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Incidence of *NTRK* genes fusion in adult brain tumours : a prospective cohort of 140 patients with cerebral gliomas and brain metastases

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Background

The *NTRK* (Neurotrophic Tyrosine Receptor Kinase) gene family encodes three tropomyosin-related kinase (TRK) receptors. *NTRK* genes (*NTRK1*, *NTRK2*, or *NTRK3*) are subject to alterations, including fusions. Oncogenic TRK fusions induce cancer cell proliferation and engage critical cancer-related downstream signalling pathways. These TRK fusions occur rarely, in a diverse spectrum of tumour histologies. TRK fusion kinase receptor inhibitors, specifically larotrectinib and entrectinib have emerged as potent, safe, and promising TRK inhibitors. They demonstrated encouraging antitumor activity with response rates (>75%), with acceptable toxicity profile in patients with *NTRK*-rearranged malignancies. Due to the excellent efficacy of TRK inhibitor therapy, it is clinically important to accurately and efficiently identify patients with oncogenic TRK fusions. In this retrospective study, we provide unique data on the incidence of oncogenic *NTRK* gene fusions in adult patients with brain metastases (BM) and gliomas.

Methods

Design study : retrospective study

Population : 140 samples fixed and paraffin-embedded tissue of adult patients (59 of gliomas [19 of WHO grade II, 20 of WHO grade III and 20 glioblastomas] and 81 of BM of different primary tumours) are analysed.

Identification of *NTRK* gene fusions : RNA-based next-generation sequencing (NGS) technology on the Ion Torrent S5XL automaton with the OncoPrint Focus RNA assay kit (ThermoFisher) was used. The analysis is carried out using the Ion Reporter software. A minimum of 50,000 mapped reads is required to allow interpretation of the result.

Results

Table 1: Patient's Characteristics.

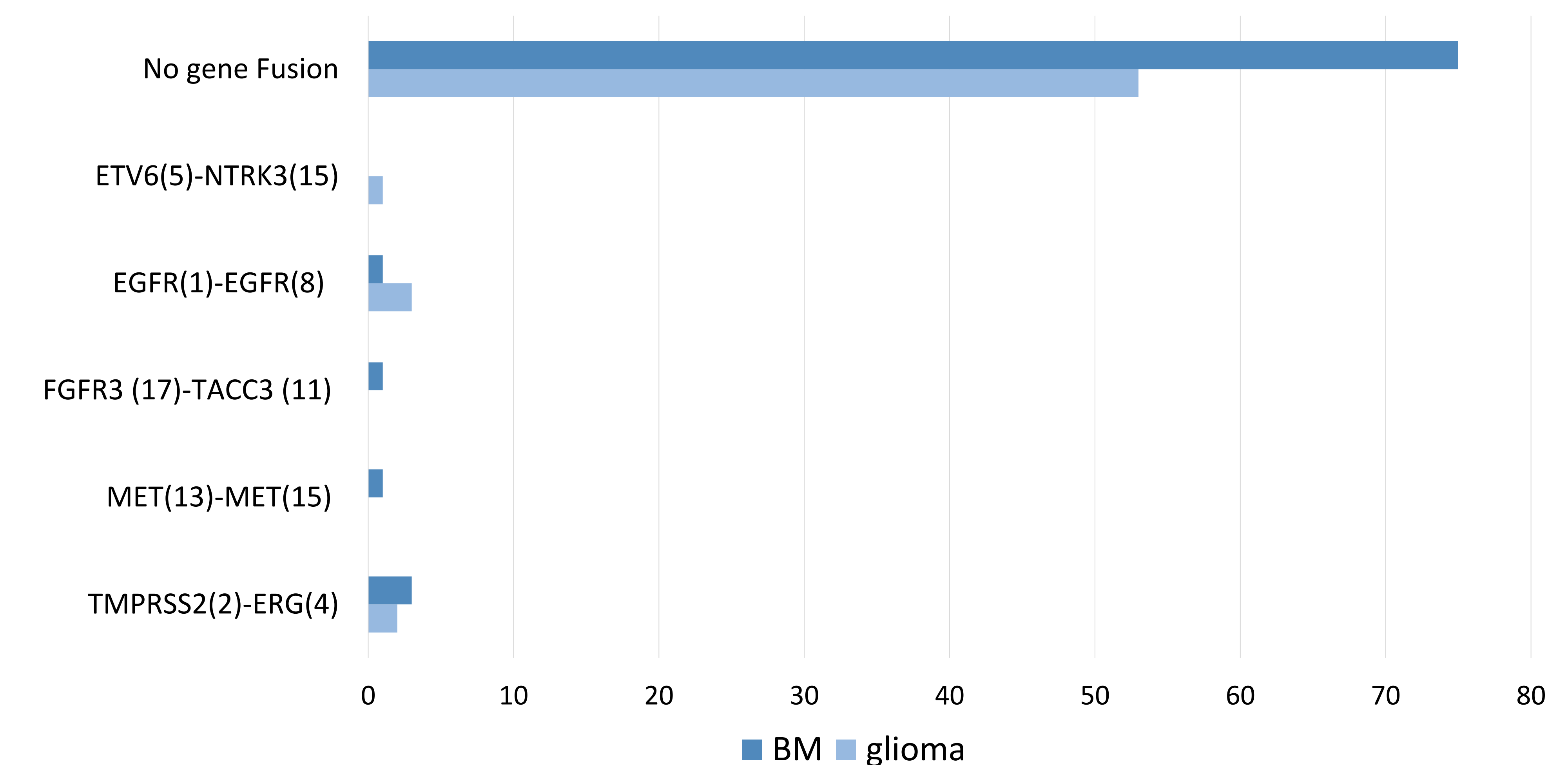
Characteristics	Gliomas n = 59	BMs n = 81
Age at surgery, yrs		
Median	50.4	66.0
Mean +/- SD	50.4 +/- 1.0	64.4 +/- 11.4
Range	24.8 – 85.2	31.9 – 85.7
Sex		
Males	37 (62.7%)	35 (43.2%)
Females	22 (37.3%)	46 (56.8%)
Histology		
Grade II glioma	19 (32.2%)	
Grade III glioma	20 (33.9%)	
Glioblastoma	20 (33.9%)	
Lung BM		21 (25.9%)
Breast BM		23 (28.4%)
Melanoma BM		3 (3.7%)
Colon BM		9 (11.1%)
Kidney BM		6 (7.4%)
Digestive BM		6 (7.4%)
Prostate BM		3 (3.7%)
Others* BM		10 (12.4%)

* urothelial BM, ovary BM, endometrium BM, pancreas BM, parotid BM, rectal BM

Table 2: Gene Fusion identified.

Fusion	Number Fusions n=140	Histology tumors (n; %)
NTRK gene fusion		
NTRK1	0 (0%)	
NTRK2	0 (0%)	
NTRK3	1 (0.7%)	Grade II glioma (1/59; 1.7%)
Other gene fusion		
EGFR(1)-EGFR(8)	4 (2.8%)	Glioblastoma (3/59; 5.1%) Ovary BM (1/81; 1.2%)
MET (13)-MET(15)	1 (0.7%)	Pancreas BM (1/81; 1.2%)
FGFR3(17)-TACC3(11)	1 (0.7%)	Breast BM (1/81; 1.2%)
TMPRSS2(2)-ERG(4)	5 (3.5%)	Grade II gliomas (2/59; 3.4%) Endometrium BM (1/81; 1.2%) Prostate BM (1/81; 1.2%)

Gene fusion



Among the 140 samples (glioma and BM) analysed, one *NTRK3* gene fusion was identified in a WHO grade II glioma sample

Conclusion

The rate of occurrence of *NTRK* fusions in adult-type brain tumors and BM is low with one *ETV6-NTRK3* fusion was detected in a WHO grade II glioma, due to the size of the population analysed, this study provides pioneering data on the incidence of *NTRK* gene fusions in brain tumors and suggest that it is worth looking for the *NTRK* fusions in adult-type brain tumors taking account the efficiency of TRK fusion kinase inhibitors.