Table S1A. Gene names and frequency of mutations for oligodendroglioma in the TCGA database.

Gene Name	Frequency of Mutations
IDH1	154
CIC	104
FUBP1	45
PI3K comb.	37
NOTCH1	32
PIK3CA	26
ZBTB20	16
IDH2	15
PIK3R1	12
ARID1A	11
NF1	8
SMARCA4	7
TP53	7
CREBZF	6
TCF12	6
ANKRD30A	5
RBPJ	5
ATRX	4
MYH4	4
SOX4	4
CDKN2C	3
EGFR	3
EMG1	3
MYH8	3
SLC6A3	3
ARL6	2
CXorf22	2
KEL	2
KPRP	2
KRT15	2
LHFPL1	2
NRAS	2
OR4S2	2
OR5D18	2
PDGFRA	2
SEMA3E	2
SPANXD	2
TRPA1	2
UGT2A3	2
VSIG4	2
ZNF709	2
CDH18	1
DCAF12L2	1
KRAS	1
LZTR1	1
MED9	1
MGAT4C	1
OPRK1	1
OR2A12	1
OR2A25	1
OR4P4	1
OR8K3	1
OR9G1	1
P2RY11	1
PTEN	1
PTPN11	1
RAP2C	1
RB1	1
RPL5	1
SPTA1	1
SSTR4	1
ST3GAL6	1
STK19	1
TEAD3	1
TREML2	1
TRIM58	1
TYRP1	1
ZPBP	1

Supplemental Table 1B. Gain and loss of whole chromosome arms of oligodendroglioma within the TCGA database.

Chromosome	Loss	Gain
1p	166	0
1q	12	1
4p	45	0
4q	50	0
7p	0	16
7q	0	24
9p	21	2
9q	15	3
11p	0	19
11q	0	24
12p	5	4
13q	28	0
14q	20	1
15q	27	0
17p	2	7
17q	1	8
18p	31	0
18q	33	0
19p	7	57
19q	167	0
21q	2	9
22q	4	17
Xp	33	0
Xq	32	1

Table S2. Patient demographics. Clinical characteristics of patients with pre-operative radiographic imaging from The Cancer Genome Atlas database, with confirmed diagnosis of oligodendroglioma (i.e. IDH-mutant, 1p19q co-deleted glioma).

Characteristic	**Total (N=55)**
Histological subtype – no. (%)	
Oligodendroglioma	
Grade II	23 (41.8)
Grade III	24 (43.6)
Oligoastrocytoma	
Grade II	5 (9.1)
Grade III	1 (1.8)
Astrocytoma	
Grade II	1 (1.8)
Grade III	0 (0.0)
Age at diagnosis (yrs)	
Mean	49.4 ± 13.2
Range	20–75
Radiographic features present – no./total no. (%)	
- Contrast-enhanced	20/55 (36.4)
+ Contrast-enhanced	35/55 (63.6)
Tumor location – no./total no. (%)	
Frontal lobe	40/55 (72.7)
Parietal lobe	7/55 (12.7)
Temporal lobe	3/55 (5.5)
Other	5/55 (9.1)

Table S3. Complete survival tables. Cox proportional hazard models for overall survival (OS) and progression-free survival (PFS); multivariate OS adjusted for grade and age; multivariate PFS adjusted for grade. GTR: gross total resection; mut: mutation; exp.: expression; *Significant on univariate analysis; †significant on multivariate analysis; ‡gene expression on a log2 scale, such that the hazard ratio is for each doubling of gene expression.

Predictor	OS Hazard Ratio (95% conf. interval)	*P*-value	Adjusted OS Hazard Ratio (95% conf. interval)	*P*-value
***Age (per 10 yrs)**	**3.64 (2.16-6.11)**	**<0.0001**	—	—
Histologic astrocytoma vs. oligodendroglioma	2.94 (0.046-2.70)	0.31	—	—
Extent of resection (GTR vs. less than GTR)	0.65 (0.24-1.68)	0.37	—	—
***Grade III (vs. II)**	**6.61 (2.08-20.95)**	**0.013**	—	—
***‡*MKI67* exp.**	**1.58 (1.17-2.14)**	**0.0029**	1.12 (0.84-1.50)	0.42
ATRX mut.	NA	NA	<0.0001	0.998
CIC mut.	0.65 (0.27-1.55)	0.33	0.44 (0.17-1.15)	0.095
FUBP1 mut.	1.70 (0.63-4.53)	0.31	2.60 (0.84-8.00)	0.096
NOTCH1 mut.	1.71 (0.65-4.50)	0.28	1.10 (0.37-3.27)	0.87
†*PIK3* mut.	1.97 (0.78-4.97)	0.15	**3.11 (1.02-9.47)**	**0.045**
RBPJ + *NOTCH1* mut.	1.81 (0.71-4.61)	0.210	0.85 (0.30-2.40)	0.76
TP53 mut.	1.36 (0.18-10.33)	0.77	1.16 (0.14-9.65)	0.893
7p gain	1.90 (0.42-8.52)	0.44	1.23 (0.26-5.68)	0.795
11p gain	2.08 (0.58-7.48)	0.26	0.60 (0.16-2.33)	0.463
14q loss	3.04 (0.94-9.77)	0.063	1.49 (0.39-5.62)	0.559
***15q loss**	**3.52 (1.41-8.82)**	**0.007**	1.48 (0.51-4.30)	0.47
‡*HES1* exp.	0.60 (0.35-1.05)	0.071	0.86 (0.47-1.56)	0.611
‡*HES2* exp.	1.01 (0.93-1.10)	0.76	1.00 (0.89-1.12)	0.954
†‡*HES5* exp.	0.82 (0.65-1.03)	0.086	**0.74 (0.57-0.96)**	**0.024**
***‡*HEY1* exp.**	**0.34 (0.18-0.64)**	**0.0009**	0.86 (0.38-1.95)	0.72
***‡*HEY2* exp.**	**0.35 (0.21-0.60)**	**0.0001**	0.79 (0.37-1.68)	0.54

	PFS Hazard Ratio (95% conf. interval)	***P*-value**	**Adjusted PFS Hazard Ratio (95% conf. interval)**	***P*-value**
Age (per 10 yrs)	1.12 (0.86-1.66)	0.28	—	—
***Histologic astrocytoma vs. oligodendroglioma**	**4.77 (1.09-20.78)**	**0.038**	—	—
Extent of resection (GTR vs. less than GTR)	0.66 (0.30-1.44)	0.30	—	—
***Grade III (vs. II)**	**2.24 (1.01-4.94)**	**0.046**	—	—
‡*MKI67* exp.	1.04 (0.84-1.29)	0.71	0.97 (0.78-1.21)	0.81
ATRX mut.	2.93 (0.38-22.67)	0.30	2.09 (0.27-16.3)	0.483
CIC mut.	0.61 (0.29-1.27)	0.18	0.58 (0.28-1.20)	0.140
***_FUBP1_ mut.**	**2.48 (1.14-5.38)**	**0.022**	2.14 (0.98-4.69)	0.058
NOTCH1 mut.	2.07 (0.93-4.60)	0.091	1.52 (0.66-3.53)	0.33
PIK3 mut.	1.91 (0.87-4.23)	0.11	1.98 (0.89-4.40)	0.092
***_RBPJ + NOTCH1 mut._**	**2.47 (1.14-5.34)**	**0.021**	1.86 (0.82-4.20)	0.13
TP53 mut.	2.57 (0.60-11.03)	0.21	2.57 (0.59-11.26)	0.211
7p gain	0.55 (0.07-4.11)	0.56	0.42 (0.06-3.19)	0.404
11p gain	1.31 (0.38-4.44)	0.67	1.19 (0.35-4.08)	0.779
***†14q loss**	**3.70 (1.49-9.20)**	**0.010**	**3.90 (1.56-9.74)**	**0.0035**
15q loss	1.75 (.073-4.19)	0.21	1.72 (0.70-4.22)	0.239
‡*HES1* exp.	0.75 (0.49-1.15)	0.18	0.70 (0.45-1.10)	0.118
‡*HES2* exp.	1.01 (0.96-1.08)	0.67	1.02 (0.95-1.10)	0.638
†‡*HES5* exp.	0.83 (0.68-1.02)	0.076	0.86 (0.71-1.04)	0.120
***†‡_HEY1_ exp.**	**0.41 (0.23-0.72)**	**0.0022**	**0.475 (0.26-0.88)**	**0.018**
‡*HEY2* exp.	0.87 (0.53-1.44)	0.59	0.96 (0.57-1.61)	0.869

Supplemental Figures

Figure S1. Boxplots of the Monte-Carlo cross validation of the genetic-protein and gene expression survival neural networks. The median c-index of the tested genetic-protein models was 0.8 (+/- 0.124), while the median c-index of the tested gene expression models was 0.752 (+/- 0.196).

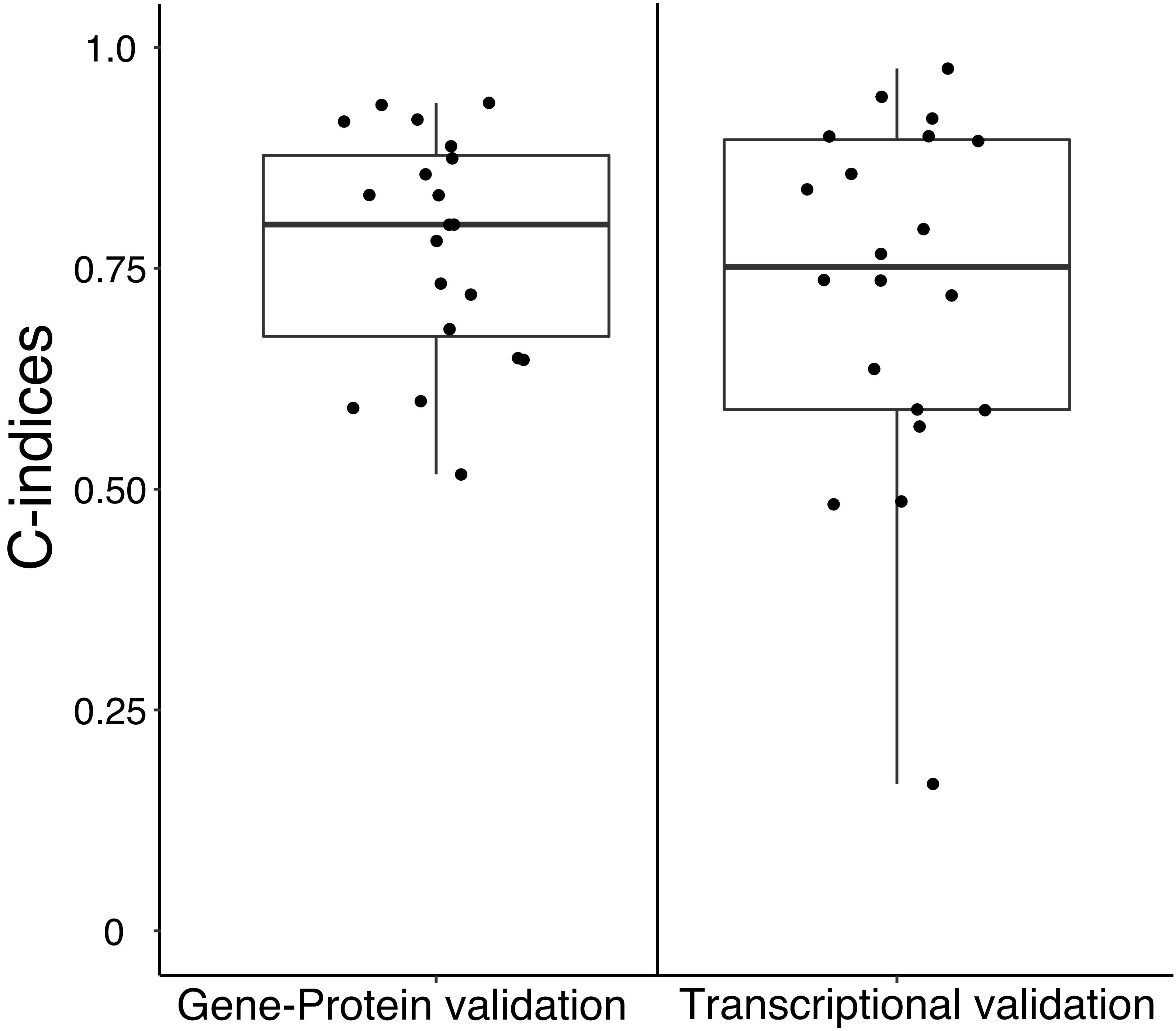
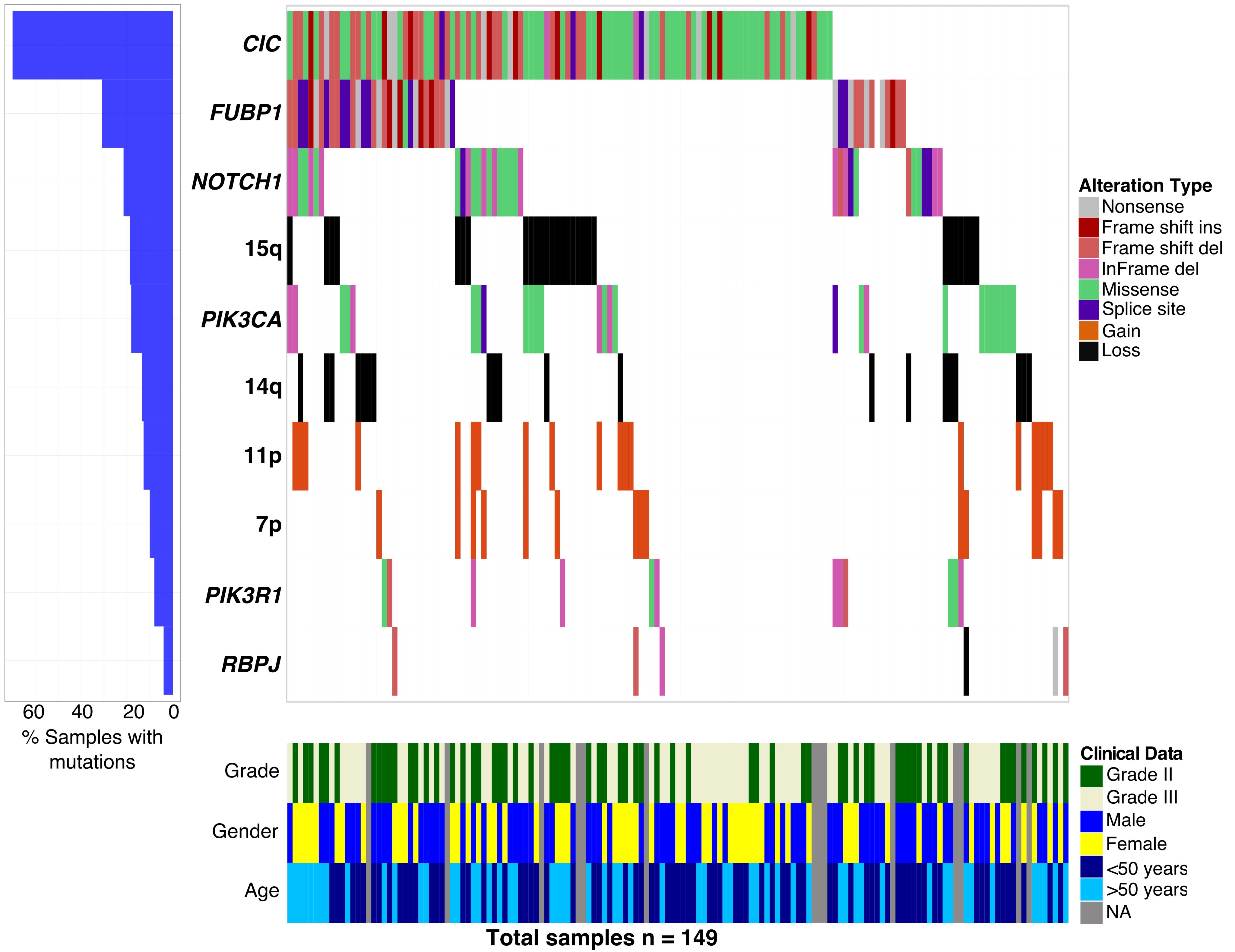

C-indices
1.0
0.75
0.50
0.25
0
Gene-Protein validation
Transcriptional validation

Figure S2. A waterfall plot of the most frequent genetic alterations found in oligodendroglioma.



CIC
FUBP1
NOTCH1
15q
PIK3CA
14q
11p
7p
PIK3R1
RBPJ
60
40
20
0
% Samples with mutations
Alteration Type
Nonsense
Frame shift ins
Frame shift del
InFrame del
Missense
Splice site
Gain
Loss
Grade
Gender
Age
Clinical Data
Grade II
Grade III
Male
Female
<50 years
>50 years
NA
Total samples n = 149

Figure S3. Boxplots demonstrating the differential cellular density using nearest neighbor distances between altered and unaltered oligodendroglioma.

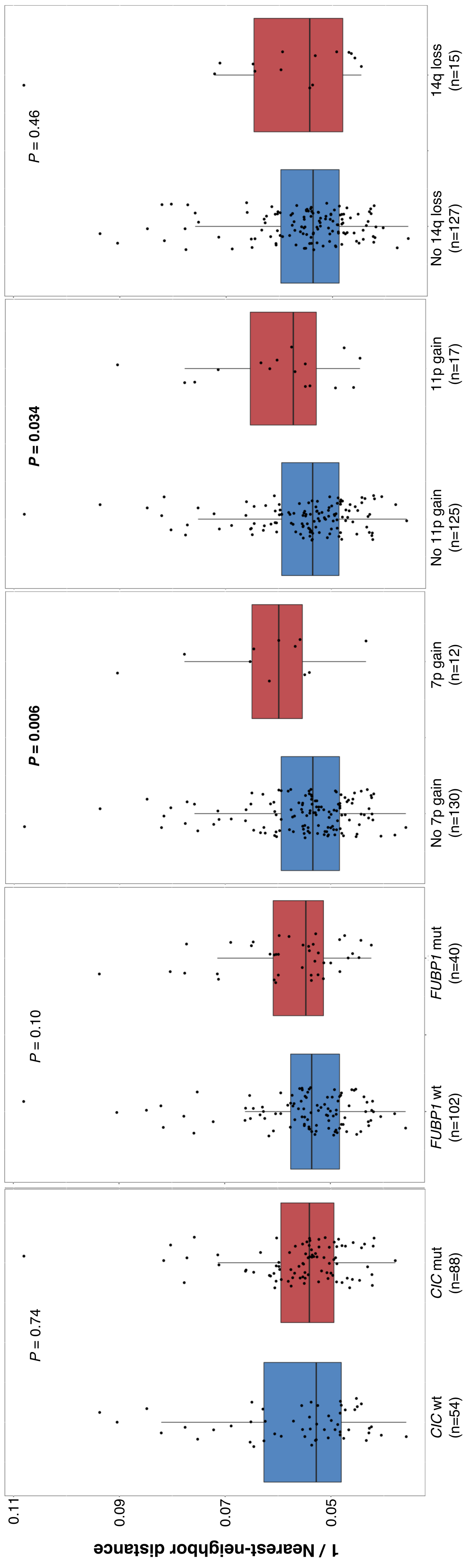

1 / Nearest-neighbor distance
0.11
0.09
0.07
0.05
P = 0.74
CIC wt (n=54)
CIC mut (n=88)
P = 0.10
FUBP1 wt (n=102)
FUBP1 mut (n=40)
P = 0.006
No 7p gain (n=130)
7p gain (n=12)
P = 0.034
No 11p gain (n=125)
11p gain (n=17)
P = 0.46
No 14q loss (n=127)
14q loss (n=15)

Figure S4. Boxplots demonstrating differences in *MKI67* gene expression, and thus cellular proliferation, between altered and unaltered oligodendroglioma.

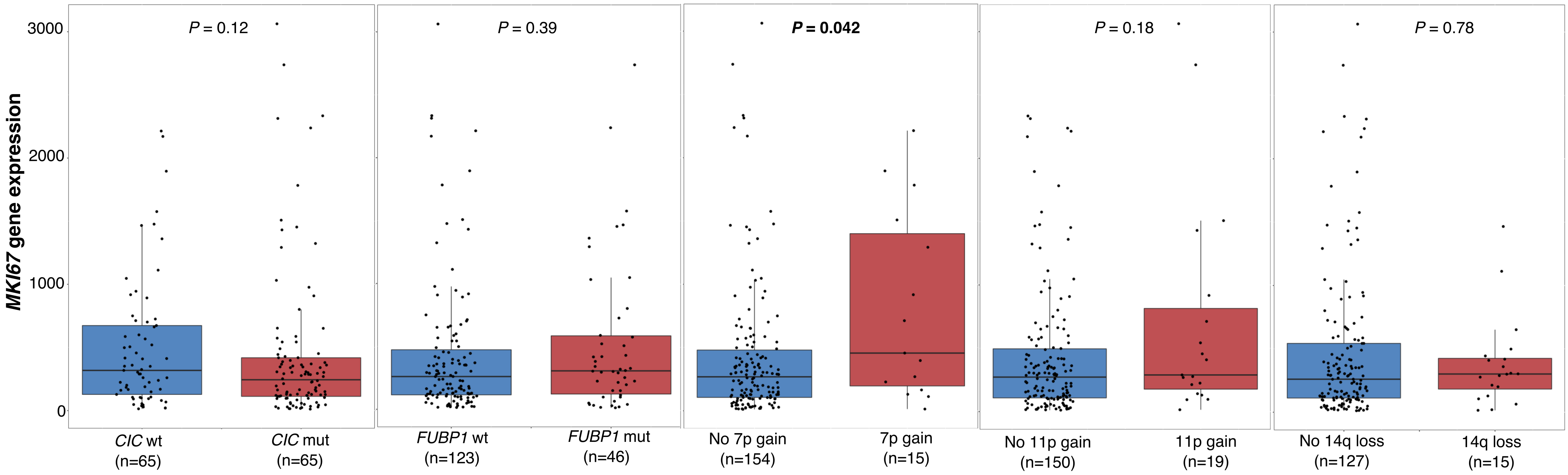
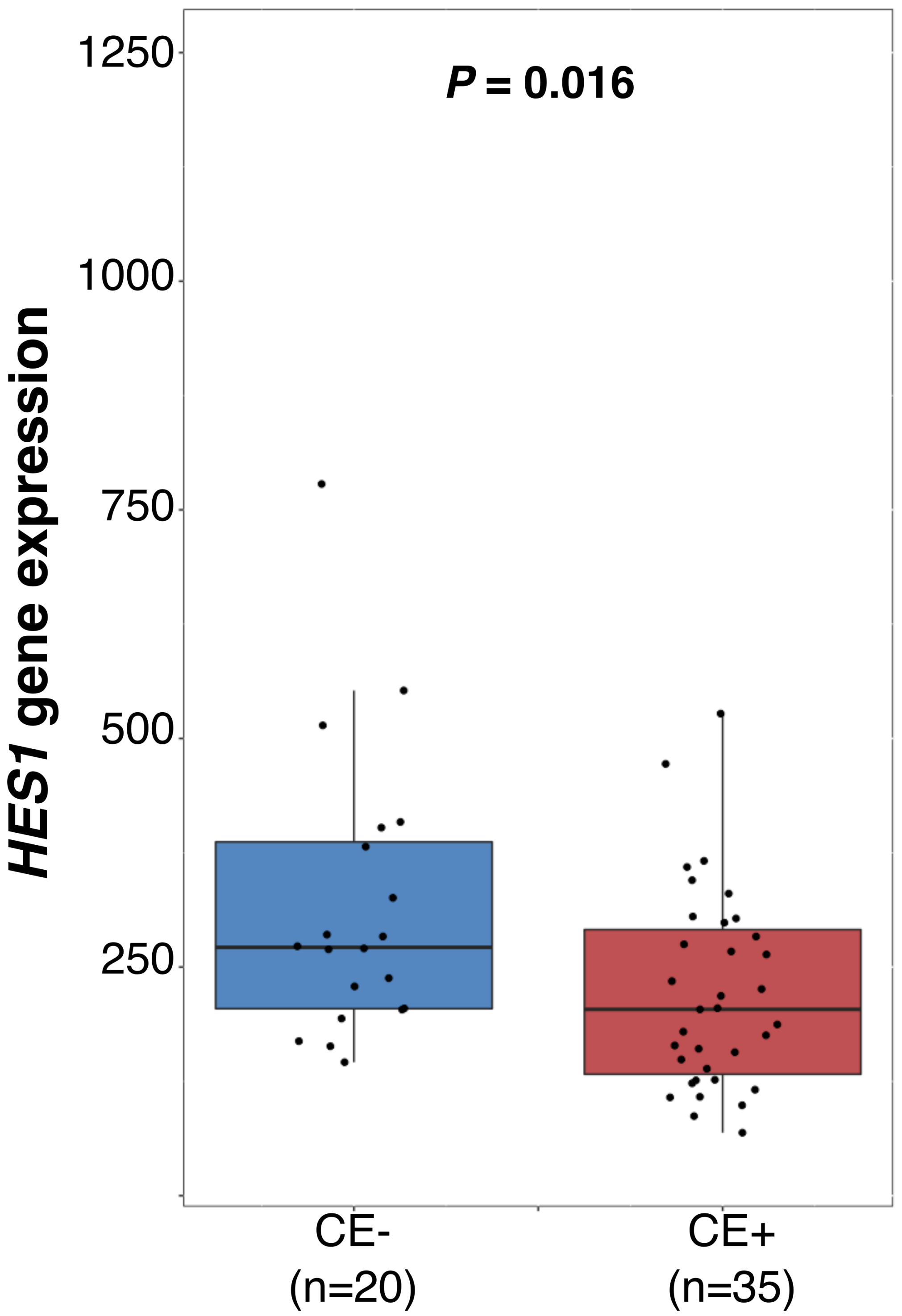

MKI67 gene expression
3000
2000
1000
0
P = 0.12
P = 0.39
P = 0.042
P = 0.18
P = 0.78
CIC wt (n=65)
CIC mut (n=65)
FUBP1 wt (n=123)
FUBP1 mut (n=46)
No 7p gain (n=154)
7p gain (n=15)
No 11p gain (n=150)
11p gain (n=19)
No 14q loss (n=127)
14q loss (n=15)

Figure S5. Boxplots illustrating differences in gene expression of downstream Notch pathway targets, HES1 and HEY1, between contrast enhancing and non-enhancing oligodendroglioma.


P = 0.016
HES1 gene expression
1250
1000
750
500
250
CE-
(n=20)
CE+
(n=35)

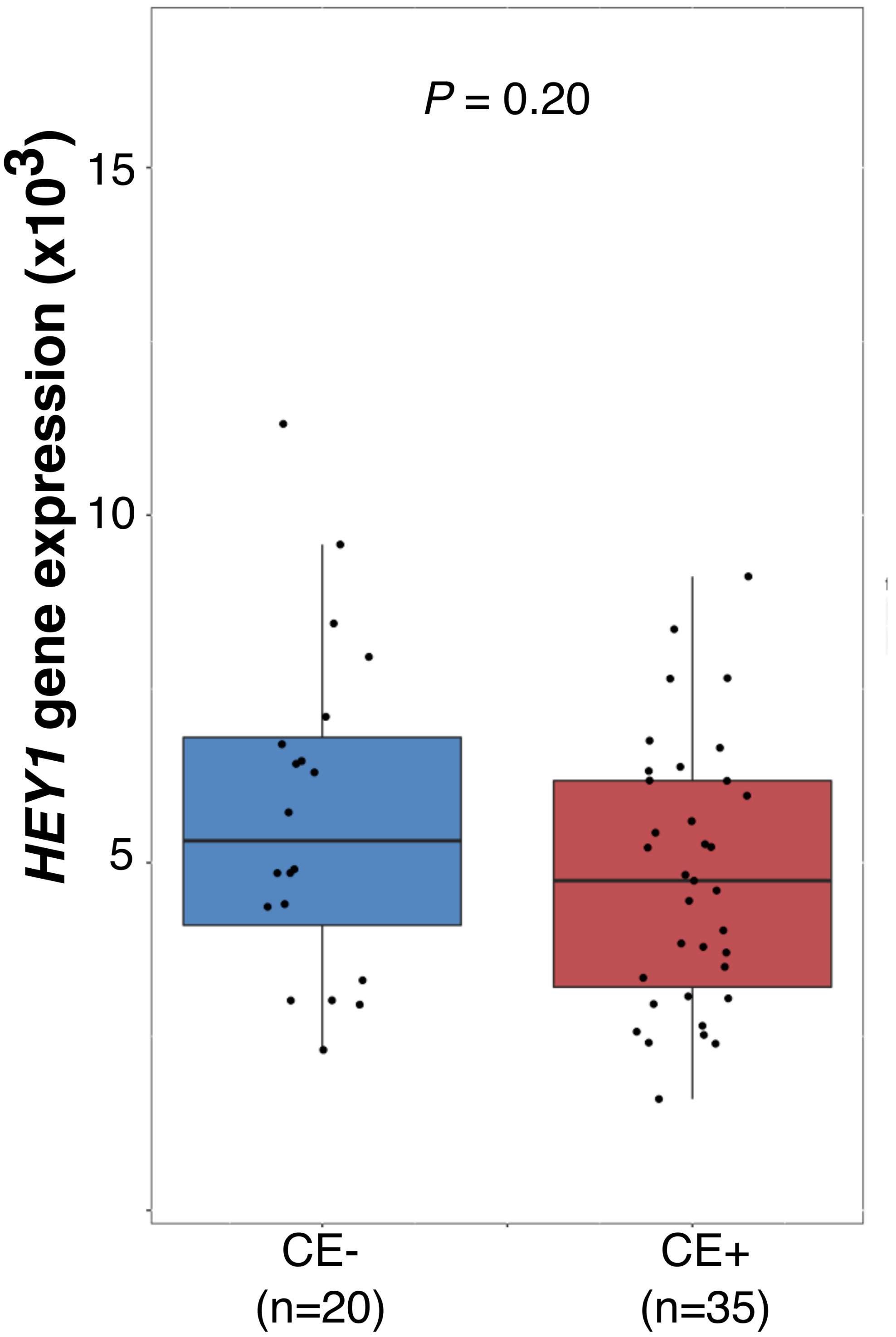

P = 0.20
HEY1 gene expression (x10³)
15
10
5
CE-
(n=20)
CE+
(n=35)

Figure S6. Boxplots demonstrating the differences in cellular density and proliferation in tumors with and without RBPJ mutations, and those tumors with both NOTCH1 and RBPJ mutations and without.

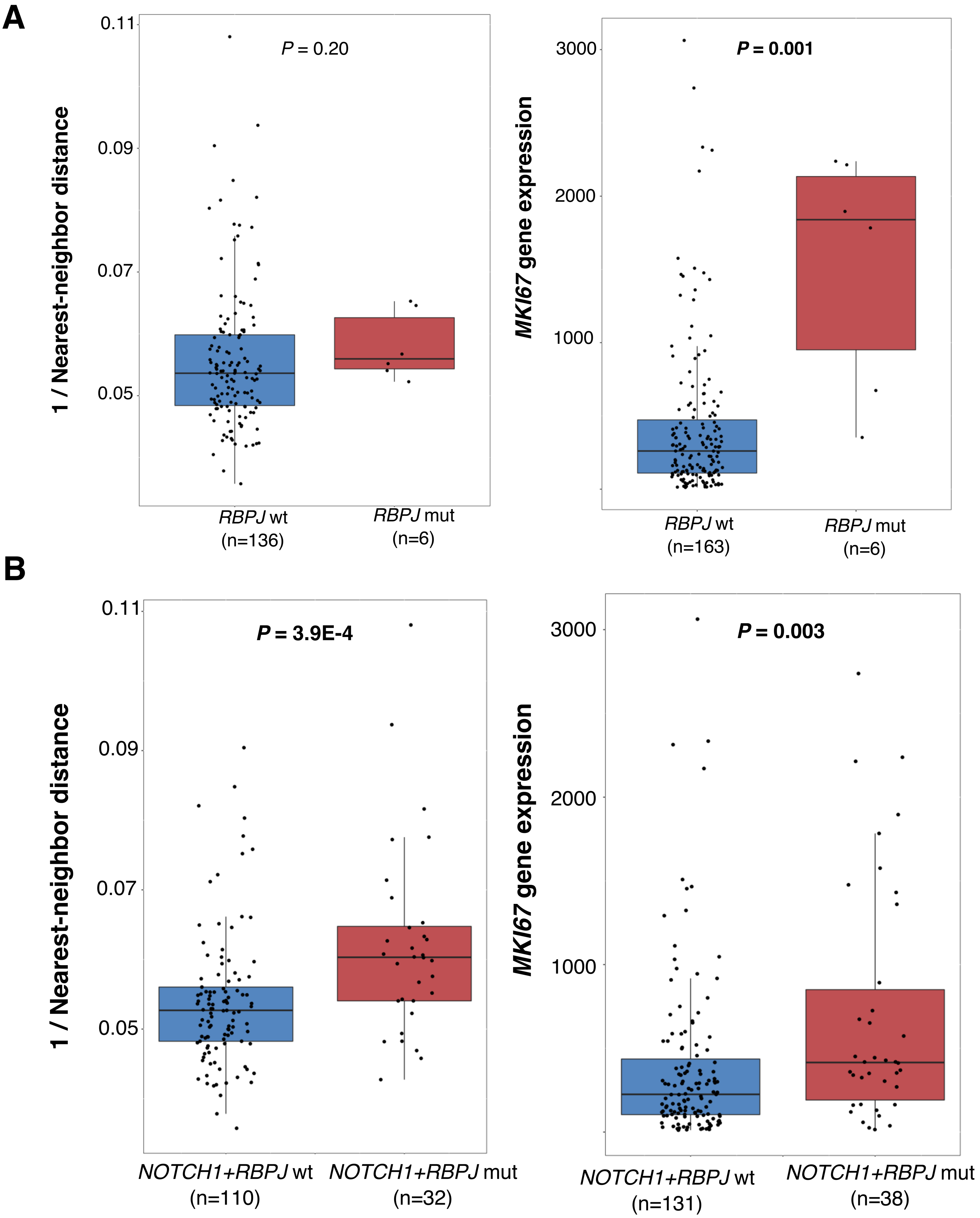

A
1 / Nearest-neighbor distance
0.11
0.09
0.07
0.05
P = 0.20
RBPJ wt (n=136)
RBPJ mut (n=6)
MKI67 gene expression
3000
2000
1000
P = 0.001
RBPJ wt (n=163)
RBPJ mut (n=6)
B
1 / Nearest-neighbor distance
0.11
0.09
0.07
0.05
P = 3.9E-4
NOTCH1+RBPJ wt (n=110)
NOTCH1+RBPJ mut (n=32)
MKI67 gene expression
3000
2000
1000
P = 0.003
NOTCH1+RBPJ wt (n=131)
NOTCH1+RBPJ mut (n=38)

Figure S7. Kaplan-Meier plots for overall survival (OS) of the key genetic alterations found in oligodendroglioma. Statistical significance was assessed using log-rank tests.

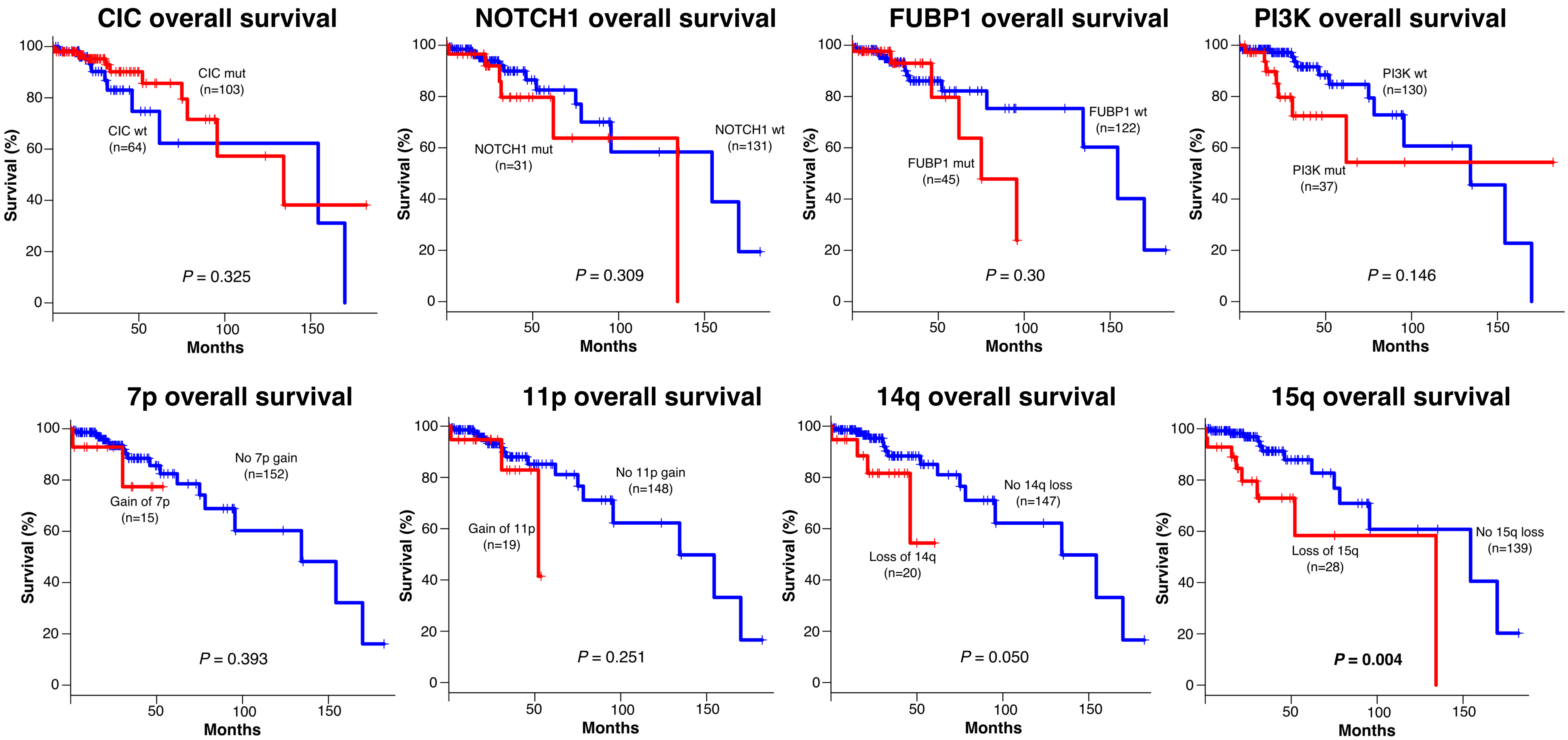
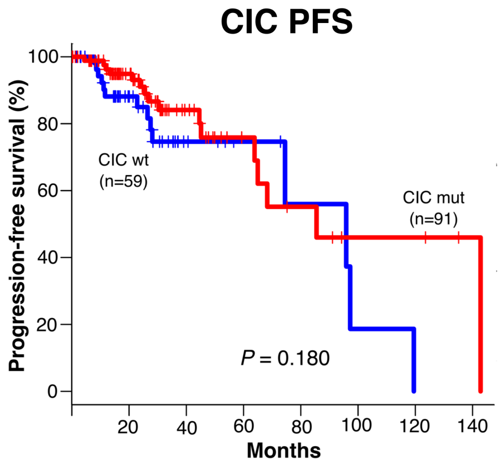
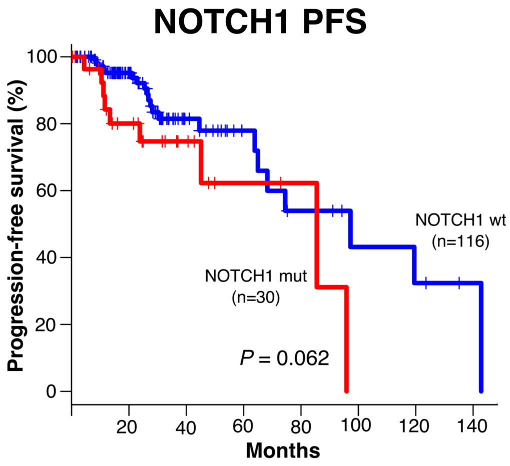
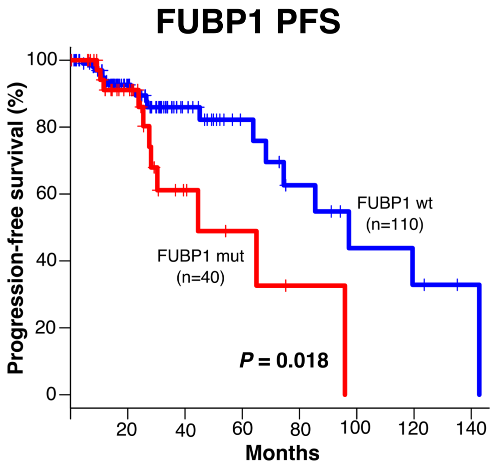
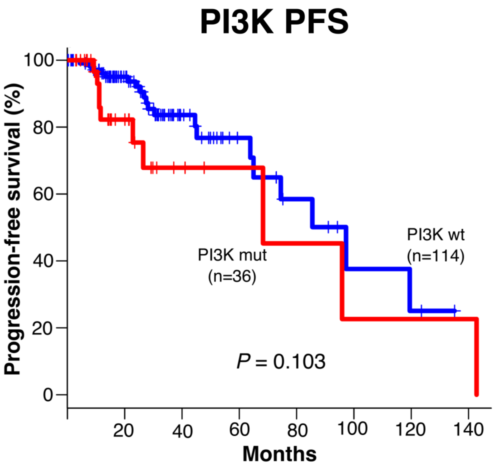

CIC overall survival
Survival (%)
100
80
60
40
20
0
50
100
150
Months
CIC mut
(n=103)
CIC wt
(n=64)
P = 0.325
NOTCH1 overall survival
NOTCH1 mut
(n=31)
NOTCH1 wt
(n=131)
P = 0.309
FUBP1 overall survival
FUBP1 mut
(n=45)
FUBP1 wt
(n=122)
P = 0.30
PI3K overall survival
PI3K wt
(n=130)
PI3K mut
(n=37)
P = 0.146
7p overall survival
No 7p gain
(n=152)
Gain of 7p
(n=15)
P = 0.393
11p overall survival
No 11p gain
(n=148)
Gain of 11p
(n=19)
P = 0.251
14q overall survival
No 14q loss
(n=147)
Loss of 14q
(n=20)
P = 0.050
15q overall survival
No 15q loss
(n=139)
Loss of 15q
(n=28)
P = 0.004

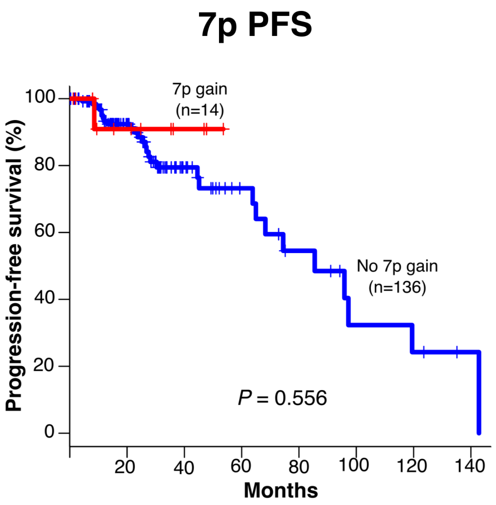
Figure S8. Kaplan-Meier plots for progression-free survival (PFS) of the key genetic alterations found in oligodendroglioma. Statistical significance was assessed using log-rank tests.

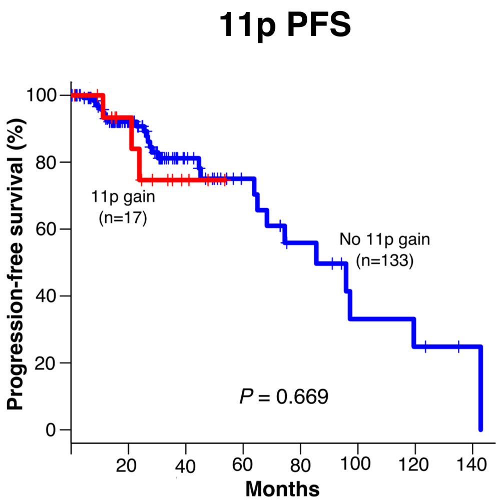

CIC PFS
Progression-free survival (%)
100
80
60
40
20
0
CIC wt
(n=59)
CIC mut
(n=91)
P = 0.180
20
40
60
80
100
120
140
Months

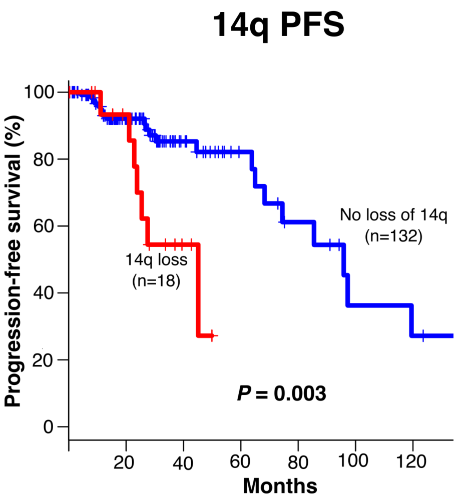

NOTCH1 PFS
Progression-free survival (%)
100
80
60
40
20
0
NOTCH1 wt
(n=116)
NOTCH1 mut
(n=30)
P = 0.062
20
40
60
80
100
120
140
Months

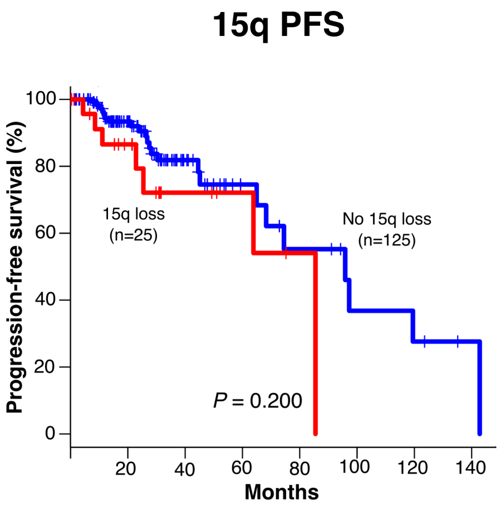

FUBP1 PFS
Progression-free survival (%)
100
80
60
40
20
0
FUBP1 wt
(n=110)
FUBP1 mut
(n=40)
P = 0.018
20
40
60
80
100
120
140
Months


PI3K PFS
Progression-free survival (%)
100
80
60
40
20
0
PI3K mut
(n=36)
PI3K wt
(n=114)
P = 0.103
20
40
60
80
100
120
140
Months


7p PFS
Progression-free survival (%)
100
80
60
40
20
0
7p gain
(n=14)
No 7p gain
(n=136)
P = 0.556
20
40
60
80
100
120
140
Months


11p PFS
Progression-free survival (%)
100
80
60
40
20
0
11p gain
(n=17)
No 11p gain
(n=133)
P = 0.669
20
40
60
80
100
120
140
Months


14q PFS
Progression-free survival (%)
100
80
60
40
20
0
No loss of 14q
(n=132)
14q loss
(n=18)
P = 0.003
20
40
60
80
100
120
Months


15q PFS
Progression-free survival (%)
100
80
60
40
20
0
15q loss
(n=25)
No 15q loss
(n=125)
P = 0.200
20
40
60
80
100
120
140
Months