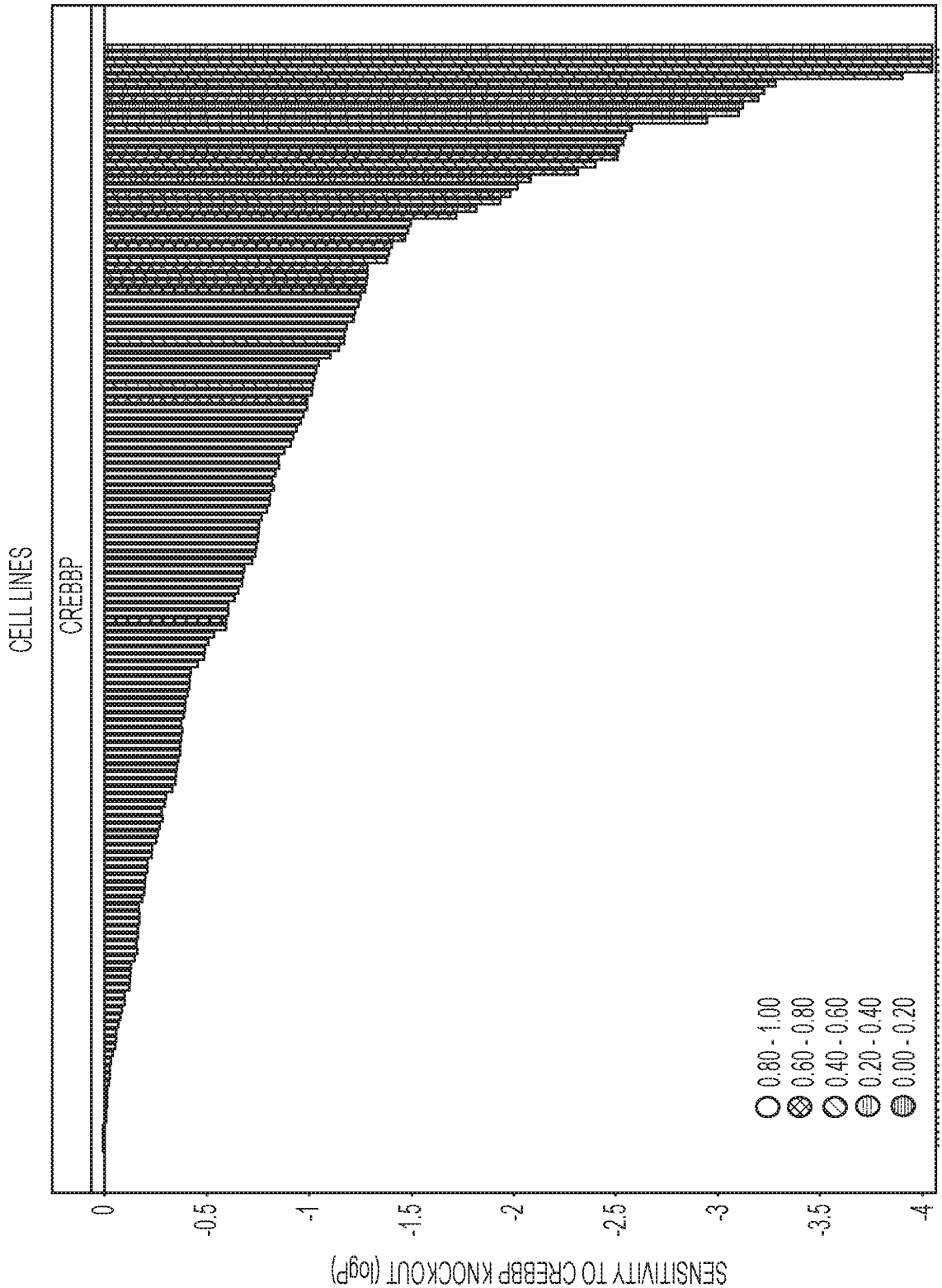

CELL LINES
CREBBP
SENSITIVITY TO CREBBP KNOCKOUT (logP)
0
-0.5
-1
-1.5
-2
-2.5
-3
-3.5
-4
0.80 - 1.00
0.60 - 0.80
0.40 - 0.60
0.20 - 0.40
0.00 - 0.20

Figure 1

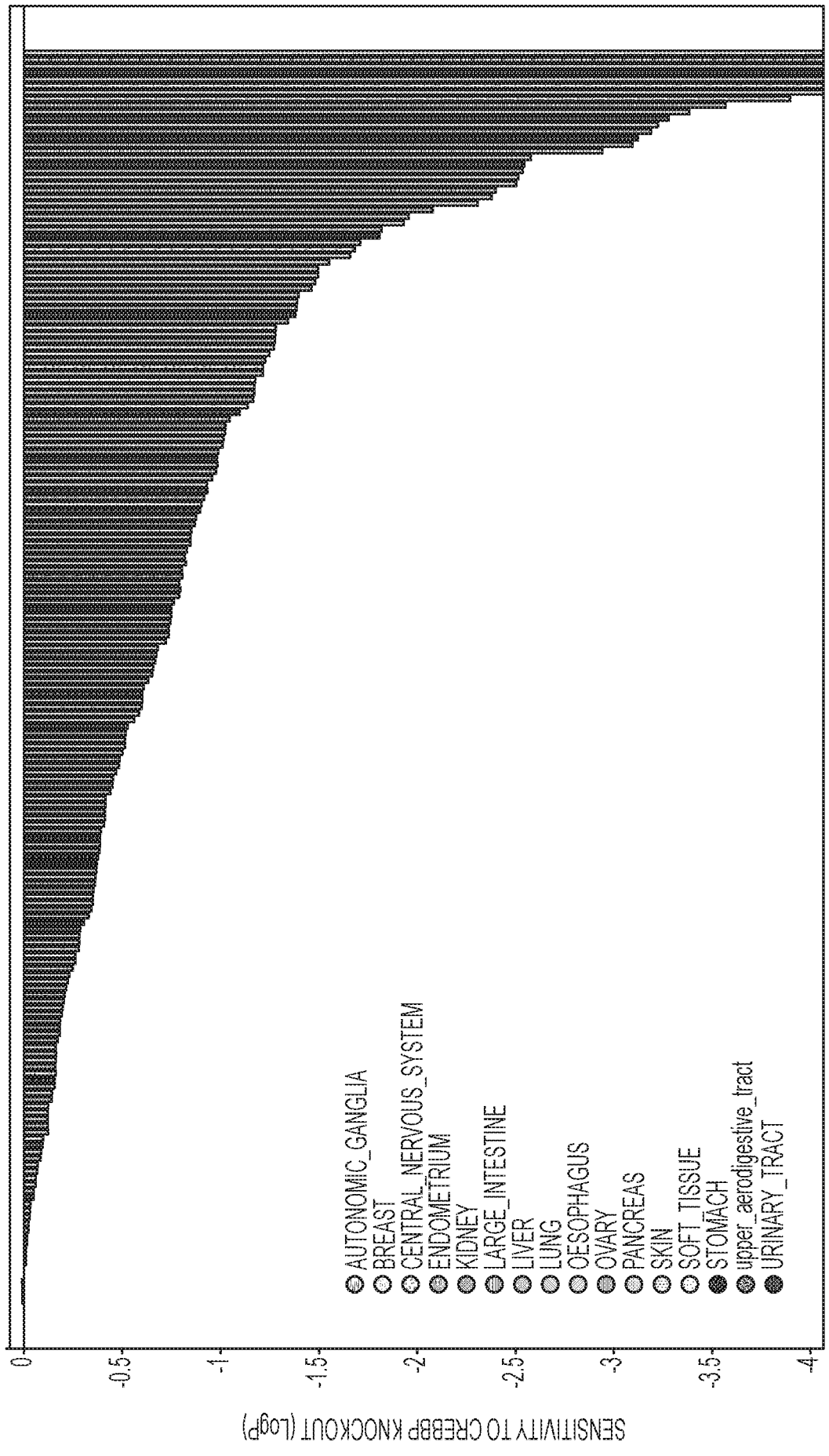

SENSITIVITY TO CREBBP KNOCKOUT (LogP)
0
-0.5
-1
-1.5
-2
-2.5
-3
-3.5
-4
AUTONOMIC_GANGLIA
BREAST
CENTRAL_NERVOUS_SYSTEM
ENDOMETRIUM
KIDNEY
LARGE_INTESTINE
LIVER
LUNG
OESOPHAGUS
OVARY
PANCREAS
SKIN
SOFT_TISSUE
STOMACH
upper_aerodigestive_tract
URINARY_TRACT

Figure 2A

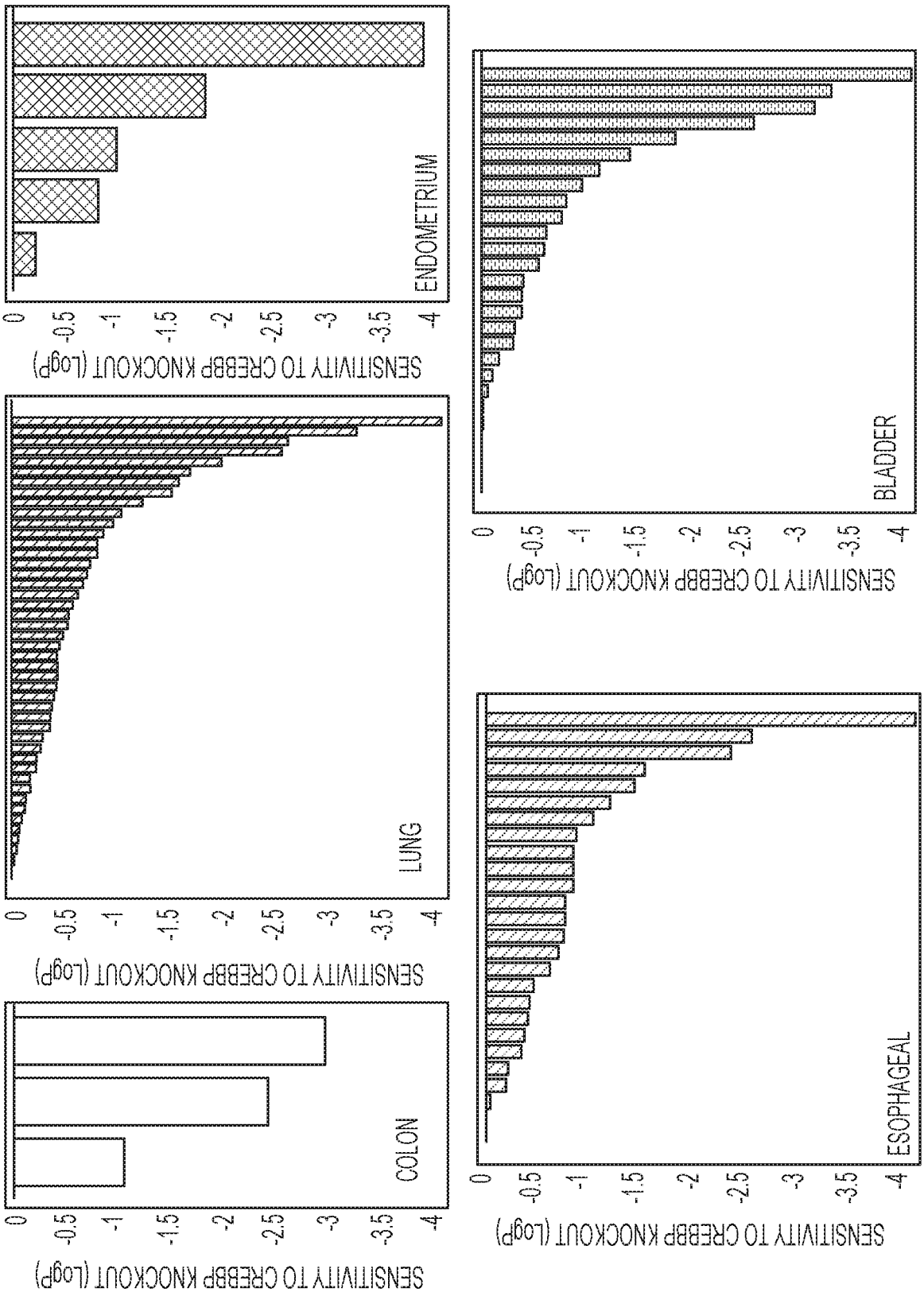

ENDOMETRIUM
SENSITIVITY TO CREBBP KNOCKOUT (LogP)
0
-0.5
-1
-1.5
-2
-2.5
-3
-3.5
-4
BLADDER
SENSITIVITY TO CREBBP KNOCKOUT (LogP)
LUNG
SENSITIVITY TO CREBBP KNOCKOUT (LogP)
ESOPHAGEAL
SENSITIVITY TO CREBBP KNOCKOUT (LogP)
COLON
SENSITIVITY TO CREBBP KNOCKOUT (LogP)

Figure 2B

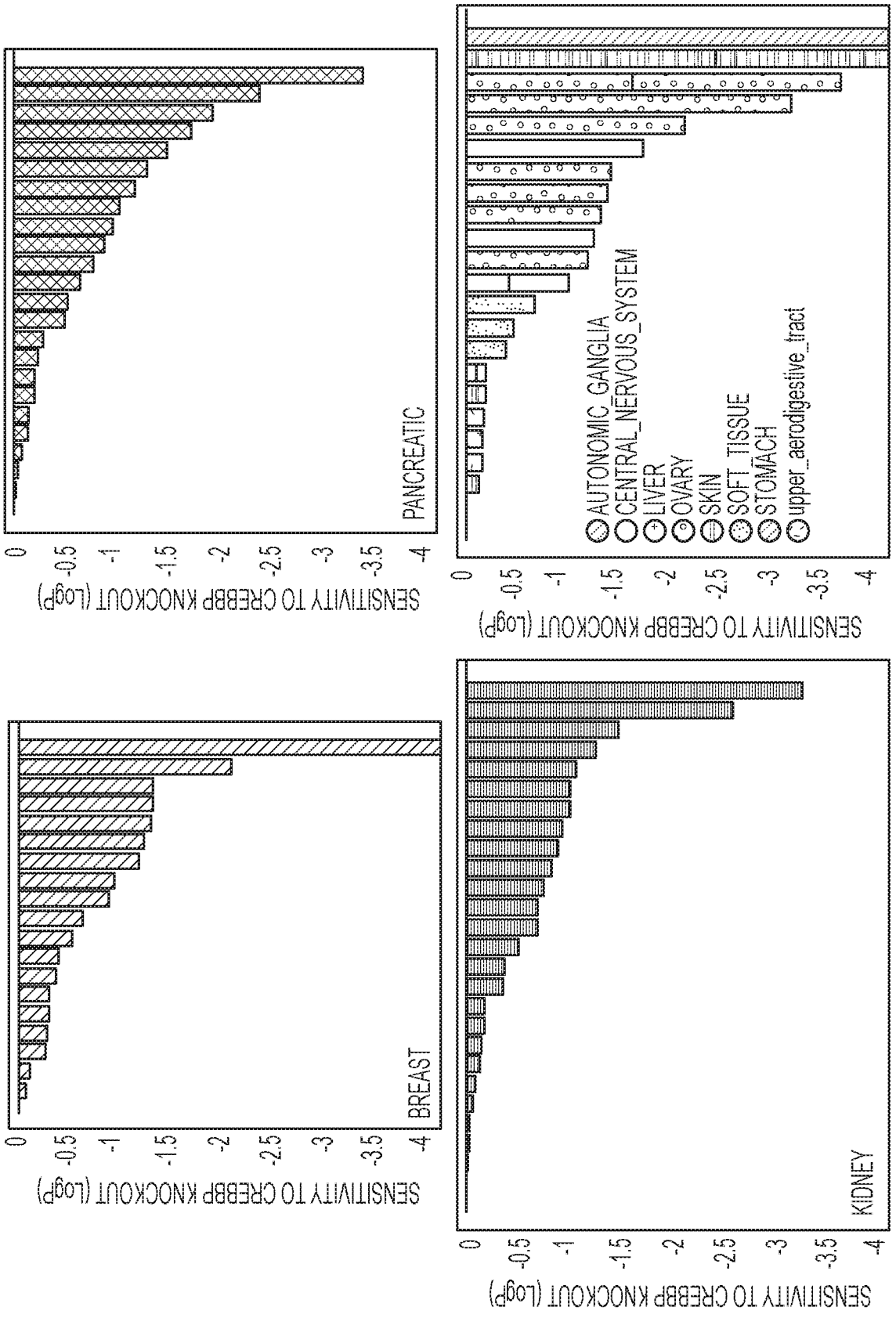



Figure 2B Cont.

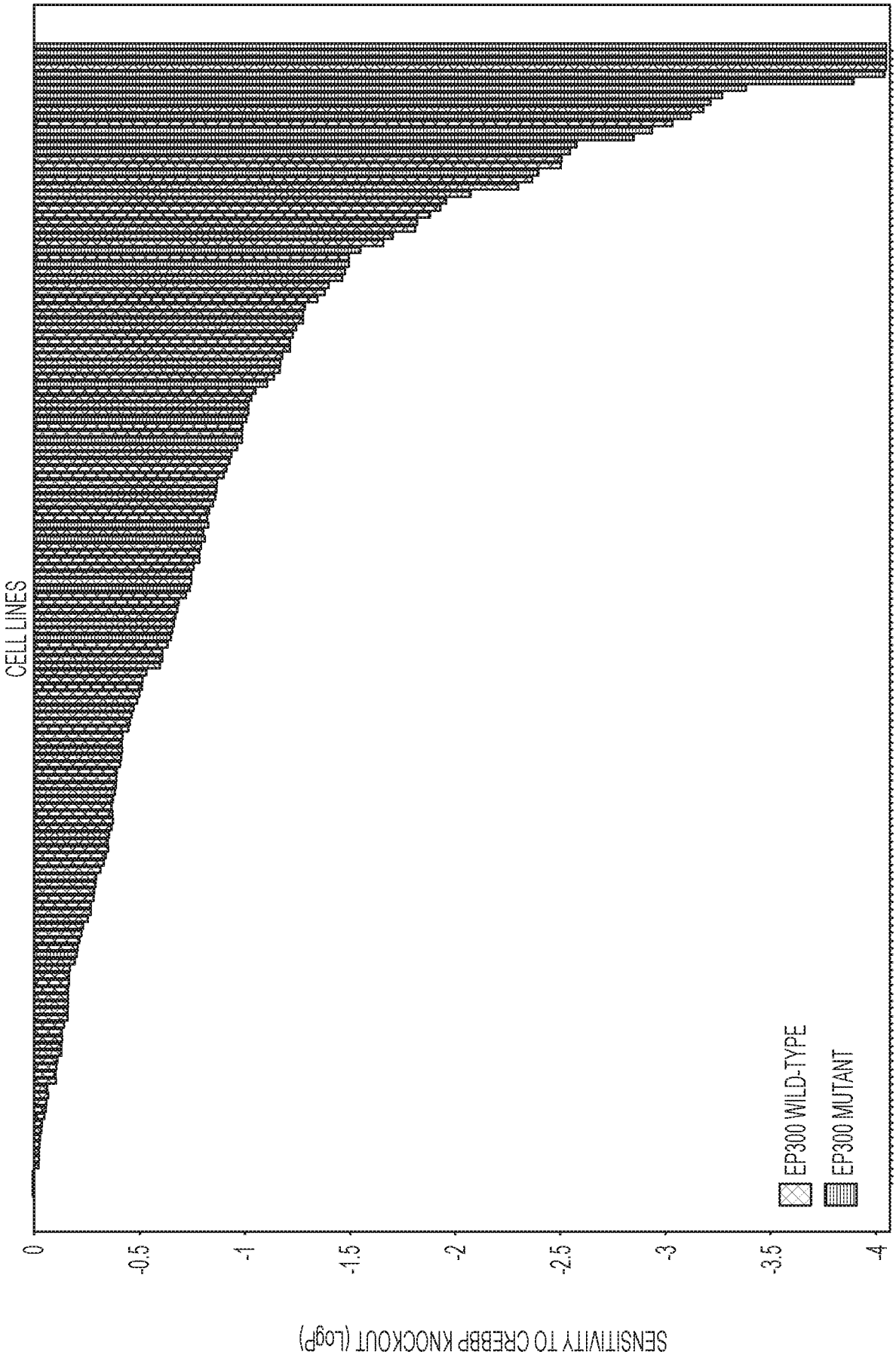

CELL LINES
SENSITIVITY TO CREBBP KNOCKOUT (LogP)
0
-0.5
-1
-1.5
-2
-2.5
-3
-3.5
-4
EP300 WILD-TYPE
EP300 MUTANT

Figure 3A

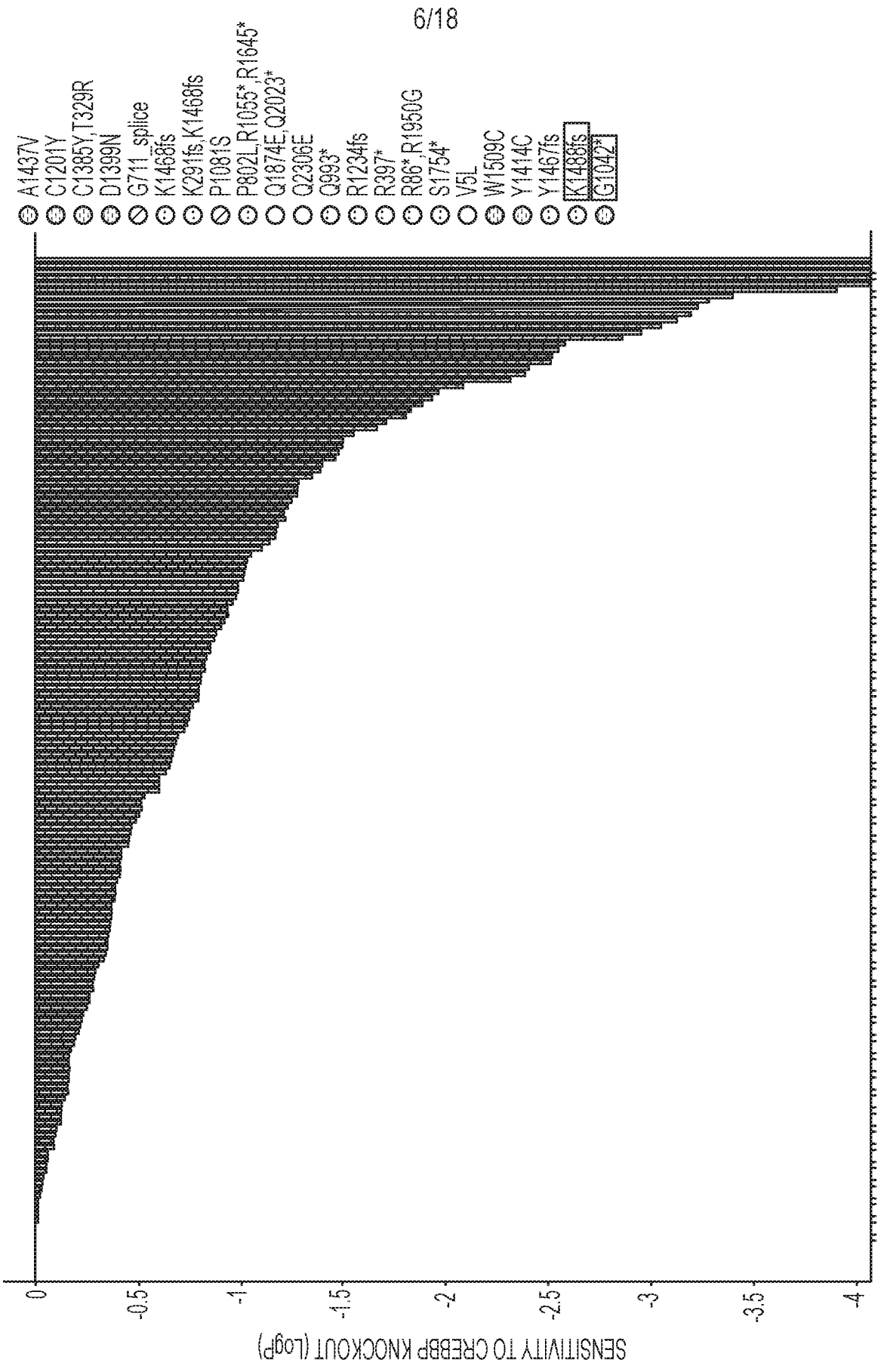

A1437V
C1201Y
C1385Y,T329R
D1399N
G711_splice
K1468fs
K2916fs,K1468fs
P1081S
P802L,R1055*,R1645*
Q1874E,Q2023*
Q2306E
Q993*
R1234fs
R397*
R86*,R1950G
S1754*
V5L
W1509C
Y1414C
Y1467fs
K1488fs
G1042*
0
-0.5
-1
-1.5
-2
-2.5
-3
-3.5
-4
SENSITIVITY TO CREBBP KNOCKOUT (LogP)

Figure 3B

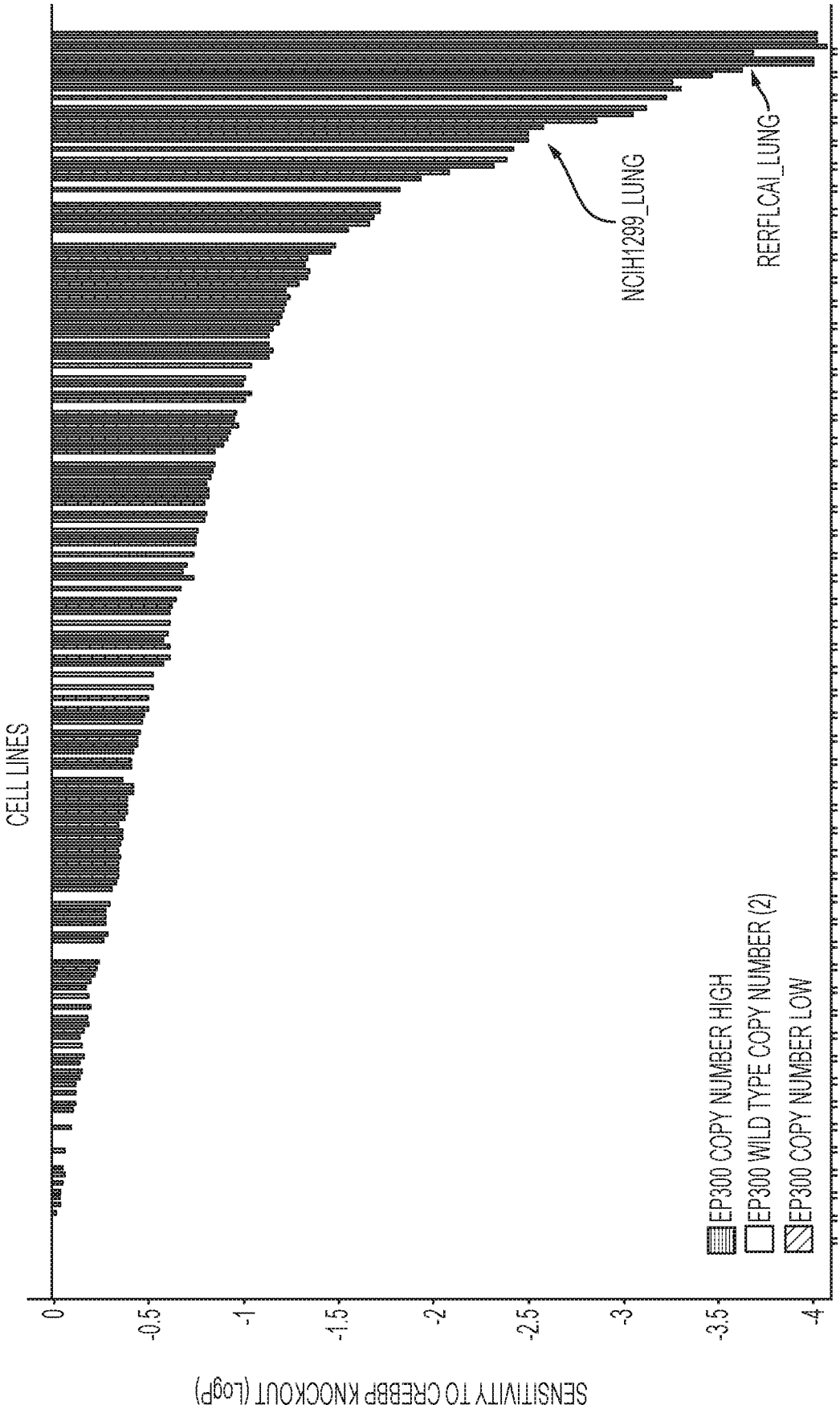

CELL LINES
SENSITIVITY TO CREBBP KNOCKOUT (LogP)
0
-0.5
-1
-1.5
-2
-2.5
-3
-3.5
-4
NCIH1299_LUNG
RERFLCAI_LUNG
EP300 COPY NUMBER HIGH
EP300 WILD TYPE COPY NUMBER (2)
EP300 COPY NUMBER LOW

Figure 3C

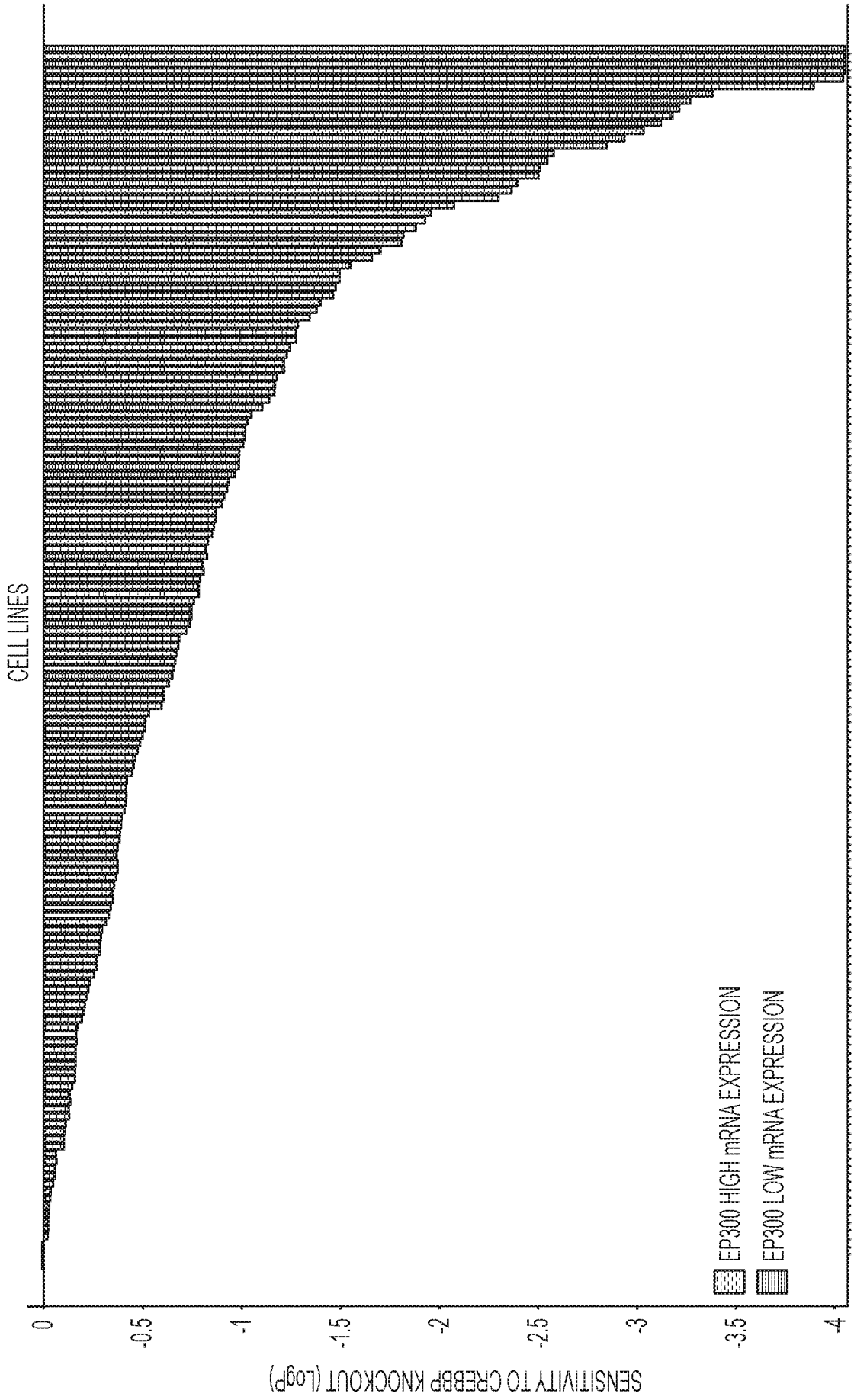

CELL LINES
SENSITIVITY TO CREBBP KNOCKOUT (LogP)
0
-0.5
-1
-1.5
-2
-2.5
-3
-3.5
-4
EP300 HIGH mRNA EXPRESSION
EP300 LOW mRNA EXPRESSION

Figure 3D

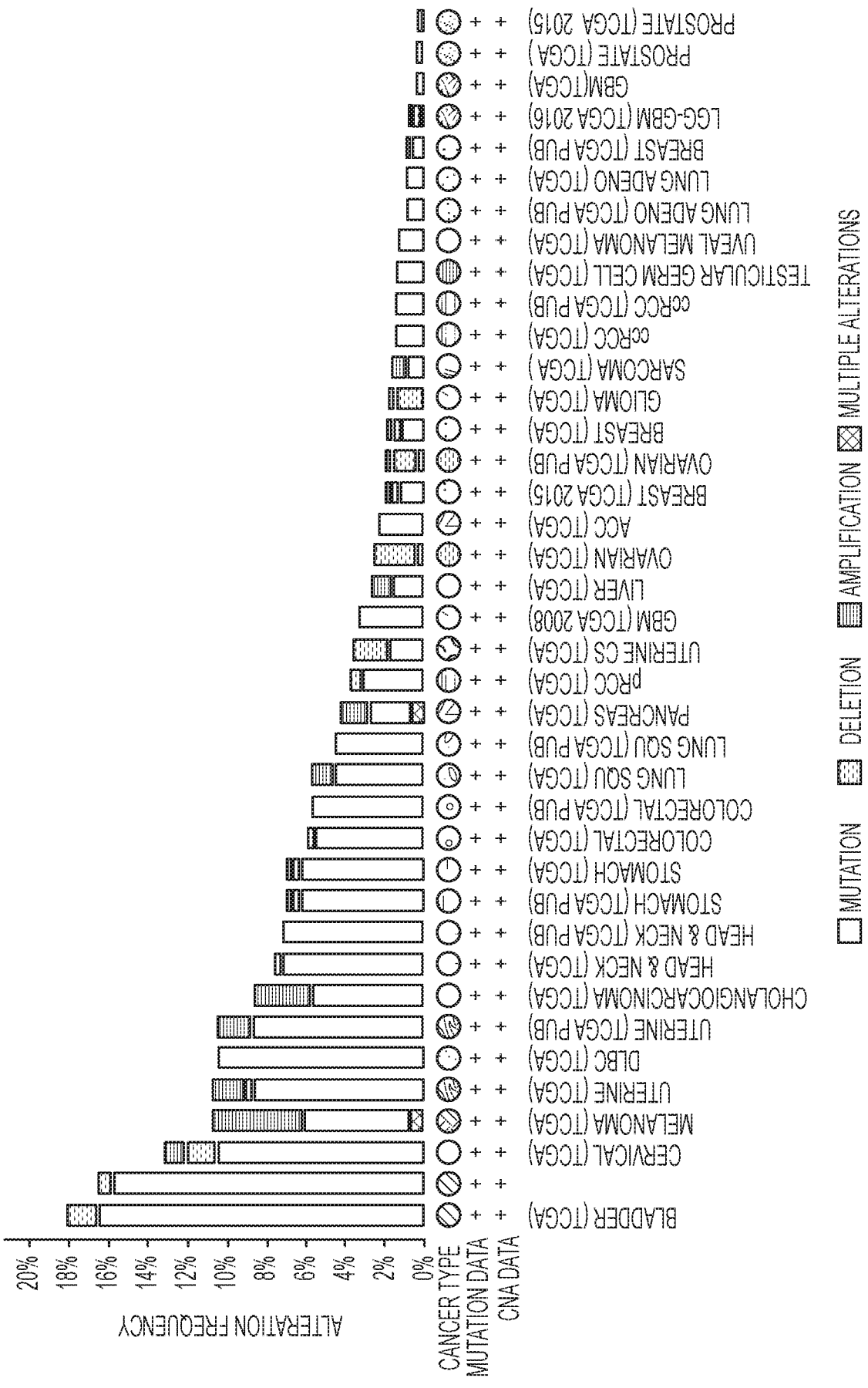

ALTERATION FREQUENCY
20%
18%
16%
14%
12%
10%
8%
6%
4%
2%
0%
CANCER TYPE
MUTATION DATA
CNA DATA
BLADDER (TCGA)
CERVICAL (TCGA)
MELANOMA (TCGA)
UTERINE (TCGA)
DLBC (TCGA)
UTERINE (TCGA PUB)
CHOLANGIOCARCINOMA (TCGA)
HEAD & NECK (TCGA)
HEAD & NECK (TCGA PUB)
STOMACH (TCGA PUB)
STOMACH (TCGA)
COLORECTAL (TCGA)
COLORECTAL (TCGA PUB)
LUNG SQU (TCGA)
LUNG SQU (TCGA PUB)
PANCREAS (TCGA)
pRCC (TCGA)
UTERINE CS (TCGA)
GBM (TCGA 2008)
LIVER (TCGA)
OVARIAN (TCGA)
ACC (TCGA)
BREAST (TCGA 2015)
OVARIAN (TCGA PUB)
BREAST (TCGA)
GLIOMA (TCGA)
SARCOMA (TCGA )
ccRCC (TCGA)
ccRCC (TCGA PUB)
TESTICULAR GERM CELL (TCGA)
UVEAL MELANOMA (TCGA)
LUNG ADENO (TCGA PUB)
LUNG ADENO (TCGA)
BREAST (TCGA PUB)
LGG-GBM (TCGA 2016)
GBM(TCGA)
PROSTATE (TCGA )
PROSTATE (TCGA 2015)
MUTATION
DELETION
AMPLIFICATION
MULTIPLE ALTERATIONS

Figure 4A

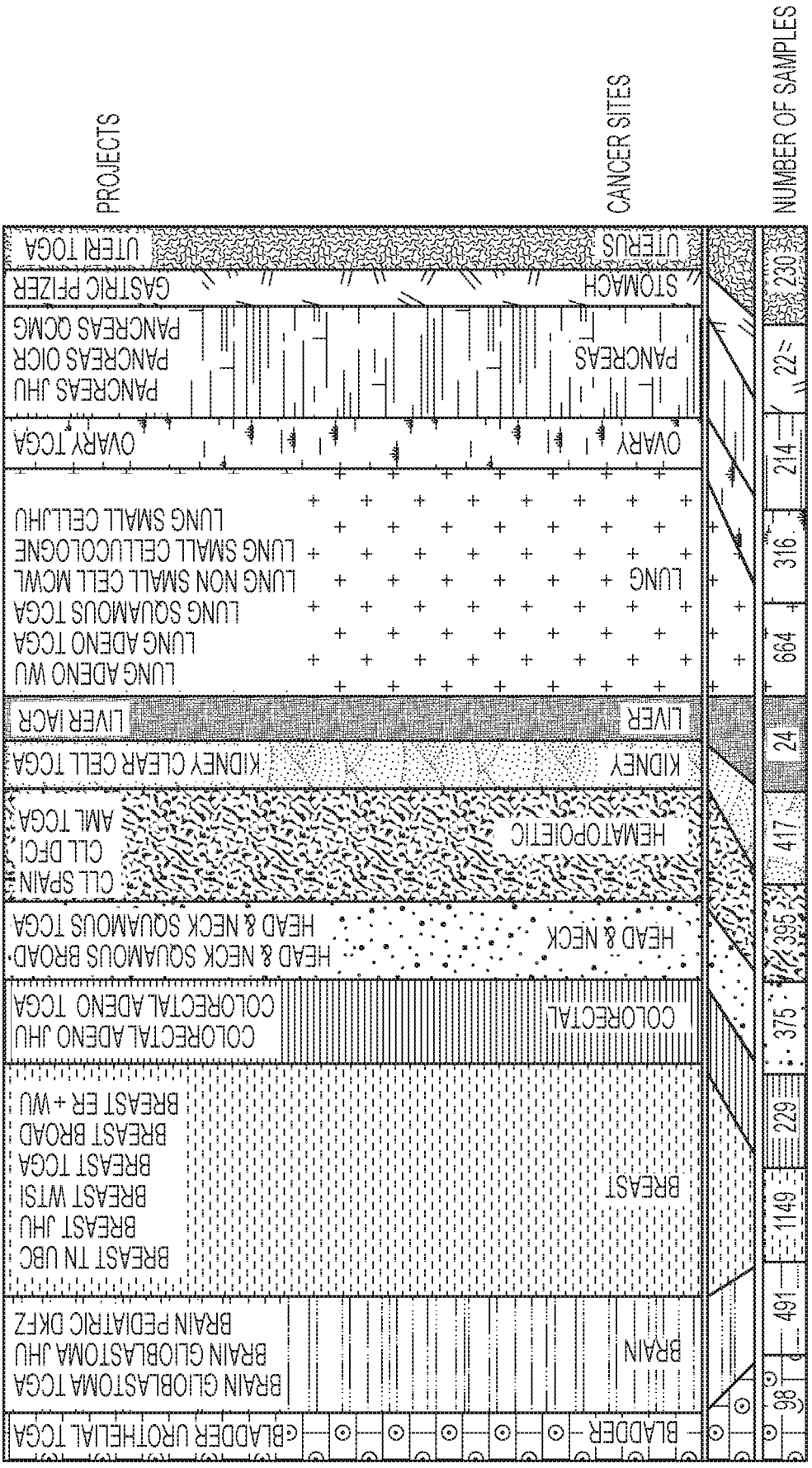
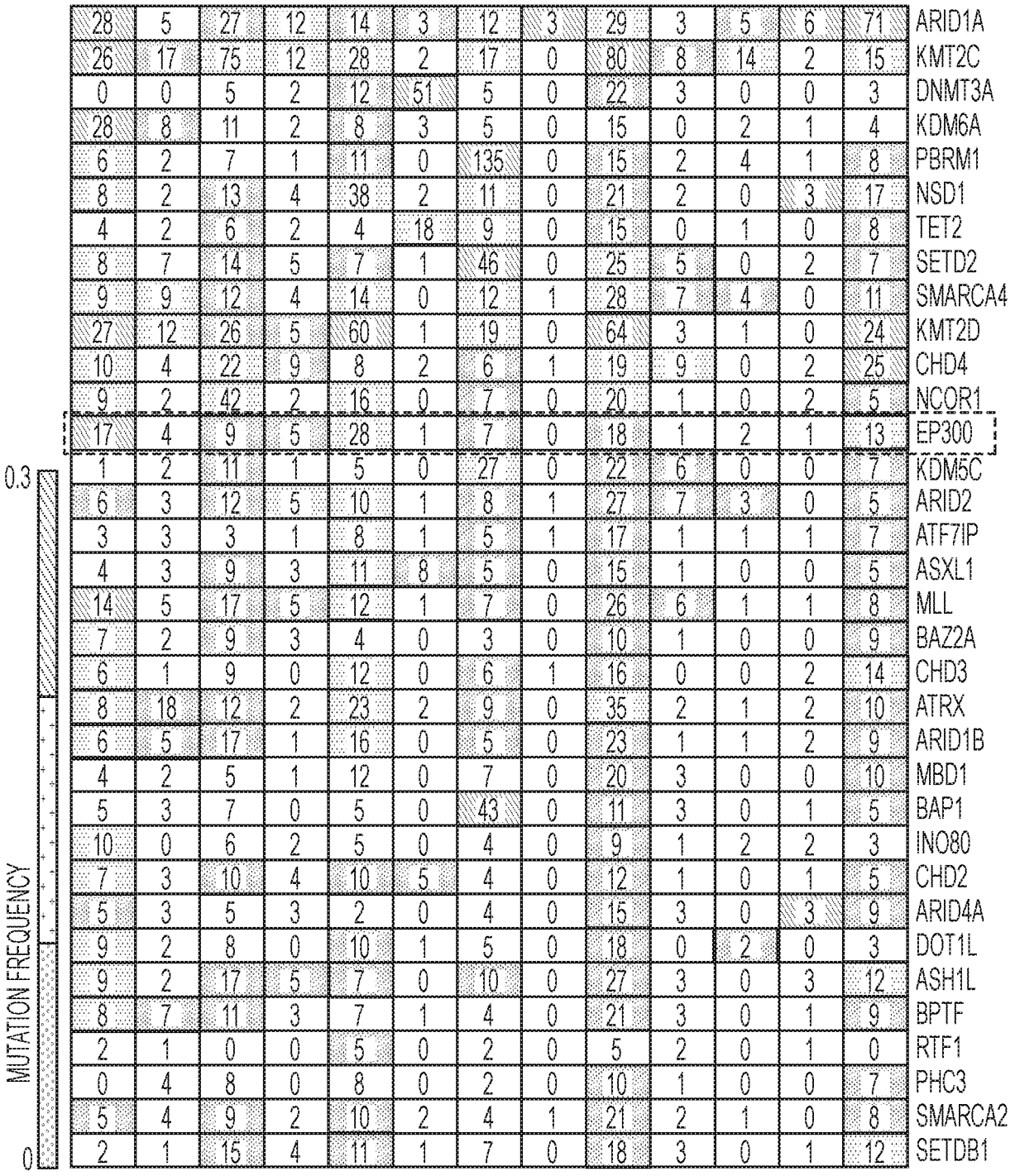

PROJECTS
CANCER SITES
NUMBER OF SAMPLES
BLADDER
BLADDER UROTHELIAL TCGA
BRAIN
BRAIN GLIOBLASTOMA TCGA
BRAIN GLIOBLASTOMA JHU
BRAIN PEDIATRIC DKFZ
BREAST
BREAST TN UBC
BREAST JHU
BREAST WTSI
BREAST TCGA
BREAST BROAD
BREAST ER + WU
COLORECTAL
COLORECTAL ADENO JHU
COLORECTAL ADENO TCGA
HEAD & NECK
HEAD & NECK SQUAMOUS BROAD
HEAD & NECK SQUAMOUS TCGA
HEMATOPOIETIC
CLL SPAIN
CLL DFCI
AML TCGA
KIDNEY
KIDNEY CLEAR CELL TCGA
LIVER
LIVER IACR
LUNG
LUNG ADENO WU
LUNG ADENO TCGA
LUNG SQUAMOUS TCGA
LUNG NON SMALL CELL MCWL
LUNG SMALL CELLUCOLOGNE
LUNG SMALL CELLJHU
OVARY
OVARY TCGA
PANCREAS
PANCREAS JHU
PANCREAS OICR
PANCREAS QCMG
STOMACH
GASTRIC PFIZER
UTERUS
UTERI TCGA
98
491
1149
229
375
395
417
24
664
316
214
22
230

Figure 4B




| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 28 | 5 | 27 | 12 | 14 | 3 | 12 | 3 | 29 | 3 | 5 | 6 | 71 | ARID1A |
| 26 | 17 | 75 | 12 | 28 | 2 | 17 | 0 | 80 | 8 | 14 | 2 | 15 | KMT2C |
| 0 | 0 | 5 | 2 | 12 | 51 | 5 | 0 | 22 | 3 | 0 | 0 | 3 | DNMT3A |
| 28 | 8 | 11 | 2 | 8 | 3 | 5 | 0 | 15 | 0 | 2 | 1 | 4 | KDM6A |
| 6 | 2 | 7 | 1 | 11 | 0 | 135 | 0 | 15 | 2 | 4 | 1 | 8 | PBRM1 |
| 8 | 2 | 13 | 4 | 38 | 2 | 11 | 0 | 21 | 2 | 0 | 3 | 17 | NSD1 |
| 4 | 2 | 6 | 2 | 4 | 18 | 9 | 0 | 15 | 0 | 1 | 0 | 8 | TET2 |
| 8 | 7 | 14 | 5 | 7 | 1 | 46 | 0 | 25 | 5 | 0 | 2 | 7 | SETD2 |
| 9 | 9 | 12 | 4 | 14 | 0 | 12 | 1 | 28 | 7 | 4 | 0 | 11 | SMARCA4 |
| 27 | 12 | 26 | 5 | 60 | 1 | 19 | 0 | 64 | 3 | 1 | 0 | 24 | KMT2D |
| 10 | 4 | 22 | 9 | 8 | 2 | 6 | 1 | 19 | 9 | 0 | 2 | 25 | CHD4 |
| 9 | 2 | 42 | 2 | 16 | 0 | 7 | 0 | 20 | 1 | 0 | 2 | 5 | NCOR1 |
| 17 | 4 | 9 | 5 | 28 | 1 | 7 | 0 | 18 | 1 | 2 | 1 | 13 | EP300 |
| 1 | 2 | 11 | 1 | 5 | 0 | 27 | 0 | 22 | 6 | 0 | 0 | 7 | KDM5C |
| 6 | 3 | 12 | 5 | 10 | 1 | 8 | 1 | 27 | 7 | 3 | 0 | 5 | ARID2 |
| 3 | 3 | 3 | 1 | 8 | 1 | 5 | 1 | 17 | 1 | 1 | 1 | 7 | ATF7IP |
| 4 | 3 | 9 | 3 | 11 | 8 | 5 | 0 | 15 | 1 | 0 | 0 | 5 | ASXL1 |
| 14 | 5 | 17 | 5 | 12 | 1 | 7 | 0 | 26 | 6 | 1 | 1 | 8 | MLL |
| 7 | 2 | 9 | 3 | 4 | 0 | 3 | 0 | 10 | 1 | 0 | 0 | 9 | BAZ2A |
| 6 | 1 | 9 | 0 | 12 | 0 | 6 | 1 | 16 | 0 | 0 | 2 | 14 | CHD3 |
| 8 | 18 | 12 | 2 | 23 | 2 | 9 | 0 | 35 | 2 | 1 | 2 | 10 | ATRX |
| 6 | 5 | 17 | 1 | 16 | 0 | 5 | 0 | 23 | 1 | 1 | 2 | 9 | ARID1B |
| 4 | 2 | 5 | 1 | 12 | 0 | 7 | 0 | 20 | 3 | 0 | 0 | 10 | MBD1 |
| 5 | 3 | 7 | 0 | 5 | 0 | 43 | 0 | 11 | 3 | 0 | 1 | 5 | BAP1 |
| 10 | 0 | 6 | 2 | 5 | 0 | 4 | 0 | 9 | 1 | 2 | 2 | 3 | INO80 |
| 7 | 3 | 10 | 4 | 10 | 5 | 4 | 0 | 12 | 1 | 0 | 1 | 5 | CHD2 |
| 5 | 3 | 5 | 3 | 2 | 0 | 4 | 0 | 15 | 3 | 0 | 3 | 9 | ARID4A |
| 9 | 2 | 8 | 0 | 10 | 1 | 5 | 0 | 18 | 0 | 2 | 0 | 3 | DOT1L |
| 9 | 2 | 17 | 5 | 7 | 0 | 10 | 0 | 27 | 3 | 0 | 3 | 12 | ASH1L |
| 8 | 7 | 11 | 3 | 7 | 1 | 4 | 0 | 21 | 3 | 0 | 1 | 9 | BPTF |
| 2 | 1 | 0 | 0 | 5 | 0 | 2 | 0 | 5 | 2 | 0 | 1 | 0 | RTF1 |
| 0 | 4 | 8 | 0 | 8 | 0 | 2 | 0 | 10 | 1 | 0 | 0 | 7 | PHC3 |
| 5 | 4 | 9 | 2 | 10 | 2 | 4 | 1 | 21 | 2 | 1 | 0 | 8 | SMARCA2 |
| 2 | 1 | 15 | 4 | 11 | 1 | 7 | 0 | 18 | 3 | 0 | 1 | 12 | SETDB1 |

Figure 4B Cont.

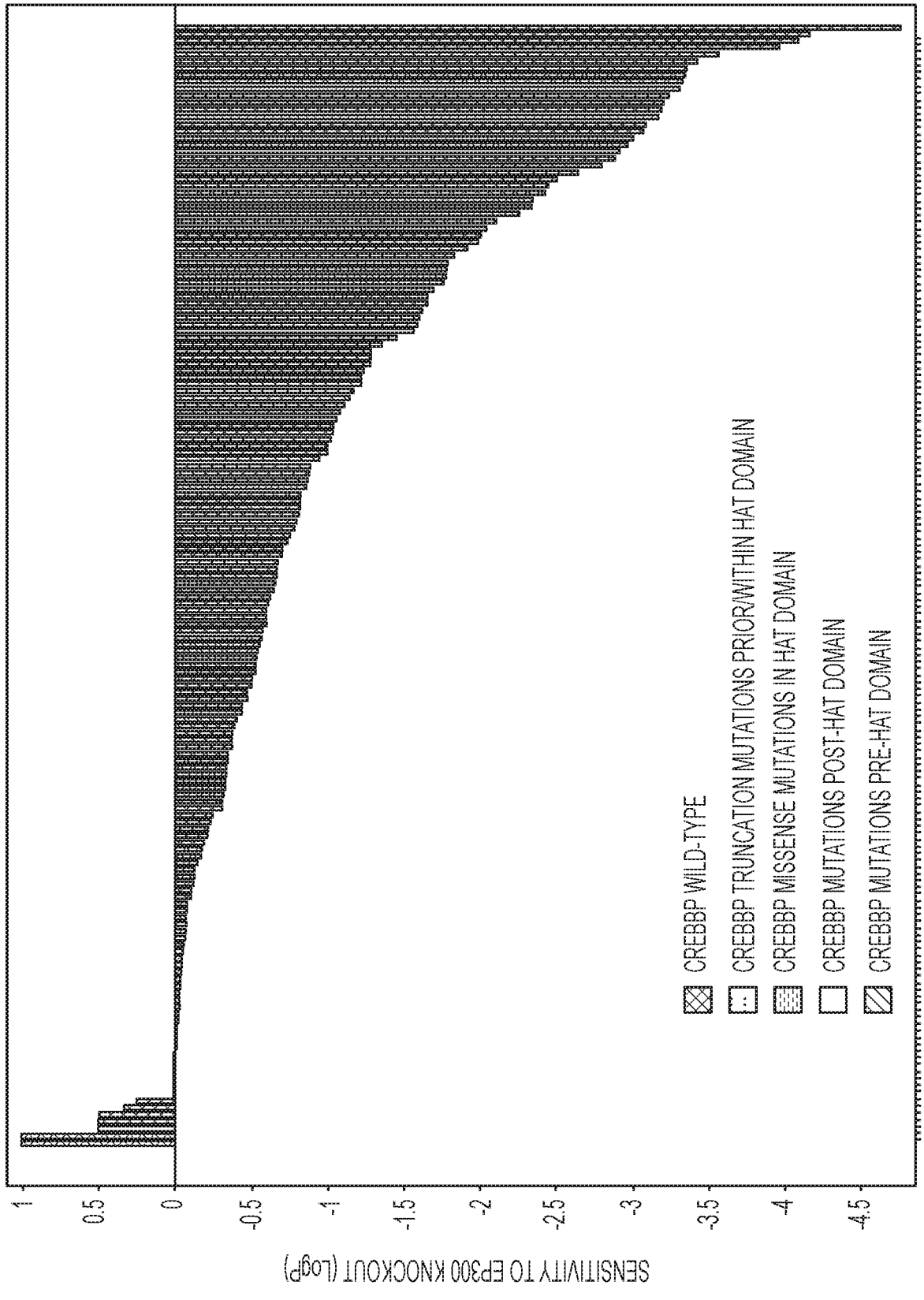

SENSITIVITY TO EP300 KNOCKOUT (LogP)
1
0.5
0
-0.5
-1
-1.5
-2
-2.5
-3
-3.5
-4
-4.5
CREBBP WILD-TYPE
CREBBP TRUNCATION MUTATIONS PRIOR/WITHIN HAT DOMAIN
CREBBP MISSENSE MUTATIONS IN HAT DOMAIN
CREBBP MUTATIONS POST-HAT DOMAIN
CREBBP MUTATIONS PRE-HAT DOMAIN

Figure 5

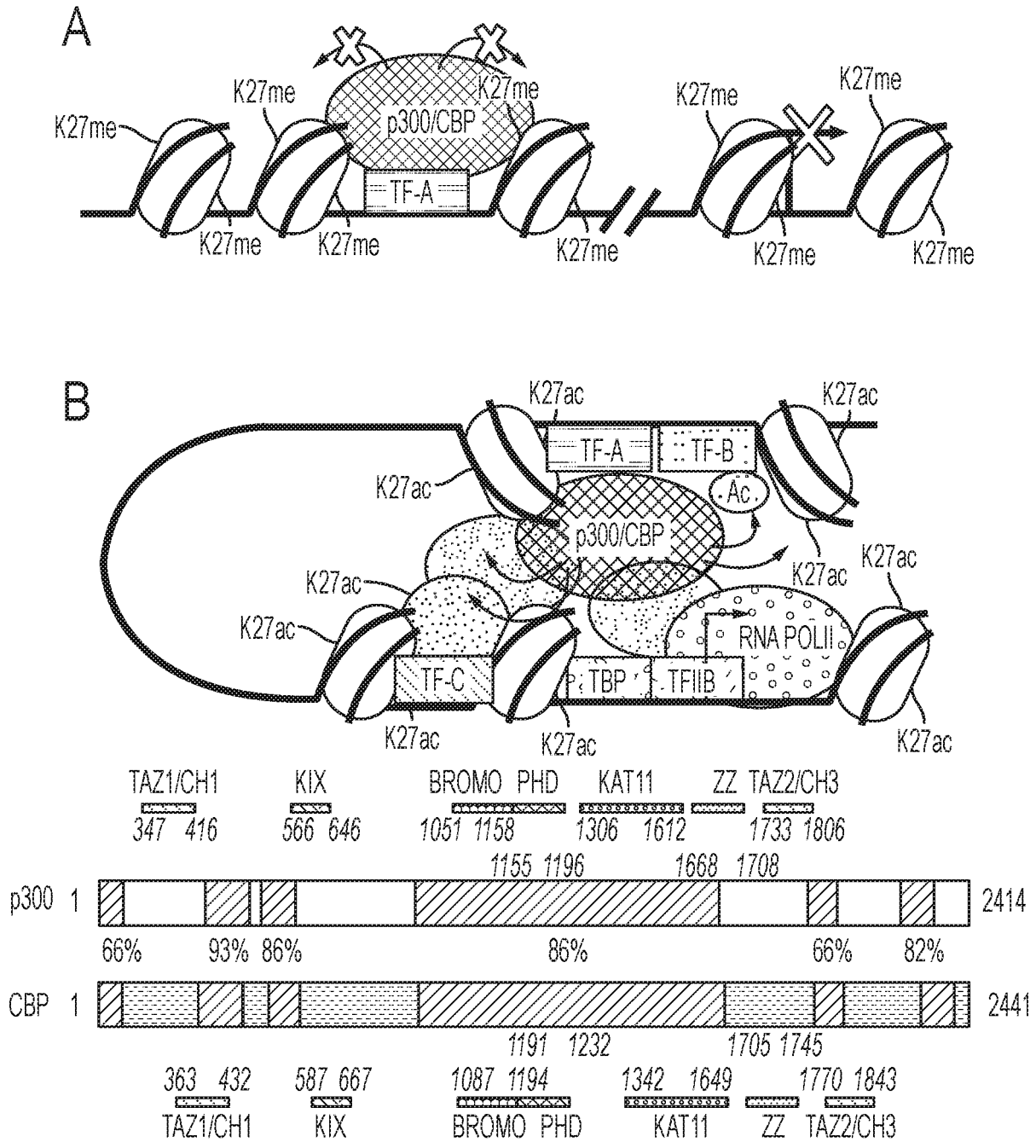

A
K27me
p300/CBP
TF-A
B
K27ac
TF-A
TF-B
Ac
p300/CBP
RNA POLII
TF-C
TBP
TFIIB
TAZ1/CH1
KIX
BROMO PHD
KAT11
ZZ TAZ2/CH3
347 416
566 646
1051 1158
1306 1612
1733 1806
1155 1196
1668 1708
p300 1
2414
66%
93%
86%
86%
66%
82%
CBP 1
2441
1191 1232
1705 1745
363 432
587 667
1087 1194
1342 1649
1770 1843
TAZ1/CH1
KIX
BROMO PHD
KAT11
ZZ
TAZ2/CH3

Figure 6

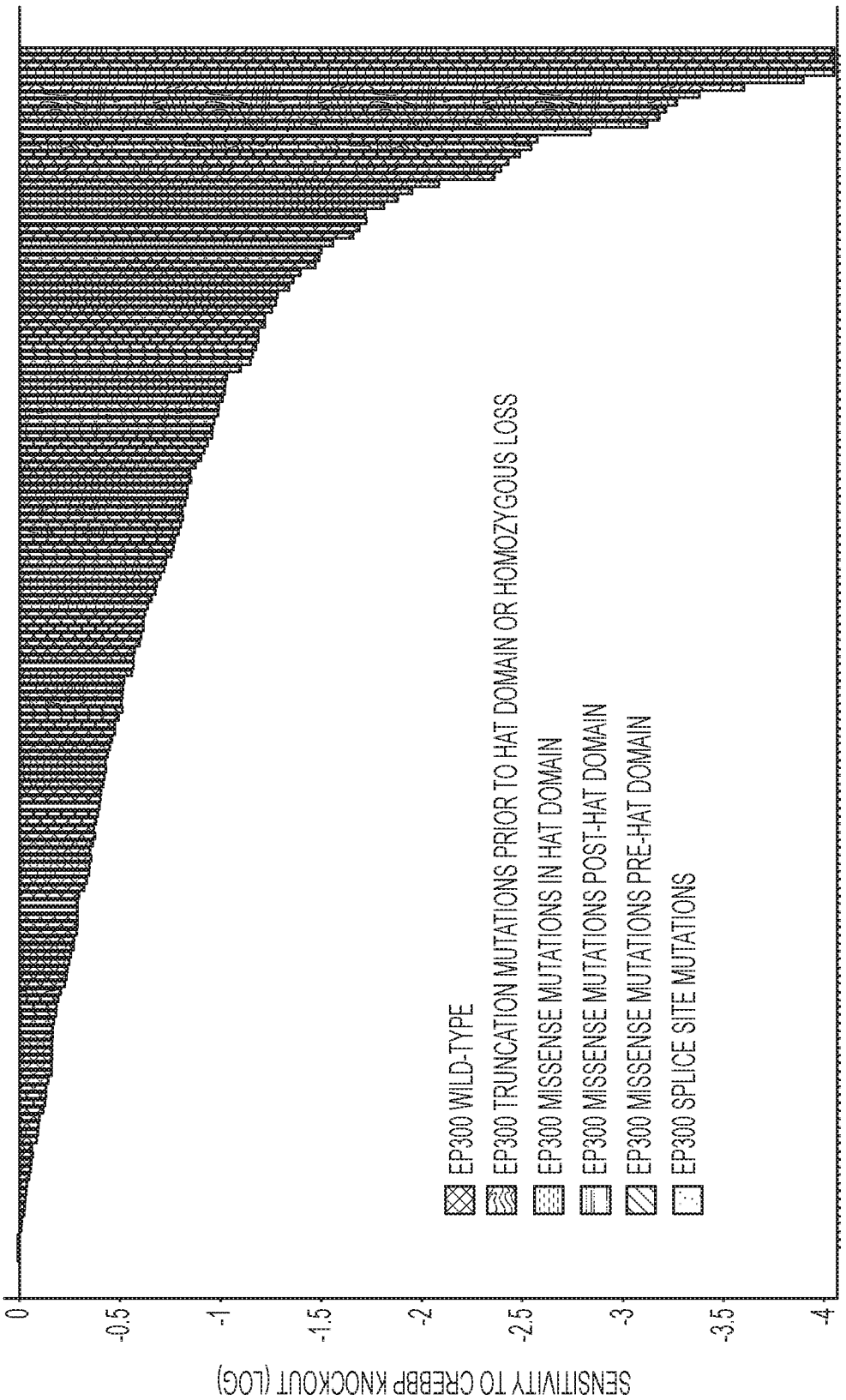

SENSITIVITY TO CREBBP KNOCKOUT (LOG)
0
-0.5
-1
-1.5
-2
-2.5
-3
-3.5
-4
EP300 WILD-TYPE
EP300 TRUNCATION MUTATIONS PRIOR TO HAT DOMAIN OR HOMOZYGOUS LOSS
EP300 MISSENSE MUTATIONS IN HAT DOMAIN
EP300 MISSENSE MUTATIONS POST-HAT DOMAIN
EP300 MISSENSE MUTATIONS PRE-HAT DOMAIN
EP300 SPLICE SITE MUTATIONS

Figure 7A

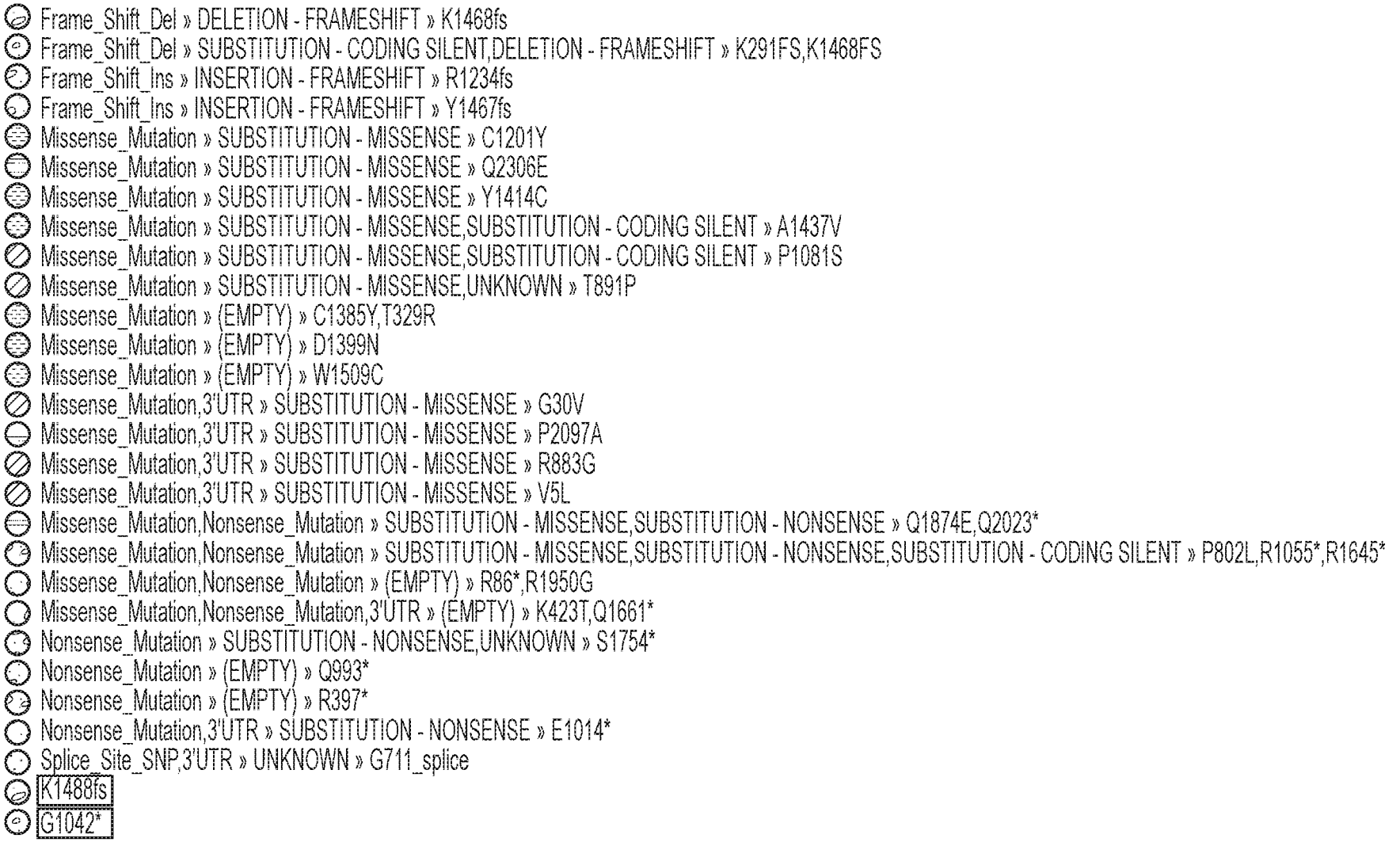



Figure 7A Cont.

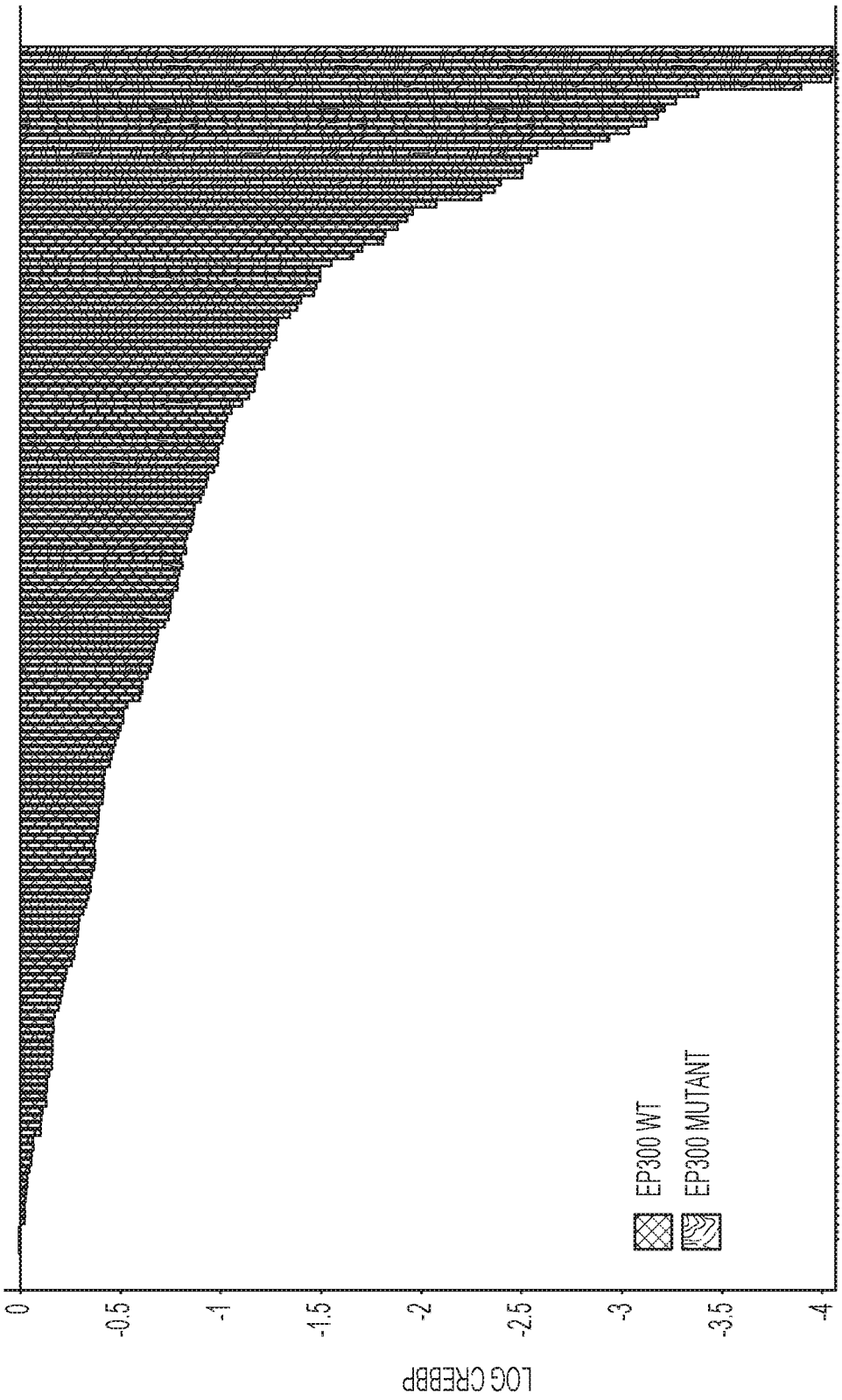
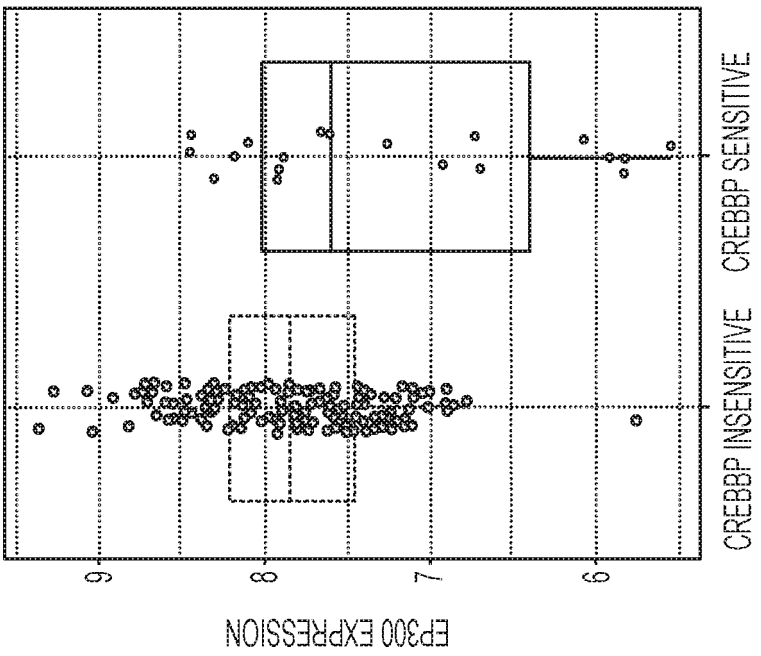
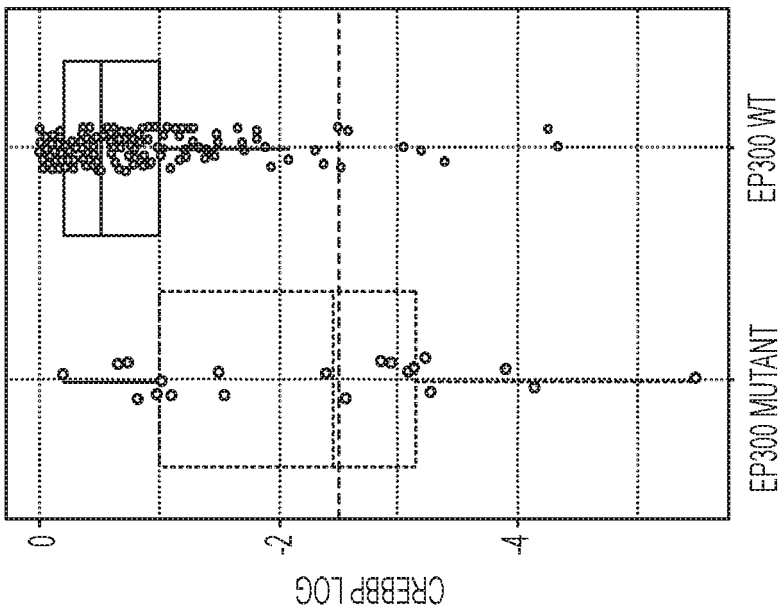



Figure 7B




| P-VALUE | ADJ. P-VALUE |
|---|---|
| 2.910e-5 | 7.950e-2 |




| P-VALUE | ADJ. P-VALUE |
|---|---|
| 3.449e-6 | 5.197e-3 |

Figure 7C

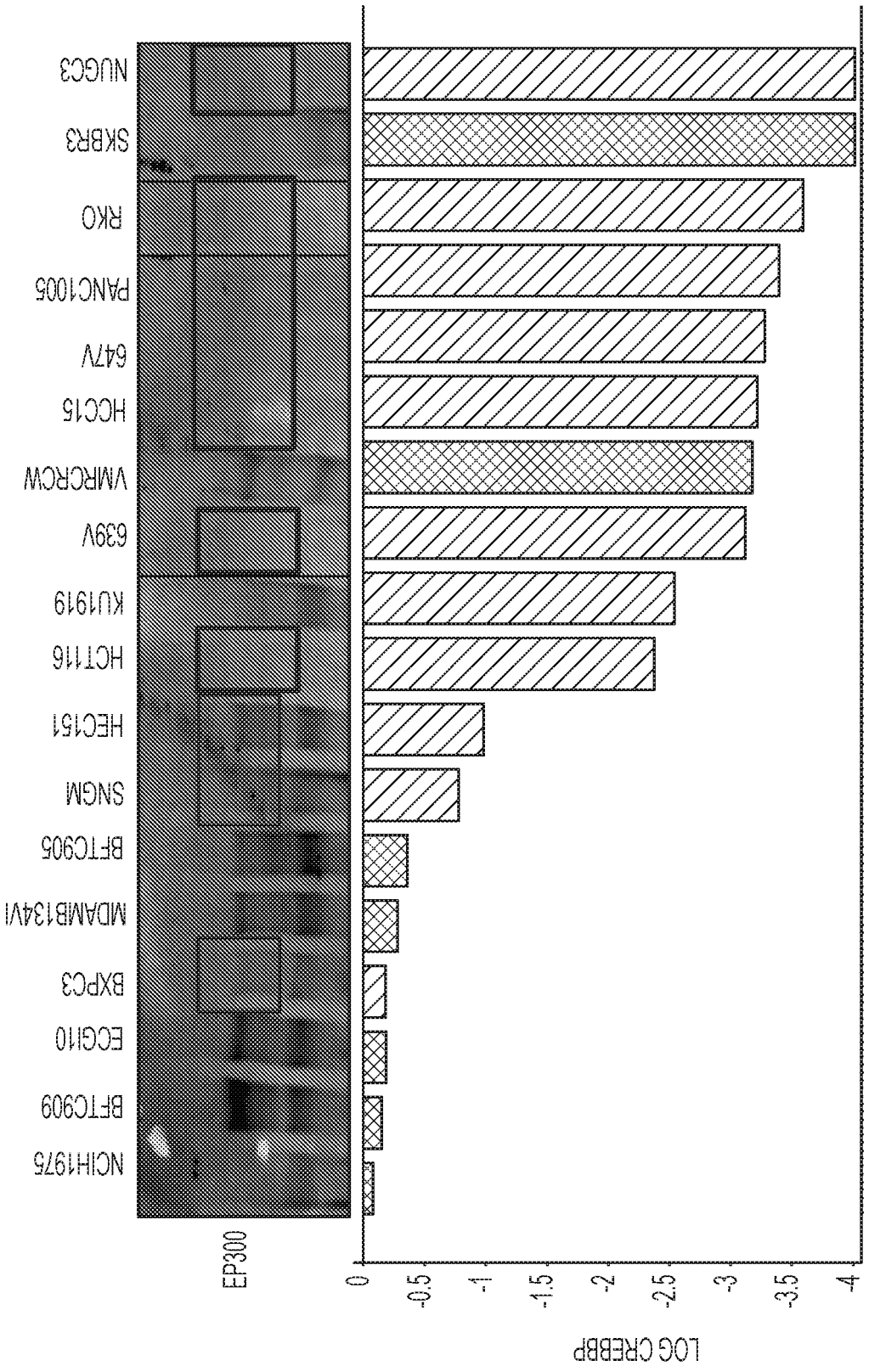

EP300
NCIH1975
BFTC909
ECGI10
BXPC3
MDAMB134VI
BFTC905
SNGM
HEC151
HCT116
KU1919
639V
VMRCRCW
HCC15
647V
PANC1005
RKO
SKBR3
NUGC3
0
-0.5
-1
-1.5
-2
-2.5
-3
-3.5
-4
LOG CREBBP

Figure 8