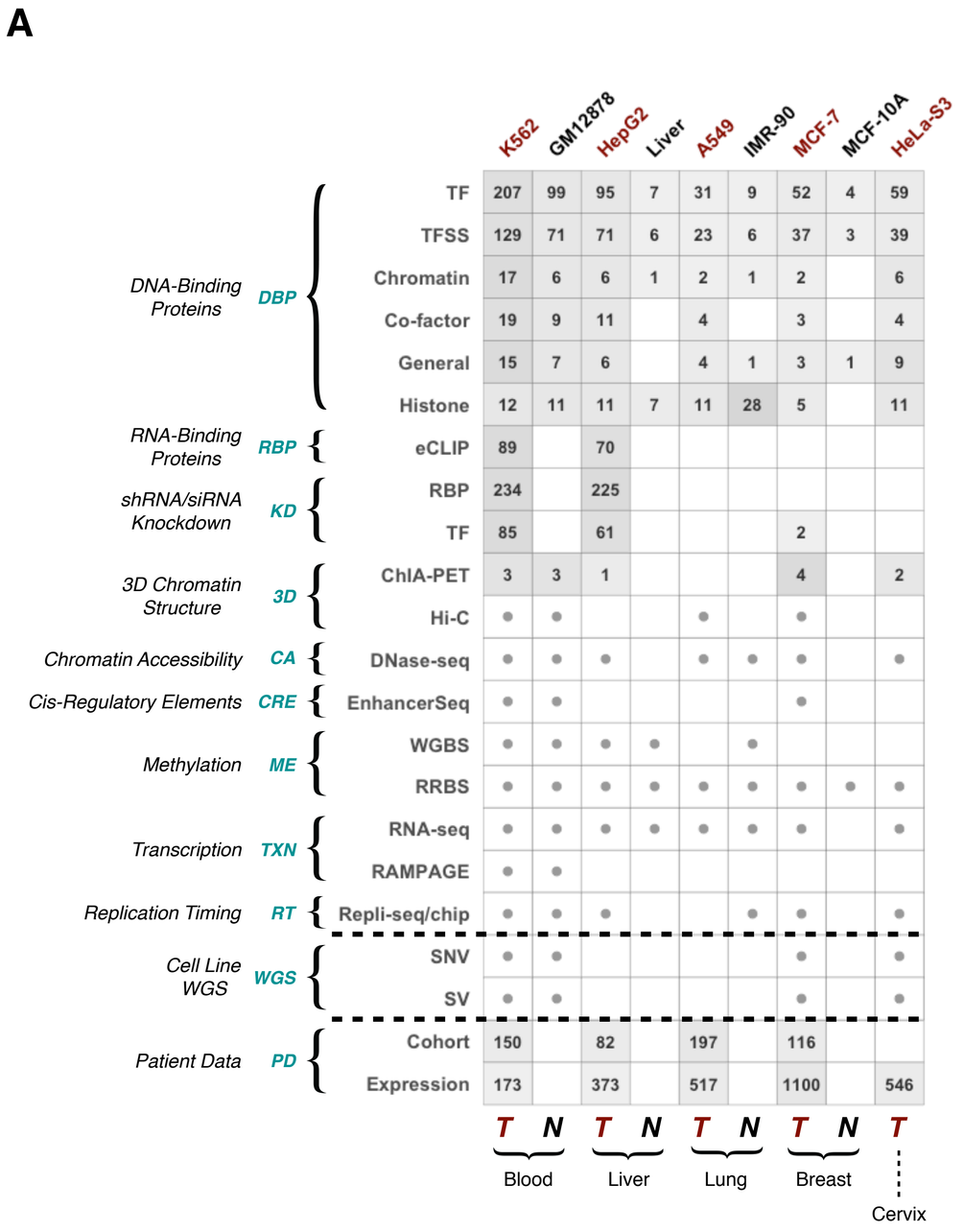
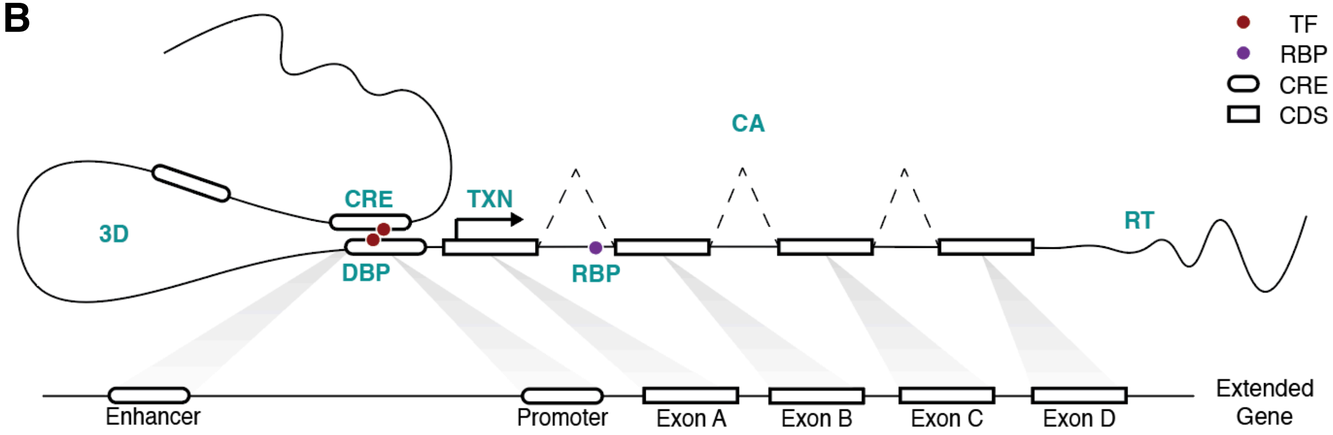
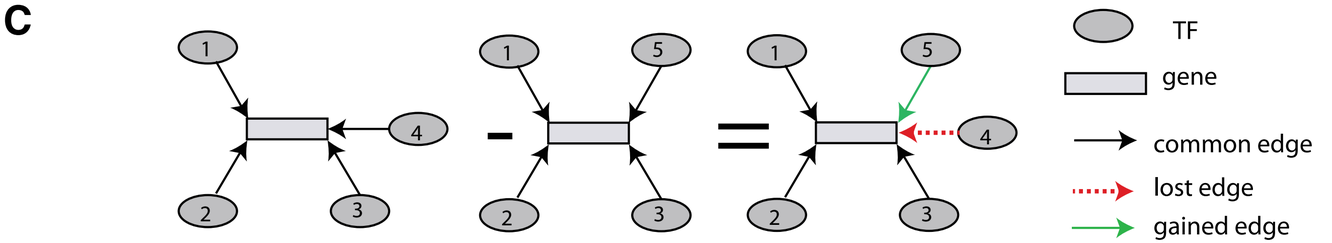
MAIN FIGURES


A
K562
GM12878
HepG2
Liver
A549
IMR-90
MCF-7
MCF-10A
HeLa-S3
DNA-Binding Proteins
DBP
TF 207 99 95 7 31 9 52 4 59
TFSS 129 71 71 6 23 6 37 3 39
Chromatin 17 6 6 1 2 1 2 6
Co-factor 19 9 11 4 3 4
General 15 7 6 4 1 3 1 9
Histone 12 11 11 7 11 28 5 11
RNA-Binding Proteins
RBP
eCLIP 89 70
shRNA/siRNA Knockdown
KD
RBP 234 225
TF 85 61 2
3D Chromatin Structure
3D
ChIA-PET 3 3 1 4 2
Hi-C
Chromatin Accessibility
CA
DNase-seq
Cis-Regulatory Elements
CRE
EnhancerSeq
Methylation
ME
WGBS
RRBS
Transcription
TXN
RNA-seq
RAMPAGE
Replication Timing
RT
Repli-seq/chip
Cell Line WGS
WGS
SNV
SV
Patient Data
PD
Cohort 150 82 197 116
Expression 173 373 517 1100 546
T N T N T N T N T
Blood
Liver
Lung
Breast
Cervix


B
TF
RBP
CRE
CDS
CA
3D
CRE
TXN
RT
DBP
RBP
Enhancer
Promoter
Exon A
Exon B
Exon C
Exon D
Extended Gene


C
1
2
3
4
5
TF
gene
common edge
lost edge
gained edge

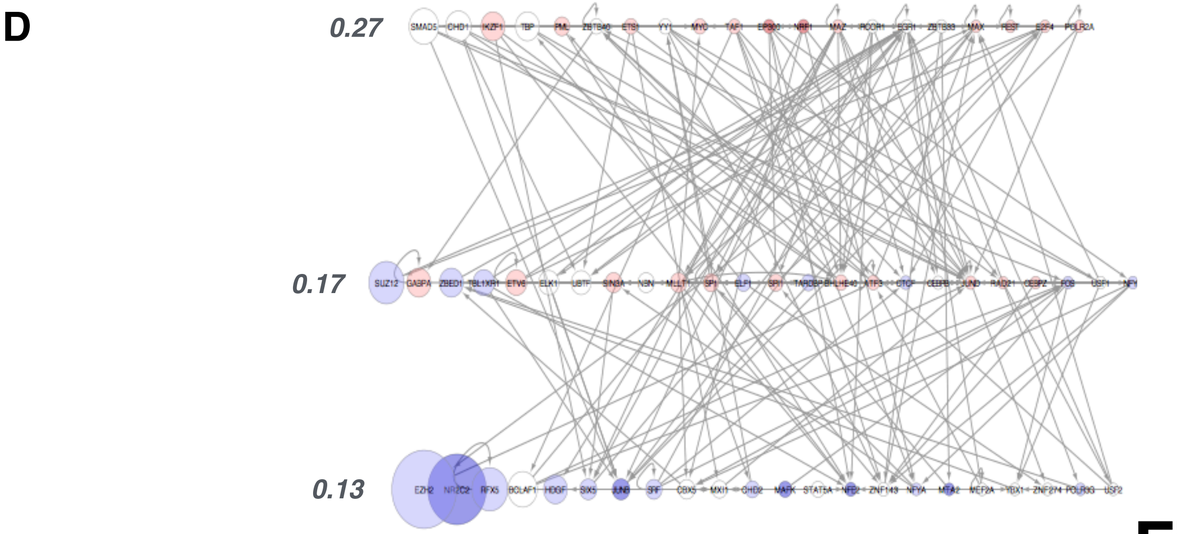

D
0.27
0.17
0.13

Figure 1

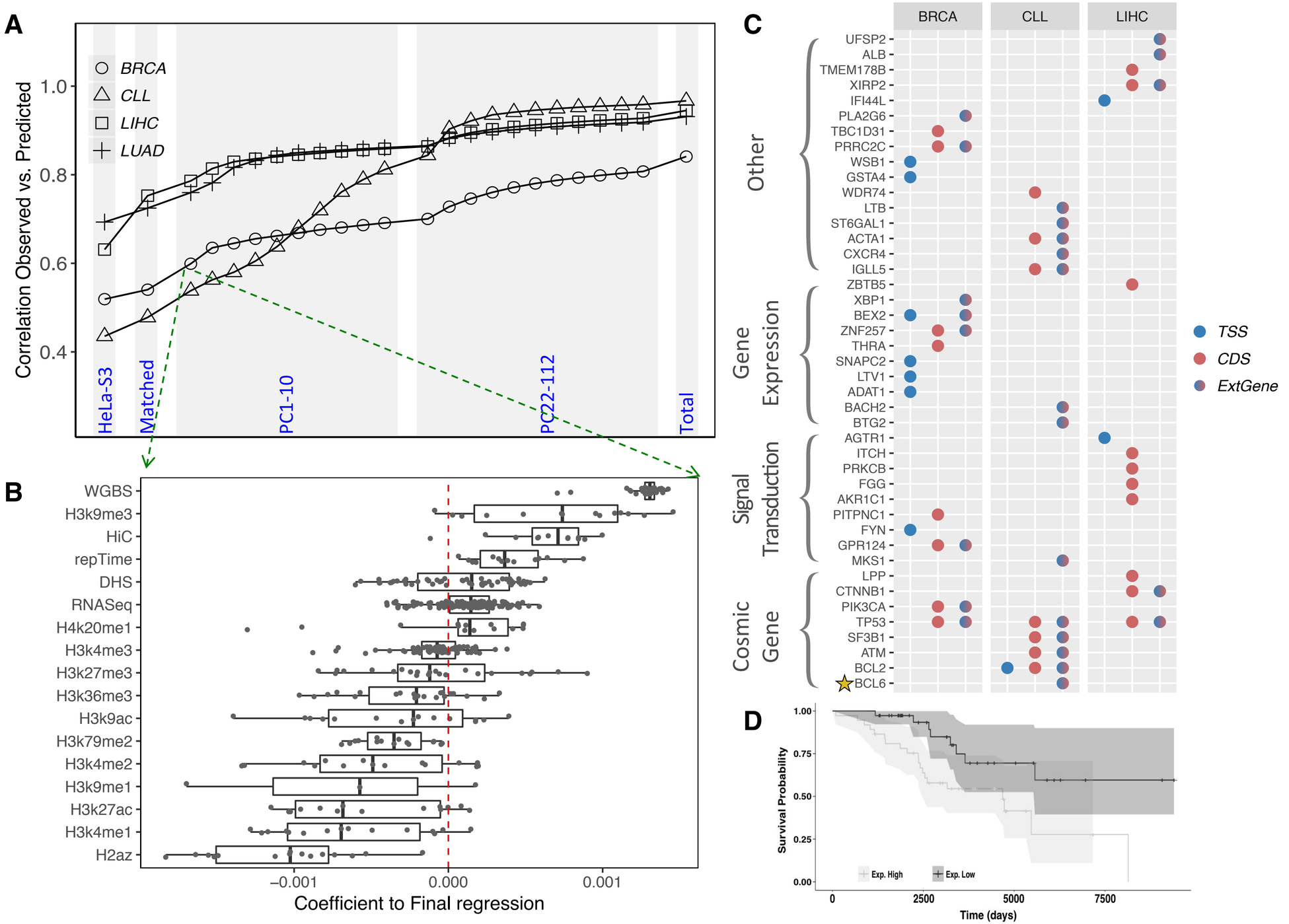

A
Correlation Observed vs. Predicted
1.0
0.8
0.6
0.4
BRCA
CLL
LIHC
LUAD
HeLa-S3
Matched
PC1-10
PC22-112
Total
B
WGBS
H3k9me3
HiC
repTime
DHS
RNASeq
H4k20me1
H3k4me3
H3k27me3
H3k36me3
H3k9ac
H3k79me2
H3k4me2
H3k9me1
H3k27ac
H3k4me1
H2az
−0.001
0.000
0.001
Coefficient to Final regression
C
BRCA
CLL
LIHC
Other
UFSP2
ALB
TMEM178B
XIRP2
IFI44L
PLA2G6
TBC1D31
PRRC2C
WSB1
GSTA4
WDR74
LTB
ST6GAL1
ACTA1
CXCR4
IGLL5
Gene Expression
ZBTB5
XBP1
BEX2
ZNF257
THRA
SNAPC2
LTV1
ADAT1
BACH2
BTG2
Signal Transduction
AGTR1
ITCH
PRKCB
FGG
AKR1C1
PITPNC1
FYN
GPR124
MKS1
Cosmic Gene
LPP
CTNNB1
PIK3CA
TP53
SF3B1
ATM
BCL2
BCL6
TSS
CDS
ExtGene
D
Survival Probability
1.00
0.75
0.50
0.25
0.00
Exp. High
Exp. Low
0
2500
5000
7500
Time (days)

Figure 2

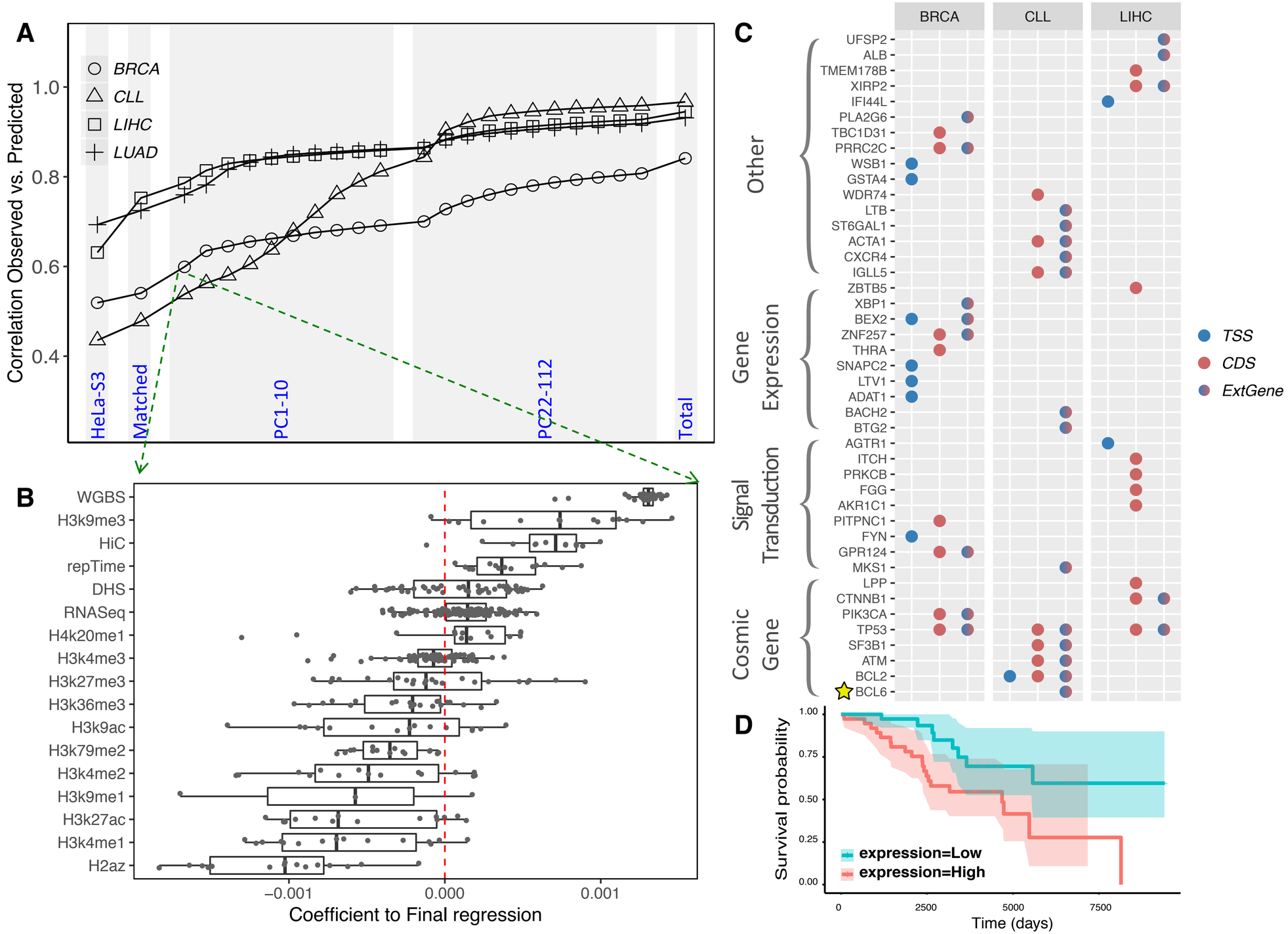

A
Correlation Observed vs. Predicted
1.0
0.8
0.6
0.4
BRCA
CLL
LIHC
LUAD
HeLa-S3
Matched
PC1-10
PC22-112
Total
B
WGBS
H3k9me3
HiC
repTime
DHS
RNASeq
H4k20me1
H3k4me3
H3k27me3
H3k36me3
H3k9ac
H3k79me2
H3k4me2
H3k9me1
H3k27ac
H3k4me1
H2az
−0.001
0.000
0.001
Coefficient to Final regression
C
BRCA
CLL
LIHC
Other
UFSP2
ALB
TMEM178B
XIRP2
IFI44L
PLA2G6
TBC1D31
PRRC2C
WSB1
GSTA4
WDR74
LTB
ST6GAL1
ACTA1
CXCR4
IGLL5
Gene Expression
ZBTB5
XBP1
BEX2
ZNF257
THRA
SNAPC2
LTV1
ADAT1
BACH2
BTG2
Signal Transduction
AGTR1
ITCH
PRKCB
FGG
AKR1C1
PITPNC1
FYN
GPR124
MKS1
Cosmic Gene
LPP
CTNNB1
PIK3CA
TP53
SF3B1
ATM
BCL2
BCL6
TSS
CDS
ExtGene
D
Survival probability
1.00
0.75
0.50
0.25
0.00
expression=Low
expression=High
0
2500
5000
7500
Time (days)

Figure 2

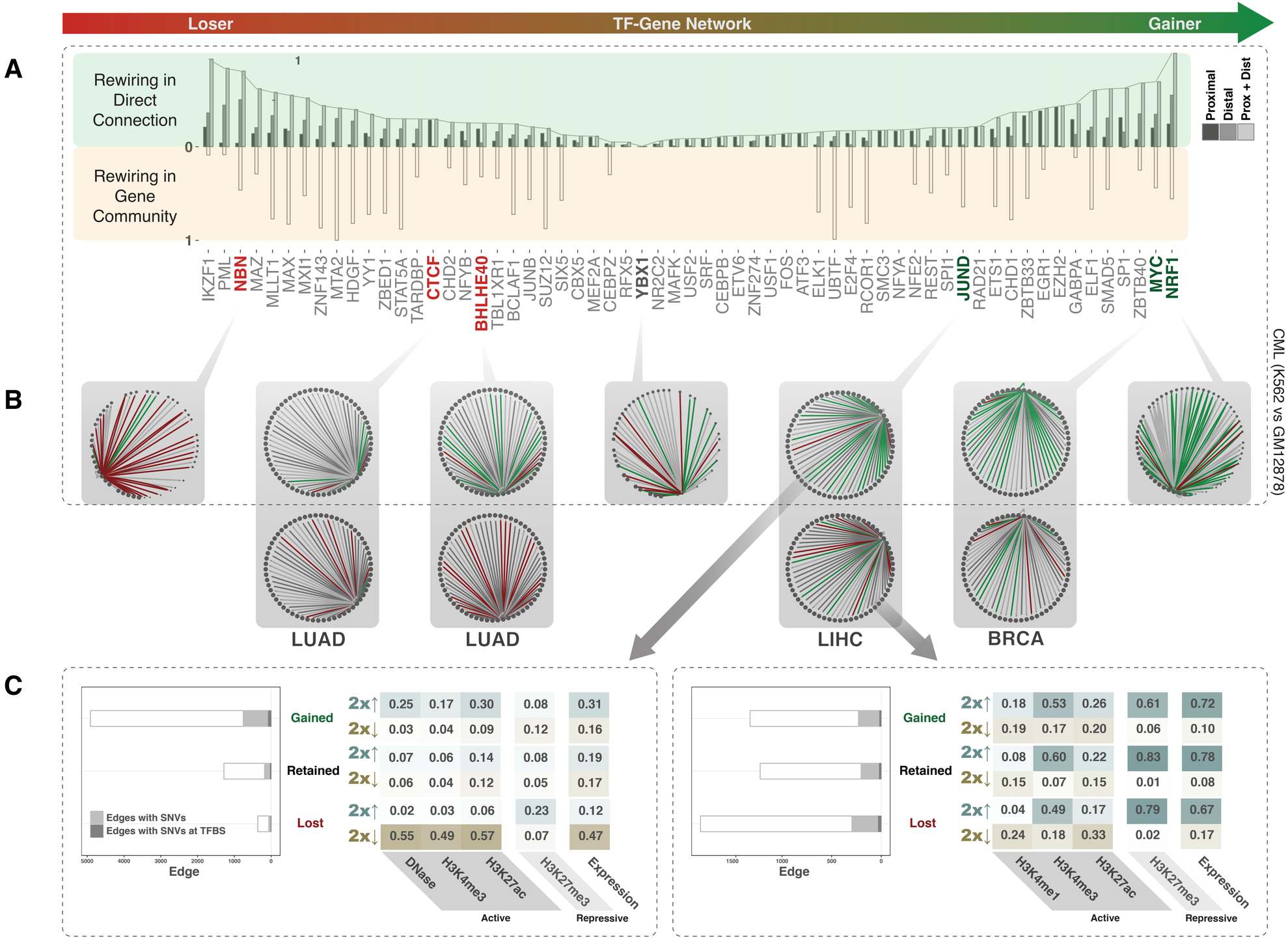

Loser
TF-Gene Network
Gainer
A
Rewiring in Direct Connection
Rewiring in Gene Community
1
0
1
Proximal
Distal
Prox + Dist
IKZF1 PML NBN MAZ MLLT1 MAX MXI1 ZNF143 MTA2 HDGF YY1 ZBED1 STAT5A TARDBP CTCF CHD2 NFYB BHLHE40 TBL1XR1 BCLAF1 JUNB SUZ12 SIX5 CBX5 MEF2A CEBPZ RFX5 YBX1 NR2C2 MAFK USF2 SRF CEBPB ETV6 ZNF274 USF1 FOS ATF3 ELK1 UBTF E2F4 RCOR1 SMC3 NFYA NFE2 REST SPI1 JUND RAD21 ETS1 CHD1 ZBTB33 EGR1 EZH2 GABPA ELF1 SMAD5 SP1 ZBTB40 MYC NRF1
CML (K562 vs GM12878)
B
LUAD
LUAD
LIHC
BRCA
C
Edges with SNVs
Edges with SNVs at TFBS
5000 4000 3000 2000 1000 0
Edge
Gained
Retained
Lost
2x↑ 0.25 0.17 0.30 0.08 0.31
2x↓ 0.03 0.04 0.09 0.12 0.16
2x↑ 0.07 0.06 0.14 0.08 0.19
2x↓ 0.06 0.04 0.12 0.05 0.17
2x↑ 0.02 0.03 0.06 0.23 0.12
2x↓ 0.55 0.49 0.57 0.07 0.47
DNase H3K4me3 H3K27ac H3K27me3 Expression
Active
Repressive
1500 1000 500 0
Edge
Gained
Retained
Lost
2x↑ 0.18 0.53 0.26 0.61 0.72
2x↓ 0.19 0.17 0.20 0.06 0.10
2x↑ 0.08 0.60 0.22 0.83 0.78
2x↓ 0.15 0.07 0.15 0.01 0.08
2x↑ 0.04 0.49 0.17 0.79 0.67
2x↓ 0.24 0.18 0.33 0.02 0.17
H3K4me1 H3K4me3 H3K27ac H3K27me3 Expression
Active
Repressive

Figure 3

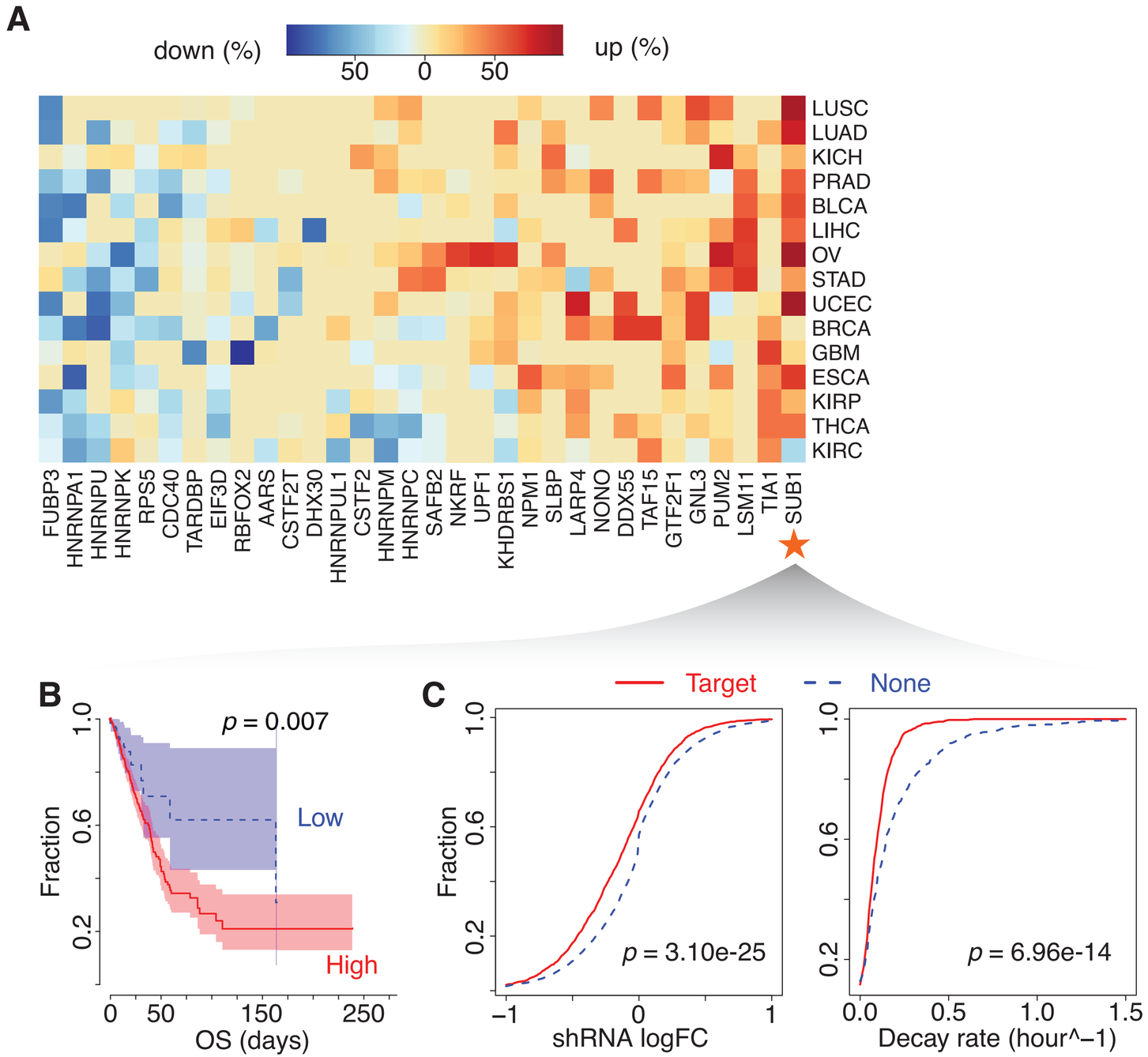

A
down (%)
50
0
50
up (%)
LUSC
LUAD
KICH
PRAD
BLCA
LIHC
OV
STAD
UCEC
BRCA
GBM
ESCA
KIRP
THCA
KIRC
FUBP3
HNRNPA1
HNRNPU
HNRNPK
RPS5
CDC40
TARDBP
EIF3D
RBFOX2
AARS
CSTF2T
DHX30
HNRNPUL1
CSTF2
HNRNPM
HNRNPC
SAFB2
NKRF
UPF1
KHDRBS1
NPM1
SLBP
LARP4
NONO
DDX55
TAF15
GTF2F1
GNL3
PUM2
LSM11
TIA1
SUB1
B
p = 0.007
Low
High
Fraction
1.0
0.6
0.2
0
50
150
250
OS (days)
C
Target
None
Fraction
1.0
0.6
0.2
p = 3.10e-25
−1
0
1
shRNA logFC
1.0
0.6
0.2
p = 6.96e-14
0.0
0.5
1.0
1.5
Decay rate (hour^−1)
D
LUSC
LUAD
PRAD
KICH
LIHC
UCEC
BRCA
BLCA
HNSC
THCA
CHOL
KIRP
KIRC
STAD
ESCA
GBM
OV
RAD21
NR2F2
YY1
FOXK2
FOXJ2
ESRRA
HMBOX1
RFX1
GLIS2
HLF
TEAD4
CHAMP1
ATF3
MYNN
ZBTB20
TRIM28
HNF4G
BHLHE40
PRDM1
SMARCA4
RFX3
CHD7
CBX5
NR3C1
JUN
CBX1
MLLT1
GATA3
SPI1
CHD1
STAT3
ZBTB33
ETV4
ZNF687
MXI1
ETV1
NRF1
CTBP2
SP1
ZZZ3
SAP130
KDM5A
E2F4
ZNF623
TAF1
HBP1
CTCF
TFDP1
ZNF121
PAF1
STAT2
IKZF1
REST
E2F1
ELF1
MYC

Figure 4

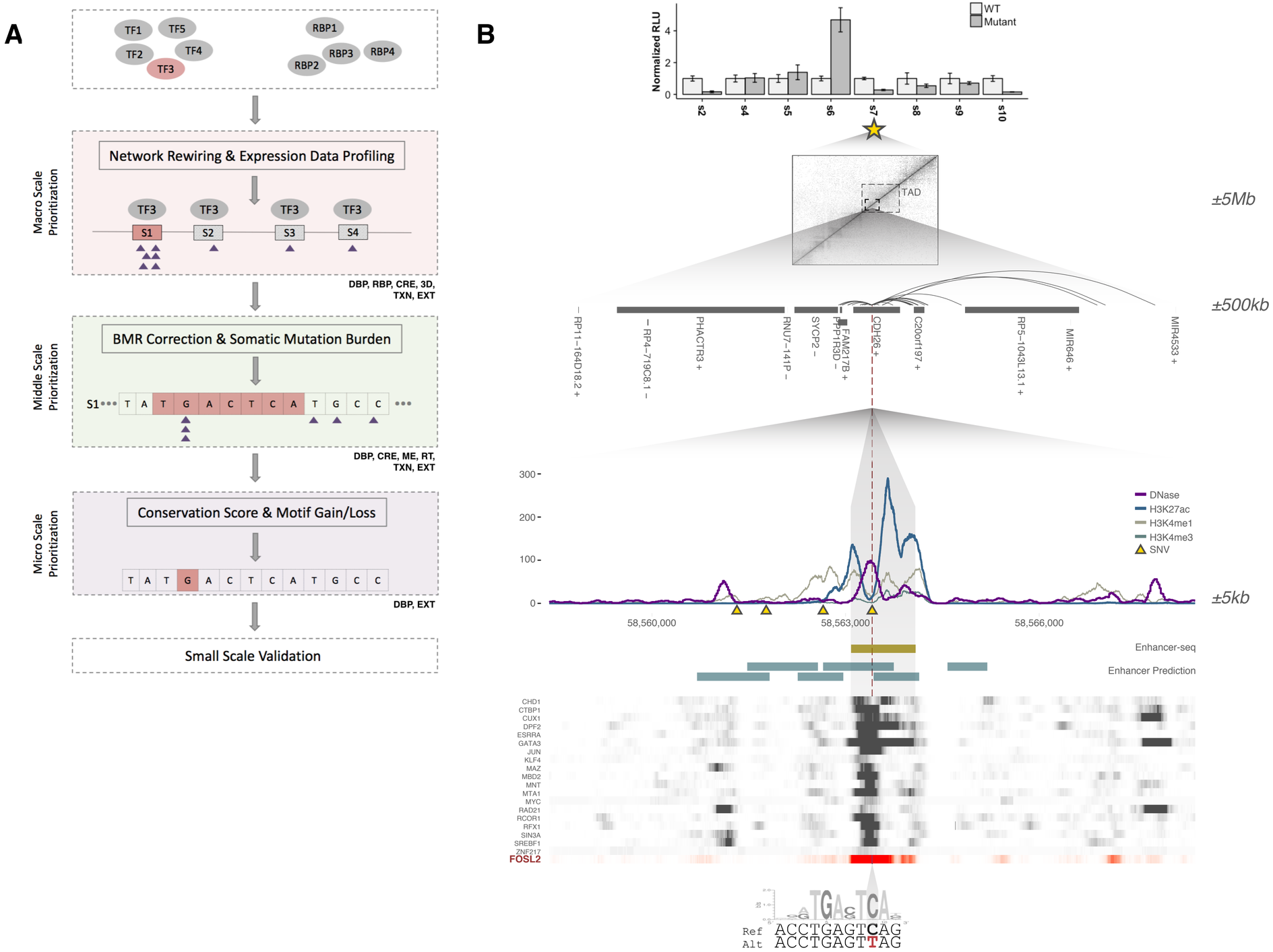

A
TF1
TF5
TF2
TF4
TF3
RBP1
RBP3
RBP4
RBP2
Macro Scale Prioritization
Network Rewiring & Expression Data Profiling
TF3
TF3
TF3
TF3
S1
S2
S3
S4
DBP, RBP, CRE, 3D, TXN, EXT
Middle Scale Prioritization
BMR Correction & Somatic Mutation Burden
S1
T A T G A C T C A T G C C
DBP, CRE, ME, RT, TXN, EXT
Micro Scale Prioritization
Conservation Score & Motif Gain/Loss
T A T G A C T C A T G C C
DBP, EXT
Small Scale Validation
B
Normalized RLU
WT
Mutant
s2
s4
s5
s6
s7
s8
s9
s10
TAD
±5Mb
±500kb
RP11−164D18.2 +
RP4−719C8.1 −
PHACTR3 +
RNU7−141P −
SYCP2 −
PPP1R3D −
FAM217B +
CDH26 +
C20orf197 +
RP5−1043L13.1 +
MIR646 +
MIR4533 +
300
200
100
0
DNase
H3K27ac
H3K4me1
H3K4me3
SNV
±5kb
58,560,000
58,563,000
58,566,000
Enhancer-seq
Enhancer Prediction
CHD1
CTBP1
CUX1
DPF2
ESRRA
GATA3
JUN
KLF4
MAZ
MBD2
MNT
MTA1
MYC
RAD21
RCOR1
RFX1
SIN3A
SREBF1
ZNF217
FOSL2
Ref ACCTGAGTCAG
Alt ACCTGAGTTAG

Figure 5