The DCCC Brain Tumor Center

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Genetic variants associated with distant recurrence in glioblastoma patients treated with standard therapy

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Background

Migratory growth is a hallmark of glioblastoma (GBM) and is a major factor in therapeutic failure.

Distant recurrence predicts poor prognosis.[1]
Unmethylated *MGMT* predicts distant recurrence.[1]

Genetic variants serve as targets for personalized therapy.[2]

Hypothesis: Genetic variants that predict distant recurrence (migratory growth) represent key treatment targets.

[1] **Abstract #: BIOM-24**, Chiranth SB et al.
[2] **Abstract #: CTNI-32**, Fougner VN et al.

Methods

Patients
All GBM IDHwt patients who received standard therapy at Rigshospitalet (year 2016-21) and underwent genomic tumor profiling were included.

Patterns of recurrence

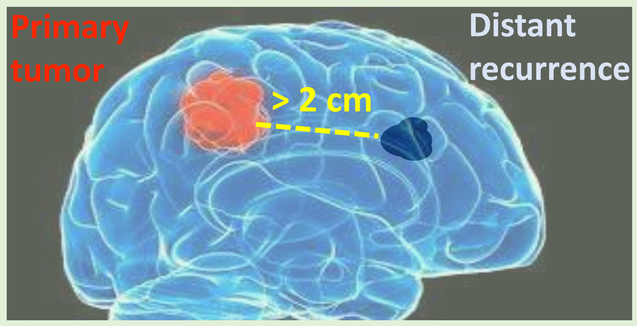

Figure 1. Distant recurrence: New tumor lesion more than 2 cm from the primary tumor.

Genomic tumor profiling
Tumor tissue was analyzed by DNA- (WES or WGS) and RNA-sequencing.

Candidate biomarkers
Pathogenic or likely-pathogenic variants, defined by the Genomic reports,[2] were grouped accordingly:

i) Gene mutations (present in >2% of samples).
ii) Number of mutations per sample.
iii) The presence of mutation in the four classical signaling pathways

Statistics
Cox regression analysis was used to model the association with time to distant recurrence.

AIM: Identify genetic variants associated with distance recurrence in glioblastoma patients

Results

Table 1. Patient characteristics, *n* = 204

Median age, years (range)	58 (18-77)
Female gender, n (%)	70 (34)
ECOG PS 0-1, n (%)	193 (96)
Subependymal, n (%)	85 (42)
Multifocal, n (%)	17 (8)
Resection, n (%)	180 (89)
MRI surgical extent, n (%)	
Measurable	39 (23)
Non-measurable	61 (37)
No residual contrast	67 (40)
Missing	13
Steroid use, n (%)	82 (40)
MGMT methylated, n (%)	91 (45)
Median PFS (95% CI), months	7.5 (7.0-8.0)
Resection at relapse, n (%)	92 (47)
Second line therapy, n (%)	160 (82)
Median OS (95% CI), months	19.5 (17.1-21.9)

Table 2. Pattern of recurrence

Local, *n* (%)	151 (81)
Distant, *n* (%)	35 (19)
No recurrence, n (%)	10
Missing, n (%)	8

Table 3. Biomarkers associated with distant recurrence (Univar.)

	HR (95%CI)
***NF1* mutation** *n* = 23 (11%)	3.46 (1.51-7.94) *p* = 0.003

Table 4. Prognostic model for distant recurrence

	HR (95%CI) *p*-value
***MGMT* unmethylated**	2.75 (1.25-6.01) 0.01
***NF1* mutation**	3.03 (1.30-7.07) 0.01

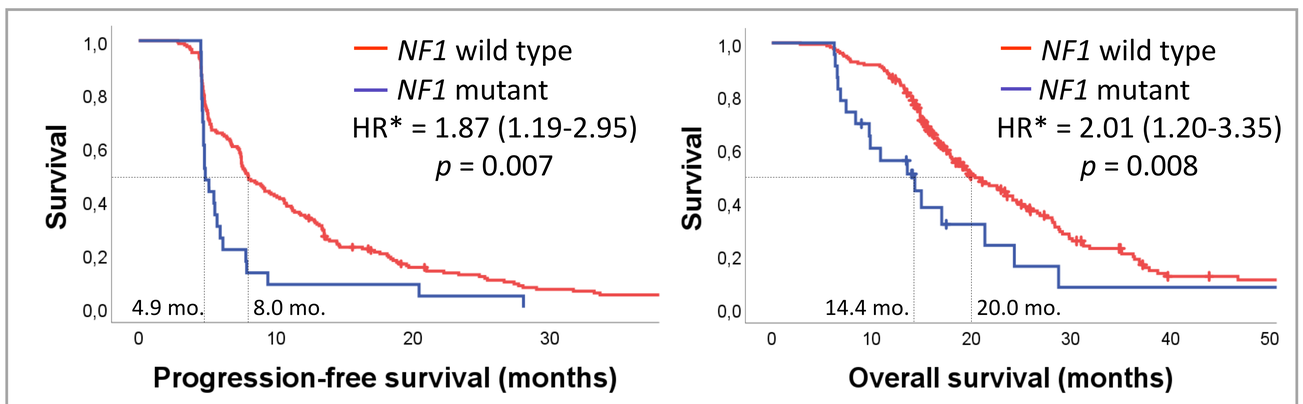

Figure 2. *NF1* mutation is an independent prognostic factor for PFS and OS.
* HR adjusted for PS, age, steroid use, MGMT, resection, and multifocal disease.

Conclusion

- *NF1* mutation predicts distance recurrence.
- *NF1* mutation is an independent predictor of poor progression-free survival and overall survival.
- *NF1* may promote migratory growth.
- Glioblastoma patients with *NF1* mutations may benefit from personalized targeted treatment.

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