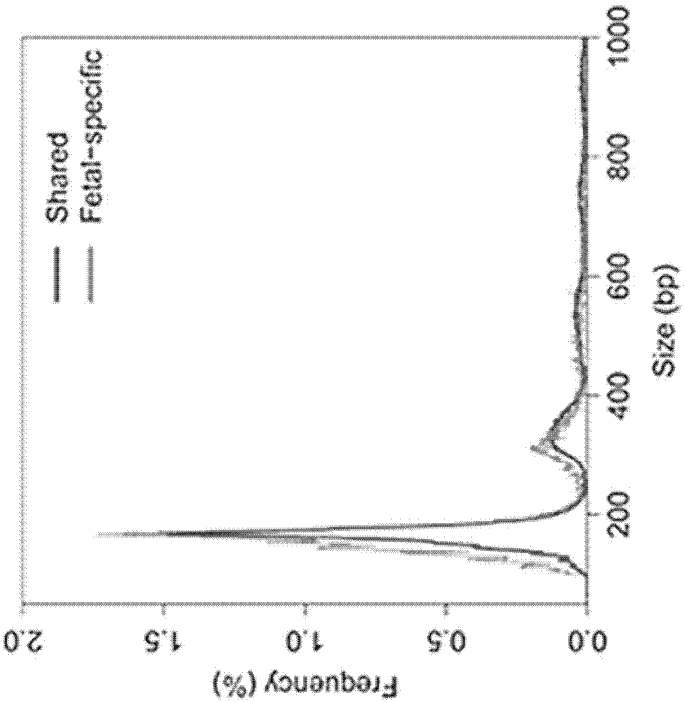


FIG. 6A

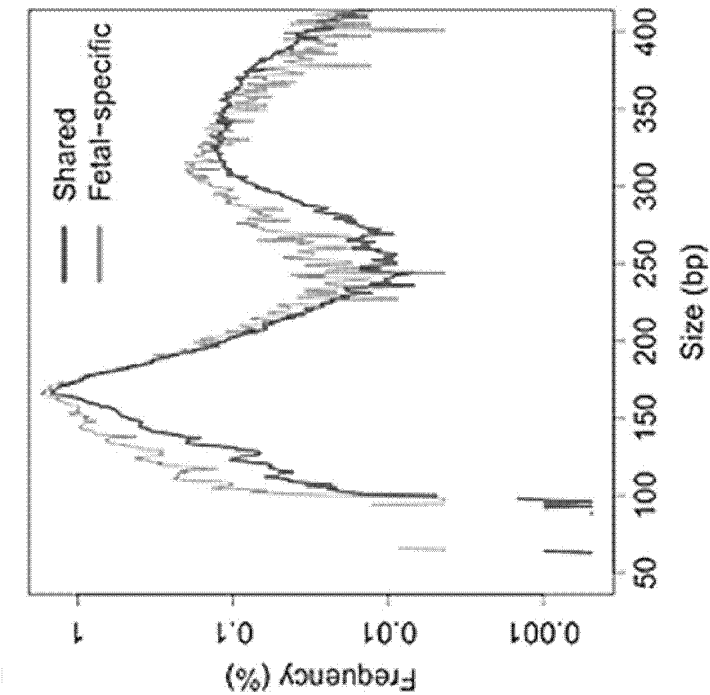


FIG. 7B

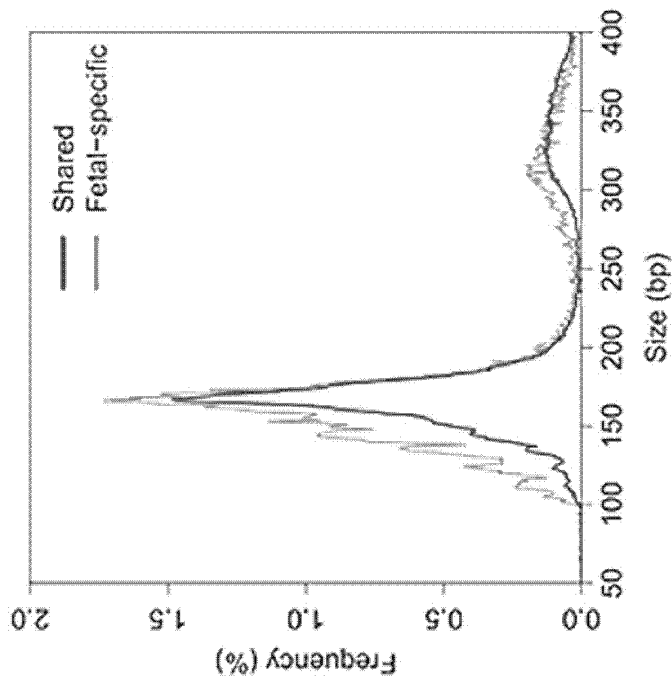


FIG. 7A

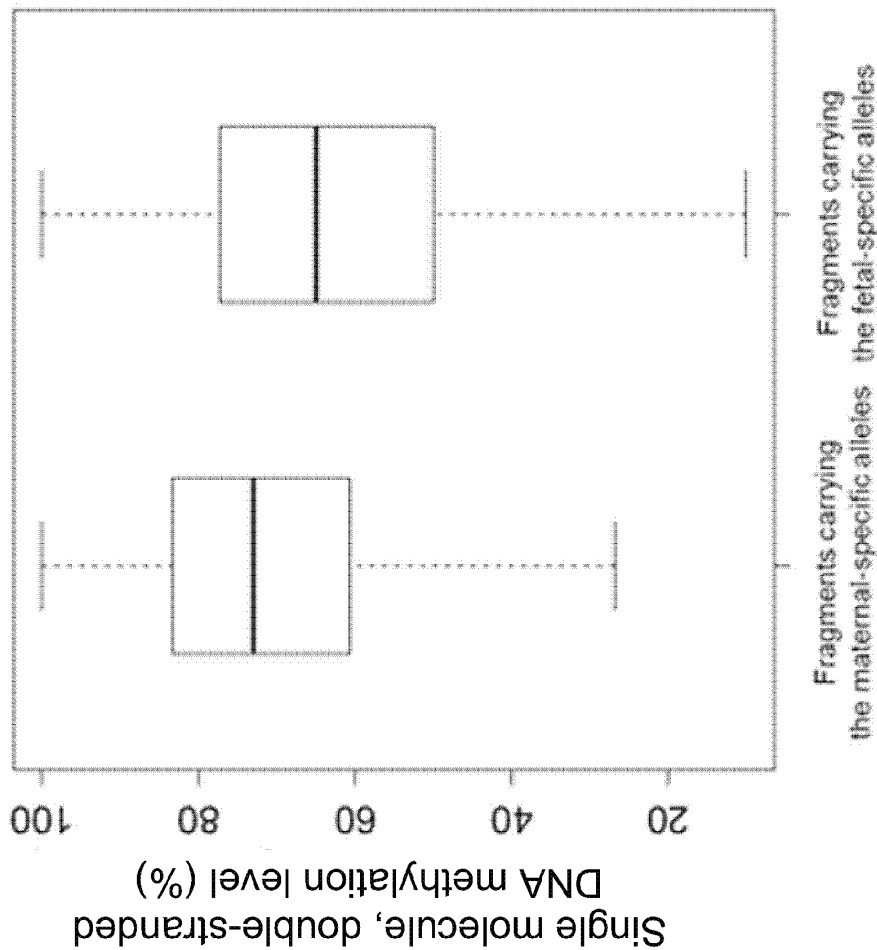


FIG. 8

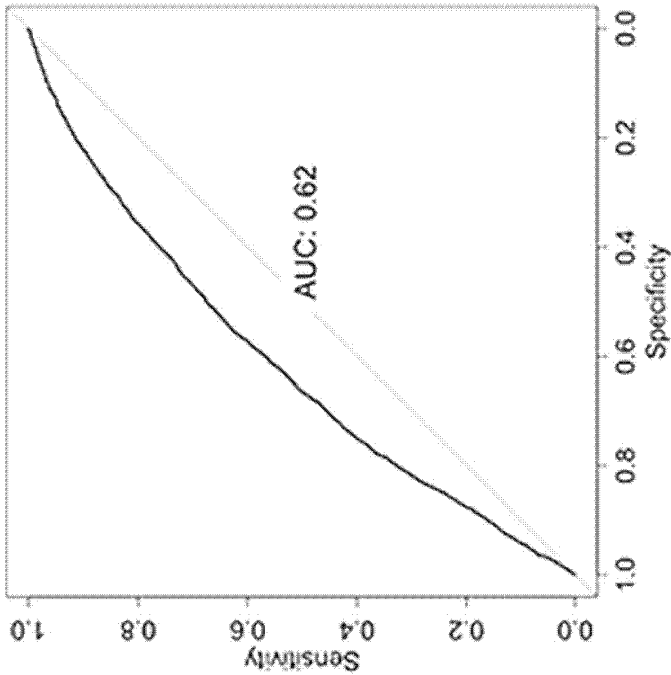


FIG. 9B

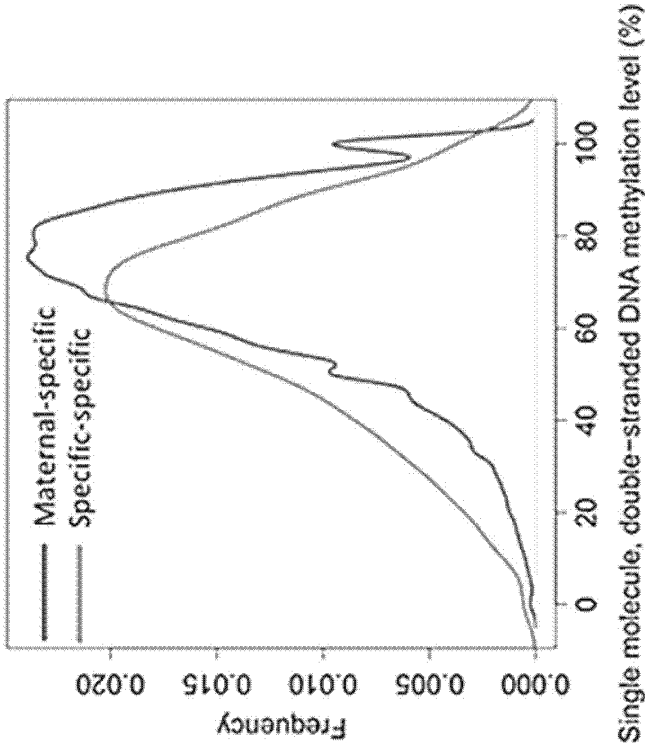


FIG. 9A

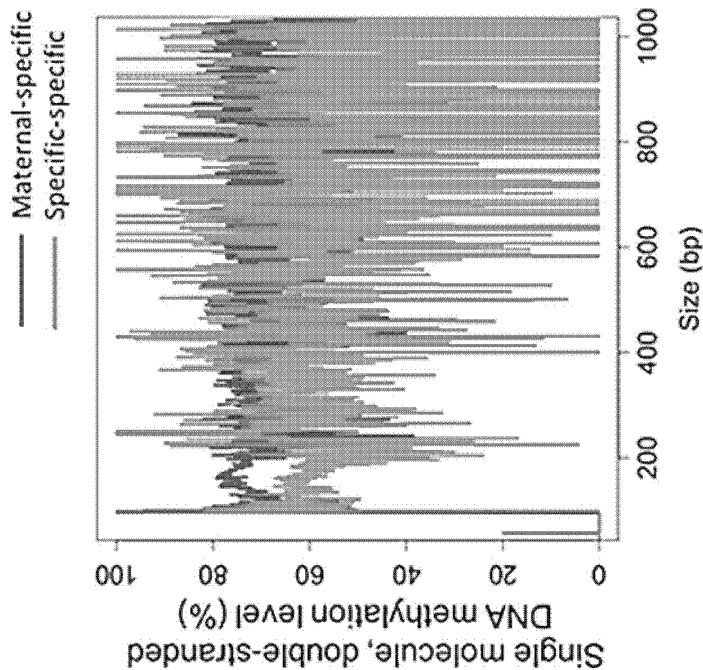


FIG. 10B

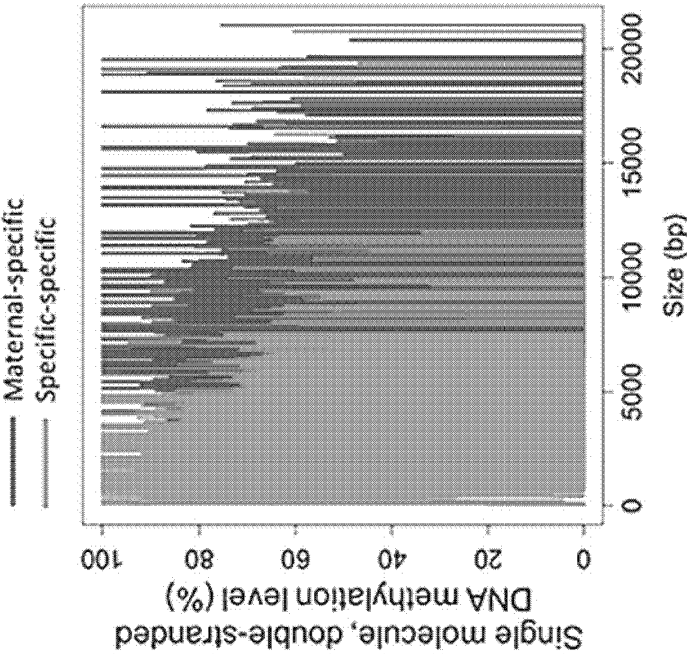
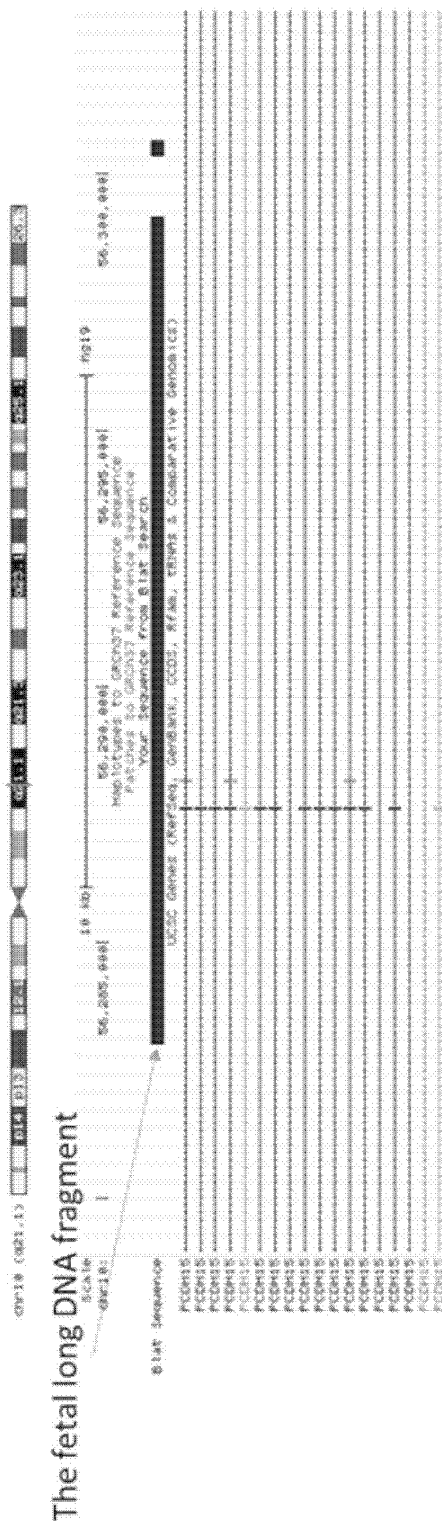


FIG. 10A



Chr	Well id	The mapping coordinates of long cell-free DNA fragment		Length	PacBio SMRT sequencing		Illumina sequencing of tissue DNA							
					Fetal-specific alleles		Sequence information	The number of CpG sites classified as methylated	The number of CpG sites classified as unmethylated	Single-molecule, double-stranded DNA methylation level	Mother genotype	Fetal genotype	Maternal haplotype	Paternal haplotype transmitted to the fetus
		Start	end											
chr20	127272846	56290381	56299166	16185	56264212	56284213	A			CC	CA	C	C	A
					56288865	56288846	C			TT	CT	T	C	
					56290387	56290388	T			CC	CT	C	T	
					56291934	56291935	C	23	60	GA	CG	G	C	
					56296882	56296883	T			CC	CC	C	T	
					56296930	56296933	T			TT	TC	T	C	
					56299345	56299347	T			CC	CT	T	C	

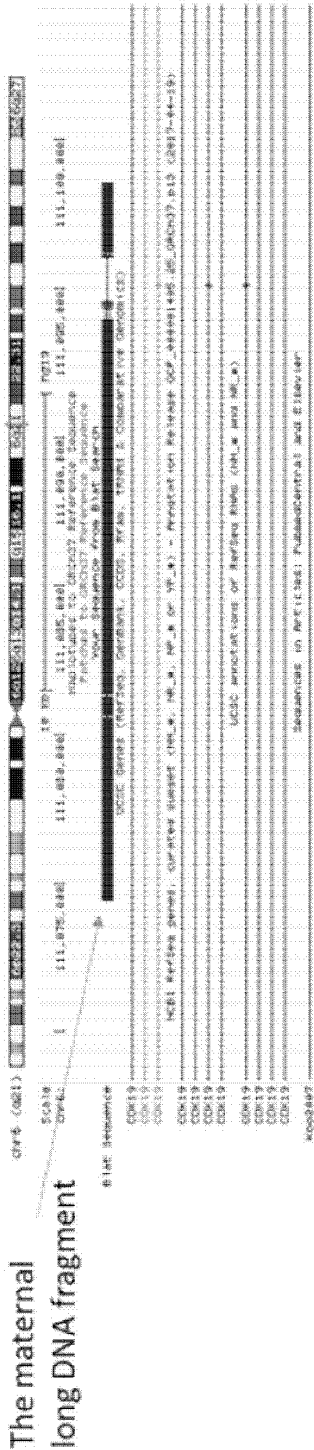


FIG. 12A

		PacBio SMRT sequence										Illumina sequencing of tissue DNA			
Chr	Well id	The mapping coordinates of		Length	Fetal-specific alleles		Sequence information	The number of CpG sites classified as methylated	The number of CpG sites classified as unmethylated	Single-molecule, double-stranded DNA methylation level	Mother genotype	Fetal genotype	Maternal haplotype	Paternal haplotype transmitted to the fetus	
		Start	End		Start	End									
chr6	128648561	111074371	111098536	24165	111075831	111075832	A	81	40	66.9	AA	AG	A	G	
					111076442	111076443	G				GG	GT	G	T	
					111076870	111076871	A				AA	AT	A	T	
					111077506	111077507	C				CC	CT	C	T	
					111078649	111078650	T				TT	CT	T	C	
					111079042	111079043	A				AA	GA	A	G	
					111081132	111081133	C				CC	CT	C	T	
					111083336	111083337	G				GG	CG	G	C	
					111084746	111084747	G				GG	TG	G	T	
					111086718	111086719	C				CC	TC	C	T	
					111087391	111087392	A				AA	AT	A	T	
					111088191	111088192	C				CC	CA	C	A	
					111091243	111091244	C				CC	TC	C	T	
					111093070	111093071	T				TT	TC	T	C	
					111093763	111093764	A				AA	GA	A	G	
					111097401	111097402	T				TT	CT	T	C	
					111097556	111097557	C				CC	CG	C	G	
					111098297	111098298	A				AA	CA	A	C	

FIG. 12B

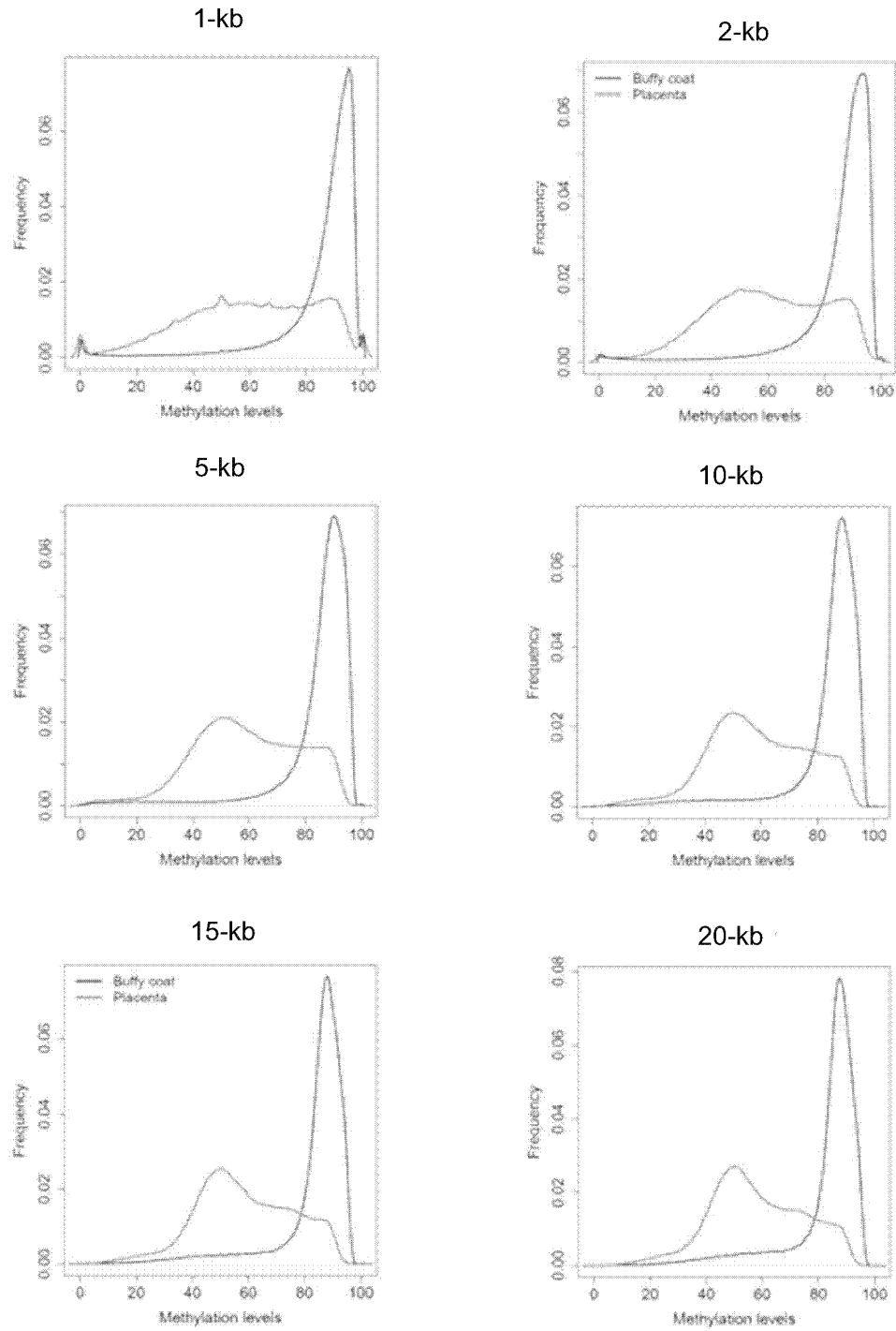


FIG. 13

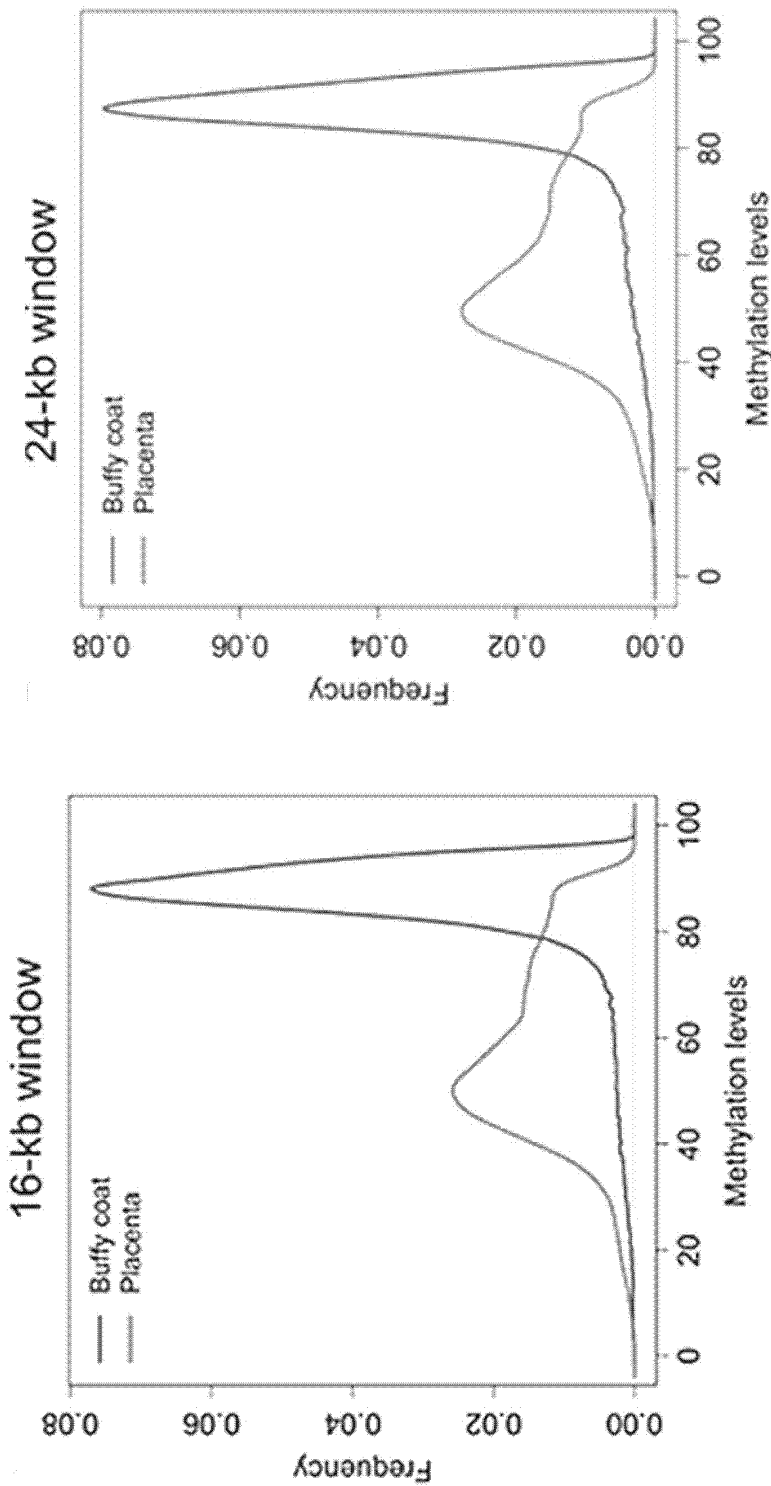


FIG. 14A

FIG. 14B

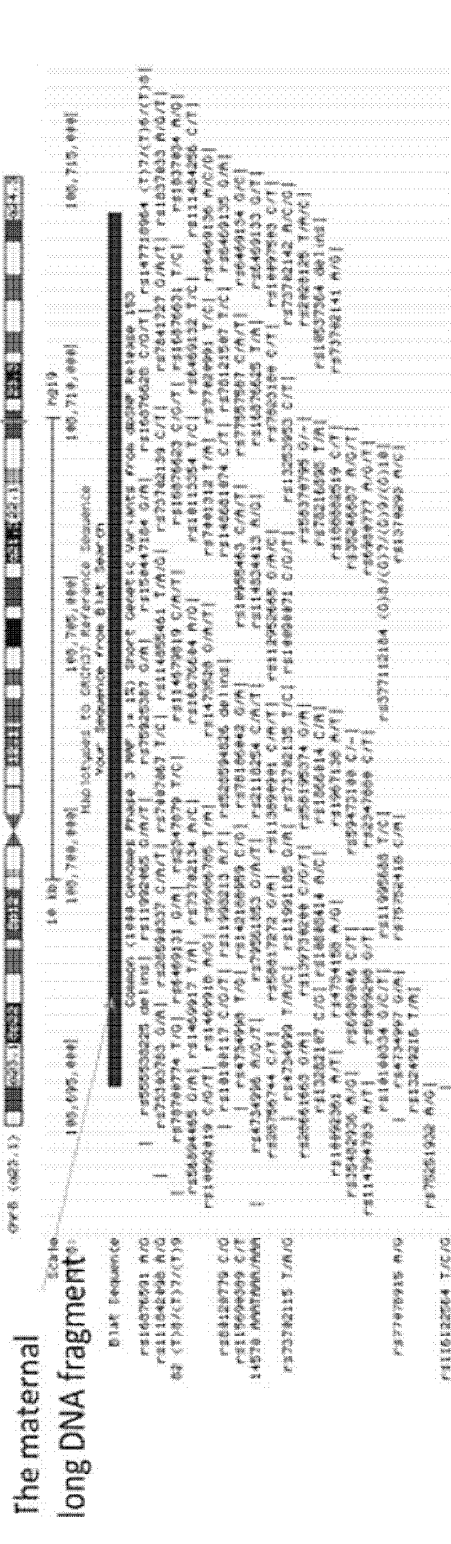


FIG. 15A

PacBio SMRT sequence														
Chr	Well id	The mapping coordinates of		Length	Fetal-specific alleles		Sequence information	The number of CpG sites classified as methylated	The number of CpG sites classified as unmethylated	Single-molecule, double-stranded DNA methylation level	Illumina sequencing of tissue DNA			
		Start	End		Start	End					Mother genotype	Fetal genotype	Maternal haplotype	Paternal haplotype transmitted to the fetus
chr8	107546586	108694010	108712904	18894	108695136	108695137	A	77	29	72.6	GA	GG	A	G
					108695137	108695138	T				CT	CC	T	C
					108697116	108697117	T				AT	AA	T	A
					108702099	108702100	T				AT	AA	T	A
					108706969	108706970	C				CT	TT	C	T
					108709180	108709181	G				GC	CC	G	C
					108712304	108712305	G				TG	TT	G	T

FIG. 15B

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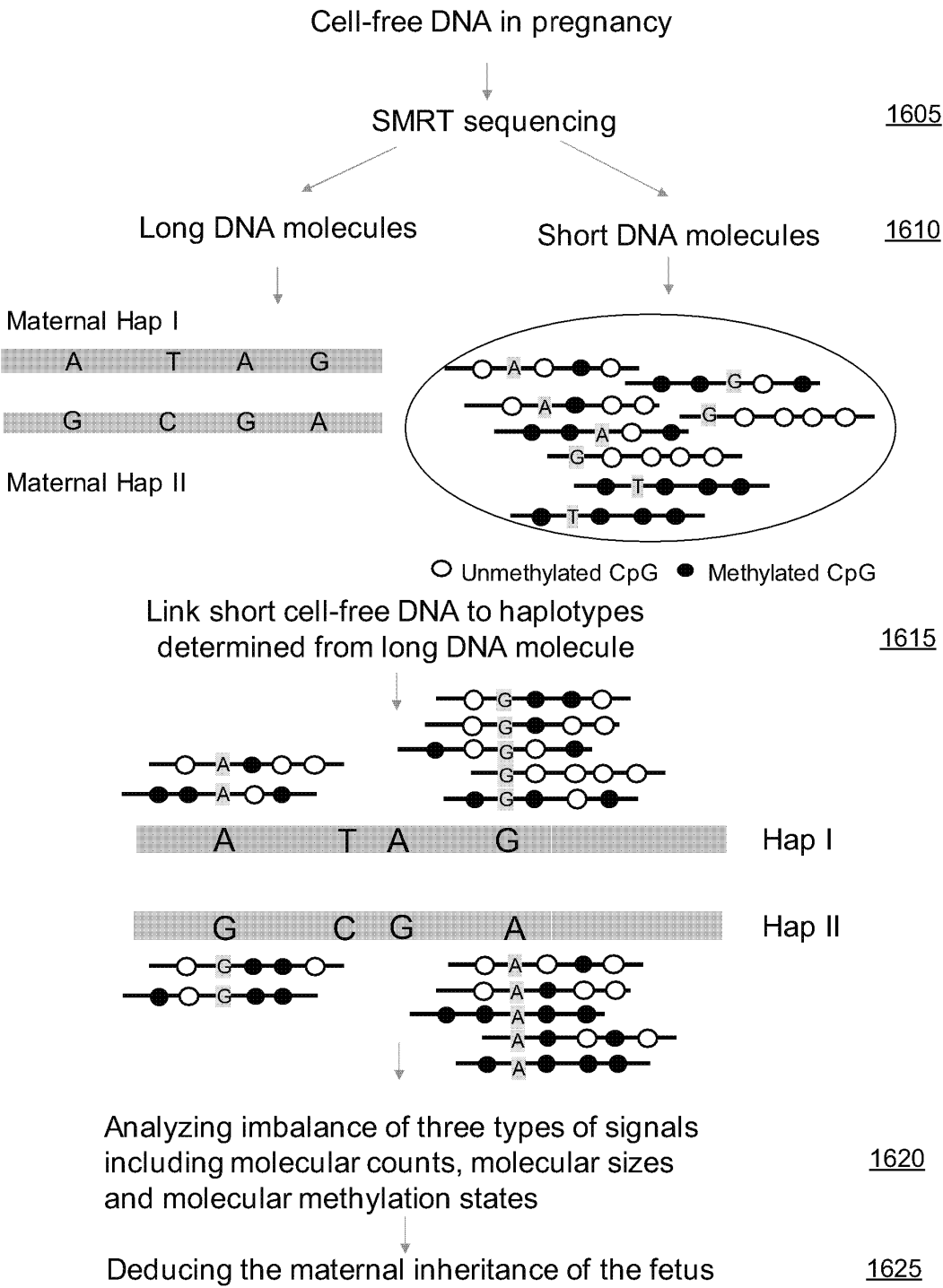


FIG. 16

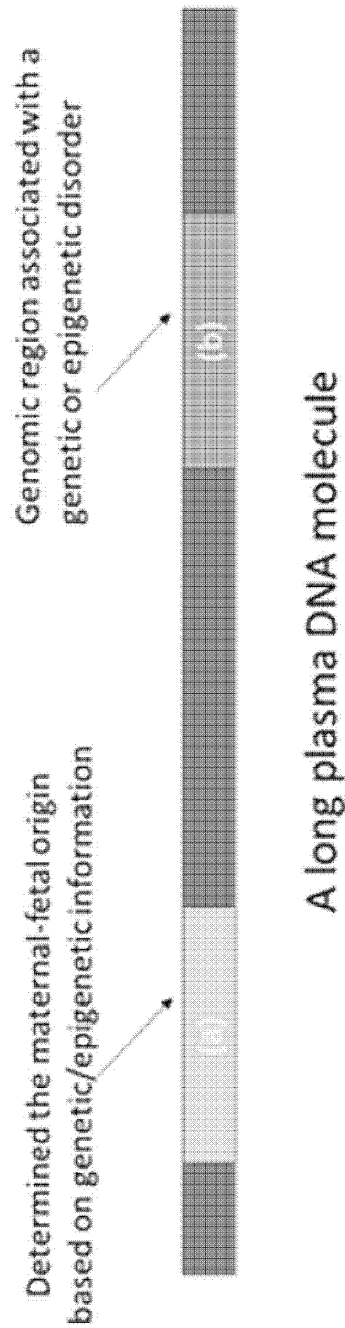


FIG. 17

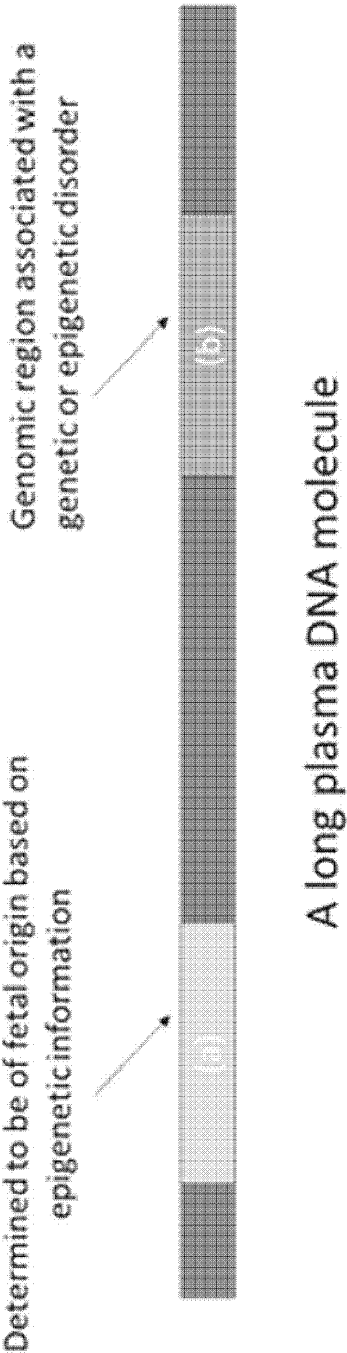


FIG. 18

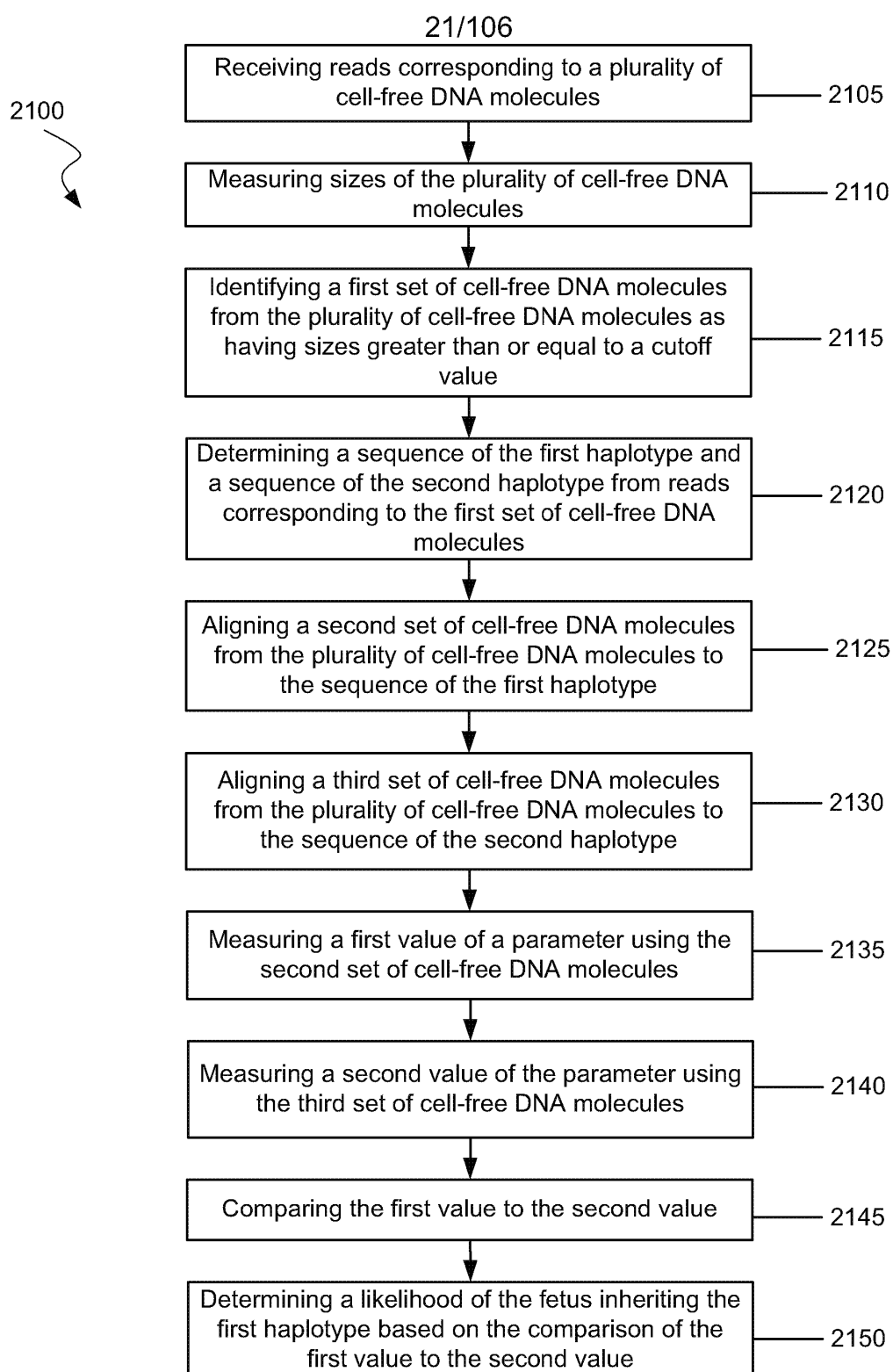
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2000


Sequencing a plurality of cell-free nucleic acid molecules, where over 20% of the plurality of the cell-free nucleic acid molecules sequenced have lengths greater than 200 nt

2010

FIG. 20

**FIG. 21**

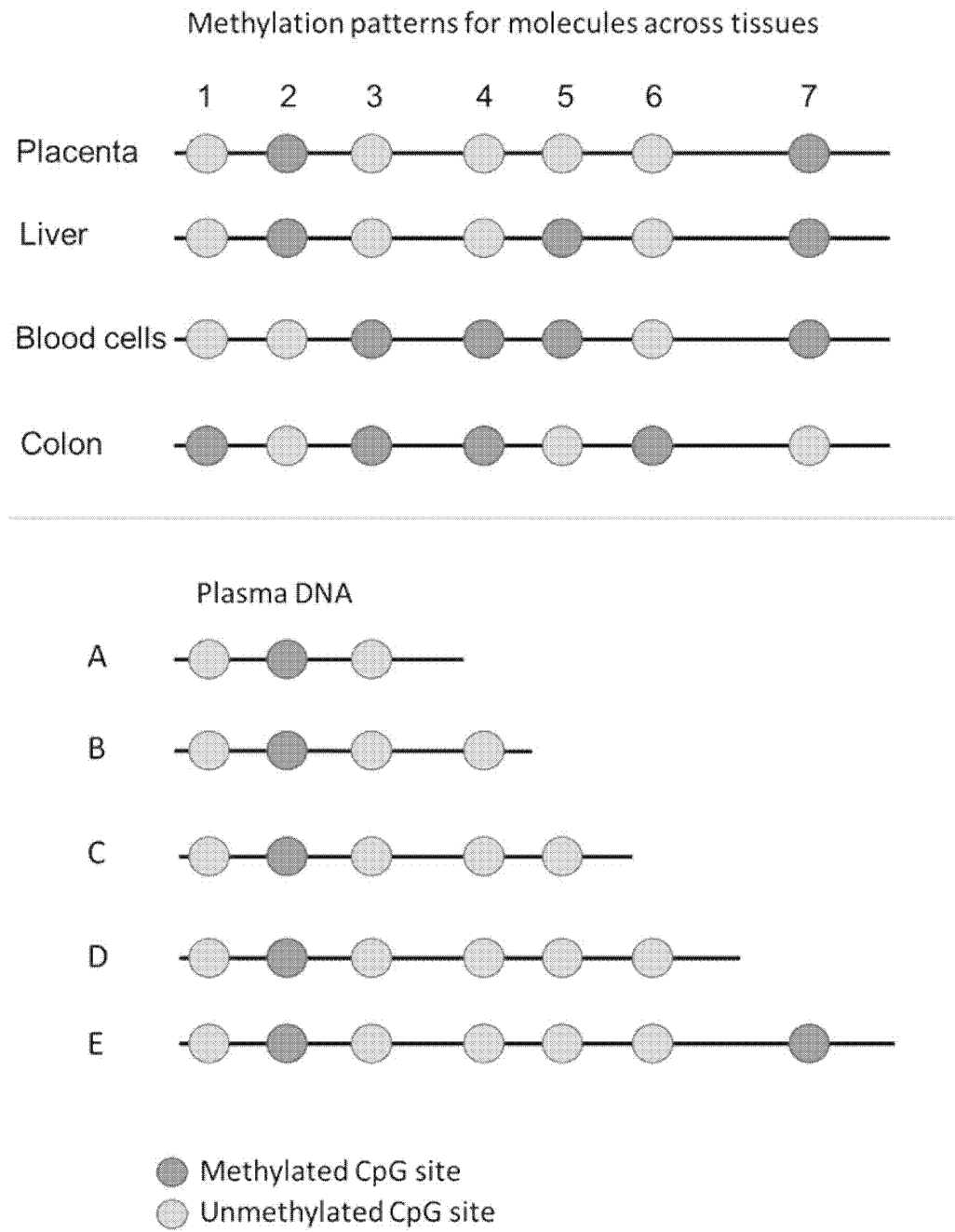


FIG. 22

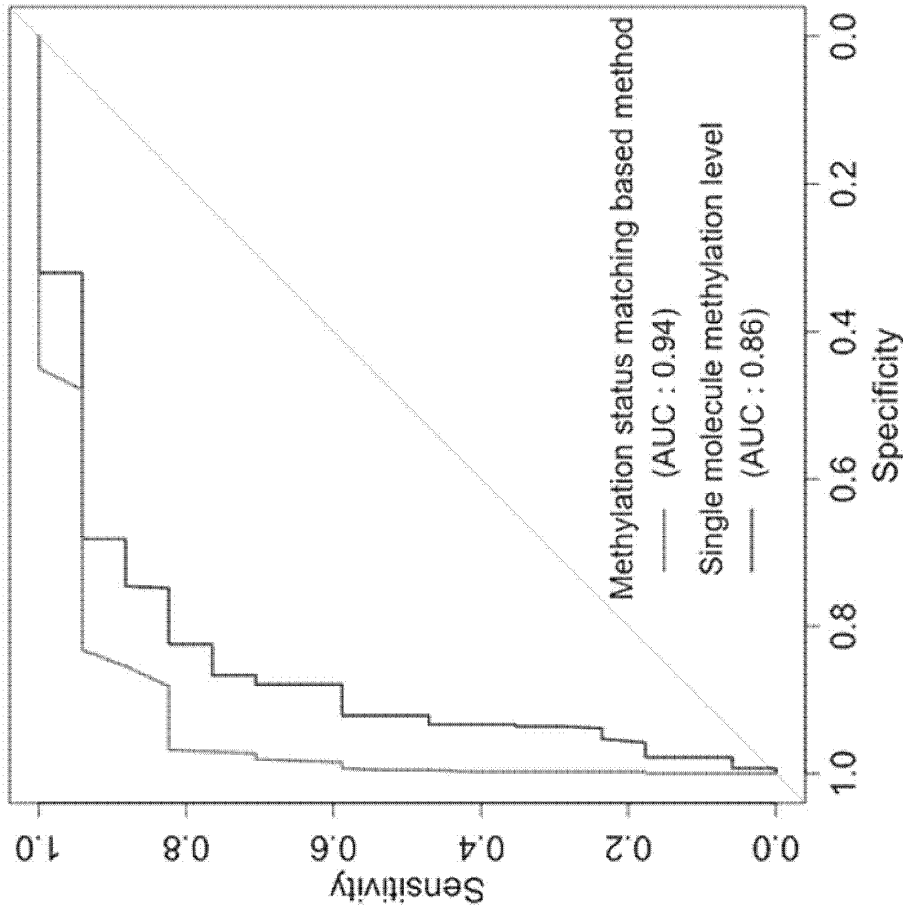


FIG. 23

Pair-wise methylation patterns

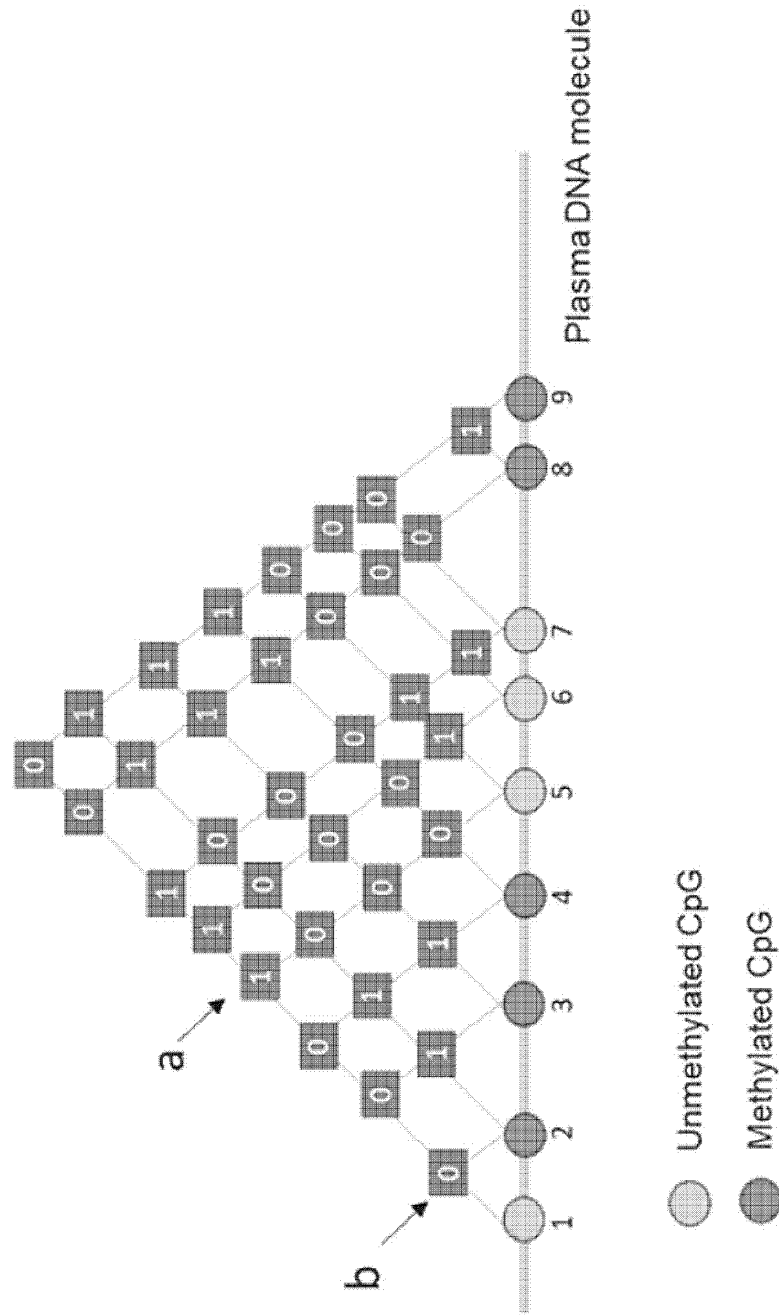


FIG. 24

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Chromosome	Number of marker regions
1	22418
2	20311
3	14559
4	15700
5	15363
6	12758
7	15108
8	15172
9	11742
10	13914
11	13545
12	13697
13	10449
14	9523
15	7132
16	13962
17	11177
18	8186
19	15622
20	8264
21	5960
22	7004

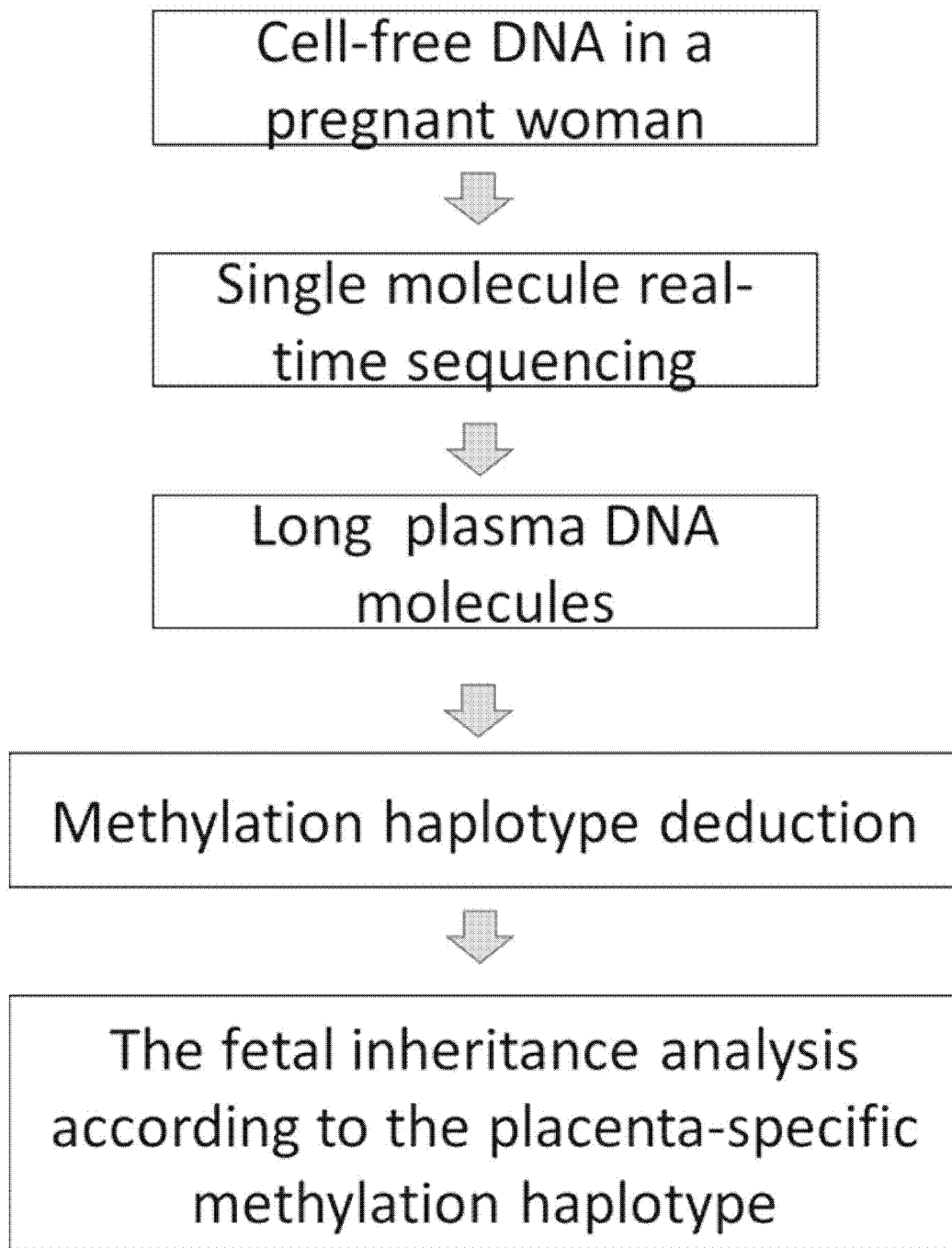
FIG. 25

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Percentage of buffy coat DNA molecules having a mismatch score of greater than 0.3 (%)		Classification based on the single-molecule methylation pattern		Percentage of DNA molecules with correct classification (%)
		Placenta-specific	Not specific for placenta	
> 60	Plasma DNA molecules covering a fetal-specific allele	24	17	58.5
	Plasma DNA molecules covering a maternal-specific allele	63	597	90.5
> 70	Plasma DNA molecules covering a fetal-specific allele	23	14	62.2
	Plasma DNA molecules covering a maternal-specific allele	53	550	91.2
> 75	Plasma DNA molecules covering a fetal-specific allele	20	13	60.6
	Plasma DNA molecules covering a maternal-specific allele	45	493	91.6
> 80	Plasma DNA molecules covering a fetal-specific allele	17	11	60.7
	Plasma DNA molecules covering a maternal-specific allele	34	433	92.7
> 85	Plasma DNA molecules covering a fetal-specific allele	14	11	56.0
	Plasma DNA molecules covering a maternal-specific allele	21	342	94.2
> 90	Plasma DNA molecules covering a fetal-specific allele	9	7	56.3
	Plasma DNA molecules covering a maternal-specific allele	10	209	95.4

FIG. 26

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**FIG. 27**

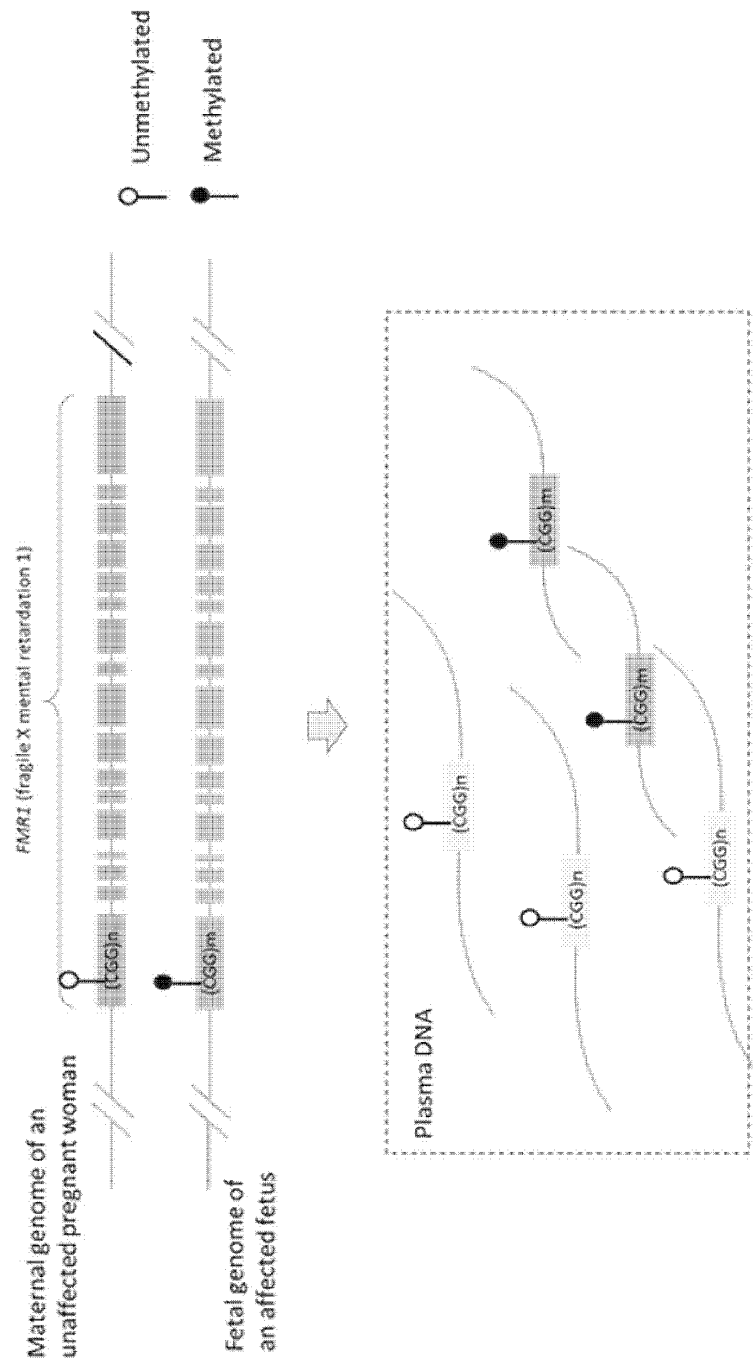
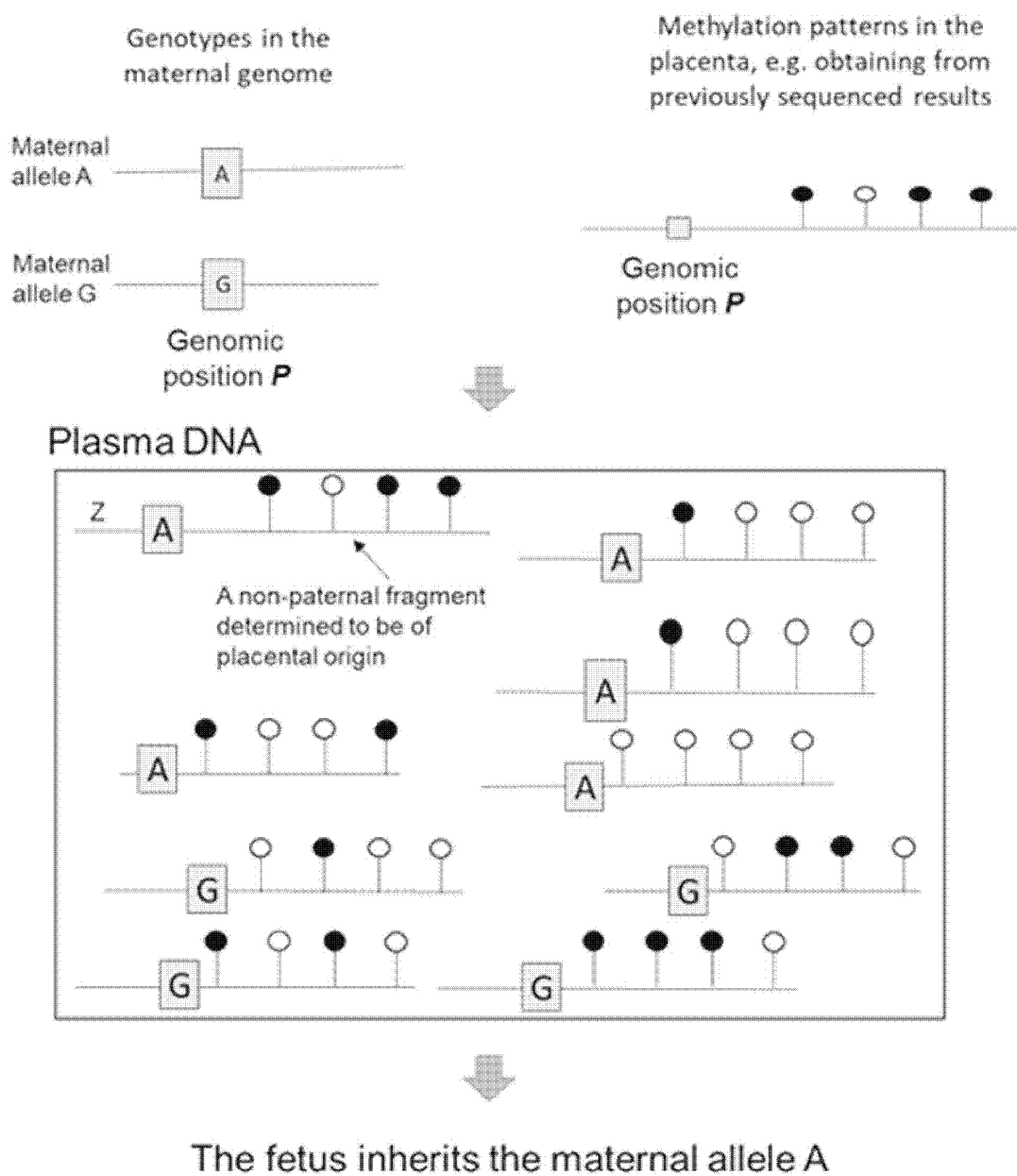


FIG. 28

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**FIG. 29**

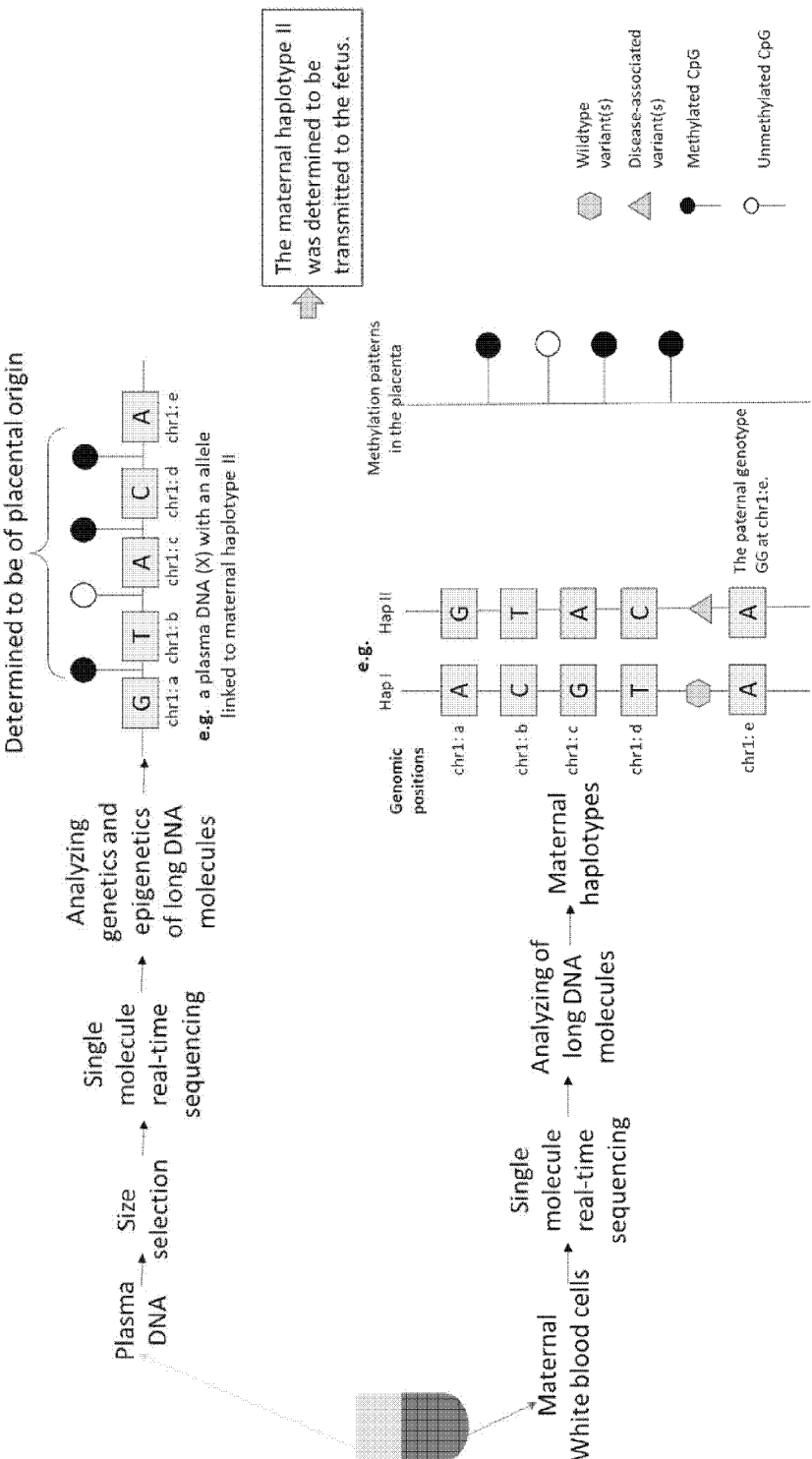
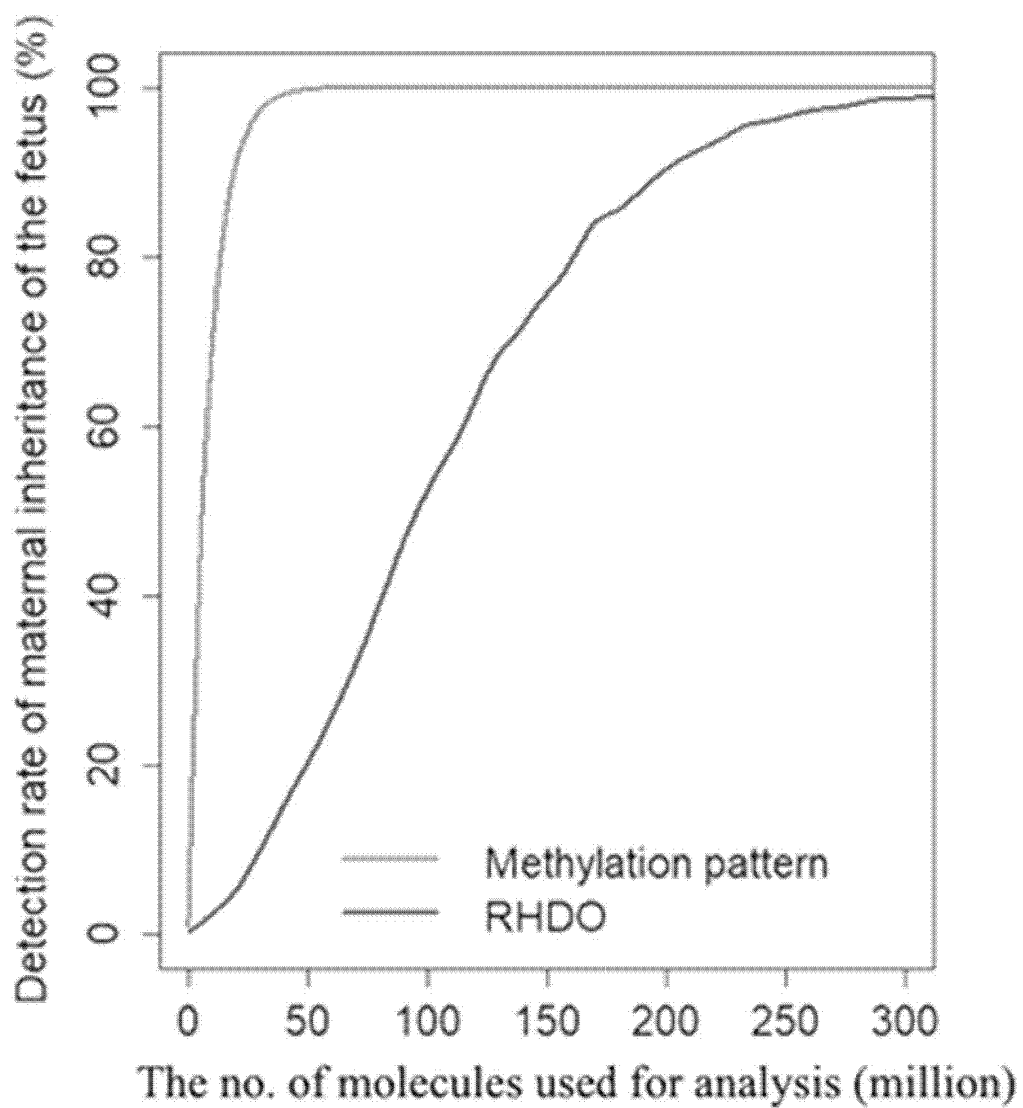


FIG. 30

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**FIG. 31**

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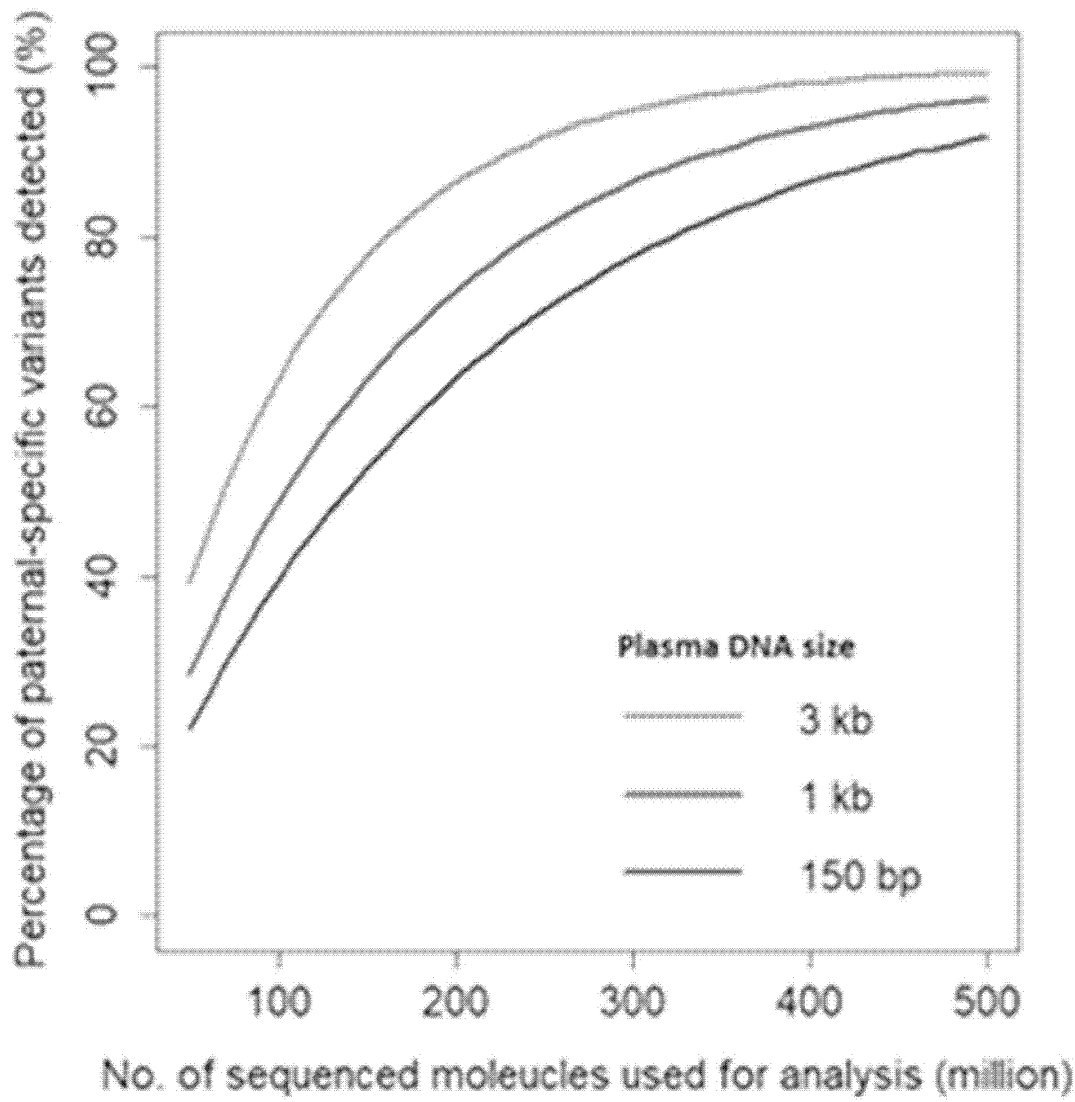


FIG. 32

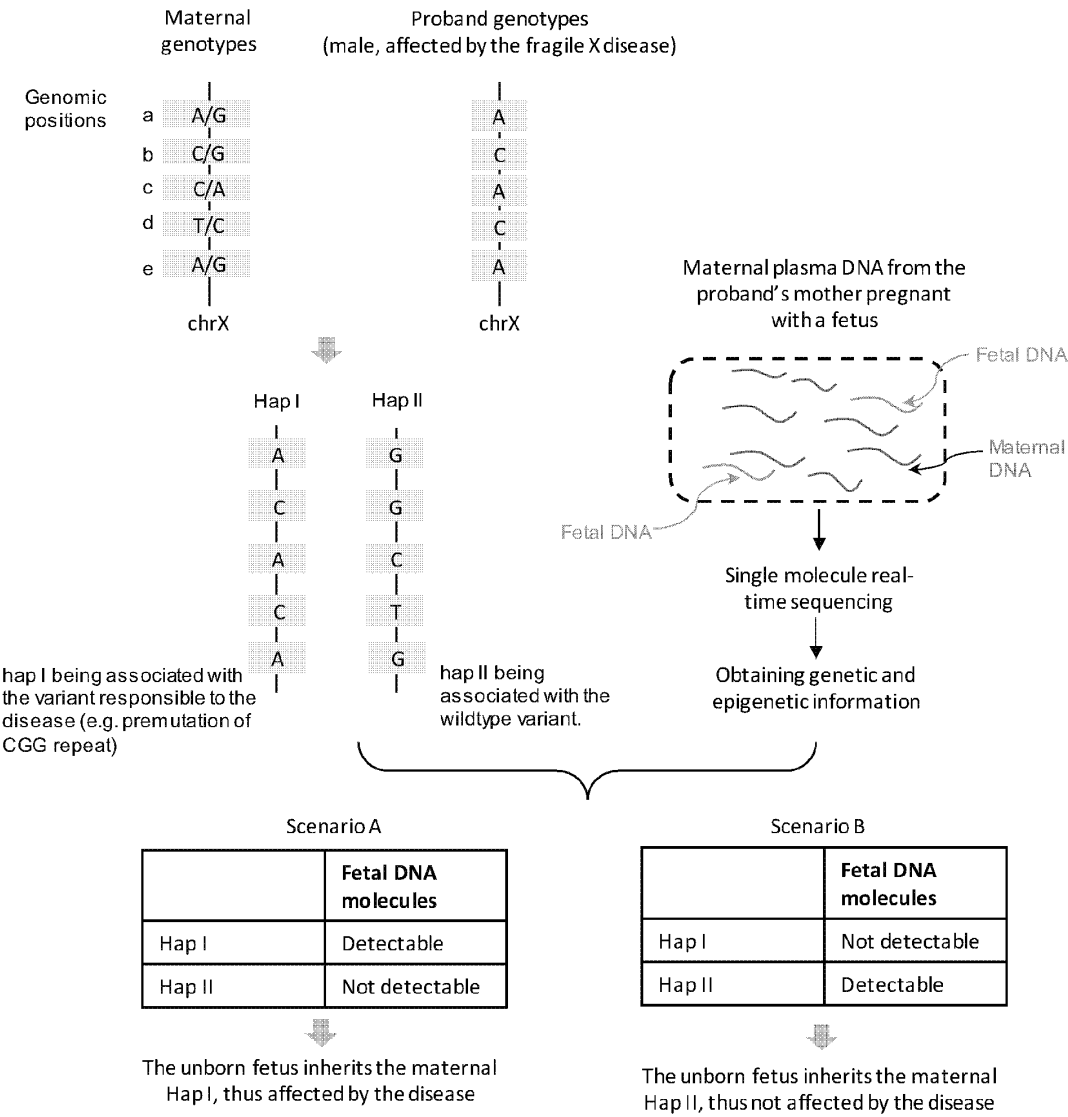


FIG. 33

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chrX: 143,782,435 - 143,782,707

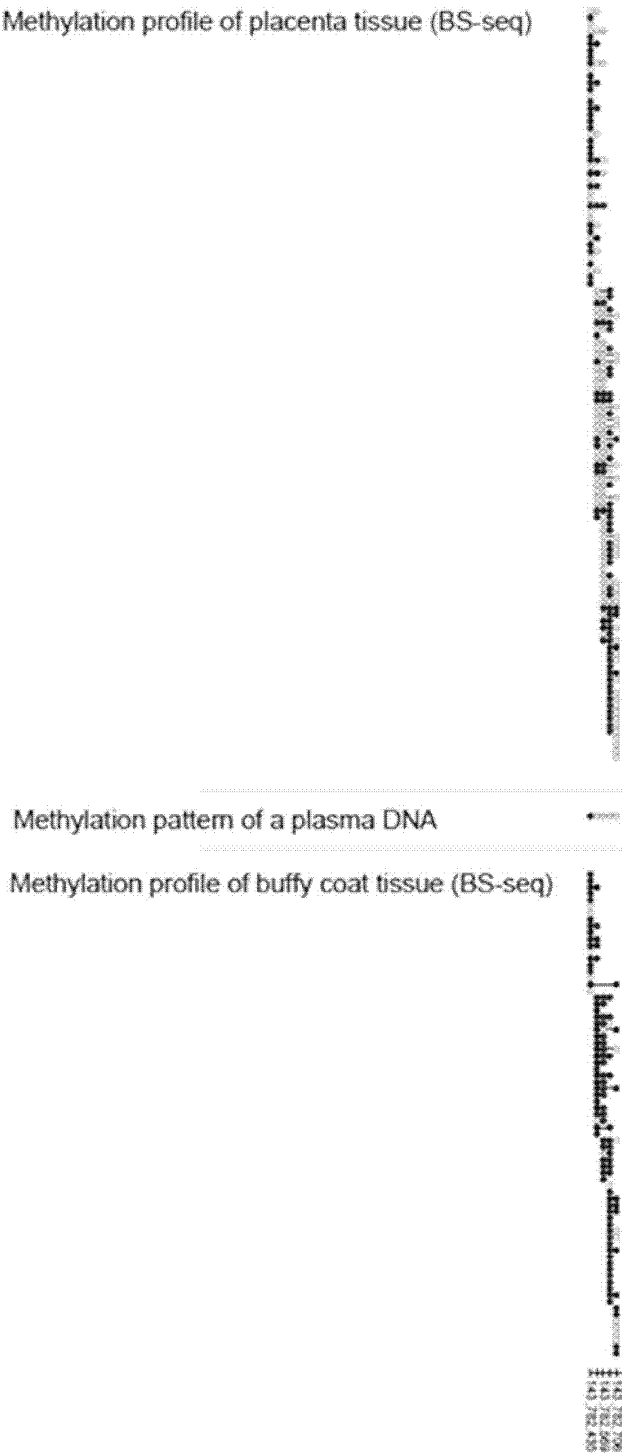


FIG. 34

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No. of CpG sites	No. of regions	Proportion (%)
≥1 CpG sites	5,333,526	86.14
≥2 CpG sites	4,534,728	73.24
≥3 CpG sites	3,604,867	58.22
≥4 CpG sites	2,782,129	44.94
≥5 CpG sites	2,141,548	34.59
≥6 CpG sites	1,668,019	26.94
≥7 CpG sites	1,317,812	21.28
≥8 CpG sites	1,052,634	17.00
≥9 CpG sites	847,632	13.69
≥10 CpG sites	685,932	11.08

FIG. 35

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No. of CpG sites	No. of regions	Proportion (%)
≥1 CpG sites	2,837,927	91.67
≥2 CpG sites	2,752,954	88.93
≥3 CpG sites	2,587,701	83.59
≥4 CpG sites	2,353,438	76.02
≥5 CpG sites	2,085,412	67.37
≥6 CpG sites	1,817,052	58.70
≥7 CpG sites	1,570,860	50.74
≥8 CpG sites	1,356,211	43.81
≥9 CpG sites	1,173,199	37.90
≥10 CpG sites	1,018,695	32.91

FIG. 36

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No. of CpG sites	No. of regions	Proportion (%)
≥1 CpG sites	953,995	92.45
≥2 CpG sites	953,934	92.45
≥3 CpG sites	953,690	92.42
≥4 CpG sites	953,021	92.36
≥5 CpG sites	951,431	92.20
≥6 CpG sites	948,049	91.87
≥7 CpG sites	941,929	91.28
≥8 CpG sites	932,143	90.33
≥9 CpG sites	918,007	88.96
≥10 CpG sites	898,679	87.09

FIG. 37

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Sample	Hematopoietic cell contribution (%)	Liver contribution (%)	Placental contribution (%)
M13323	59.31	12.1	28.6
M13324	53.12	14.61	32.27
M13315	55.15	16.16	28.69
M13318	57.26	14.28	28.47
M13211	55.4	15.58	29.02
M13230	49.41	18.51	32.09
M13304	55.03	14.57	30.39
M13199	55.86	13.55	30.59
M13198	57.72	12.46	29.82

FIG. 38

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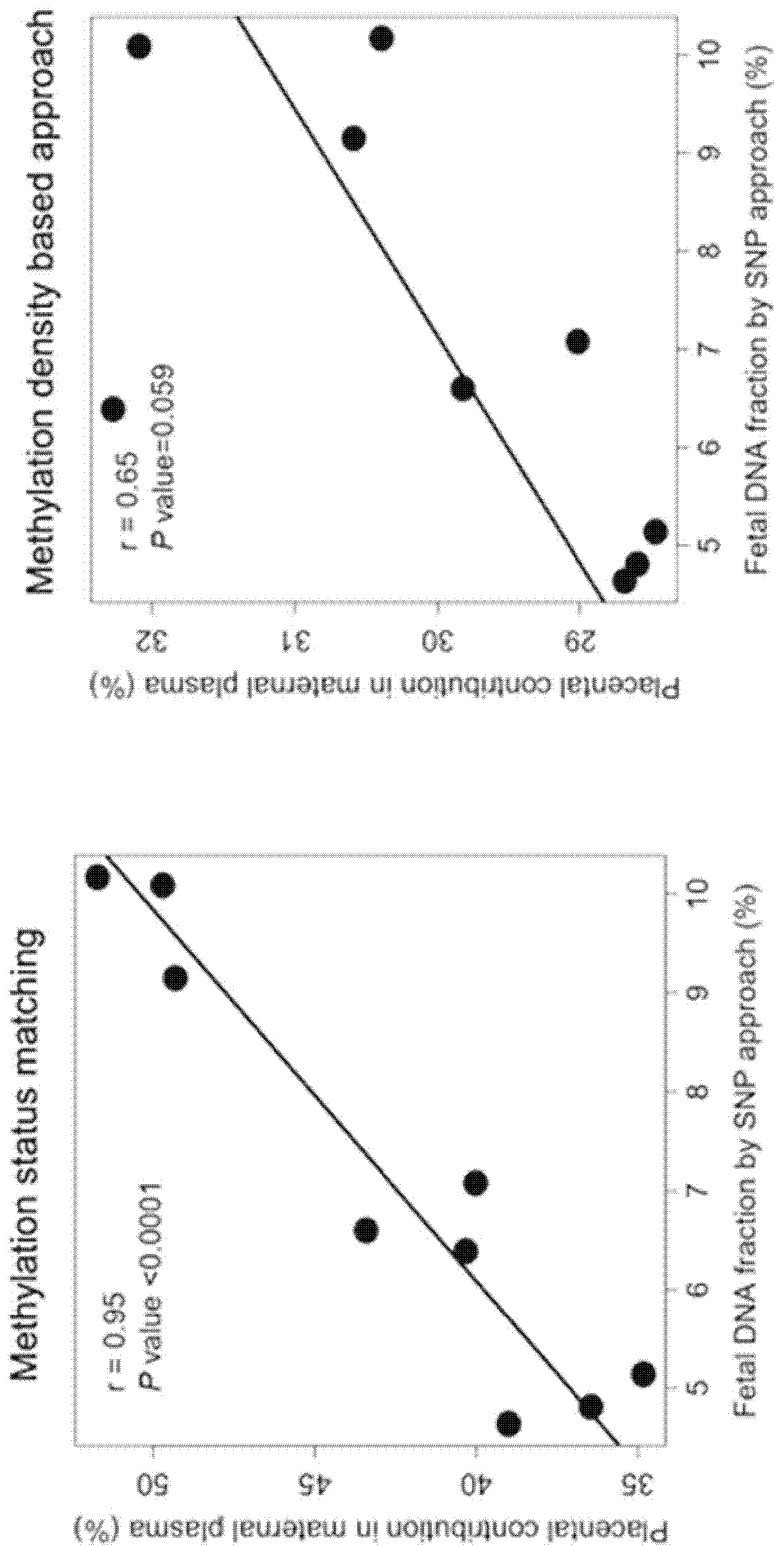
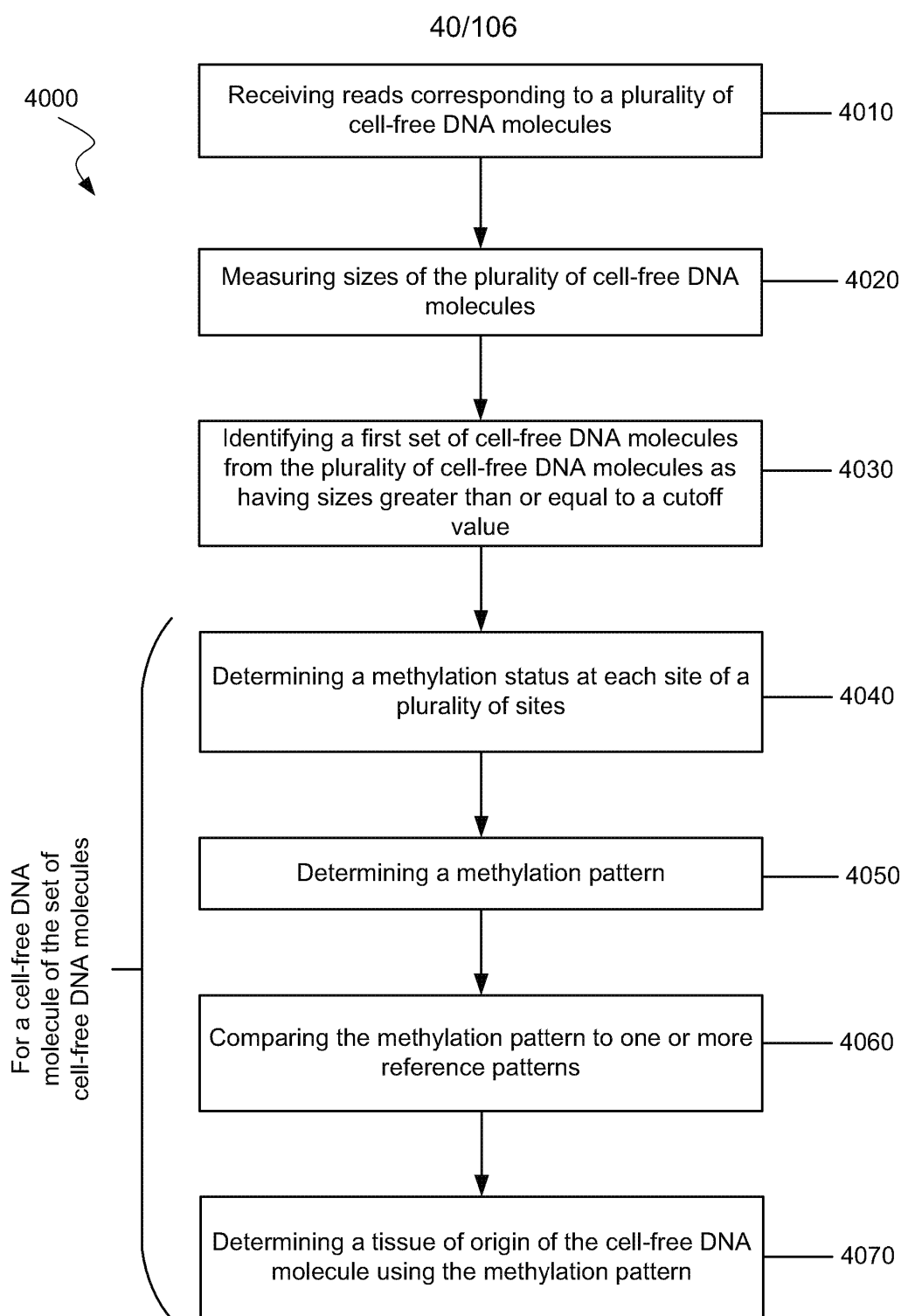


FIG. 39B

FIG. 39A

**FIG. 40**

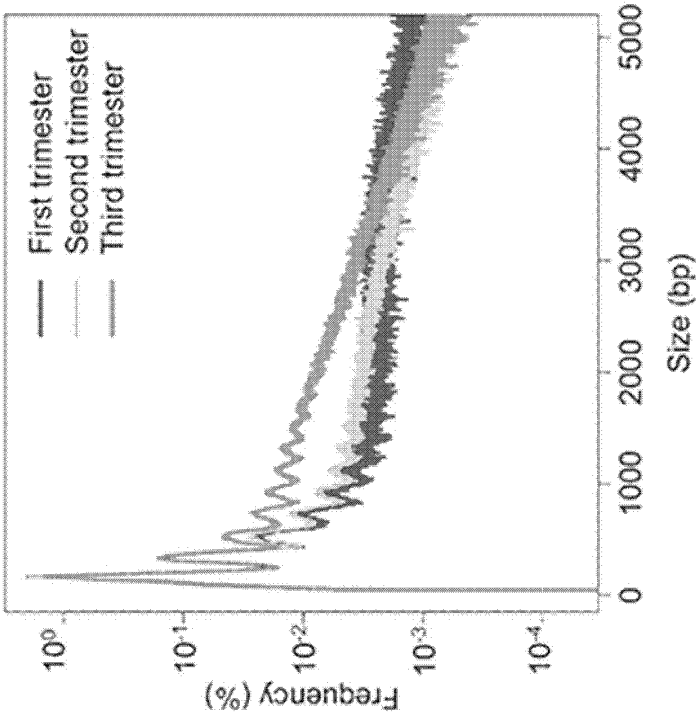


FIG. 41B

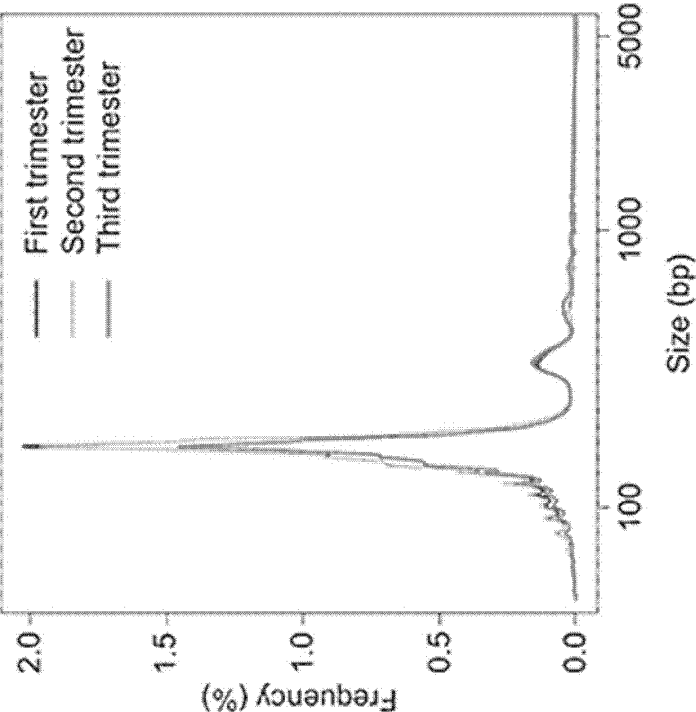


FIG. 41A

	Proportion of DNA molecules > 500 bp (%)	Proportion of DNA molecules > 1 kb (%)
First trimester maternal plasma	15.8	11.3
Second trimester maternal plasma	16.1	10.6
Third trimester maternal plasma	32.3	21.4

FIG. 42

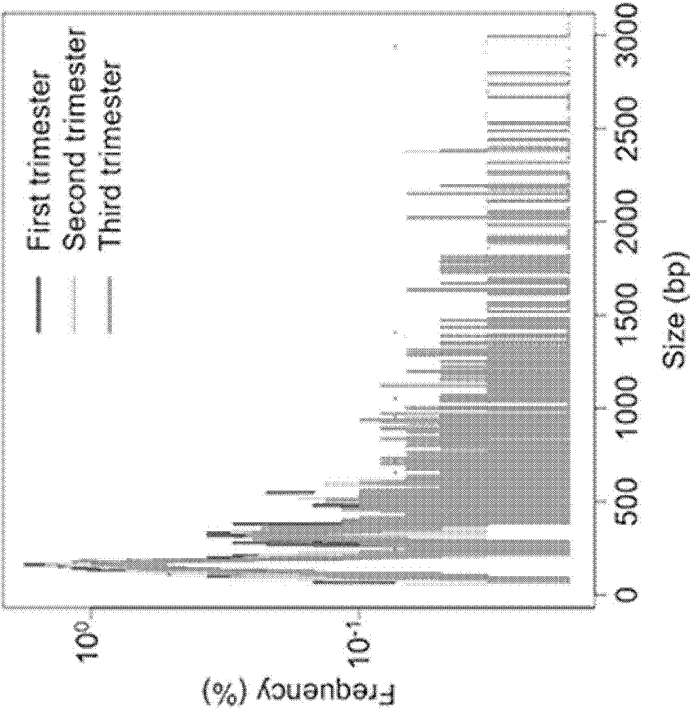


FIG. 43B

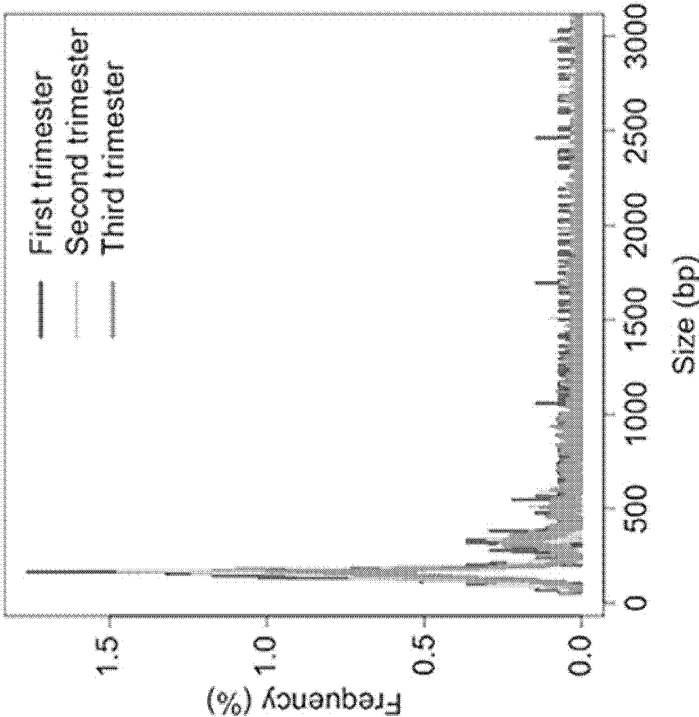


FIG. 43A

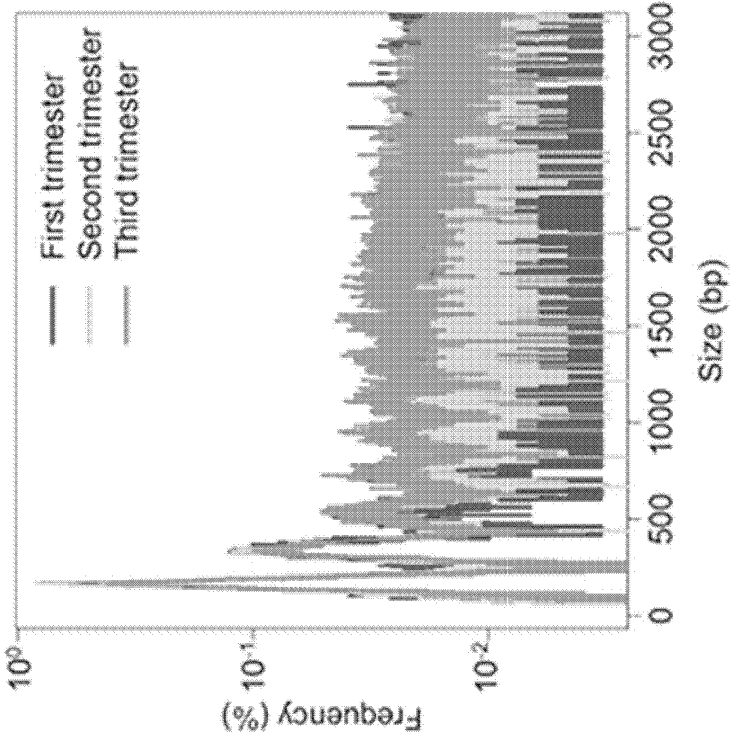


FIG. 44B

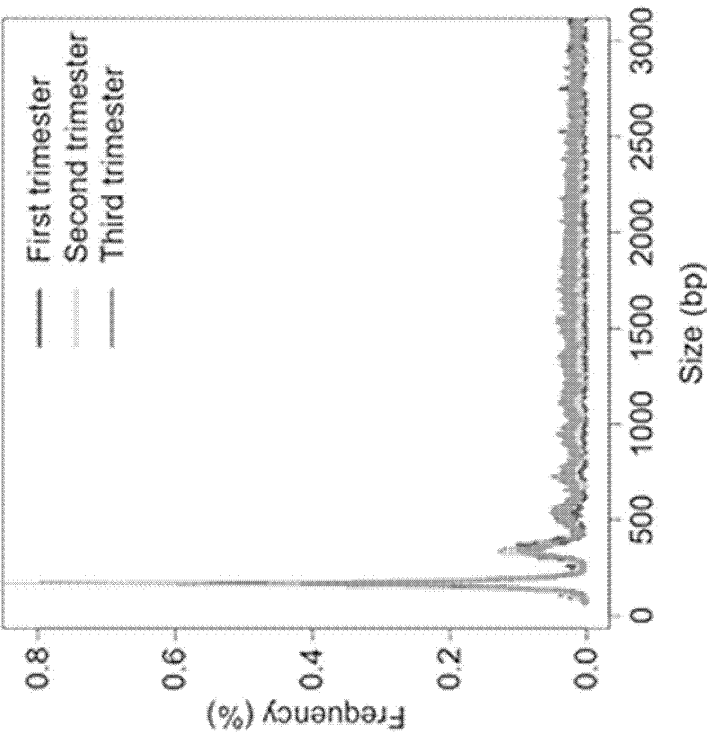


FIG. 44A

	Proportion of fetal DNA molecules > 500 bp (%)	Proportion of maternal DNA molecules > 500 bp (%)	Proportion of fetal DNA molecules > 1 kb (%)	Proportion of maternal DNA molecules > 1 kb (%)
First trimester maternal plasma	19.8	65.6	15.2	59.0
Second trimester maternal plasma	23.2	62.6	16.5	53.9
Third trimester maternal plasma	31.7	76.2	19.9	64.3

FIG. 45

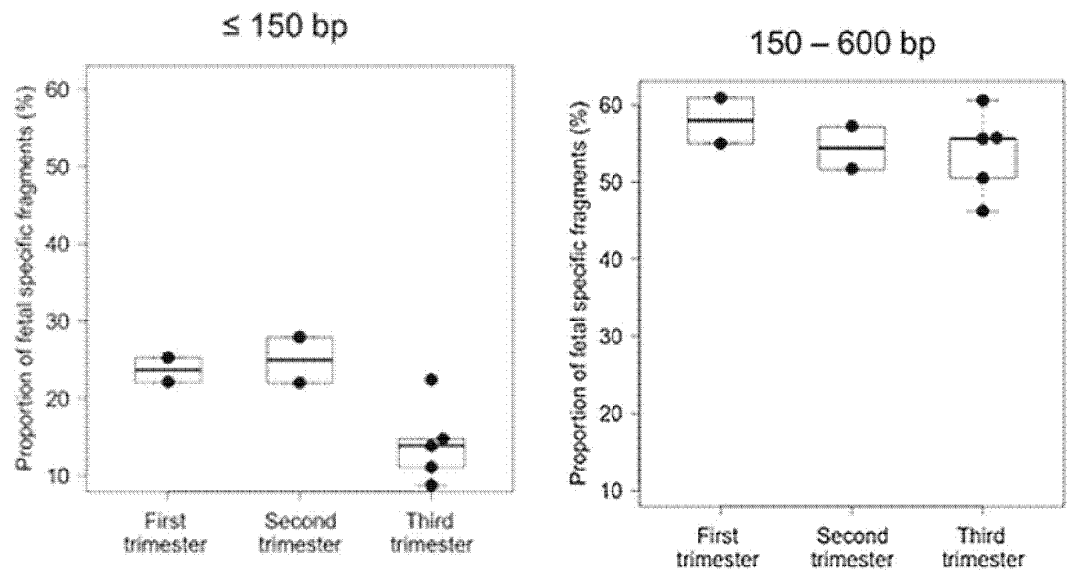


FIG. 46A

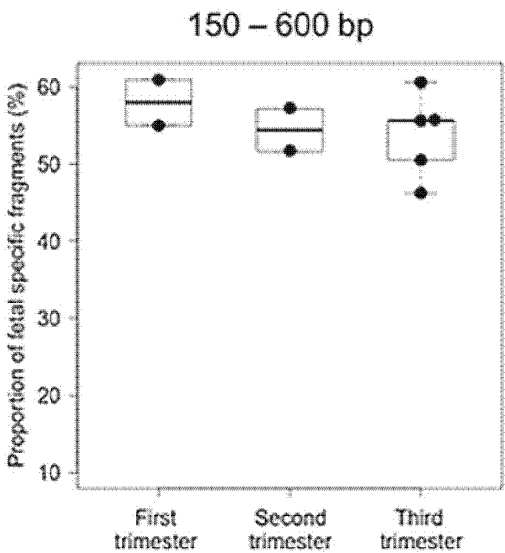


FIG. 46B

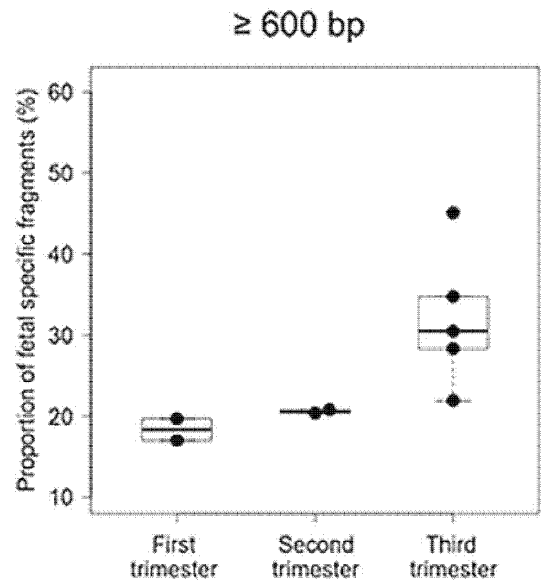


FIG. 46C

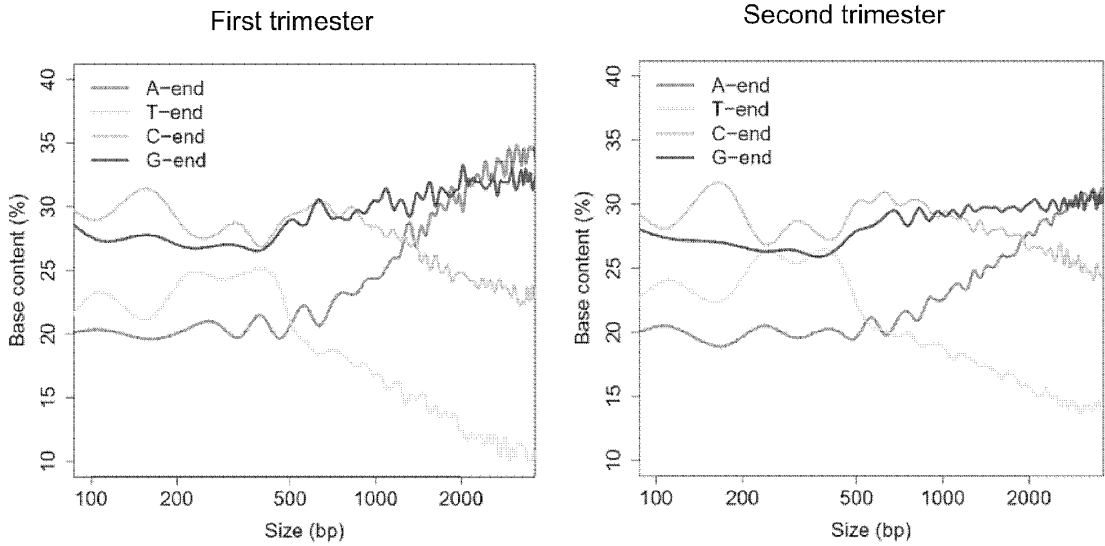


FIG. 47A

FIG. 47B

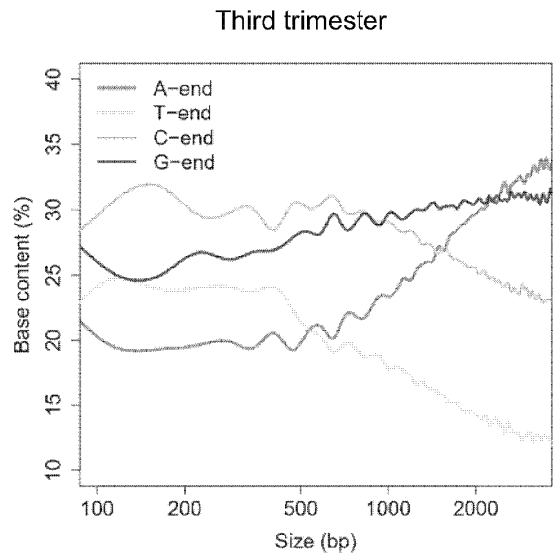


FIG. 47C

Base end	Expected proportion for an end species	First trimester maternal plasma		Second trimester maternal plasma		Third trimester maternal plasma	
		Observed proportion of an end species among fragments $\leq$ 500 bp	Observed proportion of an end species among fragments $>$ 500 bp	Observed proportion of an end species among fragments $\leq$ 500bp	Observed proportion of an end species among fragments $>$ 500 bp	Observed proportion of an end species among fragments $\leq$ 500bp	Observed proportion of an end species among fragments $>$ 500 bp
A-end	29.5	19.8	29.6	19.4	26.0	19.3	26.7
T-end	29.5	22.4	13.9	23.3	16.9	24.1	16.4
C-end	20.5	30.4	25.5	30.4	27.5	31.3	27.1
G-end	20.5	27.4	31.0	26.9	29.5	25.3	29.9

FIG. 48

Base end	Expected end-base proportions	First trimester maternal plasma		Second trimester maternal plasma		Third trimester maternal plasma	
		End-base proportions among fragments $\leq$ 500 bp	End-base proportions among fragments $>$ 500 bp	End-base proportions among fragments $\leq$ 500bp	End-base proportions among fragments $>$ 500 bp	End-base proportions among fragments $\leq$ 500bp	End-base proportions among fragments $>$ 500 bp
A-end	29.5	18.3	30.5	19.7	25.7	18.4	22.9
T-end	29.5	24.2	14.7	23.2	16.0	23.0	17.7
C-end	20.5	31.1	24.9	29.7	28.5	31.8	29.0
G-end	20.5	26.4	29.9	27.4	29.8	26.9	30.5

FIG. 49

Base end	Expected end-base proportions	First trimester maternal plasma		Second trimester maternal plasma		Third trimester maternal plasma	
		End-base proportions among fragments $\leq$ 500 bp	End-base proportions among fragments $>$ 500 bp	End-base proportions among fragments $\leq$ 500 bp	End-base proportions among fragments $>$ 500 bp	End-base proportions among fragments $\leq$ 500 bp	End-base proportions among fragments $>$ 500 bp
A-end	29.5	19.3	32.4	19.4	28.1	19.6	29.0
T-end	29.5	22.0	11.4	23.0	15.1	22.2	13.5
C-end	20.5	31.2	24.4	31.1	26.6	31.4	26.0
G-end	20.5	27.5	31.8	26.6	30.2	26.9	31.5

FIG. 50

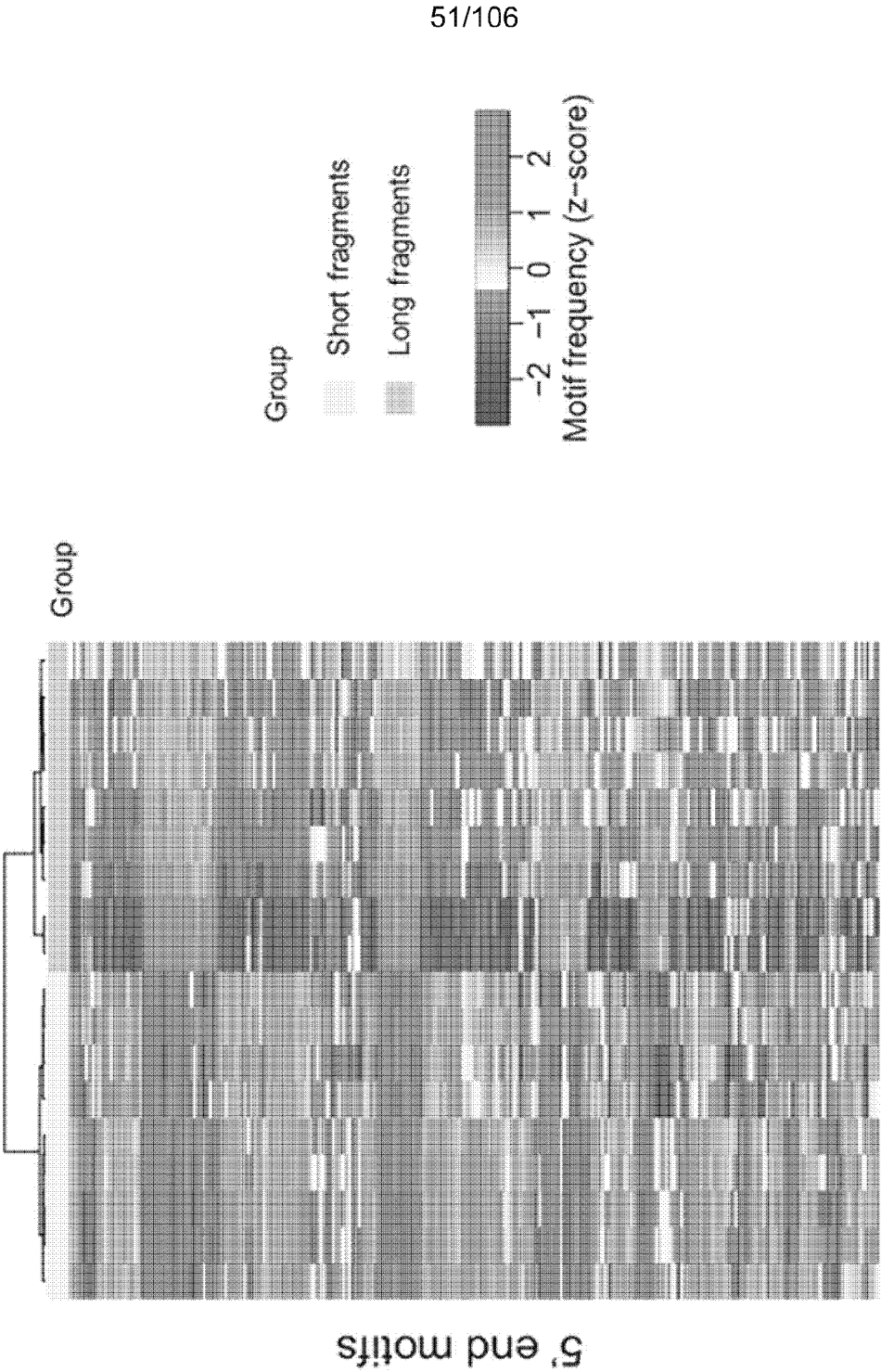


FIG. 51

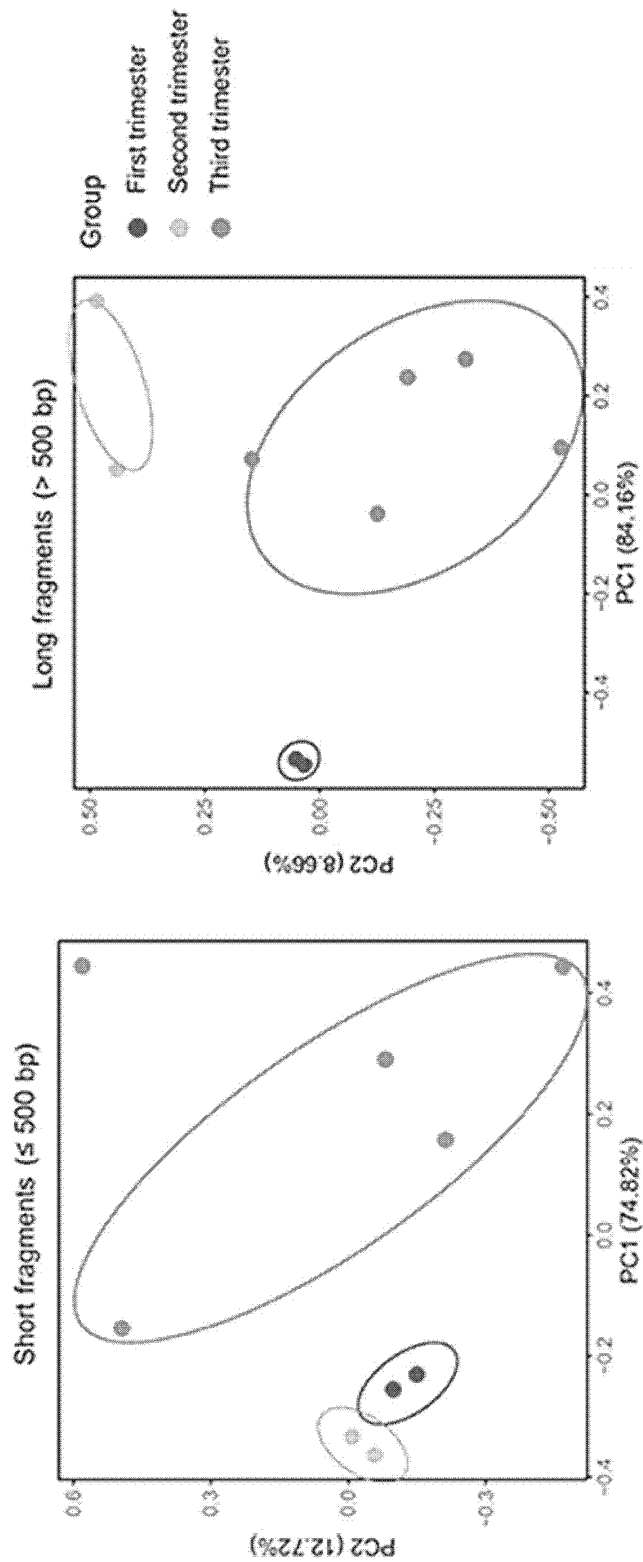


FIG. 52A

FIG. 52B

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Motif	Rank in short fragments (≤ 500 bp)	Rank in long fragments (> 500 bp)	Frequency in short fragments (%) (A)	Frequency in long fragments (%) (B)	Fold change (A/B)
CCCA	1	16	2.12	1.15	1.84
CCTG	2	17	1.67	1.10	1.52
CCAG	3	29	1.46	0.74	1.98
CCTC	4	7	1.35	1.43	0.94
CCTT	5	3	1.31	1.96	0.67
CCAA	6	30	1.26	0.74	1.70
AAAA	7	28	1.23	0.74	1.66
CCAC	8	38	1.07	0.68	1.57
CCCT	9	23	1.04	0.87	1.19
GCCT	10	10	1.03	1.29	0.80
CCAT	11	27	0.98	0.75	1.31
GCCA	12	33	0.97	0.72	1.35
CCCC	13	51	0.97	0.59	1.64
GCTG	14	19	0.97	1.01	0.95
GGAG	15	72	0.95	0.46	2.07
GGAA	16	49	0.93	0.61	1.52
CAAA	17	58	0.92	0.55	1.67
GAAA	18	43	0.86	0.66	1.30
TGTG	19	84	0.84	0.40	2.12
GCTT	20	2	0.83	2.30	0.36
TGTT	21	65	0.82	0.51	1.61
GGCT	22	15	0.82	1.17	0.70
CCTA	23	36	0.82	0.69	1.18
GGTG	24	48	0.81	0.61	1.33
CACA	25	40	0.81	0.67	1.20

FIG. 53

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Motif	Rank in short fragments (≤ 500 bp)	Rank in long fragments (> 500 bp)	Frequency in short fragments (%) (A)	Frequency in long fragments (%) (B)	Fold change (A/B)
CCCA	1	4	2.12	1.49	1.42
CCTG	2	7	1.69	1.30	1.30
CCAG	3	13	1.49	1.03	1.44
CCTC	4	5	1.28	1.33	0.96
CCTT	5	2	1.28	1.73	0.74
CCAA	6	16	1.26	0.97	1.31
AAAA	7	26	1.26	0.84	1.50
CCAC	8	28	1.07	0.82	1.31
CCCT	9	19	1.06	0.92	1.15
CCAT	10	22	1.00	0.88	1.14
GCCT	11	8	0.99	1.16	0.85
GGAG	12	46	0.97	0.63	1.54
CCCC	13	38	0.97	0.68	1.42
GCCA	14	25	0.97	0.86	1.12
CAAA	15	35	0.95	0.71	1.34
GCTG	16	14	0.94	1.01	0.93
GGAA	17	34	0.92	0.71	1.30
GAAA	18	31	0.89	0.75	1.18
TGTG	19	55	0.88	0.56	1.57
TGTT	20	48	0.85	0.61	1.40
CACA	21	32	0.82	0.75	1.09
CCTA	22	29	0.82	0.78	1.04
GCAG	23	47	0.81	0.62	1.32
TGAG	24	75	0.81	0.45	1.79
GGTG	25	40	0.80	0.66	1.21

FIG. 54

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Motif	Rank in short fragments (≤ 500 bp)	Rank in long fragments (> 500 bp)	Frequency in short fragments (%) (A)	Frequency in long fragments (%) (B)	Fold change (A/B)
CCCA	1	6	2.21	1.40	1.58
CCTG	2	7	1.80	1.28	1.40
CCAG	3	17	1.53	0.98	1.57
CCTC	4	4	1.39	1.40	0.99
CCTT	5	3	1.28	1.68	0.77
CCAA	6	22	1.26	0.89	1.42
CCAC	7	26	1.13	0.80	1.41
AAAA	8	29	1.12	0.76	1.47
CCCT	9	25	1.06	0.84	1.26
GCCA	10	24	1.05	0.87	1.21
GCCT	11	8	1.04	1.23	0.85
GGAG	12	46	1.02	0.63	1.63
CCCC	13	44	1.00	0.64	1.57
GCTG	14	14	0.98	1.03	0.95
CCAT	15	27	0.97	0.78	1.24
GGAA	16	35	0.95	0.72	1.32
GGCT	17	12	0.87	1.09	0.80
GGTG	18	38	0.87	0.70	1.24
GGCA	19	33	0.86	0.72	1.19
CAAA	20	42	0.86	0.64	1.33
TGTG	21	62	0.85	0.51	1.67
GAAA	22	34	0.83	0.72	1.15
GCTT	23	2	0.82	1.88	0.44
CACA	24	31	0.82	0.74	1.11
CCTA	25	32	0.82	0.74	1.11

FIG. 55

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Motif	Rank in long fragments (> 500 bp)	Rank in short fragments (≤ 500 bp)	Frequency in long fragments (%) (A)	Frequency in short fragments (%) (B)	Fold change (A/B)
ACTT	1	39	2.99	0.63	4.76
GCTT	2	20	2.30	0.83	2.76
CCTT	3	5	1.96	1.31	1.50
GTTT	4	40	1.77	0.63	2.82
ACCT	5	56	1.48	0.56	2.63
ACTG	6	53	1.47	0.57	2.57
CCTC	7	4	1.43	1.35	1.06
ACTC	8	76	1.34	0.48	2.79
GATT	9	83	1.29	0.46	2.81
GCCT	10	10	1.29	1.03	1.26
CTTT	11	31	1.24	0.69	1.79
AGTT	12	102	1.21	0.41	2.99
CATT	13	32	1.21	0.69	1.75
ACAT	14	75	1.17	0.48	2.42
GGCT	15	22	1.17	0.82	1.43
CCCA	16	1	1.15	2.12	0.54
CCTG	17	2	1.10	1.67	0.66
GGTT	18	36	1.09	0.65	1.69
GCTG	19	14	1.01	0.97	1.05
GCTC	20	49	0.99	0.58	1.70
ATTT	21	139	0.98	0.30	3.23
ACCA	22	43	0.97	0.61	1.60
CCCT	23	9	0.87	1.04	0.84
GAAT	24	34	0.82	0.67	1.23
CTTC	25	80	0.81	0.47	1.74

FIG. 56

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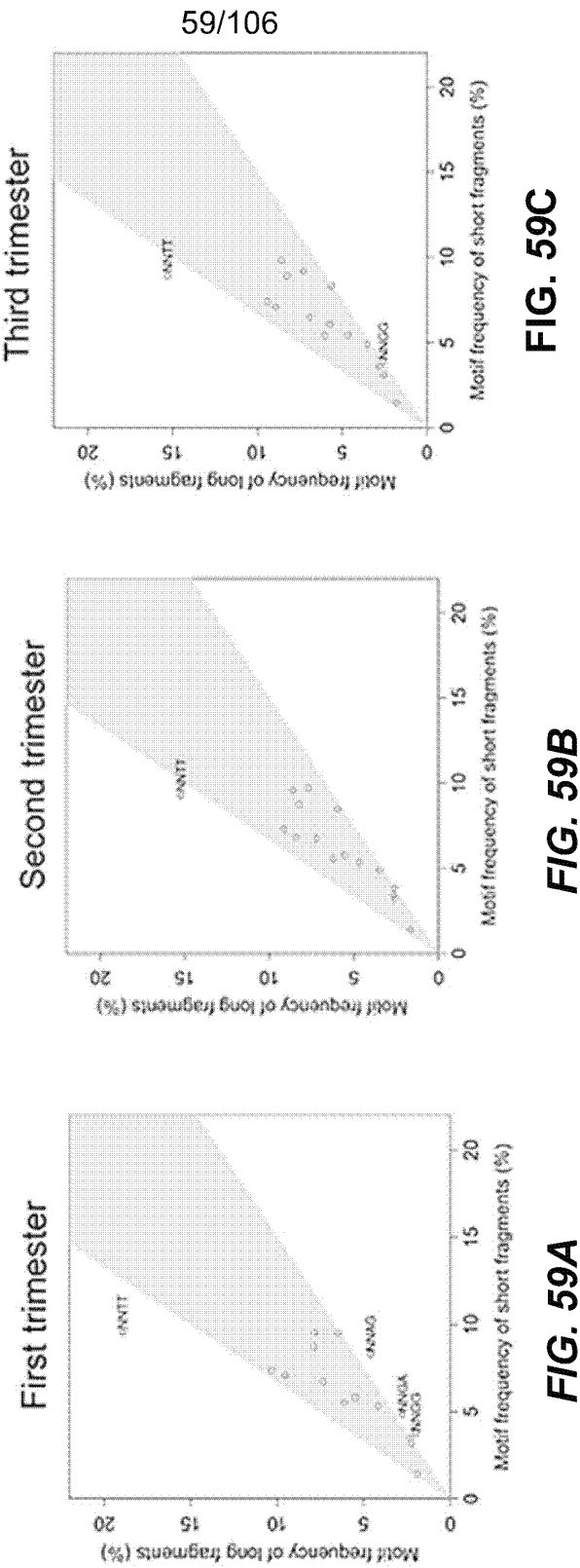
Motif	Rank in long fragments (> 500 bp)	Rank in short fragments (≤ 500 bp)	Frequency in long fragments (%) (A)	Frequency in short fragments (%) (B)	Fold change (A/B)
ACTT	1	64	2.01	0.54	3.75
CCTT	2	5	1.73	1.28	1.35
GCTT	3	29	1.68	0.76	2.20
CCCA	4	1	1.49	2.12	0.70
CCTC	5	4	1.33	1.28	1.04
GTTT	6	46	1.32	0.59	2.25
CCTG	7	2	1.30	1.69	0.77
GCCT	8	11	1.16	0.99	1.17
ACCT	9	66	1.15	0.53	2.17
ACTG	10	63	1.09	0.54	2.02
CTTT	11	32	1.07	0.69	1.56
CATT	12	31	1.05	0.69	1.52
CCAG	13	3	1.03	1.49	0.69
GCTG	14	16	1.01	0.94	1.07
ACTC	15	94	1.00	0.43	2.32
CCAA	16	6	0.97	1.26	0.77
GGCT	17	26	0.96	0.79	1.21
GATT	18	89	0.93	0.43	2.13
CCCT	19	9	0.92	1.06	0.87
ACAT	20	79	0.92	0.47	1.98
ACCA	21	44	0.88	0.60	1.47
CCAT	22	10	0.88	1.00	0.88

FIG. 57

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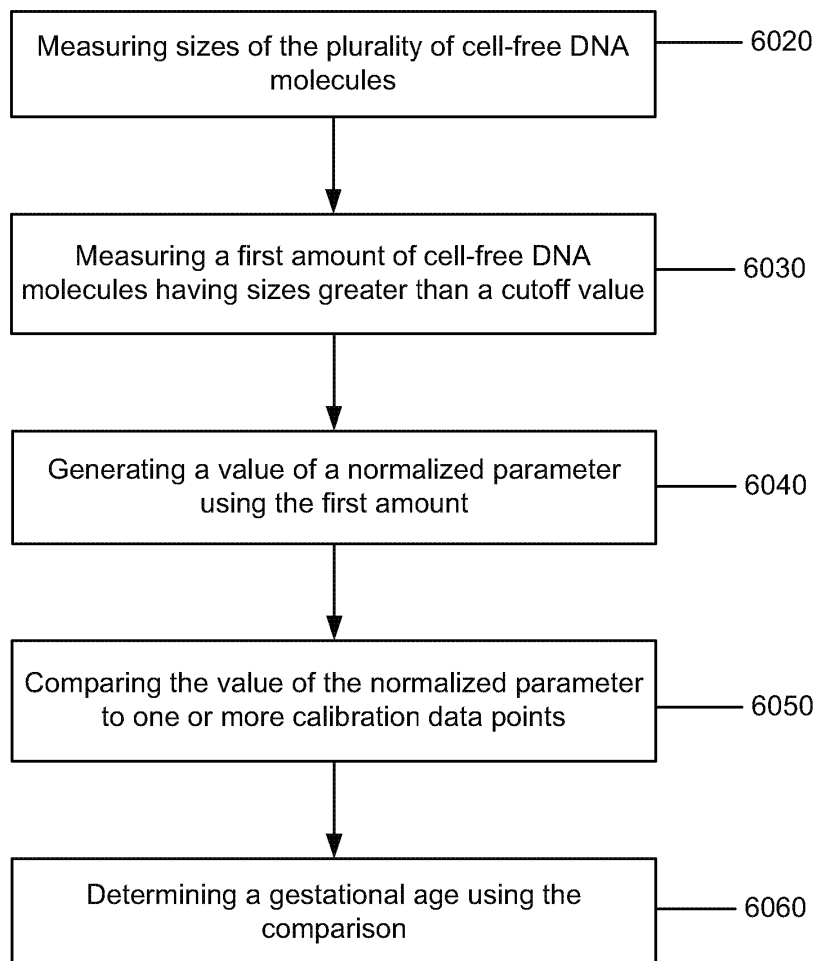
Motif	Rank in long fragments (> 500 bp)	Rank in short fragments (≤ 500 bp)	Frequency in long fragments (%) (A)	Frequency in short fragments (%) (B)	Fold change (A/B)
ACTT	1	57	2.06	0.57	3.61
GCTT	2	23	1.88	0.82	2.29
CCTT	3	5	1.68	1.28	1.30
CCTC	4	4	1.40	1.39	1.01
GTTT	5	49	1.40	0.59	2.40
CCCA	6	1	1.40	2.21	0.63
CCTG	7	2	1.28	1.80	0.71
GCCT	8	11	1.23	1.04	1.18
ACTG	9	47	1.20	0.59	2.05
ACCT	10	59	1.18	0.56	2.09
ACTC	11	78	1.12	0.48	2.36
GGCT	12	17	1.09	0.87	1.25
CTTT	13	41	1.04	0.61	1.71
GCTG	14	14	1.03	0.98	1.05
CATT	15	34	1.00	0.64	1.57
GATT	16	92	0.99	0.43	2.30
CCAG	17	3	0.98	1.53	0.64
GGTT	18	33	0.95	0.64	1.49
ACAT	19	80	0.92	0.46	1.99
GCTC	20	40	0.92	0.61	1.50
AGTT	21	115	0.91	0.37	2.46
CCAA	22	6	0.89	1.26	0.70

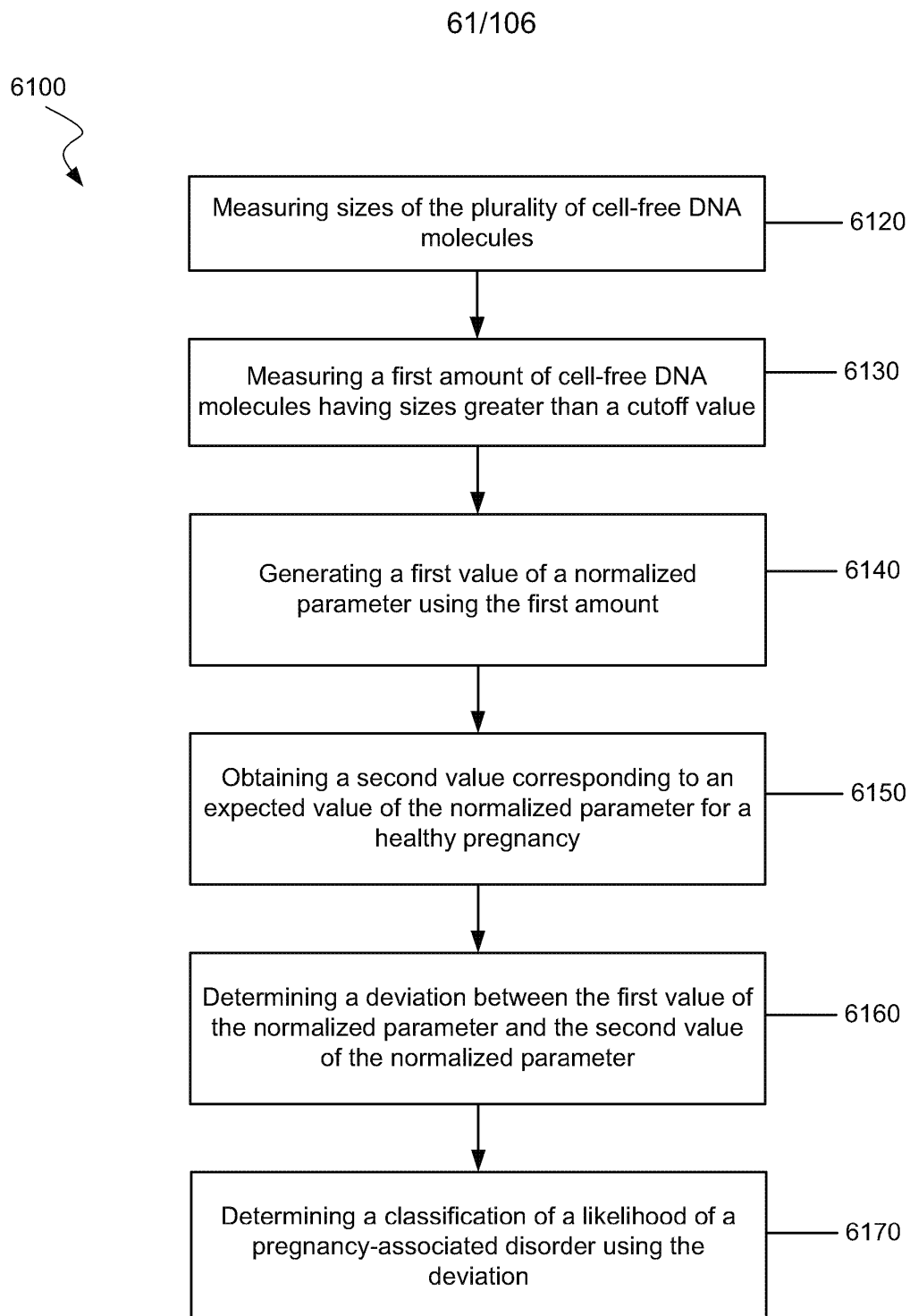
FIG. 58



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**FIG. 60**

**FIG. 61**

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Case number	Gestational age at blood sampling (week)	Fetal sex	Clinical information
M12804	34 3/7	F	Severe PET with pre- existing IgA nephropathy
M12873	37	M	Chronic hypertension with superimposed mild PET
M12876	36	F	Severe late-onset PET
M12903	35 5/7	M	Severe late-onset PET with IUGR

FIG. 62

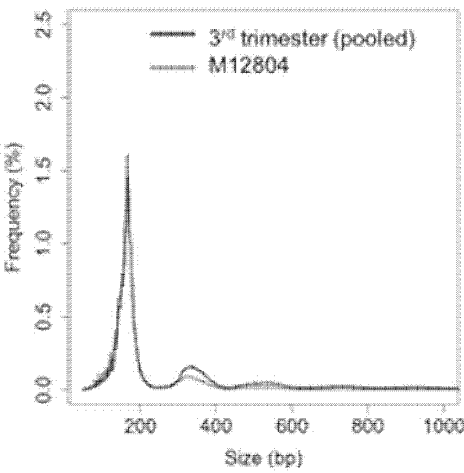


FIG. 63A

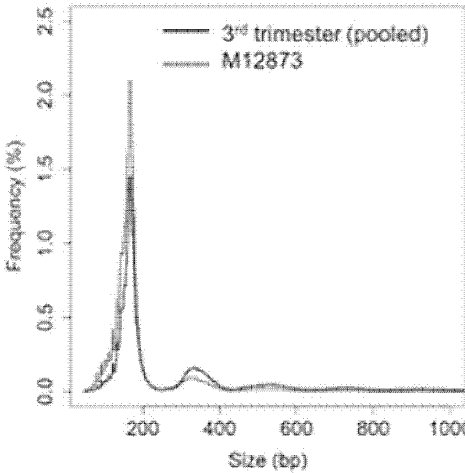


FIG. 63B

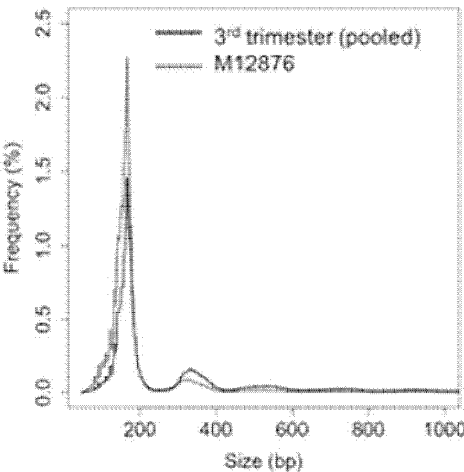


FIG. 63C

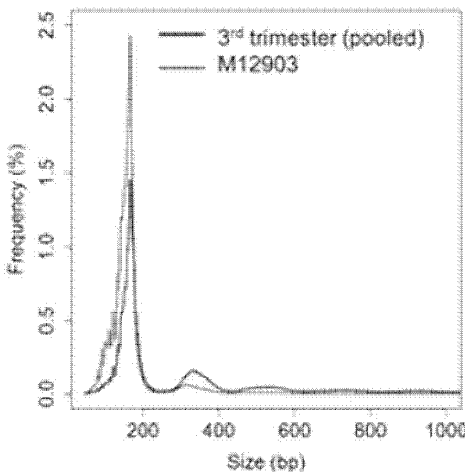


FIG. 63D

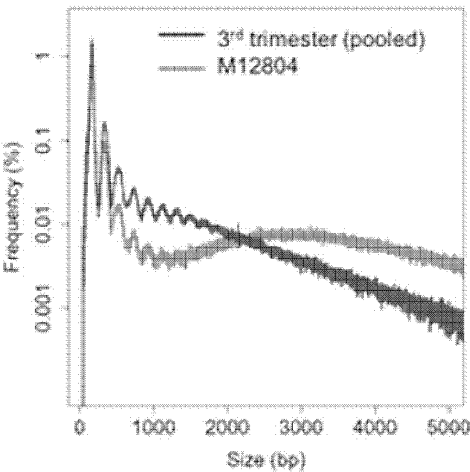


FIG. 64A

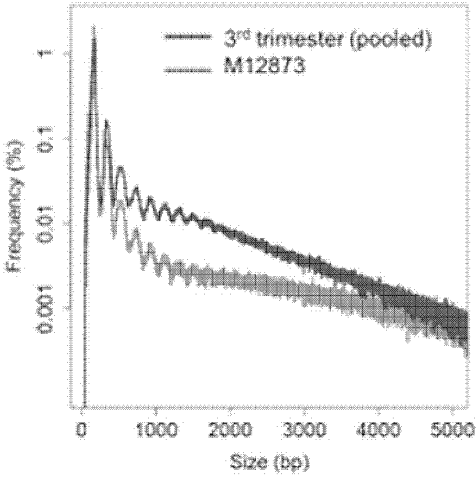


FIG. 64B

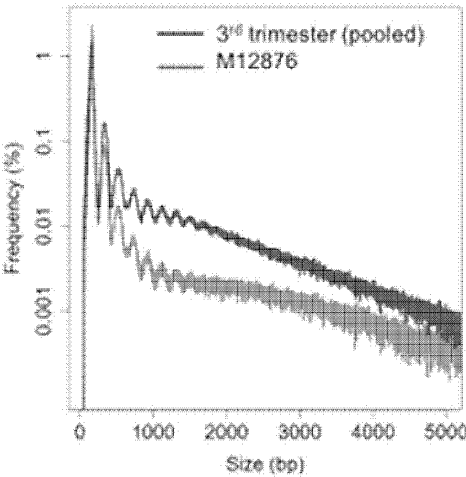


FIG. 64C

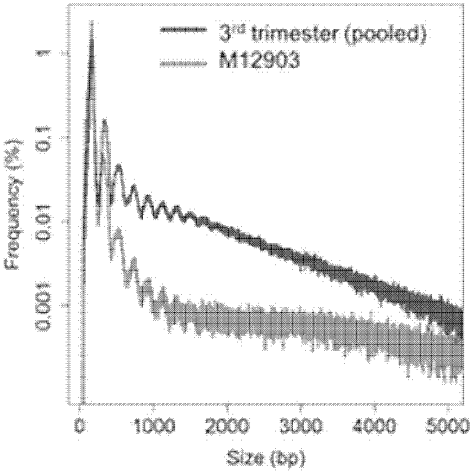


FIG. 64D

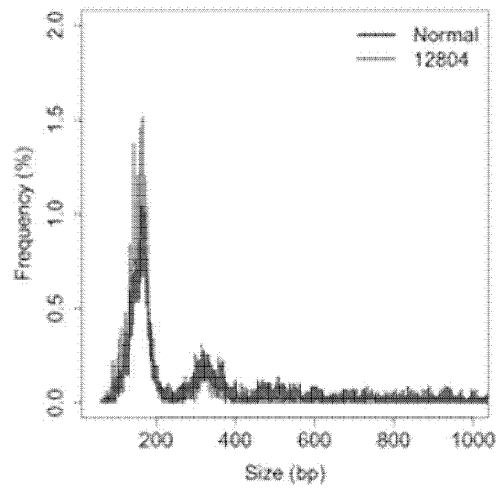


FIG. 65A

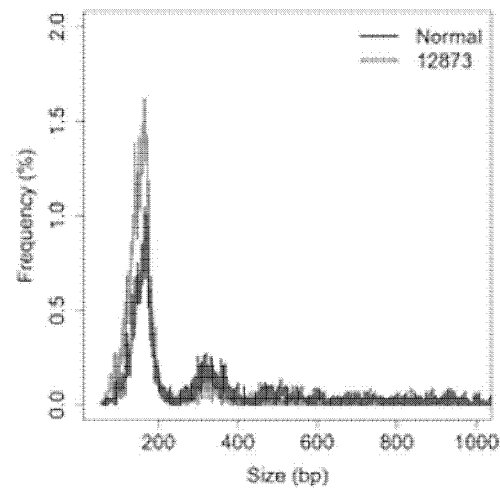


FIG. 65B

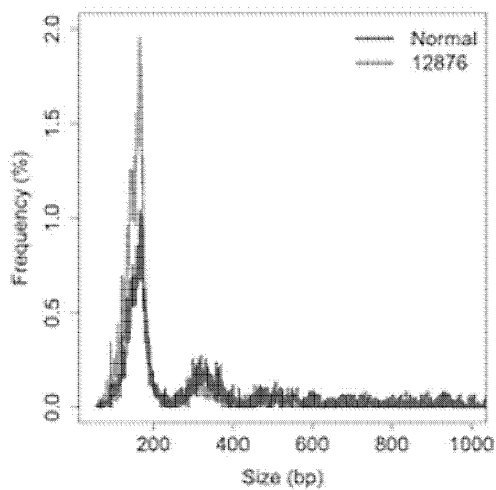


FIG. 65C

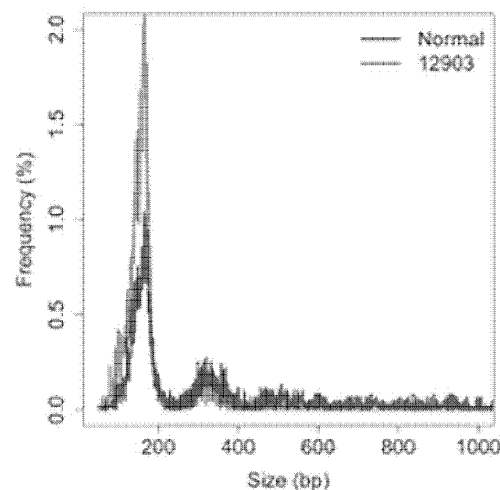


FIG. 65D

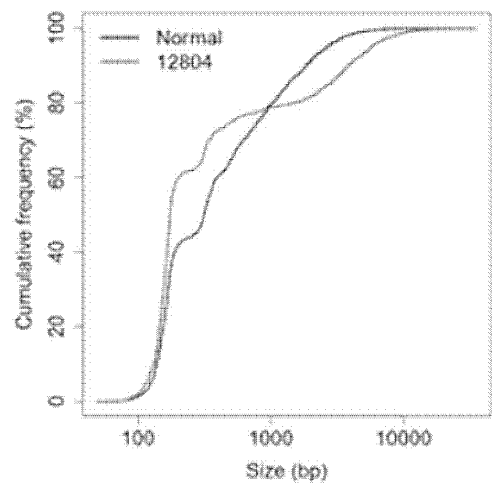


FIG. 66A

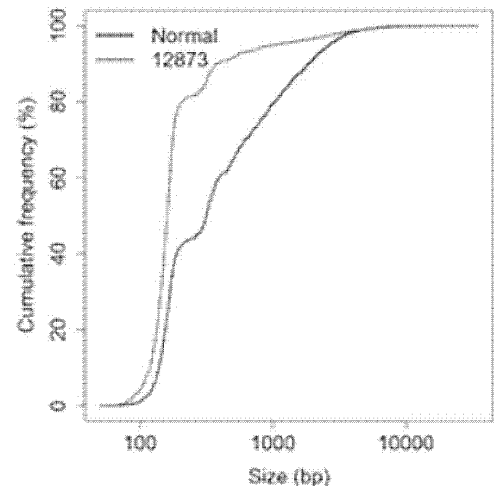


FIG. 66B

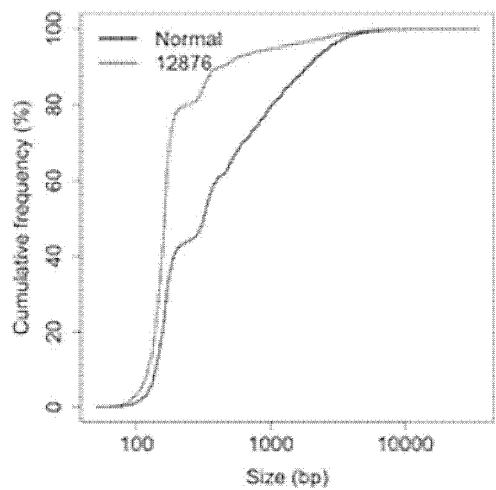


FIG. 66C

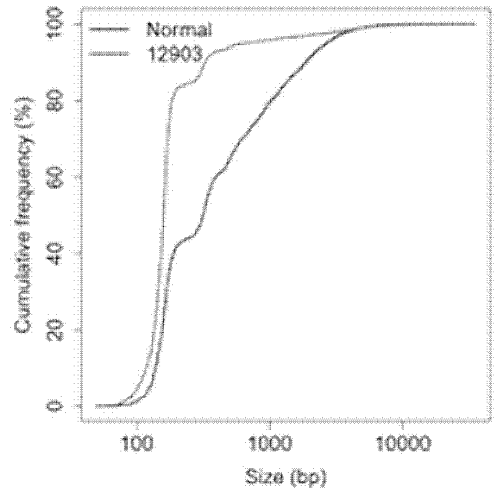
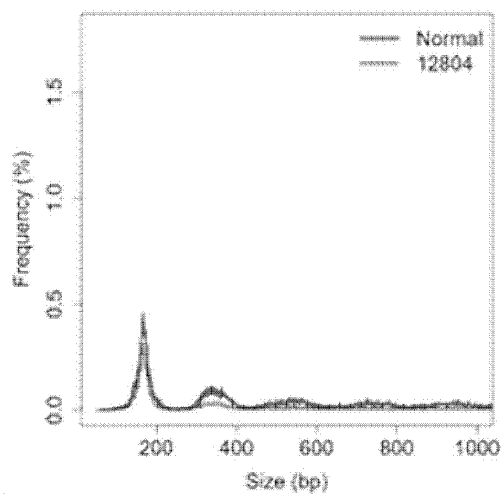
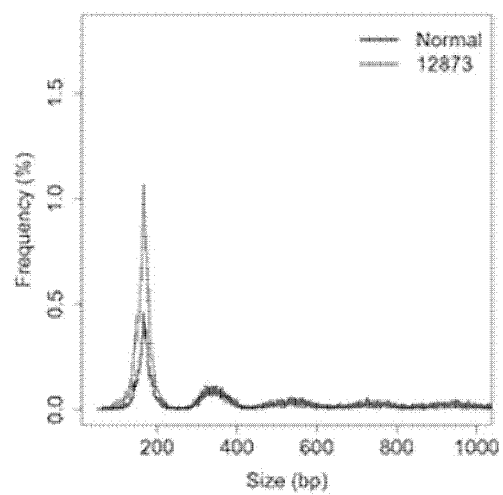
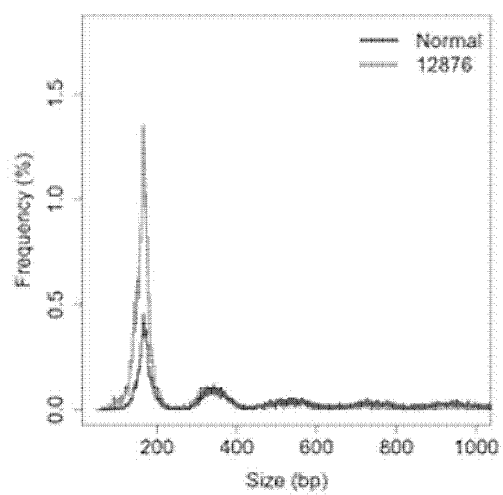
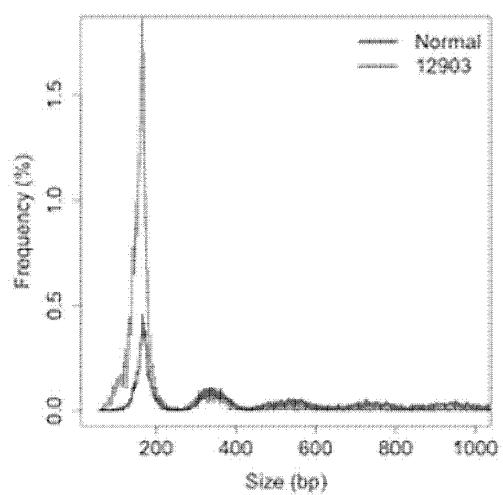


FIG. 66D

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**FIG. 67A****FIG. 67B****FIG. 67C****FIG. 67D**

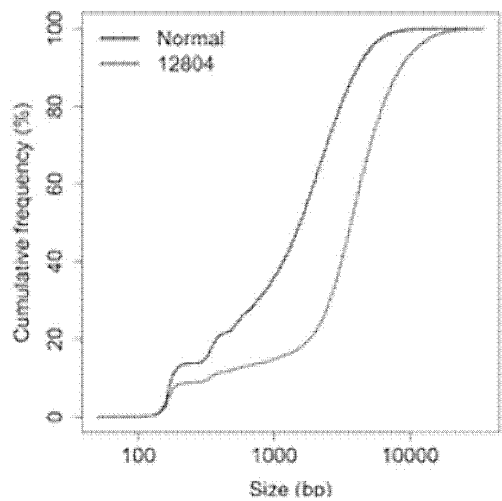


FIG. 68A

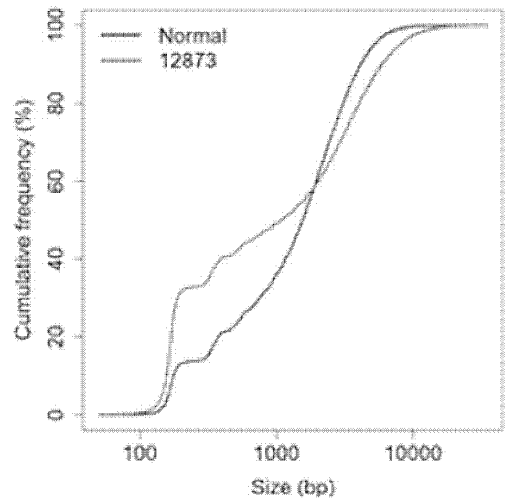


FIG. 68B

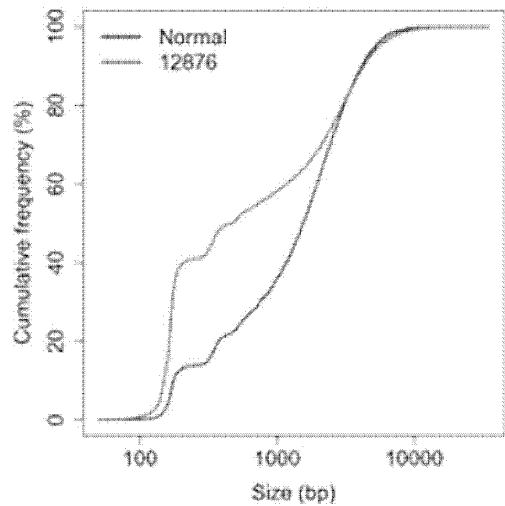


FIG. 68C

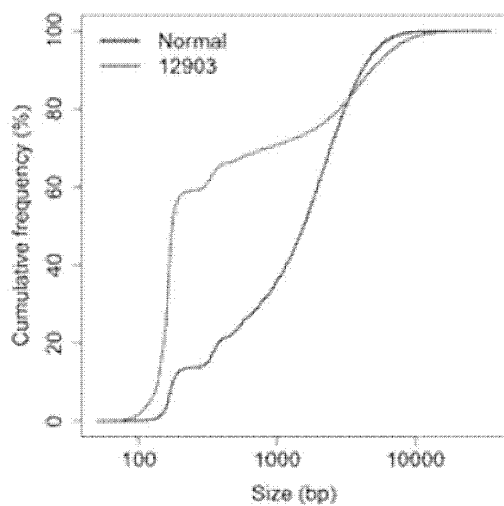


FIG. 68D

Plasma DNA molecules covering maternal-specific alleles

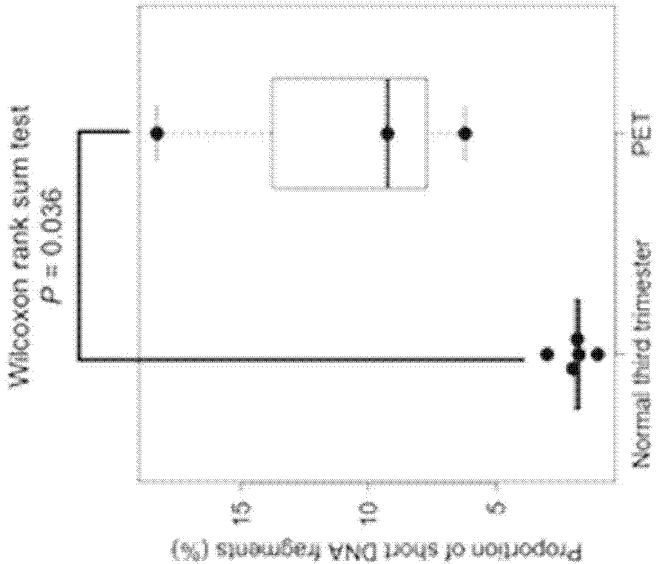


FIG. 69B

Plasma DNA molecules covering fetal-specific alleles

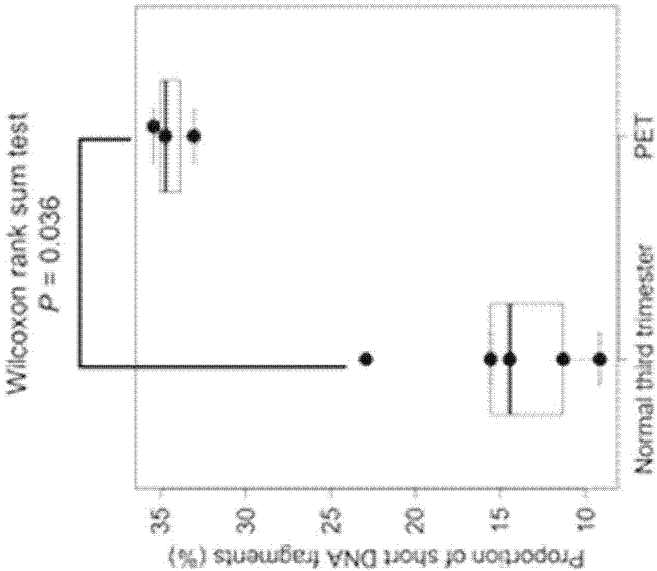


FIG. 69A

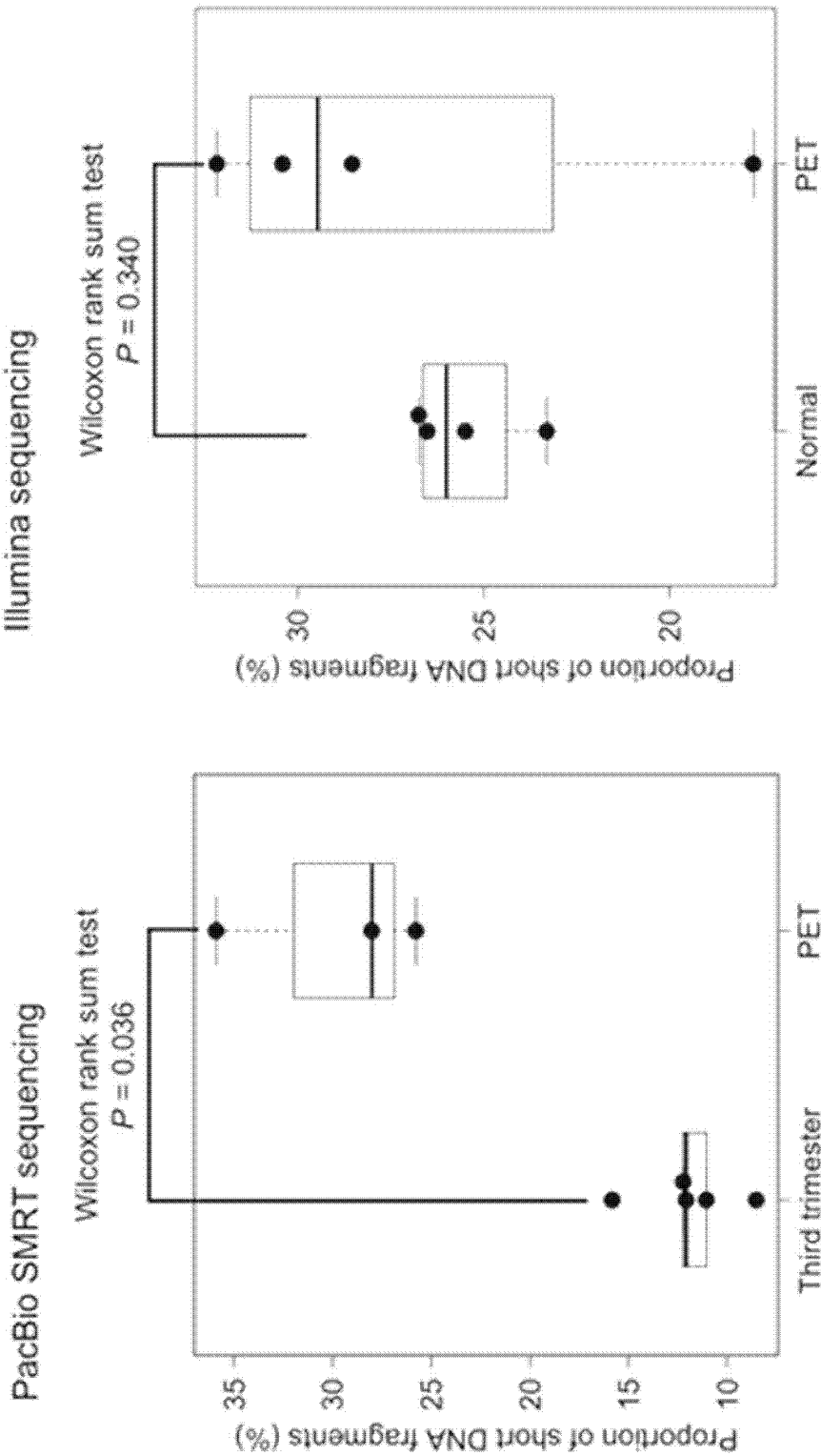


FIG. 70B

FIG. 70A

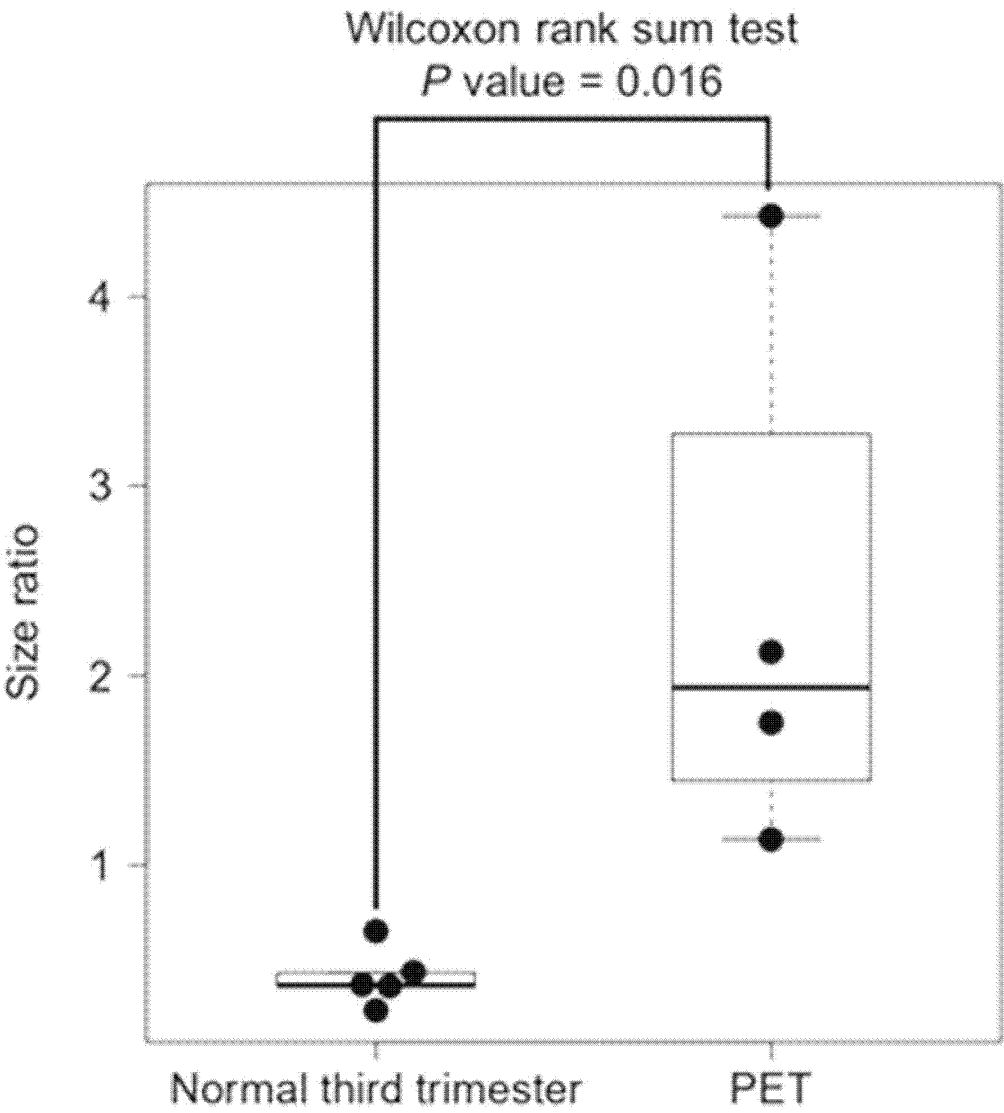


FIG. 71

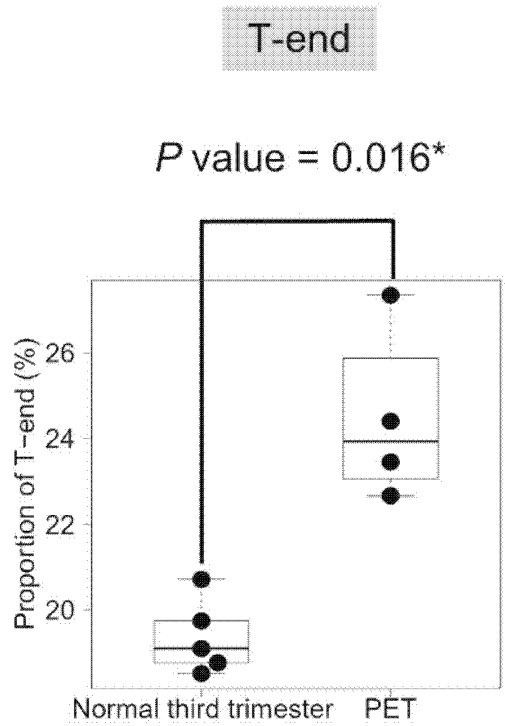


FIG. 72A

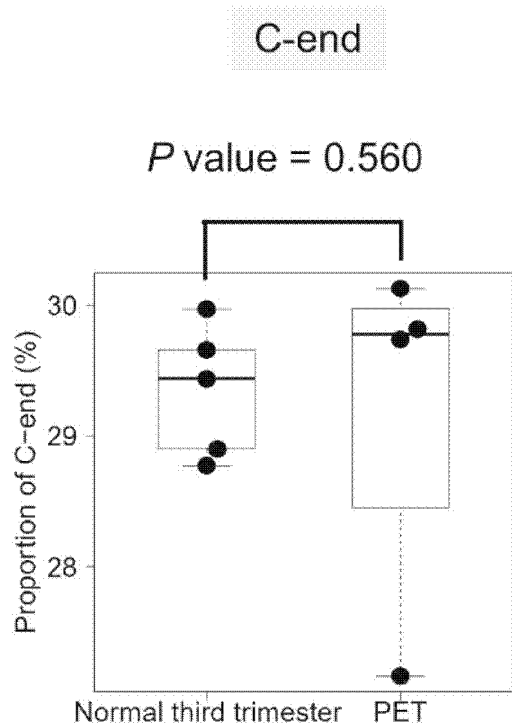


FIG. 72B

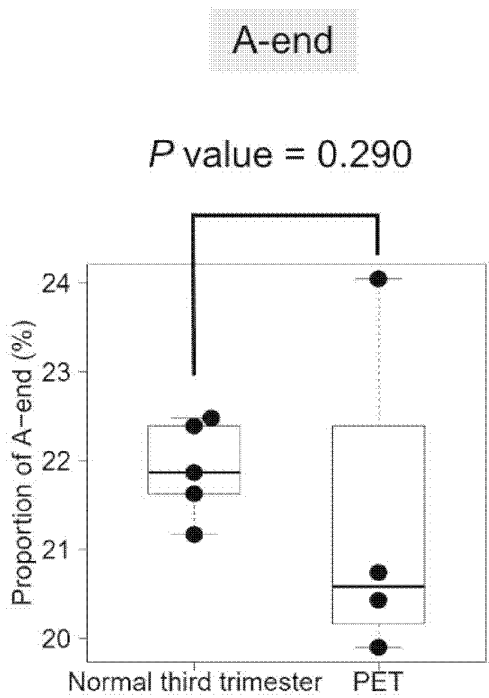


FIG. 72C

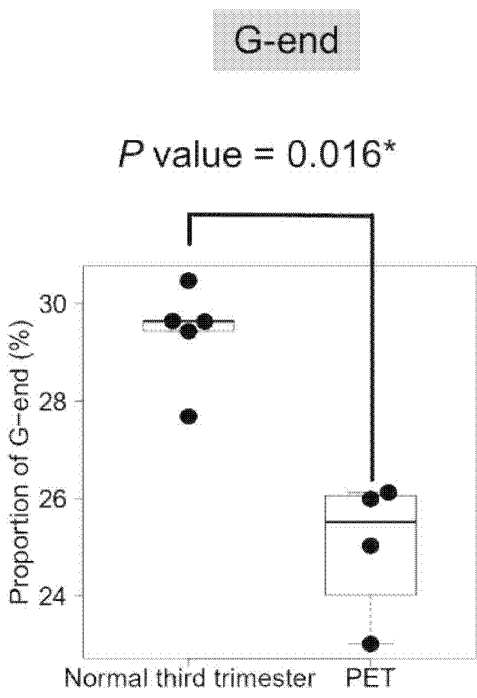


FIG. 72D

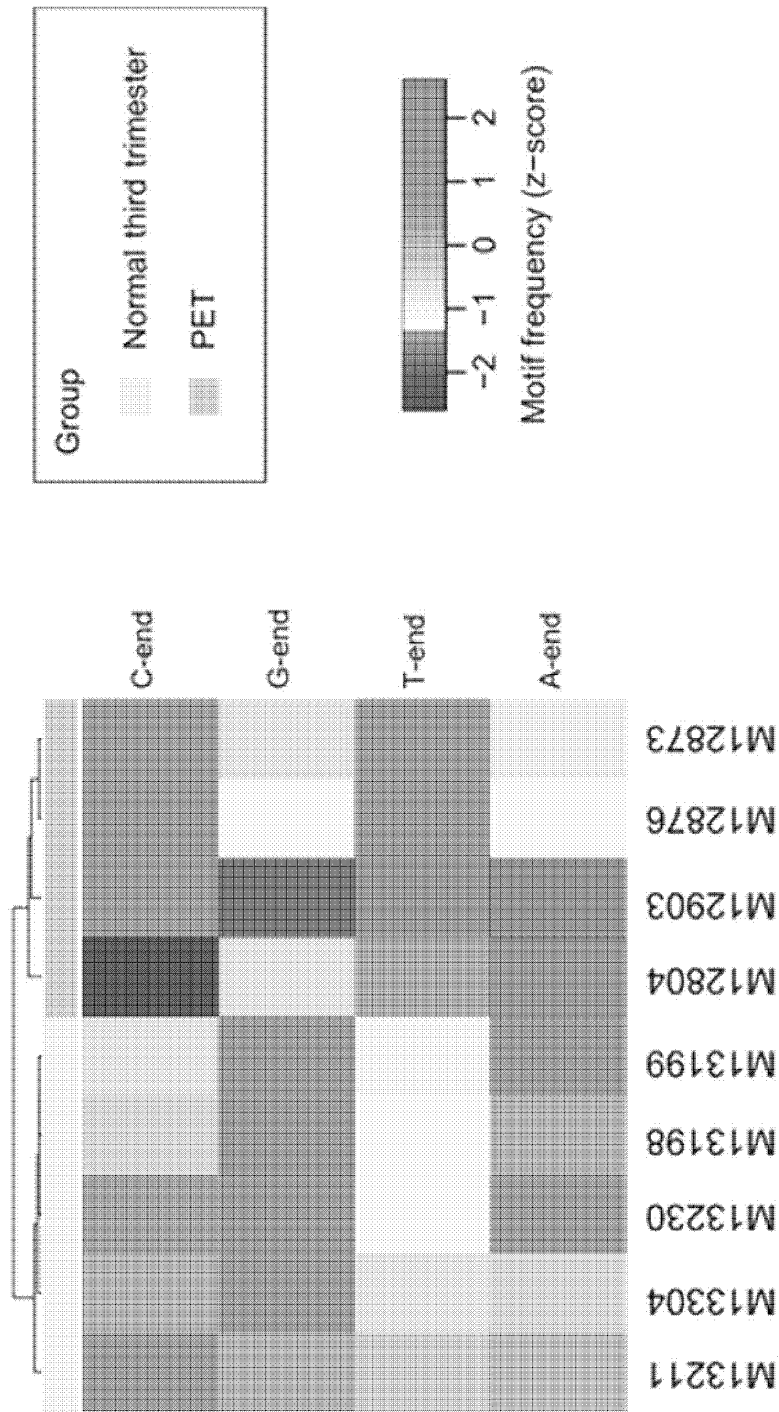


FIG. 73

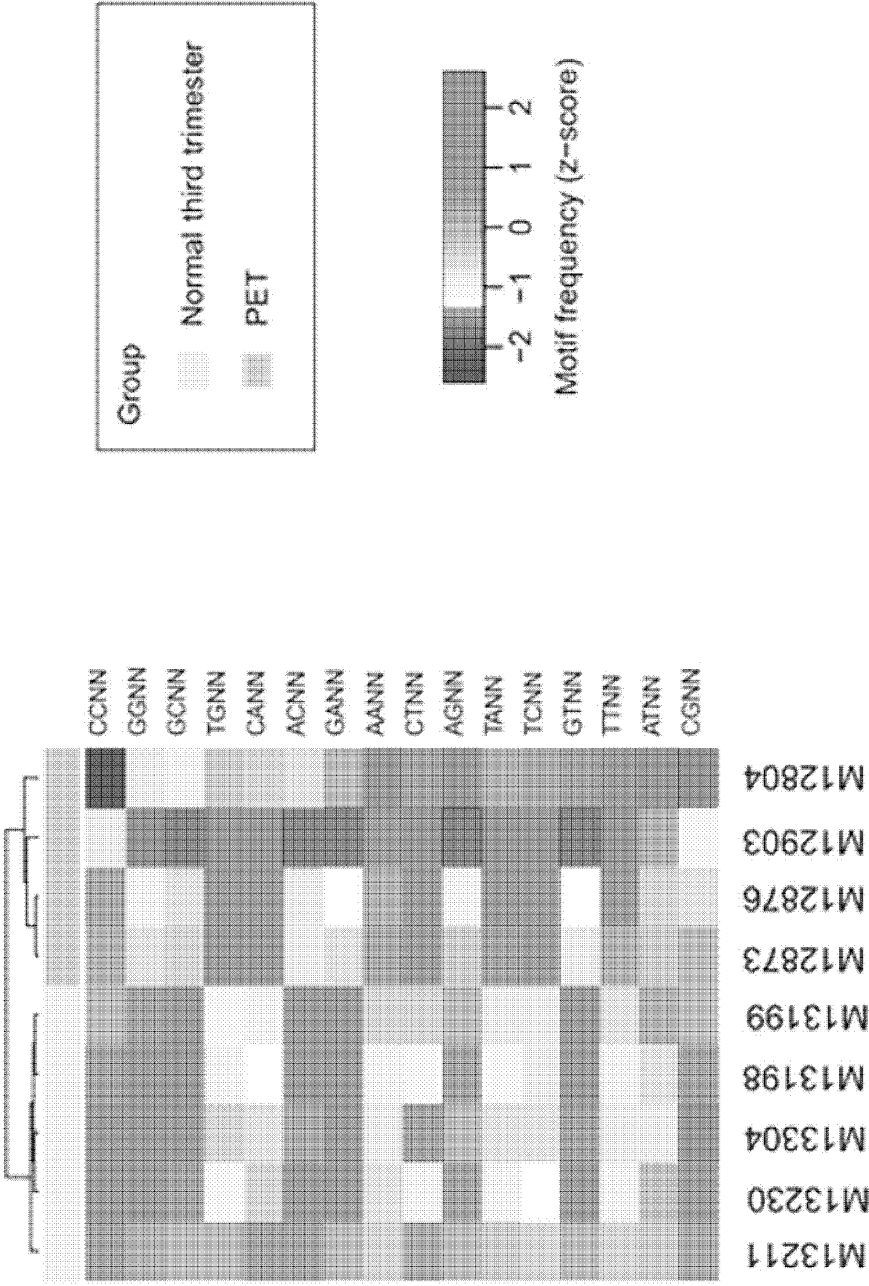


FIG. 74

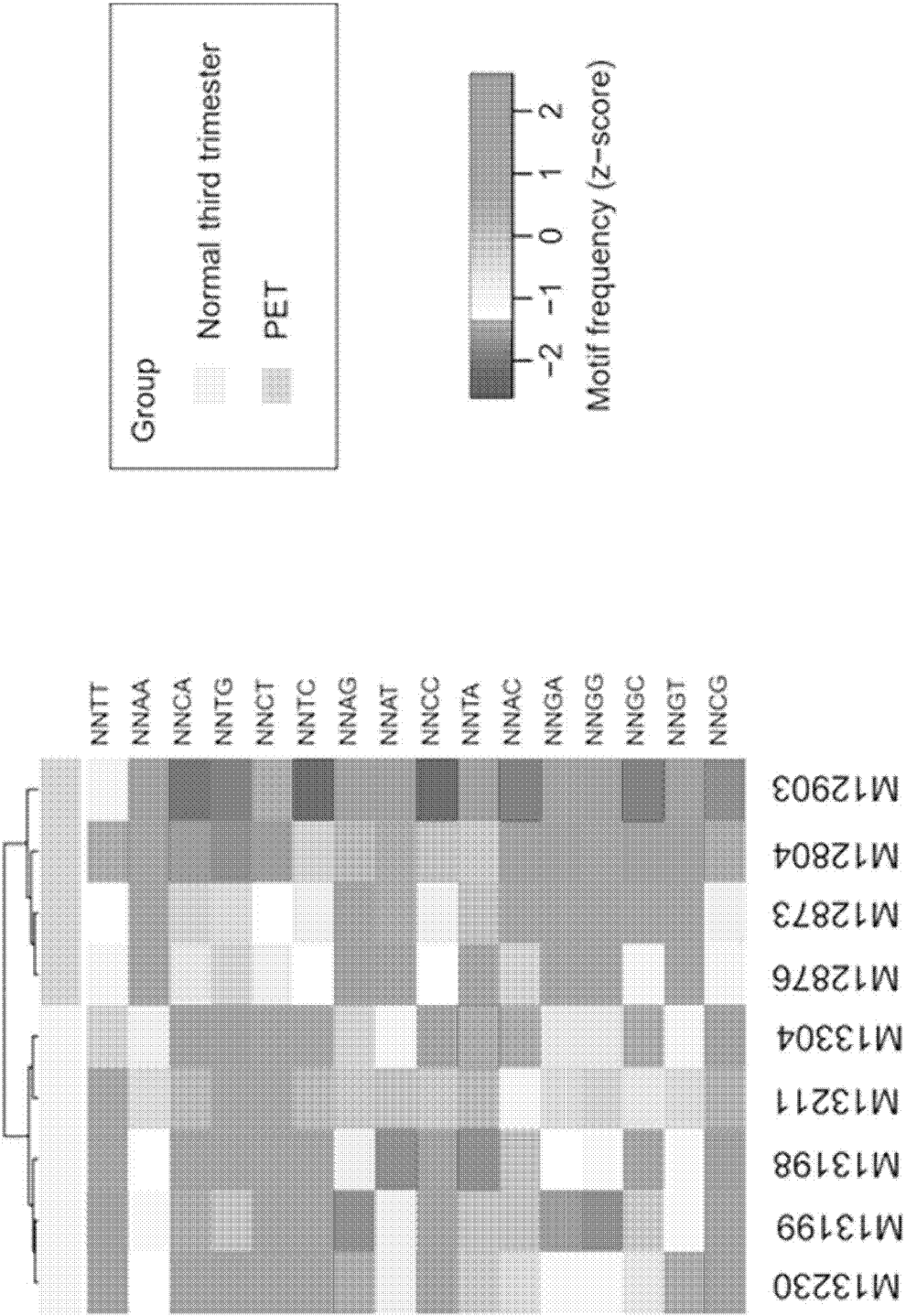


FIG. 75

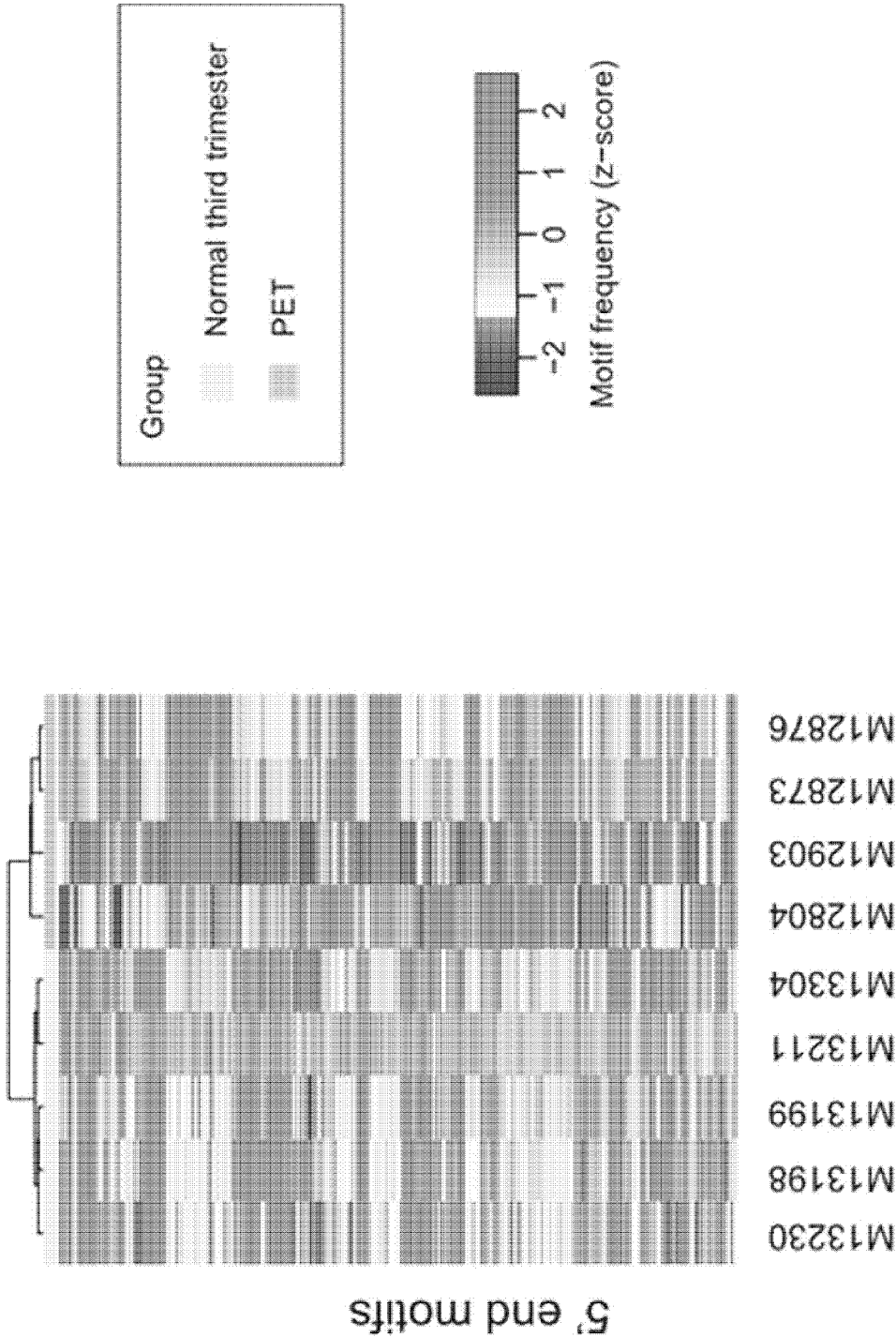


FIG. 76

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T-end

P value = 0.570

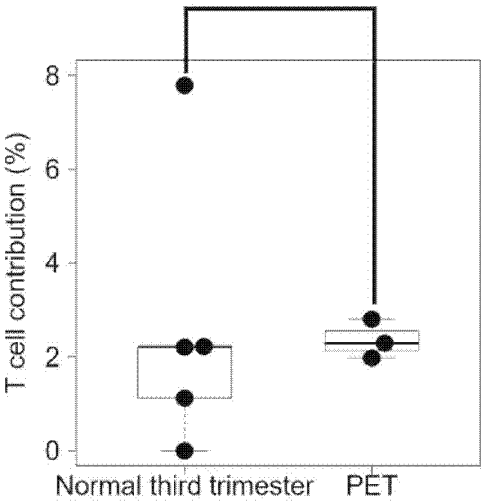


FIG. 77A

C-end

P value = 0.250

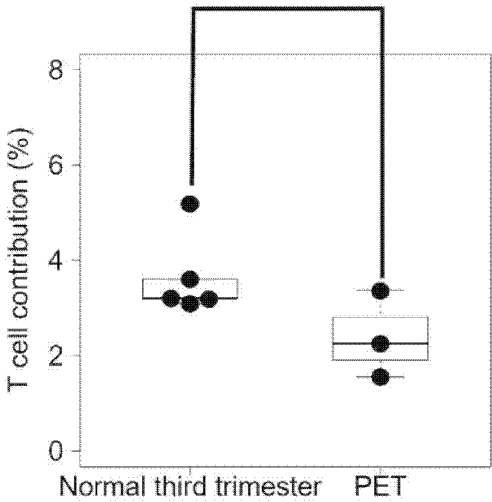


FIG. 77B

A-end

P value = 0.390

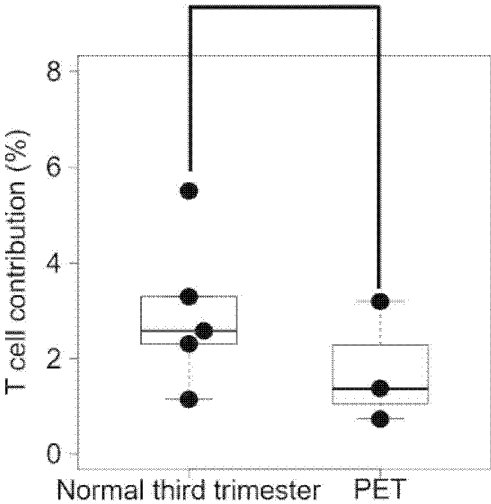


FIG. 77C

G-end

P value = 0.036*

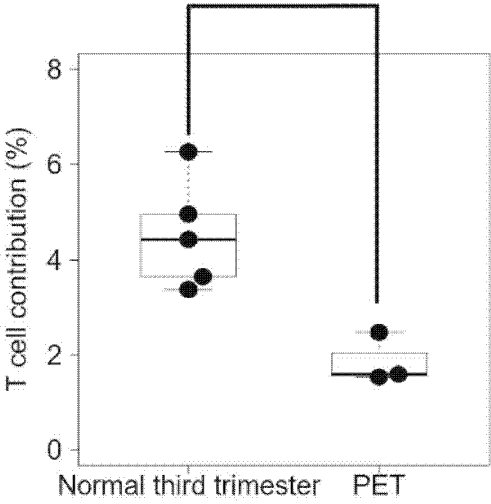
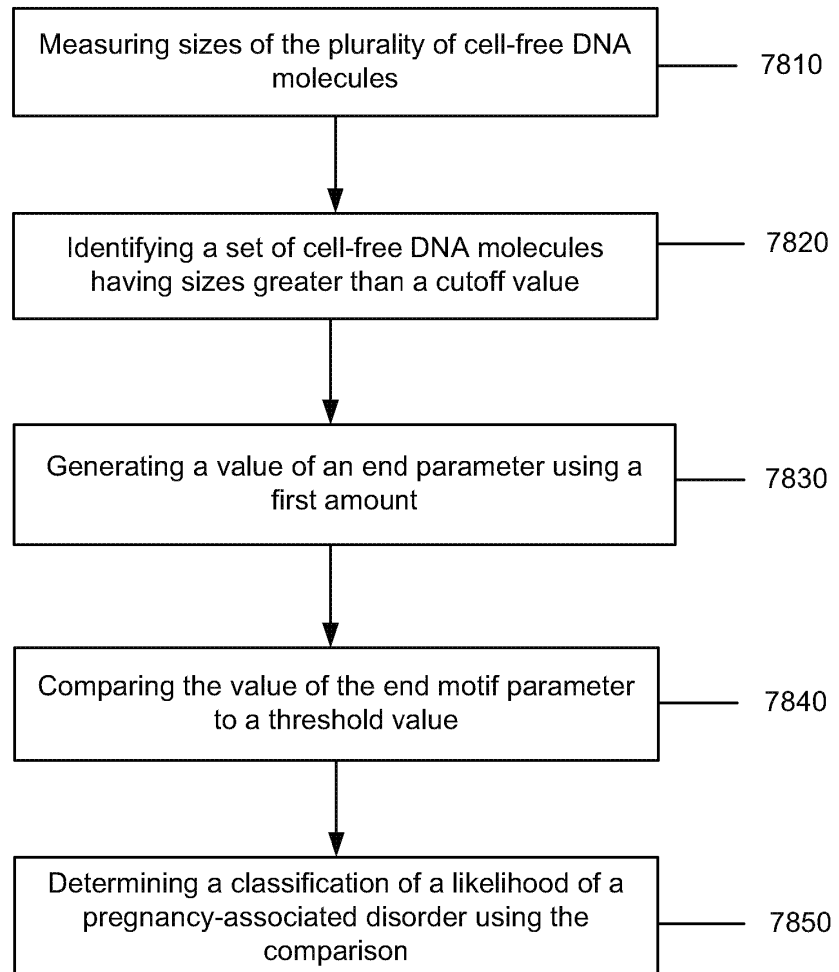


FIG. 77D

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7800

**FIG. 78**

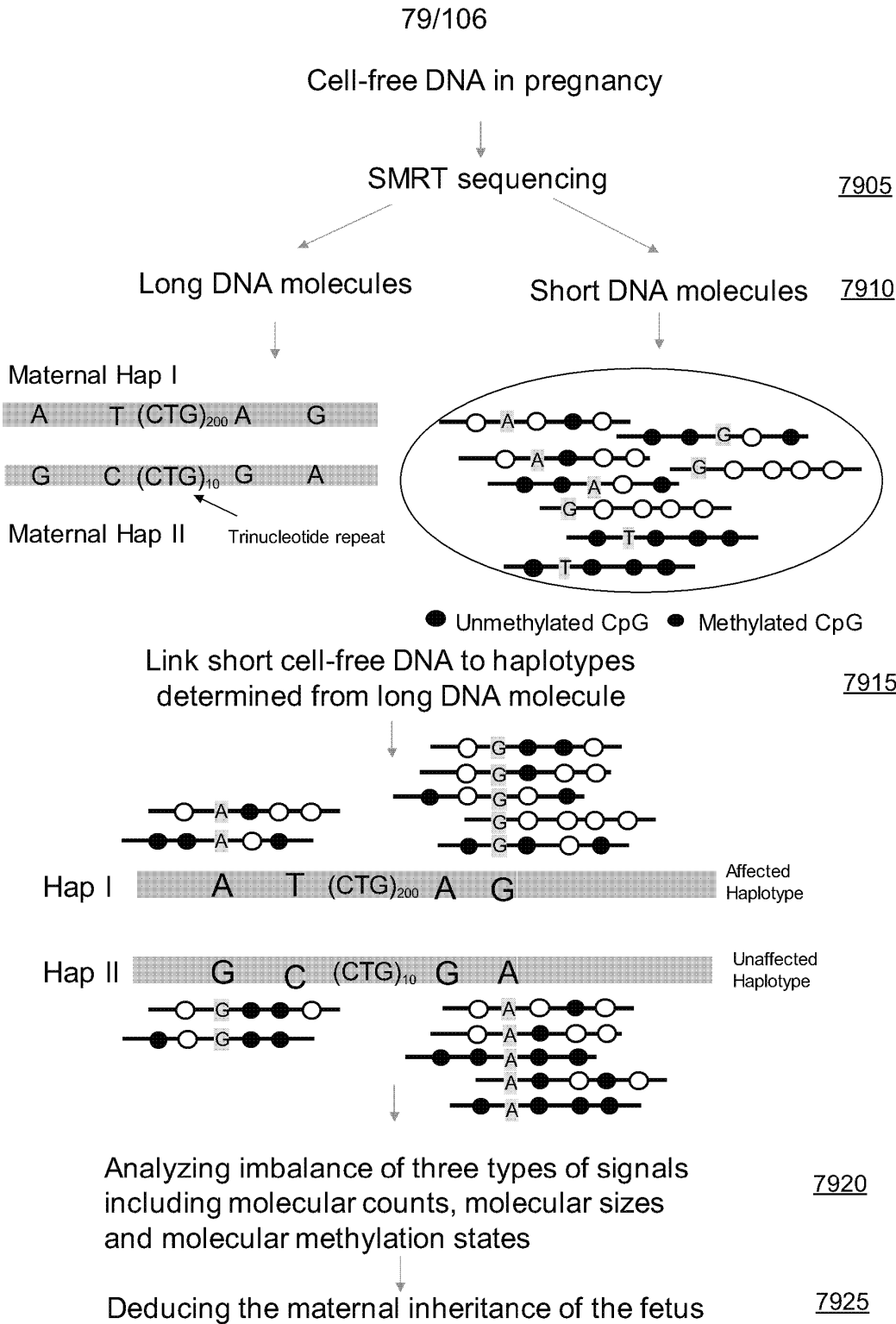


FIG. 79

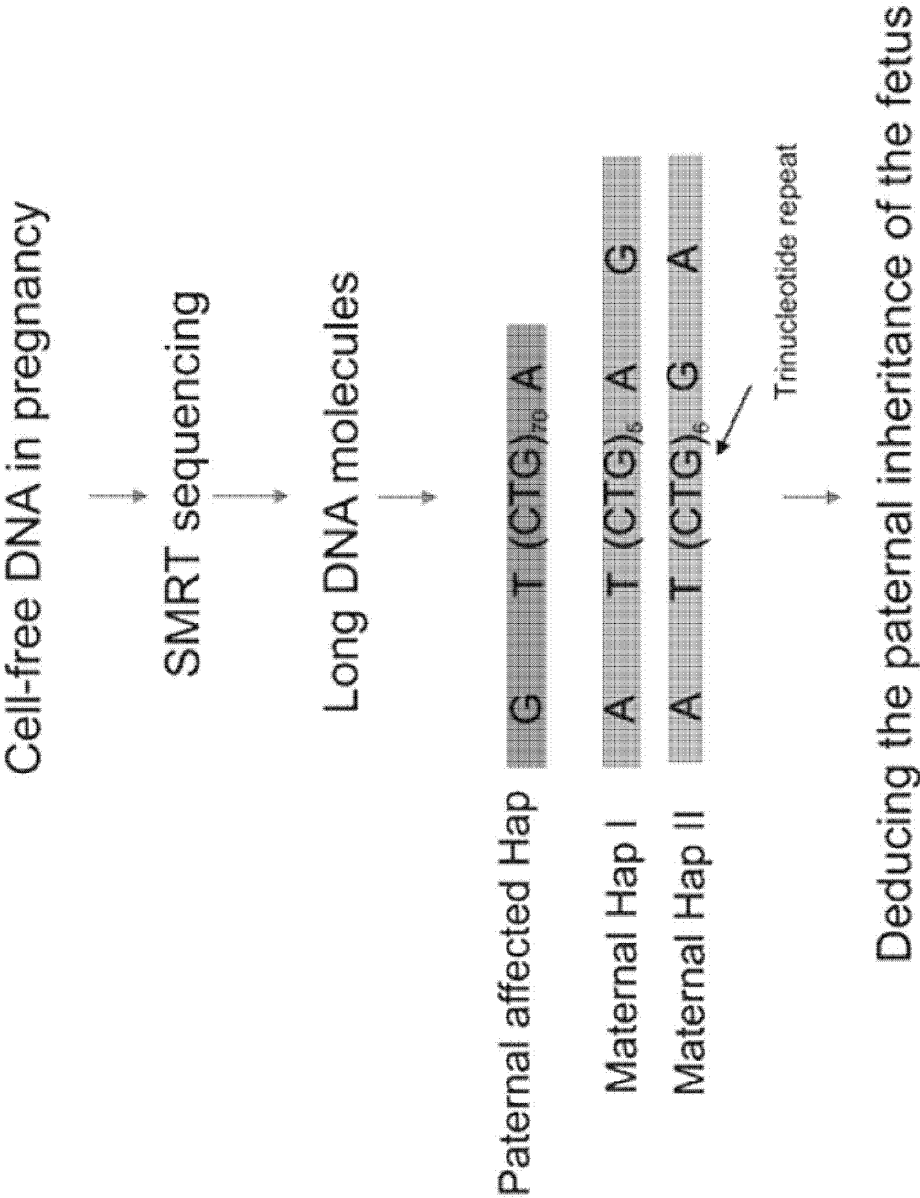


FIG. 80

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Repeat expansion related diseases	Repeat types	No. of repeats in normal subjects	No. of repeats in diseased subjects	Genetic locations related to repeats	Gene names	Patterns of inheritance
Spinocerebellar Ataxia 1	CAG	6-39	41-83	CDS	ataxin 1	autosomal dominant
Spinocerebellar Ataxia 2	CAG	<31	33-200	CDS	ataxin 2	autosomal dominant
Spinocerebellar Ataxia 3	CAG	<44	52-86	CDS	ataxin 3	autosomal dominant
Spinocerebellar Ataxia 6	CAG	<18	20-33	CDS	calcium channel, voltage-dependent, P/Q type, alpha 1A subunit	autosomal dominant
Spinocerebellar Ataxia 7	CAG	<28	>36	CDS	ataxin 7	autosomal dominant
Spinocerebellar Ataxia 17	CAG	25-44	47-63	CDS	TATA box binding protein	autosomal dominant
Spinal and Bulbar Muscular Atrophy	CAG	<34	>38	CDS	androgen receptor	x-linked recessive
Dentatorubral-Pallidoluysian Atrophy, Naito-Oyanagi Disease	CAG	6-35	49-88	CDS	atrophin 1	autosomal dominant
Huntington Disease	CAG	9-29	36-121	CDS	huntingtin	autosomal dominant
Spinocerebellar Ataxia 8	CAG	15-50	71-1300	CDS	Ataxin 8	autosomal dominant
Spastic Paraplegia 4, Autosomal Dominant	CAG	<16	>60	CDS	spastin	autosomal dominant
Epiphyseal Dysplasia, Multiple, 1	GAC	5	6-7	CDS	cartilage oligomeric matrix protein	Autosomal dominant
Vacterl Association, X-linked, with or without Hydrocephalus	GCC	10	12	CDS	Zic family member 3	x-linked recessive x-linked recessive
Neuropathy, Hereditary Sensory and Autonomic, Type VIII	GCC	12	18-19	CDS	PR/SET domain 12	autosomal recessive
Oculopharyngeal Muscular Dystrophy	GCG	10	12-17	CDS	poly(A) binding protein, nuclear 1	autosomal dominant
Synpolydactyly 1	GCG	15	22-29	CDS	homeobox D13	autosomal dominant
Hand-Foot-Genital Syndrome	GCG	18	24-26	CDS	homeobox A13	autosomal dominant
Epileptic Encephalopathy, Early Infantile, 1	GCG	10-16	17-23	CDS	aristaless related homeobox	x-linked recessive
Partington X-Linked Mental Retardation Syndrome	GCG	N/A	24-bp duplication	CDS	aristaless related homeobox	x-linked recessive
Central Hypoventilation Syndrome, Congenital	GCG	20	24-33	CDS	paired-like homeobox 2b	autosomal dominant
Holoprosencephaly 5	GCG	15	25	CDS	Zic family member 2	autosomal dominant

FIG. 81

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Repeat expansion related diseases	Repeat types	No. of repeats in normal subjects	No. of repeats in diseased subjects	Genetic locations related to repeats	Gene names	Patterns of inheritance
Blepharophimosis, Ptosis, and Epicanthus Inversus Syndrome	GCG	14	22-24	CDS	forkhead box L2	autosomal dominant
Cleidocranial Dysplasia	GCN	17	27	CDS	runt-related transcription factor 2	autosomal dominant
Mental Retardation, X-linked	GCN	11	15-26	CDS	SRY-box 3	x-linked recessive
Spinocerebellar Ataxia 12	CAG	7-32	51-78	5' UTR	protein phosphatase 2, regulatory subunit B, beta	autosomal dominant
Myoclonic Epilepsy of Unverricht and Lundborg	CCCCGCCCCGCG	2-3	30-75	5' UTR	cystatin B	autosomal recessive
Mental Retardation, X-Linked, Associated with Fragile Site Frax	CGG	4-39	>200	5' UTR	AF4/FMR2 family member 2	x-linked recessive
Jacobsen Syndrome	CCG	11	>100	5' UTR	Cbl proto-oncogene	isolated cases
Fragile X Tremor/ataxia Syndrome	CGG	<55	>200	5' UTR	fragile X mental retardation 1	x-linked dominant
Fragile X Mental Retardation Syndrome	CGG	6-52	231-2000	5' UTR	fragile X mental retardation 1	X-linked dominant
Premature Ovarian Failure 1	CGG	7-40	55-200 45-54	5' UTR	FMR1 fragile X mental retardation 1	x-linked inheritance
Mental retardation, FRA12A type	CGG	12-26	>150	5' UTR	DIP2 disco-interacting protein 2 homolog B	autosomal dominant
Oculopharyngodistal Myopathy	CGG	13-45	>51	5' UTR	LDL receptor related protein 12	autosomal dominant
Oculopharyngeal Myopathy with Leukoencephalopathy	CGG	11-16	>52	5' UTR	NOTCH2NLC	autosomal dominant
Robin Sequence with Cleft Mandible and Limb Anomalies	CACA/CGCA	3-12	14-16	5' UTR	eukaryotic translation initiation factor 4A3	autosomal recessive
Myotonic Dystrophy 1	CTG	5-37	50-5,000	3' UTR	DM1 protein kinase	autosomal dominant
Huntington Disease-Like 2	CTG	6-28	>41	3' UTR	junctophilin 3	autosomal dominant
Oculopharyngeal Myopathy with Leukoencephalopathy	CGG	<7	>37	exon	NUTM2B-AS1	autosomal dominant
Spinocerebellar Ataxia 8	CTG	15-34	90-250	exon	ATXN8 opposite strand	autosomal dominant
Spinocerebellar Ataxia 10	ATTCT	10-29	400-4500	intron 9	ataxin 10	autosomal dominant
Spinocerebellar Ataxia 37	ATTTC	<30	46-71	intron 11	DAB1; reelin adaptor protein	autosomal dominant
Myotonic Dystrophy 2	CCTG	<30	75-11,000	intron 1	CCHC-type zinc finger nucleic acid binding protein	autosomal dominant

FIG. 82

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Repeat expansion related diseases	Repeat types	No. of repeats in normal subjects	No. of repeats in diseased subjects	Genetic locations related to repeats	Gene names	Patterns of inheritance
Fuchs Endothelial Corneal Dystrophy	CTG	<40	>50	intron 3	transcription factor 4	autosomal dominant
Duchenne Muscular Dystrophy	GAA	11-33	59-82	intron 62	dystrophin	x-linked recessive
Friedreich Ataxia 1	GAA	5-30	>70	intron 1	frataxin	autosomal recessive
Spinocerebellar Ataxia 36	GGCCCTG	3-14	650-2500	intron 4	NOP56 ribonucleoprotein	autosomal dominant
Frontotemporal Degeneration and Amyotrophic Lateral Sclerosis	GGGGCC	2-19	250-1600	intron 1	chromosome 9 open reading frame 72	autosomal dominant
Spinocerebellar Ataxia 31	TGGAA	26	2.5-3.8 kb	intron 1	brain expressed, associated with NEDD4, 1	autosomal dominant
Familial Adult Myoclonic Epilepsy-1	TTTCA/TTTCA	7-20	440-3680	intron	sterile alpha motif domain containing 12	autosomal dominant
Benign Adult Familial Myoclonic Epilepsy 6	TTTTA/TTTCA	18	>22	intron	Trinucleotide repeat containing 6A	autosomal dominant
Benign Adult Familial Myoclonic Epilepsy 7	TTTTA/TTTCA	12	>22	intron	Rap guanine nucleotide exchange factor 2	autosomal dominant

FIG. 83

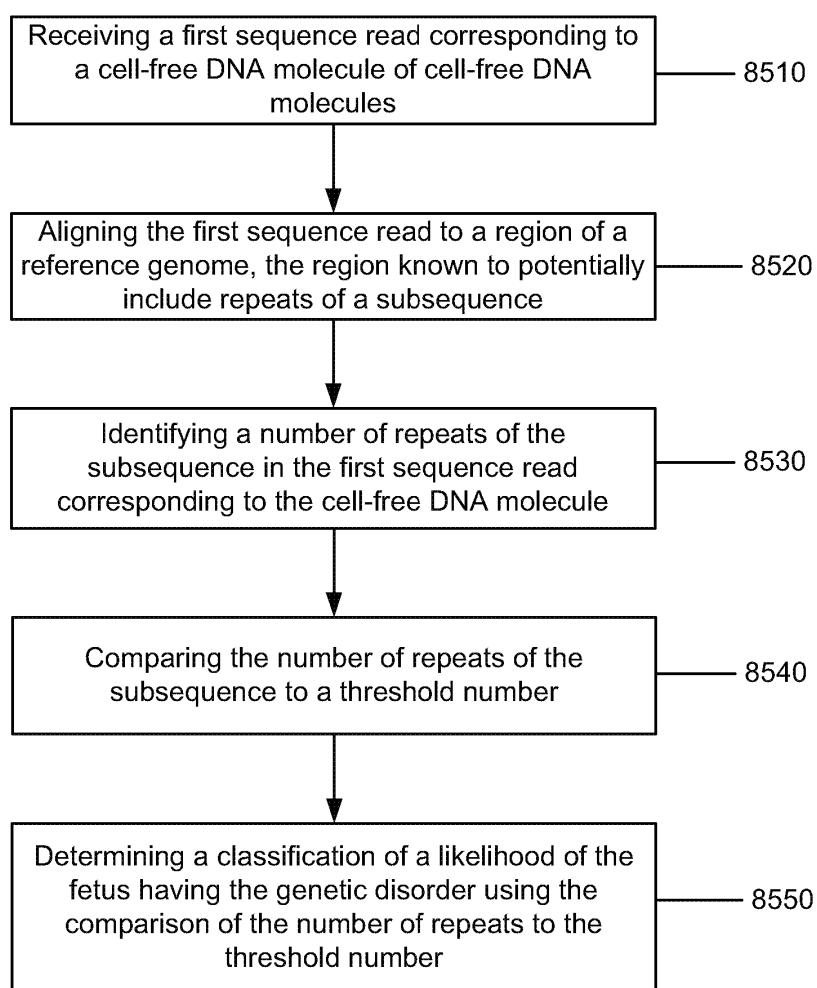
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Repeat types	Repeat unit	Genomic locations	Reference bases	Paternal genotypes (Allele 1 / Allele 2)	Maternal genotypes (Allele 1 / Allele 2)	Fetal genotypes (Allele 1 / Allele 2)	Fetal DNA methylation level linked to paternal alleles (%)	Fetal DNA methylation level linked to maternal alleles (%)
1 bp	A	chr1:244287246-244287247	C	C(A) ₂₀ /C(A) ₂₀	C/C	C(A) ₂₀ /C	51.06	45.83
1 bp	T	chr2:831609-831610	C	C(T) ₂₂ /C(T) ₂₂	C/C	C(T) ₂₂ /C	52.15	52.46
2 bp	TG	chr1:199547268-199547269	C	C(TG) ₁₁ /C(TG) ₁₁	C/C(TG) ₁₁	C(TG) ₁₁ /C(TG) ₁₁	55.67	64.08
2 bp	TG	chr11:24818036-24818037	C(TG) ₅	C/C	C(TG) ₅ /C(TG) ₅	C/C(TG) ₅	35.57	31.91
2 bp	AC	chr18:64408776-64408777	A(AC) ₃	A/A	A(AC) ₃ /A(AC) ₃	A/A(AC) ₃	43.26	44.92
3 bp	AAT	chr22:42422276-42422277	A(AAT) ₃	A(AAT) ₃ /A(AAT) ₃	A/A	A(AAT) ₃ /A	79.78	82.43
4 bp	TAAA	chr4:73237157-73237158	G(TAAA) ₂	G/G	G(TAAA) ₂ /G(TAAA) ₂	G/G(TAAA) ₂	62.84	95.65
4 bp	GATA	chr3:192384705-192384706	T(GATA) ₃	T(GATA) ₃ /T(GATA) ₃	T/T	T(GATA) ₃ /T	50.98	62.9

FIG. 84

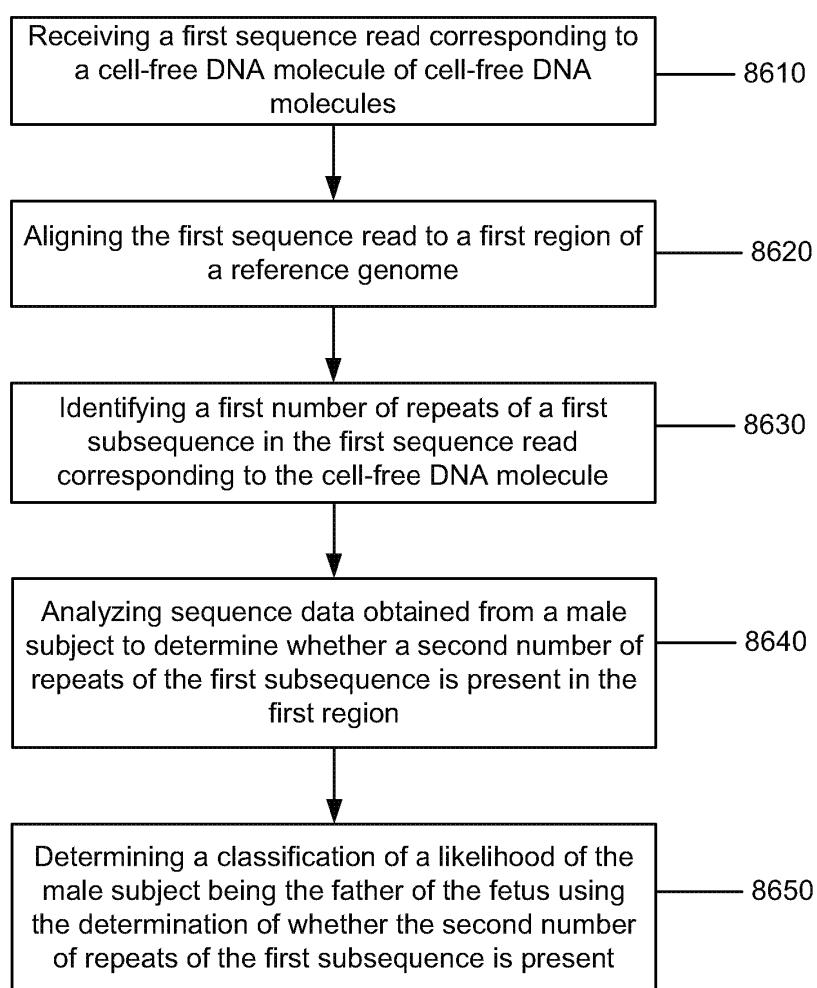
85/106

8500

**FIG. 85**

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8600

**FIG. 86**

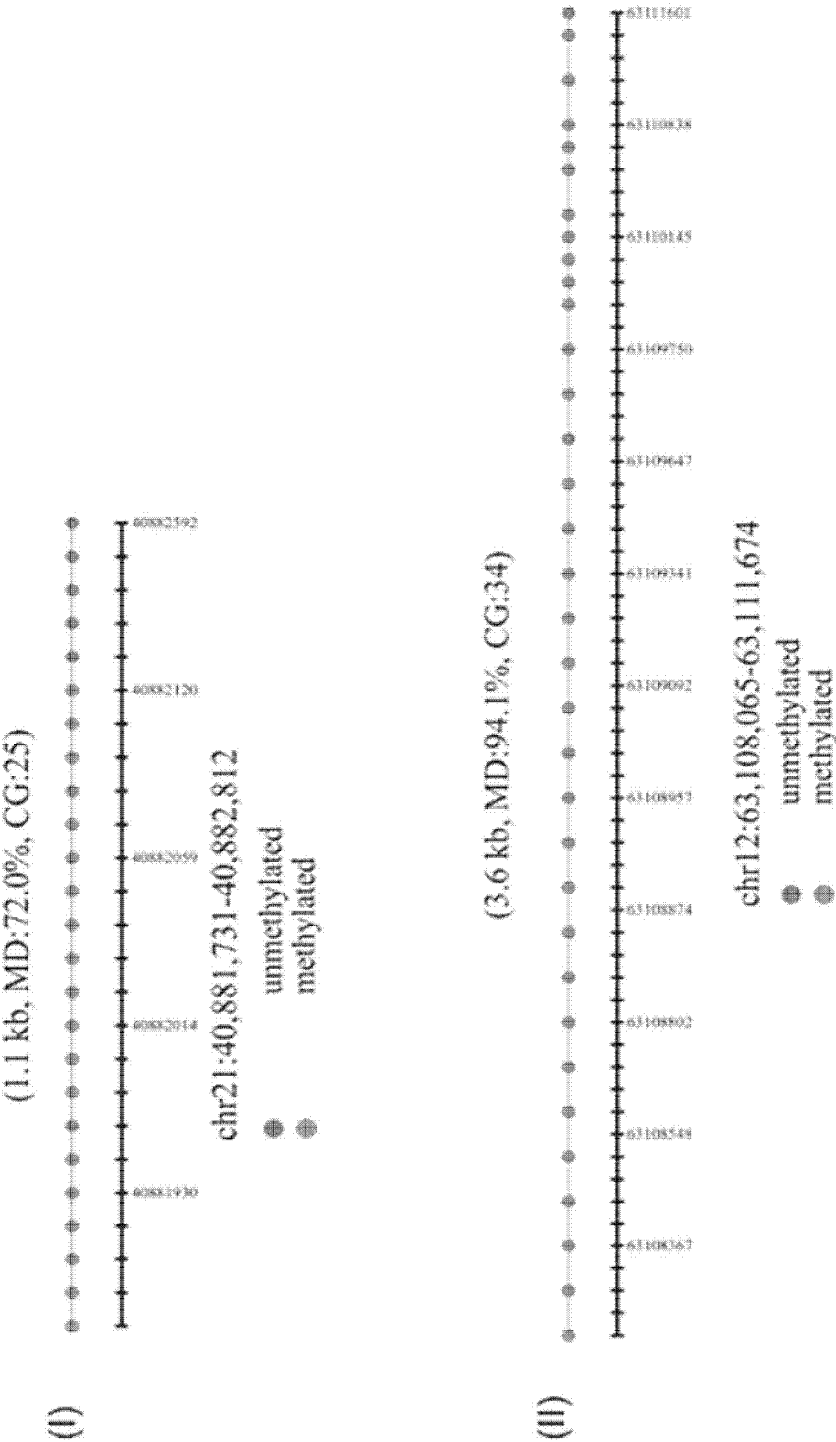


FIG. 87

Samples	Groups	No. of sequenced molecules	Mean subread depths (x)	Median fragment sizes (bp)	Proportion of fragments ≥ 500 bp (%)
299	Without size selection	2,525,216	91	176	27.3
300	Without size selection	3,057,511	67	512	50.5
B299	With size selection	4,103,718	18	2,463	97.6
B300	With size selection	1,987,264	19	2,170	97.4

FIG. 88

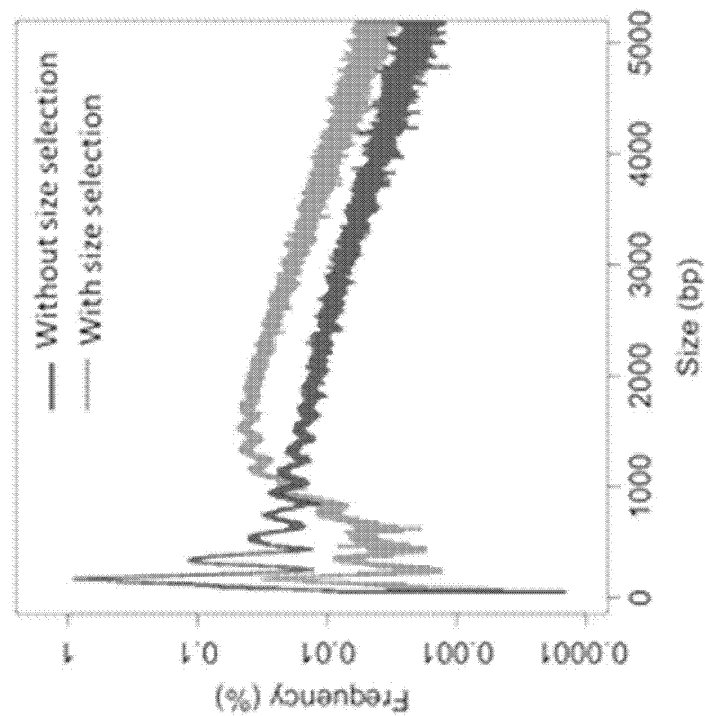


FIG. 89B

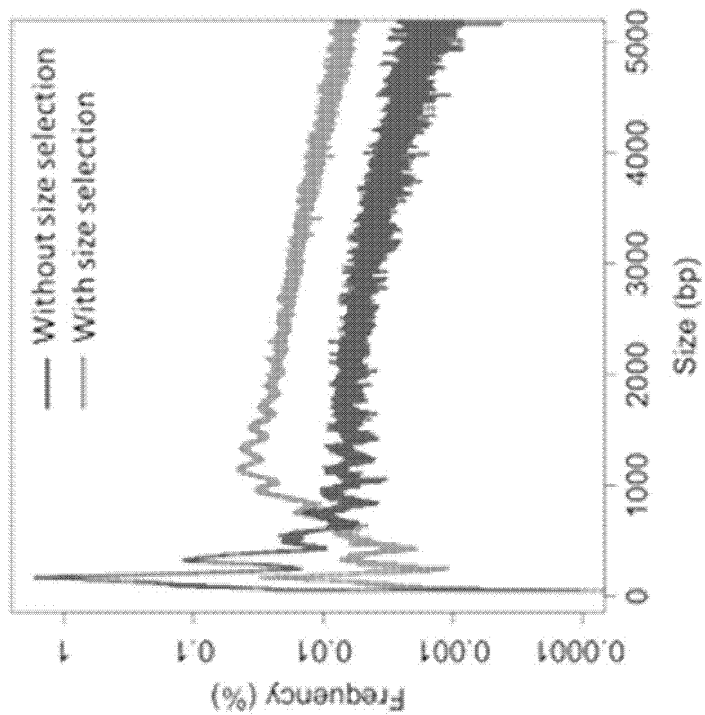


FIG. 89A

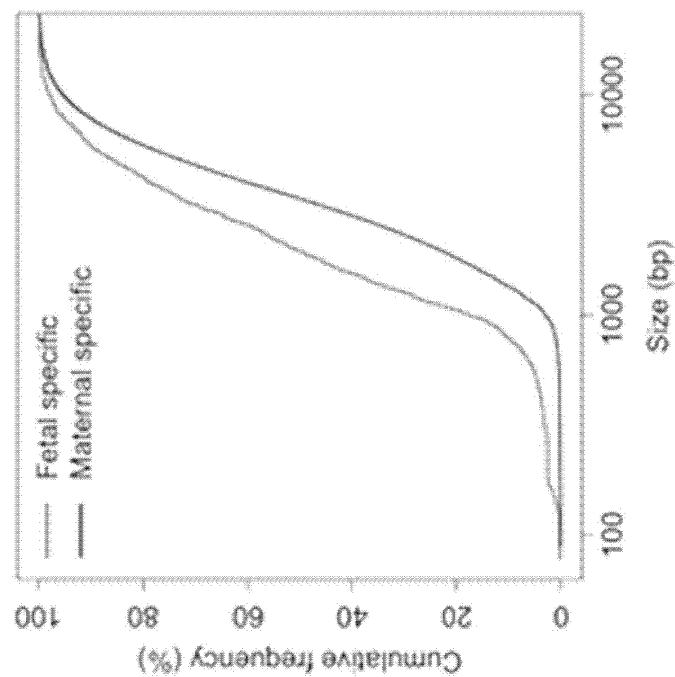


FIG. 90B

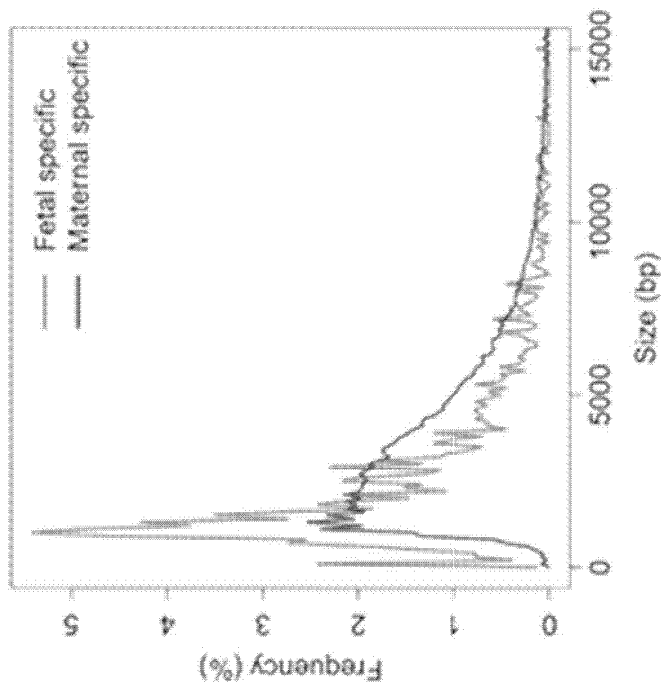


FIG. 90A

Sample	Total no. of plasma DNA molecules being analyzed	No. of plasma DNA molecules carrying informative SNPs	Percentage of plasma DNA molecules carrying informative SNPs
Sample 299 (Without size selection)	1,092,062	70,730	6.5%
Sample B299 (With size selection)	1,633,040	336,539	20.6%

FIG. 91

Sample	Group	Methylated CpG sites	Unmethylated CpG sites	Methylation level (%)
299	Without size selection	600,998	268,364	69.1
300	Without size selection	934,996	413,638	69.3
B299	With size selection (>500 bp)	1,358,631	541,425	71.5
B300	With size selection (>500 bp)	817,043	327,869	71.4

FIG. 92

Sample	Group1	Group2	Methylated CpG sites	Unmethylated CpG sites	Methylation level (%)
299	Without size selection	Fetal specific plasma DNA molecules	1,277	932	57.81
		Maternal specific plasma DNA molecules	17,500	8,003	68.62
B299	With size selection (>500 bp)	Fetal specific plasma DNA molecules	2,682	1,570	63.08
		Maternal specific plasma DNA molecules	85,741	33,062	72.17

FIG. 93

Rank	Without size selection				With size selection			
	M13299		M13300		B-M13299		B-M13300	
	Motif	Frequency (%)	Motif	Frequency (%)	Motif	Frequency (%)	Motif	Frequency (%)
1	CCCA	1.76	ACTT	1.87	ACTT	3.99	ACTT	3.37
2	CCTG	1.47	CCTT	1.67	GCTT	2.73	GCTT	2.27
3	CCTT	1.46	CCCA	1.66	CCTT	2.31	CCTT	2.05
4	GCTT	1.41	GCTT	1.53	ACTG	1.98	GTTT	1.80
5	CCTC	1.37	CCTG	1.47	GTTT	1.88	ACCT	1.54
6	ACTT	1.36	CCTC	1.27	ACCT	1.81	ACTG	1.49
7	CCAG	1.19	GCCT	1.15	GGCT	1.64	CTTT	1.42
8	GGCT	1.18	GTTT	1.14	ACAT	1.59	ACTC	1.38
9	GCCT	1.17	ACCT	1.14	CTTT	1.47	ATTT	1.35
10	GCTG	1.05	CCAG	1.12	GATT	1.46	ACAT	1.35

FIG. 94

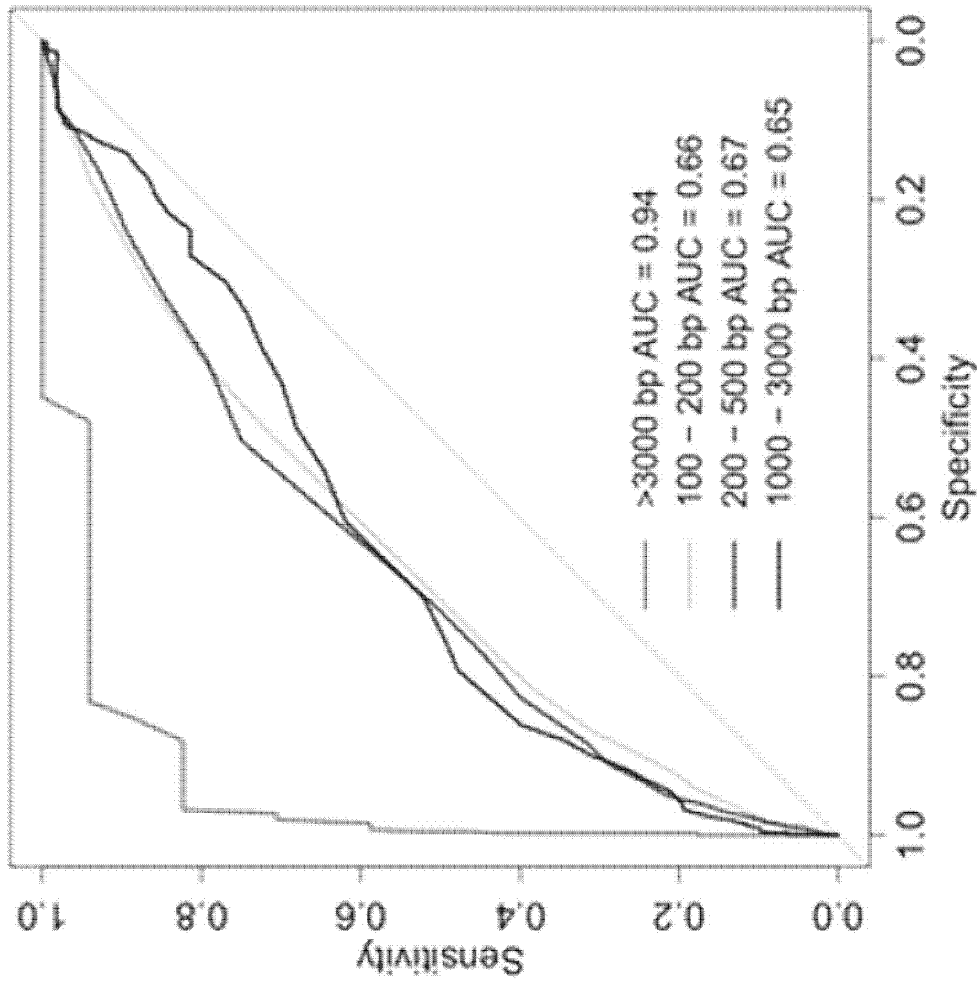


FIG. 95

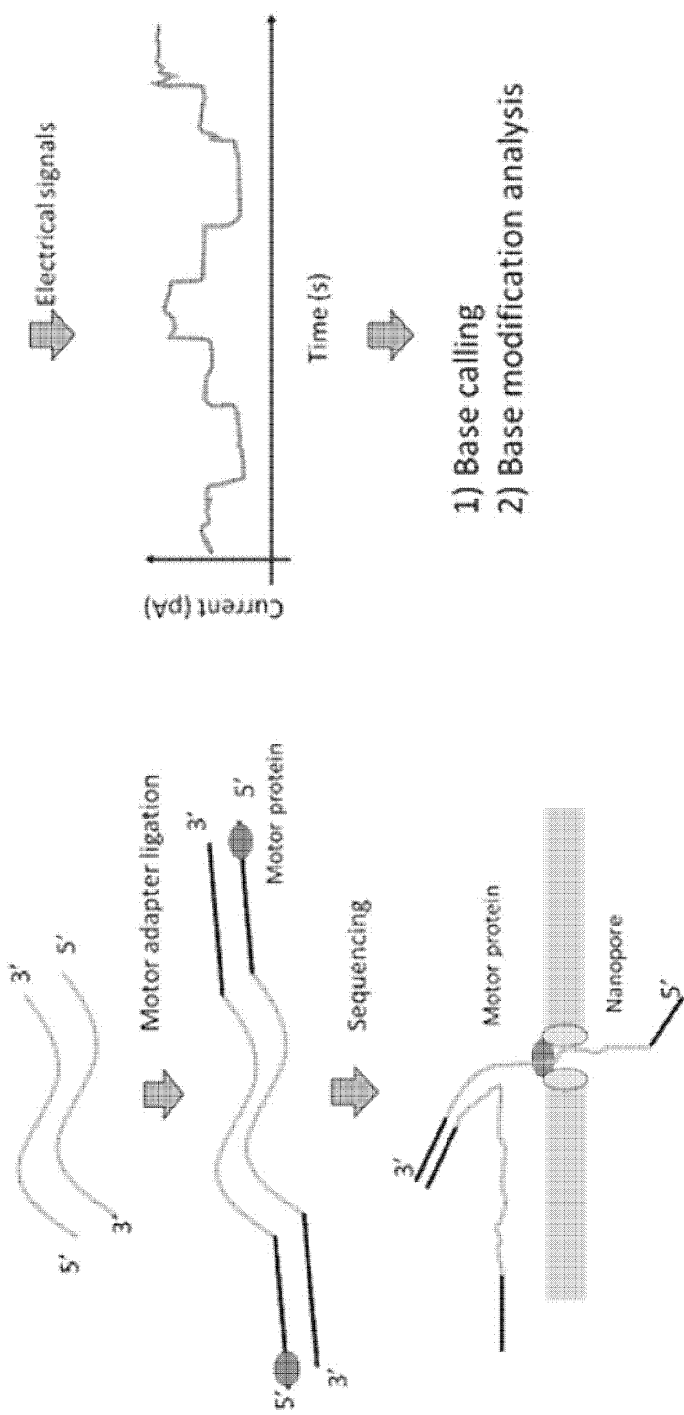


FIG. 96

M12970						
Fragment size (bp)	No. of fragments	Frequency (%)	Methylated CpG	Unmethylated CpG	Methylation level (%)	
≥500	636,828	16.63%	1,247,858	698,271	64.12%	
≥600	393,108	10.26%	955,061	529,299	64.34%	
≥1000	119,185	3.11%	463,660	231,835	66.67%	
≥2000	23,518	0.61%	151,939	62,893	70.72%	

M12985						
Fragment size (bp)	No. of fragments	Frequency (%)	Methylated CpG	Unmethylated CpG	Methylation level (%)	
≥500	201,170	7.63%	644,985	346,663	65.04%	
≥600	104,416	3.96%	426,580	222,633	65.71%	
≥1000	25,204	0.96%	168,044	72,768	69.78%	
≥2000	4,090	0.16%	46,989	15,562	73.94%	

M12969						
Fragment size (bp)	No. of fragments	Frequency (%)	Methylated CpG	Unmethylated CpG	Methylation level (%)	
≥500	590,634	12.55%	1,781,670	1,033,066	63.30%	
≥600	350,143	7.44%	1,306,833	759,671	63.24%	

FIG. 97

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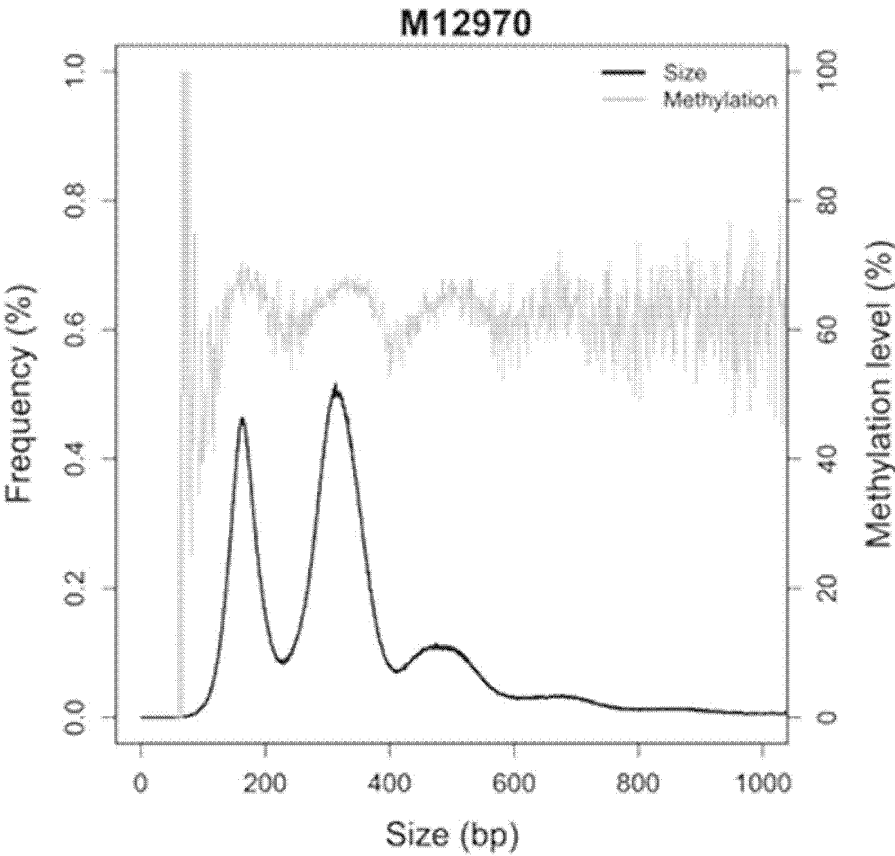


FIG. 98

Sample	No. of molecules carrying the shared alleles	No. of molecules carrying the fetal-specific alleles	Fetal DNA fraction (%)
M12970	84,911	17,776	34.6%
M12985	52,059	7,385	24.9%
M12969	95,273	17,007	30.3%

FIG. 99

Sample	Fetal-specific DNA			Maternal-specific DNA		
	Methylated CpG	Unmethylated CpG	Methylation level (%)	Methylated CpG	Unmethylated CpG	Methylation level (%)
M12970	17,340	10,434	62.43%	61,268	29,770	67.30%
M12985	9,426	5,682	62.39%	41,465	19,561	67.95%
M12969	26,440	16,563	61.48%	94,573	45,879	67.33%

FIG. 100

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Fragment size (bp)	M12970									
	fetal-specific DNA					maternal-specific DNA				
	No. of fragments	Frequency (%)	Methylated CpG	Unmethylated CpG	Methylation level (%)	No. of fragments	Frequency (%)	Methylated CpG	Unmethylated CpG	Methylation level (%)
>=500	5328	31.2%	9887	5633	63.7%	16464	41.2%	39224	19781	66.5%
>=600	3715	21.8%	8366	4622	64.4%	11927	29.8%	34222	17134	66.6%
>=1000	1596	9.3%	4901	2434	66.8%	5693	14.2%	23366	10516	69.0%
>=2000	500	2.9%	2003	839	70.5%	1793	4.5%	10926	4327	71.6%

Fragment size (bp)	M12985									
	fetal-specific DNA					maternal-specific DNA				
	No. of fragments	Frequency (%)	Methylated CpG	Unmethylated CpG	Methylation level (%)	No. of fragments	Frequency (%)	Methylated CpG	Unmethylated CpG	Methylation level (%)
>=500	1261	17.6%	3789	2092	64.4%	5132	20.4%	19235	9055	68.0%
>=600	749	10.4%	2788	1539	64.4%	3157	12.5%	15039	6870	68.6%
>=1000	290	4.0%	1502	854	63.8%	1193	4.7%	8718	3433	71.7%
>=2000	82	1.1%	597	433	58.0%	317	1.3%	3448	1174	74.6%

Fragment size (bp)	M12969									
	fetal-specific DNA					maternal-specific DNA				
	No. of fragments	Frequency (%)	Methylated CpG	Unmethylated CpG	Methylation level (%)	No. of fragments	Frequency (%)	Methylated CpG	Unmethylated CpG	Methylation level (%)
>=500	4713	28.8%	14412	8634	62.5%	14762	33.0%	53302	26440	66.8%
>=600	3200	19.6%	11820	7188	62.2%	10128	22.6%	44137	21631	67.1%
>=1000	1418	8.7%	7283	4380	62.4%	4600	10.3%	28579	13254	68.3%
>=2000	449	2.7%	3205	1594	66.8%	1403	3.1%	13004	4950	72.4%

FIG. 101

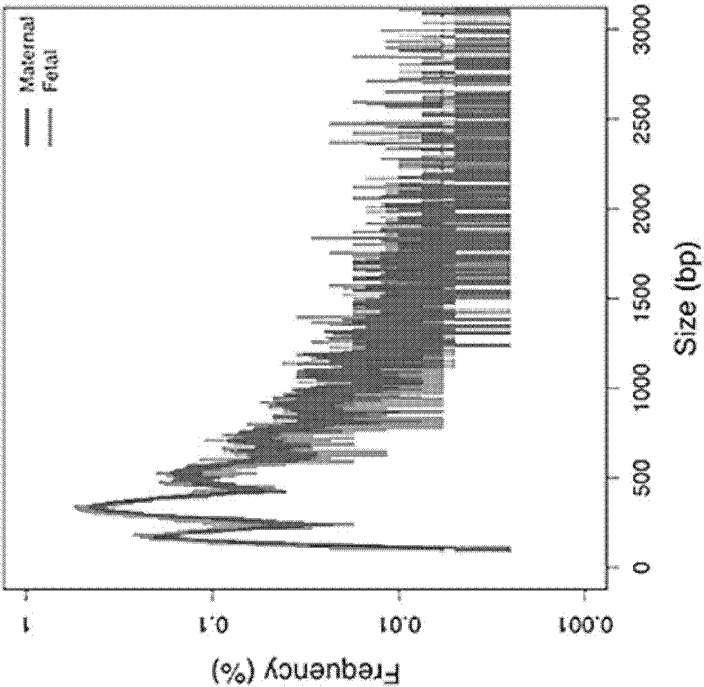


FIG. 102B

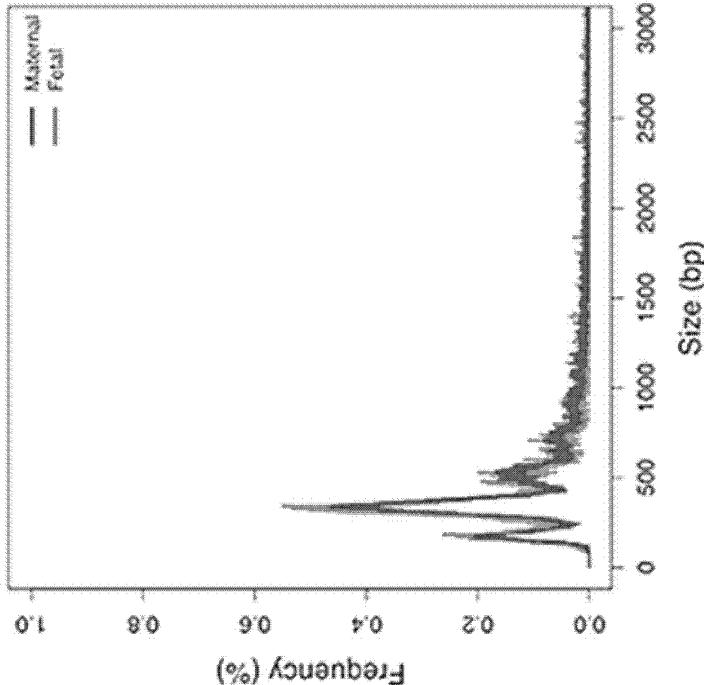


FIG. 102A

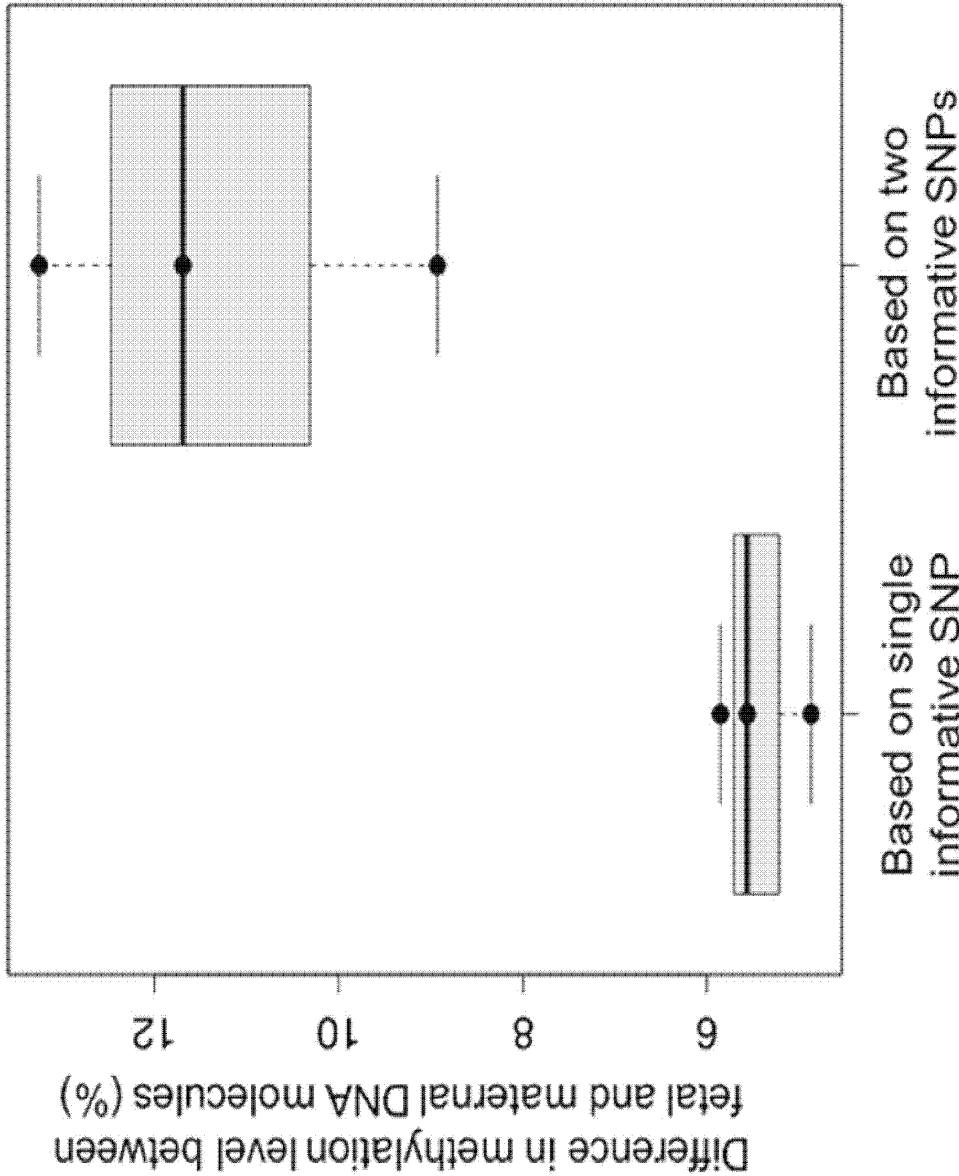


FIG. 103

Sample	Fetal-specific DNA			Maternal-specific DNA		
	Methylated CpG	Unmethylated CpG	Methylation level (%)	Methylated CpG	Unmethylated CpG	Methylation level (%)
M12970	682	522	56.64	8,634	4,001	68.33
M12985	245	177	58.06	4,175	1,680	71.31
M12969	1,065	751	58.65	13,399	6,429	67.58

FIG. 104

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10500

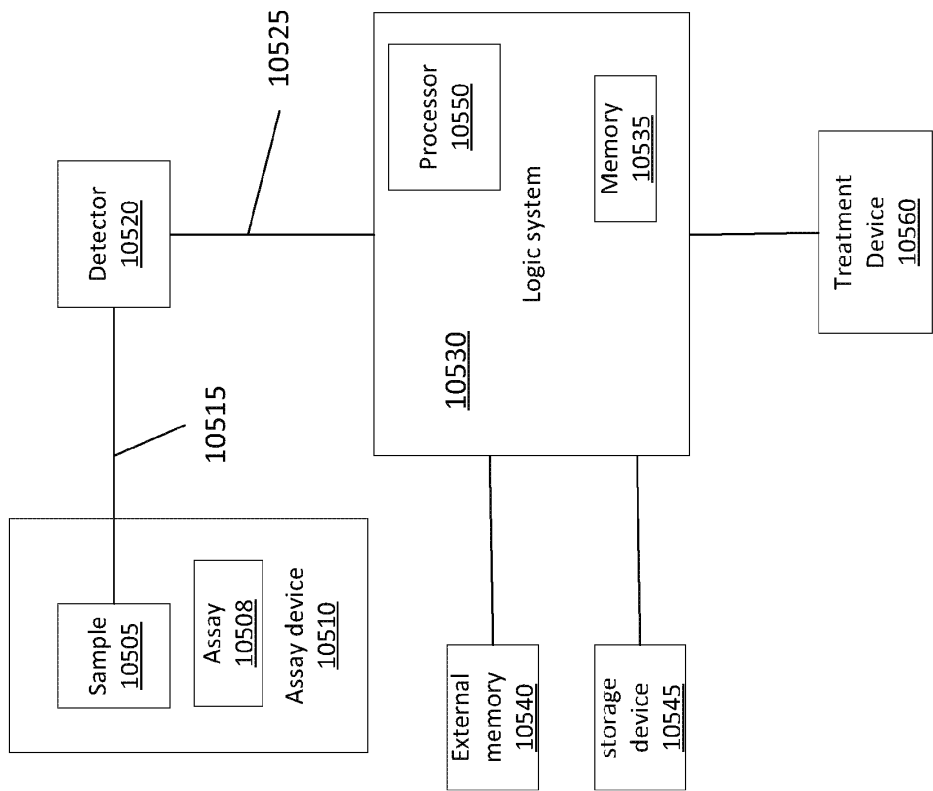


FIG. 105

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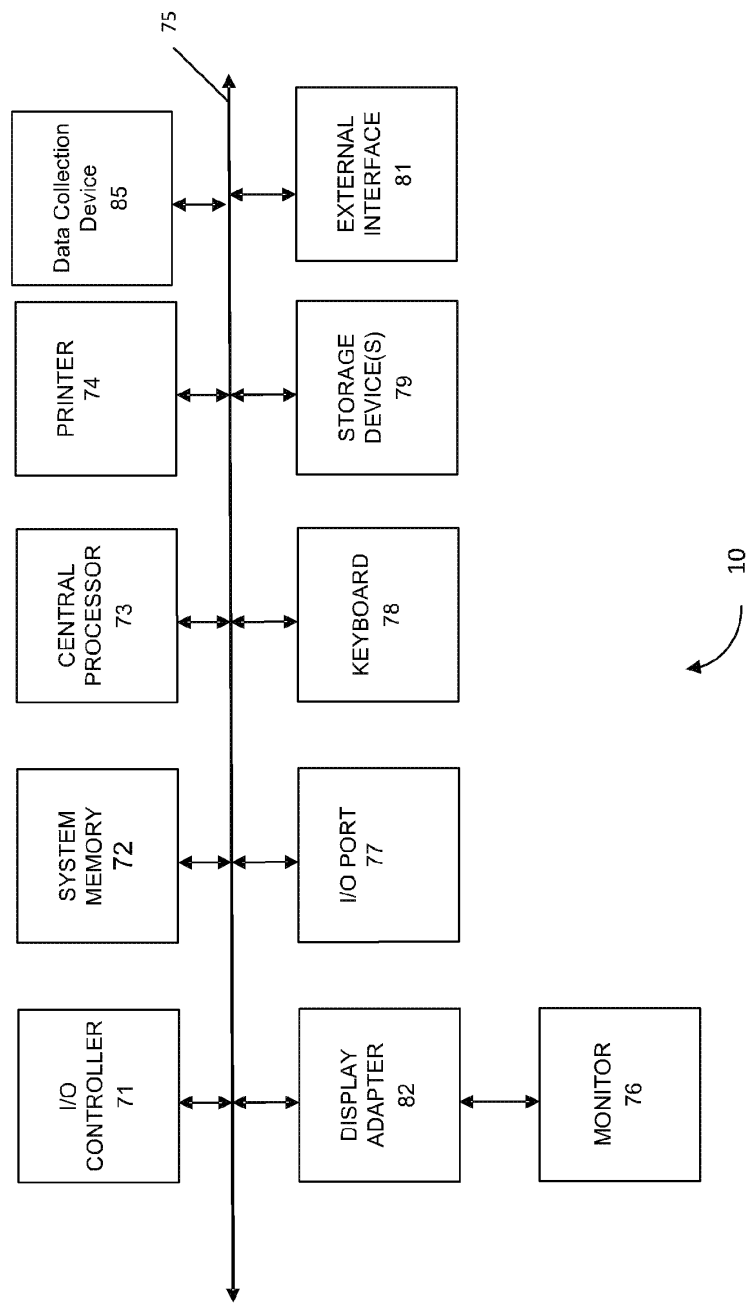


FIG. 106