	Cases	Controls
Placental tissues	**First trimester**	**Third trimester**
Chorionic villus (CHVL)	5	10
Placental cells	**Early first trimester**	**Late first trimester**
Villous cytotrophoblasts (VCTB)	9	10
Cancer tissues	**Tumor**	**Normal**
Bladder urothelial carcinoma (BLCA)	359	21
Breast invasive carcinoma (BRCA)	501	80
Colon adenocarcinoma (COAD)	251	36
Esophageal carcinoma (ESCA)	87	13
Head & neck squamous cell carcinoma (HNSC)	506	50
Liver hepatocellular carcinoma (LIHC)	352	50
Lung adenocarcinoma (LUAD)	278	26
Lung squamous cell carcinoma (LUSC)	341	41
Pancreatic adenocarcinoma (PAAD)	142	7
Prostate adenocarcinoma (PRAD)	453	50
Rectum adenocarcinoma (READ)	90	6
Thyroid carcinoma (THCA)	357	46
Uterine corpus endometrioid carcinoma (UCEC)	398	34

Supplementary Table 1

Placenta and cancer samples included in this study.*

*First trimester chorionic villi samples were obtained between 6 and 10 weeks of gestation (WG), and third trimester chorionic villi samples were obtained between 32 and 39 WG. Early first trimester villous cytotrophoblast samples were isolated from chorionic villi obtained before entrance of maternal blood into the intervillous space (8-10 WG), and late first trimester villous cytotrophoblast samples were isolated from chorionic villi samples obtained after entrance of maternal blood into the intervillous space (12-14 WG).

	CHVL	VCTB	BLCA	BRCA	COAD	ESCA	HNSC	LIHC	LUAD	LUSC	PAAD	PRAD	READ	THCA	UCEC
Island-hyper	5.8	1.2	19	26	27	23	23	20	24	20	15	22	13	4	19
Shore-hyper	11	3.2	13	24	20	16	19	11	18	18	12	23	8.2	4.7	19
Shelf-hyper	9.1	5.5	6.8	15	7.7	8.6	11	4.5	10	10	8	15	5	3.5	14
OpenSea-hyper	10	5.8	7.9	17	7.5	8.4	11	4.3	12	12	8.2	20	4.8	4.7	16
Island-hypo	5.2	1.8	10	5.2	4.5	3.4	6.5	10	5.6	8.8	3.1	3.3	3.4	1.4	8.7
Shore-hypo	17	8.7	34	18	18	13	24	33	20	29	11	12	12	7	28
Shelf-hypo	25	13	50	29	32	21	40	52	31	46	14	18	18	10	35
OpenSea-hypo	26	14	53	35	37	24	42	58	36	48	16	20	21	12	39

Supplementary Table 2

Percent of probes displaying significant hypo- and hyper- methylation in each region in placenta and cancers.*

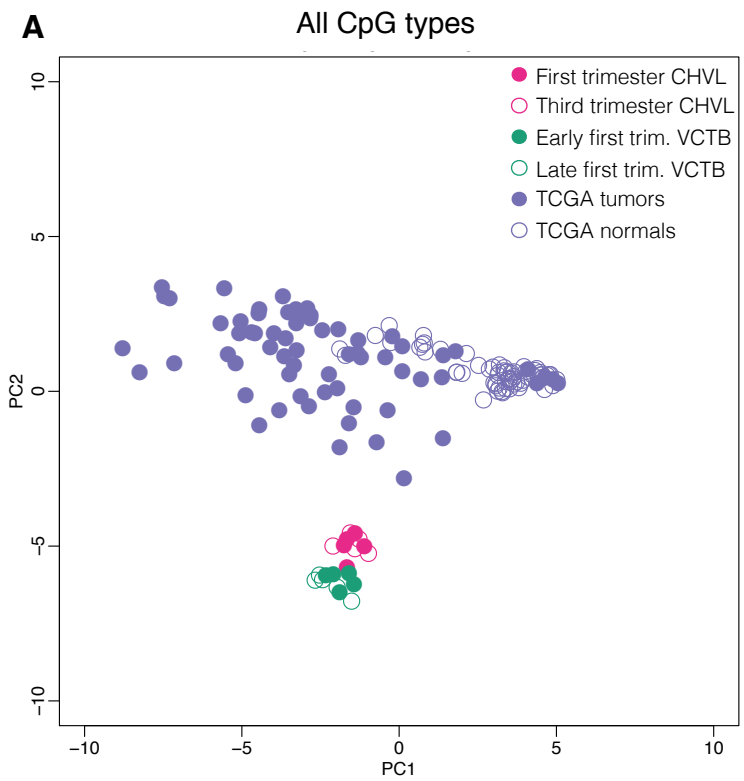
*Four first rows: percent of hypomethylation in individual island, shore, and open sea CpG probes (q value < 0.05 and difference < -0.05). Four last rows: percent of hypermethylation in individual island, shore, and open sea CpG probes (q value < 0.05 and difference > 0.05). Abbreviations as in Supplementary Table 1.

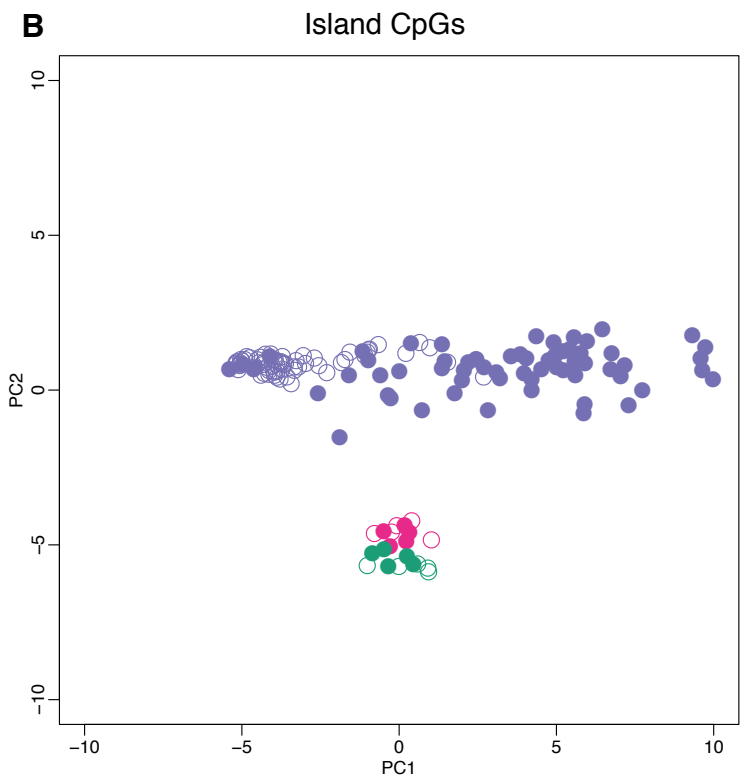
	Baseline low methylation (N)	Significant hypermethylation (N)	Significant hypermethylation (%)
CHVL	65263	3937	6.0
VCTB	69921	401	0.6
BLCA	71551	18001	25.0
BRCA	72139	26106	36.0
COAD	68939	26928	39.0
UCEC	73234	19277	26.0
ESCA	69283	22939	33.0
HNSC	71543	23322	33.0
LIHC	70122	19705	28.0
LUAD	71222	23669	33.0
LUSC	73825	20299	27.0
PAAD	72600	16665	23.0
PRAD	71257	21913	31.0
READ	68670	13487	20.0
THCA	73995	3766	5.1

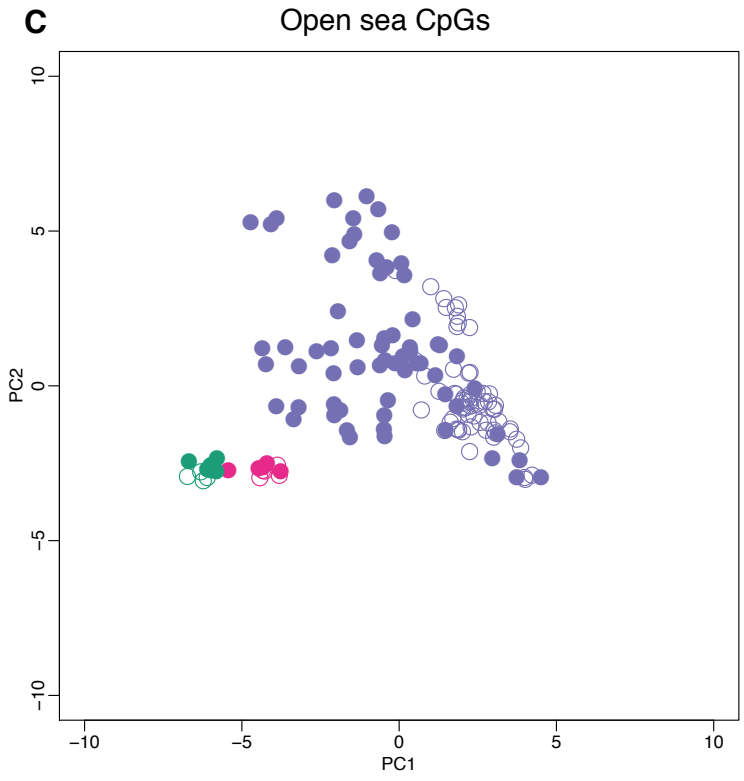
Supplementary Table 3

CpG island hypermethylation events in chorionic villi, villous cytotrophoblasts and 13 cancer types*

*Baseline low methylation is defined as methylation < 0.20 at island probes in third trimester CHVL, late first trimester VCTB or other normal tissues. Significant hypermethylation corresponds to methylation differences > 0.05 and FDR q-value < 0.05 at island probes in first *vs*. third trimester CHVL, early *vs*. late first trimester VCTB, and tumors *vs*. corresponding normal tissues. Abbreviations as in Supplementary Table 1.







Supplementary Figure 1

PCA and heatmap visualization of placenta and cancers . (A) Principal component analysis (PCA) of the methylation at island, shore, shelf and open sea probes; (B) at island probes; (C) and at open sea probes. For each condition, the 500 most variable probes were selected and plot for five samples. (D) Heatmap representing levels of methylation correspond to the 10 000 most differentially methylated probes in tumors *vs*. corresponding normal tissues for the 13 cancer types included in the study. Rows were ordered using the ward.2 method for hierarchical clustering built in the R software environment. Abbreviations as in Supplementary Table 1.

Supplementary Figure 2 (1/3)

Individual probe methylation in each region for chorionic villi and 13 cancer types. For each region, 10,000 probes were randomly sampled. Abbreviations as in Supplementary Table 1.

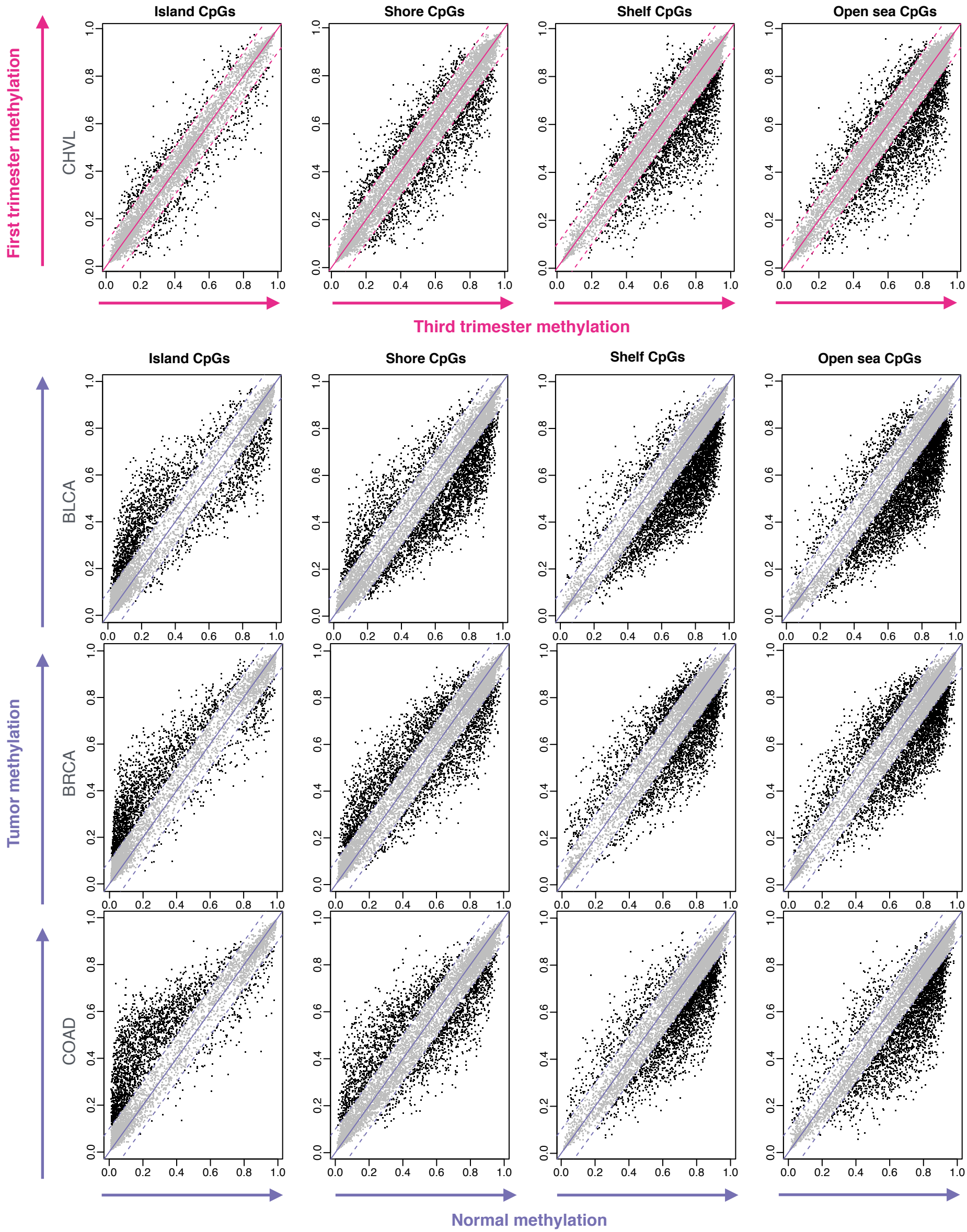


Fig. S2
(2/3)

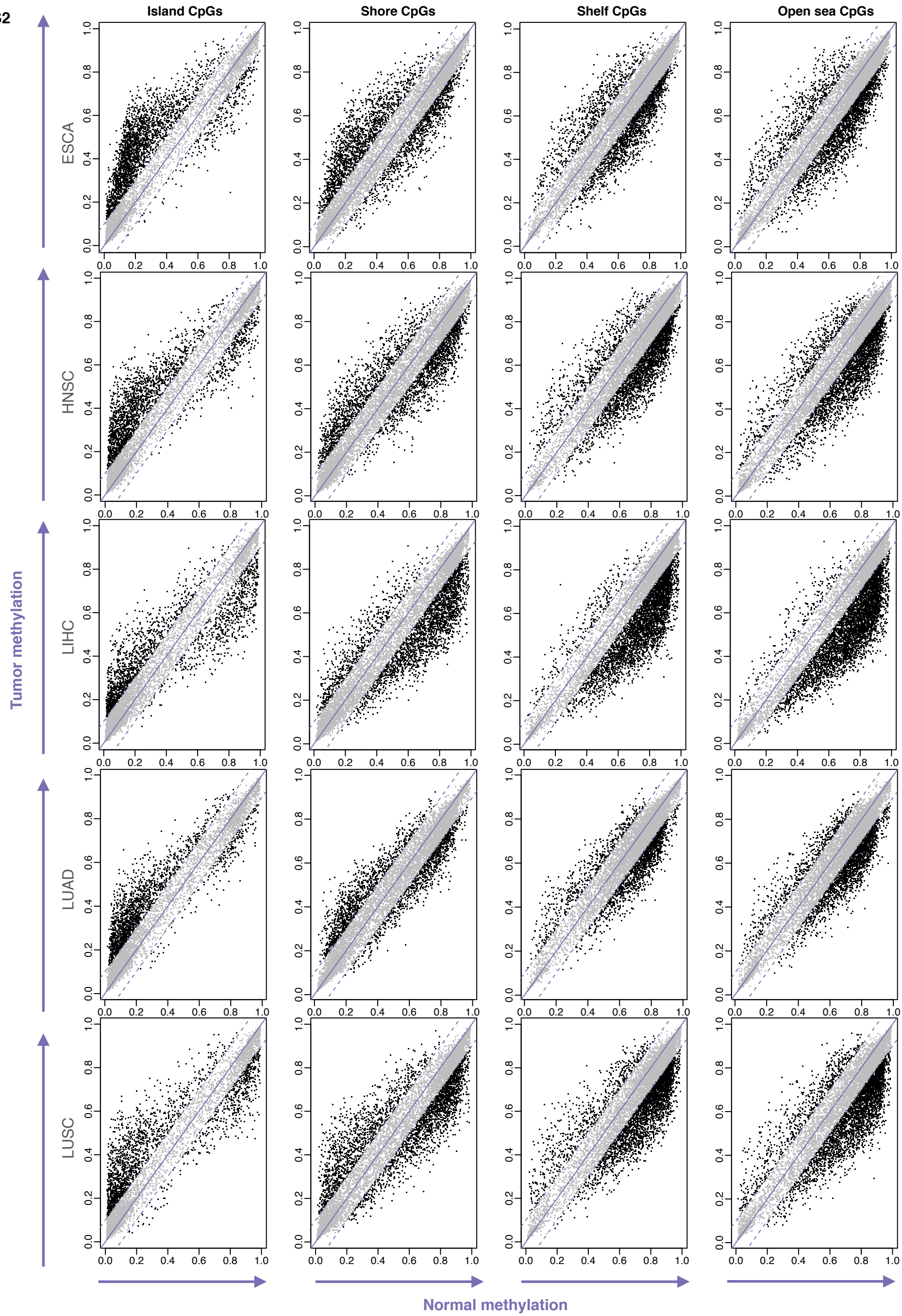
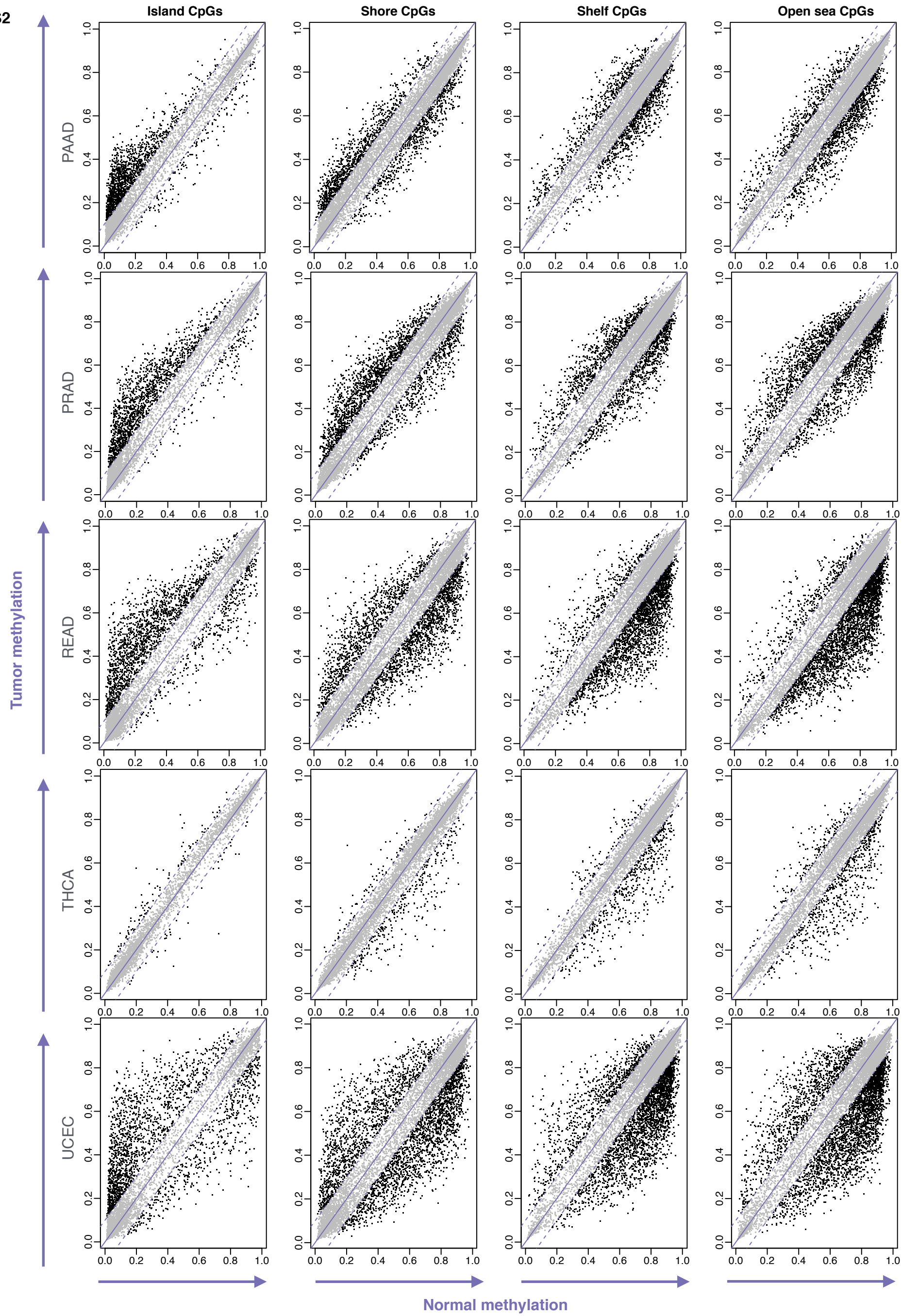
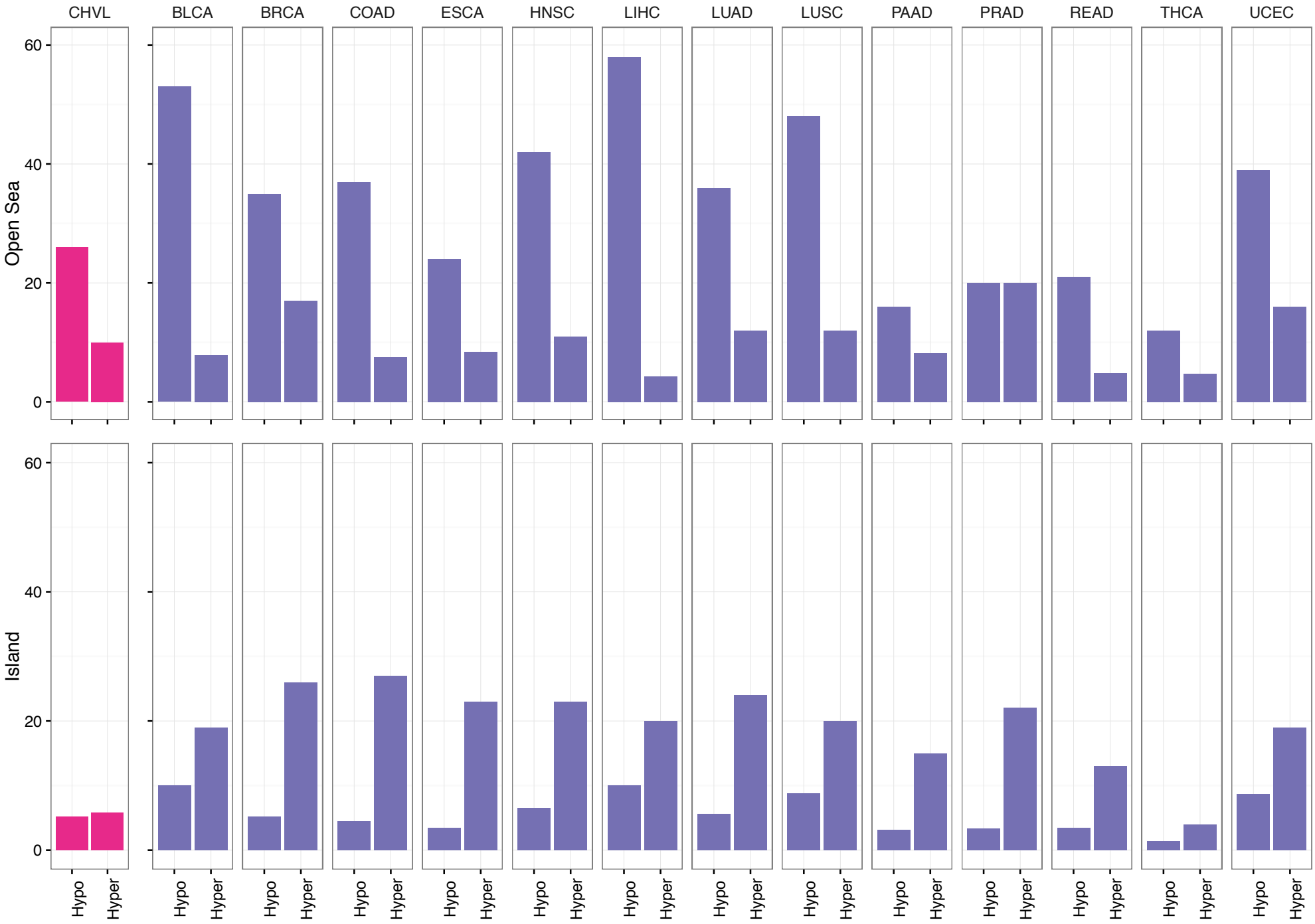

Island CpGs
Shore CpGs
Shelf CpGs
Open sea CpGs
ESCA
HNSC
LIHC
LUAD
LUSC
Tumor methylation
Normal methylation
0.0
0.2
0.4
0.6
0.8
1.0

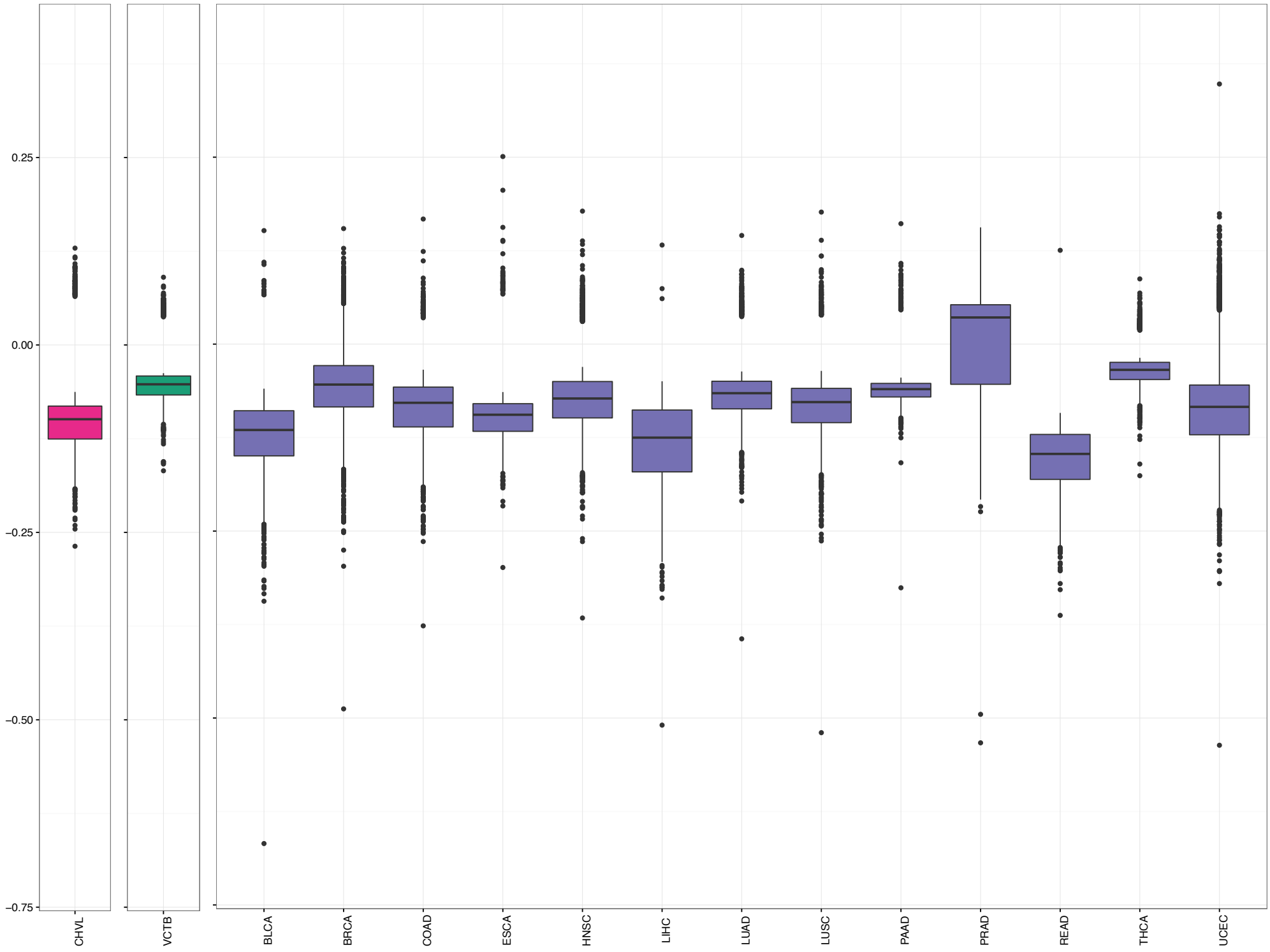
Fig. S2
(3/3)


Island CpGs
Shore CpGs
Shelf CpGs
Open sea CpGs
PAAD
PRAD
READ
THCA
UCEC
Tumor methylation
Normal methylation
0.0
0.2
0.4
0.6
0.8
1.0



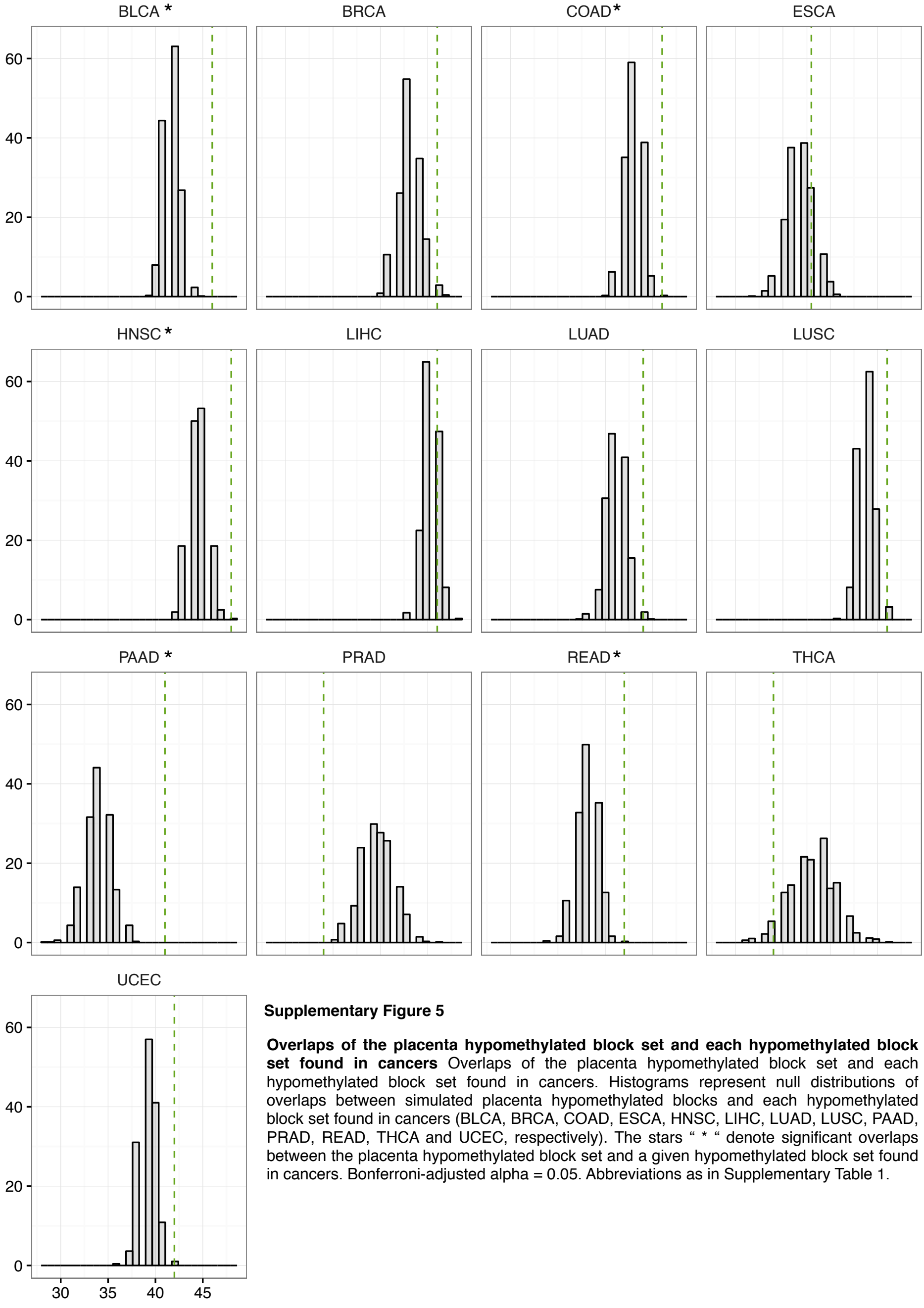
Supplementary Figure 3

Main DNA methylation changes in open sea and island CpGs. Percent of CpG probes displaying a significant (q value < 0.05) hypomethylation (difference < -0.05) and hypermethylation (difference > 0.05) in open sea regions (top), and island regions (bottom).Pink denotes placenta samples, and purple denotes cancer samples (13 types). Abbreviations as in Supplementary Table 1.



Supplementary Figure 4

Distributions of the median of methylation difference in placenta, cytotrophoblast and cancer hypomethylated blocks. Distributions of the median of the average difference of methylation in cytotrophoblast hypomethylated blocks in green, in placenta hypomethylated blocks in pink and cancer hypomethylated blocks in purple.

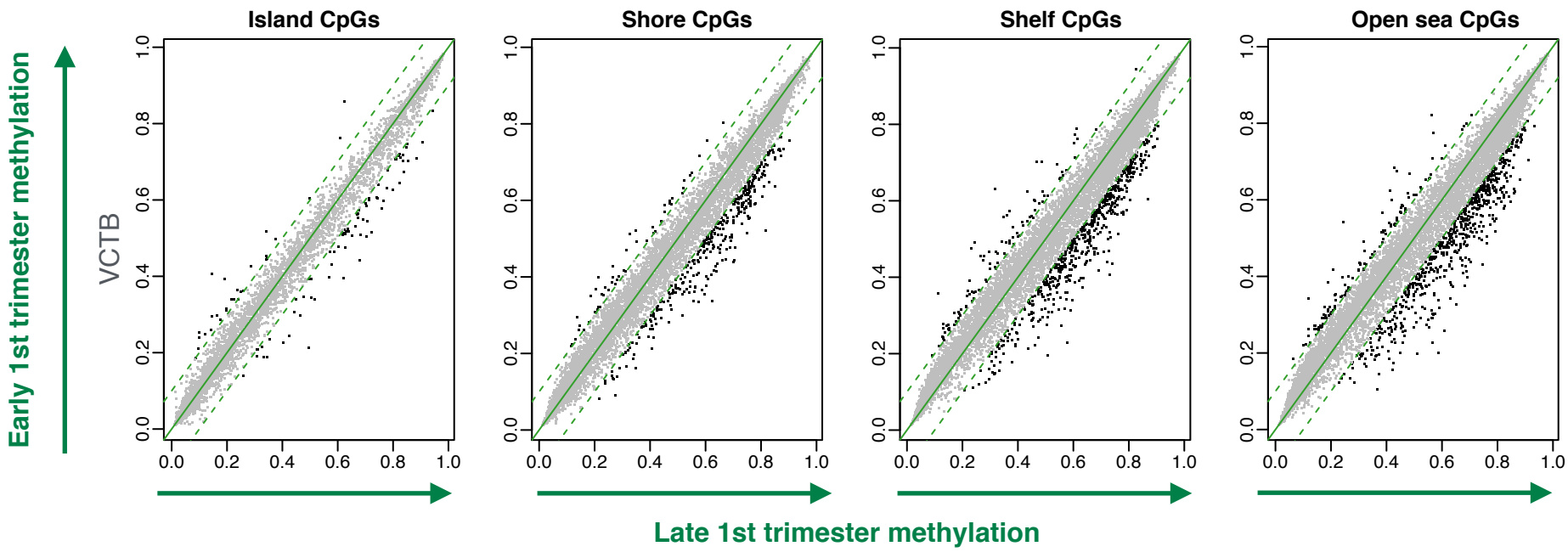


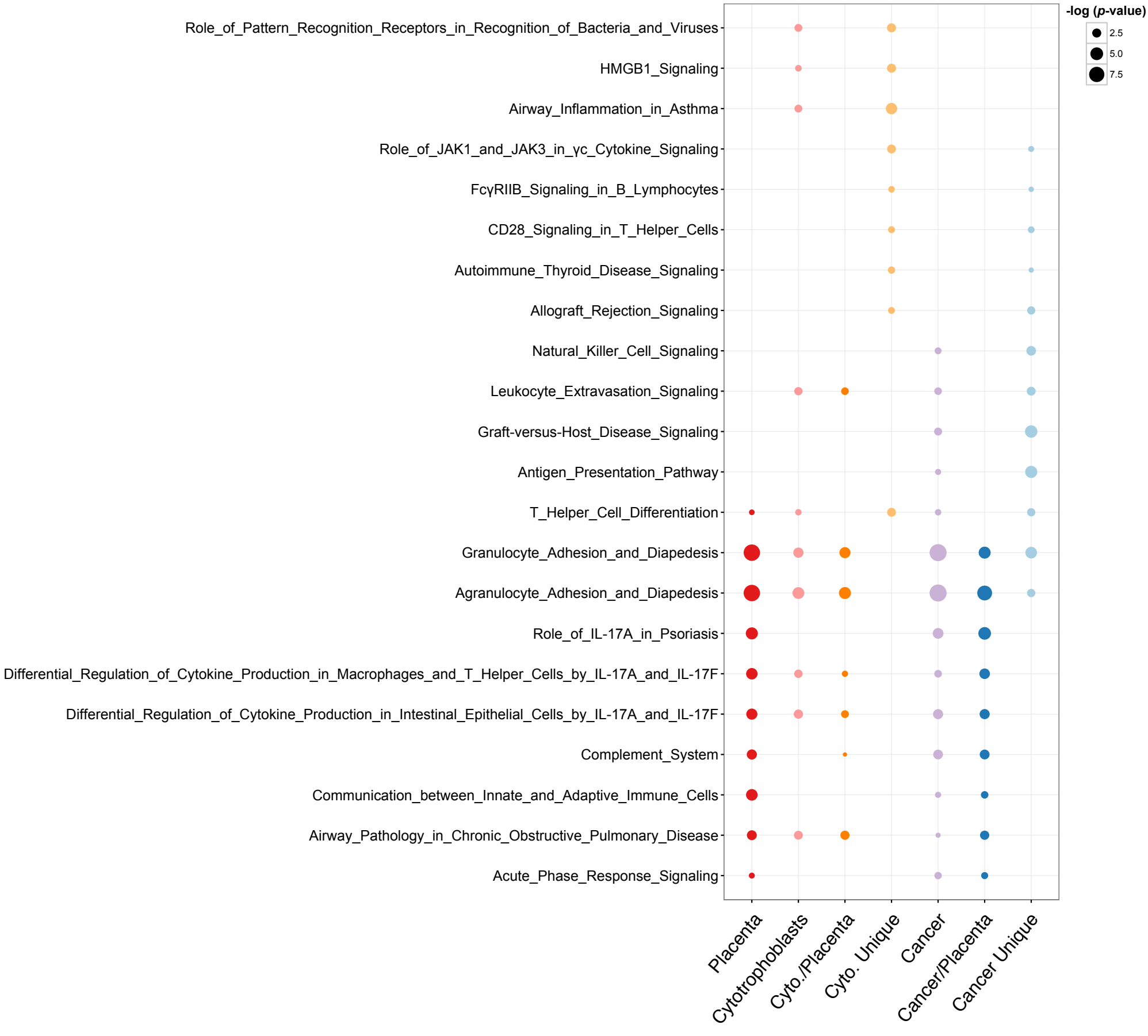
Supplementary Figure 5

Overlaps of the placenta hypomethylated block set and each hypomethylated block set found in cancers Overlaps of the placenta hypomethylated block set and each hypomethylated block set found in cancers. Histograms represent null distributions of overlaps between simulated placenta hypomethylated blocks and each hypomethylated block set found in cancers (BLCA, BRCA, COAD, ESCA, HNSC, LIHC, LUAD, LUSC, PAAD, PRAD, READ, THCA and UCEC, respectively). The stars " * " denote significant overlaps between the placenta hypomethylated block set and a given hypomethylated block set found in cancers. Bonferroni-adjusted alpha = 0.05. Abbreviations as in Supplementary Table 1.

Supplementary Figure 6

Individual probe methylation in each region for villous cytotrophoblasts. For each region, 10,000 probes were randomly sampled. Abbreviations as in Supplementary Table 1.





Supplementary Figure 7

Bubble chart representing the enrichment of IPA gene sets related to immune response in placenta and cancer hypomethylated blocks (colon adenocarcinoma). “Cancer/Placenta” (“Cancer Unique”) represents genes in cancer hypomethylated blocks that co-localize (do not co-localize) with a placenta hypomethylated block. Only the significant enrichments (p-value < 0.05) are presented. Abbreviations as in Supplementary Table 1.