Table S1. Methyl index of individual site determined from Top-Down measurement

A. Methyl Index

H3.1 MMSET-Low

Methyl-Eq	1	2	3	4	5	6	7	8
K9	0.3	0.7	1.0	1.3	1.3	1.3	1.5	1.5
K27	0.9	1.9	2.9	3.9	3.7	3.2	3.9	3.5
K36	1.0	2.0	2.9	3.9	4.8	3.4	4.0	4.3

H3.1 MMSET-High

Methyl-Eq	1	2	3	4	5	6	7	8
K9	0.2	0.7	0.8	1.1	1.4	1.6	1.6	1.4
K27	0.2	1.0	1.7	2.5	3.1	3.9	4.7	3.2
K36	1.0	2.0	2.9	3.9	4.8	5.8	6.5	4.8

H3.3 MMSET-Low

Methyl-Eq	1	2	3	4	5	6	7	8
K9	0.2	0.4	0.7	1.0	1.1	1.0	1.1	1.0
K27	1.0	1.9	2.6	3.4	2.7	3.1	3.4	3.5
K36	1.0	2.0	2.9	3.8	4.6	3.6	4.0	4.5

H3.3 MMSET-High

Methyl-Eq	1	2	3	4	5	6	7	8
K9	0.4	0.5	0.6	0.8	1.2	1.1	1.1	1.0
K27	1.0	1.0	1.9	2.4	2.8	3.6	4.0	3.2
K36	1.0	2.0	3.0	3.9	4.8	5.5	6.5	4.9

B. Δ Methyl Index

H3.1 MMSET-Low

Methyl-Eq	1	2	3	4	5	6	7	8
K27	0.7	1.2	1.8	2.6	2.4	1.9	2.5	2.0
K36	0.1	0.1	0.1	0.0	1.1	0.2	0.1	0.8

H3.1 MMSET-High

Methyl-Eq	1	2	3	4	5	6	7	8
K27	0.1	0.2	0.9	1.4	1.7	2.3	3.1	1.8
K36	0.8	1.0	1.3	1.4	1.7	1.9	1.9	1.6

H3.3 MMSET-Low

Methyl-Eq	1	2	3	4	5	6	7	8
K27	0.8	1.5	1.9	2.5	1.7	2.1	2.3	2.4

K36	0.0	0.1	0.3	0.3	1.8	0.5	0.6	1.0

H3.3 MMSET-High

Methyl-Eq	1	2	3	4	5	6	7	8
K27	0.6	0.4	1.3	1.6	1.7	2.6	2.9	2.2
K36	0.0	1.0	1.1	1.5	2.0	1.9	2.5	1.7

Methyl Index (MI) calculated from normalized modification levels. Methylation Index (MI) = ∑ *(%methylation * number of methyl groups present in fragment ion).* The convolving effect of methylation is eliminated in this scheme because a single di- or tri-methylation contributed equally to MI as two or three mono-methylations. The difference of MI from two consecutive sites (Δ MI) was then used to represent the overall levels of methylation at three individual sites, namely K9, K27, and K36. Note that K4 was mainly unmodified in all four samples and therefore MI of K9 was used directly as indicator of K9 methylation.