Figure 1

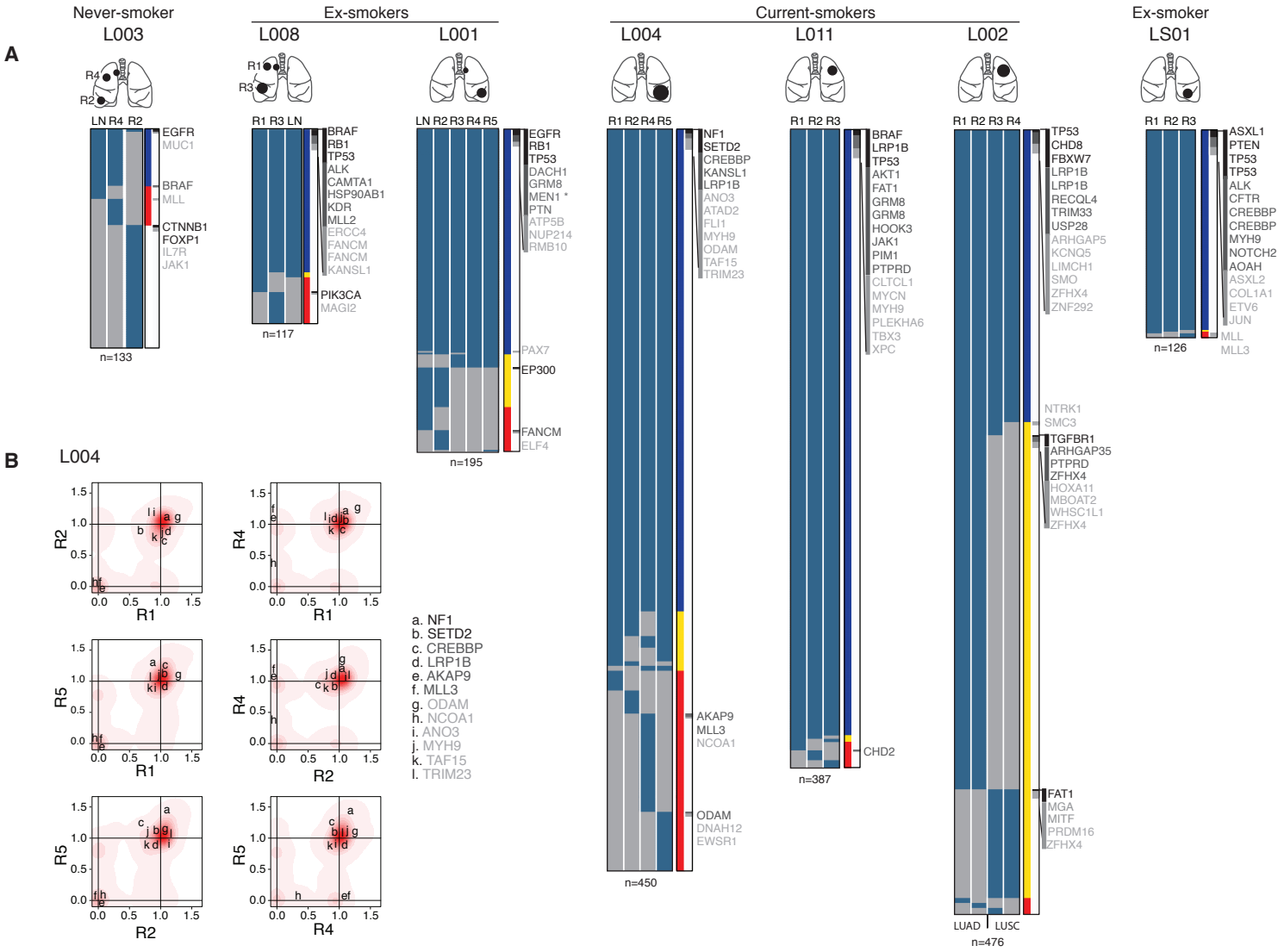

A
Never-smoker
Ex-smokers
Current-smokers
Ex-smoker
L003
L008
L001
L004
L011
L002
LS01
R4
R2
R1
R3
LN R4 R2
EGFR
MUC1
BRAF
MLL
CTNNB1
FOXP1
IL7R
JAK1
n=133
R1 R3 LN
BRAF
RB1
TP53
ALK
CAMTA1
HSP90AB1
KDR
MLL2
ERCC4
FANCM
FANCM
KANSL1
PIK3CA
MAGI2
n=117
LN R2 R3 R4 R5
EGFR
RB1
TP53
DACH1
GRM8
MEN1 *
PTN
ATP5B
NUP214
RMB10
PAX7
EP300
FANCM
ELF4
n=195
R1 R2 R4 R5
NF1
SETD2
CREBBP
KANSL1
LRP1B
ANO3
ATAD2
FLI1
MYH9
ODAM
TAF15
TRIM23
AKAP9
MLL3
NCOA1
ODAM
DNAH12
EWSR1
n=450
R1 R2 R3
BRAF
LRP1B
TP53
AKT1
FAT1
GRM8
GRM8
HOOK3
JAK1
PIM1
PTPRD
CLTCL1
MYCN
MYH9
PLEKHA6
TBX3
XPC
CHD2
n=387
R1 R2 R3 R4
TP53
CHD8
FBXW7
LRP1B
LRP1B
RECQL4
TRIM33
USP28
ARHGAP5
KCNQ5
LIMCH1
SMO
ZFHX4
ZNF292
NTRK1
SMC3
TGFBR1
ARHGAP35
PTPRD
ZFHX4
HOXA11
MBOAT2
WHSC1L1
ZFHX4
FAT1
MGA
MITF
PRDM16
ZFHX4
LUAD
LUSC
n=476
R1 R2 R3
ASXL1
PTEN
TP53
TP53
ALK
CFTR
CREBBP
CREBBP
MYH9
NOTCH2
AOAH
ASXL2
COL1A1
ETV6
JUN
MLL
MLL3
n=126
B
L004
R2
R1
R4
R5
a. NF1
b. SETD2
c. CREBBP
d. LRP1B
e. AKAP9
f. MLL3
g. ODAM
h. NCOA1
i. ANO3
j. MYH9
k. TAF15
l. TRIM23

Figure 2

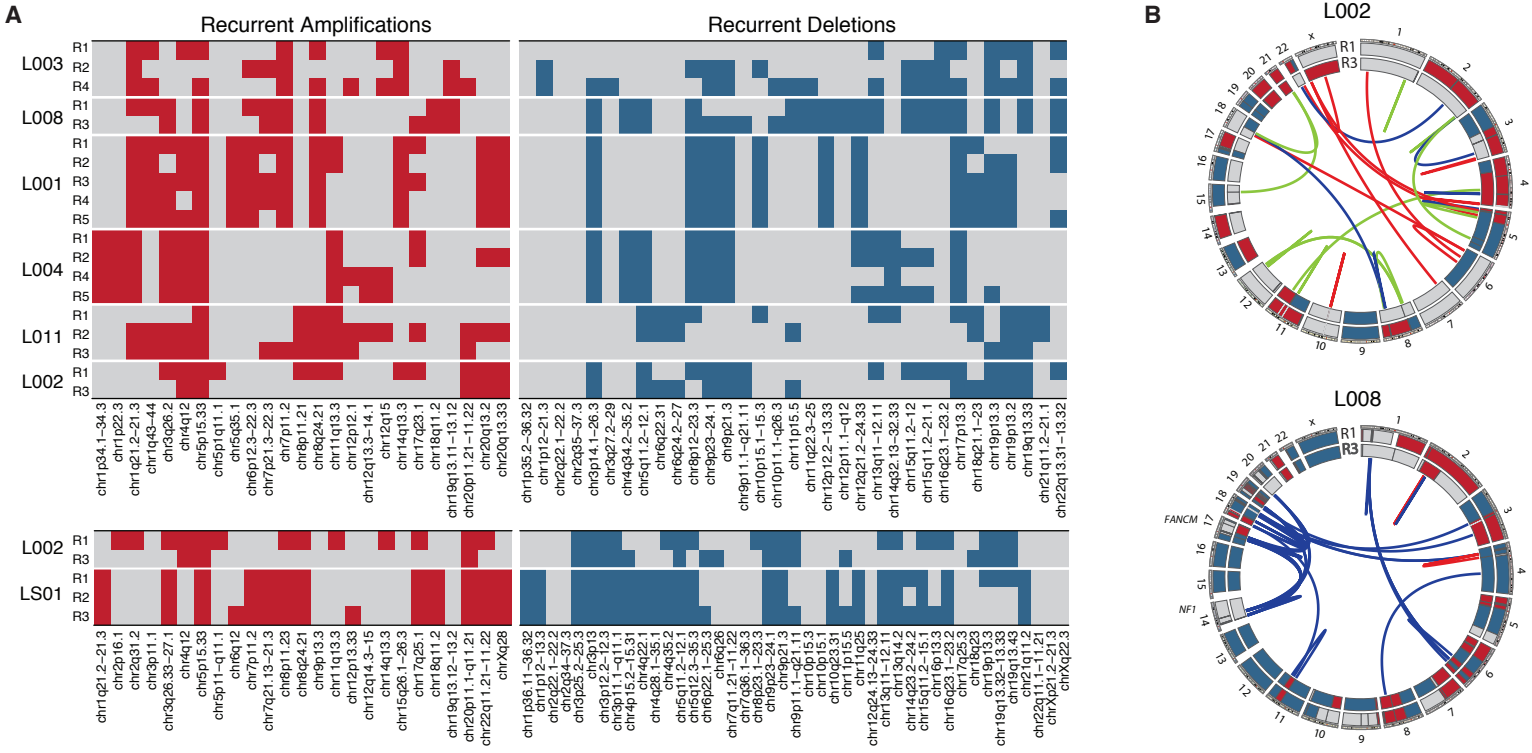

A
Recurrent Amplifications
Recurrent Deletions
L003
L008
L001
L004
L011
L002
LS01
R1
R2
R3
R4
R5
B
L002
L008
R1
R3
FANCM
NF1

Figure 3

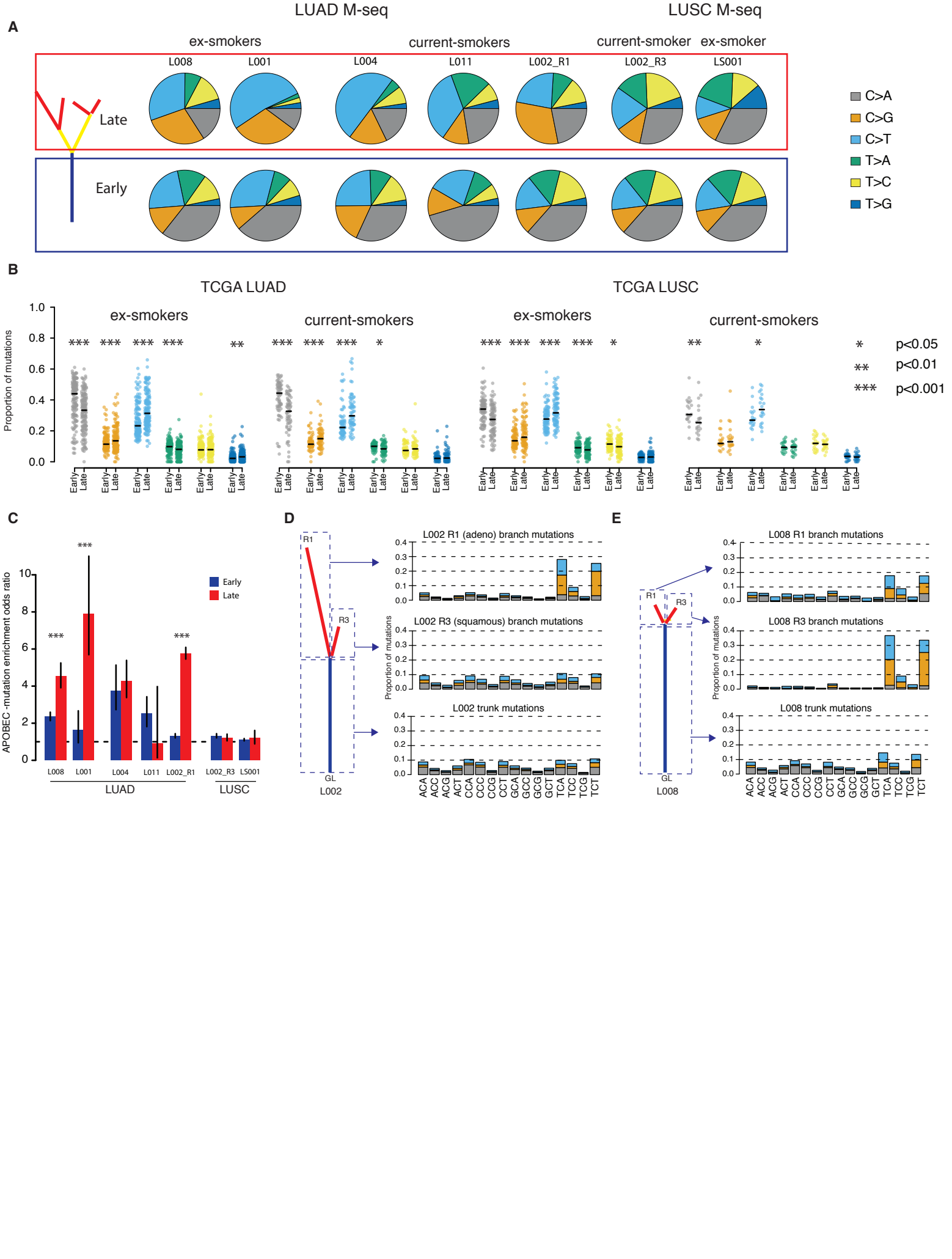
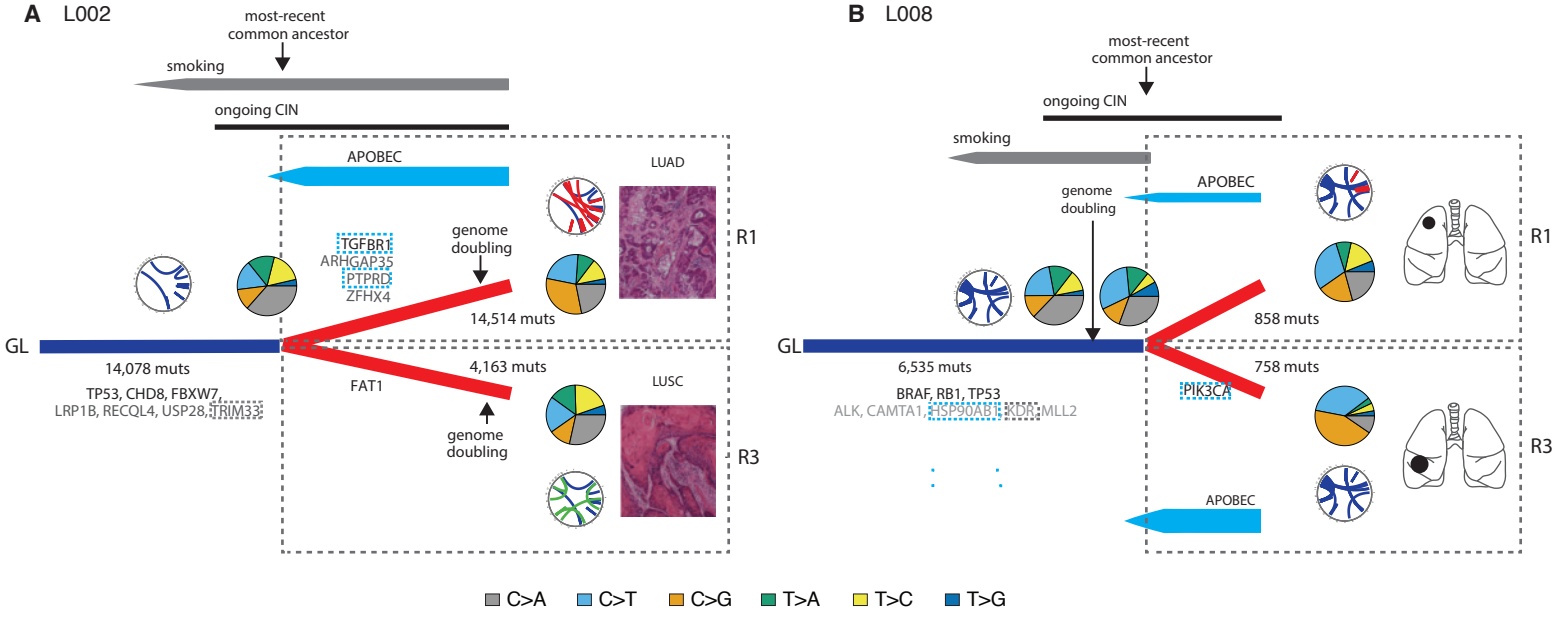

A
LUAD M-seq
LUSC M-seq
ex-smokers
current-smokers
current-smoker
ex-smoker
L008
L001
L004
L011
L002_R1
L002_R3
LS001
Late
Early
C>A
C>G
C>T
T>A
T>C
T>G
B
TCGA LUAD
TCGA LUSC
ex-smokers
current-smokers
Proportion of mutations
p<0.05
p<0.01
p<0.001
C
APOBEC -mutation enrichment odds ratio
Early
Late
LUAD
LUSC
D
R1
R3
GL
L002
L002 R1 (adeno) branch mutations
L002 R3 (squamous) branch mutations
L002 trunk mutations
E
L008
L008 R1 branch mutations
L008 R3 branch mutations
L008 trunk mutations

Figure 4


A L002
most-recent common ancestor
smoking
ongoing CIN
APOBEC
LUAD
TGFBR1
ARHGAP35
PTPRD
ZFHX4
genome doubling
R1
GL
14,078 muts
TP53, CHD8, FBXW7, LRP1B, RECQL4, USP28, TRIM33
14,514 muts
FAT1
4,163 muts
genome doubling
LUSC
R3
B L008
most-recent common ancestor
ongoing CIN
smoking
genome doubling
APOBEC
R1
GL
6,535 muts
BRAF, RB1, TP53
ALK, CAMTA1, HSP90AB1, KDR, MLL2
858 muts
758 muts
PIK3CA
APOBEC
R3
C>A
C>T
C>G
T>A
T>C
T>G