Supplemental Methods

Search Strategy:

Of the 153 834 samples in the AACR GENIE (v12) database, 9515 had identifiable BRAF mutations. 2022 of these samples harbored unclassifiable mutations or variants of unknown significance (VUS), and were excluded from further analyses. Unclassifiable mutations were BRAF mutations with mechanisms of actions that did not follow the kinase activity, RAS-dependency, and dimerization requirements of the BRAF classification system. Variants of uncertain significance were BRAF mutations whose function and association to disease are unknown. 1274 pediatric samples were removed, 1079 samples were excluded due to incomplete information on age and gender, and 20 duplicate samples were removed. Of the 153 834 samples in the AACR GENIE (v12) database, a total of 5120 samples with BRAF Class 1, 2, 3 mutations and BRAF Fusions were included in the study (**Supplemental Figure S1**).

Genomic Analysis:

Genomic alteration data was obtained using the GENIEv12 database. BRAF fusions were excluded from the genomic analysis due to small sample size. Additional inclusion criteria for NSCLC, CRC, and melanoma cancer-type specific analyses required genes to have been tested in at least 50% of the samples evaluated. We excluded samples from Oncoprints for which sequencing data was not available for all queried genes. 1264 samples were used to generate oncoprints across all BRAF mutant cancers, 221 samples in NSCLC, 462 samples in CRC, and 579 samples in melanoma.

Transcriptomic Analysis:

Using the TCGA database, RNA sequencing data was obtained for BRAF mutant melanoma, NSCLC and CRC. Data pre-processing of these samples was performed in MATLAB verifying Spearman correlation, total counts, and IQR values of the samples. Outliers were removed and data was normalized in R using the DESeq2 normalization algorithm. Heatmaps were generated in R using the ComplexHeatmap package with an absolute LogFold ≥ 2 (BRAF Class 1 vs non-V600 BRAF), baseMean ≥ 50, and padj ≤ 0.01 (**Supplemental Tables S19-S21**). The TCGA Melanoma dataset included 167 BRAF Class 1, 11 Class 2, 14 Class 3, and 3 Fusions. The NSCLC

RNAseq data included 9 BRAF Class 1, 9 Class 2, and 14 Class 3. The CRC RNAseq data included 45 BRAF Class 1, 2 Class 2, 5 Class 3, and 1 Fusion. Fusion samples were excluded from the GSEA analyses. The GSEA analysis was performed using the MSigDB Hallmark gene sets, 1000 permutations by phenotype, and using the Ratio of classes metric.

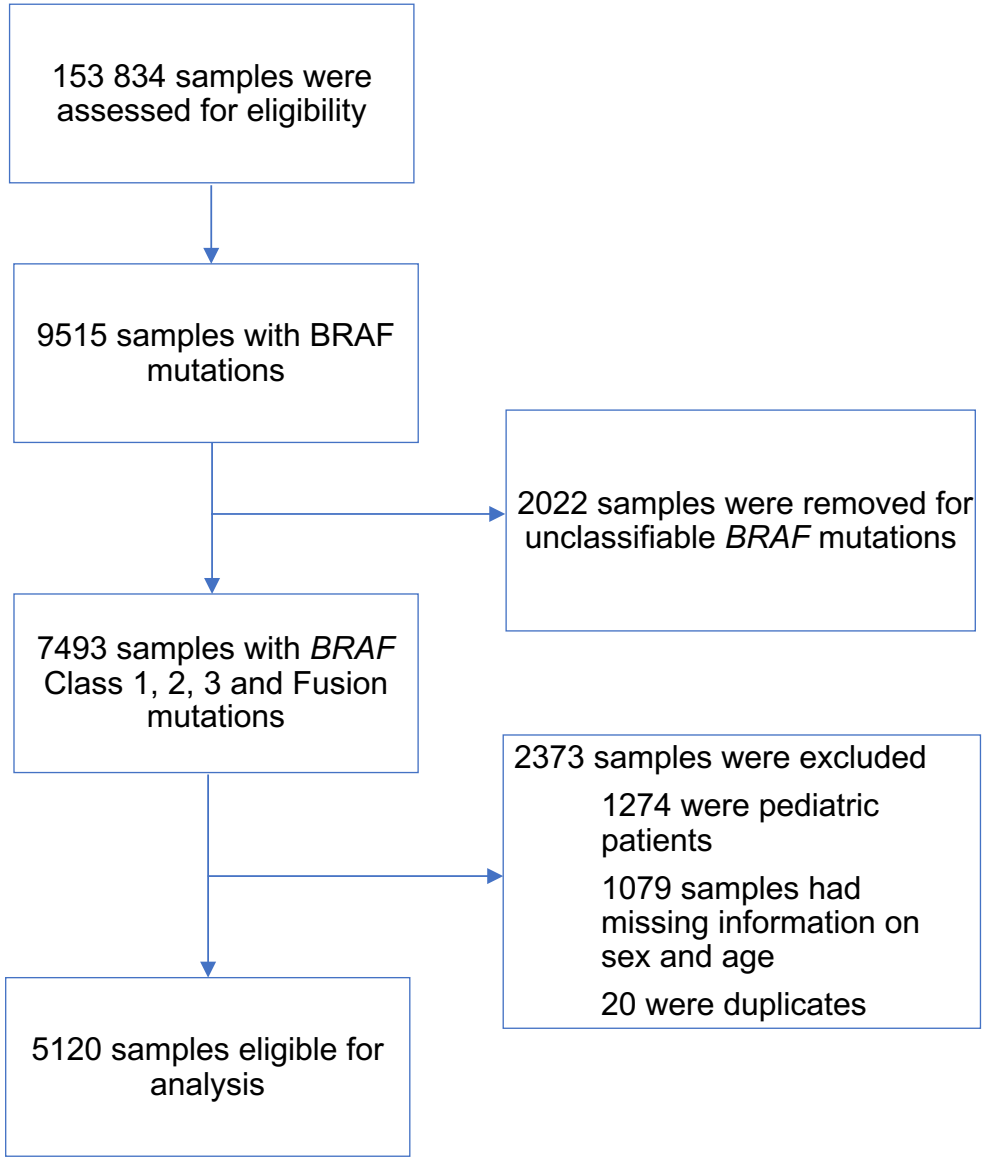

153 834 samples were assessed for eligibility
9515 samples with BRAF mutations
2022 samples were removed for unclassifiable *BRAF* mutations
7493 samples with *BRAF* Class 1, 2, 3 and Fusion mutations
2373 samples were excluded
1274 were pediatric patients
1079 samples had missing information on sex and age
20 were duplicates
5120 samples eligible for analysis

Figure S1

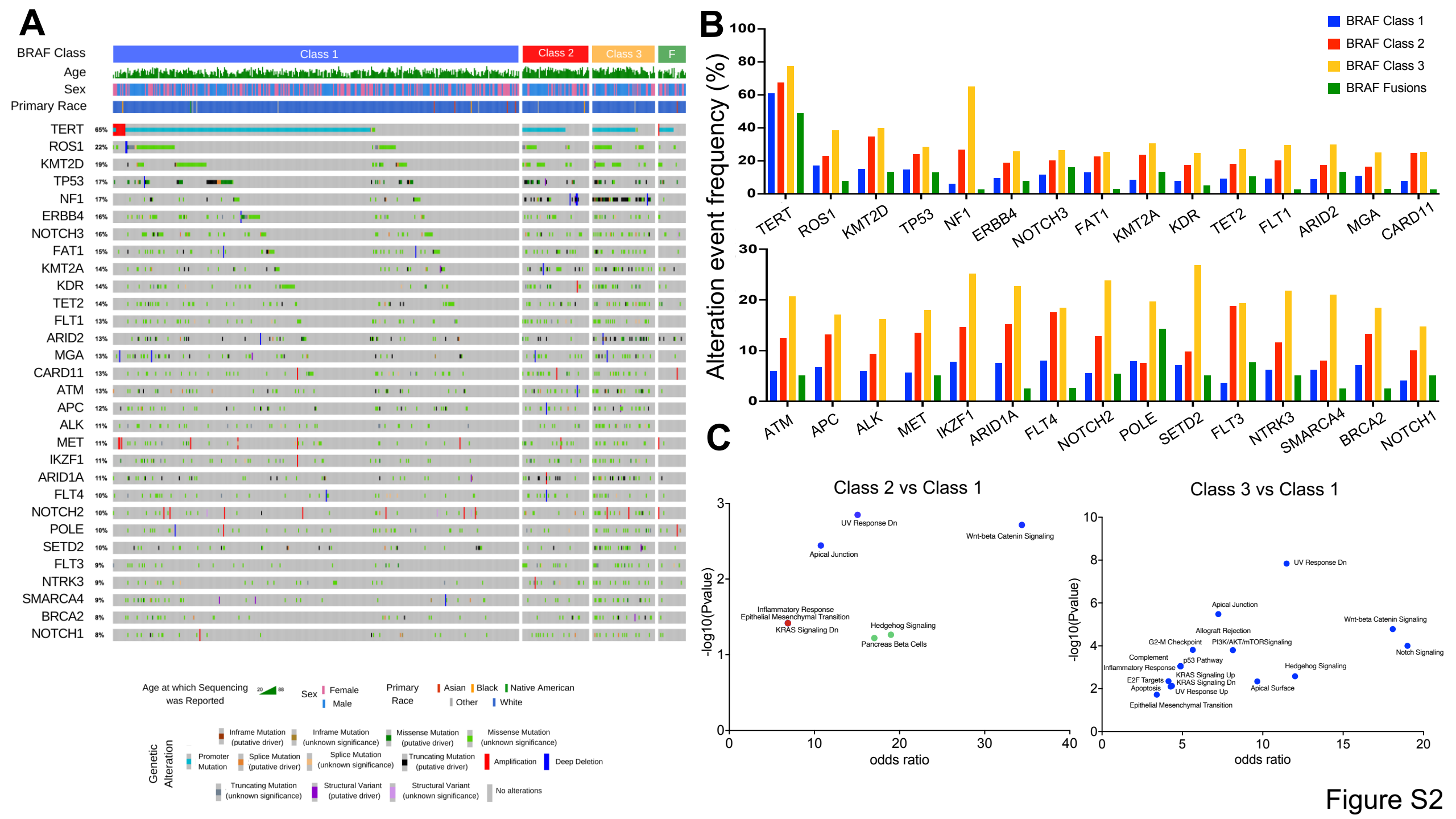
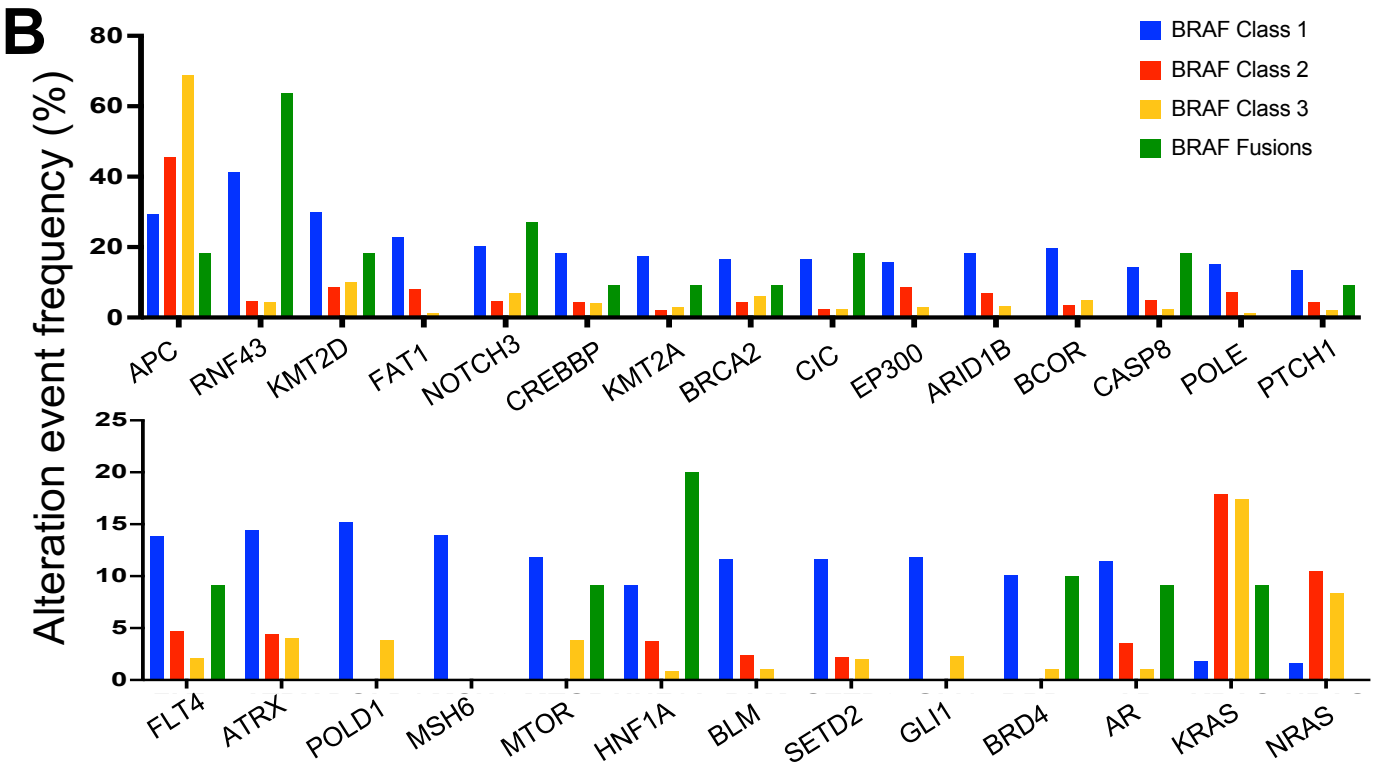

A
BRAF Class
Class 1
Class 2
Class 3
F
Age
Sex
Primary Race
TERT 65%
ROS1 22%
KMT2D 19%
TP53 17%
NF1 17%
ERBB4 16%
NOTCH3 16%
FAT1 15%
KMT2A 14%
KDR 14%
TET2 14%
FLT1 13%
ARID2 13%
MGA 13%
CARD11 13%
ATM 13%
APC 12%
ALK 11%
MET 11%
IKZF1 11%
ARID1A 11%
FLT4 10%
NOTCH2 10%
POLE 10%
SETD2 10%
FLT3 9%
NTRK3 9%
SMARCA4 9%
BRCA2 8%
NOTCH1 8%
Age at which Sequencing was Reported
20
68
Sex
Female
Male
Primary Race
Asian
Black
Native American
Other
White
Genetic Alteration
Inframe Mutation (putative driver)
Inframe Mutation (unknown significance)
Missense Mutation (putative driver)
Missense Mutation (unknown significance)
Promoter Mutation
Splice Mutation (putative driver)
Splice Mutation (unknown significance)
Truncating Mutation (putative driver)
Amplification
Deep Deletion
Truncating Mutation (unknown significance)
Structural Variant (putative driver)
Structural Variant (unknown significance)
No alterations
B
BRAF Class 1
BRAF Class 2
BRAF Class 3
BRAF Fusions
Alteration event frequency (%)
100
80
60
40
20
0
TERT
ROS1
KMT2D
TP53
NF1
ERBB4
NOTCH3
FAT1
KMT2A
KDR
TET2
FLT1
ARID2
MGA
CARD11
30
20
10
0
ATM
APC
ALK
MET
IKZF1
ARID1A
FLT4
NOTCH2
POLE
SETD2
FLT3
NTRK3
SMARCA4
BRCA2
NOTCH1
C
Class 2 vs Class 1
-log10(Pvalue)
odds ratio
UV Response Dn
Wnt-beta Catenin Signaling
Apical Junction
Inflammatory Response
Epithelial Mesenchymal Transition
KRAS Signaling Dn
Hedgehog Signaling
Pancreas Beta Cells
Class 3 vs Class 1
-log10(Pvalue)
odds ratio
UV Response Dn
Apical Junction
Wnt-beta Catenin Signaling
Allograft Rejection
G2-M Checkpoint
PI3K/AKT/mTORSignaling
Notch Signaling
Complement
p53 Pathway
Inflammatory Response
Hedgehog Signaling
KRAS Signaling Up
E2F Targets
KRAS Signaling Dn
Apoptosis
UV Response Up
Apical Surface
Epithelial Mesenchymal Transition

Figure S2


A
BRAF Class
Class 1
Class 2
Class 3
F
Age
Sex
Primary Race
APC 40%
RNF43 38%
KMT2D 28%
FAT1 19%
NOTCH3 18%
CREBBP 17%
KMT2A 14%
BRCA2 14%
CIC 14%
EP300 14%
ARID1B 13%
BCOR 13%
CASP8 13%
POLE 13%
PTCH1 13%
FLT4 12%
ATRX 12%
POLD1 12%
MSH6 11%
MTOR 10%
HNF1A 10%
BLM 10%
SETD2 9%
GLI1 9%
BRD4 9%
AR 8%
KRAS 5%
NRAS 4%
Age at which Sequencing was Reported
20
87
Sex
Female
Male
Primary Race
Asian
Black
Native American
Other
White
Genetic Alteration
Inframe Mutation (putative driver)
Inframe Mutation (unknown significance)
Missense Mutation (putative driver)
Missense Mutation (unknown significance)
Splice Mutation (putative driver)
Splice Mutation (unknown significance)
Truncating Mutation (putative driver)
Amplification
Deep Deletion
Truncating Mutation (unknown significance)
Structural Variant (putative driver)
No alterations


B
Alteration event frequency (%)
BRAF Class 1
BRAF Class 2
BRAF Class 3
BRAF Fusions
APC
RNF43
KMT2D
FAT1
NOTCH3
CREBBP
KMT2A
BRCA2
CIC
EP300
ARID1B
BCOR
CASP8
POLE
PTCH1
FLT4
ATRX
POLD1
MSH6
MTOR
HNF1A
BLM
SETD2
GLI1
BRD4
AR
KRAS
NRAS

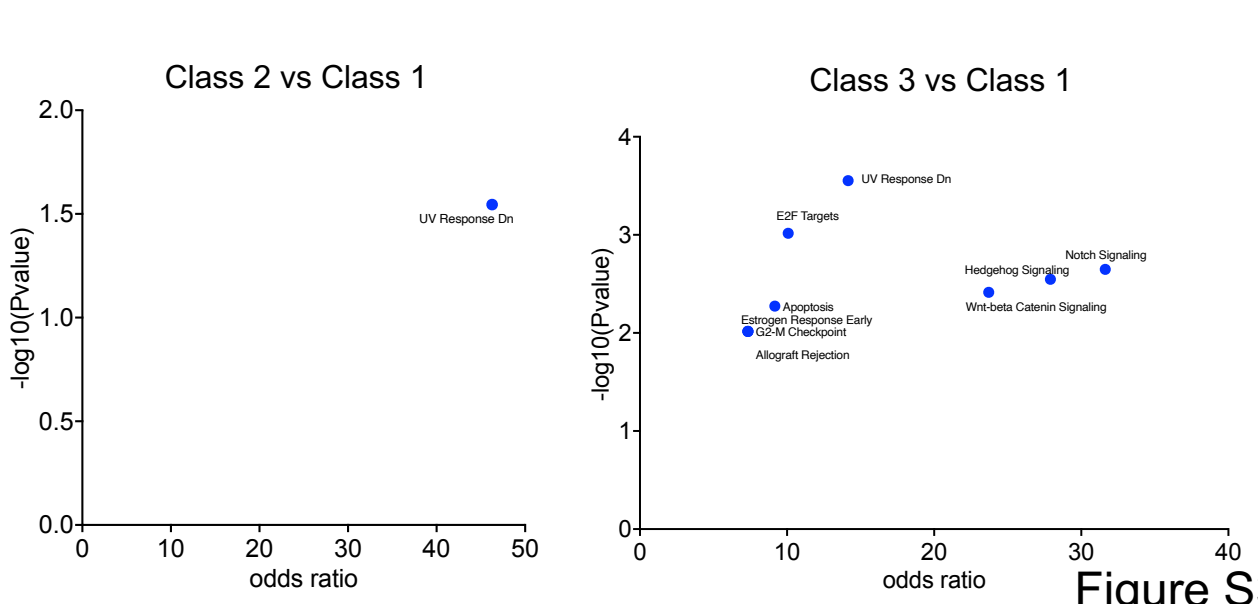

C
Class 2 vs Class 1
-log10(Pvalue)
odds ratio
UV Response Dn
Class 3 vs Class 1
-log10(Pvalue)
odds ratio
UV Response Dn
E2F Targets
Notch Signaling
Hedgehog Signaling
Wnt-beta Catenin Signaling
Apoptosis
Estrogen Response Early
G2-M Checkpoint
Allograft Rejection

Figure S3

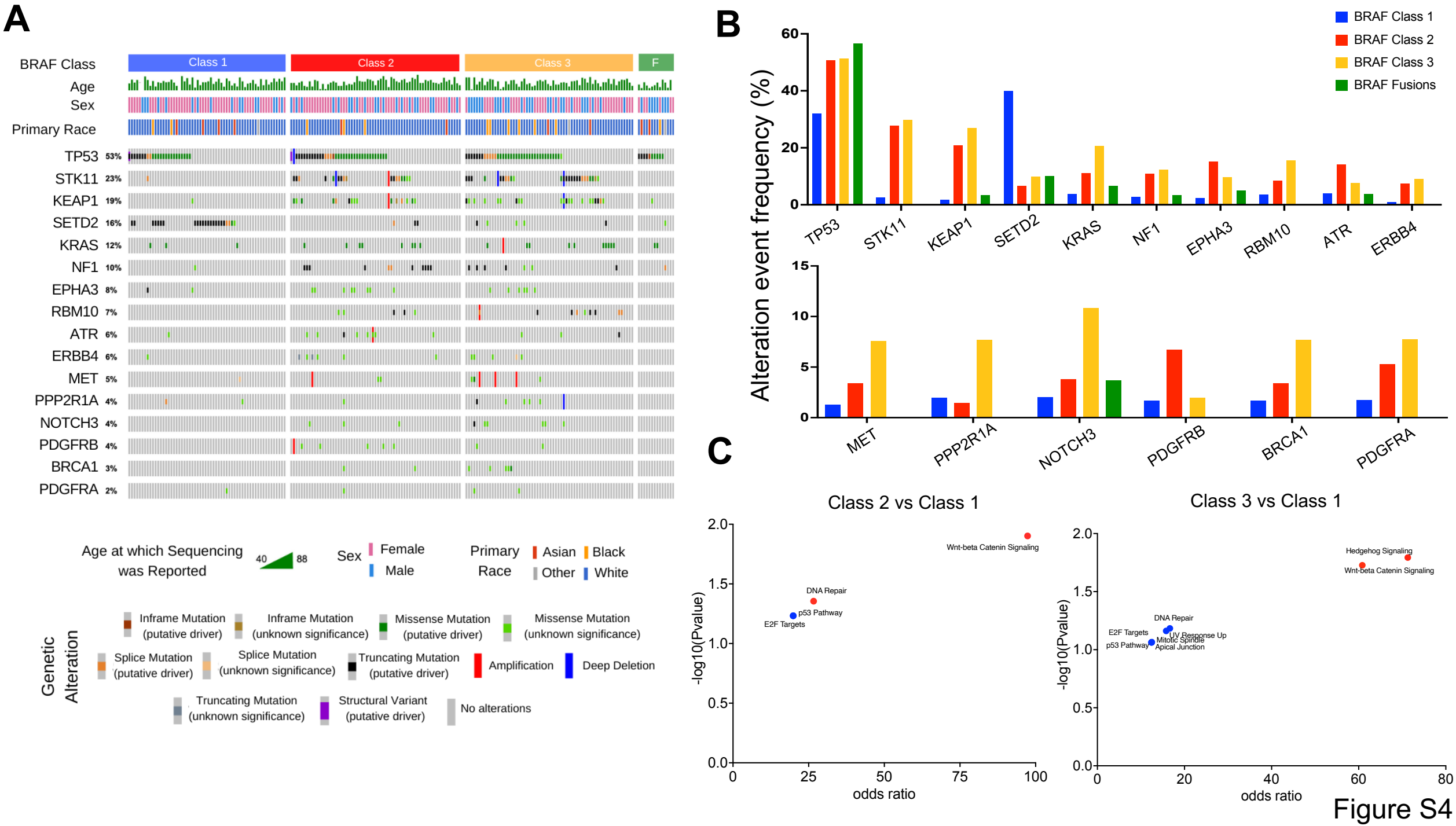
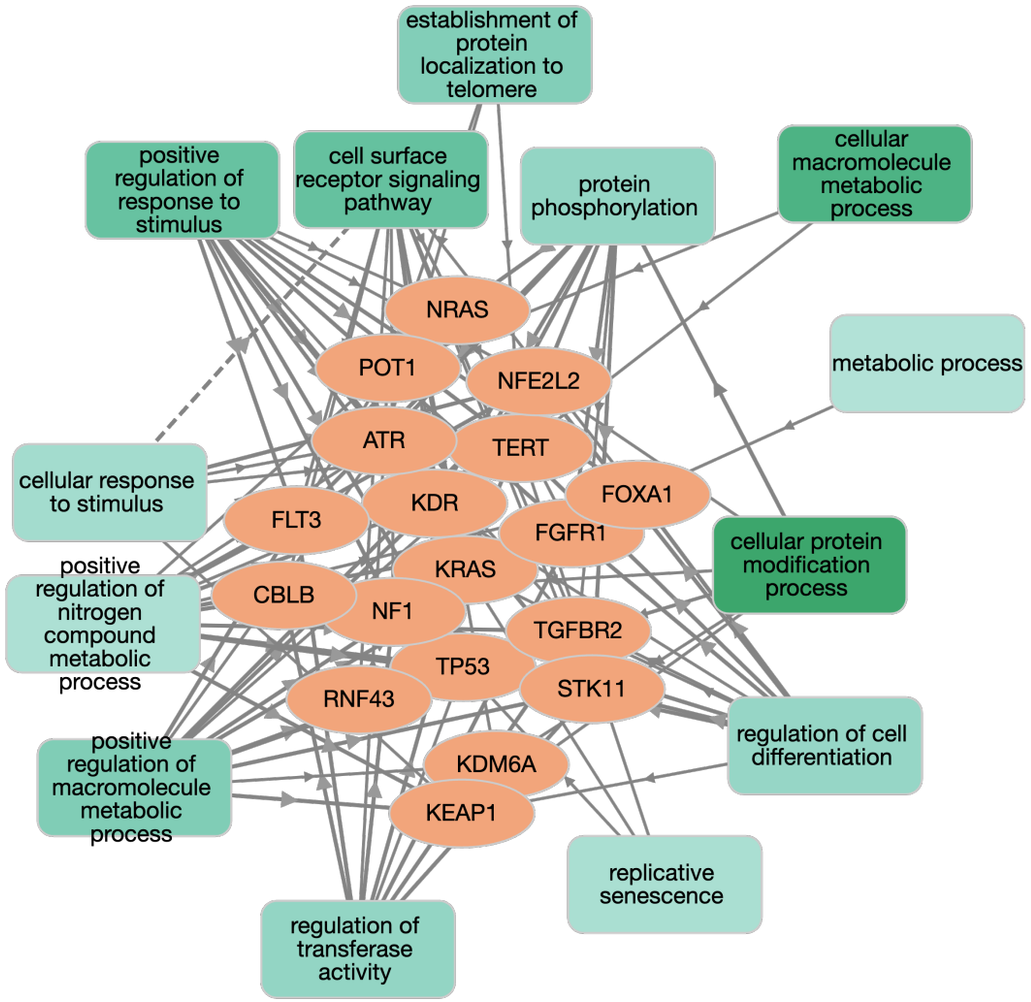

A
BRAF Class
Class 1
Class 2
Class 3
F
Age
Sex
Primary Race
TP53 53%
STK11 23%
KEAP1 19%
SETD2 16%
KRAS 12%
NF1 10%
EPHA3 8%
RBM10 7%
ATR 6%
ERBB4 6%
MET 5%
PPP2R1A 4%
NOTCH3 4%
PDGFRB 4%
BRCA1 3%
PDGFRA 2%
Age at which Sequencing was Reported
40
88
Sex
Female
Male
Primary Race
Asian
Black
Other
White
Genetic Alteration
Inframe Mutation (putative driver)
Inframe Mutation (unknown significance)
Missense Mutation (putative driver)
Missense Mutation (unknown significance)
Splice Mutation (putative driver)
Splice Mutation (unknown significance)
Truncating Mutation (putative driver)
Amplification
Deep Deletion
Truncating Mutation (unknown significance)
Structural Variant (putative driver)
No alterations
B
BRAF Class 1
BRAF Class 2
BRAF Class 3
BRAF Fusions
Alteration event frequency (%)
60
40
20
0
TP53
STK11
KEAP1
SETD2
KRAS
NF1
EPHA3
RBM10
ATR
ERBB4
15
10
5
0
MET
PPP2R1A
NOTCH3
PDGFRB
BRCA1
PDGFRA
C
Class 2 vs Class 1
Wnt-beta Catenin Signaling
DNA Repair
p53 Pathway
E2F Targets
-log10(Pvalue)
odds ratio
Class 3 vs Class 1
Hedgehog Signaling
Wnt-beta Catenin Signaling
DNA Repair
E2F Targets
UV Response Up
p53 Pathway
Mitotic Spindle
Apical Junction
-log10(Pvalue)
odds ratio

Figure S4

A. **Class 2 vs. Class 1**



B. **Class 3 vs. Class 1**

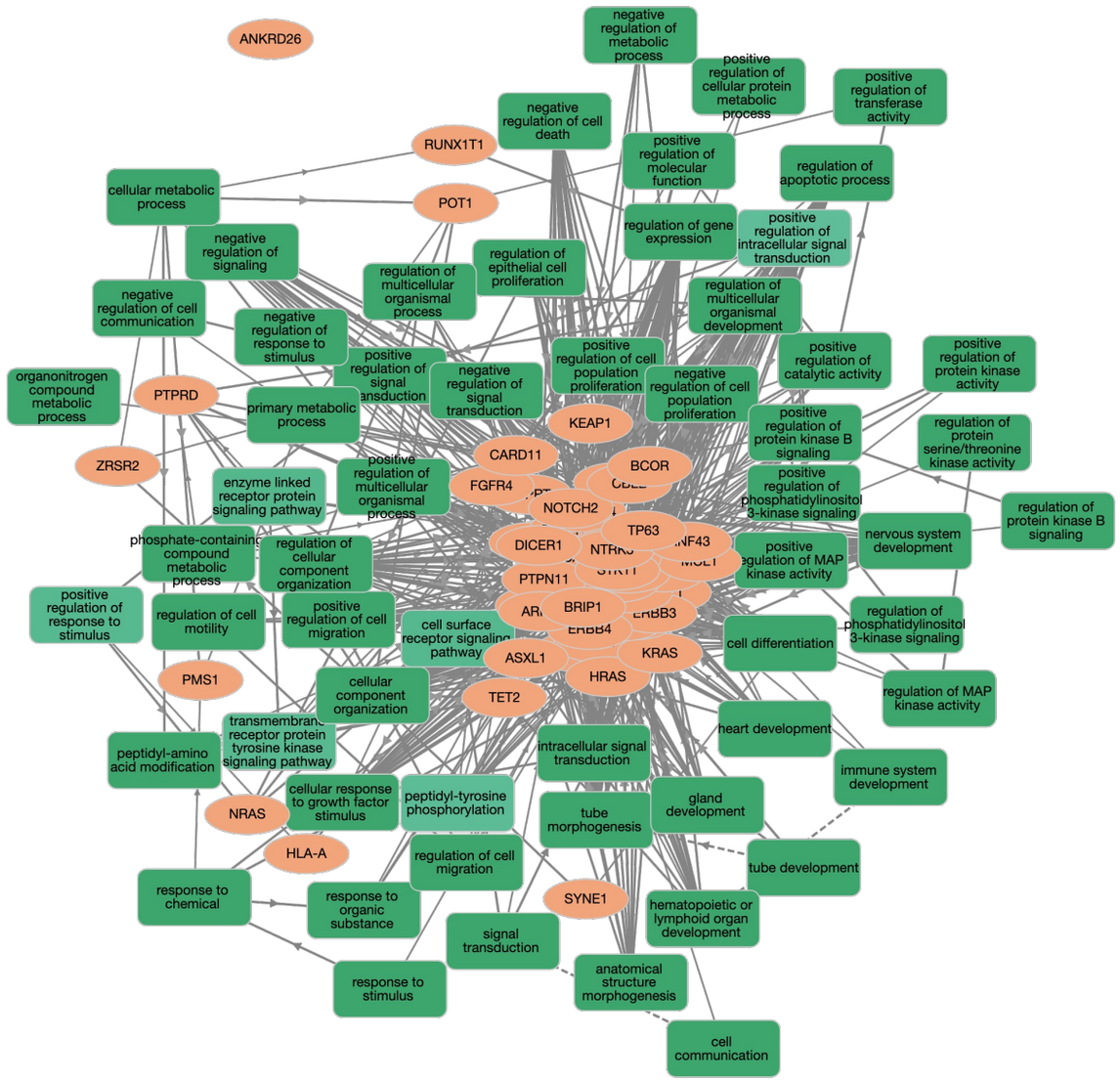


Figure S5

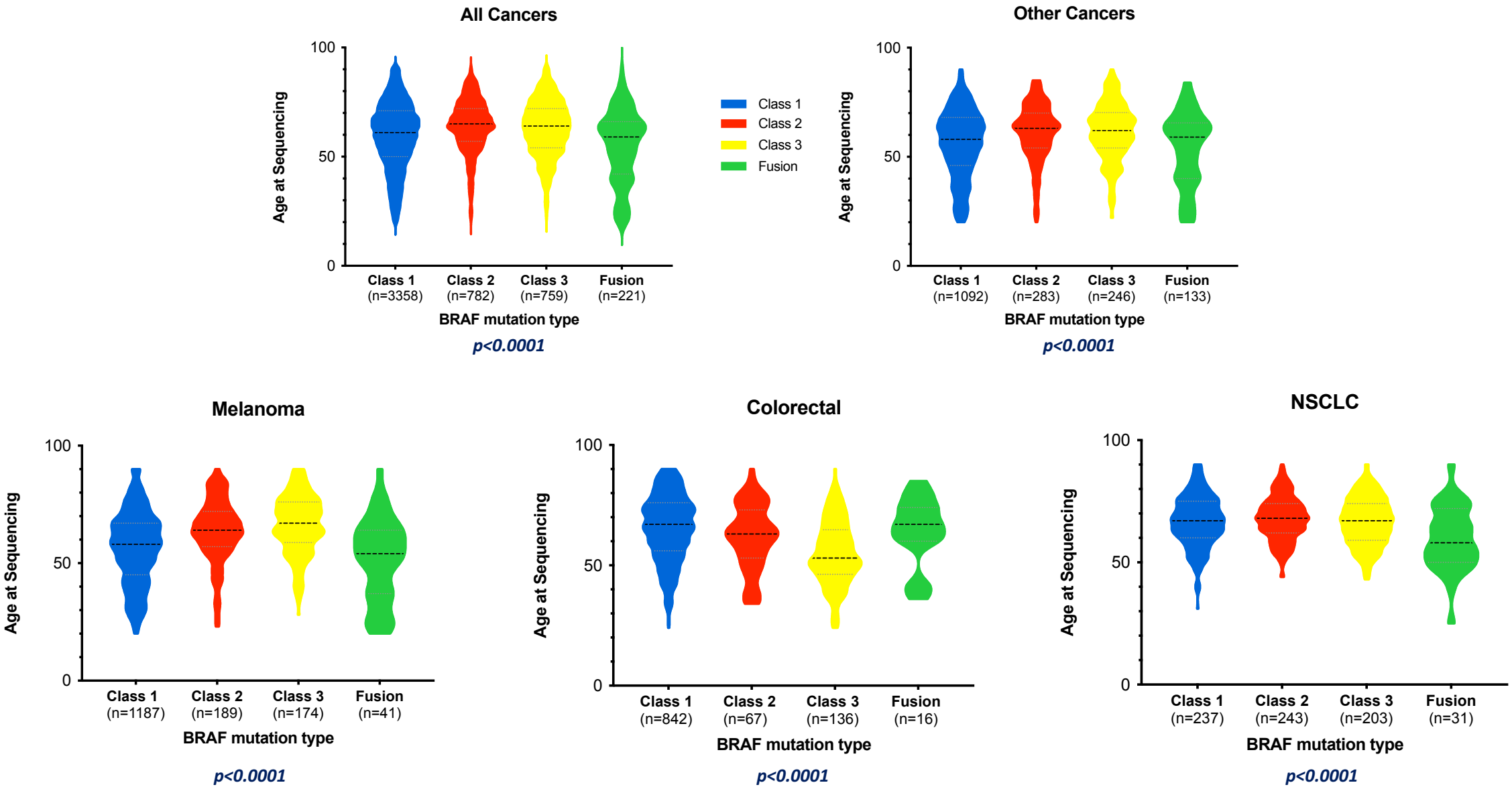

All Cancers
Age at Sequencing
100
50
0
Class 1
Class 2
Class 3
Fusion
Class 1 (n=3358)
Class 2 (n=782)
Class 3 (n=759)
Fusion (n=221)
BRAF mutation type
p<0.0001
Other Cancers
Class 1 (n=1092)
Class 2 (n=283)
Class 3 (n=246)
Fusion (n=133)
BRAF mutation type
p<0.0001
Melanoma
Class 1 (n=1187)
Class 2 (n=189)
Class 3 (n=174)
Fusion (n=41)
BRAF mutation type
p<0.0001
Colorectal
Class 1 (n=842)
Class 2 (n=67)
Class 3 (n=136)
Fusion (n=16)
BRAF mutation type
p<0.0001
NSCLC
Class 1 (n=237)
Class 2 (n=243)
Class 3 (n=203)
Fusion (n=31)
BRAF mutation type
p<0.0001

Figure S6