Molecular biomarkers in meningioma (Review)

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Abstract. Meningioma is the most common type of primary intracranial tumor. These tumors are typically slow-growing and benign [World Health Organization (WHO) grade 1]. However, 20% of meningiomas (WHO grade 2 and 3) can be difficult to treat owing to their aggressive characteristics and higher recurrence rate, which presents a significant therapeutic challenge. Histopathological grading can yield inconsistent results due to interexaminer variability, which calls for more reliable biomarkers. Genetic and epigenetic alterations may define biological behavior and predict the prognosis of meningioma. The present review highlights the relevant genetic mutations, DNA methylation status in meningioma and their associations with relevant histomorphology, location and prognosis. Mutations in TNF receptor-associated factor 7, Krüppel-like factor 4 (KLF4), v-Akt murine thymoma viral oncogene homolog (AKT1), Smoothened frizzled-class receptor (SMO), Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), and RNA polymerase II subunit A (POLR2A) were associated with a good prognosis and a low recurrence rate. By contrast, mutations in NF2, TERT promoter, SMARCB1, SMARCE1, CDKN2A/B and BAP1 are associated with poor prognosis and higher recurrence rates. DNA methylation status plays a role in diagnosis, predicting tumor recurrence and prognosis. Combining the WHO grading and molecular biomarkers may lead to better diagnosis, prognosis, and targeted therapy for meningioma.

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Contents

1. Introduction

Meningioma is the most common type of intracranial tumor that arises from the meningothelial cells in the arachnoid layer. Three membranous envelopes or meninges surround the brain and spinal cord, the arachnoid, pia and dura mater (1). It is hypothesized that arachnoidal cap cells are the precursor cells of meningioma; however, this theory warrants further experimentation (2). A previous study suggests that precursors of meningiomas are the meningothelial arachnoid cells with different embryogenesis origins based on their location, which can be from the neural crest or mesodermal structure that develops the brain convexity (1). These differences affect the histological features and the recurrent somatic mutations in meningioma (1).

Meningioma is a type of primary intracranial tumor that accounts for ~36% of all such tumors. Most meningiomas are located within the brain, accounting for ~78.9% of all cases, whereas 4.2% occur in the spine. The remaining 15.2% cannot be attributed to a specific location within the meninges (3). Meningiomas tend to develop in people aged ≥35 years, with a higher incidence rate in female (87%) than in male patients (13%) (1,4). This may be related to hormonal factors, such as the presence of estrogen, androgen and progesterone receptors in meningioma (5). Exposure to ionizing radiation is a significant risk factor for children who develop meningiomas (6). Notably, male patients and children generally have lower incidences of meningiomas, but, when they do occur, tumors tend to be relatively more aggressive (6).

The histopathological grade of meningioma is determined by characteristics such as tumor morphology, proliferation index and invasion of brain tissues (7). According to the 2016 World Health Organization (WHO) classification, meningiomas can be classified into the following grades: I (benign), II (atypical) and III (anaplastic) (8). The 2021 WHO Classification

provided additional information about molecular biomarkers that could be used to classify and grade meningiomas, and the Arabic grading system had been applied (9). These biomarkers include SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily E member (SMARCE1; for clear cell subtype), BRCA1-associated protein 1 (BAP1; for rhabdoid and papillary subtypes), Krüppel-like factor 4 (KLF4) and TNF receptor-associated factor 7 (TRAF7) (for secretory subtype), and Telomerase reverse transcriptase (TERT) promoter mutation and homozygous deletion of Cyclin-dependent kinase inhibitor 2A and 2B (CDKN2A/B) (for CNS WHO grade 3) (9).

A total of ~80% of meningiomas are benign or classified as WHO grade 1 tumors, and patients with grade 1 tumors are usually managed with surveillance imaging (10,11). The 10-year overall survival (OS) rate for this group is 80-90%. Grade 2 and 3 meningiomas, which represent 15-18% and 2-4% of all meningiomas, respectively, are more challenging to treat owing to their aggressive nature and higher recurrence rate, which often occurs within 5 years (10). There is controversy surrounding the postoperative management options for patients with WHO grade 2 tumors, as some physicians use upfront adjuvant radiation therapy to prevent or delay recurrence, while others prefer close surveillance imaging with delayed radiation at the time of recurrence (12). Grade 3 malignant meningiomas have poor prognosis, with a 10-year OS rate of 14-34% (10). Because of the limited efficacy and the lack of chemotherapeutic or targeted therapies available for these tumors, adjuvant radiation is preferred (11).

Histopathological grading of meningioma can produce inconsistent results when assessed by different examiners. Therefore, there is need for reliable biomarkers. Past studies have demonstrated that identifying genetic and epigenetic alterations in meningiomas can define their biological behavior and predict their prognosis (4,7,12). A recent study indicated that use of either DNA methylation or genetic expression status may exceed the predictive capabilities of WHO grading in assessing responses to radiotherapy (RT) (12). DNA methylation has demonstrated superior performance as an independent predictor platform compared with genetic expression status (12).

Neurofibromatosis type 2 (NF2) is one of the most commonly mutated genes in meningiomas, with >50% of sporadic meningioma cases harboring an NF2 mutation and other tumors exhibiting alterations in genes involved in meningioma oncogenesis (13). Each specific mutation develops in different intracranial and skull base meningioma location (14,15). The DNA methylation levels may be a more accurate indicator of tumor aggressiveness and predict recurrence better than WHO grading. Epigenetic changes may contribute to overall genomic instability in meningioma by silencing genes that control DNA repair and cell cycling (16). In addition, deficiency in the regulation of epigenetics is key for tumorigenesis and genomic mutations can only partially explain the early stages of tumorigenesis (17).

The present study aimed to review genetic mutations and DNA methylation in meningioma and their associations with histomorphology, location, and prognosis to support diagnosis as well as effective treatment decisions.

2. Genetic mutations in meningioma

Meningiomas are a type of tumor with genetic changes classified into NF2 and non-NF2 mutations (10,13,18-25). Non-NF2 mutations include genes such as TRAF7 (6,13,23,25-27), KLF4 (23,25,28,29), v-Akt murine thymoma viral oncogene homolog 1 (AKT1) (14,23,27,30-32), smoothened frizzled-class receptor (SMO) (18,23,27,31,33-35), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PI3KCA) (15,36,37), RNA polymerase II subunit A (POLR2A) (15), telomerase reverse transcriptase (TERTp) (38-41), SMARCB1, SMARCE1 (42-44), CDKN2A/B (45-48) and BAP1 (49-51). Table I presents a concise overview of genomic biomarkers associated with meningioma, including their frequency, histology, location, genetic alteration and prognosis.

NF2. NF2 is a tumor suppressor gene located on chromosome 22q. It encodes NF2, which is a cytoskeleton scaffold protein of 69 kDa (13). A germline mutation in NF2 on 22q12.2 can lead to familial syndrome, characterized by development of multiple benign nervous system tumors, such as vestibular schwannoma and meningioma (18). A loss of function in NF2 as a tumor suppressor gene can cause upregulation of oncological pathways, increased cellular proliferation, migration and invasion, and decreased apoptosis (13). The loss of chromosome 22 is a recurrent genetic alteration in meningioma, which was first established by a fluorescence technique in the 1970s (19). In the 1990s, mutation of NF2 on chromosome 22 was identified as a major driver and detected in 60-70% of all meningiomas (20). Most meningiomas with NF2 mutations present as a fibrous or transitional phenotype and are generally more aggressive than sporadic tumors (21). NF2-mutated meningiomas harbor more genetic alterations than NF2-non-mutated tumors, even within the same grade. Thus, chromosomal instability is increased with NF2 mutation (22). Tumors with NF2 mutations are commonly located in the cerebral convexity or posterior fossa skull base and rarely in the midline skull base (23). Several studies have reported that mutations of NF2 do not occur with TRAF7, AKT1, KLF4, SMO, or POLR2A mutations, which are all found in benign meningiomas (12,14,15). This observation implies that most high-grade meningiomas are characterized by loss of NF2 and no other significantly recurring somatic mutations (10). Meningiomas with NF2 mutation have a higher recurrence rate than other genetic mutations. Within 2 years, the recurrence rate is 16.77% and the mean time to recur is 14.5 months, which is <19.6 months reported for those without such a mutation (23,24). NF2 mutations are associated with poor survival rates. Patients with this mutation have a median progression-free survival (PFS) of 29 months and a 5-year OS rate of 63% (25).

TRAF7. TRAF7 is a protein that transmits signals within the TNF receptor family, which is located on chromosome 16p13 (13). TRAF proteins serve a role in transporting various stimuli into the cell and are involved in physiological processes, such as embryonal development, immune regulation and stress response, which are necessary for tissue homeostasis (26). TRAF7 is a key genetic factor responsible for meningiomas. In meningiomas that do not have NF2 mutation, TRAF7 mutations are the most common genetic anomaly

Table I. Genomic biomarkers of meningioma.

Gene	Frequency (%)	Predominant histology	Predominant locations	Genetic alterations	Prognosis	(Refs.)
NF2	60-70	Fibrous transitional	Convexity or posterior fossa skull base	*SMARCB1 TERTp*	Poor, high recurrence rate	(21,23-25)
TRAF7	25	Meningothelial transitional	Lateral middle fossa and median posterior fossa skull base	*AKT1, PIK3CA, KLF4 SMO*	Good, low recurrence rate	(6,23,25,27)
KLF4	9-12	Secretory	Anterior and middle cranial skull base	*TRAF7*	Good, low recurrence rate	(23,25,29)
AKT1	7-12	Meningothelial transitional	Midline anterior skull base (olfactory groove, tuberculum sellae, anterior clinoid, and medial sphenoid wing)	*TRAF7*	Good, low recurrence rate	(14,23,27,31)
SMO	1-5	Meningothelial	Medial anterior skull base near the midline	*TRAF7*	Good, low recurrence rate	(27,31,35)
PIK3CA	4-7	Meningothelial transitional	Right temporal convexity	*TRAF7*	Good, low recurrence rate	(14,36,37)
POLR2A	6	Meningothelial	Tuberculum sellae of the skull base		Good, low recurrence rate	(15)
TERTp	6-8	Atypical (secondary)	Convexity skull base	*NF2*	Poor, high recurrence rate	(40,41)
SMARCB1	5		Falx cerebri	*NF2* or none	Good, low recurrence rate	(17,42,43)
SMARCE1	3-4	Atypical, clear cell	Convexity skull, spinal cord		Poor, high recurrence rate	(17,44)
CDKN2A/B	<5	Atypical, anaplastic	Convexity skull base	*NF2*	Poor, high recurrence rate	(47)
BAP1	<1	Rhabdoid	Convexity skull base		Poor, high recurrence rate	(49,51)

NF2, neurofibromatosis type 2; TRAF7, TNF receptor-associated factor 7; KLF4, kruppel-like factor 4; AKT1, v-Akt murine thymoma viral oncogene homolog; SMO, smoothened, frizzled class receptor; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; POLR2A, RNA polymerase II subunit A; TERTp, telomerase reverse transcriptase; SMARCB1, SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1; CDKN2A/B, cyclin-dependent kinase inhibitor 2A and 2B; BAP1, BRCA1-associated protein 1.

observed (6,11,13). A total of ~25% of sporadic meningiomas with TRAF7 mutations manifest as benign meningothelial histology (6,23). TRAF7 mutations can coexist with other mutations, such as AKT1 and KLF4: Mutations in TRAF7 and AKT1 are mainly detected in the anterior fossa, median middle fossa, or anterior calvarium; most of these mutations are classified as histological-type meningothelial or transitional meningioma (27). Meanwhile, meningiomas with mutations in TRAF7 and KLF4 are most commonly found in secretory meningioma and occur in the anterior fossa, lateral middle fossa, median middle fossa and median posterior fossa (23,27). Several studies have shown that mutations in TRAF7 are associated with favorable prognosis, demonstrating ≥90% 5-year PFS and OS rates (23,25,27). The recurrence rate after 2 years is 14.71%, which was lower than that of patients with mutant NF2 meningioma (23,27).

KLF4. KLF4 gene, which is located on chromosome 9 at position q31, encodes a transcription factor that belongs to KLF. Genes of this family are involved in various physiological processes such as proliferation, apoptosis, development and pluripotency (28). Approximately 25% of meningiomas without NF2 mutations have KLF4 mutations, which corresponds to 9-12% of all meningioma cases (23). The mutations of KLF4 often occur alongside TRAF7 mutations. These mutations are detected in almost all secretory meningiomas because they contain cytokeratin-positive globules (23,29). This is related to the regulatory role of KLF4 in cytokeratin 4 and 19 (29). Tumors harboring KLF4 mutations are linked to significant peritumoral brain edema, which primarily occurs in the anterior and middle cranial skull base (23). Recurrence rate is lower for mutations of KLF4 and TRAF7 compared to other genetic mutations, with only 2% occurring at 2 years of

follow-up (23,27). Overall, KLF4 mutation is associated with improved PFS and OS prognosis when compared with NF2 mutation, with 5-year PFS and OS rates of 95% (25).

AKT1. Activation of PI3K, an oncogenic pathway involved in numerous types of cancers, including CNS, breast, prostate, urothelial and ovarian cancers, leads to AKT1 phosphorylation and subsequent activation of mTOR (30). AKT1 primarily regulates cell proliferation, division, and apoptosis (31). AKT1 mutations cause uncontrolled cell proliferation and are found in proteus syndrome, a rare disorder that causes overgrowth of the bone, skin, and other tissues, resulting in meningioma (32). The AKT1 mutation is found in 7-12% of grade 1 meningiomas and is rare in grade 2 or 3 (23). Mutations of AKT1 and TRAF7 commonly co-occur in meningioma with meningothelial or transitional histology (27,31). Tumors with AKT1 mutations are typically detected in the midline anterior skull base, which includes the olfactory groove, tuberculum sellae, anterior clinoid and medial sphenoid wing. AKT1 and KLF4 mutations can occur alongside TRAF7 mutations, but they do not have mutations in NF2 or SMO (14). AKT1 is associated better prognosis than meningioma with NF2 mutations, with lower recurrence rates. Its occurrence in higher grade meningioma is rare and the PFS and 5-year OS are ~95% (23,27).

SMO. Loss of heterozygosity has been reported in meningioma concerning the human homolog of the Drosophila patched gene (PTCH1) and suppressor of fused (SUFU) (15). PTCH1 protein should inhibit SMO, but inactivation of PTCH1 leads to the upregulation of SMO, which, in turn, activates the hedgehog pathway (SHH) essential to embryonic development (33,34). When SUFU is inactivated, it leads to dysregulated hedgehog signaling (33,34). This pathway must be strictly regulated in adult tissue. Uncontrolled activation of the SHH pathway can induce nevoid basal cell carcinoma syndrome, which leads to meningioma initiation (18). SMO mutations are responsible for 1-5% of meningiomas that are not caused by NF2 mutations (23). SMO mutations rarely occur with TRAF7 mutations. These mutations are primarily associated with the meningothelial histological type and grade I. They are primarily located in the medial anterior region of the skull base near the midline (31). Most meningioma cases with SMO mutations are low-grade but have two mutation hotspots in 7q32.1. These hotspots are p. Leu412Phe and p. Trp535Leu mutations. The p. Leu412Phe mutation has been reported in 28% of olfactory groove meningioma cases and is associated with a larger tumor volume and a high risk of recurrence (35). In addition to TRAF7, AKT1, and KLF4, past studies have confirmed that SMO mutations are associated with good prognosis, are primarily detected in benign meningiomas and rarely develop into malignancy (27,31).

PIK3CA. PIK3CA is encoded by PIK3CA, which is part of the PI3K/AKT/mTOR signaling pathway (14). PIK3CA mutations, such AKT1, may induce tumorigenesis. These mutations occur in 4-7% of meningiomas and involve NF2, AKT1 and SMO, sometimes with TRAF7 mutations (14,36). The tumors are primarily located at the base of the skull and demonstrate histological findings of meningothelial or transitional grade 1 meningioma (36). A previous case of meningioma with PIK3CA mutation demonstrated high-grade features (WHO grade 1 with atypical features) and was located in the right temporal convexity and pushed into the Sylvian fissure (14). Notably, no tumors with PIK3CA mutations have been reported to recur following surgical resection (14). Currently, therapeutics targeting the PI3K pathway are under development for multiple types of cancer, including meningiomas (37).

POLR2A. POLR2A, which is located at locus 17p13.1, encodes RNA polymerase II subunit A. Its primary function is to form the transcription preinitiation complex (15). Mutations in POLR2A affect gene transcription and lead to the growth of meningiomas. These mutations are detected in ~6% of all meningiomas, are not present with the other mutations, and typically occur in meningothelial histology type WHO grade 1 tumors, which have a low risk of recurrence and are typically located in the tuberculum sellae of the skull base (15).

TERTp. TERT, which is located on the 5p1533 locus, maintains telomeres by adding small DNA repeats to the end of a chromosome. Mutations in TERT inhibit the process of apoptosis in most somatic cells, promoting the proliferation of tumor cells. The incidence of TERT mutations is 6-8% in all meningiomas (38-40). Meningiomas harboring TERT mutations exhibit aggressive behavior and poor prognosis, regardless of WHO grading. Individuals with the TERT promoter mutation have a median time of tumor progression of 10.1 months, whereas those without have a median time of 179 months (40,41). Patients with TERT mutations in the WHO-1 and WHO-2 grade tumors should be treated and monitored similarly to those in the WHO-3 category. Thus, patients with TERT mutation should receive aggressive management for surgical planning, RT and follow-up, regardless of WHO grade, so as to improve their prognosis. TERT promoter mutations are primarily found in secondary atypical meningioma, with a higher recurrence rate and a greater likelihood of malignant transformation than de novo atypical meningioma (40,41). Therefore, analysis of TERT-promoter mutations should be integrated as a standard laboratory test in histopathological diagnosis of meningiomas.

SMARCB1 and SMARCE1. SMARCB1 and SMARCE1 are subunits of the SWI/SNF complex. This complex regulates gene activity by remodeling chromatin and is a tumor suppressor (15). SMARCB1 and SMARCE1 mutations are frequently reported in familial syndromes with multiple meningiomas (15,17). However, germline mutations associated with schwannomatosis in SMARCB1 confer a lower risk (~5%) of recurrence and commonly occur in grade 1 meningiomas with or without NF2 mutation (17). SMARCB1 mutation predominantly occurs at the falx cerebri (42,43). The exact germline mutations of SMARCE1 are unknown. However, these mutations are estimated to occur in 3-4% of all meningioma cases. Conversely, SMARCE1 mutations are often detected in spinal cord meningioma (17). Most of these mutations tend to occur in young males. The reason for this preference is unclear but may be attributed to the hormonal stimulus involved. Meningiomas that are classified as clear cell grade 2 histological type and that occur in the cranial and spinal regions with SMARCE1 mutations have a higher recurrence rate compared with grade 1 tumors (44).

Table II. Classification of DNA methylation-based on genetic mutations, histology, location, gender predisposition, and prognosis.

Characteristics	MC ben-1	MC ben-2	MC ben-3	MC int-A	MC int-B	MC mal
Genetic mutation (%)	*NF2* (63)	*NF2* (7), *TRAF7* (49), *AKT1* (33), *KLF4* (15), *SMO* (7)	*NF2* (32), *PIK3CA* (11)	*NF2* (53)	*NF2* (35), *TERT* (20) *SUFU* (5)	*NF2* (31), *TERT* (3) *SUFU* (6)
Histology	Fibroblastic transitional atypical	Secretory transitional meningothelial	Angiomatous transitional atypical	Fibroblastic transitional atypical	Atypical anaplastic	Anaplastic
Location	Frontal, central convexity	Skull base	Frontal, central convexity	Frontal, central convexity	Frontal, central convexity	Central convexity
Sex predominance (%)	Female (76) > Male (24)	Female (85) > Male (15)	Female (64) > Male (36)	Female (55) > Male (45)	Female (64) > Male (36)	Male (55) > Female (45)
Prognosis Progression-free survival	Good >80% at 120 months	Good >80% at 120 months	Good >80% at 120 months	Intermediate 50% at 120 months	Intermediate 40% at 120 months	Poor 0% at 60 months

MC, methylation class; *NF2*, neurofibromatosis type 2; *AKT1*, v-akt murine thymoma viral oncogene homolog 1; *KLF4*, Krupple-like factor 4; *SMO*, smoothened homologue; *SUFU*, suppressor of fused; *TERT*, telomerase reverse transcriptase; *TRAF7*, TNF receptor-associated factor 7; ben, benign; int, intermediate; mal, malignant.

CDKN2A/B. CDKN2A/B are well-known tumor suppressor genes on chromosome 9p21. They are frequently altered in various types of human tumor, including meningioma (45). CDKN2A encodes p16INK4a protein, a regulator of the G1/S-phase transition by inhibiting the CDK4/6 activity (46). A high frequency of somatic mutations and homozygous deletions of CDKN2A and CDKN2B have been observed in anaplastic meningioma, which is categorized as WHO grade 2-3 and constitutes <5% of all meningiomas. This finding highlights the possible involvement of these genes in malignant progression of meningiomas (47). Homozygous losses of CDKN2A and CDKN2B are associated with higher rates of meningioma in mice with inactivated NF2 (45,48). Patients with tumors carrying CDKN2A/B homozygous deletions have significantly worse outcomes and more rapid progression from the time of surgery (12,17,47). CDKN2A/B homozygous deletion has an independent adverse effect on time to progression of patients with meningiomas (47). Therefore, the CDKN2A/B status can be a valuable biomarker for identifying patients at high risk of early recurrence. CDKN2A/B homozygous deletion itself may be a target for inhibitors of the CDK4/6 axis, such as ribociclib or palbociclib (47).

BAP1. BAP1 is crucial in various cellular pathways, including DNA damage signaling and repair (49). The loss of BAP1 function is associated with alterations in the methylation status and uncontrolled cell proliferation (50). BAP1 mutations were first reported to be associated with meningioma in a case series of three affected families (49). Certain patients with meningiomas caused by BAP1 mutations inherit BAP1 mutations and are diagnosed with BAP1 tumor predisposition syndrome (50,51). BAP1 mutant meningioma is a high-grade and aggressive type characterized by rhabdoid features (51). Rhabdoid meningiomas are a specific type of tumor, classified as WHO grade 3. These tumors primarily consist of rhabdoid cells with a high proliferation index, with other characteristics indicating malignancy. There is also a less aggressive type of meningioma that displays rhabdoid features in certain areas and lacks other features indicating malignancy, called meningioma with rhabdoid features (1,5,50,51). BAP1 mutants are associated with significantly decreased time to recurrence in both grade 3 rhabdoid meningioma and lower-grade meningiomas with rhabdoid features (49).

3. Epigenetic alteration in meningioma

Epigenetic alterations refer to modifications in the gene expression without modifying the DNA sequence (52). Various factors, including environmental exposure and lifestyle, can influence these alterations. In cancer, epigenetic changes can be particularly significant as they lead to the activation of oncogenes or silencing of tumor suppressor genes. This event can cause uncontrolled cell proliferation and division that characterizes tumorigenesis (53,54). Understanding these epigenetic changes is key for developing effective cancer prevention and treatment strategies (52). Past studies on genome-wide DNA methylation have provided data on epigenetic subclassification of meningioma and their association with clinical evolution (53,54). Global hypermethylation of DNA could serve as a biomarker for malignant meningioma (16). In 2017, Sahm *et al* (55) proposed a new classification system that measures the DNA methylation status in tumor samples (55). This system predicts the PFS and postresection recurrence rates of meningioma more effectively than the 2016 WHO

grading system. This system identifies six methylation classes of meningioma based on DNA methylation profiling by combining distinct driver mutations and specific copy number variations. The methylation classes MC ben-1-3 are designated benign tumors. Meanwhile, MC int-A and MC int-B are for intermediate-level tumors, with a higher rate of progression to malignancy and chance of recurrence after resection. MC mal includes tumors with the highest probability of malignancy and recurrence (55,56). Better patient stratification within the controversial grade 1 and 2 borderline is made possible by this MC categorization, which identifies subgroups with worse and better prognoses within grade 1 and 2 meningiomas, respectively (57). Table II distinguishes the six methylation classes based on their mutation patterns, histology, and prognosis. DNA methylation is a reliable biomarker that accurately differentiates meningioma from other intracranial tumors (such as solitary fibrous tumors, hemangiopericytoma, schwannoma, malignant peripheral nerve sheath tumors, chordoma, chondrosarcoma, hemangioblastoma, fibrous dysplasia, gliosarcoma, leiomyosarcoma, neurofibroma and fibromatosis) (54,55). Understanding of meningioma characteristics in specific populations is limited, particularly in cases such as NF2-associated schwannomatosis, radiation-induced meningiomas (RIM) and pediatric patients. These groups are largely omitted from current molecular studies, which impedes a comprehensive understanding of meningioma characteristics within these populations (8,9,12,55). The lack of sequencing resources and the absence of high-fidelity preclinical models limit translation of basic research into clinical application and the lack of a standardized molecular classification scheme complicates the comparison and integration of results from various studies, impacting the design of clinical trials and optimization of treatment strategies. Existing studies are not sufficient in exploring the impact of quality of life and association with molecular biomarkers, which limits the advancement of personalized and patient-centered care (8,9,12,55). It is key to standardize molecular classification, improve sequencing resources and investigate the link between molecular biomarkers and quality of life to advance personalized, patient-centered care in the future.

4. Conclusion

Numerous studies have confirmed the applicability of molecular biomarkers in understanding characteristics of meningioma and predicting its prognosis (12,15,55). Specific gene mutations, such as TRAF7, KLF4, AKT1, SMO, PIK3CA and POLR2A, are associated with a good prognosis and lower recurrence rate. Conversely, mutations in genes such as NF2, TERT promoter, SMARCB1, SMARCE1, CDKN2A/B and BAP1 are linked to a poor prognosis and a higher recurrence rate. DNA methylation status affects the diagnosis, prediction of tumor recurrence, and prognosis. For a detailed diagnosis of meningioma, further investigation of each molecular gene is necessary with reference to the current WHO classification. Surgery not only removes tumors but also provides samples for further molecular investigation in meningioma. In the future, molecular biomarkers combined with the WHO grading system may facilitate the selection of an effective treatment option for meningioma and allow more accurate diagnosis, prognosis and treatment.

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Authors' contributions

EKD, YPK and RGB designed the study and wrote the manuscript. RGM wrote the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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