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Moderate-to-strong expression of FGFR3 and TP53 alterations in a subpopulation of choroid plexus tumors

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Summary. Deregulation of fibroblast growth factor receptor (FGFR) signaling is tightly associated with numerous human malignancies, including cancer. Indeed, FGFR inhibitors are being tested as anti-tumor drugs in clinical trials. Among gliomas, FGFR3 fusions occur in IDH wild-type diffuse gliomas leading to high FGFR3 protein expression and both, FGFR3 and FGFR1, show elevated expression in aggressive ependymomas. The aim of this study was to uncover the expression of FGFR1 and FGFR3 proteins in choroid plexus tumors and to further characterize *FGFR*-related as well as other genetic alterations in FGFR3 expressing tumors.

Expression levels of FGFR1 and FGFR3 were detected in 15 choroid plexus tumor tissues using immunohistochemistry of tissue microarrays and 6 samples were subjected to whole mount FGFR3 staining. Targeted sequencing was used for deeper molecular analysis of two FGFR3 positive cases.

Moderate expression of FGFR1 or FGFR3 was evidenced in one third of the studied choroid plexus tumors. Targeted sequencing of a choroid plexus carcinoma and an atypical choroid plexus papilloma, both with moderate-to-strong FGFR3 expression, revealed lack of protein-altering mutations or fusions in *FGFR1* or *FGFR3,* but *TP53* was altered in both tumors.

FGFR3 and FGFR1 proteins are expressed in a subpopulation of choroid plexus tumors. Further studies using larger cohorts of patients will allow identification of the clinicopathological implications of FGFR1 and FGFR3 expression in choroid plexus tumors.

Key words: Tissue microarray, Deep-sequencing, FGFR gene fusion, Immunohistochemical staining, Brain tumor

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Introduction

The fibroblast growth factor receptor (FGFR) family belongs to the receptor tyrosine kinase superfamily and is comprised of four members (FGFR1-FGFR4). All in all, FGFR signaling is associated with regulation of such cellular responses as cell growth, proliferation, differentiation and survival. Furthermore, the oncogenic properties of FGFRs are well established in a variety of cancers (Wesche et al., 2011; Parker et al., 2014). In glioblastoma, recurrent *FGFR* gene fusions have been detected (Singh et al., 2012; Parker et al., 2013), leading to good expectations for therapies based on FGFR inhibitors for those brain tumors that harbor *FGFR* alterations. Various mechanisms of FGFR activation exist in brain tumors, varying by tumor type, and including oncogenic *FGFR3* and *FGFR1* fusions, *FGFR1* rearrangements, and *FGFR1* mutations (Rand et al., 2005; Singh et al., 2012; Jones et al., 2013; Parker et al., 2013, 2014; Zhang et al., 2013; Di Stefano et al., 2015). For *FGFR3*, gene fusions seem to be the sole

recurrent oncogenic alteration found in brain tumors. *FGFR3* is commonly fused to the transforming acidic coiled-coil-containing protein 3 (*TACC3*) gene, and other fusion partners exist as well (Granberg et al., 2017). There are currently several FGFR inhibitors under pre-clinical and clinical evaluation, with recent reports showing good treatment responses in *FGFR3* fusion positive cells and tumors (Dieci et al., 2013; Dienstmann et al., 2014; Di Stefano et al., 2015). A good example of successful results is the use of JNJ-42756493 (Erdafitinib) for the treatment of urothelial cancers with actionable FGFR alterations, which was recently granted the Breakthrough Therapy Designation by the U.S. Food and Drug Administration (FDA). Although most of the FGFR inhibitor studies to date have been performed on carcinomas, positive responses have also been reported in glioblastoma patients (Di Stefano et al., 2015; Tabernero et al., 2015). Choroid plexus tumors are rare intraventricular neuroepithelial tumors derived from the choroid plexus of the brain. Their classification ranges from benign choroid plexus papillomas (CPP, WHO grade I) to malignant choroid plexus carcinomas (CPC, WHO grade III) (Safaee et al., 2013; Louis et al., 2016). While CPP may be effectively treated with surgical resection, patients with CPC have a 5-year overall survival rate of approximately 50% (Merino et al., 2015). Choroid plexus tumors can affect both pediatric and adult patients, CPC being more frequent among children and CPP among adults (Cannon et al., 2015; Dudley et al., 2015). Over half of the patients with CPC (and around 5 % of those with CPPs) carry somatic *TP53* mutations (Safaee et al., 2013; Merino et al., 2015) and carrying two copies of mutant *TP53* is associated with the worst survival (Merino et al., 2015). DNA copy number alterations also appear to be distinctively different for these specific tumor subtypes, suggesting different routes for tumor development (Rickert et al., 2002; Merino et al., 2015).

FGFR3 protein level is certainly an informative marker for fusion status in diffuse gliomas (Granberg et al., 2017). In a cohort of 791 cases, most of the tumors were devoid of any detectable FGFR3 protein expression, while all the fusion-positive cases were strongly stained (sensitivity 100 % and specificity 88% for fusion detection). Among non-diffuse gliomas, *FGFR1* alterations are commonly found in a subset of pilocytic astrocytomas that lack other usual MAPK pathway alterations (Jones et al., 2013; Zhang et al., 2013). Furthermore, FGFR1 and FGFR3 expression levels are elevated in aggressive ependymomas (Lehtinen et al., 2017). Thus far, however, *FGFR* fusions or increased FGFR protein expression levels have not been reported to occur in choroid plexus tumors. In the present study, we sought to investigate the expression of FGFR3 and FGFR1 in neuroepithelial tumors of the choroid plexus. We used immunohistochemistry to detect FGFR1 and FGFR3 protein levels and targeted sequencing of selected FGFR3-positive samples to identify genetic alterations in relevant genes.

Materials and methods

Patient samples

The study cohort included 15 choroid plexus tumors from 13 patients (Table 1) that underwent neurosurgical operation between 1989 and 2005 at Tampere University Hospital. This study was approved by the Ethical Committee of Tampere University Hospital and the National Authority for Medico-legal Affairs in Finland. All procedures involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or

Table 1. Patient demographics and clinical characteristics within the study cohort.

Patients	13
Male	6
Female	7
Age (years)	
Median (Mean ± SD)	4 (30±34)
Minimum	0
Maximum	78
Follow-up for primary tumor patients	
Survivors in the end of the follow-up	5
Follow-up time for survivors (m) (median (mean ± SD))	135 (133±94)
5-year recurrence-free survival (%)	60
5-year overall survival (%)	80
Survival and FGFR3 staining	
5-year recurrence-free survival (%)	
FGFR3 positive	65
FGFR3 negative	80
5-year overall survival (%)	
FGFR3 positive	100
FGFR3 negative	75
Survival and FGFR1 staining	
5-year recurrence-free survival (%)	
FGFR1 positive	75
FGFR1 negative	75
5-year overall survival (%)	
FGFR1 positive	75
FGFR1 negative	90
Tumors	15
Primary	8
Second	6
Third	1
Histological grade	
I	10
II	1
III	4
Topography	
Supratentorial	11
Infratentorial	4

Patient age and follow-up information were calculated using primary cases. No statistically significant differences were found between survivals of FGFR1/3 positive and negative cases. Follow-up times are shown in months (m). SD: standard deviation.

comparable ethical standards.

Tissue histopathology, tissue microarrays and immunohistochemistry

Processing of tissue samples for histopathological evaluation, construction of the tissue microarrays (TMAs) and immunohistochemistry were performed as previously described (Lehtinen et al., 2017) with the following addition: mouse monoclonal TP53 antibody (790-2912 0.5 μg/ml, Roche, Basel, Switzerland) was used for TP53 staining. Briefly, tissue sections from formalin-fixed paraffin-embedded (FFPE) samples were typed and graded from hematoxylin and eosin stained samples, and TMAs were constructed from representative sample regions. Staining of whole mount sections was done as described before (Lehtinen et al., 2017) for the two samples stained for FGFR1 and for two out of six samples stained with FGFR3. The remaining four FGFR3-stained samples were detected using N-Histofine High Stain HRP (MULTI) kit (Nichirei Biosciences, Tokyo, Japan) according to the manufacturer's instructions. Immunohistochemical staining for FGFR1 and FGFR3 was followed by scoring by a 4-step scale as follows: 0 (no staining), 1 (weak immunostaining), 2 (moderate immunostaining), or 3 (strong immunostaining). TP53 staining was scored using a binary code where 1 is given when more than five percent of the nuclei are positive and 0 when the proportion is five or less.

Targeted sequencing and data analysis

Targeted sequencing was performed as described before (Lehtinen et al., 2017). Briefly, DNA was extracted from FFPE samples using the AllPrep DNA/RNA Mini Kit (Qiagen, Hilden, Germany) and 1 μg was used as input for targeted sequencing with the SureSelect XT Target enrichment system (Agilent Technologies, Santa Clara, CA) and custom-designed RNA probes, including *FGFR1, FGFR3* and miR-99a loci, *EGFR* gene, the promoter of *TERT*, all exons from *RB1, PTPRD, TACC1, TACC3, CDKN2A, PTEN, PTPN11, PDGFRA* and *MET*, all exons in the coding region of *PIK3CA*, and certain exons from *ATRX, TP53, IDH1, IDH2, RELA,* and *BRAF*. The precise coordinates for all the targeted regions have been published elsewhere (Lehtinen et al., 2017). The analysis flow for detection of point mutations as well as copy number analyses have been described previously (Lehtinen et al., 2017).

Results

We performed immunohistochemical (IHC) staining on 15 choroid plexus tumor samples (Table 1) by using an anti-FGFR3 antibody that targets amino acids 25–124 in the N-terminus and an anti-FGFR1 antibody that detects the C-terminal part of the protein. Both FGFR3 and FGFR1 staining were localized to the cytoplasm and plasma membrane (Fig. 1A). Furthermore, one sample showed stronger FGFR3 staining on the apical side of the cells (Fig. 1A), but intracellular distribution of FGFR3 staining was more even in other samples.

Variable FGFR1 and FGFR3 expression in choroid plexus tumors

We investigated FGFR3 and FGFR1 protein levels from TMAs that included four grade III CPCs, one atypical grade II CPP and 10 grade I CPPs (Fig. 1B, Table 1). There were four (27% out of total) FGFR3-immunoreactive choroid plexus tumors, one showing weak, two showing moderate and one showing strong immunopositivity. Also, four tumors (27% out of total) were positive for FGFR1 immunoreactivity, one of which was weakly immunopositive and the other three showed moderate signal. When considering the different tumor entities separately, positive staining for either FGFR3 or FGFR1 was evidenced in two out of four CPCs and four out of ten CPPs. The sole sample from atypical CPP had moderate FGFR3 signal and was negative for FGFR1. In total, six cases (40%) showed moderate-to-strong immunoreactivity for either FGFR1 or FGFR3, while none was moderately positive for both proteins. These six tumors were subjected to whole mount FGFR3 staining (Table 2), evidencing rather heterogenous expression and good correlation of the TMA results with whole mount score ranges. Overall, positive FGFR1 or FGFR3 staining was observed in both CPCs and CPPs, both pediatric and elderly patients, and both females and males.

TP53 alteration in two selected choroid plexus tumors with moderate-to-high FGFR3 staining

Two tumor samples showing moderate FGFR3 immunostaining on the TMA, Plex001 from CPC and the only atypical CPP (Plex013), were selected for targeted sequencing analysis. In contrast to the results obtained using TMAs, staining of whole-mount tissue slides showed strong (instead of moderate) FGFR3

Table 2. Staining scores for FGFR3 from whole mount sections.

	FGFR3 score	
	Whole mount	TMA
Plex001	1-3	2
Plex008	0	0
Plex009	0-3	3
Plex013	2-3	2
Plex014	0-1	1
Plex015	0	0

Score ranges for whole mount tissue stains of 6 cases are compared with scores obtained from TMA stains.

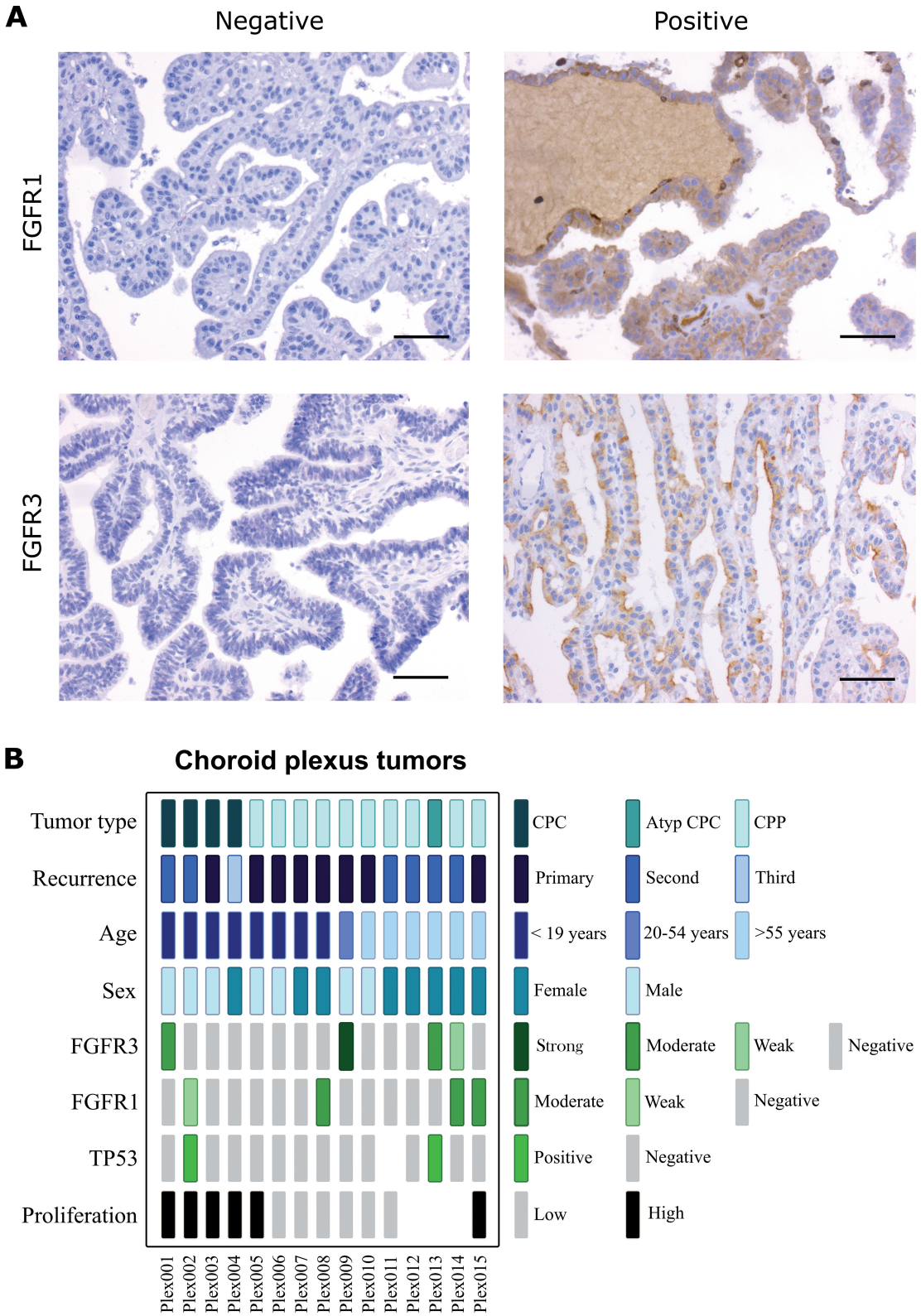
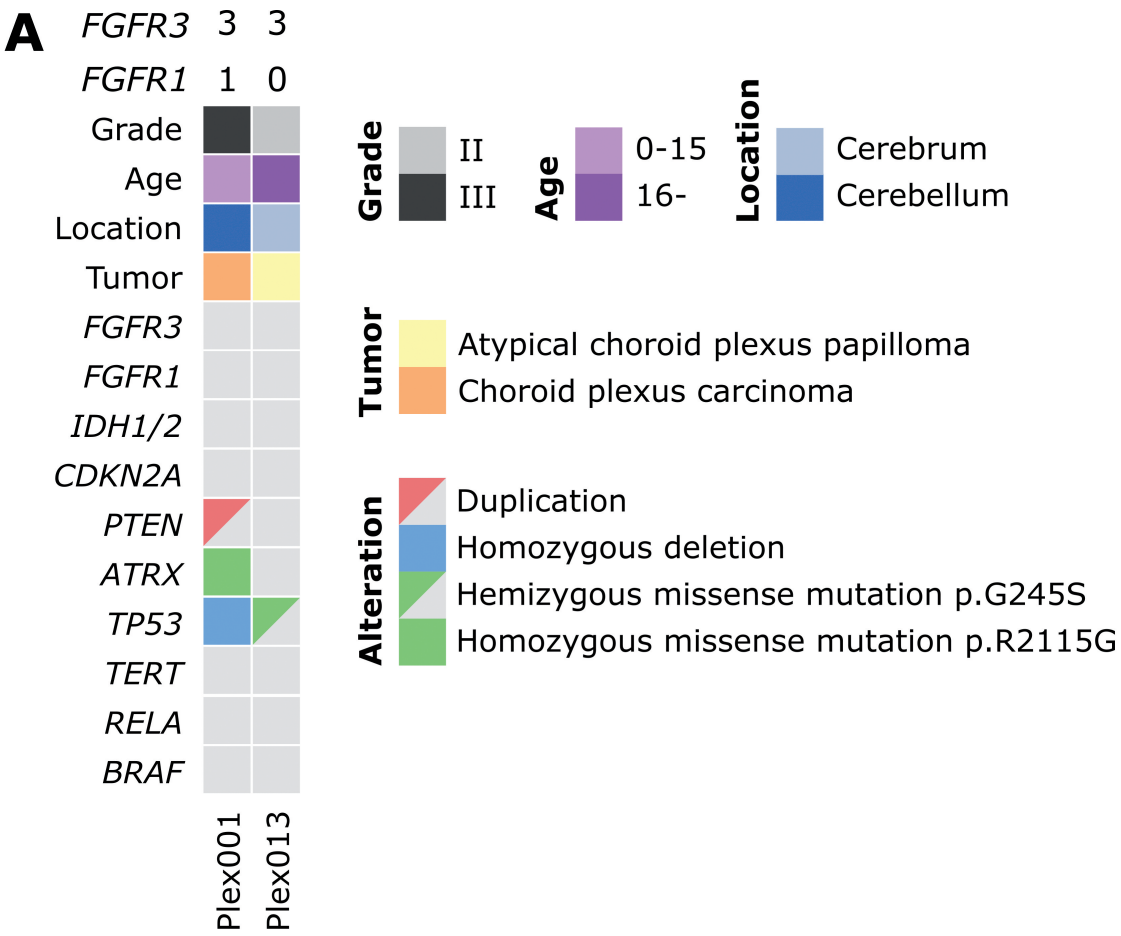


Fig. 1. FGFR3, FGFR1 and TP53 staining in choroid plexus tumor TMA. **A.** Representative immunohistochemical images of FGFR1 and FGFR3 in choroid plexus tumor samples from TMAs. **B.** Summary of FGFR3, FGFR1 and TP53 expression levels throughout the 15 choroid plexus tumor samples analyzed. Other tumor and patient characteristics (tumor type, primaries and recidives, patient age, patient sex, and tumor proliferation rate) are also depicted in the figure. Empty spaces depict cases for which data was not available. Positive TP53 staining means more than 5% of the nuclei are positive. Scale bar: 50 μm.



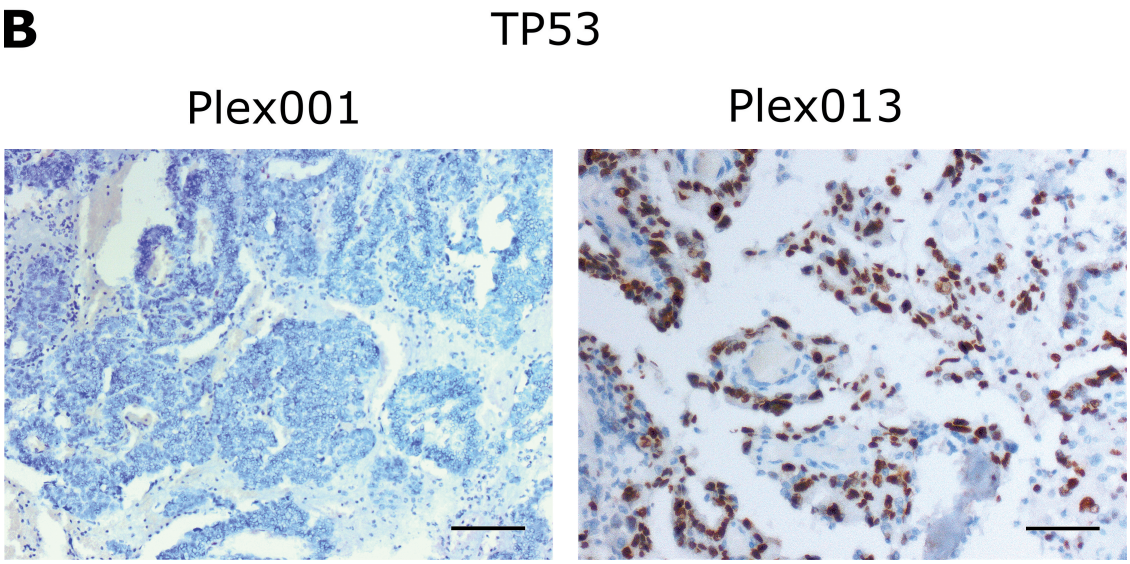


Fig. 2. Genetic alterations in choroid plexus tumors with high FGFR3 expression. **A.** Genetic alterations found in one CPC and one atypical CPP sample analyzed using targeted DNA sequencing. No coding mutations or gene fusions were detected in FGFR3 or FGFR1, but TP53 was altered in both cases. FGFR1 and FGFR3 immunohistochemical staining scores from whole-mount tissue slides are shown above the figure. **B.** IHC staining of Tp53 in samples that were analyzed with targeted sequencing. High frequency of positive staining is considered as an indication of TP53 mutation. Scale bar: 50 μm.

immunopositivity in both tumors (Table 2). In addition to *FGFR3* and *FGFR1*, the sequencing panel contained genes with reported alterations in gliomas, including *IDH1, IDH2, CDKN2A, PTE, ATRX, TP53, TERT, RELA* and *BRAF*. We did not detect *FGFR* coding mutations or fusions in either of the samples (Fig. 2A). Both tumors selected for analysis carried a *TP53* alteration, Plex001 containing a homozygous deletion and Plex013 having a missense mutation. Consistently, TP53 staining was fully negative for Plex001 and clearly positive for Plex013 (Fig. 2B). Additionally, the CPC sample (Plex001) showed a duplication in *PTEN* and a hemizygous missense mutation in *ATRX* (Fig. 2A) that led to total loss of ATRX expression (data not shown). No other alterations were found in the interrogated genomic regions.

Discussion

Our results demonstrate that moderate-to-strong FGFR3 or FGFR1 immunostaining is detectable in approximately one third of choroid plexus tumors. Even though the majority of studied cases showed no detectable FGFR3, the proportion of patients with moderate-to-strong FGFR3 immunostaining (20%) was higher in choroid plexus tumors when compared to pilocytic astrocytomas (9%) (Lehtinen et al., 2017) or diffuse astrocytomas (5%) (Granberg et al., 2017) and similar to that observed in ependymomas (22%) (Lehtinen, et al, 2017). Additional analyses of larger patient cohorts will be required to elucidate the association of FGFR1 and/or FGFR3 expression with clinical variables in choroid plexus tumor patients. For example, high expression of both proteins is associated with poor clinical prognosis in ependymomas (Lehtinen et al., 2017). Importantly, lack of *FGFR* alterations does not conclusively imply unresponsiveness to FGFR inhibitor-based treatments. For instance, in head and neck squamous cell tumors and various lung cancers, expression of FGFR1 was more informative than genomic alterations in terms of ability to predict treatment responses (Wynes et al., 2014; Göke et al., 2015). Moreover, an *FGFR1* Lys656 mutation has been detected in pilocytic astrocytomas that were negative for FGFR1 protein expression (Becker et al., 2015), suggesting that immunohistochemical data may serve as a valuable additional marker when therapeutically targeting tumors with *FGFR* alterations. Furthermore, the anatomical location of choroid plexus tumors may allow direct drug delivery via cerebrospinal fluid, leading to a less systemic treatment modality.

In the present study, targeted sequencing did not reveal any *FGFR* fusions or coding mutations in choroid plexus tumors with moderate-to-strong FGFR3 expression. This same sequencing panel and methodology was previously used to detect *FGFR3* fusions with high sensitivity (Lehtinen et al., 2017), suggesting that the lack of detectable *FGFR* fusions was not due to methodological limitations. Intracranial *FGFR3* gene fusions have only been detected in aggressive IDH wild-type diffuse gliomas (Singh et al., 2012; Zhang et al., 2013; Parker et al., 2013; Di Stefano et al., 2015; Granberg et al., 2017). *FGFR1* fusions are rarely observed in brain tumors and they are not restricted to diffuse gliomas (Zhang et al., 2013). Exceptionally, a highly frequent occurrence of FGFR1:TACC1 fusion was recently revealed in extraventricular neurocytoma (Sievers et al., 2018). In addition to gene fusions, various other *FGFR1* alterations have been observed in pilocytic astrocytomas (Jones et al., 2013; Zhang et al., 2013). Interestingly, *TP53* gene was affected in both FGFR3-staining positive tumors sequenced by us: one carrying a *TP53* missense mutation and the other showing a homozygous loss of *TP53*. Although *TP53* mutations are common in choroid plexus tumors (Brennan et al., 2013; Merino et al., 2015), homozygous *TP53* deletions are rare. As *TP53* mutation is associated with poor prognosis and the poorest survival is observed in patients with full inactivation of TP53 through genetic alterations (Merino et al., 2015), moderate-to-strong FGFR3 staining might indicate tumor aggressiveness. Of note, IHC staining of TP53 would not have clearly revealed the TP53 homozygous loss present in Plex001 sample. Further studies are needed to confirm the possible interaction between FGFR3 staining and tumor aggressiveness and to reveal the responsiveness of FGFR3-positive choroid plexus tumors to FGFR inhibition.

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