Original Article

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Expression of NF2, TRAF7, PI3KCA, and PGR in Skull Base vs Non-Skull Base Meningiomas: A Quantitative Cross-Sectional Study

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Abstract:

Objective: Meningiomas exhibit distinct genetic mutations. The association between NF2, TRAF7, PIK3CA, and progesterone receptor (PGR) mutations with tumor location remains elusive. This study aimed to quantify and compare the immunoexpression of these biomarkers across meningioma subtypes.

Material and Methods: A cross-sectional analysis was performed on 70 formalin-fixed paraffin-embedded (FFPE) meningioma tissue samples (35 skull base, 35 non-skull base) from Dr. Arifin Achmad Hospital, Indonesia (2021–2023). Immunohistochemistry assessed NF2, TRAF7, PIK3CA, and PGR expression levels based on predefined cell-positivity thresholds. Tumor location, WHO grade, demographic data, and hormonal contraceptive history were also analyzed.

Results: In patients with skull base meningiomas, 85.7% were categorized as benign, compared to 62.9% in those with non-skull base meningiomas (p-value<0.020). The immunohistochemical expression levels of NF2, TRAF7, and PIK3CA between the two study groups showed significant differences (p-value<0.001). Skull base meningiomas exhibited a higher expression of NF2, TRAF7, and PIK3CA. This study also demonstrated a positive relationship between the duration of hormonal contraceptive use and the percentage of PGR expression, where longer use of hormonal contraceptives was associated with increased PGR expression in meningiomas (p-value<0.05). There were no significant differences in sex, age, or contraceptive usage prevalence between the groups (p-value>0.05).

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Conclusion: Skull base meningiomas demonstrate distinct molecular profiles characterized by NF2 presence and TRAF7/PIK3CA overexpression, suggesting non-NF2 tumorigenesis pathways. Non-skull-base meningiomas frequently lack NF2, correlating with higher malignancy. PGR expression is ubiquitous and linked to hormonal contraceptive duration. These findings support the location-based molecular stratification of meningiomas and the development of targeted therapies for difficult-to-resect tumors.

Keywords: immunohistochemistry, NF2, non skull base meningioma, PGR, skull base meningioma

Introduction

Meningiomas are intracranial tumors arising from arachnoid cap cells[1], with histological and genetic variations influenced by embryological differences between the brain surface and the skull base meninges[2]. Meningiomas are the most common intracranial tumors, with an incidence of 7.86 cases per 100,000 annually[3,4]. Incidence peaks at ages 35–39 years, accounting for 25.1% of intracranial tumors[5]. In surgical practice, meningiomas are classified as skull base origin (51%), non-skull base origin (39%), and other locations (10%)[6]. The male-to-female ratio is 1:3.15, suggesting a hormonal factor in pathogenesis, and progesterone receptor (PGR) expression has been documented in meningiomas[2,6,7].

Meningioma is a solid tumor characterized by consistent chromosomal aberrations, with cytogenetic analysis revealing monosomy or partial loss of chromosome 22 in 70% of cases[8]. More recent studies have identified multiple mutations contributing to meningiomagenesis[2,9]. Mutations in neurofibromin 2 (*NF2*), tumor necrosis factor receptor-associated factor 7 (*TRAF7*), phosphatidylinositol-4,5 biphosphate 3-kinase catalytic subunit alpha (*PIK3CA*), and *PGR* have been documented in meningiomas[2,8–11].

Genetic mutations in meningioma most commonly involve *NF2*, a tumor suppressor gene on chromosome 22q. Loss of heterozygosity (LOH) in this region is observed in 40–80% of sporadic meningiomas[12], with *NF2* inactivating mutations present in approximately 60% of cases, supporting the classic two-hit hypothesis in meningioma pathogenesis[12]. Recent studies highlight the role of non-*NF2* mutations in meningioma development. Furthermore, *TRAF7*, a tumor suppressor gene on chromosome 16p13, is frequently mutated in non-*NF2* meningiomas[13]. TRAF7 protein regulates multiple cellular processes, including nuclear factor kappa B (NF-ĸB) transcription modulation, cellular stress response activation, and apoptosis induction[13,14]. It also facilitates the SUMOylation of proto-oncogene products, influencing hematopoietic cell proliferation and differentiation[13,14].

PIK3CA mutations are common in various cancers, including gliomas, and lead to the constitutive activation of PI3K. Hotspot mutations such as *H1047R, E542K*, and *E545K* are implicated in meningioma pathogenesis. Studies have identified *PIK3CA* point mutations in atypical and malignant meningiomas[15] with an overall mutation prevalence of approximately 7% in non-*NF2* cases[2]. Another relevant mutation involves *PGR*, a progesterone-activated protein encoded by a gene on chromosome 11q22[16]. A previous study reported that *PGR* mRNA expression is present in 64% of women with meningiomas, suggesting a hormonal influence on tumor development[16].

The surgical treatment of meningiomas is challenging due to their proximity to the neurovascular structures. Incomplete resection leads to recurrence[17]. Recent advancements in biomolecular characterization offer promising therapeutic targets for meningiomas[18]. Novel

therapies are needed for the challenging cases, especially for the skull base, metastatic, or recurrent meningiomas[19]. Agents such as hydroxyurea, temozolomide, and somatostatin analogs are common, with ongoing trials exploring molecular therapies, such as AKT inhibitors and FAK inhibitors, based on genetic changes like *AKT1*, *SMO*, and *NF2*[2,19]. These highlight the potential of molecular therapies to transform meningioma treatment, particularly in difficult-to-resect tumors[17,18].

With clinical challenges posed by meningiomas, particularly those that are difficult to access surgically, recurrent, or metastatic, and the limitations of current treatment options, there is a pressing need for a deeper understanding of the genetic and molecular basis of meningioma pathogenesis. While genetic mutations in meningiomas have been explored, the association between *NF2, TRAF7, PIK3CA*, and *PGR* mutations and tumor location remains under-examined. This study aimed to analyze the immunoexpression of NF2, TRAF7, PIK3CA, and PGR in both skull base and non-skull base meningiomas.

Material and Methods

Study design

All surgical procedures for the treatment of meningiomas were performed at the Neurosurgery Division, Department of Surgery, Arifin Achmad Hospital, Pekanbaru, Indonesia, from January 2021 to November 2023. All tissue specimens were formalin-fixed paraffin-embedded (FFPE). For the immunohistochemical analyses, FFPE specimens were sent to the Pathology Department, Faculty of Medicine, Gadjah Mada University, Yogyakarta, Indonesia. After staining, the immunoexpression levels of NF2, TRAF7, PIK3CA, and PGR were independently evaluated by at least two blinded pathologists. In case of disagreement, a third pathologist was consulted. The immunohistochemical data were analyzed based on the anatomical location of meningiomas.

Sample collection

Thirty-five samples from each study group (skull base and non-skull base meningiomas) were included. Inclusion criteria required tumor samples from FFPE diagnosed as meningiomas based on the latest guidelines[20]. Exclusion criteria removed samples from secondary meningiomas (post-radiotherapy) or those with difficult-to-assess tissue antigens. All specimens from January 2021 to December 2023 were confirmed as meningiomas by pathologists at Arifin Achmad Hospital. The clinical dependent variables (gender, age, hormonal contraception use, and WHO grade) were obtained from medical records.

Tumor location

Tumor location (skull base and non-skull base) serves as an independent variable in this study. To minimize bias, the determination of tumor origin was reassessed using pre-operative CT or MRI imaging by a panel of neurosurgeons. Skull base location was defined as cavernous sinus, cerebellopontine angle, clinoid, clivus, foramen magnum, jugular foramen, middle fossa, olfactory groove, orbital, parasellar, petroclival, petrous, planum sphenoidale, posterior fossa, skull base, sphenoid wing, and tuberculum sellae. While convexity, falx, parasagittal, and tentorium were defined as non-skull base. Large tumors comprising multiple regions in the skull with undetermined origin were excluded. Intraventricular meningiomas were also excluded.

Tissue sample preparation

A total of 70 FFPE tumor tissues were obtained following the surgical treatment of meningiomas. Under a material transfer agreement, all FFPE samples were delivered to the Department of Pathology, Faculty of Medicine, Gadjah Mada University, Yogyakarta, for immunohistochemical analyses.

Immunohistochemical examination

The immunohistochemistry examination was performed as follows: paraffin blocks from meningioma specimens were sectioned to a thickness of 0.3 microns using a microtome. The sections were placed on slides and heated on a hot plate at 60 °C for 60 minutes. Dehydration, washing, and rinsing were performed using the standard protocol. The slides were immersed in preheated Target Retrieval Solution and heated in a microwave at 800 watts for 2.5–3 minutes or 100 watts for 10 minutes. After cooling for 20 minutes, the slides were rinsed with wash buffer or Phosphate-Buffered Saline with Tween-20, followed by blocking with DAKO FLEX Peroxidase for 5 minutes. The primary antibody MIB-1/Ki-67 was applied and incubated for 20–60 minutes. Following another rinse, the slides were incubated with DAKO FLEX HRP and rinsed. After incubation with DAKO FLEX DAB (3,3′-Diaminobenzidine) for 5 minutes, the slides were rinsed with running water and counterstained with hematoxylin. Dehydration, xylene immersion, and mounting were performed using the standard protocol[21]. Primary antibodies used were NF2 Rabbit mAb, TRAF7 Rabbit pAb, and PIK3CA Rabbit pAb (Abclonal Technology, Woburn, USA); and PGR mAb (Novocastra Laboratories, Newcastle upon Tyne, UK), all at a dilution of 1:200. Positive results were visualized by a color change in the tissue, with DAB producing a stable brown precipitate.

Immunoexpression analysis

Immunoexpression of NF2, TRAF7, PIK3CA, and PGR was evaluated in 3 non-consecutive high-power fields (400×) using an Olympus microscope. DAB staining location was used to determine immunopositivity: cytoplasmic[22] for NF2 (Figure 1) and TRAF7 (Figure 2), perimembranous[22] for PIK3CA (Figure 3), and nuclear[23] for PGR (Figure 4). Each marker has distinct staining characteristics and intensity profiles due to subcellular localization and biological roles. After optimization of the staining protocol, the average percentage of positive tumor cells per 100 cells was recorded and classified as follows:

NF2: absent (0%), low (<10%), moderate (10–50%), high (>50%)

TRAF7: absent (0%), low (<10%), moderate (10–30%), high (>30%)

PIK3CA: absent (<5%), low (5–25%), moderate (25–50%), high (>50%)

PGR: absent (0%), low (<15%), moderate (15–50%), high (>50%)

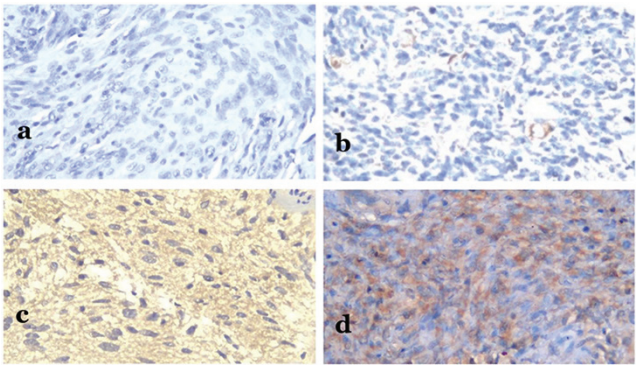

Figure 1 Representative NF2 immunohistochemistry in meningioma with 400x magnification. a. Absent (0%) b. Low (<10%) c. Moderate (10–50%) d. High (>50%)

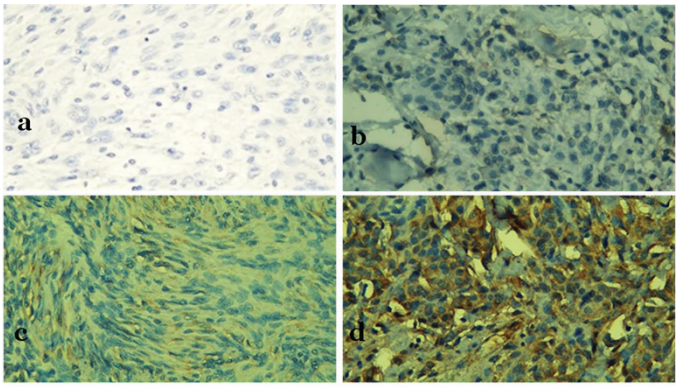

Figure 2 Representative TRAF7 immunohistochemistry in meningioma with 400x magnification. a. Absent (0%) b. Low (<10%) c. Moderate (10 – <30%) d. High (>30%)

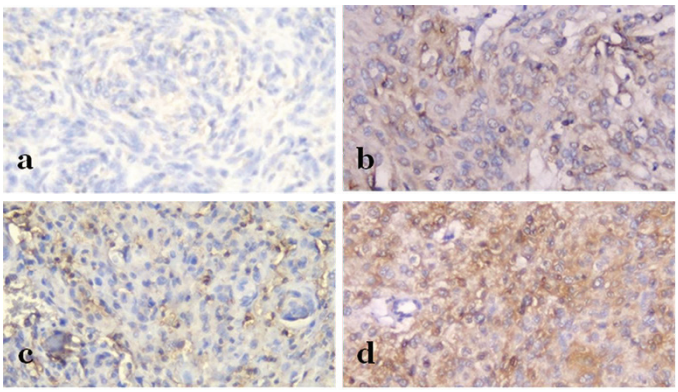

Figure 3 Representative PIK3CA immunohistochemistry in meningioma with 400x magnification. a. Absent (<5%) b. Low (5 – <25%) c. Moderate (25 – <50%) d. High (>50%)

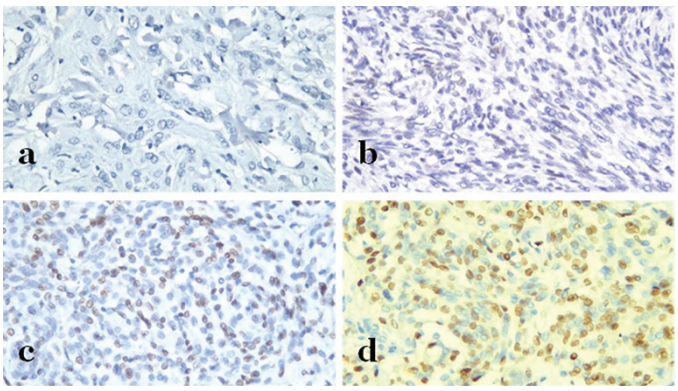

Figure 4 Representative progesterone receptor (PGR) immunohistochemistry in meningioma with 400x magnification. a. Absent b. Low (<15%) c. Moderate low (16–50%) d. High (>50%)

Statistical analysis

Statistical analyses were performed using SPSS version 29 (IBM SPSS, New York, USA), with a p-value of <0.05 considered statistically significant. The Kolmogorov-Smirnov test assessed data normality. Fisher's exact test and the chi-squared test were used for categorical data, while the independent t-test was employed for continuous data with a normal distribution, and the Mann-Whitney U test was used for non-normally distributed data. The chi-squared test analyzed differences in NF2, TRAF7, PIK3CA, and PGR expression across locations. Spearman's rank correlation examined correlations between variables.

Results

Different profiles of skull base and non-skull base meningiomas

In this study, there were no significant differences between skull base and non-skull base meningiomas in the demographic profiles. Both groups had a similar sex proportion (p-value=0.477), mean age (p-value=0.506), proportion of hormonal contraceptive users (p-value=0.232), and duration of contraceptive usage (p-value=0.353). Apart from technical differences during the surgery, skull base and non-skull base meningiomas also differ in their biological profiles. The skull base group was mostly benign (Grade I =85.7%), while the non-skull base group had a lower proportion of benign tumors (Grade I =62.9%, p-value=0.002).

We conducted an immunohistochemical analysis (NF2, TRAF7, PIK3CA, and PGR) to evaluate the biological profile of skull base and non-skull base meningiomas. The immunoexpression levels of NF2 showed a distinct profile in the skull base group; the majority of specimens had a higher number of immunopositive cells (n=21, 60.0%), while in the non-skull base group, the majority of specimens had absent (n=26, 74.3%) and low expression (n=6, 17.1%, p-value<0.001). The absence of NF2 expression in non-skull base meningiomas suggests a deletion of *NF2;* hence, the protein is not produced[22].

The immunoexpression levels of TRAF7 were also distinct between skull base and non-skull base. In the skull base group, the majority of specimens had a higher number of immunopositive cells (n=29, 82.9%), while in the non-skull base group, the majority of specimens were absent (n=21, 60.0%, p-value<0.001). The high expression of TRAF7 in skull base meningiomas suggests an overactivation of *TRAF7*[22].

The immunoexpression levels of PIK3CA were distinct between skull base and non-skull base. In the skull base group, the majority of specimens had a higher number of immunopositive cells (n=25, 71.4%), while in the non-skull base group, the majority of specimens were absent (n=22, 62.9%, p-value<0.001). The high expression of PIK3CA in skull base meningiomas suggests an overactivation of *PIK3CA*[22].

We could obtain PGR expression in almost all specimens, but the proportion of high PGR expression in skull base (n=24, 68.6%) and non-skull base (n=25, 71.4%) did not differ. The detailed characteristics are presented in Table 1.

Correlation between clinical profiles and immunoexpression

To investigate whether any clinical variable might play a role in meningiomagenesis, we performed a correlation analysis between clinical variables (age, duration of hormonal contraceptive usage, and histological grade) and immunoexpression. In this regard, age did not correlate with the immunoexpression levels of NF2, TRAF7, PIK3CA, or PGR in either skull base or non-skull base meningiomas (p-value>0.05).

We found that the duration of hormonal contraceptive usage is positively correlated with the immunoexpression level of PGR in both skull base (r=0.564, p-value<0.001)

and non-skull base meningiomas (r=0.513, p-value=0.002). The other immunoexpressions did not correlate with the duration of hormonal contraceptive usage.

Furthermore, we found that WHO Grade is negatively correlated with NF2 expression in non-skull base meningiomas (r=-0.399, p-value<0.001). The other immunoexpressions did not correlate with WHO grade in both skull base and non-skull base meningiomas. The detailed analysis is presented in Table 2.

Correlation between immunoexpressions

We further investigated the correlation between each immunoexpression level. In this regard, only TRAF7 expression is positively correlated with PIK3CA expression in skull base meningiomas (r=0.365, p-value=0.003). The other immunoexpressions did not show any correlation. The detailed analysis is presented in Table 3.

Table 1 Characteristics of skull base and non-skull base meningiomas

Variables	Skull base (n=35)	Non-skullbase (n=35)	p-value
Sex			0.477[a]
Male	3 (8.6%)	6 (17.1%)	
Female	32 (91.4%)	29 (82.9%)	
Age (years), mean±S.D.	45.9±10.8	44±12.7	0.506[b]
Female with hormonal contraceptive	30 (85.7%)	26 (74.3%)	0.232[c]
Duration of hormonal contraceptive usage	17.0±4.5	16.0±4.0	0.353[d]
Meningioma grade			0.002[c]*
I	30 (85.7%)	22 (62.9%)	
II	5 (14.3%)	11 (31.4%)	
III	0 (0.0%)	2 (5.7%)	
NF2 expression			<0.001[c]*
0% (absent)	3 (8.6%)	26 (74.3%)	
<10% (low)	4 (11.4%)	6 (17.1%)	
10–50% (moderate)	7 (20.0%)	3 (8.6%)	
>50% (high)	21 (60.0%)	0 (0.0%)	
TRAF7 expression			<0.001[c]*
0% (absent)	0 (0.0%)	21 (60.0%)	
<10% (low)	3 (8.6%)	4 (11.4%)	
10 – <30% (moderate)	3 (8.6%)	10 (28.6%)	
>30% (high)	29 (82.9%)	0 (0%)	
PIK3CA expression			<0.001[c]*
<5% (absent)	1 (2.9%)	22 (62.9%)	
5 – <25% (low)	3 (8.6%)	9 (25.7%)	
25 – <50% (moderate)	6 (17.1%)	4 (11.4%)	
≥50% (high)	25 (71.4%)	0 (0%)	
PGR expression			0.971[c]
0% (absent)	2 (5.7%)	2 (5.7%)	
<15% (low)	2 (5.7%)	1 (2.9%)	
16–50% (moderate)	7 (20%)	7 (20%)	
>50% (high)	24 (68.6%)	25 (71.4%)	

[a]Analyzed using Fisher Exact test, [b]Analyzed using Independent t-test, [c]Analyzed using Chi-Squared test, [d]Analyzed using Mann-Whitney U test, *statistically significant at p-value<0.050

Table 2 Correlation of age, duration of hormonal contraceptive usage, histological grading with NF2, TRAF7, PIK3CA, and PGR expression on skull base vs non-skull base meningiomas

Variables		Skull base		Non-skull base	
		R	p-value	R	p-value
Age	NF2	-0.057	0.743	0.068	0.696
	TRAF7	-0.117	0.204	0.106	0.545
	PIK3CA	0.013	0.941	-0.025	0.887
	PGR	-0.718	0.305	-0.119	0.497
Duration of hormonal contraceptive usage	NF2	-0.129	0.461	0.244	0.157
	TRAF7	-0.221	0.203	0.120	0.494
	PIK3CA	0.074	0.674	-0.043	0.805
	PGR	0.563	<0.001*	0.513	0.002*
WHO grade	NF2	-0.238	0.169	-0.399	0.001*
	TRAF7	0.012	0.944	0.321	0.060
	PIK3CA	0.283	0.100	0.046	0.791
	PGR	0.078	0.655	0.025	0.885

*p-value<0.005, Analyzed with Spearman's rank correlation
PGR=progesterone receptor

Table 3 Correlation between percentage of NF2, TRAF7, PIK3CA, and PGR expression on skull base vs non-skull base meningiomas

Cut off value	Skull base		Non-skull base	
	R	p-value	R	p-value
NF2 with TRAF7	-0.026	0.883	-0.084	0.631
NF2 with PIK3CA	0.216	0.213	-0.070	0.688
NF2 with PGR	0.081	0.643	-0.211	0.223
TRAF7 with PIK3CA	0.365	0.003*	0.078	0.657
TRAF7 with PGR	-0.031	0.859	-0.115	0.509
PIK3CA with PGR	-0.025	0.887	0.004	0.980

PGR=progesterone receptor

Discussion

Meningiomas are generally benign, but their location and size can significantly affect symptoms and treatment outcomes[2,7-11]. Skull base meningiomas often present with more complex neurological symptoms due to their proximity to neurovascular structures[6,7,24,25]. Non-skull base meningiomas, although more easily accessible for surgical resection, can still cause significant morbidity depending on their size and location[6,7,24,25]. Meningioma recurrence remains a major issue, particularly in difficult-to-resect tumors and high-grade meningiomas[5,6,17,18]. Targeted therapy, a patient-tailored medicine that is emerging in neuro-oncology, is a novel option in meningioma treatment[17,18,26].

Previous studies have consistently found a higher prevalence of meningiomas in women, which may be linked to hormonal factors, as these tumors are more common in females[7,27,28]. The location of the meningioma (whether skull base or non-skull base) does not appear to correlate strongly with either gender or age in this study, suggesting that other factors, such as genetic predispositions or environmental influences, might play a role in meningioma location[6,8,22]. Of note, prolonged hormonal contraceptive use is a risk factor for meningiomas[27-30]. We found that prolonged hormonal contraceptive use (>5 years) is associated with higher expression of PGR, suggesting that PGR may act more as the promoter of meningioma growth than the initiator of meningioma formation[27-30].

We confirmed that skull base and non-skull base meningiomas have different biomolecular signatures. In this regard, skull base meningiomas typically exhibit a non-NF2 (TRAF7 and PIK3CA) pathway of meningiomagenesis, while non-skull base meningiomas are more commonly NF2-related. We found that NF2 expression is relatively high in skull base meningiomas and correlates with the normal function of NF[22,31]. In contrast, NF2 expression is absent in the majority of non-skull base meningiomas. These differences have been reported to influence tumor behaviour, growth pattern, invasiveness, and the malignant progression of meningiomas[31,32,33].

Mutations in the NF2 gene disrupt the function of Merlin, impairing cell-to-cell adhesion and removing its inhibitory effect on cell proliferation. This leads to the malignant progression of meningioma[22,33]. We confirmed that hypofunction or absence of NF2 in non-skull base is correlated with a higher WHO grade, highlighting a crucial role of NF2 in meningiomagenesis. Together, these findings explain the tendency of higher-grade meningioma in non-skull base locations and also aid in the development of novel therapeutic interventions for meningiomas[32-34].

In this study, we found that the majority of skull base meningiomas have overactivation of TRAF7 and PIK3CA. Both markers also showed a strong correlation. TRAF7 is recognized as a tumor suppressor that regulates the MEKK3 and NF-κB pathways, both of which are crucial for controlling cell proliferation, apoptosis, and inflammation[35]. Meanwhile, PIK3CA activation, commonly identified in various cancers, including gliomas, results in the activation of PI3 kinase, a key pathway involved in cell growth, survival, and metabolism[36]. This finding suggests a unique non-NF2 meningiomagenesis[22,33-36]. From an embryological perspective, the skull base meningeal layer is derived from the para-axial mesoderm, while the cranial vault meningeal layer is derived from the neural crest[22]. The epigenetic modification during differentiation of the meningeal layer contributes to mutation patterns during malignancy[22]. Further investigation is needed to elucidate the process of meningiomagenesis.

To the best of our knowledge, this is the first study to evaluate the immunoexpression levels of NF2, TRAF7, PIK3CA, and PGR in meningiomas. We confirmed distinct biomolecular characteristics in both skull base and non-skull base meningiomas using a simple immunohistochemistry examination, which demonstrated a similar profile to previous studies with genome sequencing[22,33,34]. Hence, our method is applicable for a limited-resource setting to aid in the molecular stratification of meningiomas.

The relatively small sample size is a notable limitation, which may affect the generalizability of the findings. Further investigations involving multiple institutions would enhance the heterogeneity of the sample population and minimize center-specific biases, thereby improving the study's external validity. In this study, we did not provide a long-term follow-up to correlate this molecular examination with recurrence or disease progression. The other limitation is that the investigated proteins were not tested to confirm their role in meningiomagenesis.

In the future, it is important to consider the potential implications of immunohistochemical profiling in the management of meningiomas. Biomarkers such as NF2, TRAF7, PIK3CA, and PGR may offer valuable prognostic information that could inform surgical decision-making, risk stratification, and postoperative surveillance strategies. For instance, certain expression patterns may be associated with more aggressive tumor behavior, higher recurrence rates, or distinct responses to adjuvant therapy. Understanding these molecular signatures could help clinicians tailor treatment approaches more precisely, potentially reducing overtreatment in low-risk cases while prompting more aggressive management in high-risk patients.[37,38]

Conclusion

Skull base meningiomas exhibit higher expression of TRAF7, PIK3CA, and NF2. Meanwhile, NF2 hypoactivation is predominantly observed in non-skull base meningiomas. This hypoactivation of NF2 is correlated with a higher proportion of malignant meningiomas in non-skull base meningiomas. Although PGR expression is detected in the majority of meningiomas, it did not contribute to the difference in meningioma location. These findings could enhance the understanding of meningiomas, highlighting the potential for novel therapies, particularly for difficult-to-resect tumors.

Ethics approval

This study received ethical approval from the Ethics Commission of XXXX No. B/014/UN19.5.1.1.8/UEPKK/2024. The authors received hospital approval before performing data collection. Before data collection, all patients were informed about the study objectives and provided written informed consent.

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Conflict of interest

All the authors declare that there are no conflicts of interest.

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