Figure 1

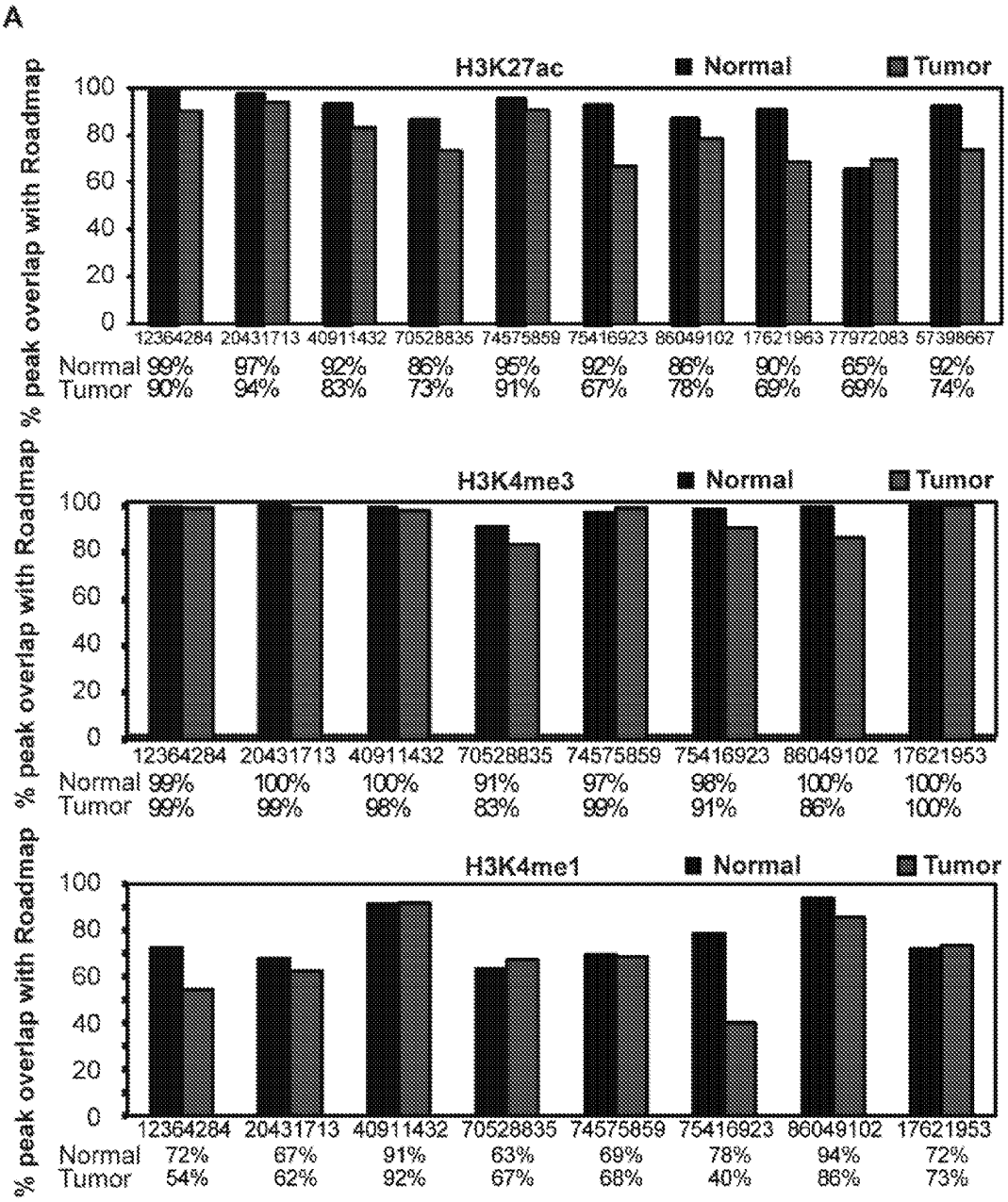

A
% peak overlap with Roadmap
H3K27ac
Normal
Tumor
100
80
60
40
20
0
12364284 20431713 40911432 70528835 74575859 75416923 86049102 17621963 77972083 57398667
Normal 99% 97% 92% 86% 95% 92% 86% 90% 65% 92%
Tumor 90% 94% 83% 73% 91% 67% 78% 69% 69% 74%
H3K4me3
Normal
Tumor
12364284 20431713 40911432 70528835 74575859 75416923 86049102 17621953
Normal 99% 100% 100% 91% 97% 98% 100% 100%
Tumor 99% 99% 98% 83% 99% 91% 86% 100%
H3K4me1
Normal
Tumor
12364284 20431713 40911432 70528835 74575859 75416923 86049102 17621953
Normal 72% 67% 91% 63% 69% 78% 94% 72%
Tumor 54% 62% 92% 67% 68% 40% 86% 73%

Figure 1 continued

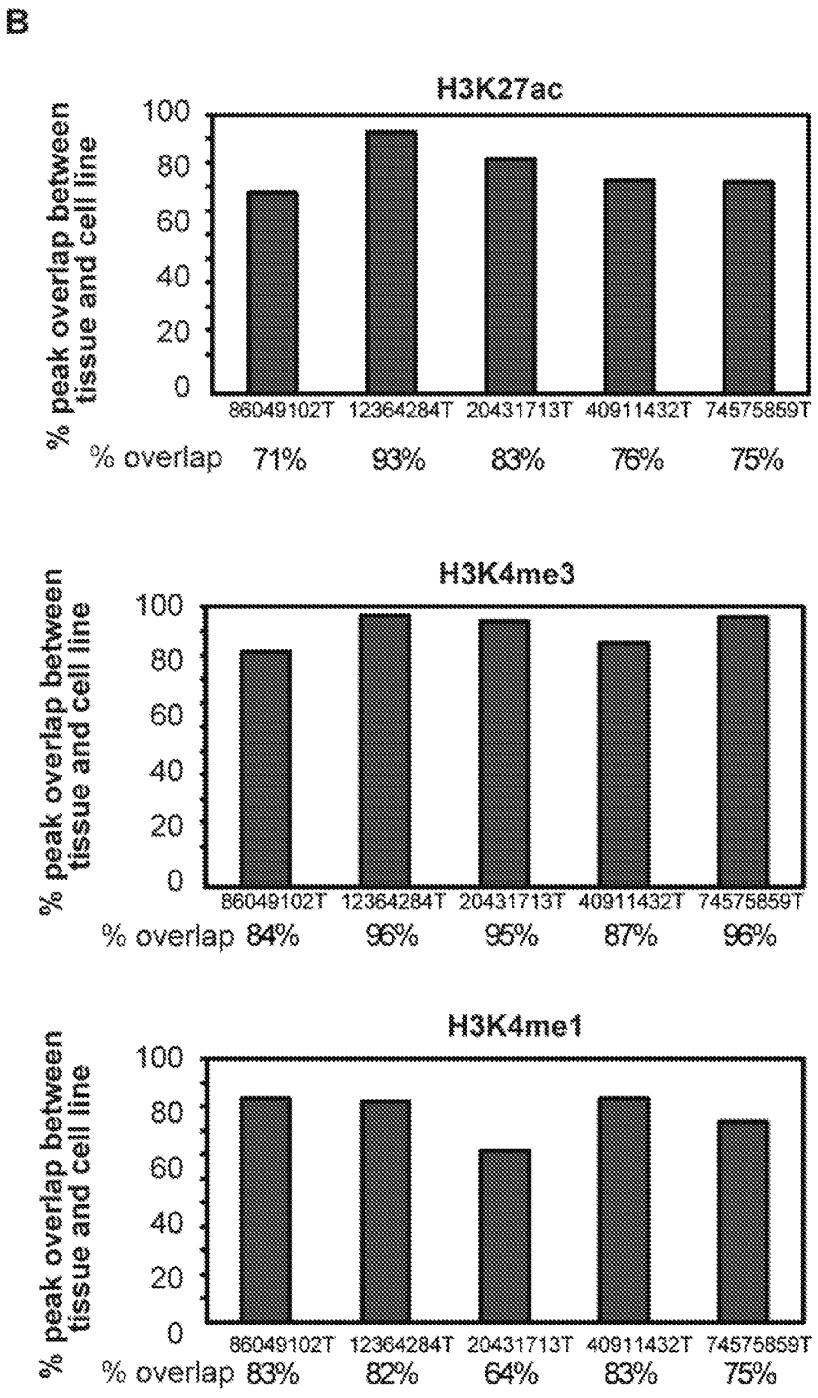
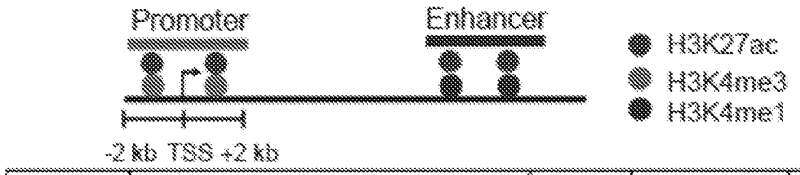


Figure 1 continued

C



Regions	Definition	Total	Recurrently gained in tumor	Recurrently lost in tumor
Promoter	H3K27ac$^+$/H3K4me3$^+$/±2 kb TSS	17,497	4,719	592
Enhancer	H3K27ac$^+$/H3K4me1$^+$/promoter-	66,448	4,906	5,654

D

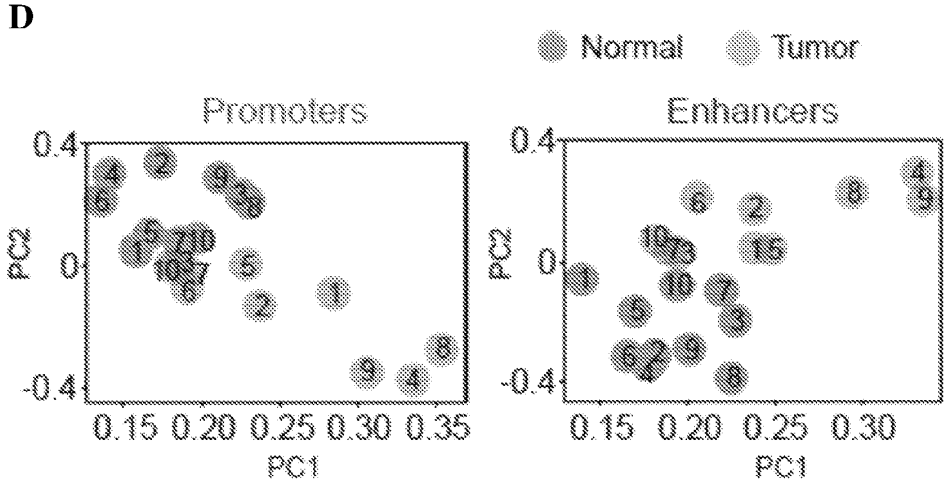


Figure 1 continued

E

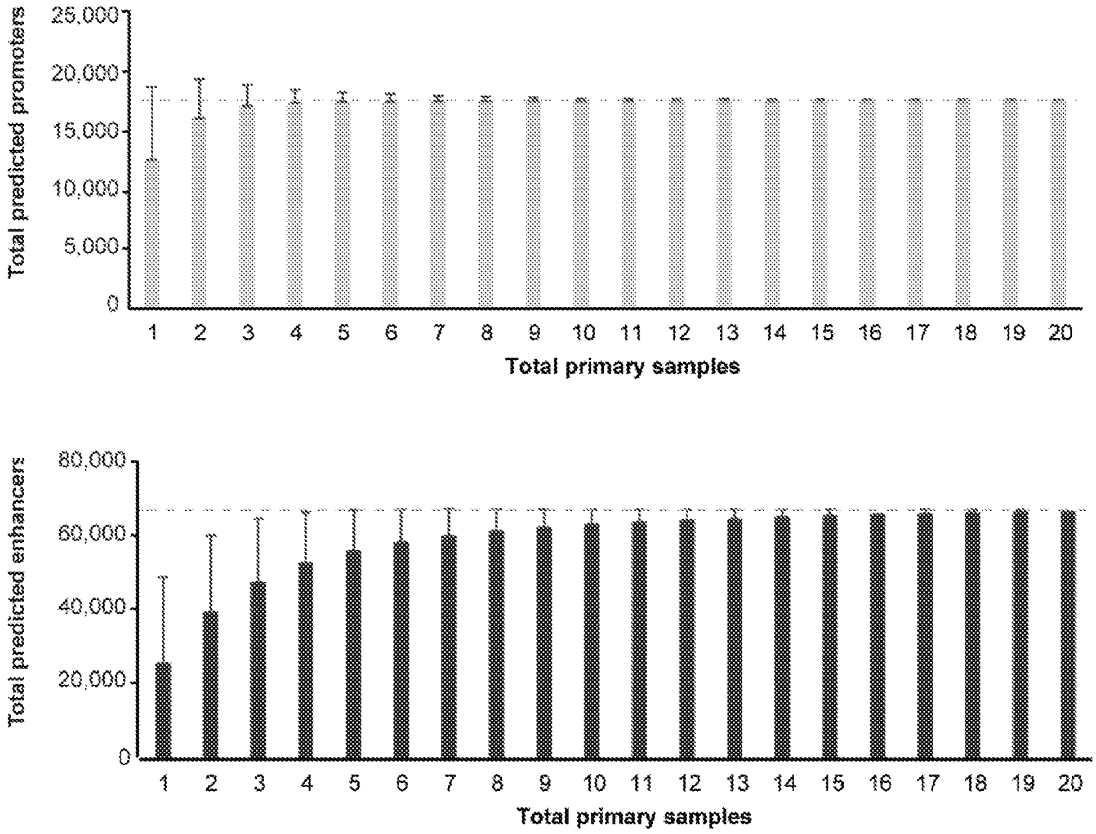


Figure 1 continued

F

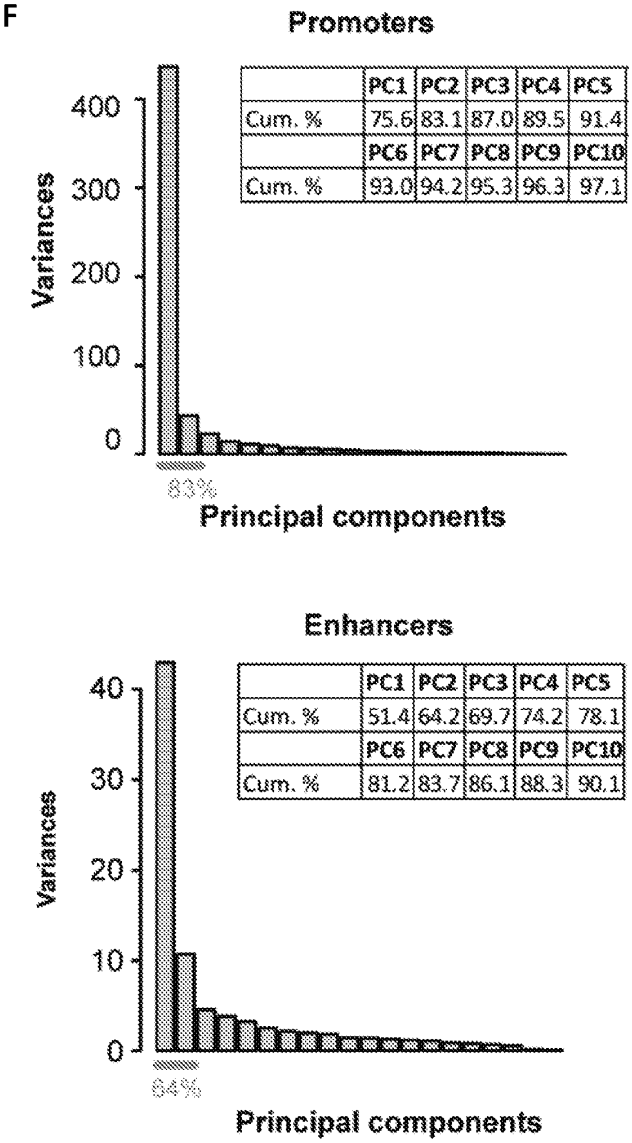


Figure 1 continued

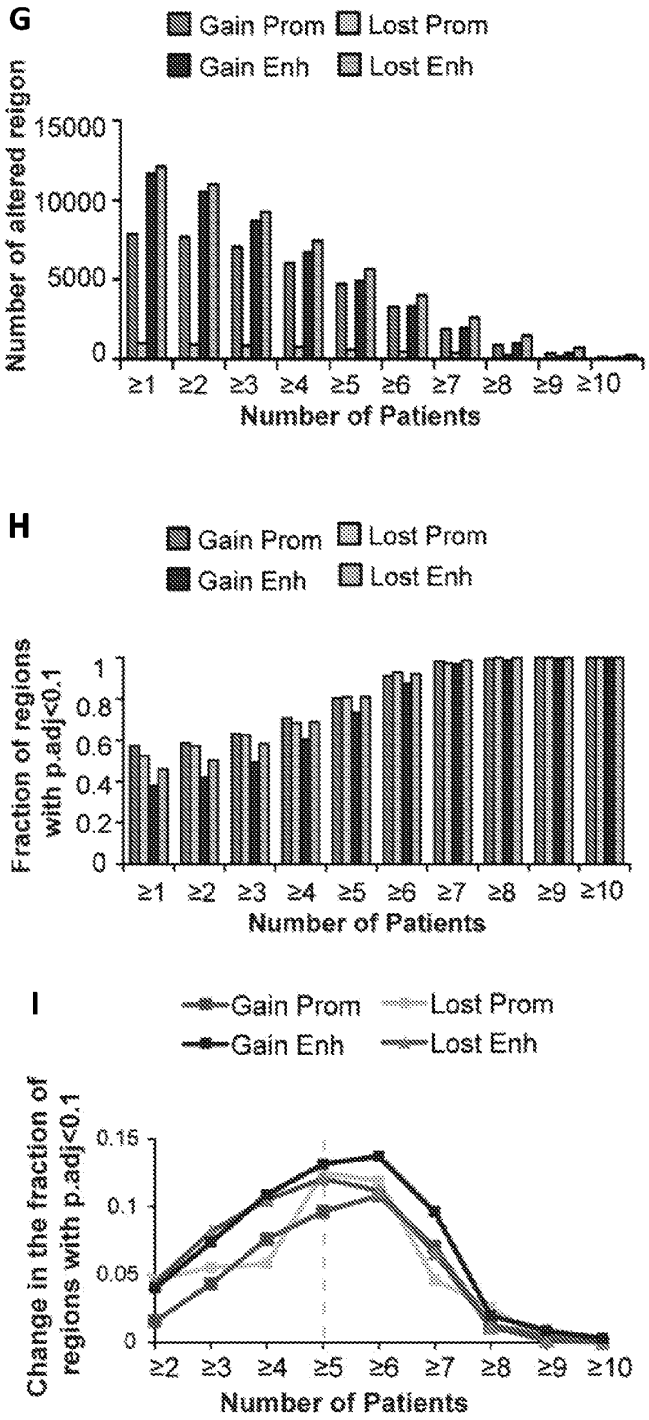


Figure 1 continued

J

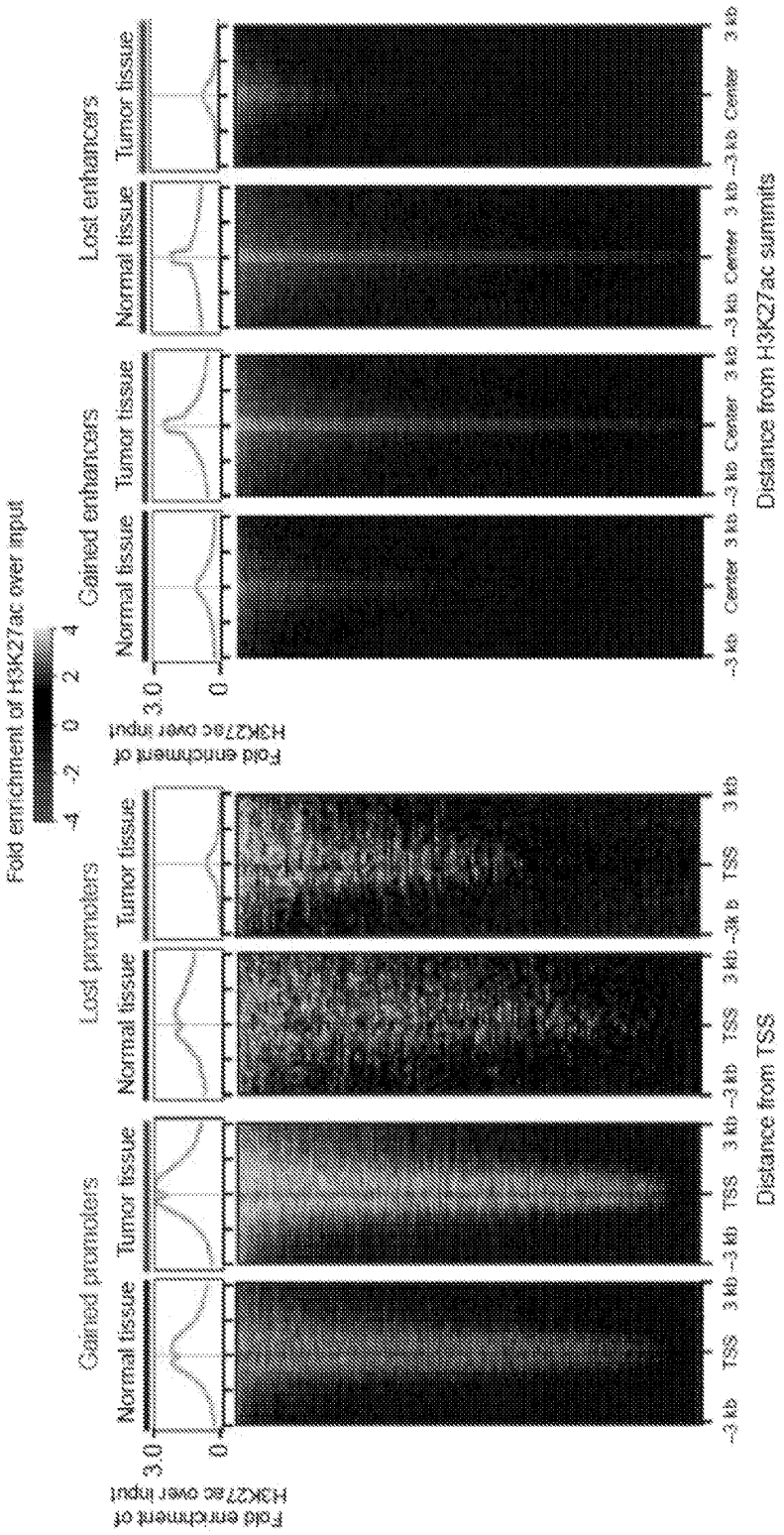


Figure 1 continued

K i)

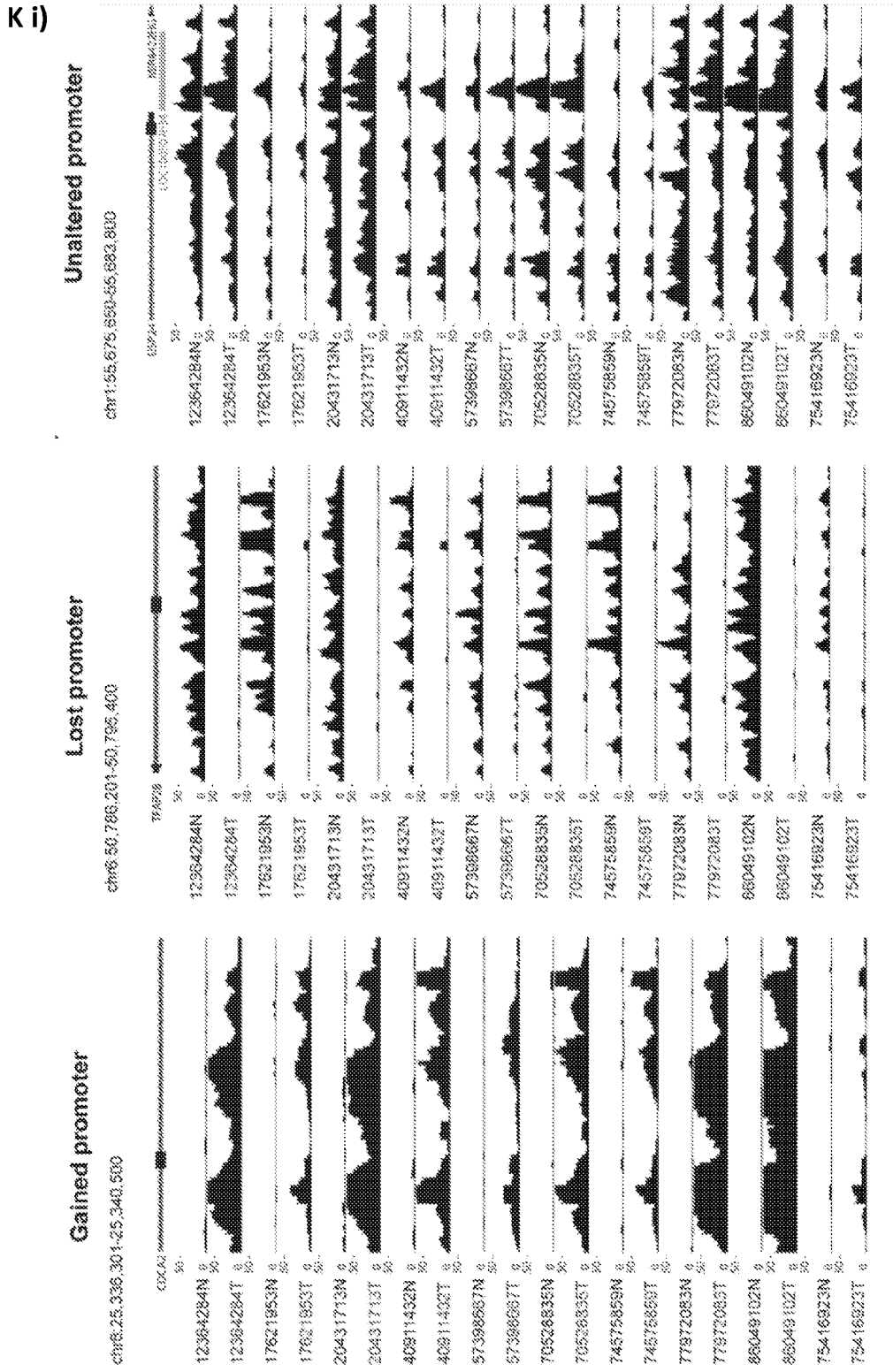


Figure 1 continued

K ii)

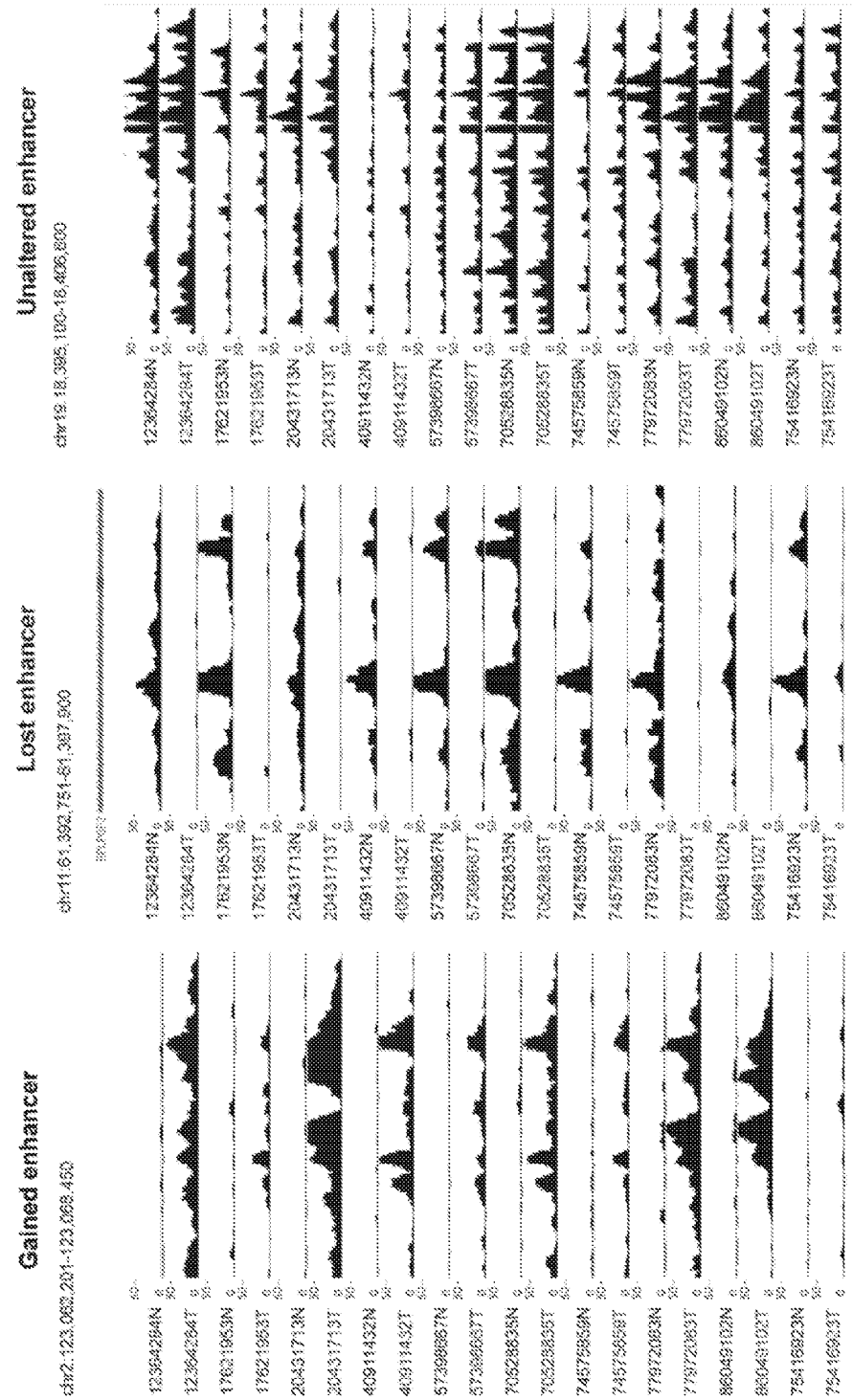


Figure 1 continued

L

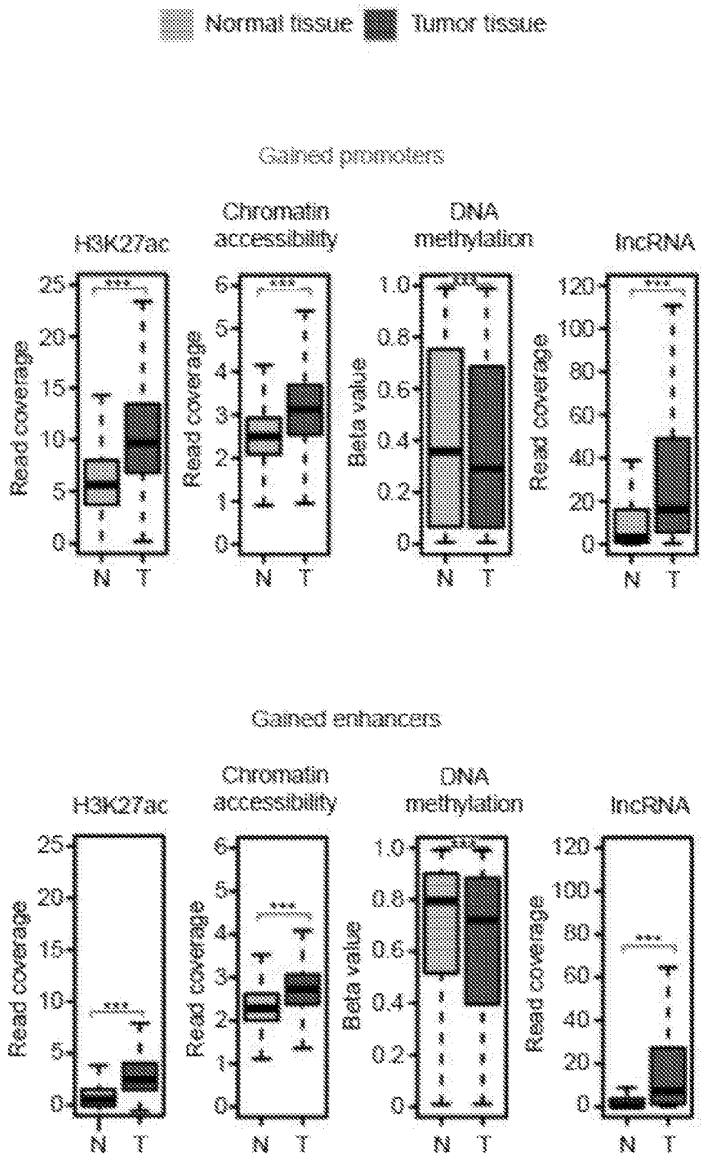


Figure 1 continued

M

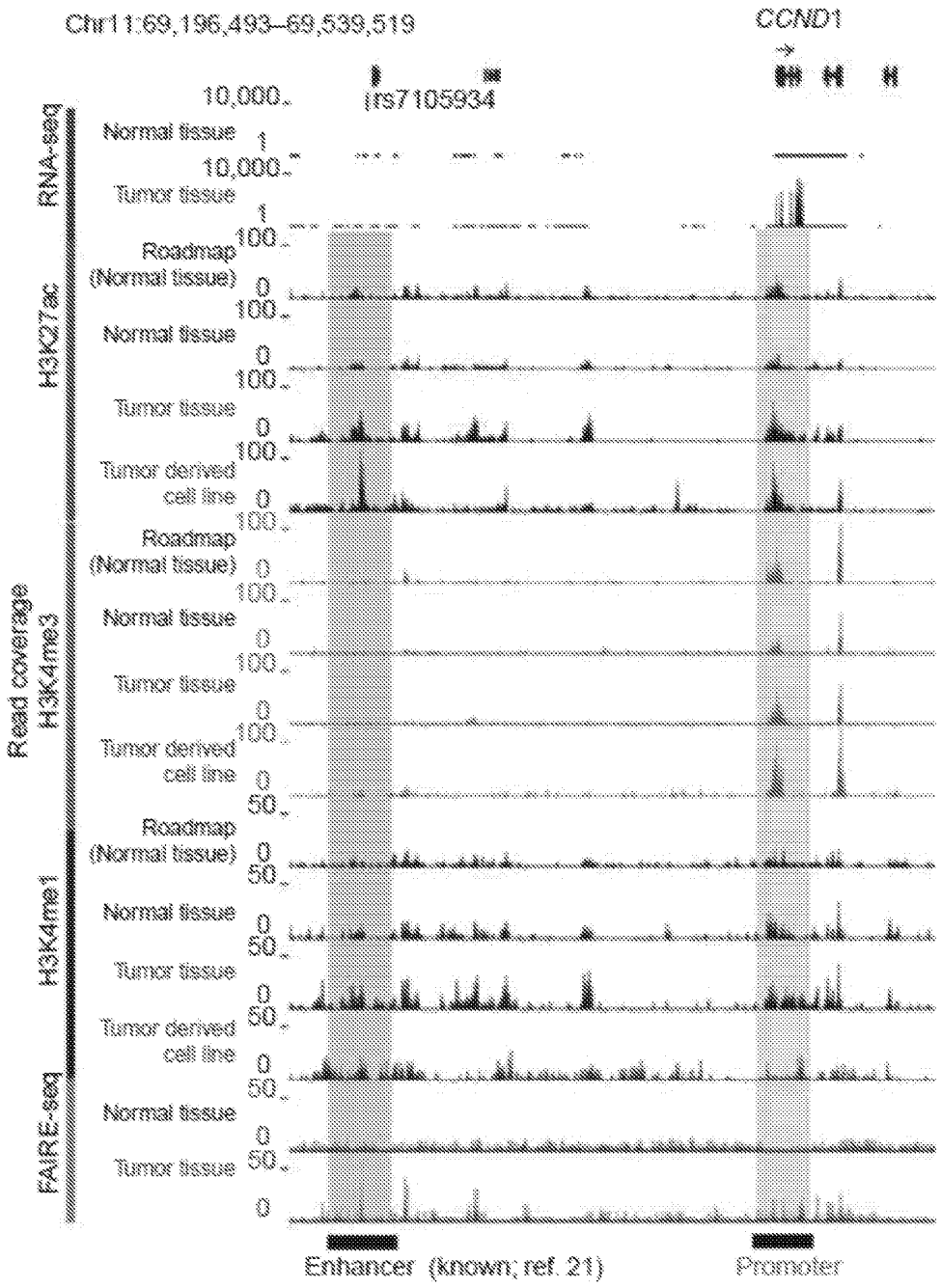


Figure 2

A

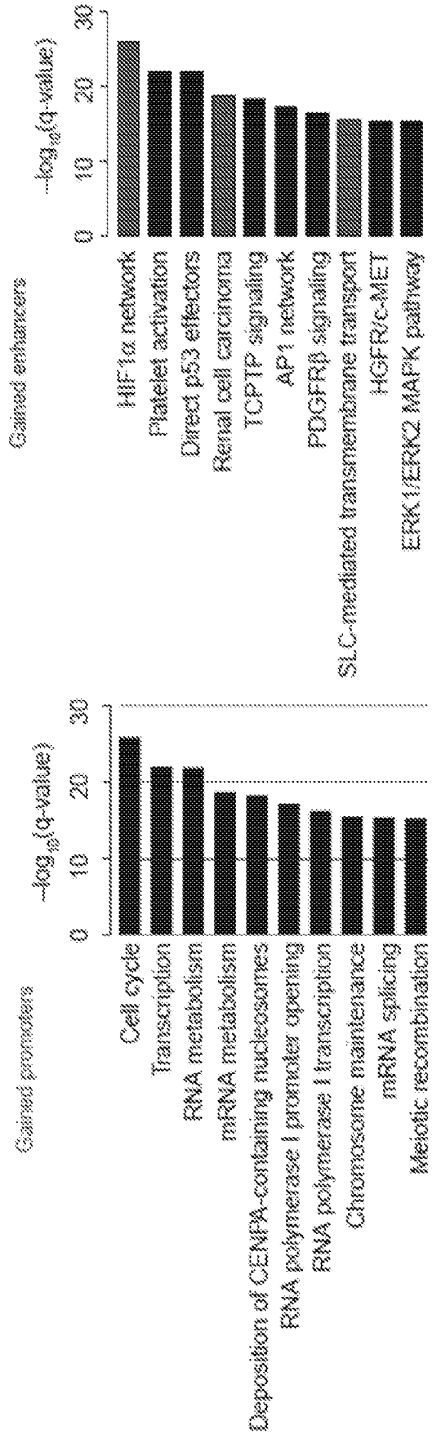

Gained enhancers
−log10(q-value)
0
10
20
30
HIF1α network
Platelet activation
Direct p53 effectors
Renal cell carcinoma
TCPTP signaling
AP1 network
PDGFRβ signaling
SLC-mediated transmembrane transport
HGFR/c-MET
ERK1/ERK2 MAPK pathway
Gained promoters
−log10(q-value)
0
10
20
30
Cell cycle
Transcription
RNA metabolism
mRNA metabolism
Deposition of CENPA-containing nucleosomes
RNA polymerase I promoter opening
RNA polymerase I transcription
Chromosome maintenance
mRNA splicing
Meiotic recombination

Figure 2 continued

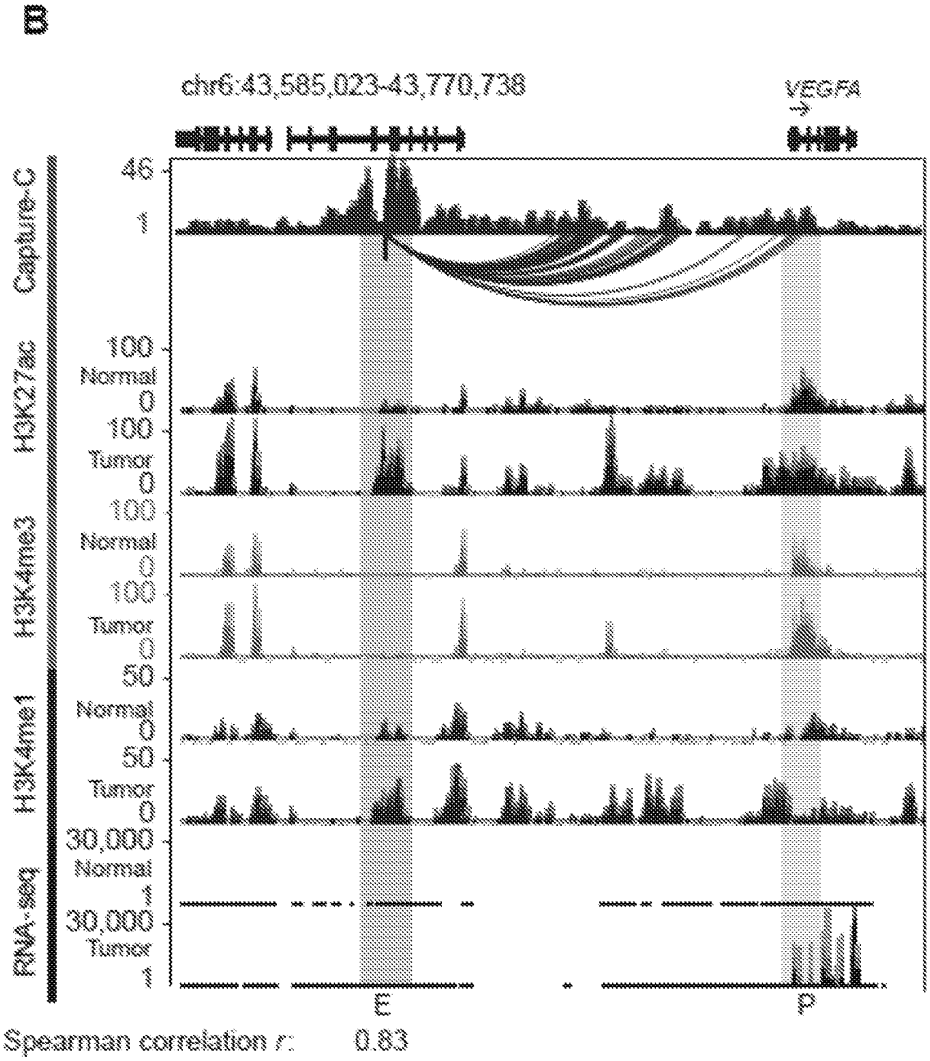


Figure 2 continued

C

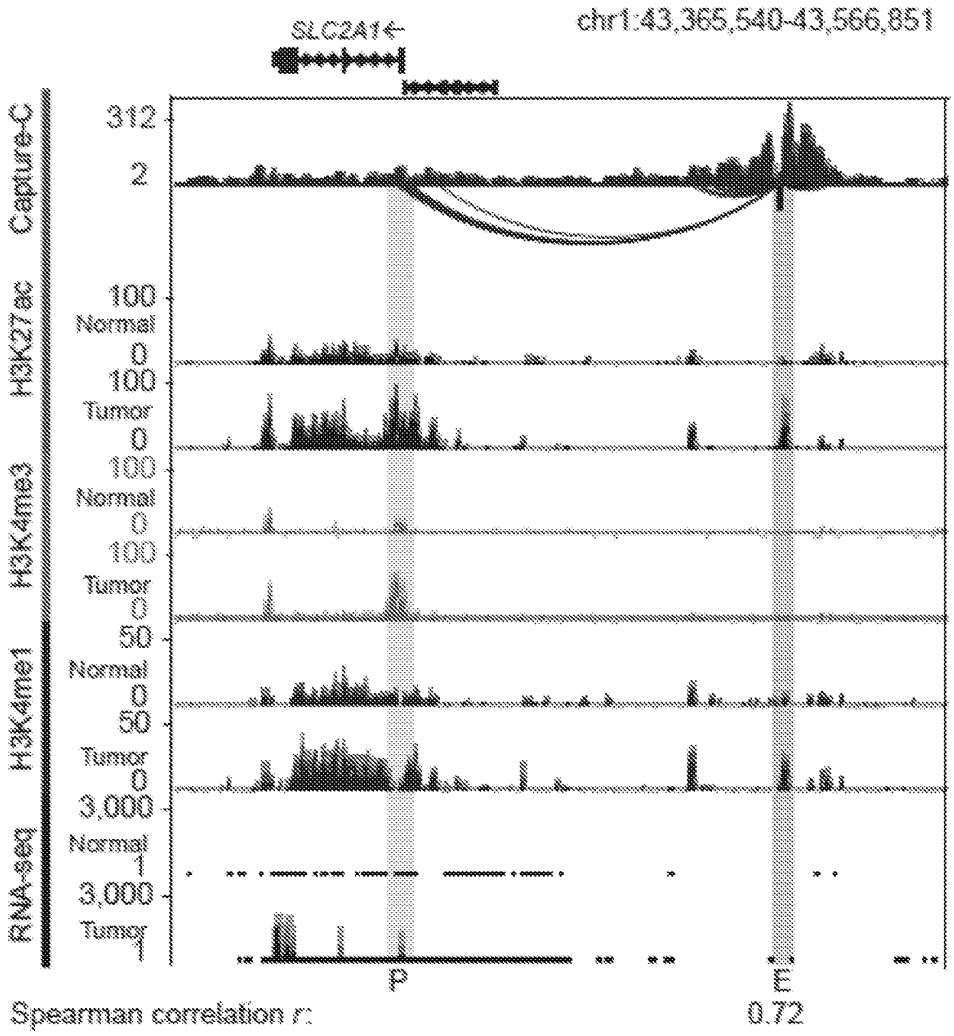


Figure 2 continued

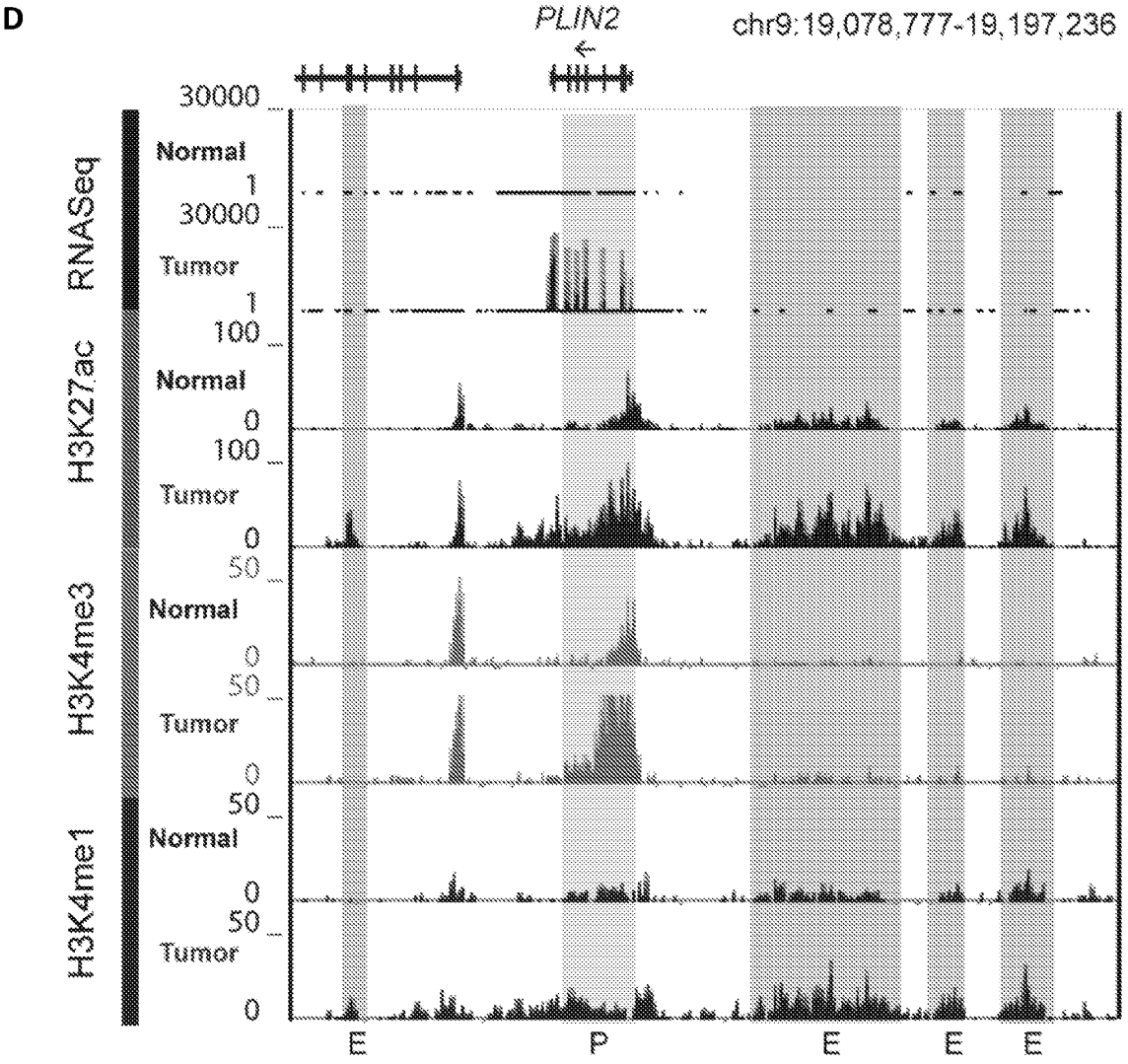


Figure 2 continued

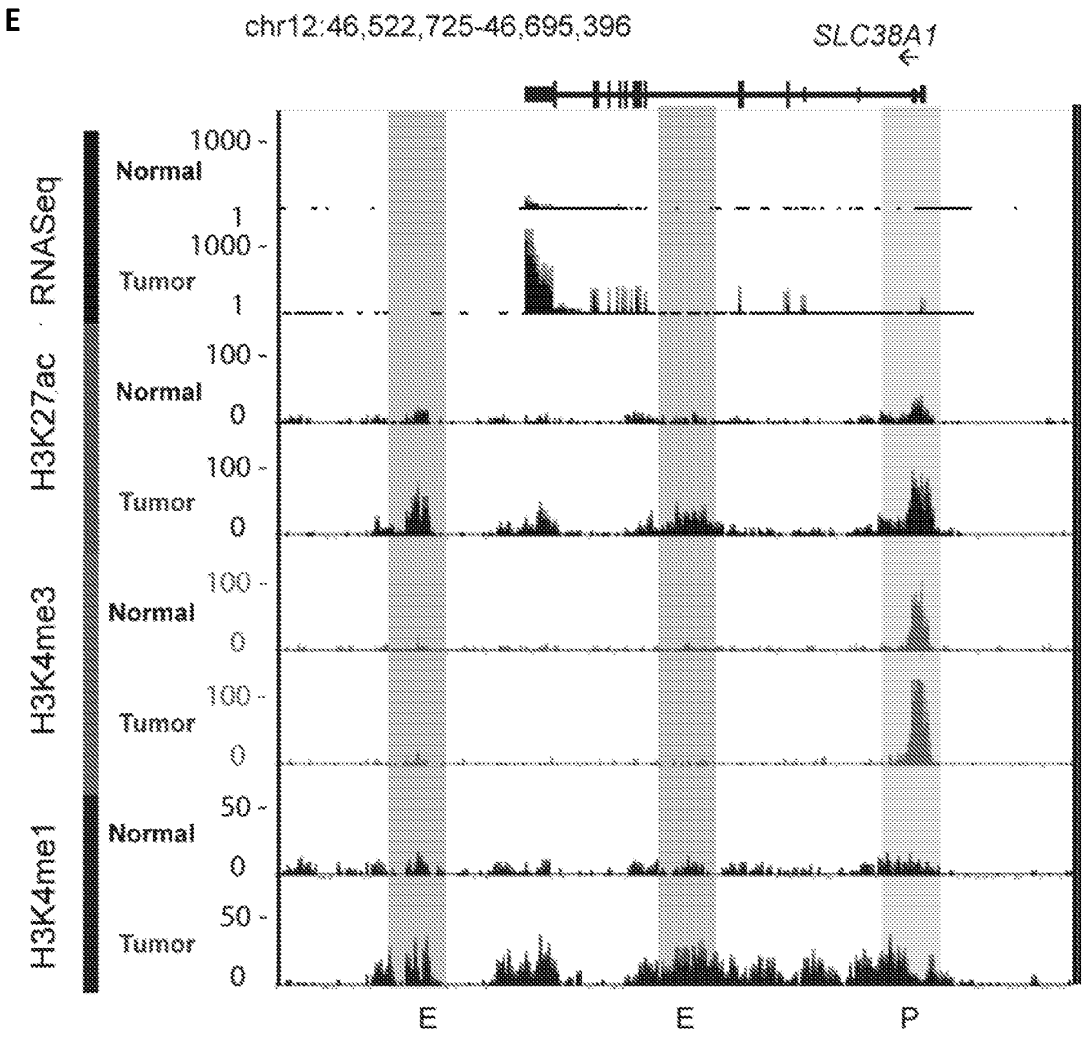


Figure 2 continued

F

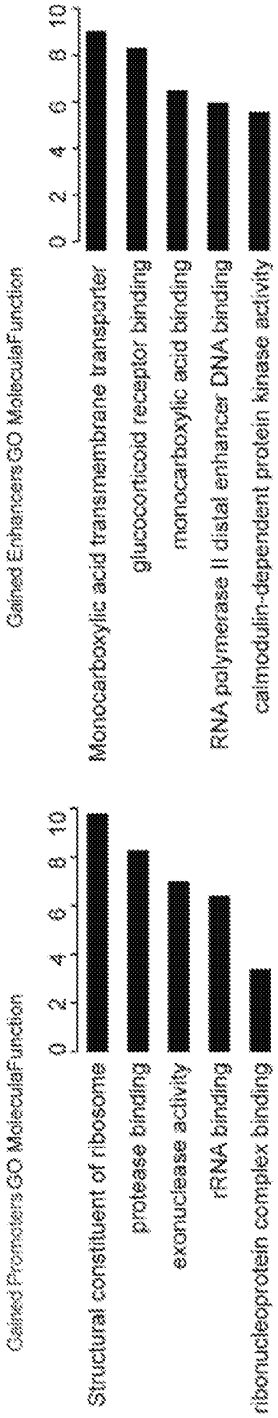
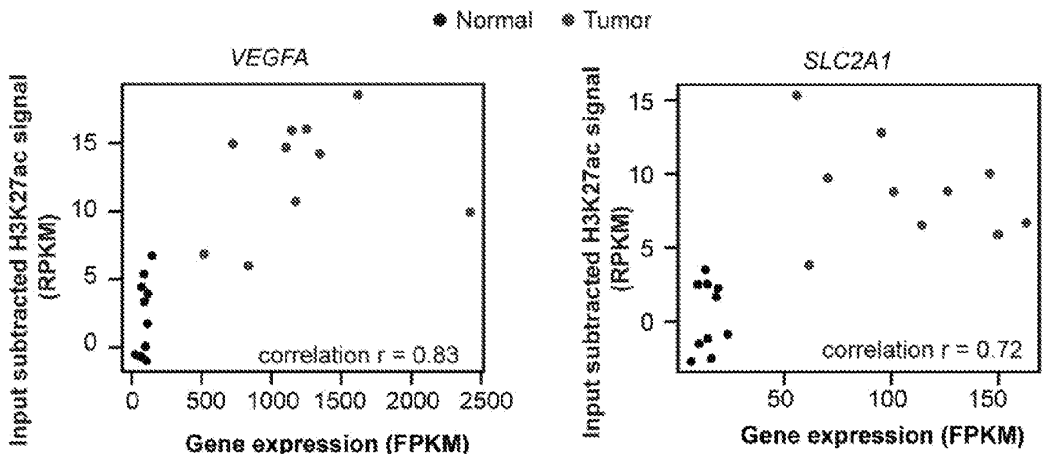


Figure 2 continued

G



H

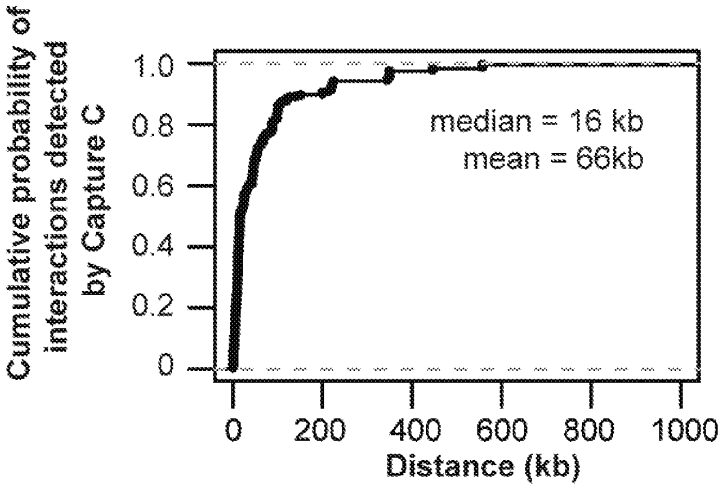


Figure 3

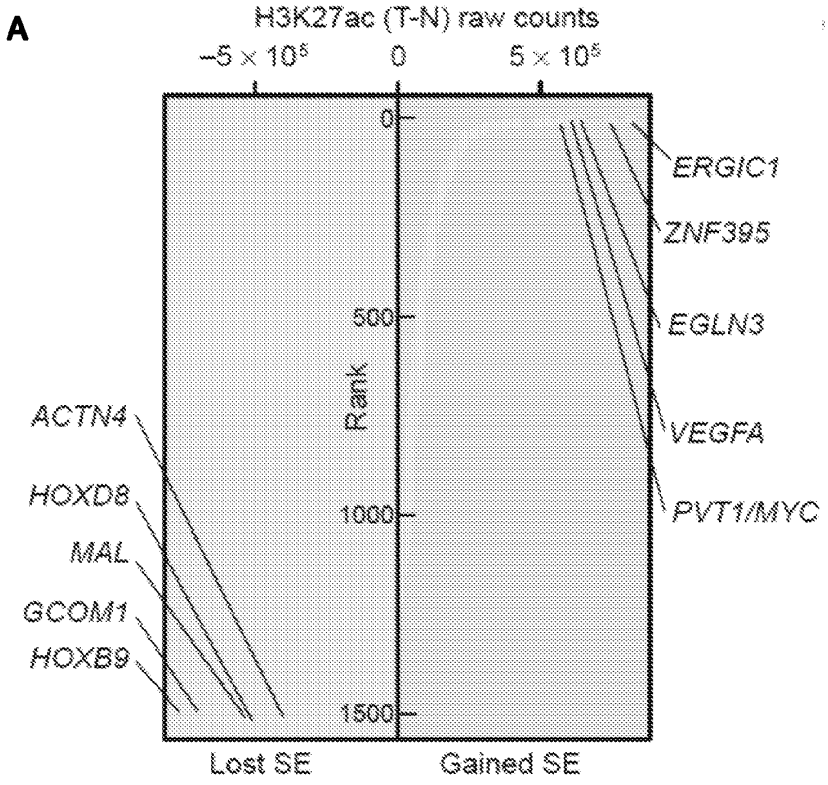

A
H3K27ac (T-N) raw counts
−5 × 10^5
0
5 × 10^5
0
500
1000
1500
Rank
ERGIC1
ZNF395
EGLN3
VEGFA
PVT1/MYC
ACTN4
HOXD8
MAL
GCOM1
HOXB9
Lost SE
Gained SE

Figure 3 continued

B

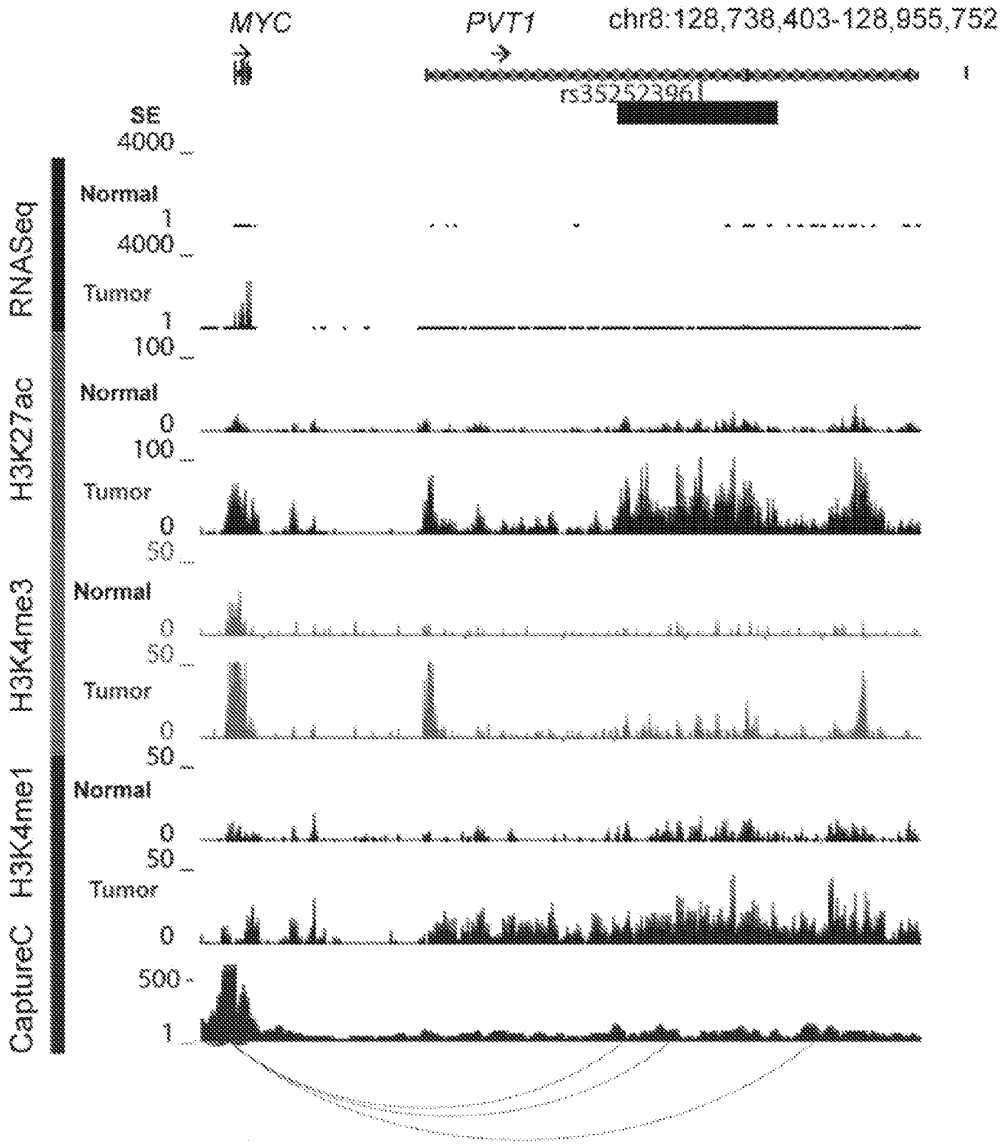


Figure 3 continued

C

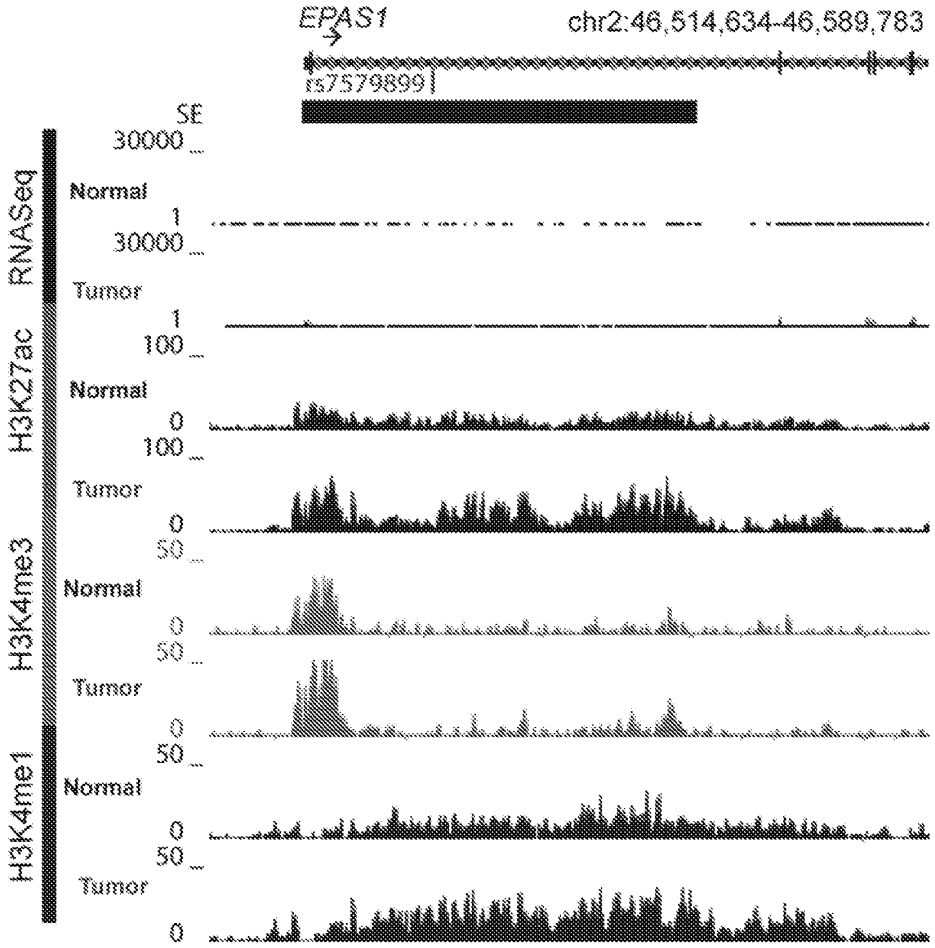


Figure 3 continued

D

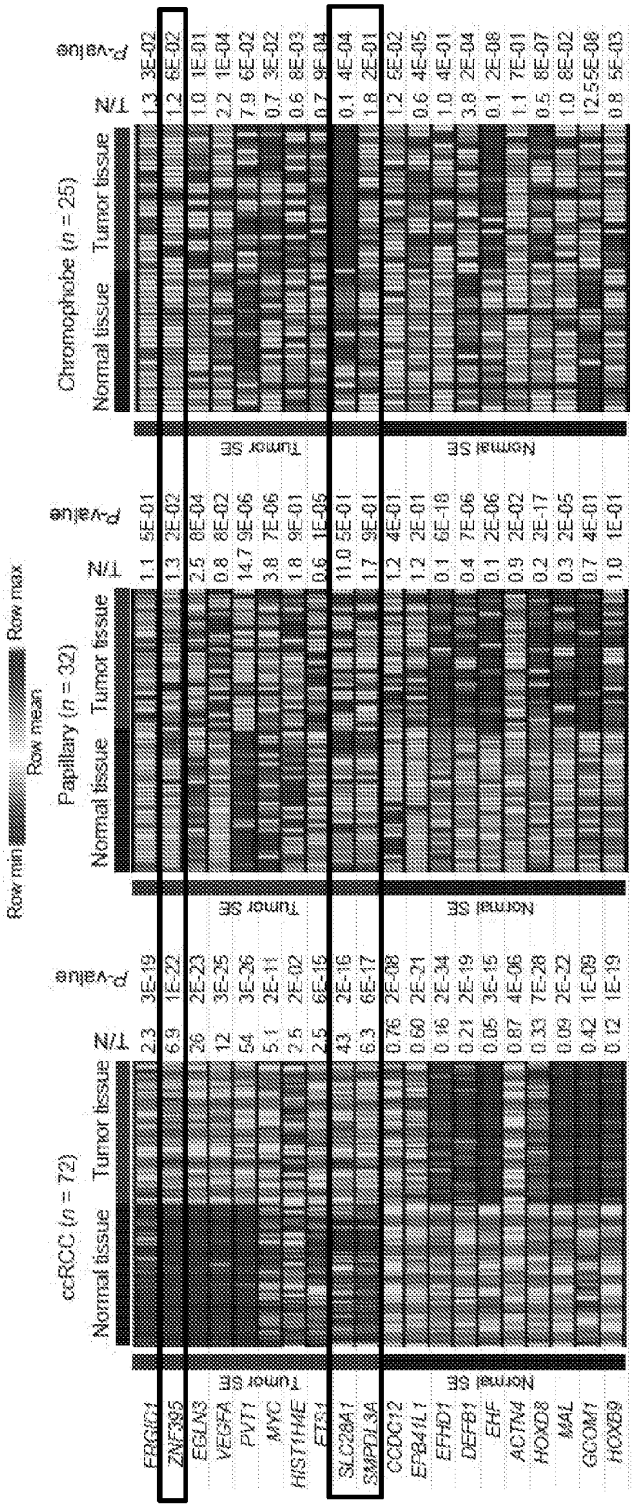
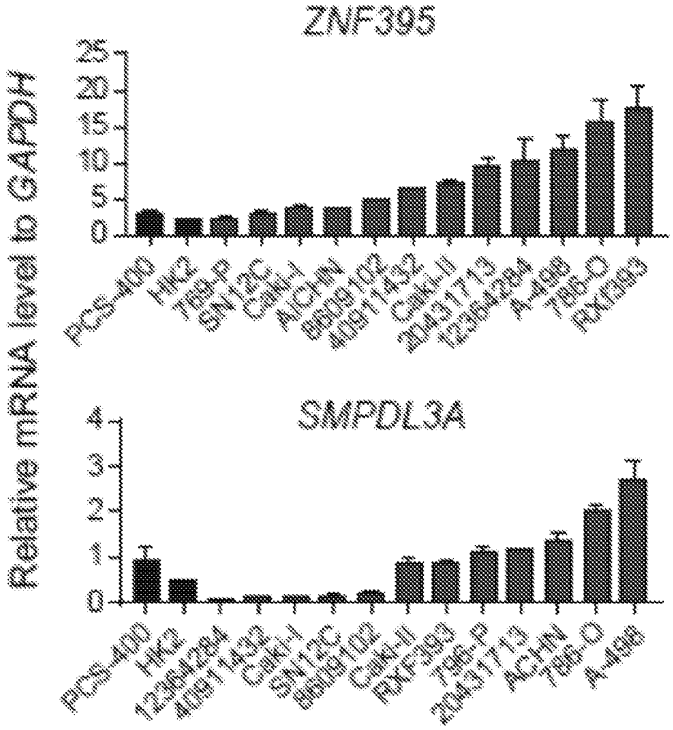


Figure 3 continued

E



F

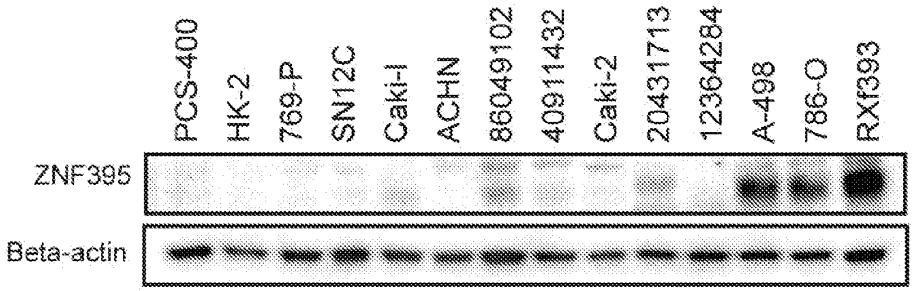
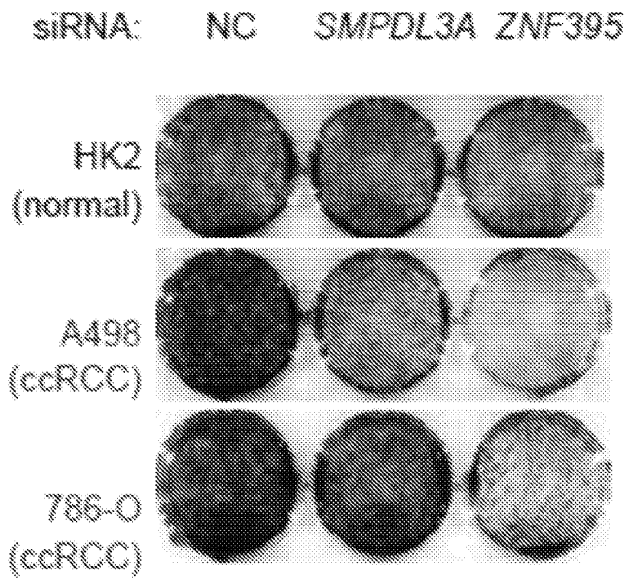


Figure 3 continued

G



H

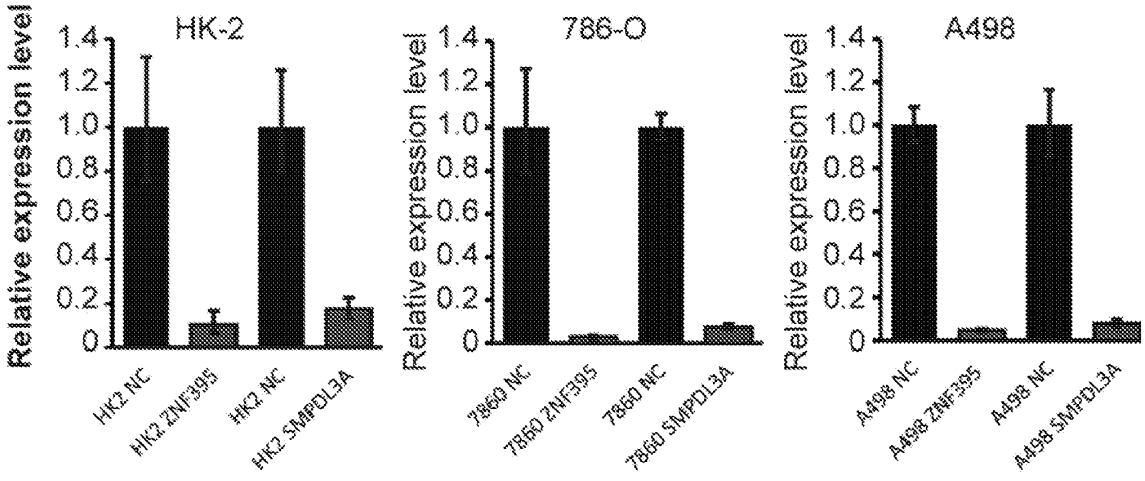


Figure 3 continued

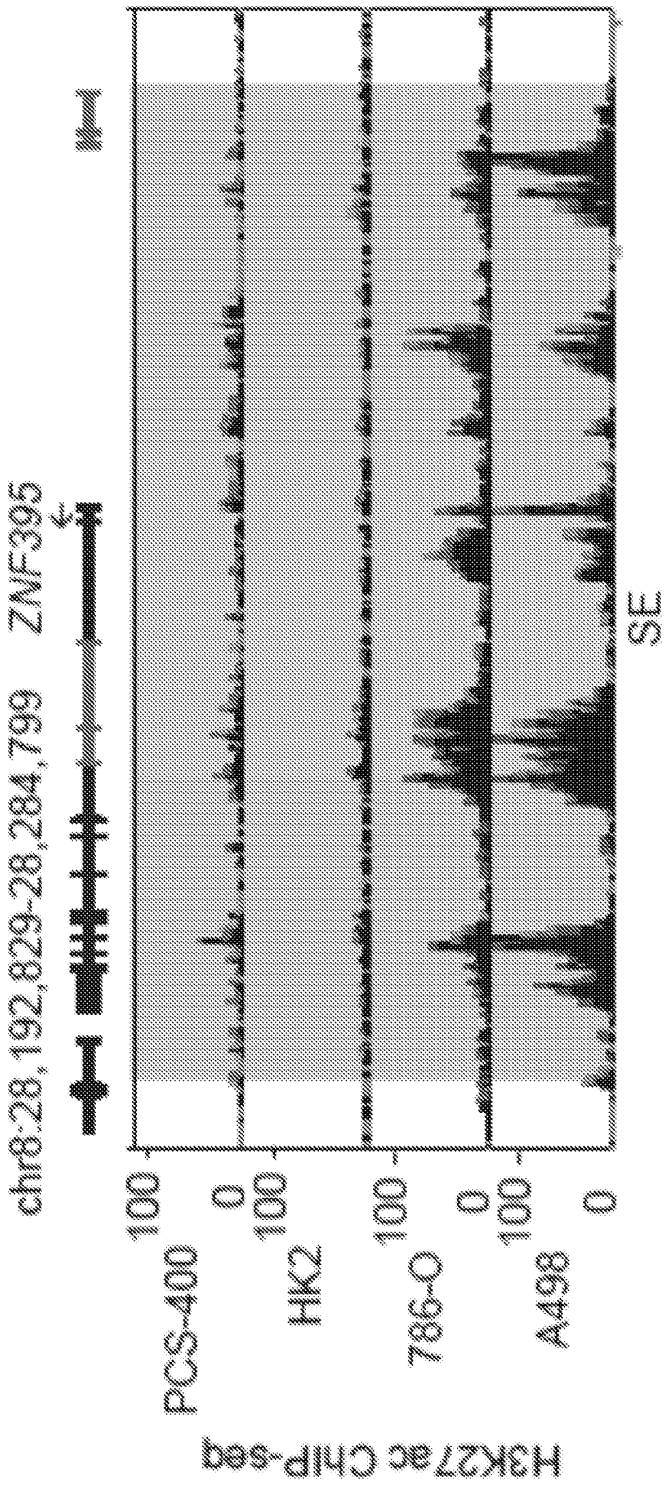


Figure 3 continued

J

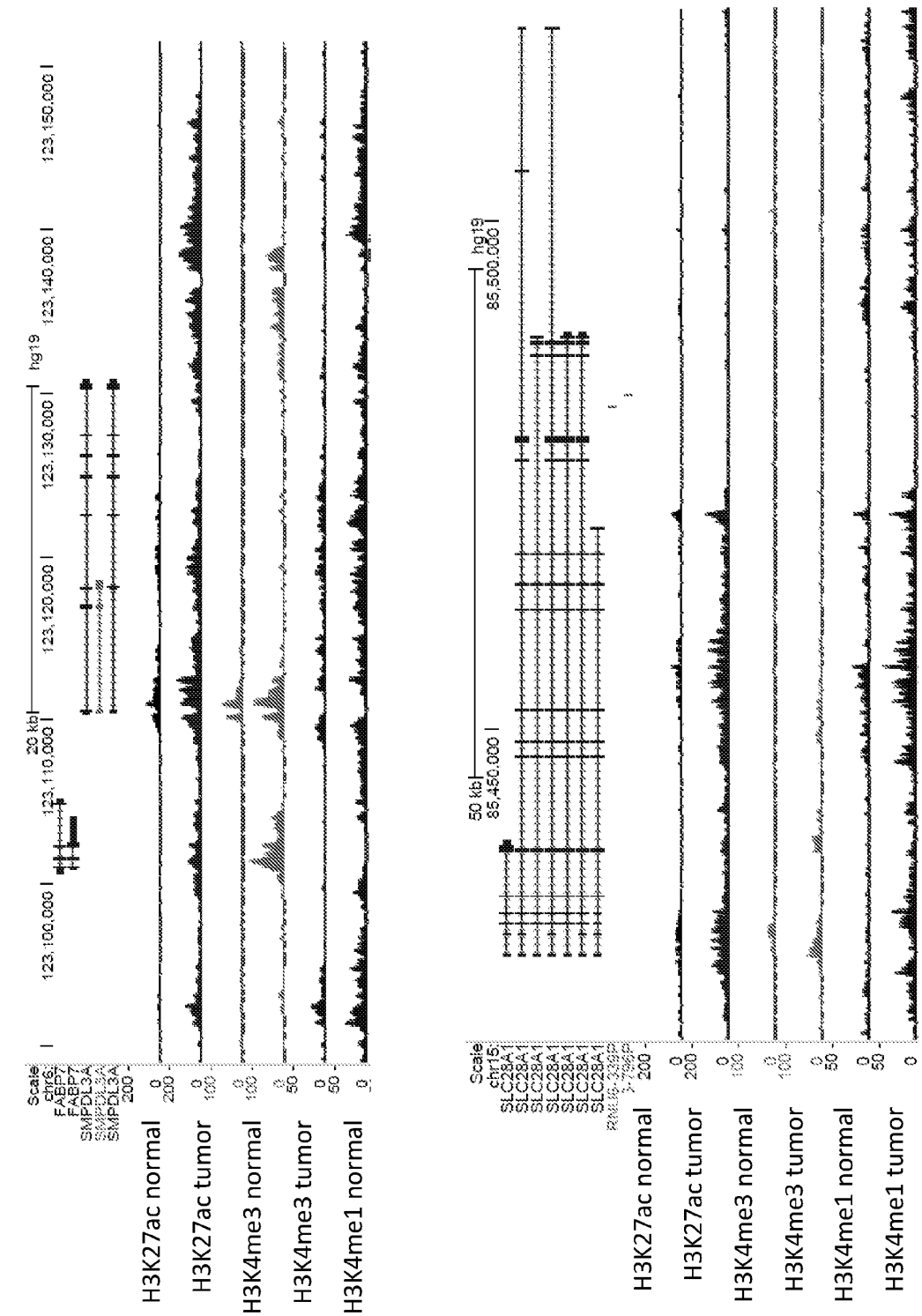


Figure 3 continued

K i)

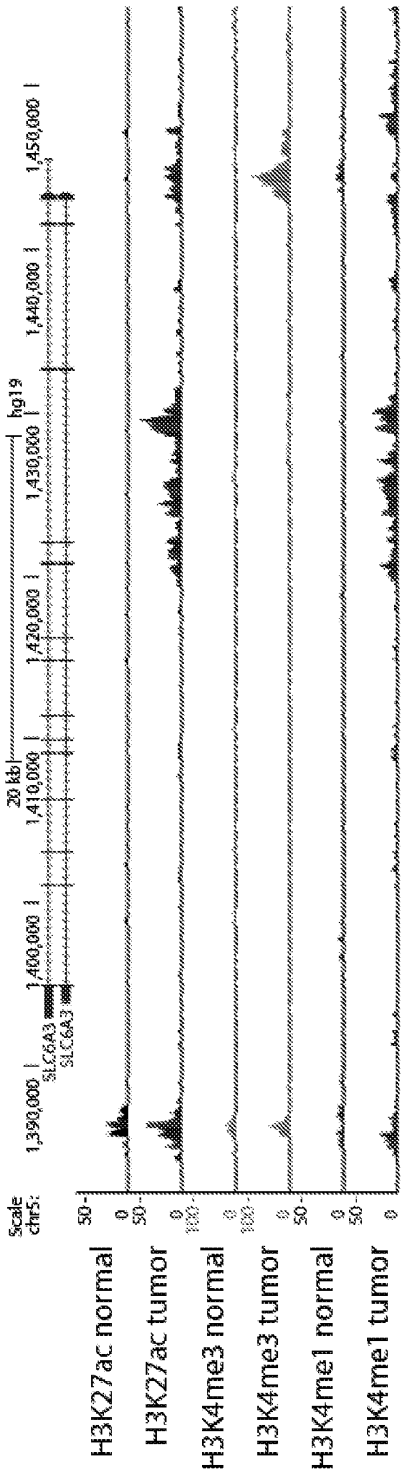


Figure 3 continued

K ii)

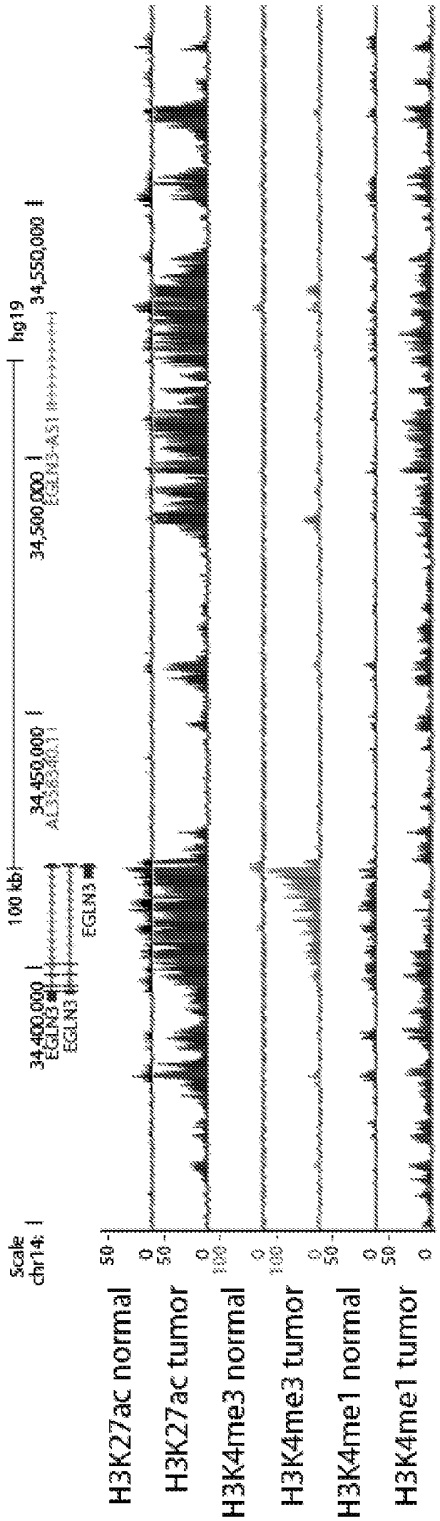


Figure 3 continued

K iii)

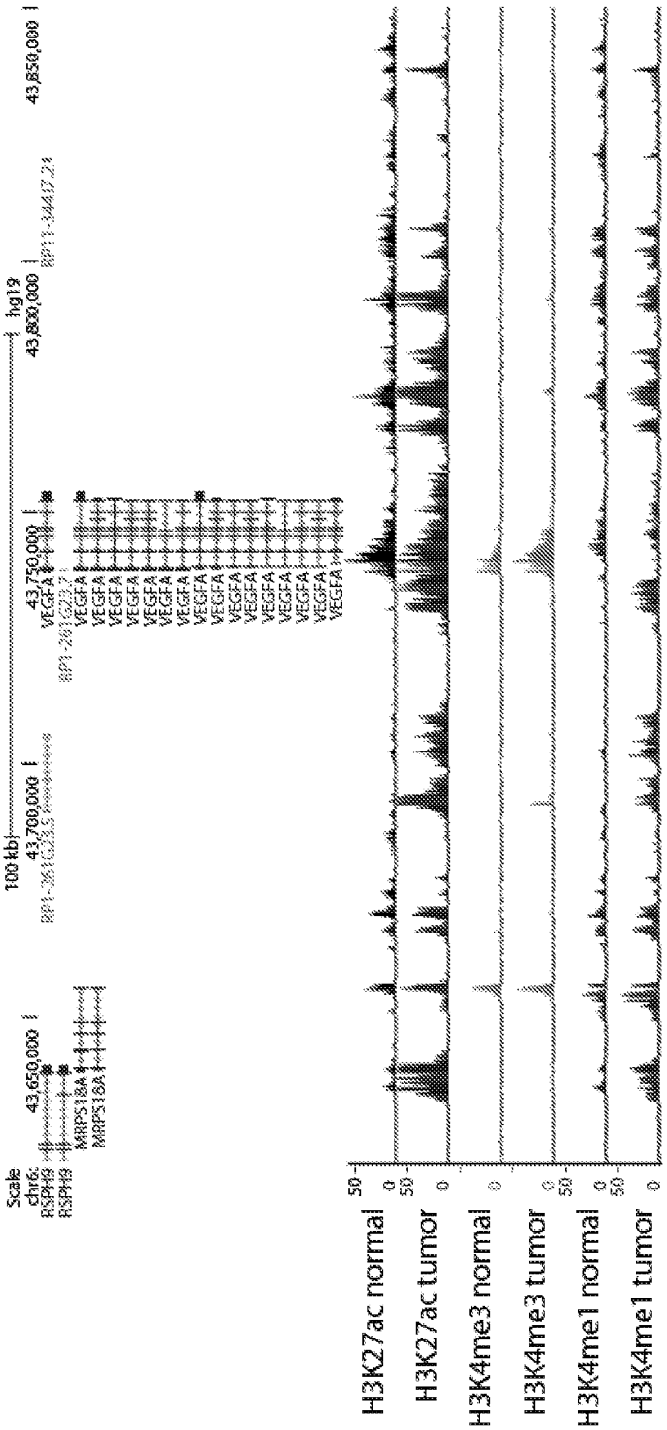


Figure 3 continued

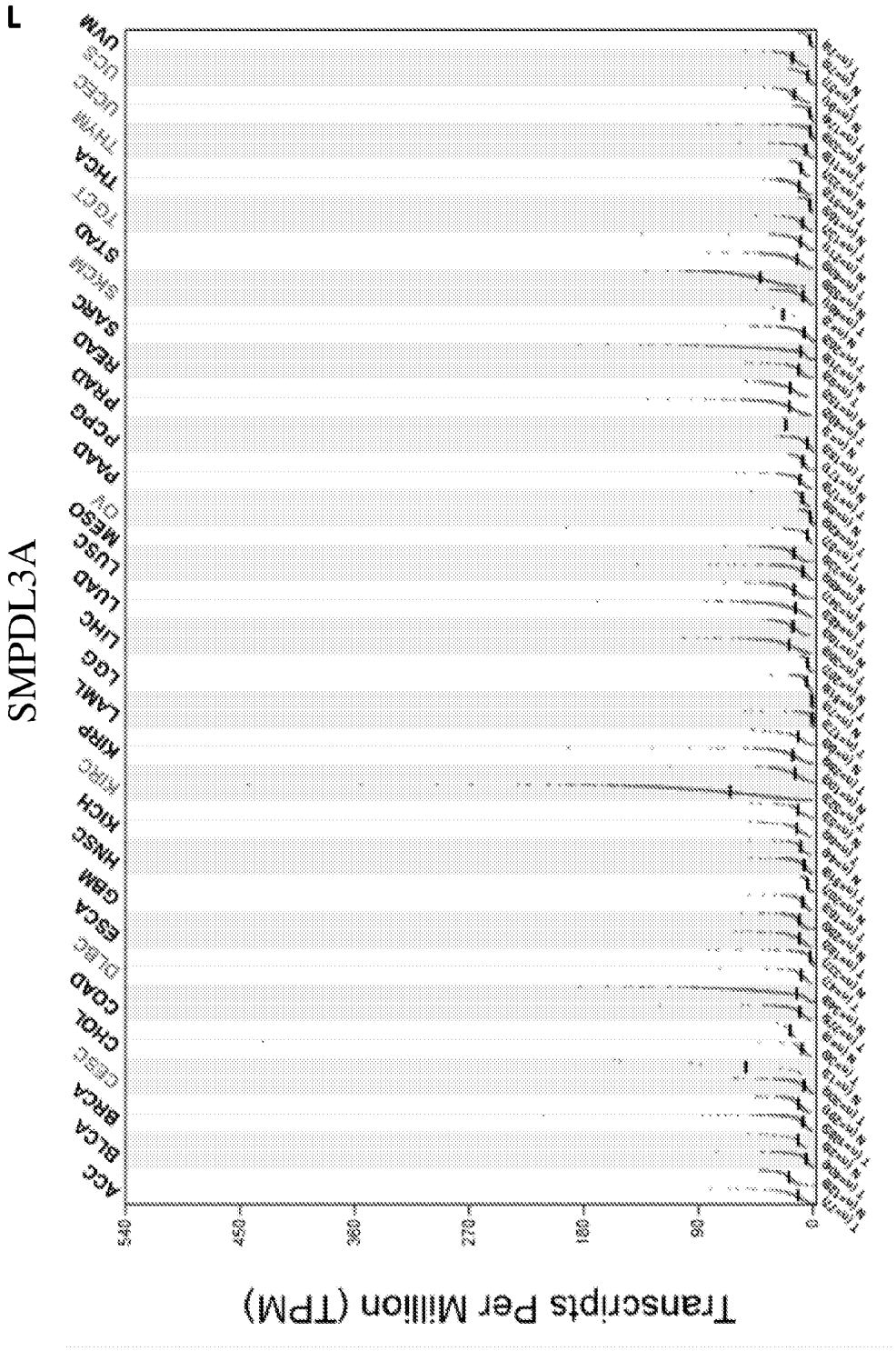


Figure 3 continued

M

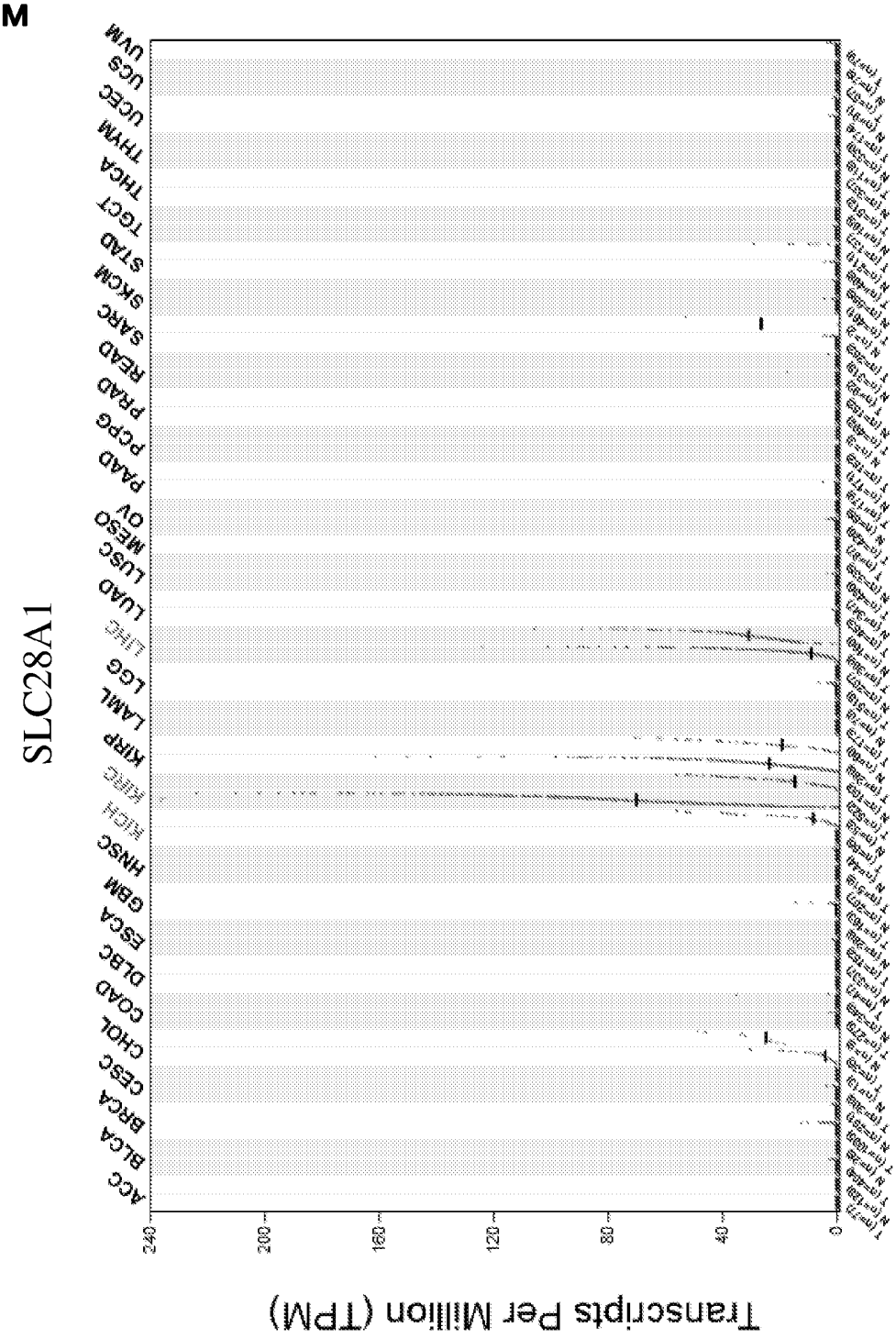


Figure 3 continued

N

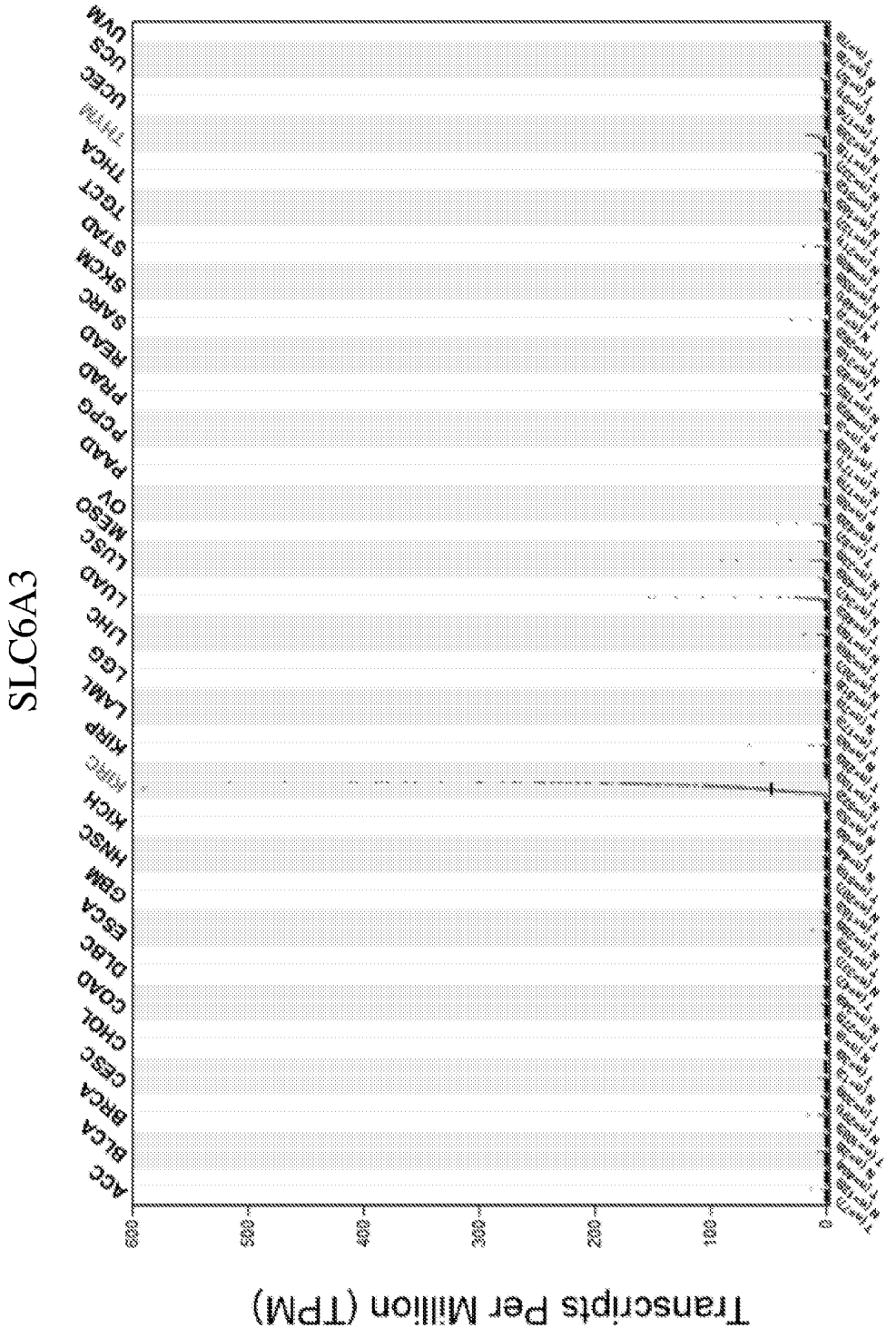


Figure 3 continued

o

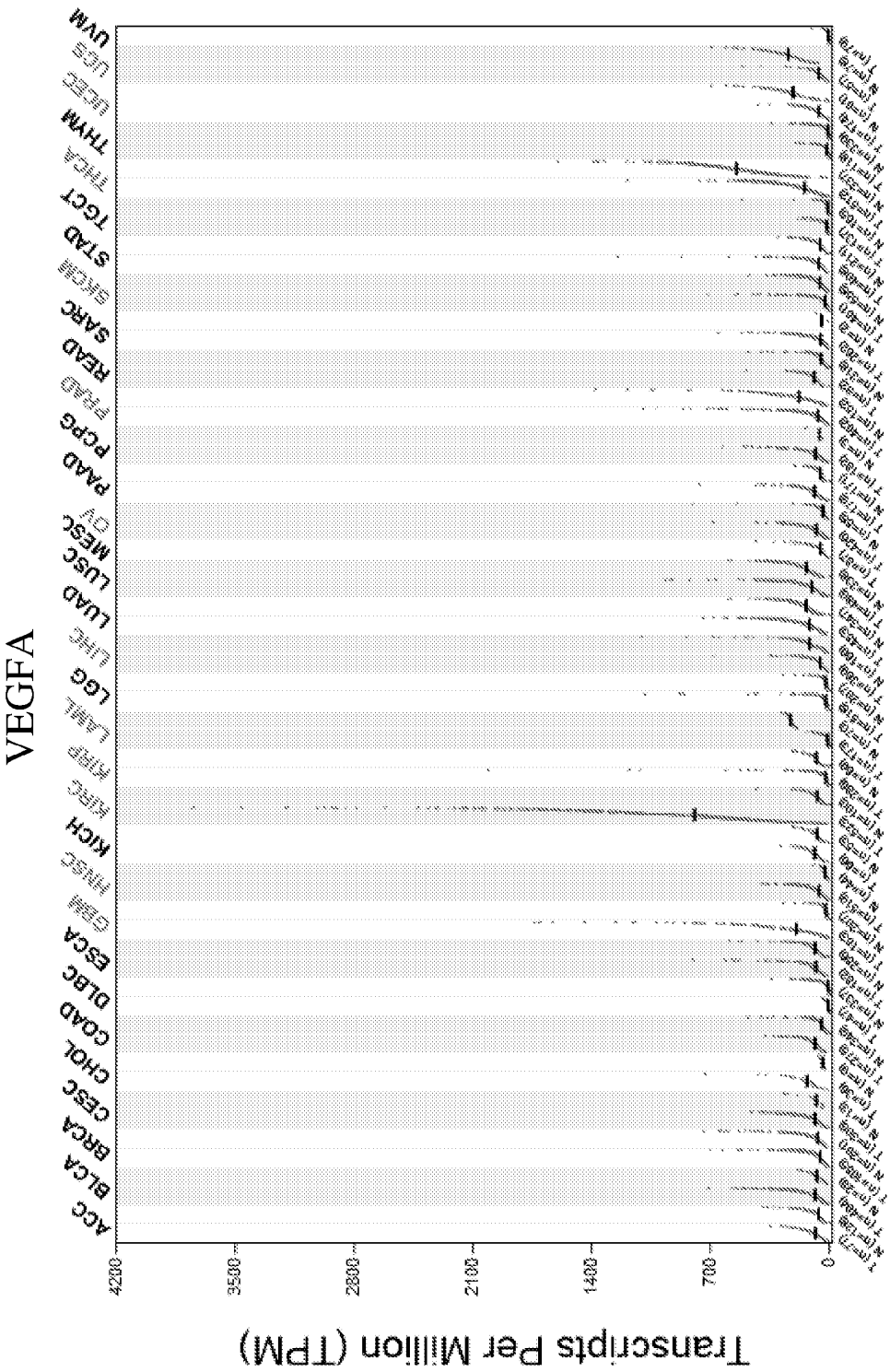


Figure 3 continued

P

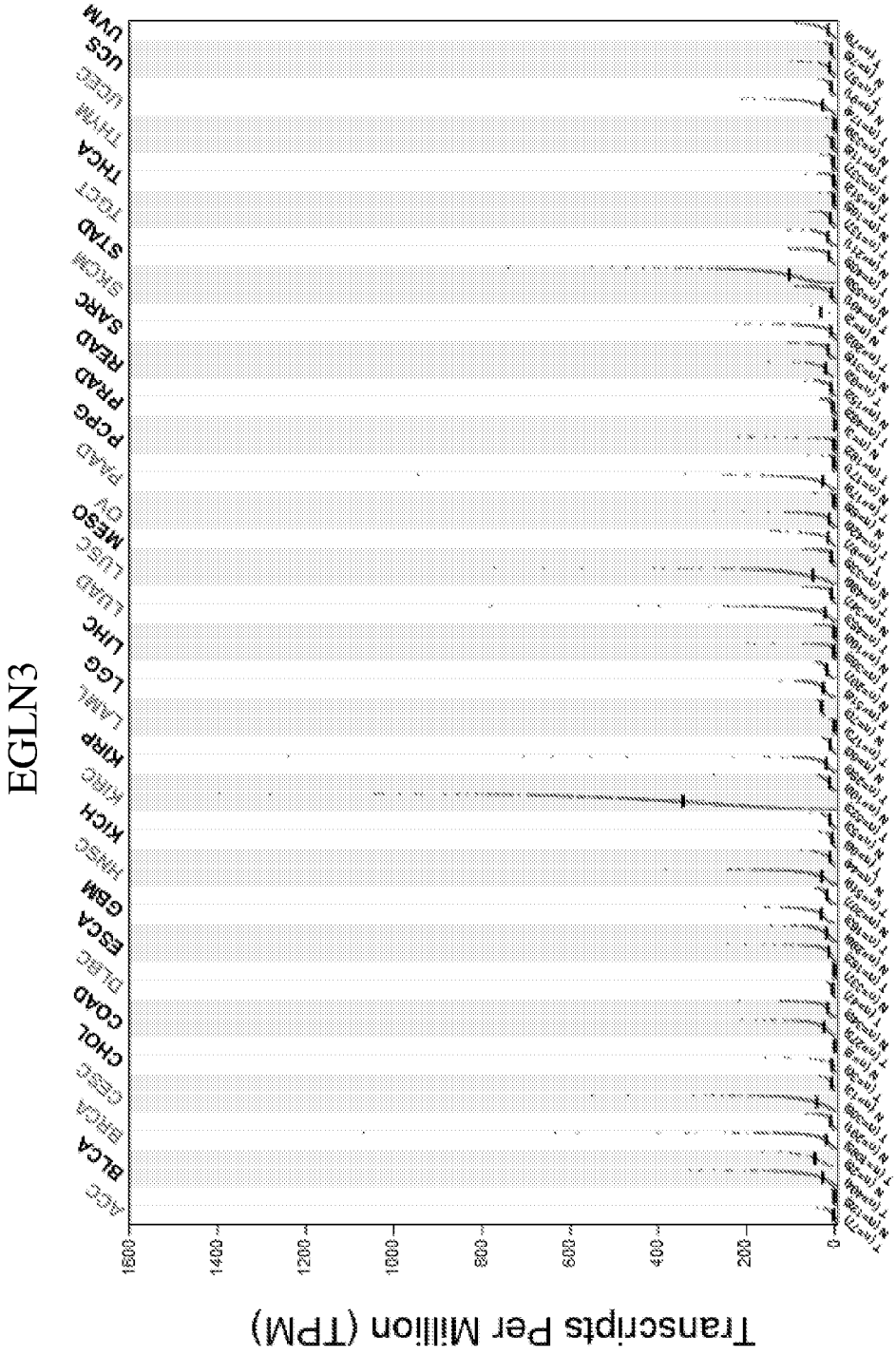
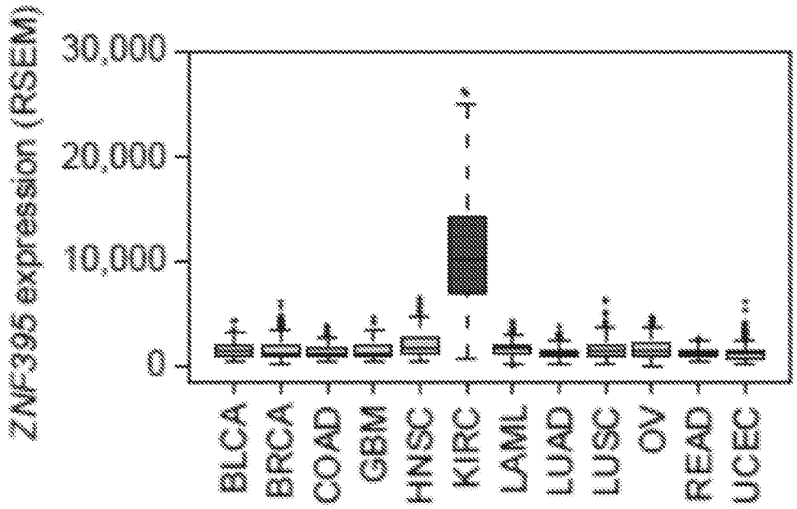


Figure 3 continued

Q



R

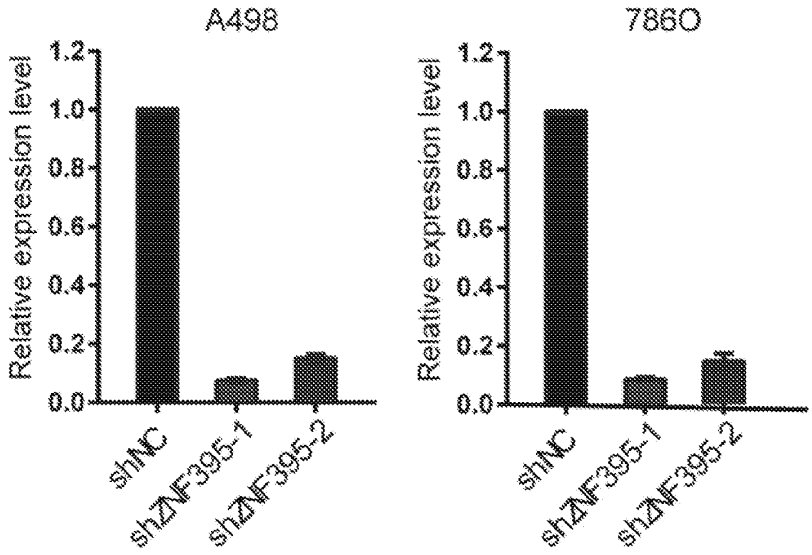
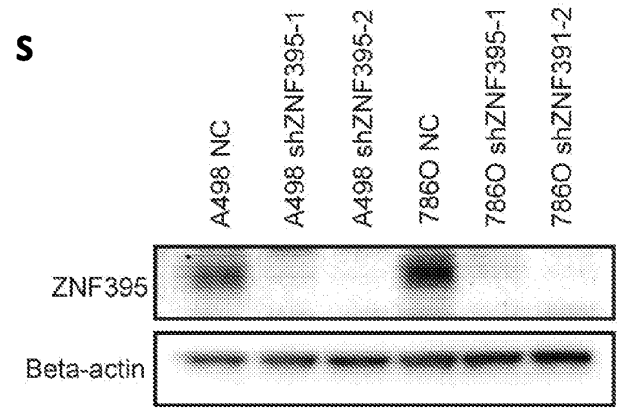


Figure 3 continued



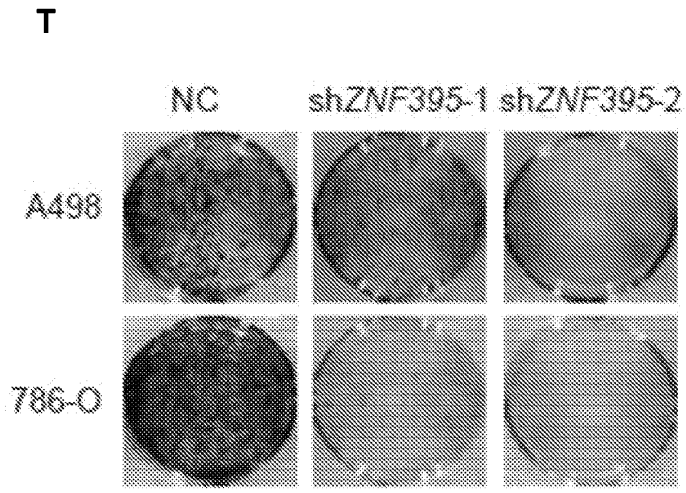
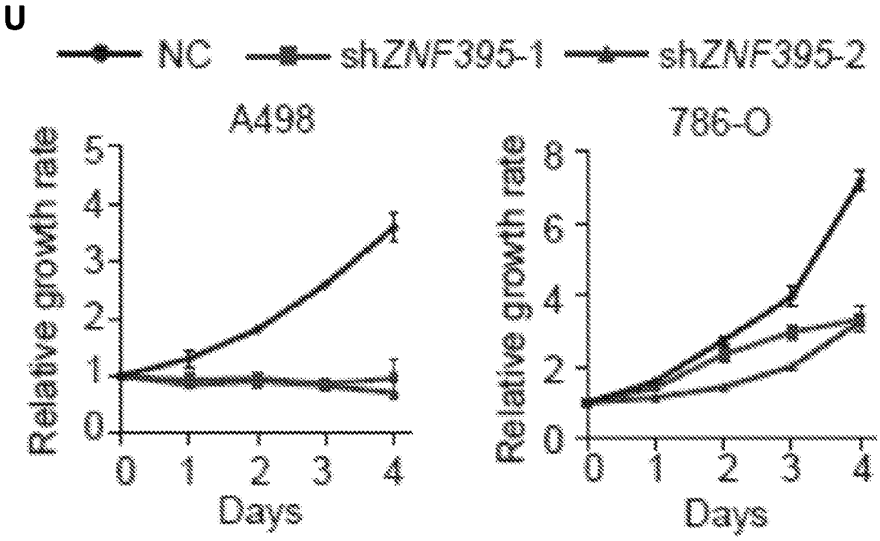
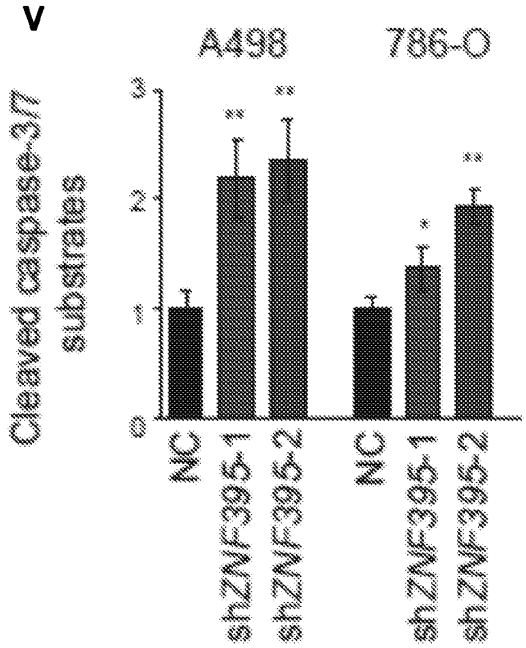


Figure 3 continued





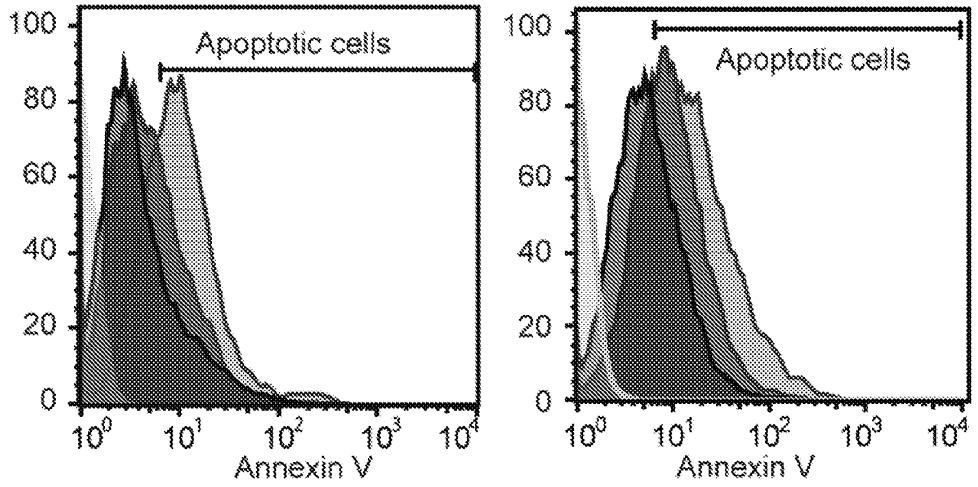
W

Figure 3 continued

Sample	% AnnexinV+
786-O unstained	0.12
786-O NC	24.3
786-O shZNF395-1	69.7
786-O shZNF395-2	35.5

Sample	% AnnexinV+
A498 unstained	0
A498 NC	39.9
A498 shZNF395-1	66.6
A498 shZNF395-2	79.1

X



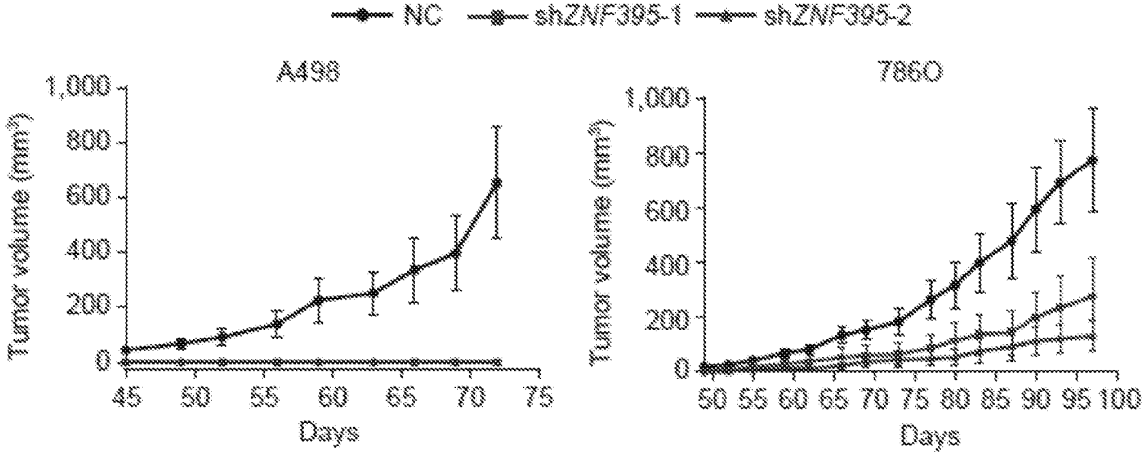


Figure 4

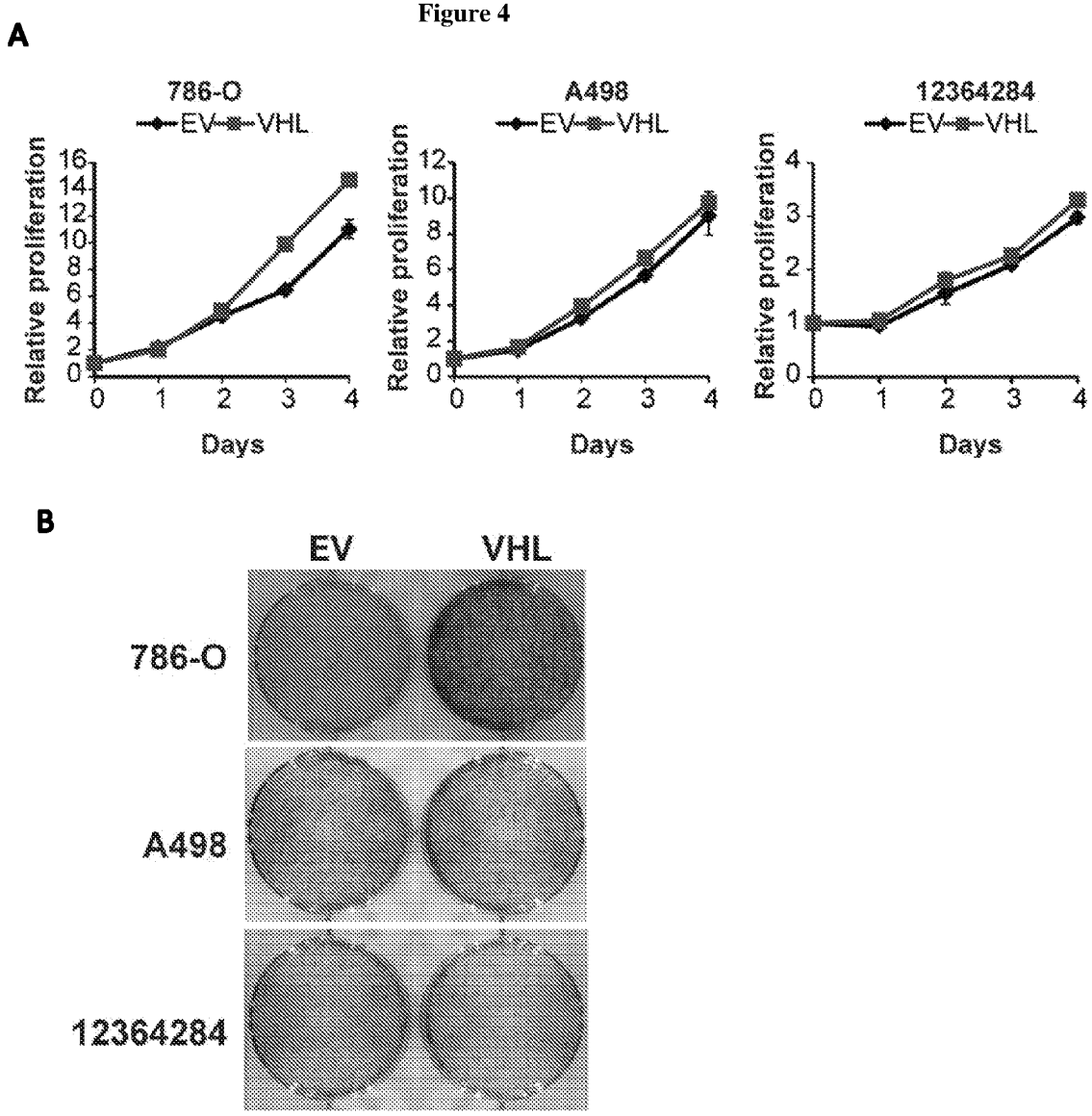
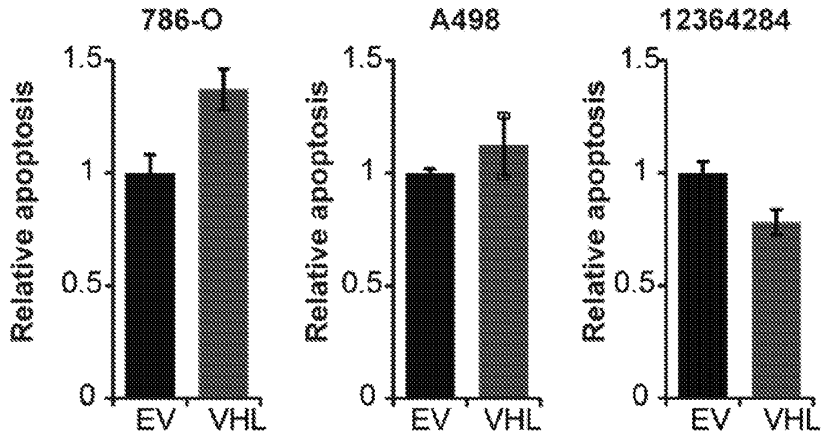

A
786-O
EV
VHL
Relative proliferation
Days
A498
12364284
B
EV
VHL
786-O
A498
12364284

Figure 4 continued

C



D

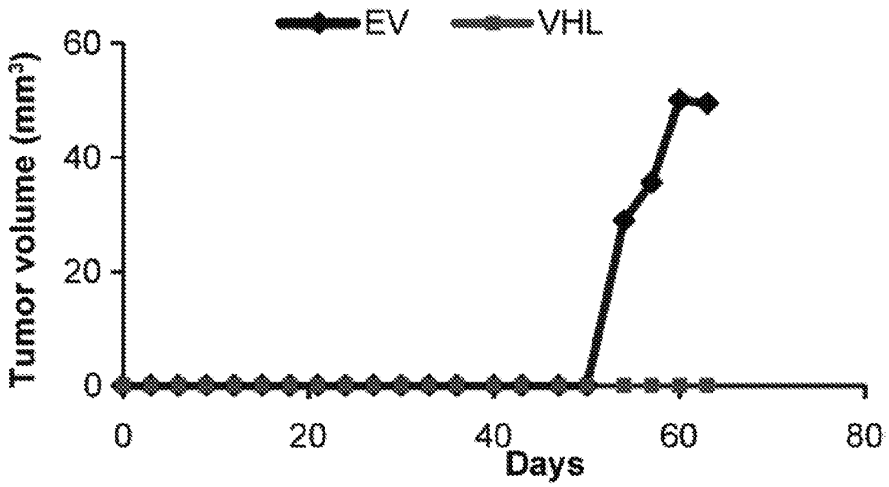


Figure 4 continued

E

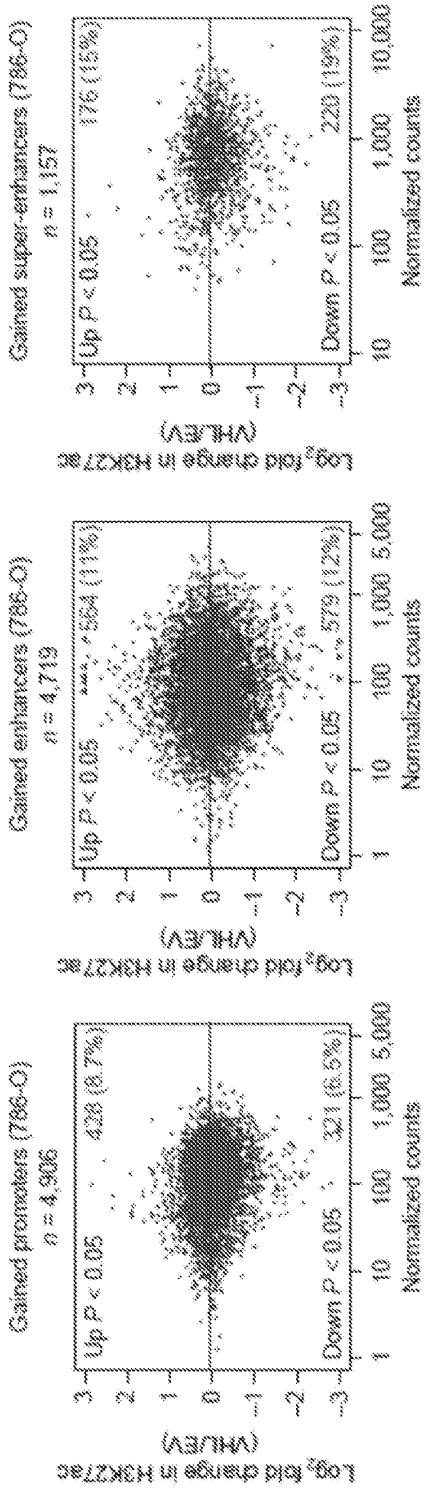


Figure 4 continued

F

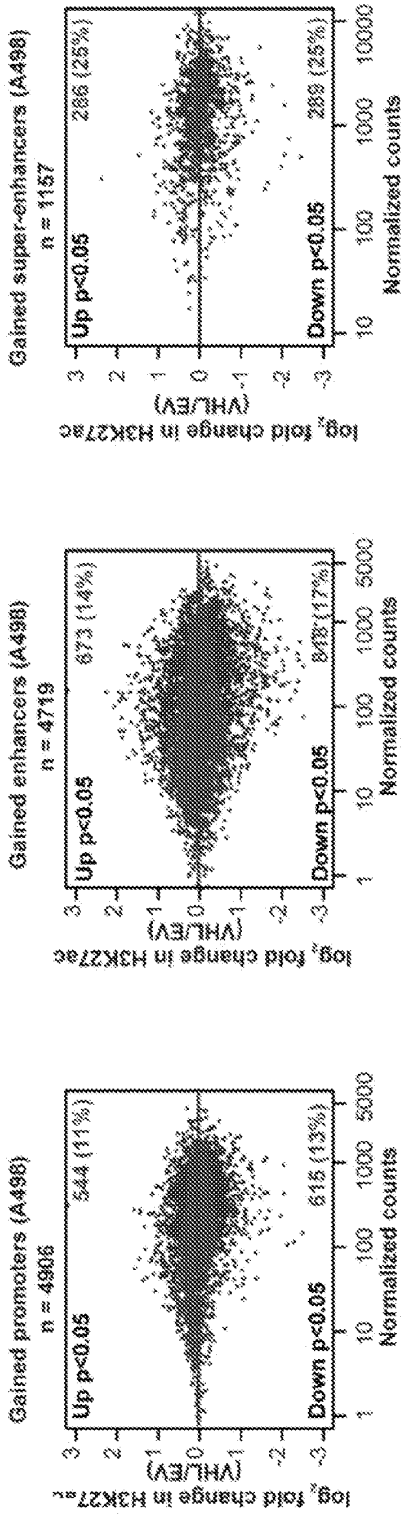


Figure 4 continued

G

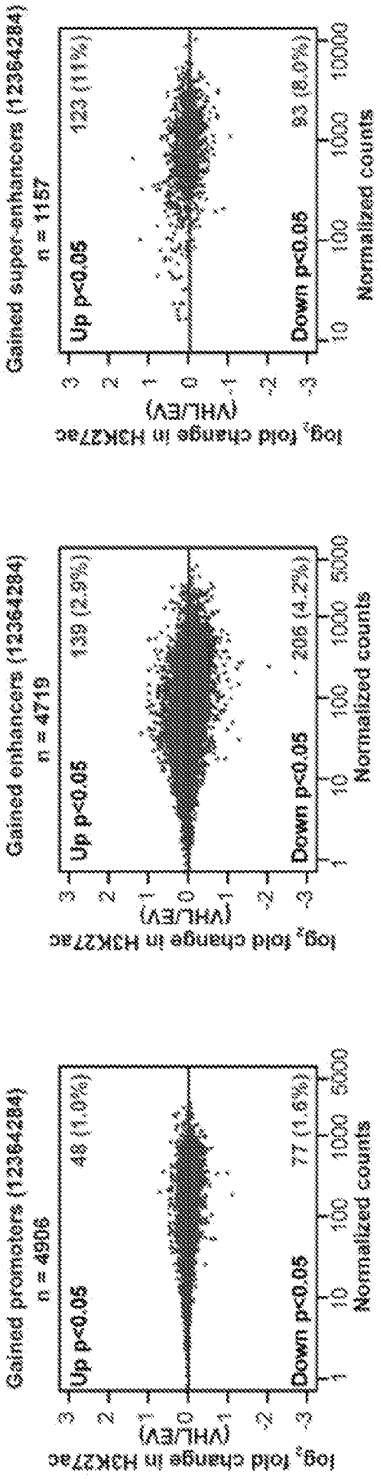


Figure 4 continued

H

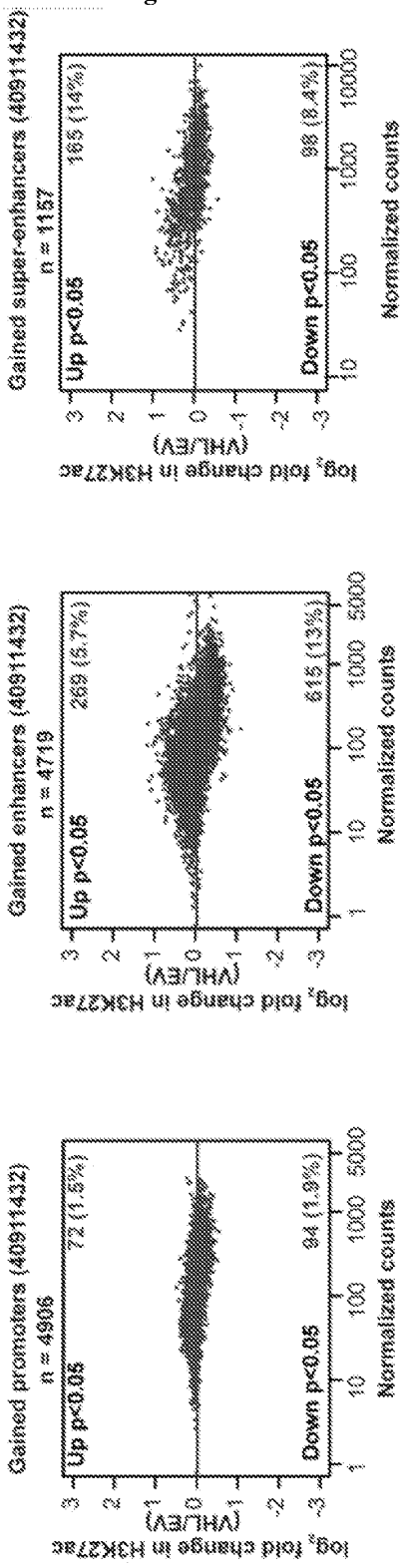
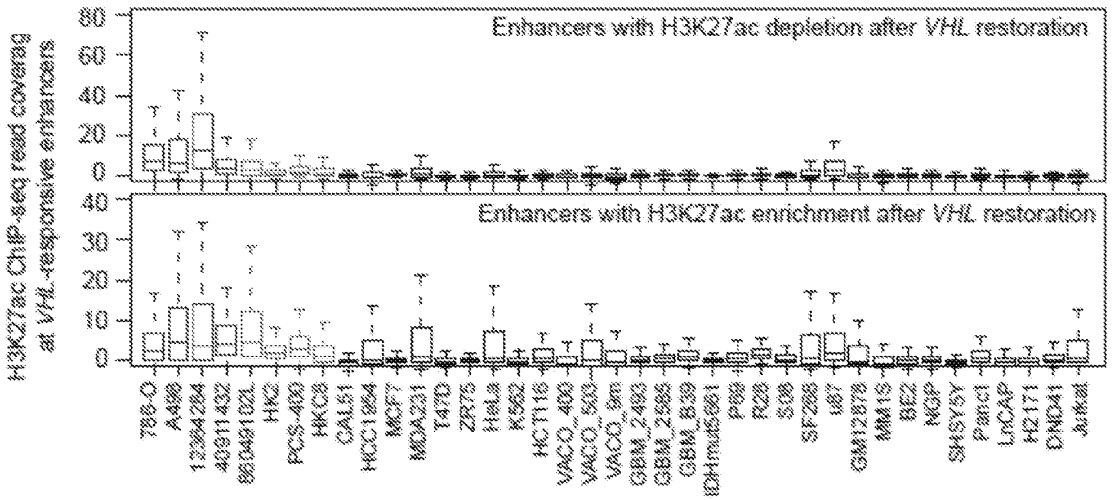
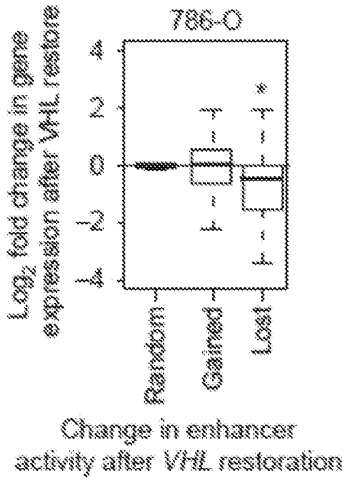


Figure 4 continued

I



J



K

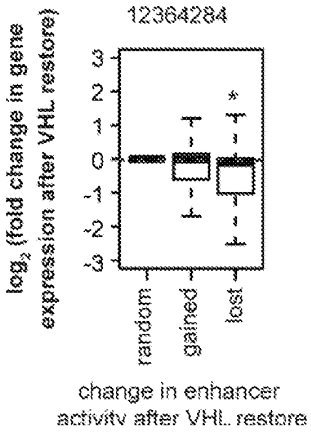
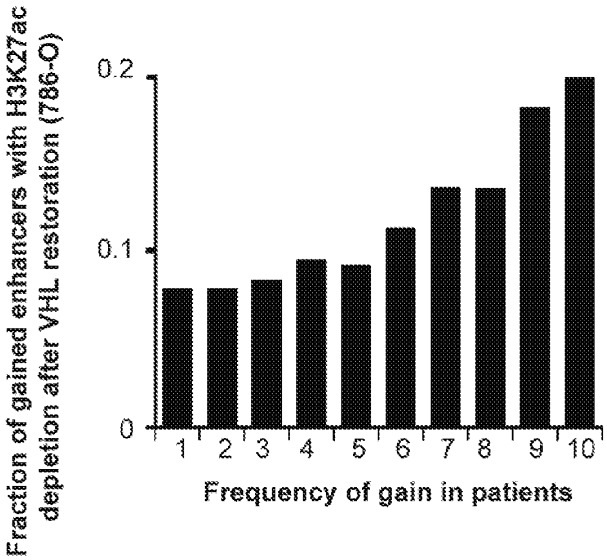


Figure 4 continued

L



M

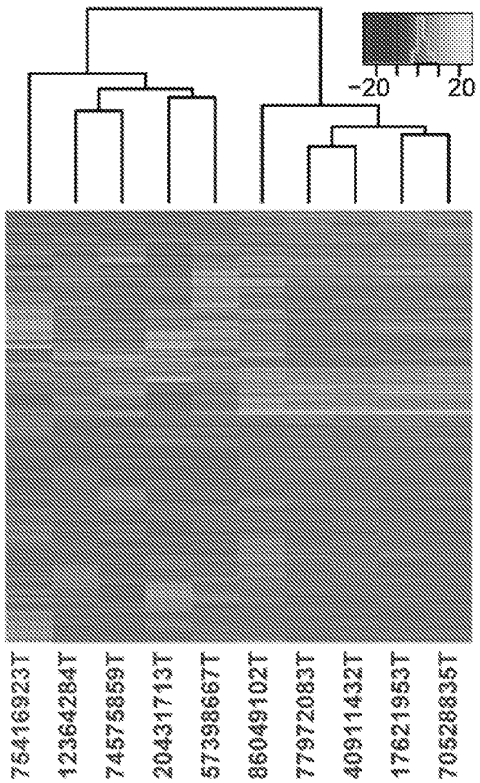


Figure 4 continued

N

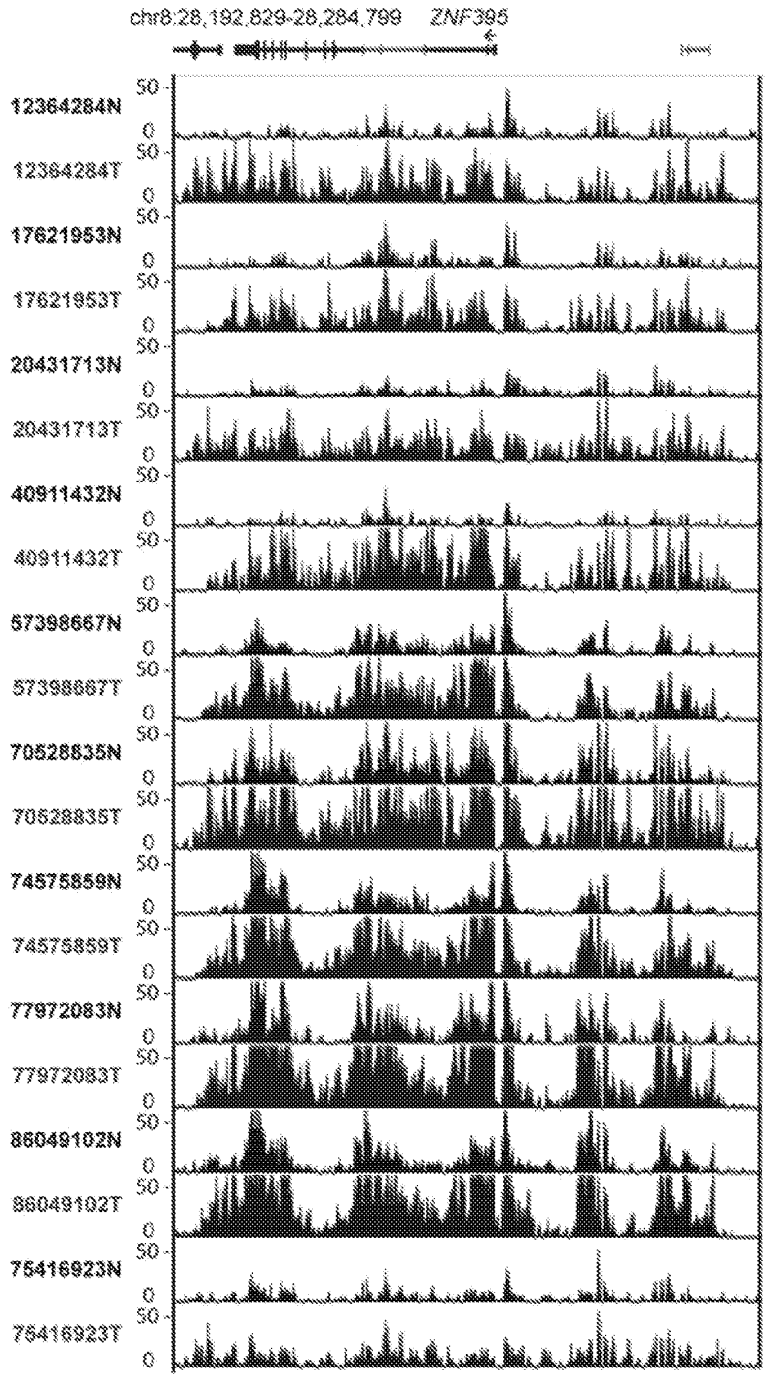
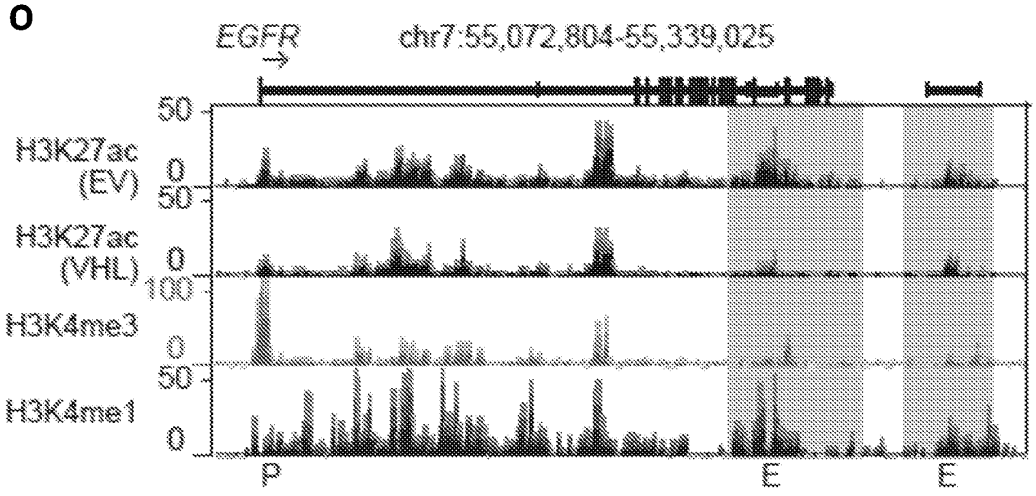
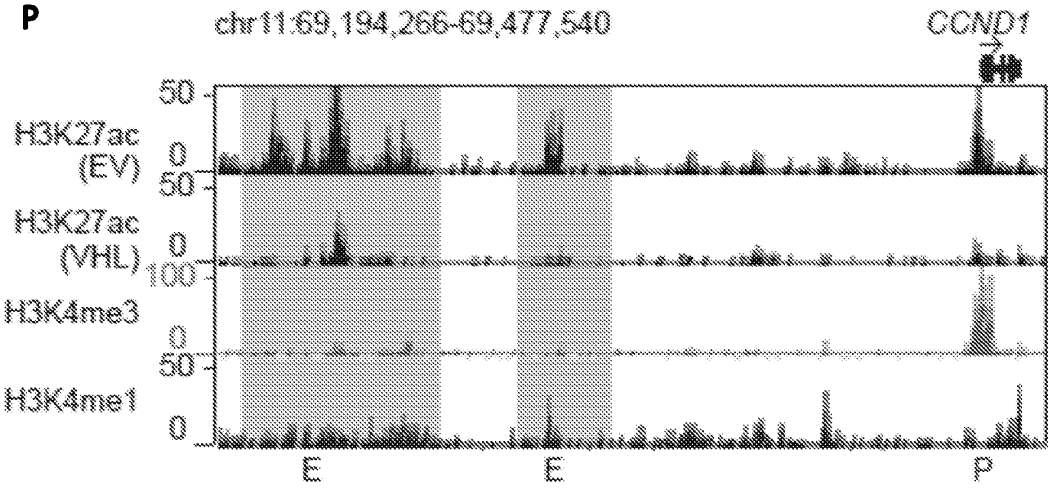


Figure 4 continued





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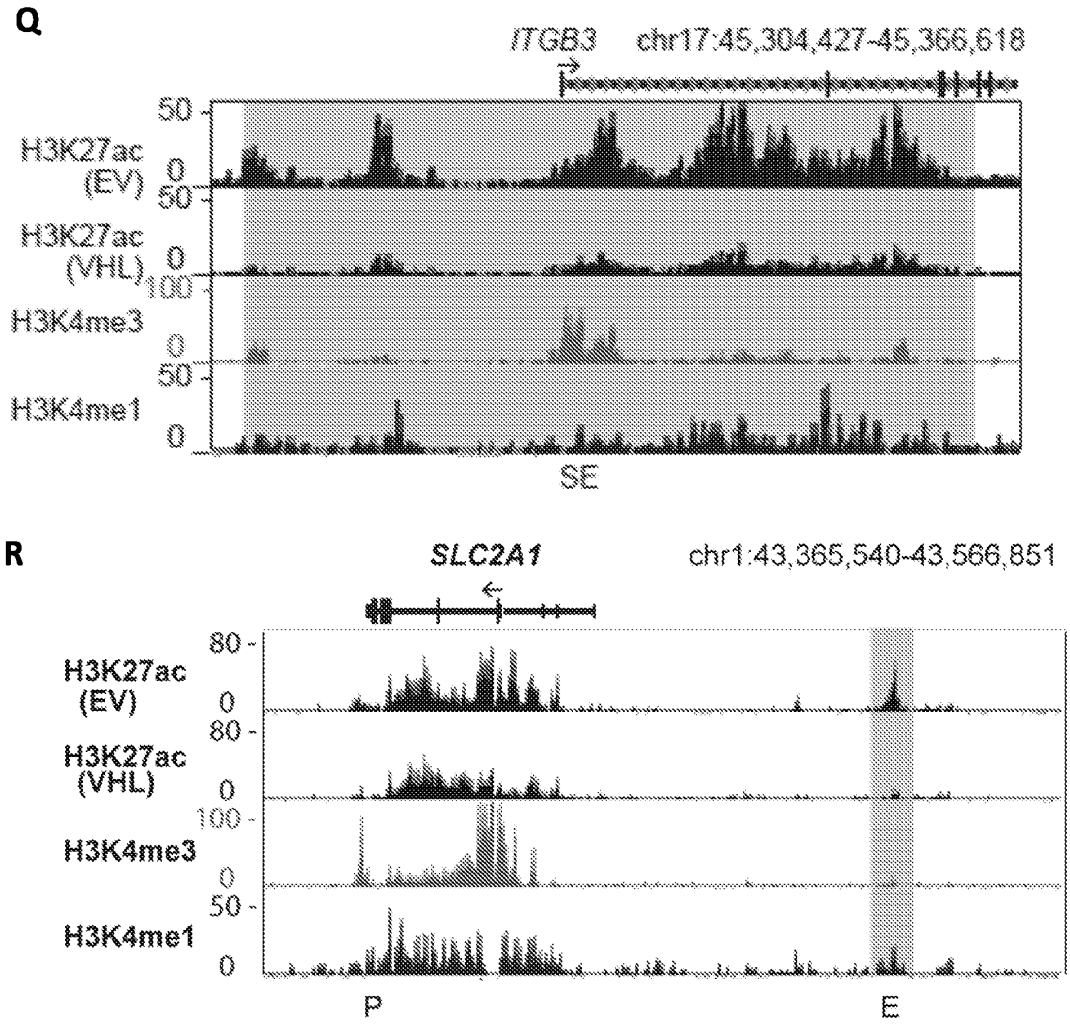
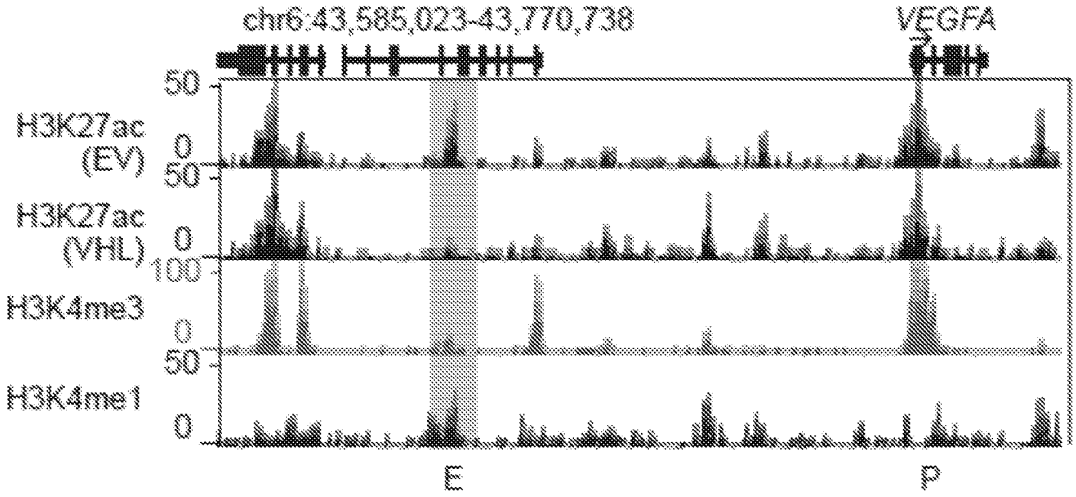


Figure 4 continued

S



T

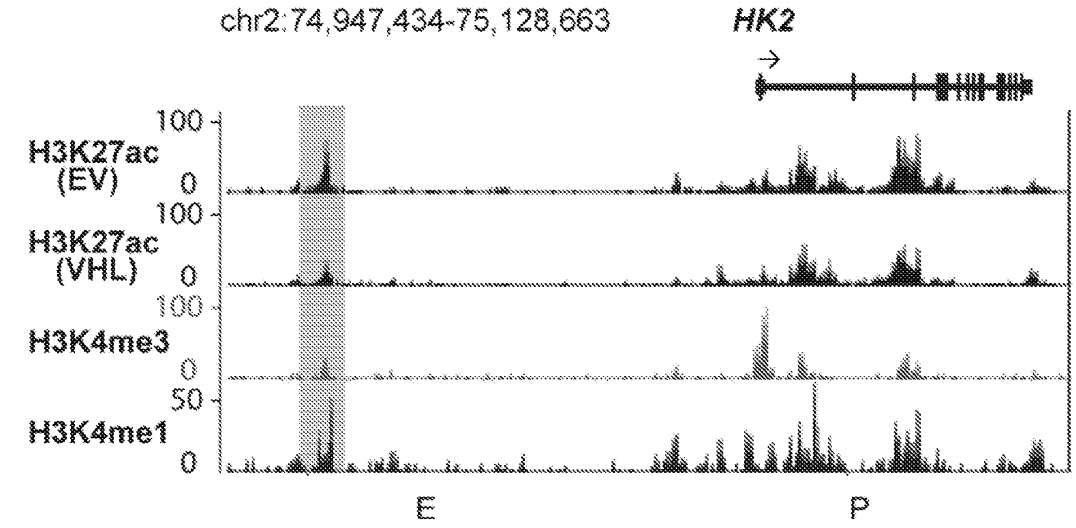
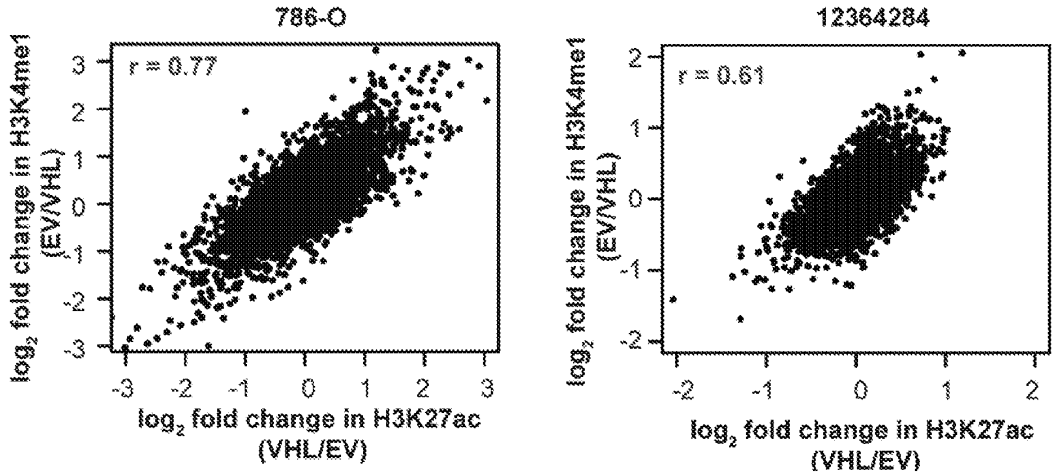


Figure 4 continued

U



V

I

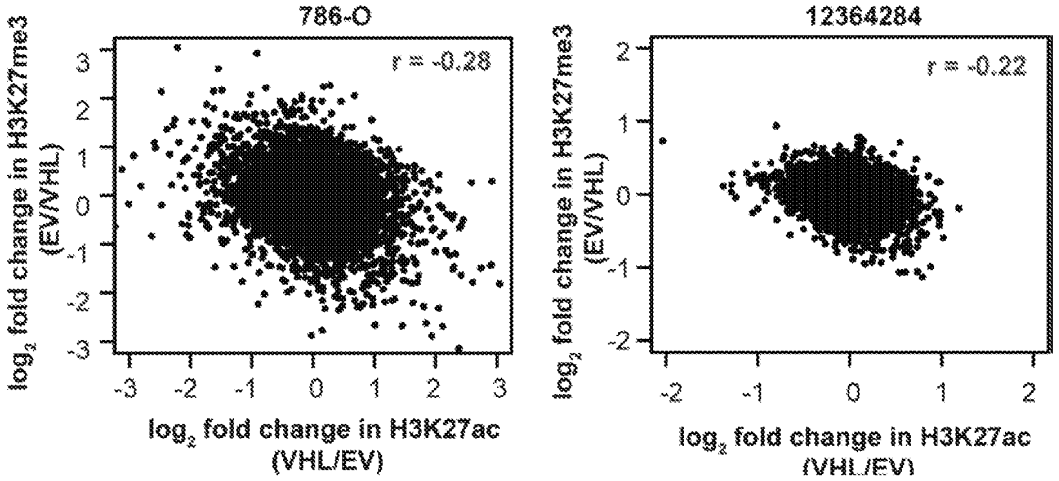


Figure 4 continued

W

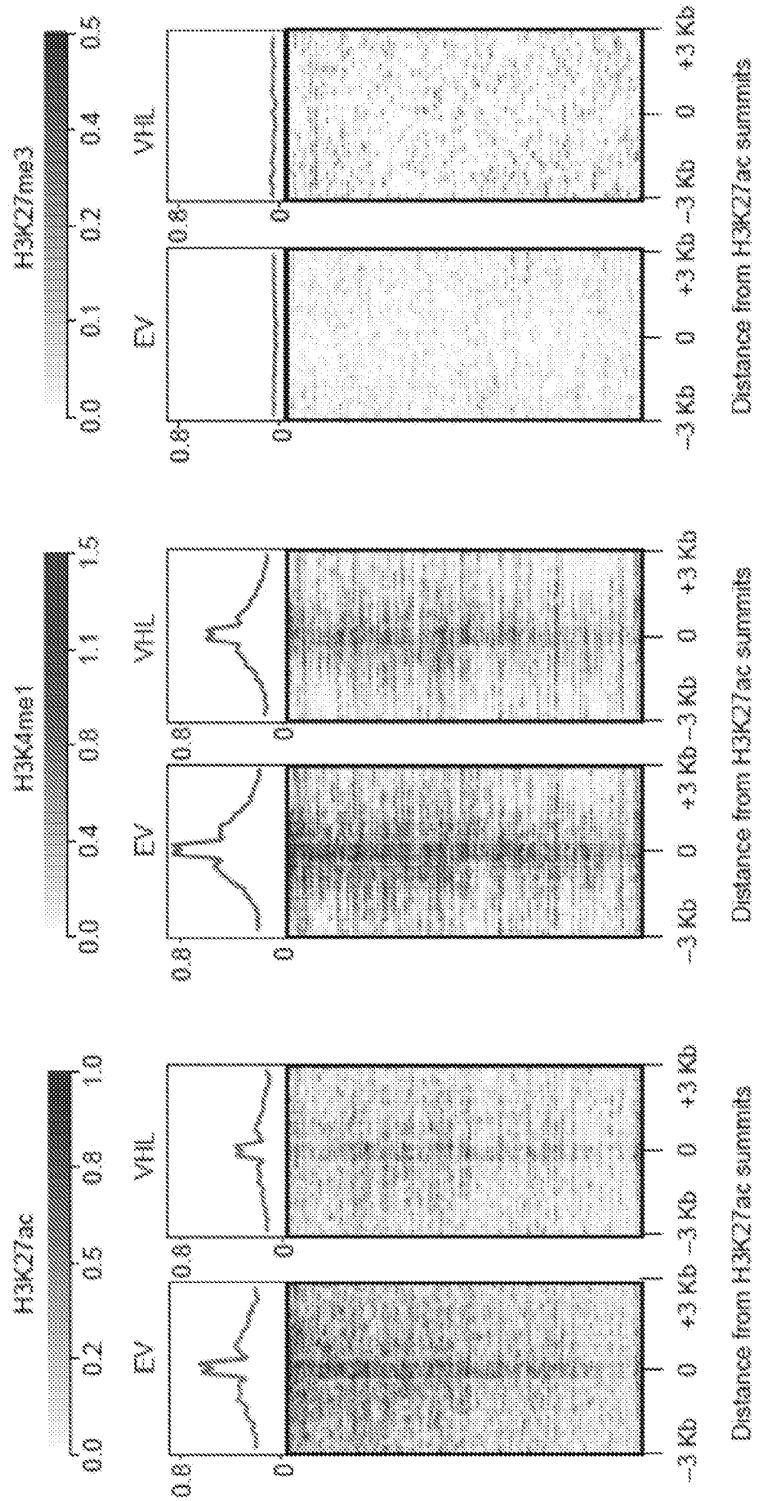
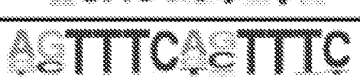


Figure 5

A

Motif	Family	Members	*p*
	bZIP	FOSL2, JUN-AP1, BACH2, FRA1, BATF, ATF3, AP1, MAFK	1E-63
	ETS	ETS1-distal, PU.1, FLI1	1E-32
	RHD	NF-κB–p65–Rel	1E-25
	bHLH	HIF2α, HIF1α	1E-23
	IRF	ISRE	1E-21

B

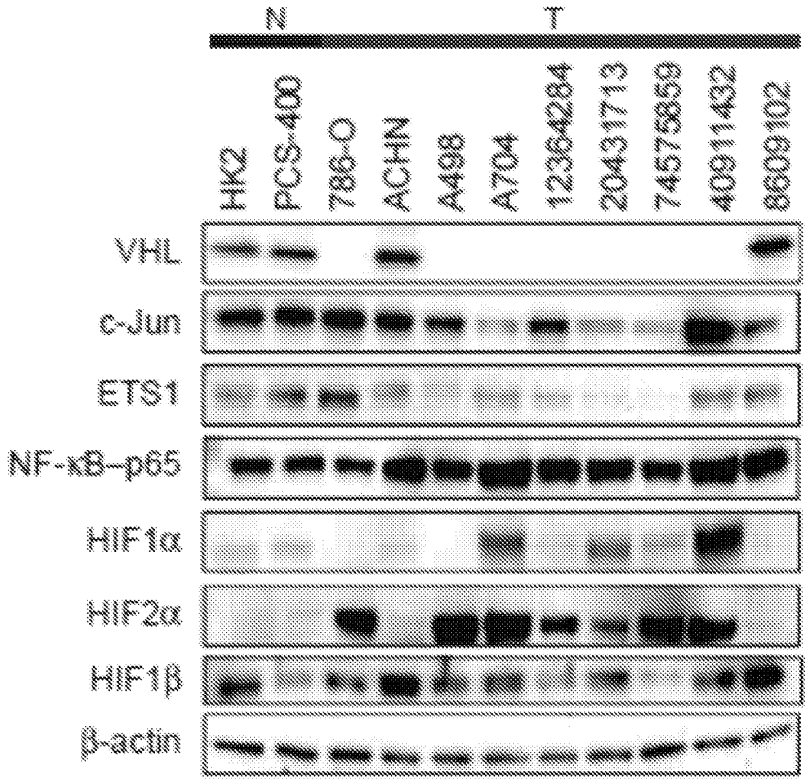


Figure 5 continued

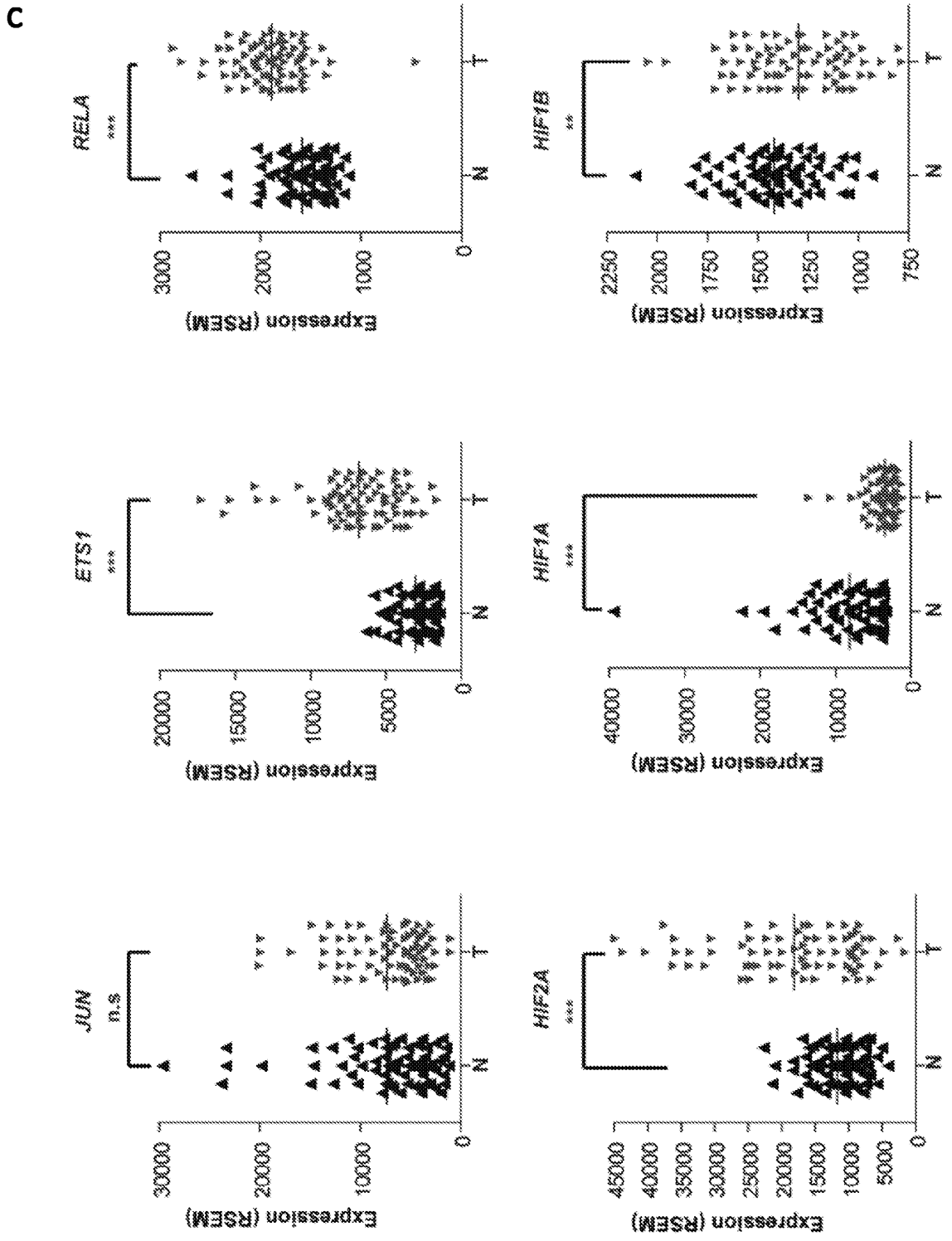


Figure 5 continued

D

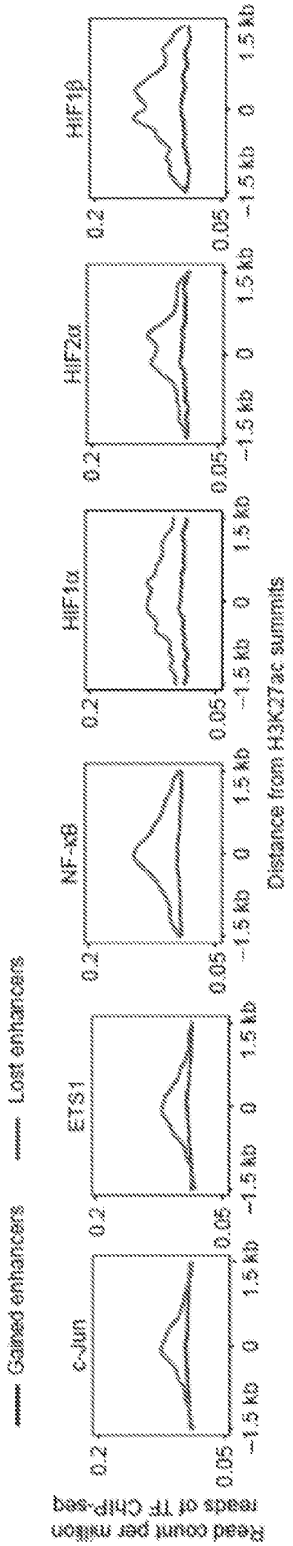
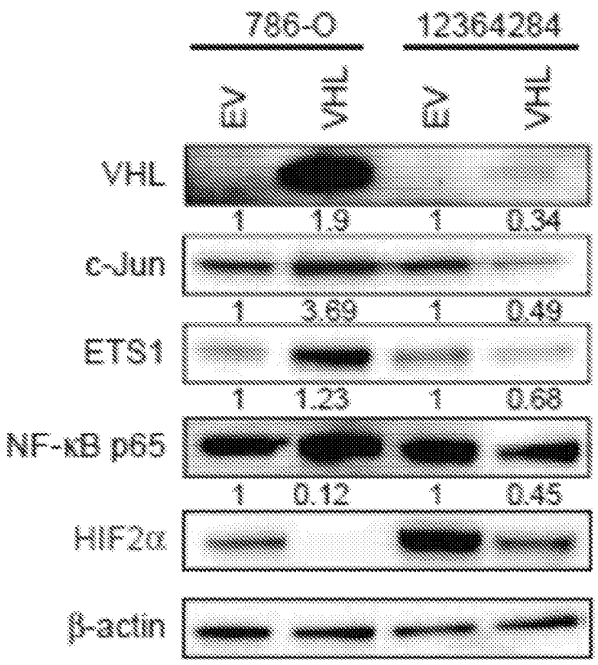


Figure 5 continued

E



F

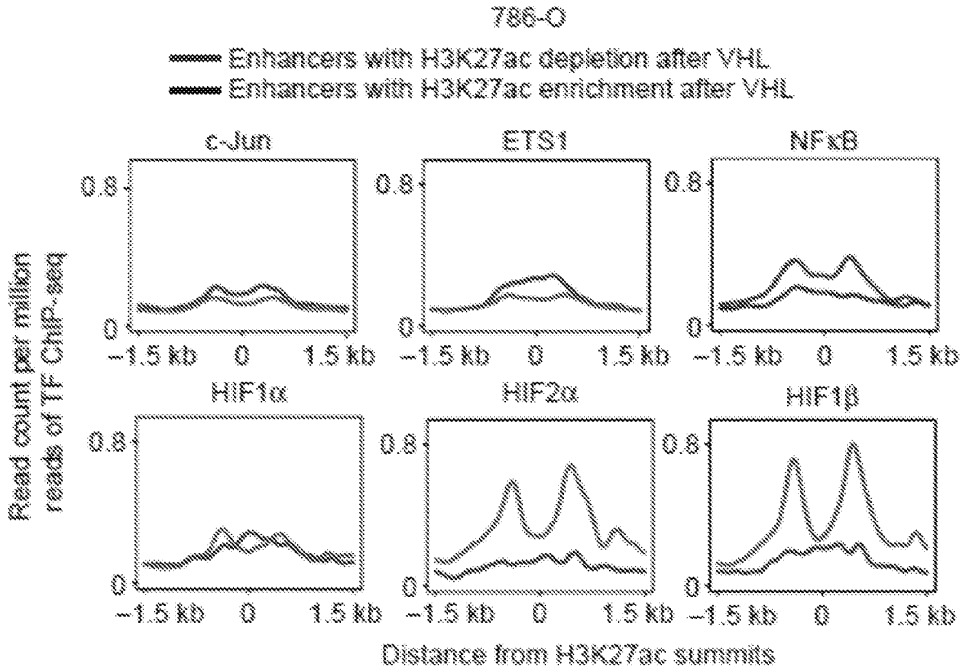


Figure 5 continued

G

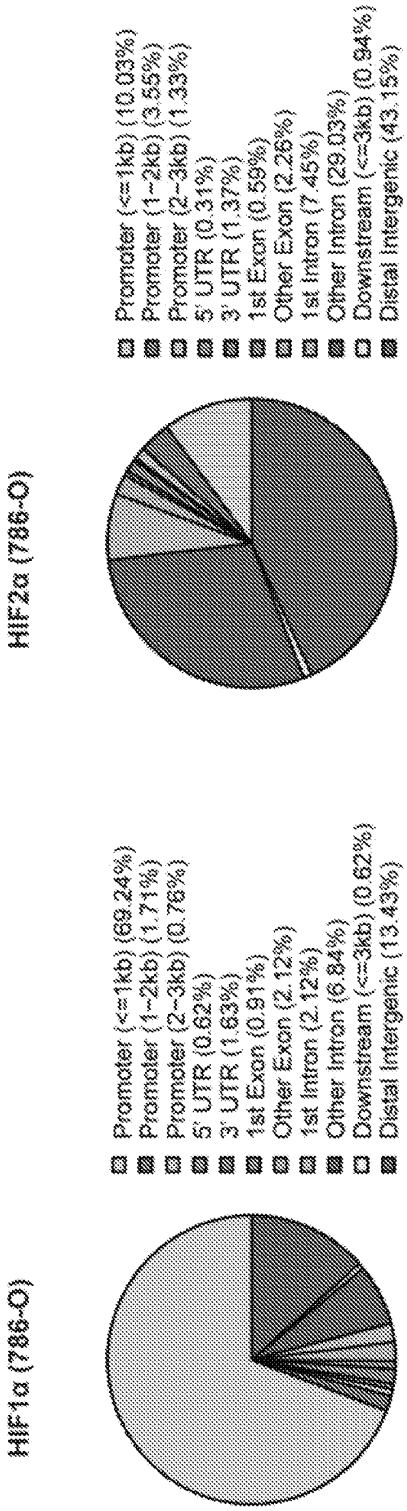
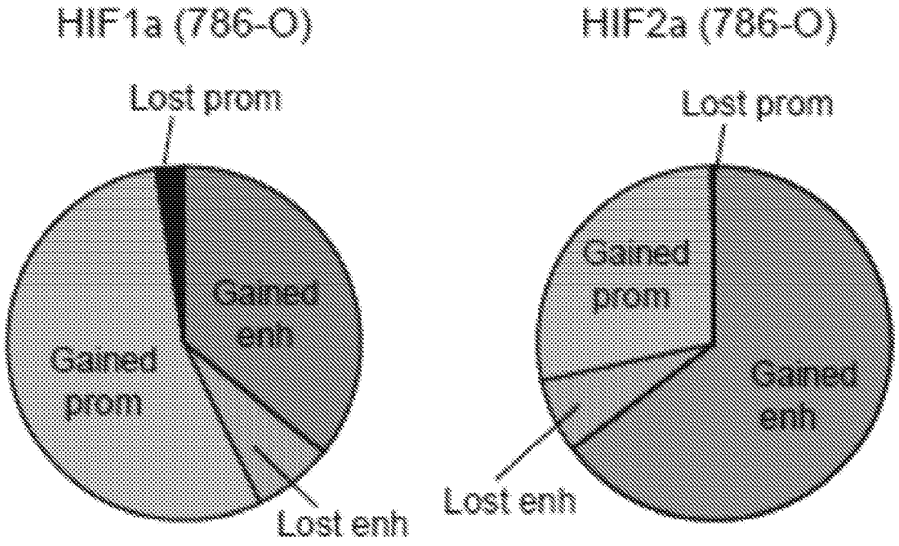


Figure 5 continued

H



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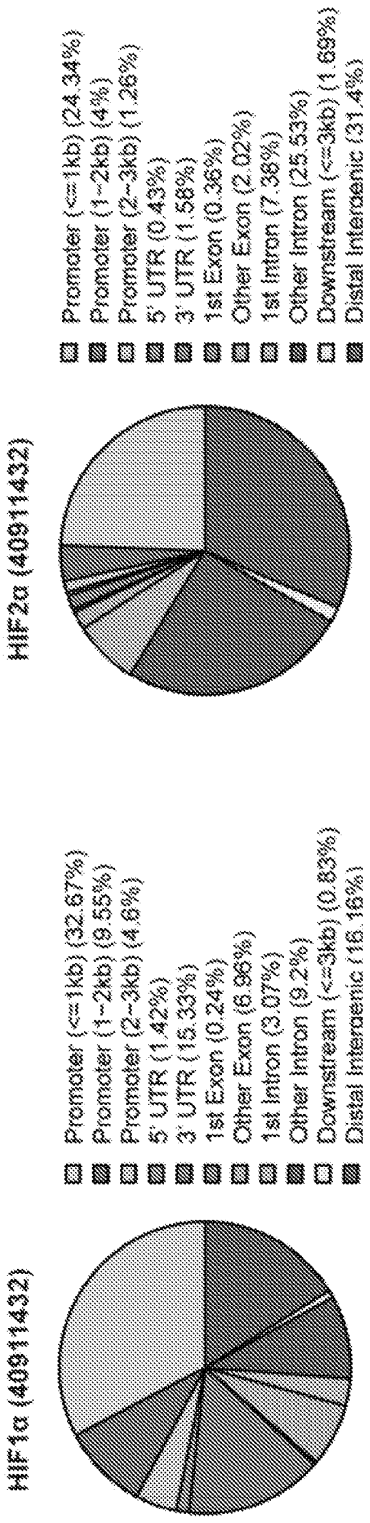
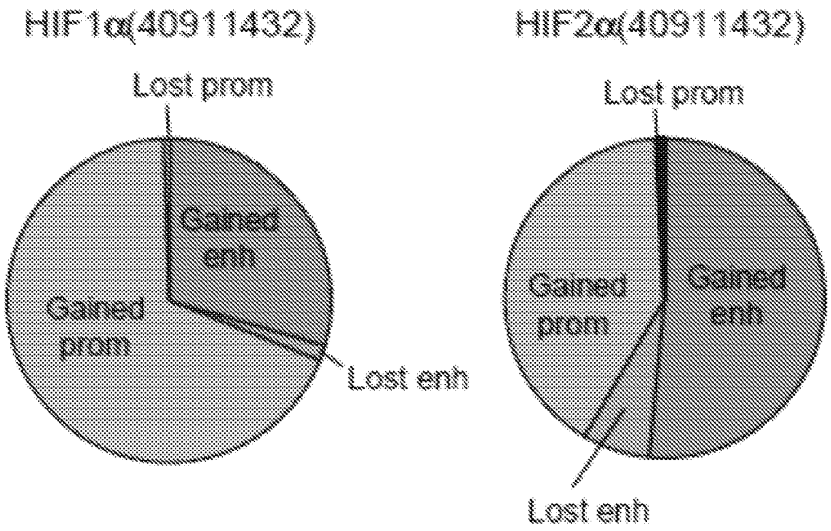


Figure 5 continued

J



K

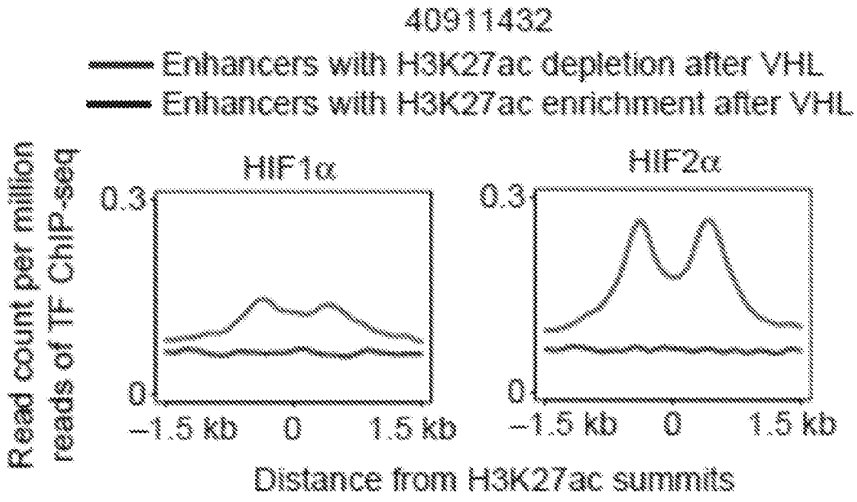
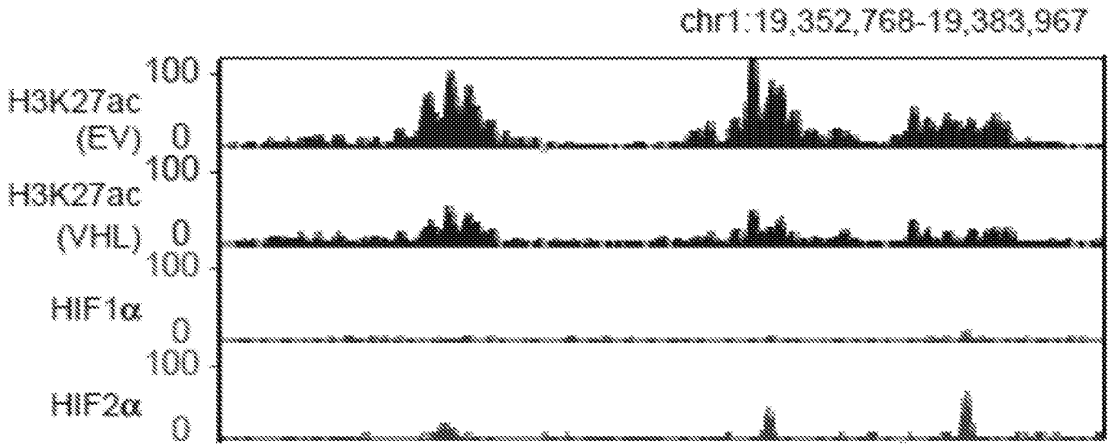


Figure 5 continued

L



M

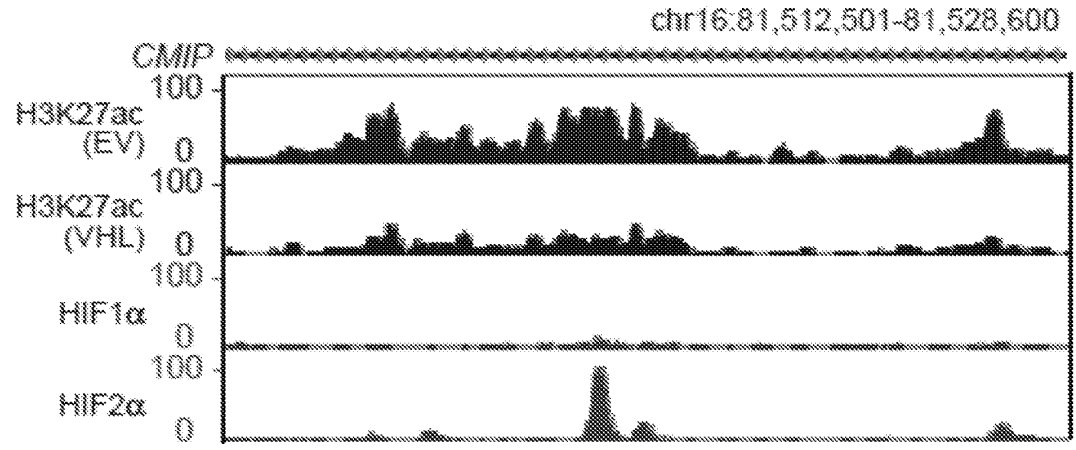


Figure 6

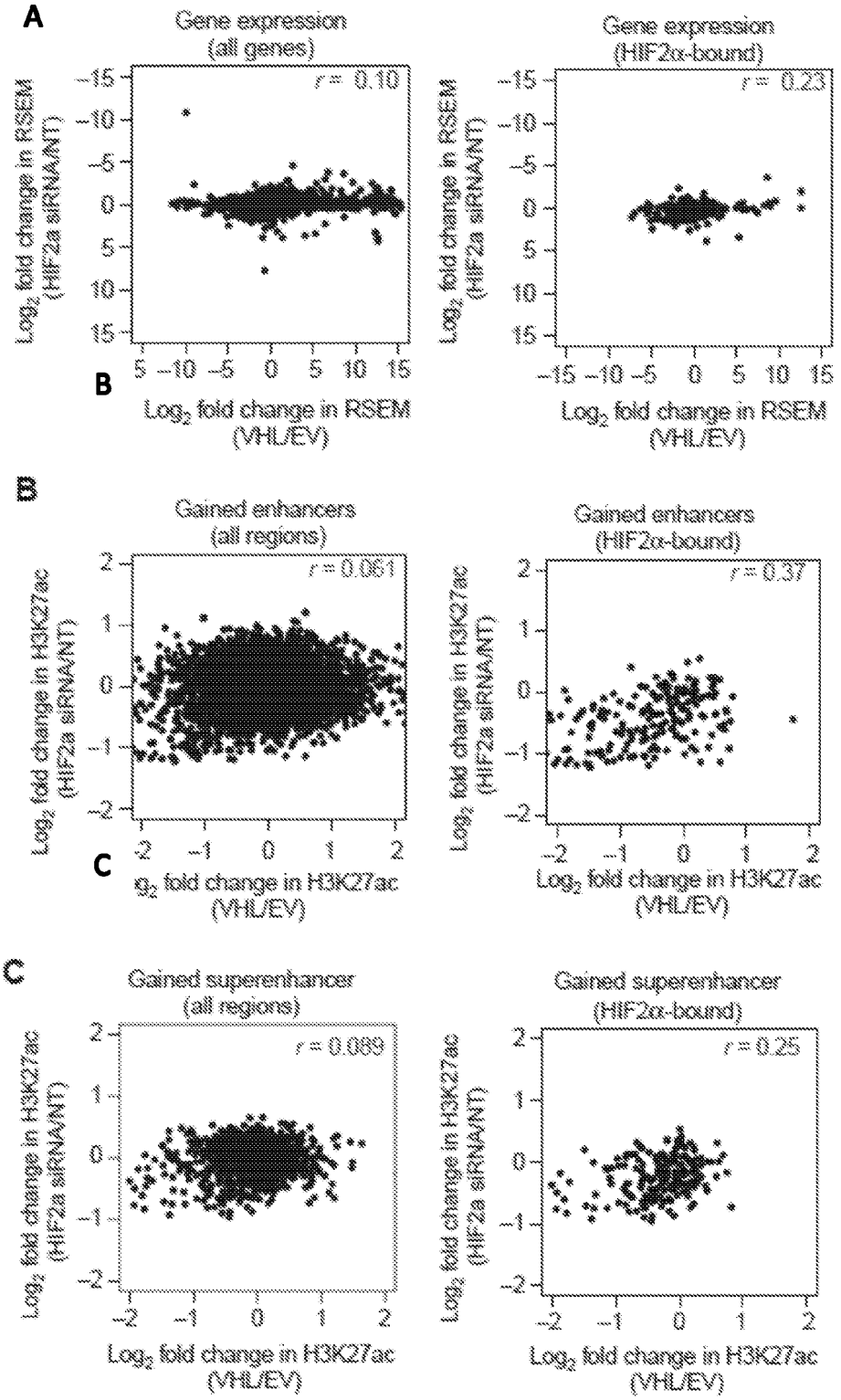
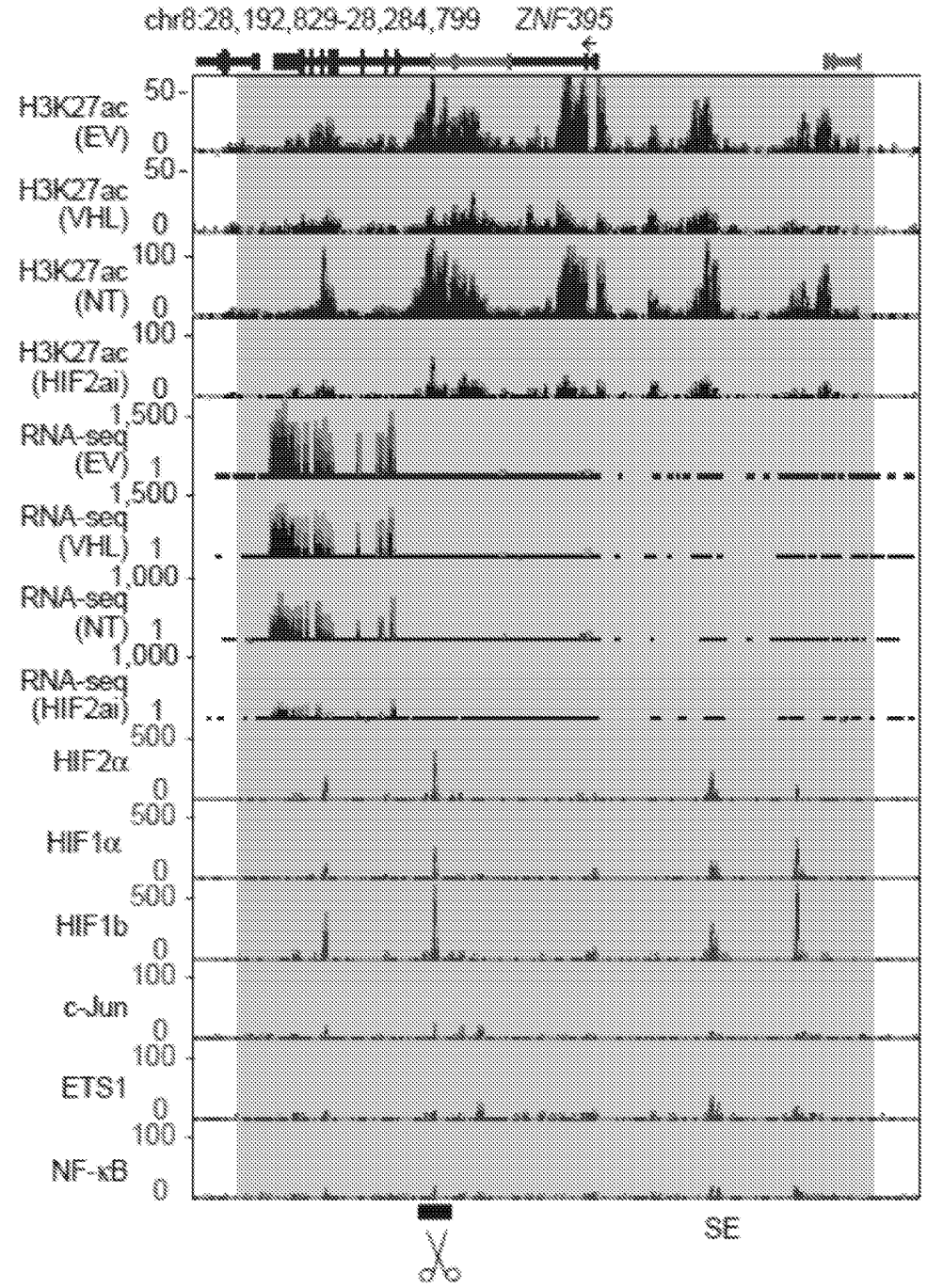

A
Gene expression
(all genes)
r = 0.10
Log2 fold change in RSEM
(HIF2a siRNA/NT)
Log2 fold change in RSEM
(VHL/EV)
Gene expression
(HIF2α-bound)
r = 0.23
Log2 fold change in RSEM
(HIF2a siRNA/NT)
Log2 fold change in RSEM
(VHL/EV)
B
Gained enhancers
(all regions)
r = 0.061
Log2 fold change in H3K27ac
(HIF2a siRNA/NT)
Log2 fold change in H3K27ac
(VHL/EV)
Gained enhancers
(HIF2α-bound)
r = 0.37
Log2 fold change in H3K27ac
(HIF2a siRNA/NT)
Log2 fold change in H3K27ac
(VHL/EV)
C
Gained superenhancer
(all regions)
r = 0.089
Log2 fold change in H3K27ac
(HIF2a siRNA/NT)
Log2 fold change in H3K27ac
(VHL/EV)
Gained superenhancer
(HIF2α-bound)
r = 0.25
Log2 fold change in H3K27ac
(HIF2a siRNA/NT)
Log2 fold change in H3K27ac
(VHL/EV)

Figure 6 continued

D



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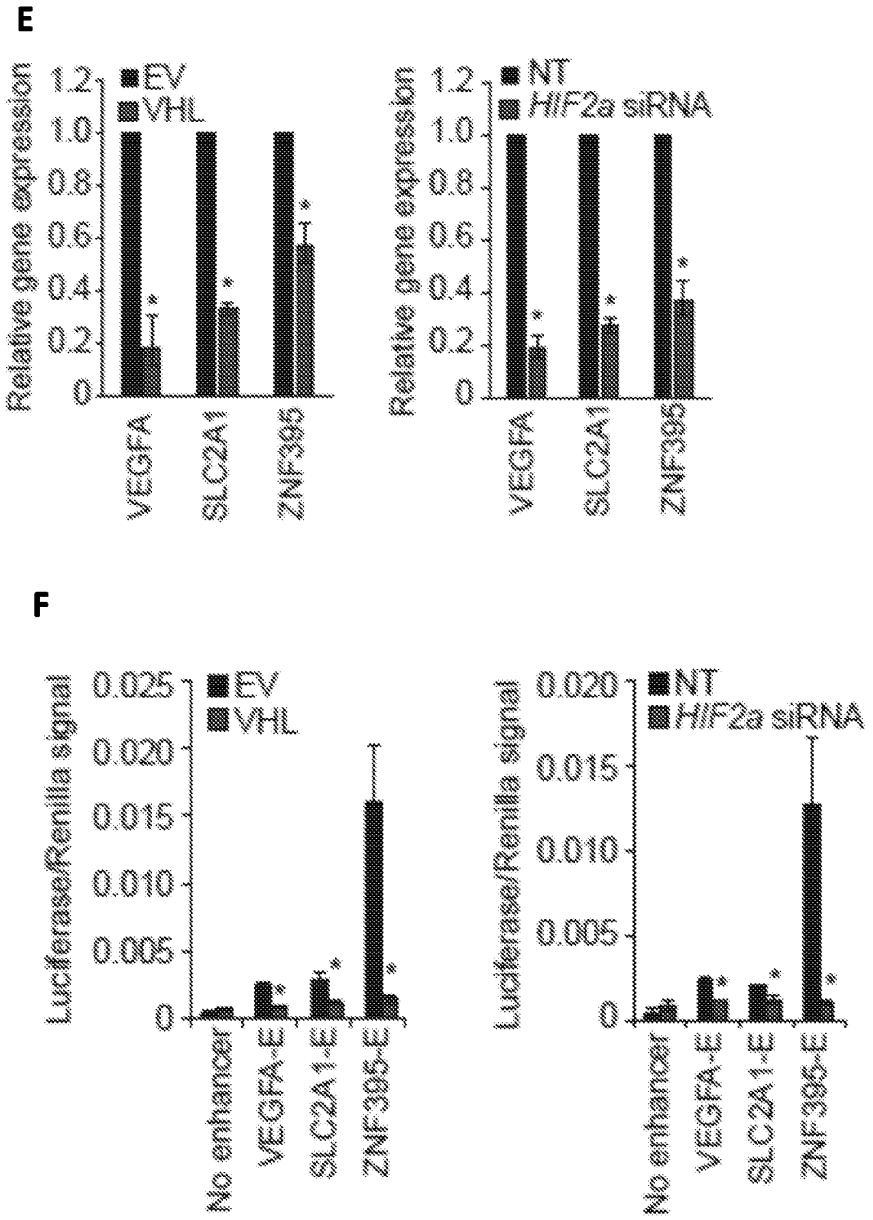


Figure 6 continued

G

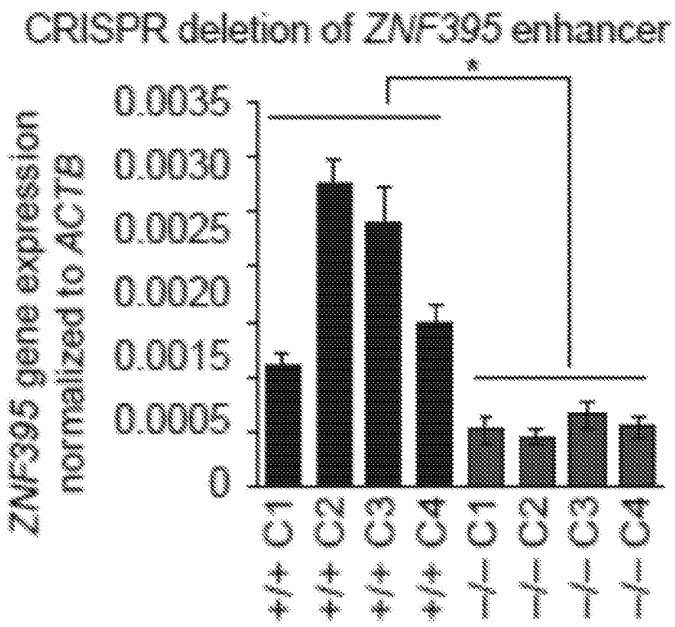
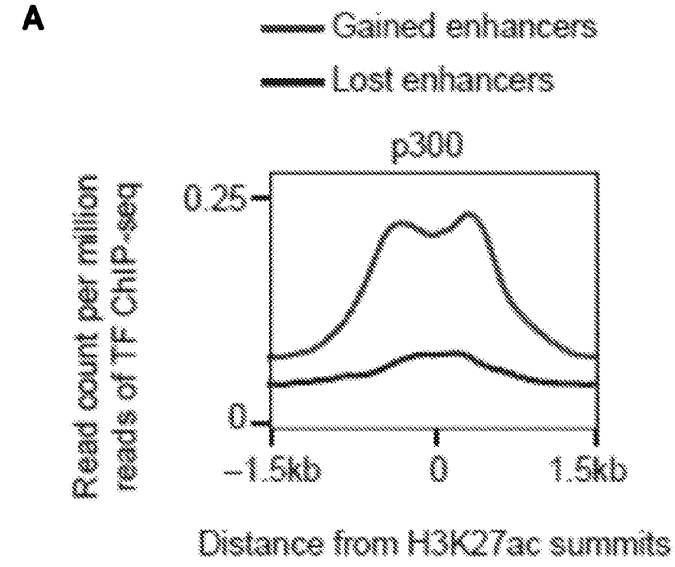


Figure 7


A
Gained enhancers
Lost enhancers
p300
Read count per million reads of TF ChIP-seq
0.25
0
−1.5kb
0
1.5kb
Distance from H3K27ac summits

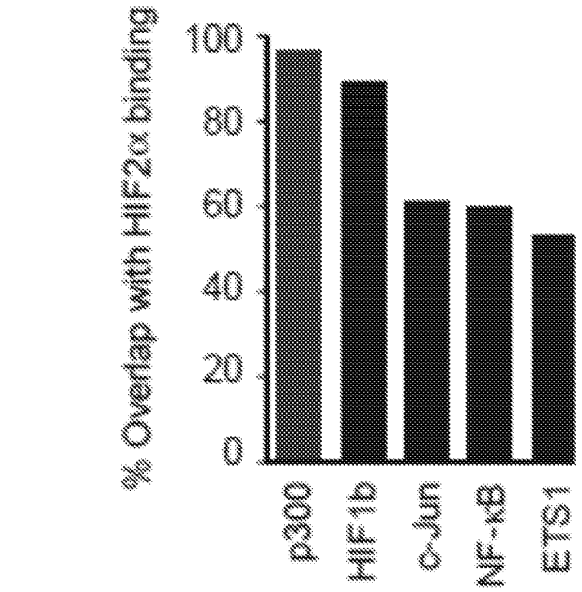
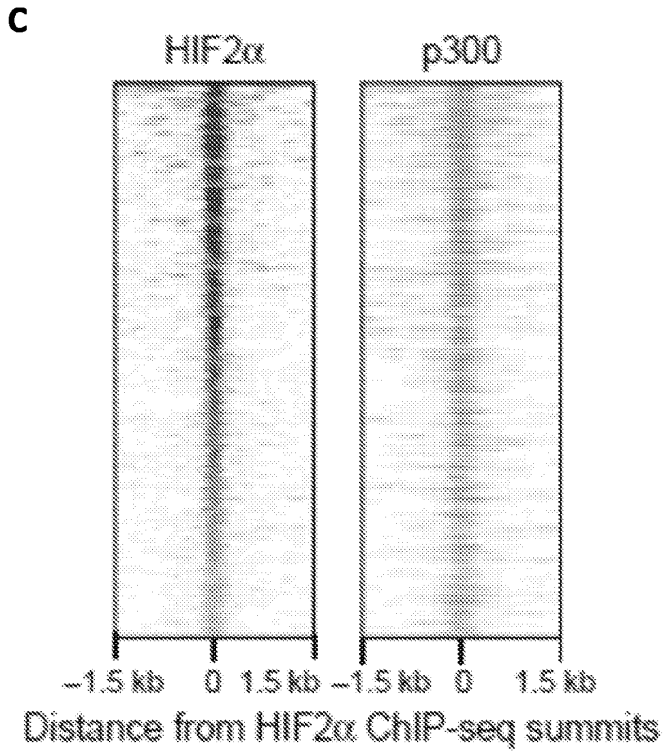

B
% Overlap with HIF2α binding
100
80
60
40
20
0
p300
HIF1b
c-Jun
NF-κB
ETS1

Figure 7 continued



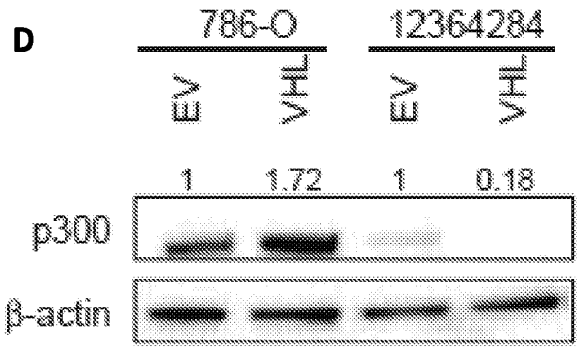


Figure 7 continued

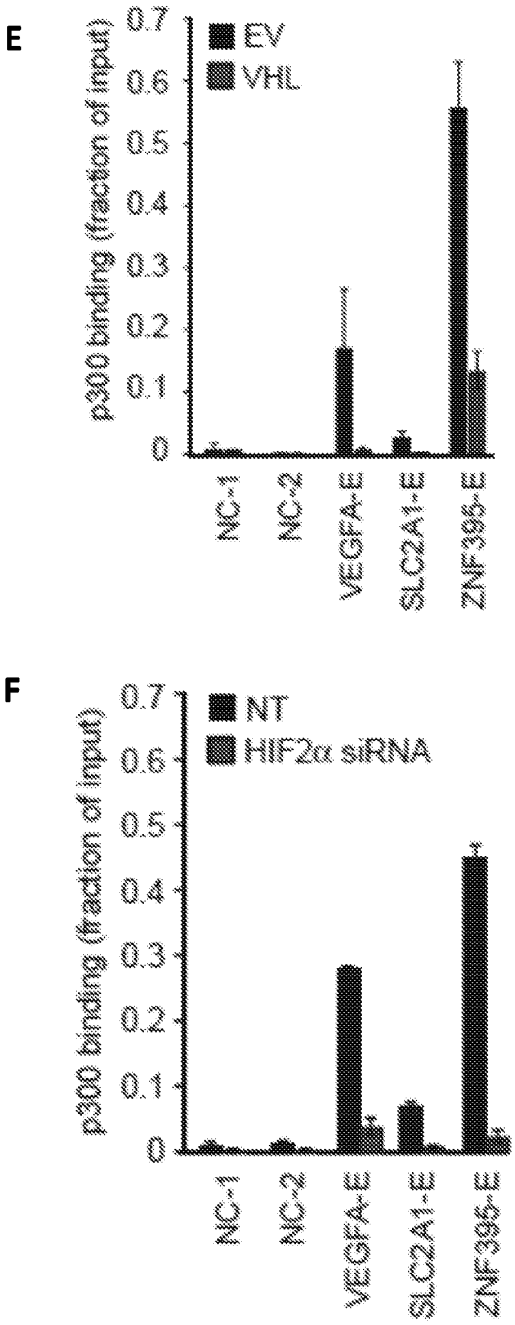
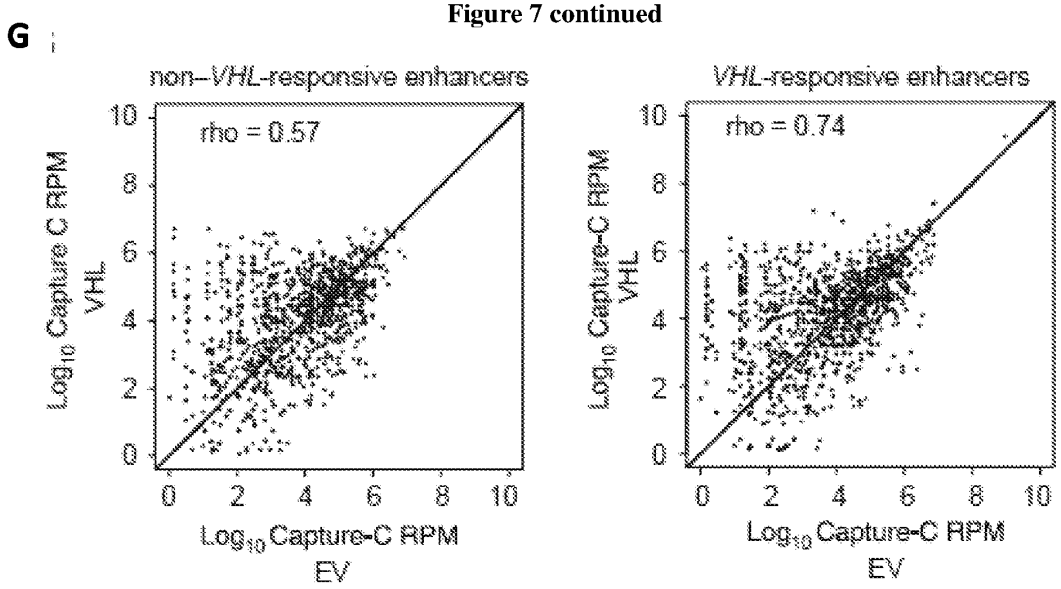


Figure 7 continued



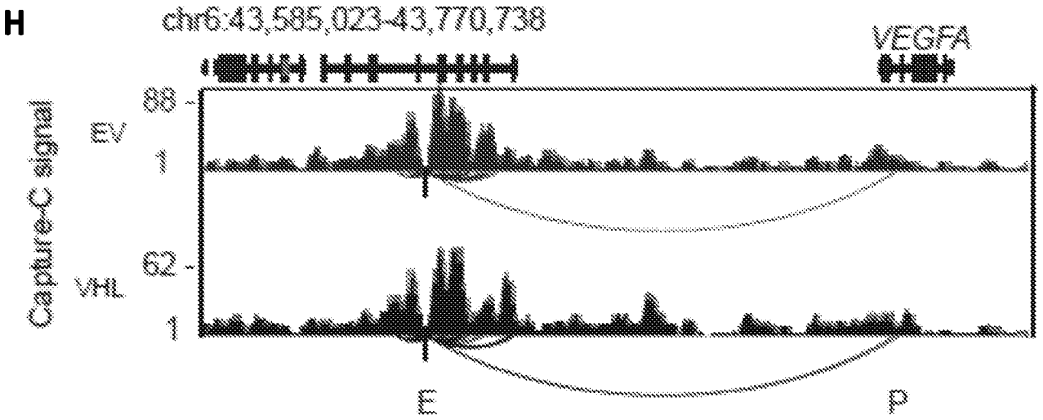
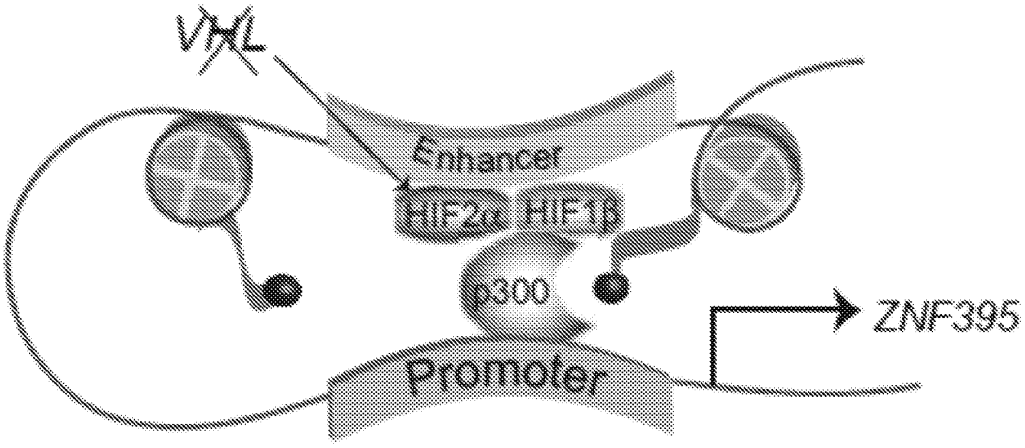


Figure 7 continued

I



J

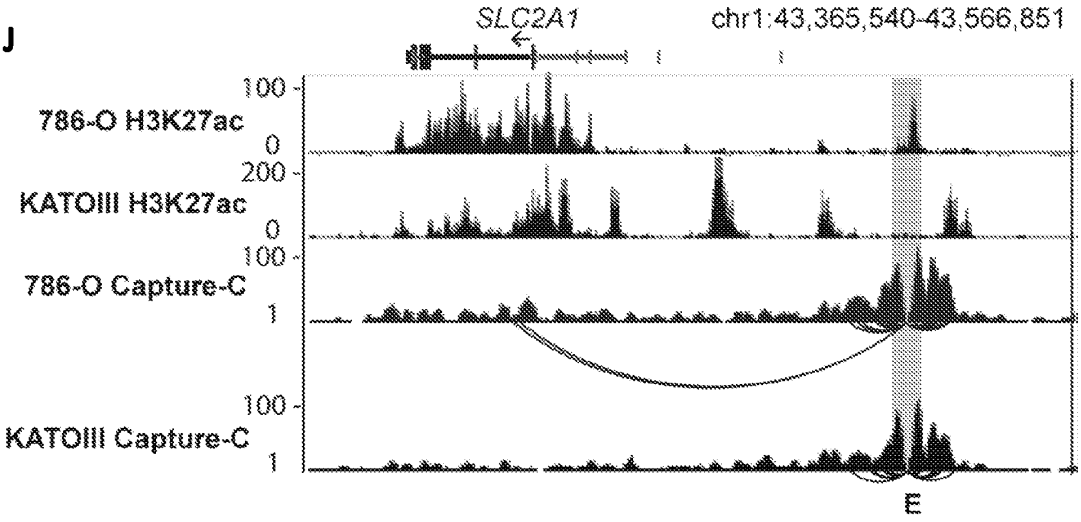


Figure 8

A

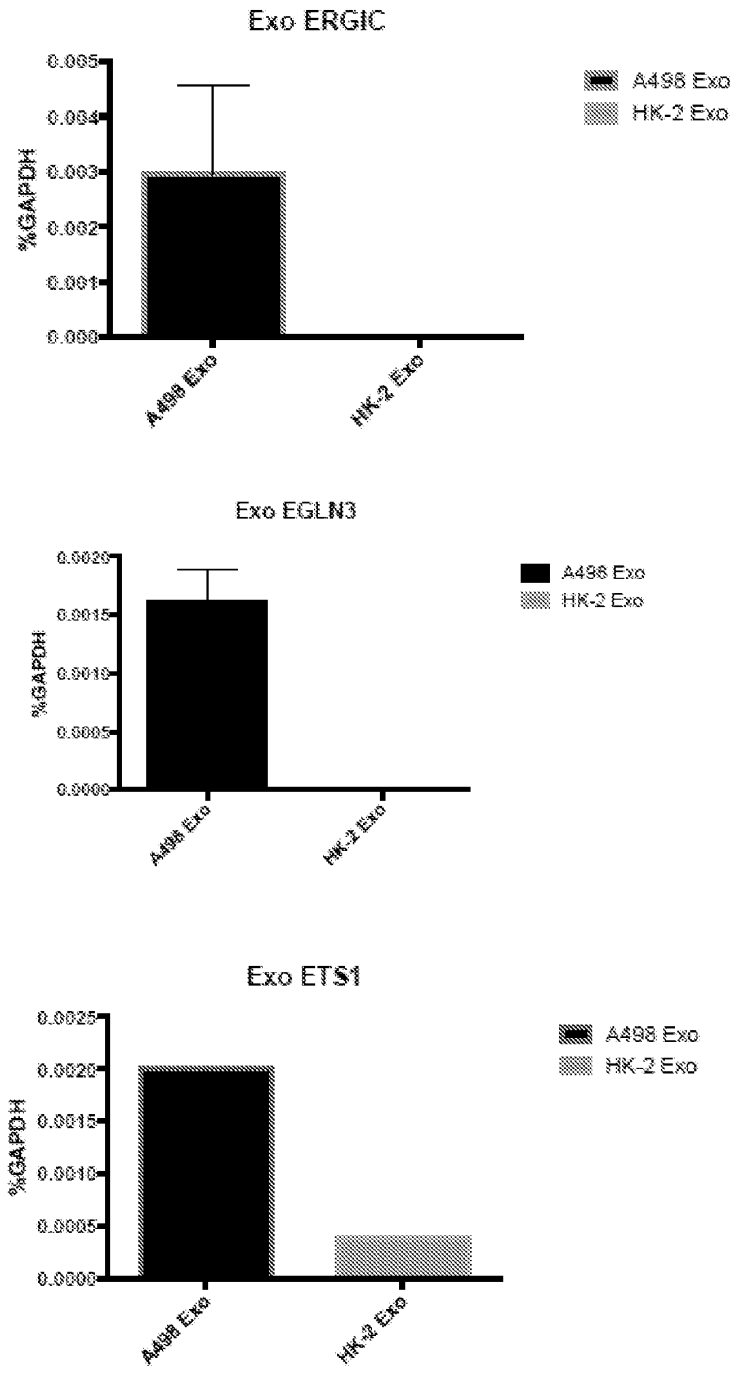
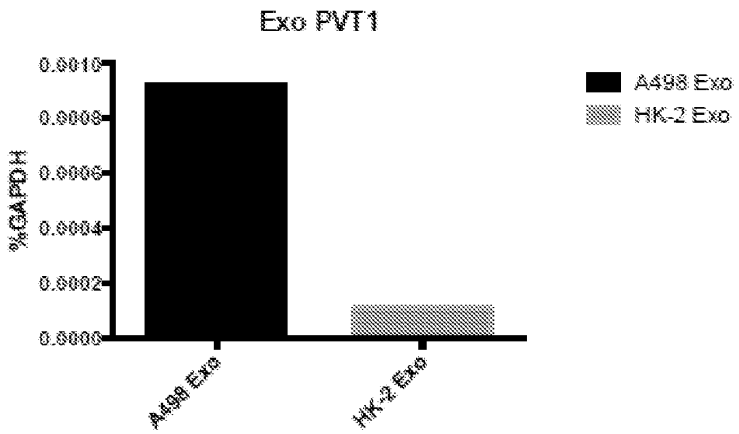
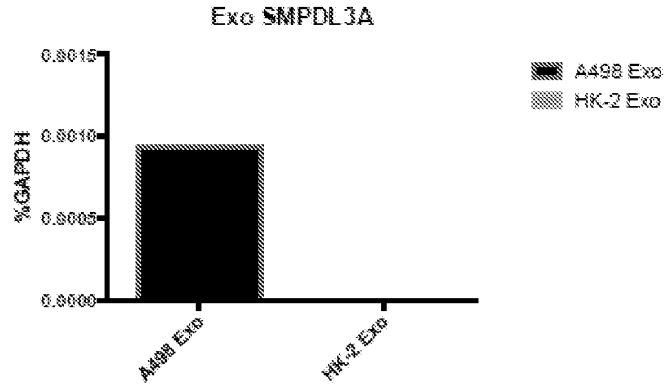

Exo ERGIC
%GAPDH
0.005
0.004
0.003
0.002
0.001
0.000
A498 Exo
HK-2 Exo
Exo EGLN3
%GAPDH
0.0020
0.0015
0.0010
0.0005
0.0000
A498 Exo
HK-2 Exo
Exo ETS1
%GAPDH
0.0025
0.0020
0.0015
0.0010
0.0005
0.0000
A498 Exo
HK-2 Exo

Figure 8 continued

B





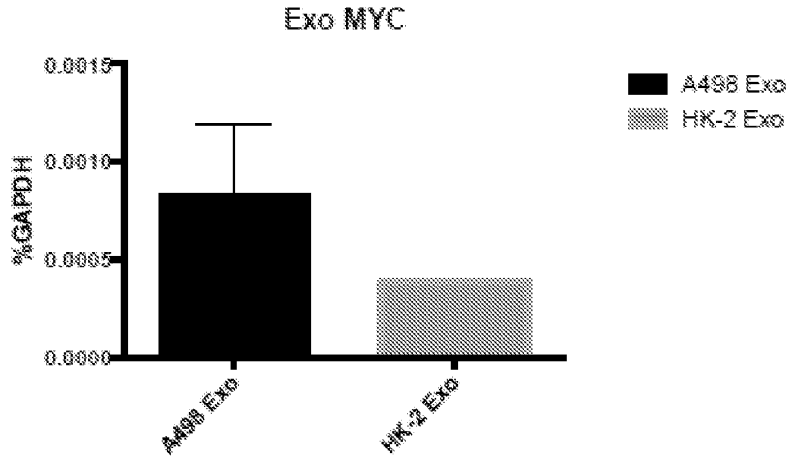


Figure 8 continued

C

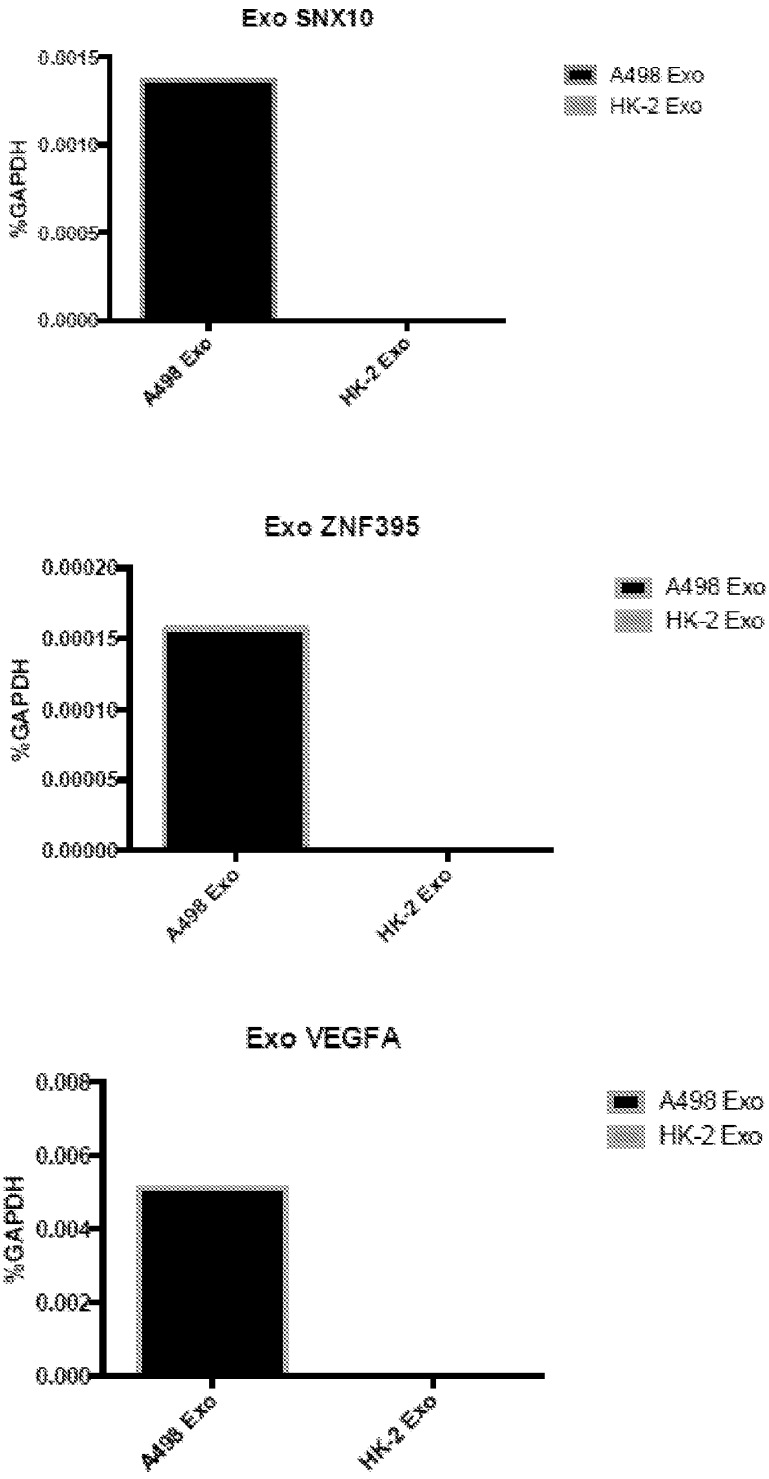
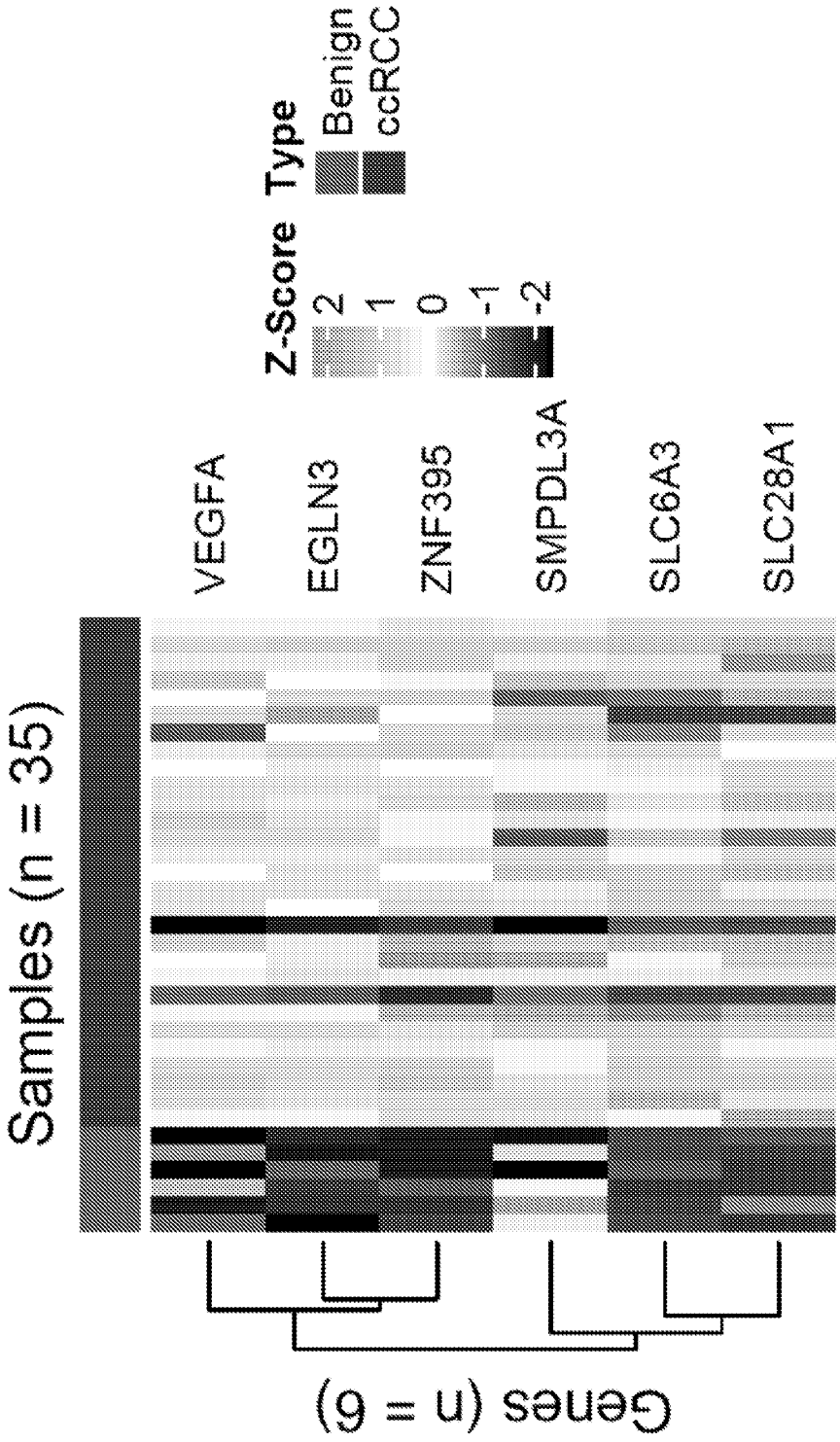


Figure 9


Type
Benign
ccRCC
Z-Score
2
1
0
-1
-2
VEGFA
EGLN3
ZNF395
SMPDL3A
SLC6A3
SLC28A1
Samples (n = 35)
Genes (n = 6)