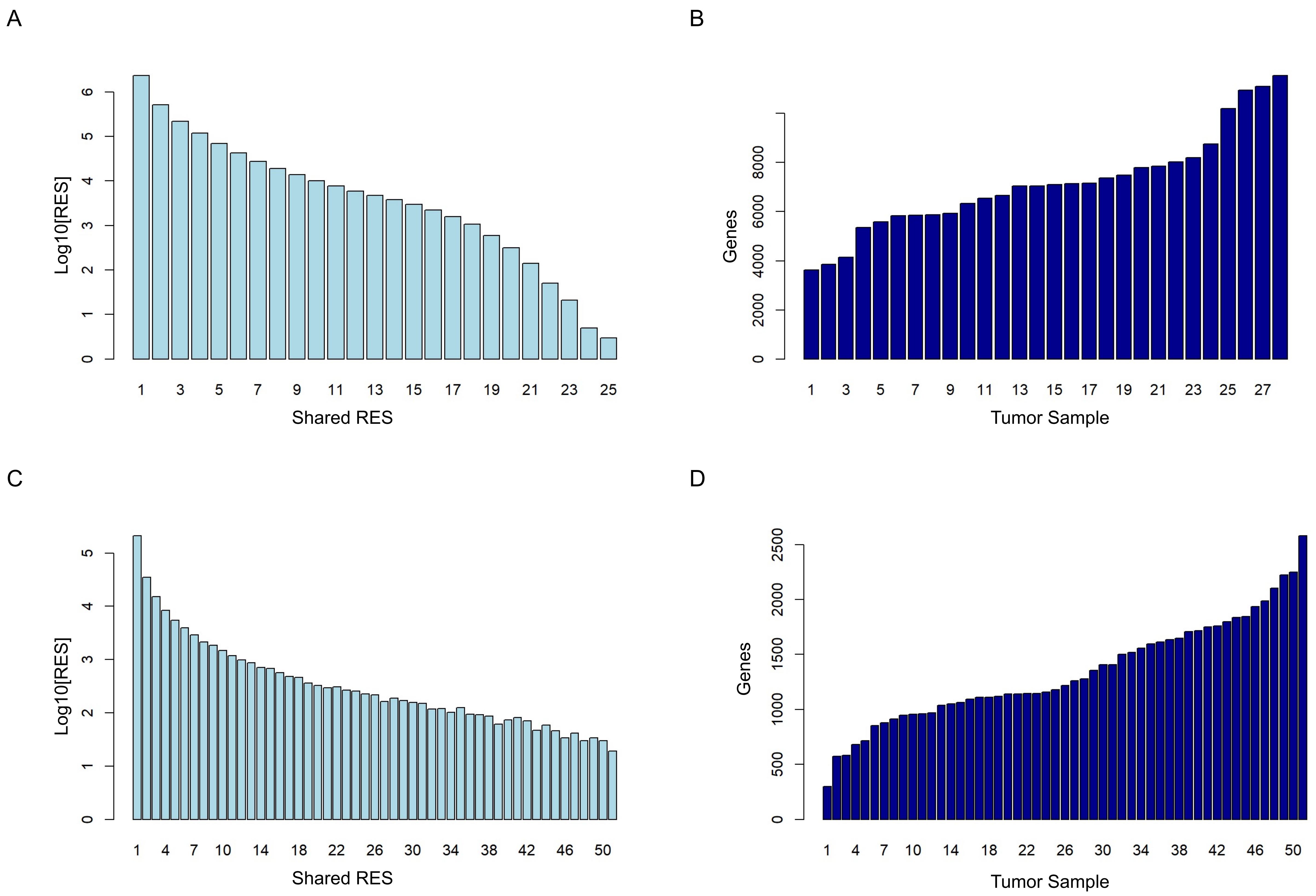
A
Log10[RES]
0
1
2
3
4
5
6
1
3
5
7
9
11
13
15
17
19
21
23
25
Shared RES
B
Genes
0
2000
4000
6000
8000
1
3
5
7
9
11
13
15
17
19
21
23
25
27
Tumor Sample
C
Log10[RES]
0
1
2
3
4
5
1
4
7
10
14
18
22
26
30
34
38
42
46
50
Shared RES
D
Genes
0
500
1000
1500
2000
2500
1
4
7
10
14
18
22
26
30
34
38
42
46
50
Tumor Sample

Figure S1

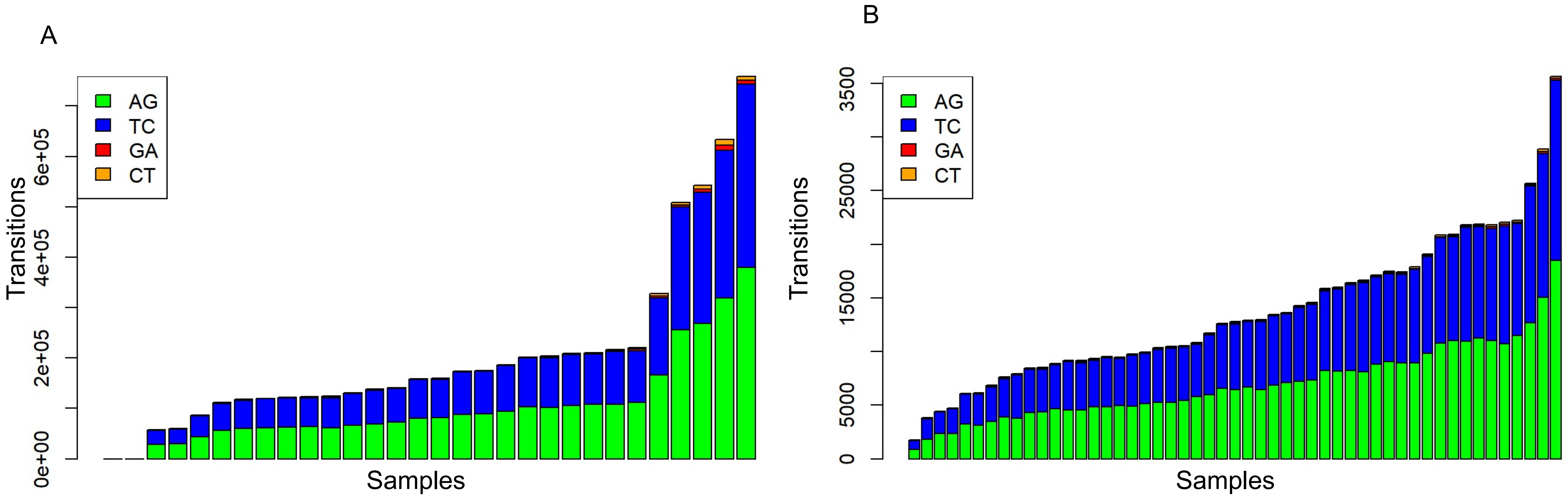
A
AG
TC
GA
CT
Transitions
0e+00
2e+05
4e+05
6e+05
Samples
B
AG
TC
GA
CT
Transitions
0
5000
15000
25000
3500
Samples

Figure S2

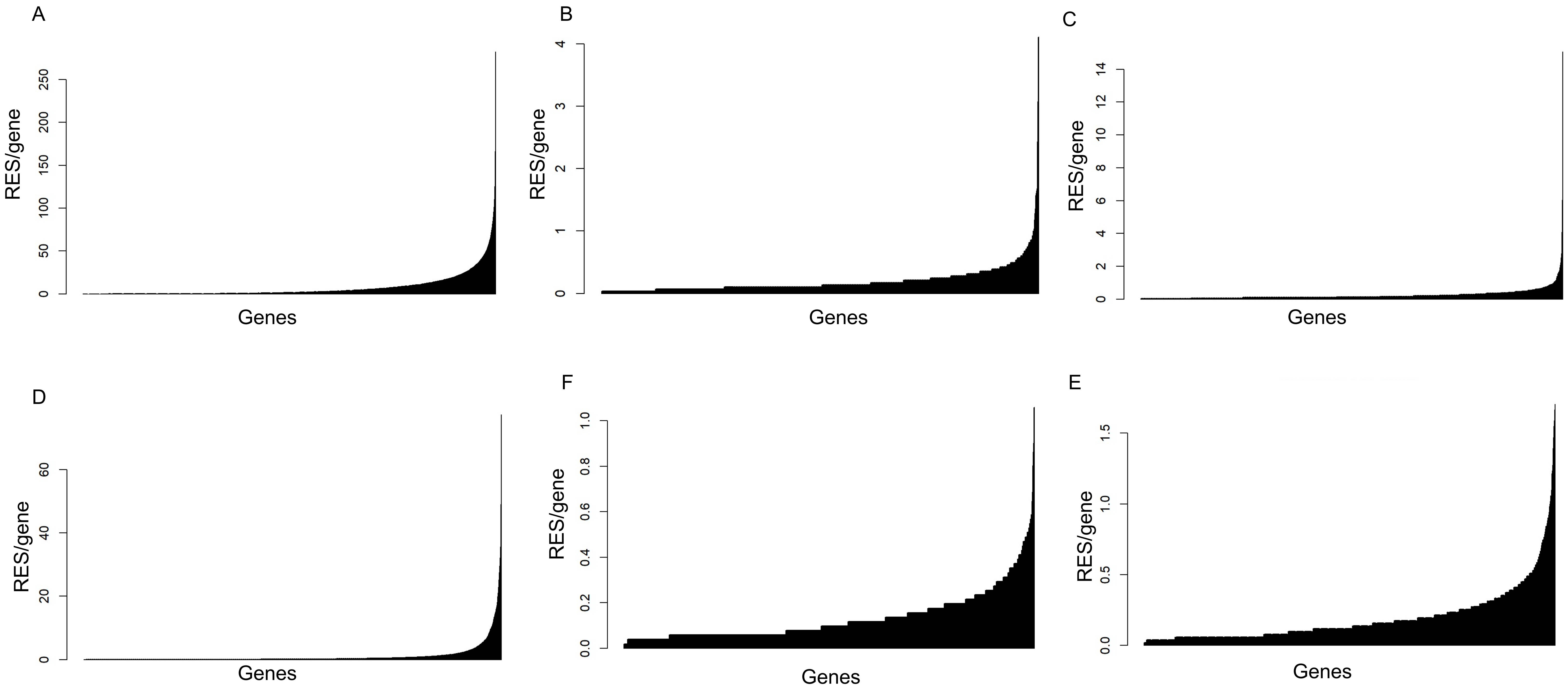
A
RES/gene
0
50
100
150
200
250
Genes
B
RES/gene
0
1
2
3
4
Genes
C
RES/gene
0
2
4
6
8
10
12
14
Genes
D
RES/gene
0
20
40
60
Genes
F
RES/gene
0.0
0.2
0.4
0.6
0.8
1.0
Genes
E
RES/gene
0.0
0.5
1.0
1.5
Genes

Figure S3

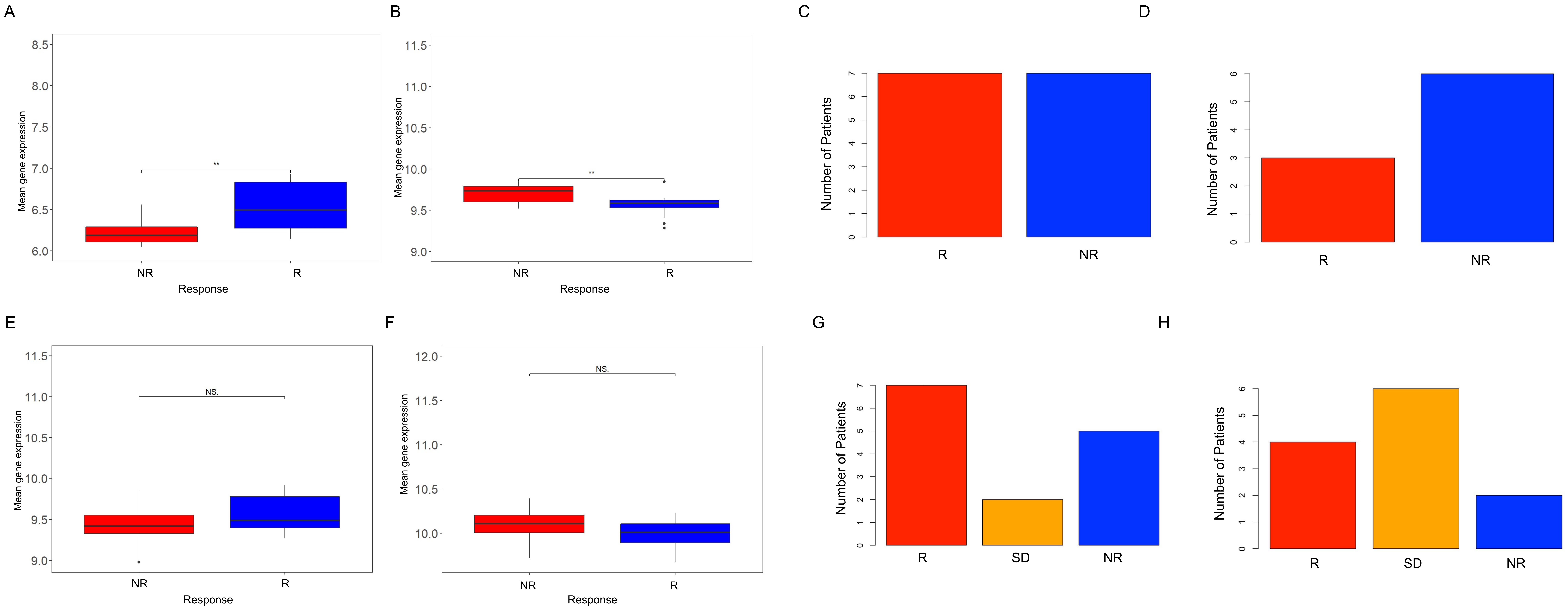
A
8.5
8.0
7.5
7.0
6.5
6.0
Mean gene expression
**
NR
R
Response
B
11.5
11.0
10.5
10.0
9.5
9.0
Mean gene expression
**
NR
R
Response
C
Number of Patients
0
1
2
3
4
5
6
7
R
NR
D
Number of Patients
0
1
2
3
4
5
6
R
NR
E
11.5
11.0
10.5
10.0
9.5
9.0
Mean gene expression
NS.
NR
R
Response
F
12.0
11.5
11.0
10.5
10.0
Mean gene expression
NS.
NR
R
Response
G
Number of Patients
0
1
2
3
4
5
6
7
R
SD
NR
H
Number of Patients
0
1
2
3
4
5
6
R
SD
NR

Figure S4

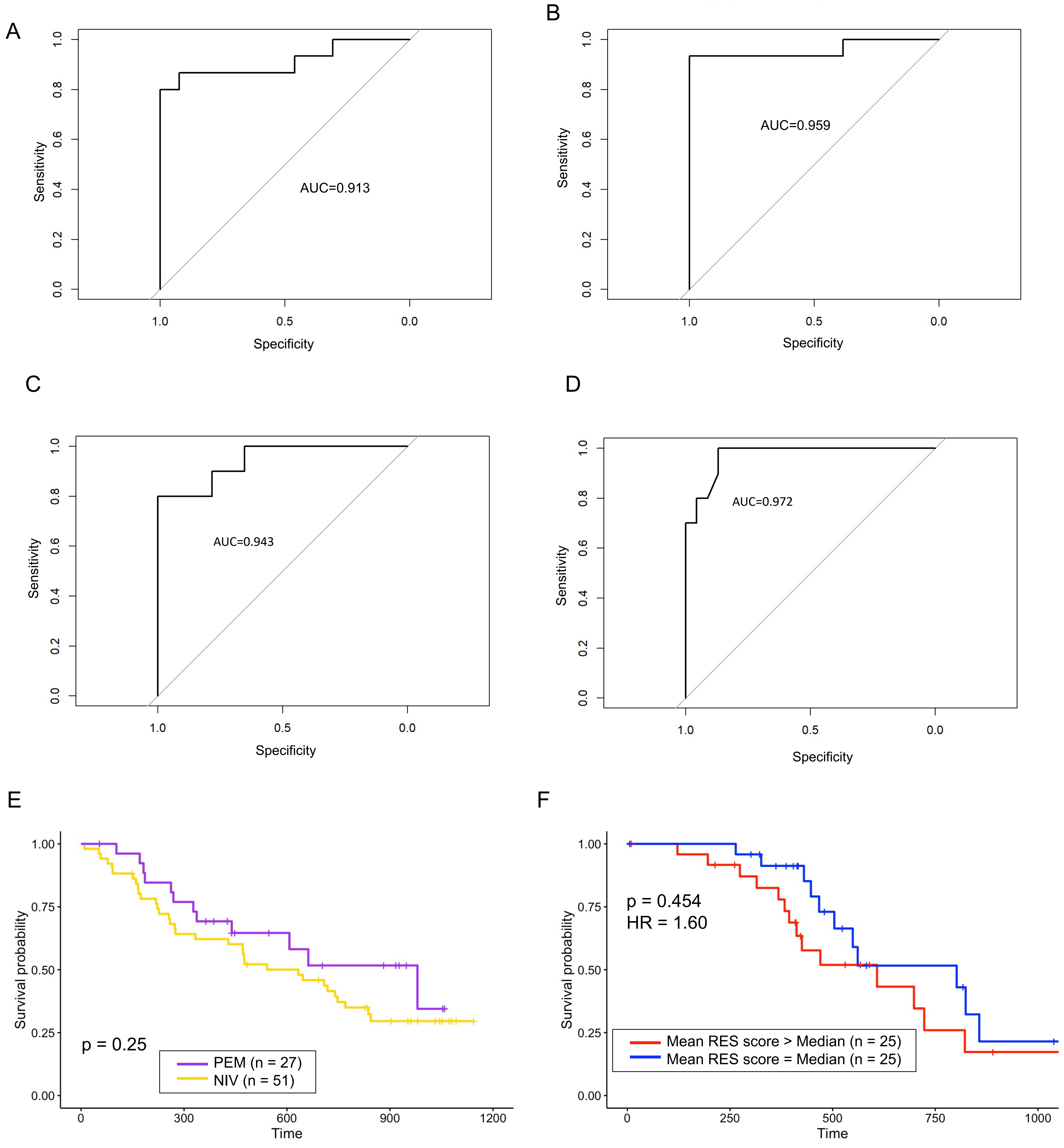
A
AUC=0.913
B
AUC=0.959
C
AUC=0.943
D
AUC=0.972
Sensitivity
Specificity
0.0
0.2
0.4
0.6
0.8
1.0
1.0
0.5
0.0
E
Survival probability
Time
p = 0.25
PEM (n = 27)
NIV (n = 51)
0.00
0.25
0.50
0.75
1.00
0
300
600
900
1200
F
p = 0.454
HR = 1.60
Mean RES score > Median (n = 25)
Mean RES score = Median (n = 25)
0
250
500
750
1000

Figure S5

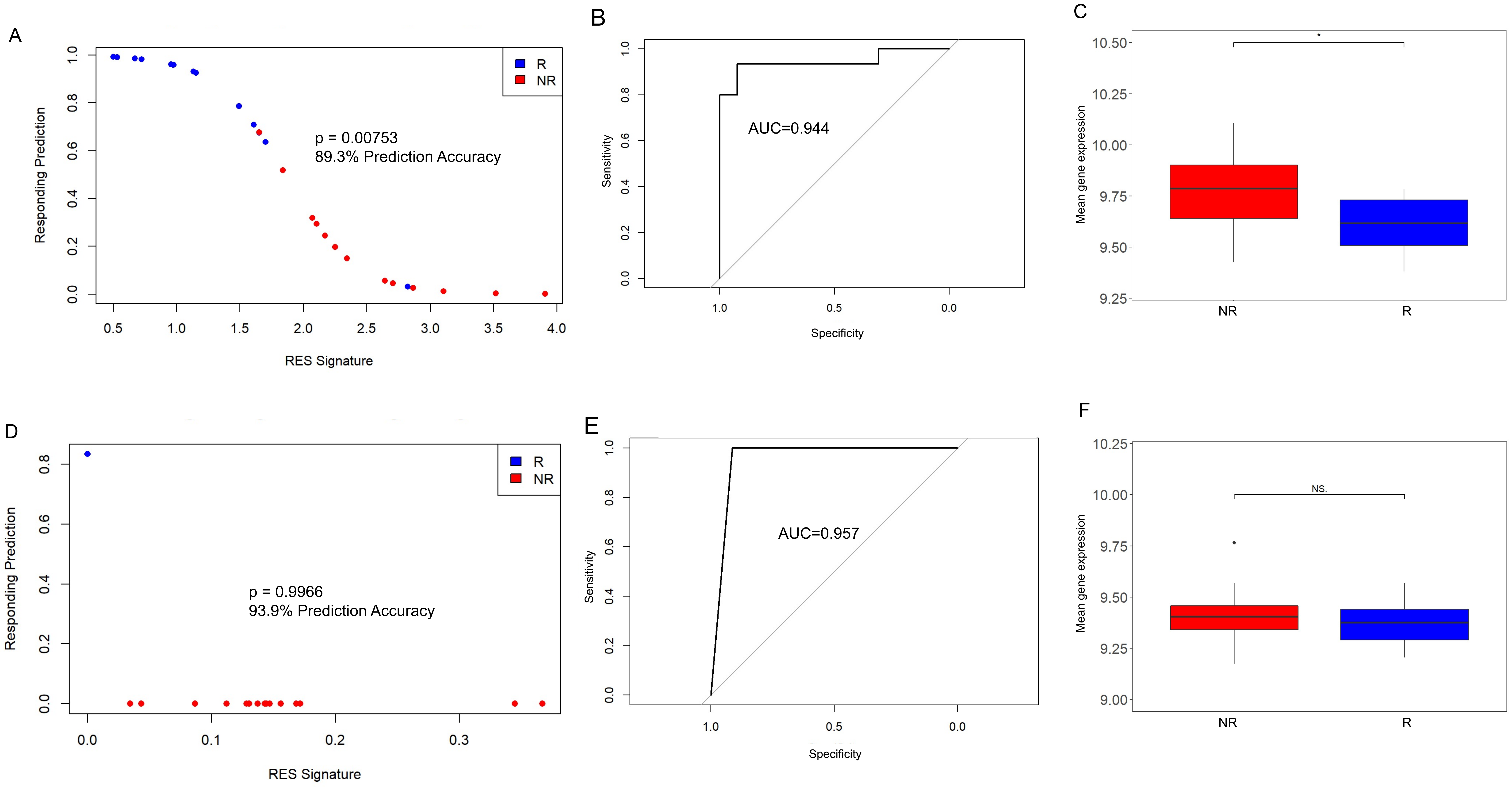
A
Responding Prediction
0.0
0.2
0.4
0.6
0.8
1.0
RES Signature
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
R
NR
p = 0.00753
89.3% Prediction Accuracy
B
Sensitivity
Specificity
1.0
0.5
0.0
AUC=0.944
C
Mean gene expression
9.25
9.50
9.75
10.00
10.25
10.50
NR
R
*
D
Responding Prediction
0.0
0.2
0.4
0.6
0.8
RES Signature
0.0
0.1
0.2
0.3
R
NR
p = 0.9966
93.9% Prediction Accuracy
E
Sensitivity
Specificity
1.0
0.5
0.0
AUC=0.957
F
Mean gene expression
9.00
9.25
9.50
9.75
10.00
10.25
NS.
NR
R

Figure S6

Figure S1: RNA editing sites and unique genes per sample. A) RNA editing sites identified per sample from Pembrolizumab treated patients. **B)** Genes identified per sample from Pembrolizumab treated patients. **C)** RNA editing sites identified per sample from Nivolumab treated patients. **D)** Genes identified per sample from Nivolumab treated patients.

Figure S2: Major RNA editing transitions by dataset. A) AG, TC, GA, and CT transitions from Pembrolizumab treated patients. **B)** AG, TC, GA, and CT transitions from Nivolumab treated patients.

Figure S3: Average RNA editing sites identified per gene. A) Average RES per gene for Pembrolizumab treated patients. **B)** Average RES per gene for Responders in Pembrolizumab treated patients. **C)** Average RES per gene for Non-Responders in Pembrolizumab treated patients. **D)** Average RES per gene for Nivolumab treated patients. **E)** Average RES per gene for Responders in Nivolumab treated patients. **F)** Average RES per gene for Non-Responders in Nivolumab treated patients.

Figure S4: Gene expression levels of RES containing genes do not correlate with outcome. A) Expression levels of 13 predictive genes that contain up-regulated RES scores in the Pembrolizumab treated patients. **B)** Expression levels of 248 predictive genes that contain down-regulated RES scores in the Pembrolizumab treated patients. **C)** BRAF mutations in responding and non-responding Pembrolizumab patients. **D)** RAS mutations in responding and non-responding Pembrolizumab patients. **E)** Expression levels of 29 predictive genes that contain up-regulated RES scores in the Nivolumab treated patients. **F)** Expression levels of 41 predictive genes that contain down-regulated RES scores in the Nivolumab treated patients. **G)** BRAF mutations in responding and non-responding Nivolumab patients. **H)** RAS mutations in responding and non-responding Nivolumab patients.

Figure S5: Logistic regression models segregate patients based on up-regulated and down-regulated RES scores.

A) ROC curves of 13 up-regulated RES score means from Pembrolizumab treated patients. **B)** ROC curves of 248 down-regulated RES score means from Pembrolizumab treated patients. **C)** ROC curves of 29 up-regulated RES score means from Nivolumab treated patients. **D)** ROC curves of 41 down-regulated RES score means from Pembrolizumab treated patients. **E)** Survival analysis comparing Pembrolizumab and Nivolumab patient cohorts. **F)** Survival analysis of patients stratified by upper 50% (red) and lower 50% (blue) means of 44 signature genes from 50 sampled patients of TCGA-SKCM cohort. **$p<0.01$.

Figure S6: Logistic models and ROC curves segregate patients from both cohorts based on 46 signature genes. A) Logistic regression models from Pembrolizumab treated patients for 46 signature RES score means and responding prediction for responder (R, blue) and non-responder (NR, red) patients. **B)** ROC curves of signature RES score means from Pembrolizumab treated patients. **C)** Mean gene expression of signature genes from Pembrolizumab treated patients. **D)** Logistic regression models from Nivolumab treated patients for 46 signature RES score means and responding prediction for responder (R, blue) and non-responder (NR, red) patients. **E)** ROC curves of signature RES score means from Nivolumab treated patients. **F)** Mean gene expression of signature genes from Nivolumab treated patients.