

Domestic Animal Models of Central Nervous System Tumors

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Intracranial primary tumors (IPTs) are aggressive forms of malignancies that cause high mortality in both humans and domestic animals. Meningiomas are frequent adult IPTs in humans, dogs, and cats, and both benign and malignant forms cause a decrease in life quality and survival. Surgery is the primary therapeutic approach to treat meningiomas, but, in many cases, it is not resolute. The chemotherapy and targeted therapy used to treat meningiomas also display low efficacy and many side effects. Therefore, it is essential to find novel pharmacological approaches to increase the spectrum of therapeutic options for meningiomas.

meningiomas

cancer

one health

veterinary medicine

1. Meningiomas

Meningiomas frequently occur in humans and domestic animals. Although they are mostly benign, they can also exhibit malignant characteristics. In humans, meningiomas are the most common type of IPT, accounting for approximately 40% of all brain cancers, with a median age of diagnosis at 67 years ^{[1][2][3]}. Meningiomas represent around 30% of all primary CNS tumors in adults but only 0.4–4.6% in pediatric patients, with a higher proportion observed in females ^[4].

In humans, the most frequent site of origin for meningiomas is the arachnoid cells in the dura mater. Additional sites include the arachnoid associated with cranial nerves or choroid plexus ^[5]. Despite being often diagnosed as benign lesions due to their histological features, these tumors can show a clinical behavior similar to malignant neoplasia, with a high recurrence rate and poor prognosis. The 10-year overall survival for non-malignant meningiomas is approximately 81.4%, whereas for malignant forms, it decreases to 57.1% ^{[1][2]}.

Meningiomas are also diagnosed in canine and feline species displaying a strong relationship with age and breeds and accounting for from 22.3% up to 50% of all brain tumors in dogs ^{[6][7][8]} and 58% in cats ^[9]. In a comparative study between canine and feline meningiomas, Wada et al. (2020) highlighted the development of tumors at median ages of 11.7 years and 14.1 years, respectively. According to the same study, the canine breeds most affected were Miniature Dachshund, Toy Poodle, Beagle, Shetland Sheepdog, Labrador Retriever, Flat-coated Retriever, Shiba Inu, Jack Russel Terrier, Welsh Corgi, and mixed breed ^[10]. A Japanese study that analyzed data from 186 canine intracranial tumors showed a breed predisposition for meningiomas in Rough Collie, Golden Retriever, Miniature Schnauzer, and Scottish Terrier ^[11]. Other studies associated a frequent meningioma diagnosis with canine dolichocephalic breeds ^{[12][13][14][15]}, while a female sex predisposition was not confirmed in more

recent studies [7][16]. In cats, Domestic Shorthair seems to be the most predisposed breed to meningioma and no significant difference between sexes exists [16]. Adamo et al. (2003) reported a higher onset of meningiomas in Persian, Domestic Shorthair, and Domestic Longhair cats [17]. In dogs, meningiomas originate in the calvarium-adjacent region, involving the olfactory and frontal regions, cranial cavity, optic chiasm, and suprasellar and parasellar regions, although it has been rarely diagnosed in other regions [18][19]. The sites in which feline meningiomas arise are mainly the tela choroidea of the third ventricle, the supratentorial meninges, and less frequently the cerebellar meninges [9][20][21]. Conversely to what happens in dogs, multiple meningiomas are frequently found in cats (about 17% of all meningioma cases) [9][16][22][23]. Three theories have been proposed to explain the occurrence of multiple meningiomas: multicentric dural foci, metastasis by blood-borne spread, and metastasis via the cerebrospinal fluid. The first hypothesis seems most plausible considering the tumor's histologically benign nature and the reports showing histological variants in the same patient [24]. However, more research is needed to confirm them.

In about 15% of cases in cats and 20% of cases in dogs, meningiomas are diagnosed in the presence of other neurological disorders [9][16], including depression, stupor, coma, ataxia, lethargy, inappetence, and anorexia in cats [9] and menace response deficits, other cranial nerve deficits, ataxia, and reduced postural reactions in dogs [25].

2. Pathogenesis

The factors contributing to the development of meningiomas in humans and domestic animals need to be further studied. Currently, several hypotheses and mechanisms have been proposed.

Ionizing radiation stands out as the primary environmental risk factor consistently linked to the development of meningiomas. Human exposure to ionizing radiation leads to a 6- to 10-fold incidence increase in this condition [26]. Furthermore, this heightened risk is notably evident among survivors of the atomic bombings in Hiroshima and Nagasaki, where a substantial increase in meningioma cases has been documented [27][28]. In addition to radiation exposure, occupational contact with herbicides and pesticides also appears to elevate the likelihood of developing meningiomas [29]. Moreover, obesity has been identified as a significant positive risk factor for tumor development, likely due to its association with chronic inflammation and the signaling of insulin or insulin-like growth factors [30][31][32][33][34].

Several receptors are over-expressed in meningiomas, particularly somatostatin receptors (SSTRs) and intracellular receptors for sexual steroid hormones, such as androgens, progesterone, and estrogen, suggesting a role for these systems in tumor pathogenesis [27][35][36][37][38]. Among SSTRs, although all the subtypes are expressed in meningiomas [39], SSTR2 expression was associated with a poor prognosis, while SSTR1 expression was associated with reduced incidence of relapses, with less strong evidence. Nevertheless, the in vitro activation of SSTRs demonstrates antiproliferative effects. This evidence led to the development of clinical trials exploring the use of selective agonists, such as octreotide and pasireotide, although, to date, no conclusive results have been reported [40]. Receptors for the steroidal hormones estrogen (ER α) and progesterone (PR) have been reported to be expressed in most meningiomas: ER α presence has been associated with increased proliferation and the

development of high-grade tumors, while the high expression of PRs has been correlated with Grade 1 tumors according to the WHO grading system [41]. It is now assumed that PR expression alone represents a favorable prognostic factor in meningiomas, while its loss or the association with ER expression correlates with a worse clinical outcome. However, pharmacovigilance data indicated that the prolonged use of androgen receptor antagonists and/or progesterone receptor agonists (cyproterone acetate, norgestrel acetate) results in increased meningioma incidence [42][43], making rather complex the prognostic or therapeutic evaluation of these receptors.

Feline and canine meningiomas also express PR [17][44]. Adamo et al. (2003) reported a high proportion of PRs and the absence of ERs in feline meningiomas. Furthermore, a high number of cells with PRs and a significantly lower number of cells with ERs in canine meningiomas were observed. According to this study, the proportion of PR-positive cells in canine benign meningiomas was >80%, while in malignant meningioma only 32% of cells were PR-positive; in cats, the percentages were >80% and 38%, respectively. In dogs, the number of PRs correlated to more aggressive progression (with nuclear pleomorphism, severe necrosis, and histological subtypes), while in cats, such a correlation was not observed [17].

In humans, meningiomas occur in several forms, sometimes associated with other syndromes. **Table 1** shows the syndromes associated with high-frequency meningioma and the gene assumed to be involved.

Table 1. Syndromes associated with a considerable frequency of meningiomas.

Associated Syndromes	Meningioma Frequency	Associated Genes	References
Neurofibromatosis type 2, schwannomatosis, spinal tumors, spinal ependymoma	35%	<i>NF2</i>	[5][45][46]
Gorlin–Goltz syndrome	1–5%	<i>PTCH1</i> , <i>P53</i>	[47][48][49] [50]
Cowden syndrome	8.25%	<i>PTEN</i>	[51]
BAP1 Tumor Predisposition Syndrome	<1%	<i>BAP-1</i>	[52]
Multiple Endocrine Neoplasia Type 1	-	<i>MEN1</i>	[53][54]
Werner syndrome	10.9%	<i>WRN</i>	[55]
Rubinstein–Taybi syndrome	Case report		[56][57]

Some of the syndromes listed in **Table 1** have also been modeled in animals or have been observed in other species. A murine model was developed to accurately replicate the human *NF2*-related schwannoma phenotype, including the deficit in hearing and balance [58]. Mice with mutations in *PTC*, an orthologue of human *PTCH1*, develop many of the characteristics of Gorlin syndrome and exhibit a high incidence of rhabdomyosarcomas [59]. *Pten*^{M3M4} missense knock-in mutant mice present megalencephalic brains and elevated nuclear proteasome activity, also observed in patients with Cowden syndrome-related mutations in *PTEN* [60]. Multiple endocrine neoplasia type-I-like syndrome was reported in two male Domestic Shorthair cats that developed symmetric

alopecia, insulin-resistant diabetes mellitus, and pituitary-dependent hyperadrenocorticism at 12 and 13 years of age [61] and in a crossbred 12-year-old male dog with abdominal enlargement, seborrhoea, and polypnea [62]. Nevertheless, the listed studies did not highlight associations with meningioma.

Few studies reported contemporaneous and unrelated neoplasms in 3–23% of dogs with IPTs, mainly in the thoracic or abdominal cavity [6][7][63].

As reported in a review by Motta et al. (2012), intracranial meningiomas in dogs as well as in cats have been diagnosed with concurrent neural (oligodendroglioma and meningioangiomatosis) [7][9][64][65] or extra-neural disorders (mucopolysaccharidosis type 1 and thymic lymphoma) [66][67]. Moreover, it has been reported that 13.9% of cats and 19% of dogs develop a meningioma in addition to another intracranial neoplasm [7][9][64][68].

In humans, the malignant forms of meningiomas increase the tumor cell invasion processes and the risk of metastasis is higher compared to non-malignant meningiomas [69]. Metastases developments are reported mainly in the lung, pleura, bone, and liver. In domestic animals, meningioma metastases have been described almost uniquely in dogs, and mainly pulmonary metastases were observed [70][71]. A study performed in cats highlighted skull osteolysis. The authors hypothesized that metastases could be responsible for osteolysis [72].

3. Histopathological Classification

The WHO classifies meningiomas in humans and domestic animals with similar criteria.

In humans, the WHO classifies meningiomas into 15 subtypes, reflecting a broad heterogeneity [73]. These are clustered into three groups, differentiated by their histological components. The first group is composed of benign forms classified in different variants: meningothelial, fibrous, and transitional, which are the most common forms. Psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte-rich, and metaplastic variants are also included in group 1, but their incidence is significantly lower. In group 2, three additional classes are clustered: atypical, choroid, and clear cell meningiomas. The third group encompasses anaplastic, papillary, and rhabdoid meningiomas, often diagnosed as a single histological type, but including different biological and oncological aspects associated with different documented genetic mutations [74][75].

In domestic animals, meningiomas are divided into subtypes, according to the morphological characteristics of the cells [76]. Initially, WHO classified domestic animal meningiomas into two categories: benign and malignant. The benign meningiomas included eight subtypes: meningotheliomatous, fibrous, transitional, psammomatous, angiomatous, papillary, granular cell, and myxoid. Malignant meningioma was classified as anaplastic. However, this classification presents some limitations, and considering the similarities between human and domestic animal meningiomas in pathological, immunological, molecular, and MRI aspects, an improved classification was defined. The benign meningioma classification must be used with caution as histological aspects sometimes lead to considering benign neoplasia that does not match with biological/oncological characteristics [73][77][78][79]. In a study on feline meningiomas, concurrent benign and malignant forms were diagnosed [68].

Dogs show a rare form of meningioma, known as cystic meningioma, characterized by cysts originating through tumoral processes, such as necrosis or release of fluids. The size of the cyst depends on the fluid volume and causes increased intracranial pressure [80].

The observed similarities in pathological, immunological, and MRI aspects between human and canine meningiomas allowed for the classification of canine meningiomas according to three grades of the 2016 WHO human histological grading system [77]. In order to evaluate the possibility of translating the human grading system to canine tumors in terms of accuracy and reproducibility, Belluco et al. (2022) evaluated veterinary neuropathologists' inter-observer agreement with the application of a human grading system to canine meningioma [77]. The reproducibility of each histologic criterion was evaluated to identify a possible disagreement. The authors proposed amendments to increase reproducibility in canine meningioma [77]. In their study, Belluco et al. (2022) proposed a criterion for canine meningioma classification (**Table 2**) based on mitotic grade in a specific area (2.37 mm²) of tumor tissue [77].

Table 2. Canine meningioma classification criteria proposed by Belluco et al. (2022) [77].

Number of Mitoses (n)	Mitotic Grade
<4 mitoses in 2.37 mm ²	Grade 1
4 ≤ n ≤ 20 in 2.37 mm ²	Grade 2: tumors with sheeting architecture, small cells, hypercellularity, macronuclei and spontaneous necrosis
>20 mitoses in 2.37 mm ²	Grade 3: high anaplasia

Commonly, canine meningiomas present characteristics similar to the group 1 WHO classification of human meningiomas. The group 1 meningioma subtypes include meningotheliomatous, fibrous (fibroblastic), transitional (mixed), psammomatous, angiomatous (angioblastic), papillary, granular cell, myxoid, and anaplastic (malignant) [81]. Canine meningiomas usually display transitional, meningothelial, microcystic, and psammonas histological aspects [82]. In some cases, canine meningiomas present chondroid, osseous, myxoid, and xanthomatous-like areas in meningotheliomatous and transitional subtypes. Another aspect highlighted in meningotheliomatous and transitional subtypes was polymorphic infiltration with or without tumor cells necrosis area. Feline meningiomas are commonly classified into the transitional and fibroblastic subtypes. However, feline meningioma histology is cytologically bland and uniform; for this reason, it is very difficult to adapt to the human WHO guidelines [82]. The Comparative Brain Tumors Consortium (CBTC) tried to establish the translational aspects of canine brain tumors as a model for their human counterparts [83]. The work of CBTC provided the foundation for a histologic atlas of canine glioma that included astrocytoma, oligodendroglioma, and undefined glioma [84]. The samples were collected from several institutions and analyzed with immunohistochemistry to evaluate the expression of specific markers [84]. Other criteria studied were infiltrations, necrosis, mitosis, and vascularization. A grading classification was built reporting these criteria [84]. The grading was compared with human tumor counterparts. Belluco et al.

(2022) evaluated the reproducibility of criteria used in the human meningioma grading when applied to canine meningioma [77].

4. Diagnosis

Meningiomas are diagnosed in both humans and domestic animals through a combination of clinical evaluations, imaging techniques, and histopathological analysis. The primary diagnostic tools employed to assess the presence of meningiomas are magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET) [85][86].

Specific conditions such as edema, cyst formation, change in vascularity, and necrosis are well detected by MRI [87], and novel imaging techniques are improving the diagnosis of brain lesions. The use of MRI contrast agents permits the distinction of the tumor from the normal tissues. Furthermore, neurosurgeons can use MRI to minimize the size of craniotomy, maximize tumor removal, and minimize damage to the surrounding brain. Moreover, diffusion-weighted imaging, magnetic resonance spectroscopy, and dynamic contrast-enhanced MRI are entering clinical practice [88][89][90][91][92], whereas cerebrospinal fluid (CSF) analysis can provide clinical parameters, such as altered protein content and leukocyte count, useful for diagnosing pathology [93]. Motta et al. (2012) reported the main MRI characteristics of dog and cat meningiomas [16]. **Table 3** summarizes meningioma MRI features observed in canine, feline, and human meningiomas [91][94][95][96].

Table 3. Common MRI features observed in canine, feline, and human meningiomas.

MRI Features	Dog	Cats	Human
Margins	Defined	Defined	Irregular
Pre-contrast	Isodense to hyperdense (T1 and T2)	Isodense to hyperdense (T1 and T2)	Isodense to hyperdense (T1 and T2)
Contrast	Marked and uniform	Marked and uniform	Nonhomogeneous
Tumor associated edema	Mild	Mild	Severe
Hyperostosis	Rare	Frequent	Occasionally
Dura tail	Frequent	Frequent	Frequent
Mass observation	Correctly observed	Correctly observed	Correctly observed

Immunohistochemistry (IHC) plays a significant role in the diagnosis of meningiomas. IHC can be performed in human, canine, and feline meningiomas, using similar markers (**Table 4**). Saito et al. (2021) described about 39 cases of feline meningiomas of various grades in which specific markers were observed to classify the tumors [97]. The study analyzed markers such as Cytokeratin, Vimentin, E-cadherin, β -catenin, N-cadherin, and Ki-67. In feline meningiomas, Cytokeratin was only recognized in particular histological phenotypes (fibrous and transitional types) and showed high immunoreactivity in some studies involving dogs and humans [97]. Vimentin tested positive in

some cases of feline meningiomas. According to Saito et al., E-cadherin remained stable in all subtypes of meningiomas, making it a reliable marker for feline meningiomas. In some studies, N-cadherin was detected in many human and canine meningiomas [98][99]. β -catenin was analyzed in both canine and feline meningiomas. In feline meningiomas, while β -catenin was detected in over half of the analyzed meningiomas, its translocation to the nucleus (indicating the active form) was observed only in specific tumor types; in particular, translocation was not evaluated in atypical and anaplastic subtypes. In dogs, β -catenin was detected at the nuclear level, mainly in anaplastic meningiomas [100]. Ki-67 is an important proliferation index associated with many tumors, as well as in meningioma [101]. In the human literature, KI-67 expression correlates with tumor aggressiveness in meningiomas [102][103][104][105]. Matiassek et al. (2009) evaluated the role of KI-67 in dog meningiomas [106] considering about 70 canine meningiomas. The samples were analyzed via immunohistochemistry and 64 cases tested positive for KI-67 [106]. Some studies reported KI-67 be predictive for the survival of dogs with non-nervous tissue tumors [107][108][109][110]. Matiassek et al. (2009) did not find the same prediction; however, this was a retrospective study performed with a small sample size [106]. Janssen et al. (2023) studied the expression of KI-67 in 68 canine meningiomas to correlate KI-67 expression with the WHO grading of meningioma [111]. Many samples positive for KI-67 were classified as WHO grade I and the authors hypothesized a possible role of KI-67 in meningioma development, in particular during the early stage of these tumors [111]. Saito et al. (2021) did not correlate Ki-67 with specific subtypes of feline meningiomas [97].

Table 4. Immunohistochemical markers evaluated in human, canine and feline meningiomas.

Species	Markers	Reference
Human	Vimentin, KL-1, Claudin-1, NSE, S-100, EMA, Leu-7, Cytokeratin, N-Cadherin, KI-67	[112]
Dog	Vimentin, EMA, Claudin-1, CD18, CD1c, CD11d, CD3, IBA-1, Cytokeratin, β -Catenin, N-Cadherin, S100, Pancytokeratin, PGP9.5, CD34	[82][113]
Cat	Vimentin, E-Cadherin, β -Catenin	[97]

Therefore, the above-mentioned observations highlight common characteristics in meningioma classification and similar markers in IHC among the three species.

5. Molecular Characteristics

Meningiomas shows numerous molecular alterations in both human and domestic animal tumors, and some similarities and differences have been reported.

In humans, many genetic alterations have been associated with meningioma development. Deletions of *NF2* seem to be a common characteristic condition of meningiomas [114]. Indeed, alterations in *NF2* have been recognized as meningioma’s driver mutation, being present in about 50% of sporadic meningiomas [114]. Neurofibromatosis type II determines the inactivation of merlin gene *NF2*, a tumor suppressor involved in cytoskeleton dynamics, tumor-associated increased motility, and the regulation of cell proliferation [115]. Another pivotal player in meningioma’s development is *EPB41L3*, also known as *DAL-1* or *4.1B*, a tumor-suppressor gene that encodes erythrocyte

membrane protein-band 4.1-like 3, involved in cell–cell interaction and having an important role in the control of motility [\[116\]\[117\]\[118\]](#). Decreased *EPB41L3* expression is observed in about 70% of meningiomas.

Alterations in chromosome 1 were frequently found in meningiomas [\[74\]\[119\]](#) and include mutations in *TP73*, *CDKN2C*, *RAD54*, *EPB41*, *GADD45A*, and *ALPL* [\[120\]\[121\]\[122\]\[123\]](#).

Loss of function in chromosome 14 is commonly found in high-grade meningiomas and includes inactivation in *NDRG* family protein 2 and maternally expressed gene 3 (*MEG3*), which were associated with a poor prognosis [\[74\]\[124\]\[125\]](#).

Loss of function in chromosome 9 due to the deletions of the cyclin-dependent kinase inhibitors 2A (*CDKN2A*) and 2B (*CDKN2B*) has been associated with the progression from Grade 2 to anaplastic meningioma (Grade 3) [\[74\]\[126\]](#).

Whole-genome sequencing approaches have identified mutations occurring in *TRAF7*, *AKT1*, *KLF4*, *PIK3CA*, and *SMO*, although these mutations seem to be mutually exclusive with those associated with *NRF-2* [\[127\]\[128\]\[129\]](#).

TRAF7 is mutated in about 20% of all meningiomas and is frequently associated with *KLF4*, *AKT1*, and *PIK3CA* mutations [\[74\]\[128\]](#).

AKT1 mutations are found in about 12% of Grade 1 meningiomas and, although less frequently, in Grade 2 and 3. Interestingly, about 50% of all *AKT1*-mutated meningiomas also show alterations in *TRAF7* [\[74\]\[128\]\[130\]](#). *PIK3CA* mutations occur in about 7% of all meningiomas; they are mutually exclusive with *NF2* and *AKT1* and often associated with *TRAF7* mutations [\[127\]](#). Other somatic mutations associated with meningiomas include *BAP1*, *SMARCB1*, *SMARCE1*, *BRAF-V600E*, *NOTCH2*, *CHEK2*, *PTEN*, *CDKN2A*, *CDKN2B*, and *DMD* [\[52\]\[131\]\[132\]\[133\]\[134\]\[135\]\[136\]\[137\]\[138\]](#).

In humans, telomerase alterations are frequently associated with an increased risk of meningioma development [\[139\]](#). Telomerase mutations occur in all grades of meningiomas, the frequency being associated with the tumor grade [\[140\]\[141\]\[142\]](#). The main somatic mutations occur in the promoter region at two specific hotspots, C228T and C250T, resulting in up-regulation of the protein and the increased survival of cancer cells [\[141\]](#). Slavik et al. (2022) performed RNA-seq in 64 meningiomas to identify novel prognostic markers for these tumors. This study found the dysregulation of many transcripts involved in the WNT signaling pathway, highlighting the importance of the WNT pathway in meningioma development, as already reported for dogs [\[143\]](#).

Initially, meningiomas were studied in athymic nude mouse models, after PDX meningioma cell inoculation. The study by Rath et al. (2011) demonstrated that meningioma PDX retained the characteristics of the original tumors and that a stabilized cell line of meningiomas exhibited similar features to the tumors of origin [\[144\]](#). A limitation of the xenograft models is the absence of the tumor microenvironment, which restricts the study of the aspects of meningiomas, including drug resistance. GEM overcomes this limit by having an intact tumor microenvironment. Peyre et al. (2018) utilized a model of transgenic mice in which alterations in *NF-2* and *CDKN2AB* were induced [\[145\]](#). Nevertheless, as above reported, studying meningiomas in mice models does not yield the same results obtained with spontaneous animal models and, in general, the existence of spontaneous models is a fundamental

tool for studying cancer and other pathologies. Indeed, they mimic key aspects in the investigation of novel therapeutical approaches that are absent in non-spontaneous models, i.e., the role of the microenvironment and of the immune system [146].

Few available studies explored the genetic factors involved in the formation of canine and feline meningiomas. However, canine and feline models are reported to be strong translational models for CNS diseases, like stroke, epilepsy, movement disorders, lysosomal storage diseases, Alzheimer's and cognitive disorders, and neuro-oncology [113]. Differential expression regulation in orthologue genes of *Homo sapiens* in canine and feline meningiomas has been reported (Table 5). Partridge et al. (2020) highlighted the advantages of using canine and feline models to study meningiomas since the larger size of the animals allows for surgical handling of the CNS; moreover, the presence of an intact immune system and the molecular, histological, and neuroimaging characteristics make them comparable to human neoplasia [113].

Table 5. Reported differentially expressed genes in canine and feline meningiomas.

Species	Gene Name	Reference
Dog	<i>CADM1</i> (also known as <i>TSLC1</i>)	[147]
Dog	<i>NF2</i>	[147]
Dog	<i>VEGF</i>	[106][148]
Dog	<i>MMP-2</i> and <i>MMP-9</i>	[149]
Cat	<i>MMP-2</i> and <i>MMP-9</i>	[149]
Dog	<i>SSTR2</i>	[150]
Dog	<i>PDGFR</i>	[151]
Dog	<i>FOLR1</i>	[152]
Dog	<i>FOSB</i> , <i>FOS</i> , <i>CTSE</i> , <i>ZC2HC1C</i> , <i>KLF5</i> , <i>BMPR1B</i> , <i>MYBL1</i> , <i>NR4A1</i> , <i>PAMR1</i> , <i>GJB2</i> , <i>GEM</i> , <i>UPK3B</i> , <i>EGR1</i> , <i>ZFP36</i> , <i>CHGA</i> , <i>NOL4</i> , <i>DACT2</i> , <i>AMPD3</i> , <i>MEDAG</i> , <i>KLKB1</i> , <i>TF</i> , <i>AMDHD1</i> , <i>GPR133</i> , <i>WNT5A</i> , <i>RIMS1</i> , <i>PDPN</i> , <i>COMP</i> , <i>LPAR3</i> , <i>NEAT1_2</i> , <i>STXBP6</i> , <i>MYRF</i> , <i>PERP</i> , <i>BMPEP</i> , <i>IRF6</i> , <i>VWA5A</i> , <i>MYC</i> , <i>ERMP1</i> , <i>DMXL2</i> , <i>WFCD2</i> , <i>NEAT1_1</i> , <i>FAM210B</i> , <i>CTPS1</i>	[153]
Dog	<i>MYOC</i> , <i>ALP</i> , <i>CILP2</i> , <i>COL14A1</i> , <i>THBS1</i> , <i>MMRN2</i> , <i>ADAMTSL1</i> , <i>PRKD1</i> , <i>COL8A1</i> , <i>SPTBN5</i> , <i>FHL5</i> , <i>MYH11</i> , <i>SFRP1</i> , <i>SCN7A</i> , <i>ARHGEF15</i> , <i>FRZB</i> , <i>SYNPO2</i> , <i>ACTC</i> , <i>PTGIR</i> , <i>TIE1</i> , <i>CD93</i> , <i>MCAM</i> , <i>FLT1</i> , <i>EMCN</i> , <i>MYCT1</i> , <i>DAAM2</i> , <i>KANK3</i> , <i>LAMC3</i> , <i>CALCRL</i> , <i>CPZ</i> , <i>DCP1/ACE</i> , <i>AQP1</i> , <i>KITLG</i> , <i>TINAGL1</i> , <i>PECAM1</i> , <i>CRISPLD2</i> , <i>OLFML3</i> , <i>ESAM</i> , <i>ADCY2</i> , <i>NOTCH3</i> , <i>FBLN2</i> , <i>FAM180A</i> , <i>STC2</i> , <i>APOD</i> , <i>PTCH2</i> , <i>APOE</i> , <i>CACNA2D2</i> , <i>PTPRB</i> , <i>FAM198B</i> , <i>MGLL</i> , <i>PDGFRL</i> , <i>TEK</i> , <i>IGFBP6</i> , <i>GAS6</i> , <i>ABCA8</i> , <i>TLL1</i> , <i>COL16A1</i> , <i>PALD1</i> , <i>PIK3R1</i> , <i>FMN2</i> , <i>MCF2L</i> , <i>NOS3</i> , <i>ARAP3</i> , <i>FMOD</i> , <i>DYSF</i> , <i>CYYR1</i> , <i>PLVAP</i> , <i>DRP2</i> , <i>ZFHX4</i> ,	[153]

Species	Gene Name	Reference
	<i>ECE1, GM2A, RCN3, AMOT, LEPREL2, TM4SF18, KALRN, PREX2, HECW, CCDC80, LIMCH1, ETS1, MYO1E, SHE</i>	

Some have demonstrated an epigenetic role in human meningioma onset [74][154][155]. These epigenetics mechanisms include DNA methylation, defective chromatin remodeling, alterations in microRNAs, and the hypermethylation of *TIMP3*. Alterations in the methylation of the *TIMP3* promoter determine inhibition of the metalloproteinases and can be associated with a poor prognosis [74][156][157]. *TP73* inactivation by hypermethylation has been investigated as a possible risk factor for malignant meningiomas [156][158]. Interestingly, experimental evidence suggests that methylation profiles might be suitable to predict the clinical outcome of patients. Indeed, some studies showed that an altered methylation profile is associated with a worse prognosis [142].

Few studies analyzed the molecular alterations driving canine and feline meningioma pathogenesis [153]. Different genes resulted in down-regulation, for instance *MYOC, ALP, PRKD1, FHL5, TIE1, MCAM* and *PECAM1*. Courtay-Cahen et al. (2008) highlighted the following alterations in canine meningiomas: histone acetyltransferase p300, PDGF- β , thioredoxin reductase 1, mutS homolog 2 and 6, Dal-1, Clusterin-like 1 (Retinal), B-cell lymphoma, T-cell differentiation protein, BCL-2-like 11, IL-1 α , and IL-1 β [159]. An RNA-seq transcriptome analysis performed in canine meningioma determined a series of over-expressed genes, for example, *FOSB, KLF5, WNT, GEM, EGR1*, and *DACT2* [153]. The entire altered gene list is reported in **Table 5** and includes also genes altered in both humans and dogs: *FOS, KLF5, BMPR1B, NR4A1, WNT5A, PDPN, MYRF, MYC, ALP, COL14A1, THSB1, MMRN2, FHL5, SFRP1, MCAM, DAAM2, AQP1, KITLG, PECAM1, OLFML3, ADCY2, NOTCH3, FBLN2, APOD, PTCH2, IGFBP6, GAS6, COL16A1, PIK3R1*, and *FMN2* [160][161][162][163][164][165][166][167][168][169][170][171][172][173][174][175][176][177][178][179][180][181][182][183][184][185][186]. A case-report study speculated about the relationship between mucopolysaccharidosis I (caused by alpha-L-iduronidase deletions) and the onset of meningiomas in cats [66].

The role of PR receptors in the pathogenesis of human and animal meningiomas has been already mentioned [17][44][187][188][189][190][191][192][193]. Other studies reported the important role of matrix metalloproteinases *MMP-2* and *MMP-9* in canine and human meningiomas, where they are involved in extracellular matrix degradation, required for tumor progression and recurrence [194][195][196][197]. Mandara et al. (2007) evaluated the expression of *MMP-2* and *MMP-9* in canine meningiomas, establishing correlations with *TIMP-1* and *TIMP-2* expression [198]. The authors found that *TIMP-1* levels were elevated in Grade 1 and Grade 2 meningiomas, but not in Grade 3 cases and hypothesized different pathways in which *TIMP-1* can be involved in the progression of meningiomas [138]. Cyclooxygenase-2 (*COX-2*) is reported to have an impact on canine meningiomas [199] and is over-expressed in some feline meningiomas [200]. However, only in humans, *COX-2* seems to be correlated with meningioma grade and local invasion [113] and is a marker used to classify the tumors [201]. Vascular Endothelial Growth Factor (*VEGF*) has been proposed as a prognostic marker in canine, where it seems to be inversely correlated with survival time [113], while in human meningiomas, it is a tumor recurrence marker [202]. The role of E-cadherin, N-cadherin, β -catenin and doublecortin (*DCX*) have been evaluated in both canine and human meningiomas. In canine tumors, N-cadherin, β -catenin, and *DCX* seem to have a positive correlation with invasion and anaplastic subtypes of meningiomas, instead in human meningiomas, it has not demonstrated a correlation and this role is still debated [99][113][203][204]. Alterations of *NF-2* in chromosome 22 do not seem to play an important role in the

onset of canine meningiomas [147], as opposed to human meningiomas, where they have been reported to predispose to the development of the tumors [203].

Glucose transporter (Glut-1) is expressed at high levels in malignant meningiomas both in dogs and humans [113]. Boozer et al. (2012) evaluated the immunological infiltrate in canine meningiomas [205], reporting a prevalence of CD18+ microglia and macrophages surrounding and infiltrating the tumors; CD11d+ cells were also present. Lymphocyte infiltrate included mainly CD3+ T-cells and a sparse number of CD79a+ B-cells. In human meningiomas, similar T-cell and B-cell infiltrate have been found, but in both cases, the biological role of this infiltrate was not determined [206][207][208][209]. The proteins altered in human and dog meningiomas are reported in **Table 6**.

Table 6. Proteins frequently altered in human and dog Meningiomas.

Genes	Species	Reference
MMP-2	Human, Dog	[149]
MMP-9	Human, Dog	[149]
TIMP-1	Human, Dog	[149]
TIMP-2	Human, Dog	[149]
COX-2	Human	[172]
VEGF	Human	[175]
N-Cadherin	Dog	[176][177]
β-Catenin	Dog	[203][204]
DCX	Dog	[203][204]
NF-2	Human	[147]
Glut-1	Human, Dog	[113]
CD18+	Dog	[206][207][208][209]
CD11d+	Dog	[206][207][208][209]
CD3+	Dog	[206][207][208][209]
CD79a+	Dog	[206][207][208][209]
CD34	Dog	[6]
NSE	Dog	[6]

Genes	Species	Reference
PGP9.5	Dog	[6]
Pancytokeratin	Dog	[6]
S100	Dog	[6]

- Ostrom, Q.T.; Gittleman, H.; Fulop, J.; Liu, M.; Blanda, R.; Kromer, C.; Wolinsky, Y.; Kruchko, C.; Barnholtz-Sloan, J.S. CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2008–2012. *Neuro Oncol.* 2015, 17 (Suppl. S4), iv1–iv62.
- Ostrom, Q.T.; Gittleman, H.; Truitt, G.; Boscia, A.; Kruchko, C.; Barnholtz-Sloan, J.S. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2011–2015. *Neuro Oncol.* 2018, 20, iv1–iv86.
- Ostrom, Q.T.; Price, M.; Neff, C.; Cioffi, G.; Waite, K.A.; Kruchko, C.; Barnholtz-Sloan, J.S. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2015–2019. *Neuro Oncol.* 2022, 24, v1–v95.
- Kotecha, R.S.; Pascoe, E.M.; Rushing, E.J.; Rorke-Adams, L.B.; Zwerdling, T.; Gao, X.; Li, X.; Greene, S.; Amirjamshidi, A.; Kim, S.K.; et al. Meningiomas in children and adolescents: A meta-analysis of individual patient data. *Lancet Oncol.* 2011, 12, 1229–1239.
- Huntoon, K.; Toland, A.M.S.; Dahiya, S. Meningioma: A Review of Clinicopathological and Molecular Aspects. *Front. Oncol.* 2020, 10, 579599.
- Miller, A.D.; Miller, C.R.; Rossmeisl, J.H. Canine Primary Intracranial Cancer: A Clinicopathologic and Comparative Review of Glioma, Meningioma, and Choroid Plexus Tumors. *Front. Oncol.* 2019, 9, 1151.
- Snyder, J.M.; Shofer, F.S.; Van Winkle, T.J.; Massicotte, C. Canine intracranial primary neoplasia: 173 cases (1986–2003). *J. Vet. Intern. Med.* 2006, 20, 669–675.
- Hayes, H.M.; Priester, W.A., Jr.; Pendergrass, T.W. Occurrence of nervous-tissue tumors in cattle, horses, cats and dogs. *Int. J. Cancer* 1975, 15, 39–47.
- Troxel, M.T.; Vite, C.H.; Van Winkle, T.J.; Newton, A.L.; Tiches, D.; Dayrell-Hart, B.; Kapatkin, A.S.; Shofer, F.S.; Steinberg, S.A. Feline intracranial neoplasia: Retrospective review of 160 cases (1985–2001). *J. Vet. Intern. Med.* 2003, 17, 850–859.
- Wada, M.; Hasegawa, D.; Hamamoto, Y.; Yu, Y.; Asada, R.; Fujiwara-Igarashi, A.; Fujita, M. Comparison of Canine and Feline Meningiomas Using the Apparent Diffusion Coefficient and Fractional Anisotropy. *Front. Vet. Sci.* 2020, 7, 614026.
- Kishimoto, T.E.; Uchida, K.; Chambers, J.K.; Kok, M.K.; Son, N.V.; Shiga, T.; Hirabayashi, M.; Ushio, N.; Nakayama, H. A retrospective survey on canine intracranial tumors between 2007 and

2017. *J. Vet. Med. Sci.* 2020, 82, 77–83.
12. Song, R.B.; Vite, C.H.; Bradley, C.W.; Cross, J.R. Postmortem evaluation of 435 cases of intracranial neoplasia in dogs and relationship of neoplasm with breed, age, and body weight. *J. Vet. Intern. Med.* 2013, 27, 1143–1152.
 13. Withrow, S.J.; Page, R.; Vail, D.M. *Small Animal Clinical Oncology*; Elsevier: Amsterdam, The Netherlands, 2013.
 14. Bagley, R.S.; Gavin, P.R. Seizures as a complication of brain tumors in dogs. *Clin. Tech. Small Anim. Pract.* 1998, 13, 179–184.
 15. Gavin, P.R.; Fike, J.R.; Hoopes, P.J. Central nervous system tumors. *Semin. Vet. Med. Surg. Small Anim.* 1995, 10, 180–189.
 16. Motta, L.; Mandara, M.T.; Skerritt, G.C. Canine and feline intracranial meningiomas: An updated review. *Vet. J.* 2012, 192, 153–165.
 17. Adamo, P.F.; Cantile, C.; Steinberg, H. Evaluation of progesterone and estrogen receptor expression in 15 meningiomas of dogs and cats. *Am. J. Vet. Res.* 2003, 64, 1310–1318.
 18. Sturges, B.K.; Dickinson, P.J.; Bollen, A.W.; Koblik, P.D.; Kass, P.H.; Kortz, G.D.; Vernau, K.M.; Knipe, M.F.; Lecouteur, R.A.; Higgins, R.J. Magnetic resonance imaging and histological classification of intracranial meningiomas in 112 dogs. *J. Vet. Intern. Med.* 2008, 22, 586–595.
 19. Patnaik, A.K.; Lieberman, P.H.; Erlandson, R.A.; Shaker, E.; Hurvitz, A.I. Paranasal meningioma in the dog: A clinicopathologic study of ten cases. *Vet. Pathol.* 1986, 23, 362–368.
 20. Kaldrymidou, E.; Polizopoulou, Z.S.; Koutinas, A.F.; Papaioannou, N.; Papadopoulos, G.; Poutahidis, T. Papillary meningioma in the cerebellum of a cat. *J. Comp. Pathol.* 2000, 123, 222–225.
 21. Mandara, M.T.; Ricci, G.; Sforza, M. A cerebral granular cell tumor in a cat. *Vet. Pathol.* 2006, 43, 797–800.
 22. Forterre, F.; Tomek, A.; Konar, M.; Vandeveld, M.; Howard, J.; Jaggy, A. Multiple meningiomas: Clinical, radiological, surgical, and pathological findings with outcome in four cats. *J. Feline Med. Surg.* 2007, 9, 36–43.
 23. Gordon, L.E.; Thacher, C.; Matthiesen, D.T.; Joseph, R.J. Results of craniotomy for the treatment of cerebral meningioma in 42 cats. *Vet. Surg.* 1994, 23, 94–100.
 24. Song, K.; Lee, H.; Jeong, J.; Roh, Y. Multiple Meningioma Resection by Bilateral Extended Rostrotentorial Craniotomy with a 3D-Print Guide in a Cat. *Vet. Sci.* 2022, 9, 512.
 25. Forward, A.K.; Volk, H.A.; Cherubini, G.B.; Harcourt-Brown, T.; Plessas, I.N.; Garosi, L.; De Decker, S. Clinical presentation, diagnostic findings and outcome of dogs undergoing surgical

- resection for intracranial meningioma: 101 dogs. *BMC Vet. Res.* 2022, 18, 88.
26. Wiemels, J.; Wrensch, M.; Claus, E.B. Epidemiology and etiology of meningioma. *J. Neurooncol.* 2010, 99, 307–314.
 27. Ogasawara, C.; Philbrick, B.D.; Adamson, D.C. Meningioma: A Review of Epidemiology, Pathology, Diagnosis, Treatment, and Future Directions. *Biomedicines* 2021, 9, 319.
 28. Sadamori, N.; Shibata, S.; Mine, M.; Miyazaki, H.; Miyake, H.; Kurihara, M.; Tomonaga, M.; Sekine, I.; Okumura, Y. Incidence of intracranial meningiomas in Nagasaki atomic-bomb survivors. *Int. J. Cancer* 1996, 67, 318–322.
 29. Samanic, C.M.; De Roos, A.J.; Stewart, P.A.; Rajaraman, P.; Waters, M.A.; Inskip, P.D. Occupational exposure to pesticides and risk of adult brain tumors. *Am. J. Epidemiol.* 2008, 167, 976–985.
 30. Shao, C.; Bai, L.P.; Qi, Z.Y.; Hui, G.Z.; Wang, Z. Overweight, obesity and meningioma risk: A meta-analysis. *PLoS ONE* 2014, 9, e90167.
 31. Lichtor, T.; Kurpakus, M.A.; Gurney, M.E. Expression of insulin-like growth factors and their receptors in human meningiomas. *J. Neurooncol.* 1993, 17, 183–190.
 32. Glick, R.P.; Gettleman, R.; Patel, K.; Lakshman, R.; Tsibris, J.C. Insulin and insulin-like growth factor I in brain tumors: Binding and in vitro effects. *Neurosurgery* 1989, 24, 791–797.
 33. Antoniades, H.N.; Galanopoulos, T.; Neville-Golden, J.; Maxwell, M. Expression of insulin-like growth factors I and II and their receptor mRNAs in primary human astrocytomas and meningiomas; in vivo studies using in situ hybridization and immunocytochemistry. *Int. J. Cancer* 1992, 50, 215–222.
 34. Kurihara, M.; Tokunaga, Y.; Tsutsumi, K.; Kawaguchi, T.; Shigematsu, K.; Niwa, M.; Mori, K. Characterization of insulin-like growth factor I and epidermal growth factor receptors in meningioma. *J. Neurosurg.* 1989, 71, 538–544.
 35. Korhonen, K.; Salminen, T.; Raitanen, J.; Auvinen, A.; Isola, J.; Haapasalo, H. Female predominance in meningiomas can not be explained by differences in progesterone, estrogen, or androgen receptor expression. *J. Neurooncol.* 2006, 80, 1–7.
 36. Baldi, I.; Engelhardt, J.; Bonnet, C.; Bauchet, L.; Berteaud, E.; Gruber, A.; Loiseau, H. Epidemiology of meningiomas. *Neurochirurgie* 2018, 64, 5–14.
 37. Wu, W.; Zhou, Y.; Wang, Y.; Liu, L.; Lou, J.; Deng, Y.; Zhao, P.; Shao, A. Clinical Significance of Somatostatin Receptor (SSTR) 2 in Meningioma. *Front. Oncol.* 2020, 10, 1633.
 38. Delgado-Lopez, P.D.; Cubo-Delgado, E.; Gonzalez-Bernal, J.J.; Martin-Alonso, J. A Practical Overview on the Molecular Biology of Meningioma. *Curr. Neurol. Neurosci. Rep.* 2020, 20, 62.

39. Arena, S.; Barbieri, F.; Thellung, S.; Pirani, P.; Corsaro, A.; Villa, V.; Dadati, P.; Dorcaratto, A.; Lapertosa, G.; Ravetti, J.L.; et al. Expression of somatostatin receptor mRNA in human meningiomas and their implication in in vitro antiproliferative activity. *J. Neurooncol.* 2004, 66, 155–166.
40. Miyagishima, D.F.; Moliterno, J.; Claus, E.; Gunel, M. Hormone therapies in meningioma-where are we? *J. Neurooncol.* 2022, 161, 297–308.
41. Pravdenkova, S.; Al-Mefty, O.; Sawyer, J.; Husain, M. Progesterone and estrogen receptors: Opposing prognostic indicators in meningiomas. *J. Neurosurg.* 2006, 105, 163–173.
42. Samoyeau, T.; Provost, C.; Roux, A.; Legrand, L.; Dezamis, E.; Plu-Bureau, G.; Pallud, J.; Oppenheim, C.; Benzakoun, J. Meningioma in patients exposed to progestin drugs: Results from a real-life screening program. *J. Neurooncol.* 2022, 160, 127–136.
43. Hoisnard, L.; Laanani, M.; Passeri, T.; Duranteau, L.; Coste, J.; Zureik, M.; Froelich, S.; Weill, A. Risk of intracranial meningioma with three potent progestogens: A population-based case-control study. *Eur. J. Neurol.* 2022, 29, 2801–2809.
44. Mandara, M.T.; Ricci, G.; Rinaldi, L.; Sarli, G.; Vitellozzi, G. Immunohistochemical identification and image analysis quantification of oestrogen and progesterone receptors in canine and feline meningioma. *J. Comp. Pathol.* 2002, 127, 214–218.
45. Abaza, M.M.; Makariou, E.; Armstrong, M.; Lalwani, A.K. Growth rate characteristics of acoustic neuromas associated with neurofibromatosis type 2. *Laryngoscope* 1996, 106, 694–699.
46. Goutagny, S.; Bah, A.B.; Henin, D.; Parfait, B.; Grayeli, A.B.; Sterkers, O.; Kalamarides, M. Long-term follow-up of 287 meningiomas in neurofibromatosis type 2 patients: Clinical, radiological, and molecular features. *Neuro Oncol.* 2012, 14, 1090–1096.
47. Albrecht, S.; Goodman, J.C.; Rajagopalan, S.; Levy, M.; Cech, D.A.; Cooley, L.D. Malignant meningioma in Gorlin's syndrome: Cytogenetic and p53 gene analysis. Case report. *J. Neurosurg.* 1994, 81, 466–471.
48. Kimonis, V.E.; Mehta, S.G.; Digiovanna, J.J.; Bale, S.J.; Pastakia, B. Radiological features in 82 patients with nevoid basal cell carcinoma (NBCC or Gorlin) syndrome. *Genet. Med.* 2004, 6, 495–502.
49. Lopes, N.N.; Caran, E.M.; Lee, M.L.; Silva, N.S.; Rocha, A.C.; Macedo, C.R. Gorlin-Goltz syndrome and neoplasms: A case study. *J. Clin. Pediatr. Dent.* 2010, 35, 203–206.
50. Narang, A.; Maheshwari, C.; Aggarwal, V.; Bansal, P.; Singh, P. Gorlin-Goltz Syndrome with Intracranial Meningioma: Case Report and Review of Literature. *World Neurosurg.* 2020, 133, 324–330.

51. Yakubov, E.; Ghoochani, A.; Buslei, R.; Buchfelder, M.; Eyupoglu, I.Y.; Savaskan, N. Hidden association of Cowden syndrome, PTEN mutation and meningioma frequency. *Oncoscience* 2016, 3, 149–155.
52. Shankar, G.M.; Abedalthagafi, M.; Vaubel, R.A.; Merrill, P.H.; Nayyar, N.; Gill, C.M.; Brewster, R.; Bi, W.L.; Agarwalla, P.K.; Thorner, A.R.; et al. Germline and somatic BAP1 mutations in high-grade rhabdoid meningiomas. *Neuro Oncol.* 2017, 19, 535–545.
53. Marini, F.; Falchetti, A.; Del Monte, F.; Carbonell Sala, S.; Gozzini, A.; Luzi, E.; Brandi, M.L. Multiple endocrine neoplasia type 1. *Orphanet J. Rare Dis.* 2006, 1, 38.
54. Asgharian, B.; Chen, Y.J.; Patronas, N.J.; Peghini, P.L.; Reynolds, J.C.; Vortmeyer, A.; Zhuang, Z.; Venzon, D.J.; Gibril, F.; Jensen, R.T. Meningiomas may be a component tumor of multiple endocrine neoplasia type 1. *Clin. Cancer Res.* 2004, 10, 869–880.
55. Lauper, J.M.; Krause, A.; Vaughan, T.L.; Monnat, R.J., Jr. Spectrum and risk of neoplasia in Werner syndrome: A systematic review. *PLoS ONE* 2013, 8, e59709.
56. Verstegen, M.J.; van den Munckhof, P.; Troost, D.; Bouma, G.J. Multiple meningiomas in a patient with Rubinstein-Taybi syndrome. Case report. *J. Neurosurg.* 2005, 102, 167–168.
57. Boot, M.V.; van Belzen, M.J.; Overbeek, L.I.; Hijmering, N.; Mendeveille, M.; Waisfisz, Q.; Wesseling, P.; Hennekam, R.C.; de Jong, D. Benign and malignant tumors in Rubinstein-Taybi syndrome. *Am. J. Med. Genet. A* 2018, 176, 597–608.
58. Gehlhausen, J.R.; Park, S.J.; Hickox, A.E.; Shew, M.; Staser, K.; Rhodes, S.D.; Menon, K.; Lajiness, J.D.; Mwanthi, M.; Yang, X.; et al. A murine model of neurofibromatosis type 2 that accurately phenocopies human schwannoma formation. *Hum. Mol. Genet.* 2015, 24, 1–8.
59. Hahn, H.; Wojnowski, L.; Zimmer, A.M.; Hall, J.; Miller, G.; Zimmer, A. Rhabdomyosarcomas and radiation hypersensitivity in a mouse model of Gorlin syndrome. *Nat. Med.* 1998, 4, 619–622.
60. He, X.; Arrotta, N.; Radhakrishnan, D.; Wang, Y.; Romigh, T.; Eng, C. Cowden syndrome-related mutations in PTEN associate with enhanced proteasome activity. *Cancer Res.* 2013, 73, 3029–3040.
61. Roccabianca, P.; Rondena, M.; Paltrinieri, S.; Pocacqua, V.; Scarpa, P.; Faverzani, S.; Scanziani, E.; Caniatti, M. Multiple endocrine neoplasia type-I-like syndrome in two cats. *Vet. Pathol.* 2006, 43, 345–352.
62. Walker, M.C.; Jones, B.R.; Guildford, W.G.; Burbidge, H.M.; Alley, M.R. Multiple endocrine neoplasia type 1 in a crossbred dog. *J. Small Anim. Pract.* 2000, 41, 67–70.
63. Bigio Marcello, A.; Gieger, T.L.; Jimenez, D.A.; Granger, L.A. Detection of comorbidities and synchronous primary tumours via thoracic radiography and abdominal ultrasonography and their

- influence on treatment outcome in dogs with soft tissue sarcomas, primary brain tumours and intranasal tumours. *Vet. Comp. Oncol.* 2015, 13, 433–442.
64. Stacy, B.A.; Stevenson, T.L.; Lipsitz, D.; Higgins, R.J. Simultaneously occurring oligodendroglioma and meningioma in a dog. *J. Vet. Intern. Med.* 2003, 17, 357–359.
65. Ginel, P.J.; Novales, M.; Blanco, B.; Perez, J.; Zafra, R.; Perez-Ecija, R.A. Meningioangiomatosis associated with fibrous meningioma in a dog. *Vet. Rec.* 2009, 164, 756–758.
66. Haskins, M.E.; Aguirre, G.D.; Jezyk, P.F.; Desnick, R.J.; Patterson, D.F. The pathology of the feline model of mucopolysaccharidosis I. *Am. J. Pathol.* 1983, 112, 27–36.
67. Lobetti, R.G.; Nesbit, J.W.; Miller, D.B. Multiple malignant meningiomas in a young cat. *J. S. Afr. Vet. Assoc.* 1997, 68, 62–65.
68. Lu, D.; Pocknell, A.; Lamb, C.R.; Targett, M.P. Concurrent benign and malignant multiple meningiomas in a cat: Clinical, MRI and pathological findings. *Vet. Rec.* 2003, 152, 780–782.
69. Enam, S.A.; Abdulrauf, S.; Mehta, B.; Malik, G.M.; Mahmood, A. Metastasis in meningioma. *Acta Neurochir.* 1996, 138, 1172–1177; discussion 1177–1178.
70. Mutnuru, P.C.; Ahmed, S.F.; Uppin, S.G.; Lachi, P.K. Pulmonary metastases from intracranial meningioma. *Lung India* 2015, 32, 661–663.
71. Schulman, F.Y.; Ribas, J.L.; Carpenter, J.L.; Sisson, A.F.; LeCouteur, R.A. Intracranial meningioma with pulmonary metastasis in three dogs. *Vet. Pathol.* 1992, 29, 196–202.
72. Dussaux, A.; Gomes, E.; Hurion, M.; Rattez, E.; Mayousse, V. Cerebral meningioma associated with extensive calvarium osteolysis and presumed intratumoral carcinoma metastasis in a cat. *JFMS Open Rep.* 2022, 8, 20551169221122849.
73. Louis, D.N.; Perry, A.; Wesseling, P.; Brat, D.J.; Cree, I.A.; Figarella-Branger, D.; Hawkins, C.; Ng, H.K.; Pfister, S.M.; Reifenberger, G.; et al. The 2021 WHO Classification of Tumors of the Central Nervous System: A summary. *Neuro Oncol.* 2021, 23, 1231–1251.
74. Lee, Y.S.; Lee, Y.S. Molecular characteristics of meningiomas. *J. Pathol. Transl. Med.* 2020, 54, 45–63.
75. Shibuya, M. Pathology and Molecular Genetics of Meningioma: Recent Advances. *Neurol. Med. Chir.* 2015, 55 (Suppl. S1), 14–27.
76. Pintus, D.; Marruchella, G.; Masia, M.; Maestrale, C.; Cancedda, M.G.; Contu, C.; Macciocu, S.; Ligios, C. Glioblastoma with oligodendroglioma component in a ewe. *J. Vet. Diagn. Investig.* 2016, 28, 449–454.
77. Belluco, S.; Marano, G.; Baiker, K.; Beineke, A.; Oevermann, A.; Seehusen, F.; Boracchi, P.; Pumarola, M.; Mandara, M.T. Standardisation of canine meningioma grading: Inter-observer

- agreement and recommendations for reproducible histopathologic criteria. *Vet. Comp. Oncol.* 2022, 20, 509–520.
78. Vernau, K.M.; Higgins, R.J.; Bollen, A.W.; Jimenez, D.F.; Anderson, J.V.; Koblik, P.D.; LeCouteur, R.A. Primary canine and feline nervous system tumors: Intraoperative diagnosis using the smear technique. *Vet. Pathol.* 2001, 38, 47–57.
79. Fages, J.; Oura, T.J.; Sutherland-Smith, J.; Jennings, S.H. Atypical and malignant canine intracranial meningiomas may have lower apparent diffusion coefficient values than benign tumors. *Vet. Radiol. Ultrasound* 2020, 61, 40–47.
80. Kitagawa, M.; Kanayama, K.; Sakai, T. Cystic meningioma in a dog. *J. Small Anim. Pract.* 2002, 43, 272–274.
81. Koestner, A. *Histological Classification of Tumors of the Nervous System of Domestic Animals*; Armed Forces Institute of Pathology: Washington, DC, USA, 1999.
82. Meuten, D.J. *Tumors in Domestic Animals*, 5th ed.; Wiley-Blackwell, Ed.: Hoboken, NJ, USA, 2020.
83. Comparative Brain Tumors Consortium. Available online: <https://ccr.cancer.gov/comparative-oncology-program/pathology-and-molecular-markers> (accessed on 6 September 2023).
84. Koehler, J.W.; Miller, A.D.; Miller, C.R.; Porter, B.; Aldape, K.; Beck, J.; Brat, D.; Cornax, I.; Corps, K.; Frank, C.; et al. A Revised Diagnostic Classification of Canine Glioma: Towards Validation of the Canine Glioma Patient as a Naturally Occurring Preclinical Model for Human Glioma. *J. Neuropathol. Exp. Neurol.* 2018, 77, 1039–1054.
85. Goldbrunner, R.; Minniti, G.; Preusser, M.; Jenkinson, M.D.; Sallabanda, K.; Houdart, E.; von Deimling, A.; Stavrinou, P.; Lefranc, F.; Lund-Johansen, M.; et al. EANO guidelines for the diagnosis and treatment of meningiomas. *Lancet Oncol.* 2016, 17, e383–e391.
86. Nowosielski, M.; Galldiks, N.; Iglseider, S.; Kickingeder, P.; von Deimling, A.; Bendszus, M.; Wick, W.; Sahm, F. Diagnostic challenges in meningioma. *Neuro Oncol.* 2017, 19, 1588–1598.
87. Turrel, J.M.; Fike, J.R.; LeCouteur, R.A.; Higgins, R.J. Computed tomographic characteristics of primary brain tumors in 50 dogs. *J. Am. Vet. Med. Assoc.* 1986, 188, 851–856.
88. Sutherland, T.; Temple, F.; Galvin, A.; Hennessy, O. Contrast-enhanced ultrasound of the spleen: An introduction and pictorial essay. *Insights Imaging* 2011, 2, 515–524.
89. Vite, C.H.; Cross, J.R. Correlating magnetic resonance findings with neuropathology and clinical signs in dogs and cats. *Vet. Radiol. Ultrasound* 2011, 52, S23–S31.
90. Zhao, W.; Zheng, X.; Liu, Y.; Yang, W.; Amirbekian, V.; Diaz, L.E.; Huang, X. An MRI study of symptomatic adhesive capsulitis. *PLoS ONE* 2012, 7, e47277.

91. Zhao, M.; Zhou, Y.; Chang, J.; Hu, J.; Liu, H.; Wang, S.; Si, D.; Yuan, Y.; Li, H. The accuracy of MRI in the diagnosis of anterior cruciate ligament injury. *Ann. Transl. Med.* 2020, 8, 1657.
92. Zhao, J.P.; Liu, X.J.; Lin, H.Z.; Cui, C.X.; Yue, Y.J.; Gao, S.; Xu, H.Z. MRI comparative study of diffuse midline glioma, H3 K27-altered and glioma in the midline without H3 K27-altered. *BMC Neurol.* 2022, 22, 498.
93. Latouche, E.L.; Arena, C.B.; Ivey, J.W.; Garcia, P.A.; Pancotto, T.E.; Pavlisko, N.; Verbridge, S.S.; Davalos, R.V.; Rossmeisl, J.H. High-Frequency Irreversible Electroporation for Intracranial Meningioma: A Feasibility Study in a Spontaneous Canine Tumor Model. *Technol. Cancer Res. Treat.* 2018, 17, 1533033818785285.
94. Filippi, C.G.; Edgar, M.A.; Ulug, A.M.; Prowda, J.C.; Heier, L.A.; Zimmerman, R.D. Appearance of meningiomas on diffusion-weighted images: Correlating diffusion constants with histopathologic findings. *AJNR Am. J. Neuroradiol.* 2001, 22, 65–72.
95. Elster, A.D.; Challa, V.R.; Gilbert, T.H.; Richardson, D.N.; Contento, J.C. Meningiomas: MR and histopathologic features. *Radiology* 1989, 170, 857–862.
96. Volckaert, V.; Royaux, E. Peritumoral (pseudo)cystic meningioma in a cat. *Vlaams Diergeneesk. Tijdschr.* 2020, 89, 215–220.
97. Saito, R.; Chambers, J.K.; Kishimoto, T.E.; Uchida, K. Pathological and immunohistochemical features of 45 cases of feline meningioma. *J. Vet. Med. Sci.* 2021, 83, 1219–1224.
98. Figarella-Branger, D.; Pellissier, J.F.; Bouillot, P.; Bianco, N.; Mayan, M.; Grisoli, F.; Rougon, G. Expression of neural cell-adhesion molecule isoforms and epithelial cadherin adhesion molecules in 47 human meningiomas: Correlation with clinical and morphological data. *Mod. Pathol.* 1994, 7, 752–761.
99. Ide, T.; Uchida, K.; Suzuki, K.; Kagawa, Y.; Nakayama, H. Expression of cell adhesion molecules and doublecortin in canine anaplastic meningiomas. *Vet. Pathol.* 2011, 48, 292–301.
100. Kepes, J.J. Presidential Address: The Histopathology of Meningiomas. A Reflection of Origins and Expected Behavior? *J. Neuropathol. Exp. Neurol.* 1986, 45, 95–107.
101. Liu, N.; Song, S.Y.; Jiang, J.B.; Wang, T.J.; Yan, C.X. The prognostic role of Ki-67/MIB-1 in meningioma: A systematic review with meta-analysis. *Medicine* 2020, 99, e18644.
102. Devaprasath, A.; Chacko, G. Diagnostic validity of the Ki-67 labeling index using the MIB-1 monoclonal antibody in the grading of meningiomas. *Neurol. India* 2003, 51, 336–340.
103. Takahashi, J.A.; Ueba, T.; Hashimoto, N.; Nakashima, Y.; Katsuki, N. The combination of mitotic and Ki-67 indices as a useful method for predicting short-term recurrence of meningiomas. *Surg. Neurol.* 2004, 61, 149–155; discussion 155–146.

104. Ferraraccio, F.; Accardo, M.; Giangaspero, F.; Cuccurullo, L. Recurrent and atypical meningiomas--a multiparametric study using Ki67 labelling index, AgNOR and DNA Feulgen staining. *Clin. Neuropathol.* 2003, 22, 187–192.
105. Hsu, D.W.; Efird, J.T.; Hedley-Whyte, E.T. MIB-1 (Ki-67) index and transforming growth factor-alpha (TGF alpha) immunoreactivity are significant prognostic predictors for meningiomas. *Neuropathol. Appl. Neurobiol.* 1998, 24, 441–452.
106. Matiasek, L.A.; Platt, S.R.; Adams, V.; Scase, T.J.; Keys, D.; Miller, J.; Adamo, F.; Long, S.; Matiasek, K. Ki-67 and vascular endothelial growth factor expression in intracranial meningiomas in dogs. *J. Vet. Intern. Med.* 2009, 23, 146–151.
107. Roels, S.; Tilmant, K.; Ducatelle, R. PCNA and Ki67 proliferation markers as criteria for prediction of clinical behaviour of melanocytic tumours in cats and dogs. *J. Comp. Pathol.* 1999, 121, 13–24.
108. Castagnaro, M.; De Maria, R.; Bozzetta, E.; Ru, G.; Casalone, C.; Biolatti, B.; Caramelli, M. Ki-67 index as indicator of the post-surgical prognosis in feline mammary carcinomas. *Res. Vet. Sci.* 1998, 65, 223–226.
109. Peña, L.L.; Nieto, A.I.; Pérez-Alenza, D.; Cuesta, P.; Castaño, M. Immunohistochemical detection of Ki-67 and PCNA in canine mammary tumors: Relationship to clinical and pathologic variables. *J. Vet. Diagn. Investig.* 1998, 10, 237–246.
110. Abadie, J.J.; Amardeilh, M.A.; Delverdier, M.E. Immunohistochemical detection of proliferating cell nuclear antigen and Ki-67 in mast cell tumors from dogs. *J. Am. Vet. Med. Assoc.* 1999, 215, 1629–1634.
111. Janssen, J.; Oevermann, A.; Walter, I.; Tichy, A.; Kummer, S.; Gradner, G. Osteopontin and Ki-67 expression in World Health Organization graded canine meningioma. *J. Comp. Pathol.* 2023, 201, 41–48.
112. Artlich, A.; Schmidt, D. Immunohistochemical profile of meningiomas and their histological subtypes. *Hum. Pathol.* 1990, 21, 843–849.
113. Partridge, B.; Rossmeisl, J.H., Jr. Companion animal models of neurological disease. *J. Neurosci. Methods* 2020, 331, 108484.
114. Rutledge, M.H.; Sarrazin, J.; Rangaratnam, S.; Phelan, C.M.; Twist, E.; Merel, P.; Delattre, O.; Thomas, G.; Nordenskjold, M.; Collins, V.P.; et al. Evidence for the complete inactivation of the NF2 gene in the majority of sporadic meningiomas. *Nat. Genet.* 1994, 6, 180–184.
115. Sato, T.; Sekido, Y. NF2/Merlin Inactivation and Potential Therapeutic Targets in Mesothelioma. *Int. J. Mol. Sci.* 2018, 19, 988.
116. Gerber, M.A.; Bahr, S.M.; Gutmann, D.H. Protein 4.1B/Differentially Expressed in Adenocarcinoma of the Lung-1 Functions as a Growth Suppressor in Meningioma Cells by

- Activating Rac1-Dependent c-Jun-NH2-kinase Signaling. *Cell Tumor Stem Cell Biol.* 2016, 66, 5295–5303.
117. Pecina-Slaus, N.; Kafka, A.; Lechpammer, M. Molecular Genetics of Intracranial Meningiomas with Emphasis on Canonical Wnt Signalling. *Cancers* 2016, 8, 67.
 118. Wang, Z.; Zhang, J.; Ye, M.; Zhu, M.; Zhang, B.; Roy, M.; Liu, J.; An, X. Tumor suppressor role of protein 4.1B/DAL-1. *Cell Mol. Life Sci.* 2014, 71, 4815–4830.
 119. Lamszus, K. Meningioma pathology, genetics, and biology. *J. Neuropathol. Exp. Neurol.* 2004, 63, 275–286.
 120. Bostrom, J.; Meyer-Puttlitz, B.; Wolter, M.; Blaschke, B.; Weber, R.G.; Lichter, P.; Ichimura, K.; Collins, V.P.; Reifenberger, G. Alterations of the tumor suppressor genes CDKN2A (p16(INK4a)), p14(ARF), CDKN2B (p15(INK4b)), and CDKN2C (p18(INK4c)) in atypical and anaplastic meningiomas. *Am. J. Pathol.* 2001, 159, 661–669.
 121. Mendiola, M.; Bello, M.J.; Alonso, J.; Leone, P.E.; Vaquero, J.; Sarasa, J.L.; Kusak, M.E.; De Campos, J.M.; Pestana, A.; Rey, J.A. Search for mutations of the hRAD54 gene in sporadic meningiomas with deletion at 1p32. *Mol. Carcinog.* 1999, 24, 300–304.
 122. Lomas, J.; Bello, M.J.; Arjona, D.; Alonso, M.E.; Martinez-Glez, V.; Lopez-Marin, I.; Aminoso, C.; de Campos, J.M.; Isla, A.; Vaquero, J.; et al. Genetic and epigenetic alteration of the NF2 gene in sporadic meningiomas. *Genes. Chromosomes Cancer* 2005, 42, 314–319.
 123. Piaskowski, S.; Rieske, P.; Szybka, M.; Wozniak, K.; Bednarek, A.; Pluciennik, E.; Jaskolski, D.; Sikorska, B.; Liberski, P.P. GADD45A and EPB41 as tumor suppressor genes in meningioma pathogenesis. *Cancer Genet. Cytogenet.* 2005, 162, 63–67.
 124. Lusi, E.A.; Watson, M.A.; Chicoine, M.R.; Lyman, M.; Roerig, P.; Reifenberger, G.; Gutmann, D.H.; Perry, A. Integrative genomic analysis identifies NDRG2 as a candidate tumor suppressor gene frequently inactivated in clinically aggressive meningioma. *Cancer Res.* 2005, 65, 7121–7126.
 125. Zhang, X.; Gejman, R.; Mahta, A.; Zhong, Y.; Rice, K.A.; Zhou, Y.; Cheunsuchon, P.; Louis, D.N.; Klibanski, A. Maternally expressed gene 3, an imprinted noncoding RNA gene, is associated with meningioma pathogenesis and progression. *Cancer Res.* 2010, 70, 2350–2358.
 126. Buschges, R.; Ichimura, K.; Weber, R.G.; Reifenberger, G.; Collins, V.P. Allelic gain and amplification on the long arm of chromosome 17 in anaplastic meningiomas. *Brain Pathol.* 2002, 12, 145–153.
 127. Abedalthagafi, M.; Bi, W.L.; Aizer, A.A.; Merrill, P.H.; Brewster, R.; Agarwalla, P.K.; Listewnik, M.L.; Dias-Santagata, D.; Thorner, A.R.; Van Hummelen, P.; et al. Oncogenic PI3K mutations are as common as AKT1 and SMO mutations in meningioma. *Neuro Oncol.* 2016, 18, 649–655.

128. Clark, V.E.; Erson-Omay, E.Z.; Serin, A.; Yin, J.; Cotney, J.; Ozduman, K.; Avsar, T.; Li, J.; Murray, P.B.; Henegariu, O.; et al. Genomic analysis of non-NF2 meningiomas reveals mutations in TRAF7, KLF4, AKT1, and SMO. *Science* 2013, 339, 1077–1080.
129. Yuzawa, S.; Nishihara, H.; Tanaka, S. Genetic landscape of meningioma. *Brain Tumor Pathol.* 2016, 33, 237–247.
130. Brastianos, P.K.; Horowitz, P.M.; Santagata, S.; Jones, R.T.; McKenna, A.; Getz, G.; Ligon, K.L.; Palescandolo, E.; Van Hummelen, P.; Ducar, M.D.; et al. Genomic sequencing of meningiomas identifies oncogenic SMO and AKT1 mutations. *Nat. Genet.* 2013, 45, 285–289.
131. Baia, G.S.; Stifani, S.; Kimura, E.T.; McDermott, M.W.; Pieper, R.O.; Lal, A. Notch activation is associated with tetraploidy and enhanced chromosomal instability in meningiomas. *Neoplasia* 2008, 10, 604–612.
132. Basu, S.; Totty, N.F.; Irwin, M.S.; Sudol, M.; Downward, J. Akt phosphorylates the Yes-associated protein, YAP, to induce interaction with 14-3-3 and attenuation of p73-mediated apoptosis. *Mol. Cell* 2003, 11, 11–23.
133. Juratli, T.A.; McCabe, D.; Nayyar, N.; Williams, E.A.; Silverman, I.M.; Tummala, S.S.; Fink, A.L.; Baig, A.; Martinez-Lage, M.; Selig, M.K.; et al. DMD genomic deletions characterize a subset of progressive/higher-grade meningiomas with poor outcome. *Acta Neuropathol.* 2018, 136, 779–792.
134. Lino, M.M.; Merlo, A. PI3Kinase signaling in glioblastoma. *J. Neurooncol.* 2011, 103, 417–427.
135. Loo, E.; Khalili, P.; Beuhler, K.; Siddiqi, I.; Vasef, M.A. BRAF V600E Mutation Across Multiple Tumor Types: Correlation Between DNA-based Sequencing and Mutation-specific Immunohistochemistry. *Appl. Immunohistochem. Mol. Morphol.* 2018, 26, 709–713.
136. Perry, A.; Banerjee, R.; Lohse, C.M.; Kleinschmidt-DeMasters, B.K.; Scheithauer, B.W. A role for chromosome 9p21 deletions in the malignant progression of meningiomas and the prognosis of anaplastic meningiomas. *Brain Pathol.* 2002, 12, 183–190.
137. Schmitz, U.; Mueller, W.; Weber, M.; Sevenet, N.; Delattre, O.; von Deimling, A. INI1 mutations in meningiomas at a potential hotspot in exon 9. *Br. J. Cancer* 2001, 84, 199–201.
138. Yang, H.W.; Kim, T.M.; Song, S.S.; Shrinath, N.; Park, R.; Kalamarides, M.; Park, P.J.; Black, P.M.; Carroll, R.S.; Johnson, M.D. Alternative splicing of CHEK2 and codeletion with NF2 promote chromosomal instability in meningioma. *Neoplasia* 2012, 14, 20–28.
139. Maier, A.D.; Stenman, A.; Svahn, F.; Mirian, C.; Bartek, J., Jr.; Juhler, M.; Zedenius, J.; Broholm, H.; Mathiesen, T. TERT promoter mutations in primary and secondary WHO grade III meningioma. *Brain Pathol.* 2021, 31, 61–69.

140. Goutagny, S.; Nault, J.C.; Mallet, M.; Henin, D.; Rossi, J.Z.; Kalamarides, M. High incidence of activating TERT promoter mutations in meningiomas undergoing malignant progression. *Brain Pathol.* 2014, 24, 184–189.
141. Koelsche, C.; Sahm, F.; Capper, D.; Reuss, D.; Sturm, D.; Jones, D.T.; Kool, M.; Northcott, P.A.; Wiestler, B.; Bohmer, K.; et al. Distribution of TERT promoter mutations in pediatric and adult tumors of the nervous system. *Acta Neuropathol.* 2013, 126, 907–915.
142. Sahm, F.; Schrimpf, D.; Stichel, D.; Jones, D.T.W.; Hielscher, T.; Schefzyk, S.; Okonechnikov, K.; Koelsche, C.; Reuss, D.E.; Capper, D.; et al. DNA methylation-based classification and grading system for meningioma: A multicentre, retrospective analysis. *Lancet Oncol.* 2017, 18, 682–694.
143. Slavik, H.; Balik, V.; Kokas, F.Z.; Slavkovsky, R.; Vrbkova, J.; Rehulkova, A.; Lausova, T.; Ehrmann, J.; Gurska, S.; Uberall, I.; et al. Transcriptomic Profiling Revealed Lnc-GOLGA6A-1 as a Novel Prognostic Biomarker of Meningioma Recurrence. *Neurosurgery* 2022, 91, 360–369.
144. Rath, P.; Miller, D.C.; Litofsky, N.S.; Anthony, D.C.; Feng, Q.; Franklin, C.; Pei, L.; Free, A.; Liu, J.; Ren, M.; et al. Isolation and characterization of a population of stem-like progenitor cells from an atypical meningioma. *Exp. Mol. Pathol.* 2011, 90, 179–188.
145. Peyre, M.; Kalamarides, M. Molecular genetics of meningiomas: Building the roadmap towards personalized therapy. *Neurochirurgie* 2018, 64, 22–28.
146. Suppiah, S.; Nassiri, F.; Bi, W.L.; Dunn, I.F.; Hanemann, C.O.; Horbinski, C.M.; Hashizume, R.; James, C.D.; Mawrin, C.; Noushmehr, H.; et al. Molecular and translational advances in meningiomas. *Neuro Oncol.* 2019, 21, i4–i17.
147. Dickinson, P.J.; Surace, E.I.; Cambell, M.; Higgins, R.J.; Leutenegger, C.M.; Bollen, A.W.; LeCouteur, R.A.; Gutmann, D.H. Expression of the tumor suppressor genes NF2, 4.1B, and TSLC1 in canine meningiomas. *Vet. Pathol.* 2009, 46, 884–892.
148. Platt, S.R.; Scase, T.J.; Adams, V.; Wieczorek, L.; Miller, J.; Adamo, F.; Long, S. Vascular endothelial growth factor expression in canine intracranial meningiomas and association with patient survival. *J. Vet. Intern. Med.* 2006, 20, 663–668.
149. Mandara, M.T.; Pavone, S.; Mandrioli, L.; Bettini, G.; Falzone, C.; Baroni, M. Matrix metalloproteinase-2 and matrix metalloproteinase-9 expression in canine and feline meningioma. *Vet. Pathol.* 2009, 46, 836–845.
150. Foiani, G.; Guelfi, G.; Chiaradia, E.; Mancini, F.; Trivelli, C.; Vitellozzi, G.; Lepri, E.; Mandara, M.T. Somatostatin Receptor 2 Expression in Canine Meningioma. *J. Comp. Pathol.* 2019, 166, 59–68.
151. Dickinson, P.J.; Roberts, B.N.; Higgins, R.J.; Leutenegger, C.M.; Bollen, A.W.; Kass, P.H.; LeCouteur, R.A. Expression of receptor tyrosine kinases VEGFR-1 (FLT-1), VEGFR-2 (KDR), EGFR-1, PDGFRalpha and c-Met in canine primary brain tumours. *Vet. Comp. Oncol.* 2006, 4, 132–140.

152. Pierce, J.T.; Cho, S.S.; Nag, S.; Zeh, R.; Jeon, J.; Holt, D.; Durham, A.; Nasrallah, M.P.; Singhal, S.; Lee, J.Y.K. Folate Receptor Overexpression in Human and Canine Meningiomas-Immunohistochemistry and Case Report of Intraoperative Molecular Imaging. *Neurosurgery* 2019, 85, 359–368.
153. Grenier, J.K.; Foureman, P.A.; Sloma, E.A.; Miller, A.D. RNA-seq transcriptome analysis of formalin fixed, paraffin-embedded canine meningioma. *PLoS ONE* 2017, 12, e0187150.
154. He, S.; Pham, M.H.; Pease, M.; Zada, G.; Giannotta, S.L.; Wang, K.; Mack, W.J. A review of epigenetic and gene expression alterations associated with intracranial meningiomas. *Neurosurg. Focus* 2013, 35, E5.
155. Galani, V.; Lampri, E.; Varouktsi, A.; Alexiou, G.; Mitselou, A.; Kyritsis, A.P. Genetic and epigenetic alterations in meningiomas. *Clin. Neurol. Neurosurg.* 2017, 158, 119–125.
156. Barski, D.; Wolter, M.; Reifengerger, G.; Riemenschneider, M.J. Hypermethylation and transcriptional downregulation of the TIMP3 gene is associated with allelic loss on 22q12.3 and malignancy in meningiomas. *Brain Pathol.* 2010, 20, 623–631.
157. Lyu, Y.; Lou, J.; Yang, Y.; Feng, J.; Hao, Y.; Huang, S.; Yin, L.; Xu, J.; Huang, D.; Ma, B.; et al. Dysfunction of the WT1-MEG3 signaling promotes AML leukemogenesis via p53-dependent and -independent pathways. *Leukemia* 2017, 31, 2543–2551.
158. Nakane, Y.; Natsume, A.; Wakabayashi, T.; Oi, S.; Ito, M.; Inao, S.; Saito, K.; Yoshida, J. Malignant transformation-related genes in meningiomas: Allelic loss on 1p36 and methylation status of p73 and RASSF1A. *J. Neurosurg.* 2007, 107, 398–404.
159. Courtay-Cahen, C.; Platt, S.R.; De Risio, L.; Starkey, M.P. Preliminary analysis of genomic abnormalities in canine meningiomas. *Vet. Comp. Oncol.* 2008, 6, 182–192.
160. Du, Z.; Brewster, R.; Merrill, P.H.; Chmielecki, J.; Francis, J.; Aizer, A.; Abedalthagafi, M.; Sholl, L.M.; Geffers, L.; Alexander, B.; et al. Meningioma transcription factors link cell lineage with systemic metabolic cues. *Neuro Oncol.* 2018, 20, 1331–1343.
161. Riva, P.; Larizza, L. Expression of c-sis and c-fos genes in human meningiomas and neurinomas. *Int. J. Cancer* 1992, 51, 873–877.
162. Aarhus, M.; Bruland, O.; Bredholt, G.; Lybaek, H.; Husebye, E.S.; Krossnes, B.K.; Vedeler, C.; Wester, K.; Lund-Johansen, M.; Knappskog, P.M. Microarray analysis reveals down-regulation of the tumour suppressor gene WWOX and up-regulation of the oncogene TYMS in intracranial sporadic meningiomas. *J. Neurooncol.* 2008, 88, 251–259.
163. Wang, A.Z.; Bowman-Kirigin, J.A.; Desai, R.; Kang, L.I.; Patel, P.R.; Patel, B.; Khan, S.M.; Bender, D.; Marlin, M.C.; Liu, J.; et al. Single-cell profiling of human dura and meningioma reveals cellular meningeal landscape and insights into meningioma immune response. *Genome Med.* 2022, 14, 49.

164. Medici, G.; Freudenmann, L.K.; Velz, J.; Wang, S.S.; Kapolou, K.; Paramasivam, N.; Mühlenbruch, L.; Kowalewski, D.J.; Vasella, F.; Bilich, T.; et al. A T-cell antigen atlas for meningioma: Novel options for immunotherapy. *Acta Neuropathol.* 2023, 146, 173–190.
165. Shintaku, M.; Honda, T.; Sakai, T. Expression of podoplanin and calretinin in meningioma: An immunohistochemical study. *Brain Tumor Pathol.* 2010, 27, 23–27.
166. Maier, A.D.; Meddis, A.; Mirian, C.; Haslund-Vinding, J.; Bartek, J.; Krog, S.M.; Nguyen, T.U.P.; Areškevičiūtė, A.; Melchior, L.C.; Heegaard, S.; et al. Gene expression analysis during progression of malignant meningioma compared to benign meningioma. *J. Neurosurg.* 2023, 138, 1302–1312.
167. Kazumoto, K.; Tamura, M.; Hoshino, H.; Yuasa, Y. Enhanced expression of the sis and c-myc oncogenes in human meningiomas. *J. Neurosurg.* 1990, 72, 786–791.
168. Ogashiwa, M.; Nishiyama, F.; Fukai, K.; Takeuchi, K.; Hirano, H. Cytochemical study of Mg²⁺-ATPase and ALPase activity in human meningiomas. *No Shinkei* 1990, 42, 497–503.
169. Zhang, L.; Wang, L.; Tan, Y.; Li, C.; Fang, C. Identification of key genes of anti-programmed death ligand 1 for meningioma immunotherapy by bioinformatic analysis. *Med. Oncol.* 2022, 40, 54.
170. Sahm, F.; Bissel, J.; Koelsche, C.; Schweizer, L.; Capper, D.; Reuss, D.; Böhmer, K.; Lass, U.; Göck, T.; Kalis, K.; et al. AKT1E17K mutations cluster with meningothelial and transitional meningiomas and can be detected by SFRP1 immunohistochemistry. *Acta Neuropathol.* 2013, 126, 757–762.
171. Serna, E.; Morales, J.M.; Mata, M.; Gonzalez-Darder, J.; San Miguel, T.; Gil-Benso, R.; Lopez-Gines, C.; Cerda-Nicolas, M.; Monleon, D. Gene expression profiles of metabolic aggressiveness and tumor recurrence in benign meningioma. *PLoS ONE* 2013, 8, e67291.
172. Tabernero, M.D.; Maillo, A.; Gil-Bellosta, C.J.; Castrillo, A.; Sousa, P.; Merino, M.; Orfao, A. Gene expression profiles of meningiomas are associated with tumor cytogenetics and patient outcome. *Brain Pathol.* 2009, 19, 409–420.
173. Marton, E.; Feletti, A.; Basaldella, L.; Dei Tos, A.P.; Bendini, M.; Longatti, P. Atypical cystic meningioma overexpressing AQP1 in early infancy: Case report with literature review. *Acta Paediatr.* 2008, 97, 1145–1149.
174. Saini, M.; Jha, A.N.; Abrari, A.; Ali, S. Expression of proto-oncogene KIT is up-regulated in subset of human meningiomas. *BMC Cancer* 2012, 12, 212.
175. Atukeren, P.; Turk, O.; Yanar, K.; Kemerdere, R.; Sayyahmelli, S.; Eren, B.; Tanriverdi, T. Evaluation of ALCAM, PECAM-1 and selectin levels in intracranial meningiomas. *Clin. Neurol. Neurosurg.* 2017, 160, 21–26.

176. Schulten, H.J.; Hussein, D. Array expression meta-analysis of cancer stem cell genes identifies upregulation of PODXL especially in DCC low expression meningiomas. *PLoS ONE* 2019, 14, e0215452.
177. Zhang, H.; Qi, L.; Du, Y.; Huang, L.F.; Braun, F.K.; Kogiso, M.; Zhao, Y.; Li, C.; Lindsay, H.; Zhao, S.; et al. Patient-Derived Orthotopic Xenograft (PDOX) Mouse Models of Primary and Recurrent Meningioma. *Cancers* 2020, 12, 1478.
178. Choudhury, A.; Cady, M.A.; Lucas, C.G.; Najem, H.; Phillips, J.J.; Palikuqi, B.; Zakimi, N.; Joseph, T.; Birrueta, J.O.; Chen, W.C.; et al. NOTCH3 drives meningioma tumorigenesis and resistance to radiotherapy. *bioRxiv* 2023.
179. Sofela, A.A.; Hilton, D.A.; Ammoun, S.; Baiz, D.; Adams, C.L.; Ercolano, E.; Jenkinson, M.D.; Kurian, K.M.; Teo, M.; Whitfield, P.C.; et al. Fibulin-2: A Novel Biomarker for Differentiating Grade II from Grade I Meningiomas. *Int. J. Mol. Sci.* 2021, 22, 560.
180. Fornelli, A.; Bacci, A.; Collina, G.; Eusebi, V. Breast carcinoma metastatic to meningioma: Review of the literature and description of 2 new cases. *Pathologica* 1995, 87, 506–512.
181. Sulman, E.P.; White, P.S.; Brodeur, G.M. Genomic annotation of the meningioma tumor suppressor locus on chromosome 1p34. *Oncogene* 2004, 23, 1014–1020.
182. Nordqvist, A.C.; Mathiesen, T. Expression of IGF-II, IGFBP-2, -5, and -6 in meningiomas with different brain invasiveness. *J. Neurooncol.* 2002, 57, 19–26.
183. Hilton, D.A.; Shivane, A.; Kirk, L.; Bassiri, K.; Enki, D.G.; Hanemann, C.O. Activation of multiple growth factor signalling pathways is frequent in meningiomas. *Neuropathology* 2016, 36, 250–261.
184. Mukherjee, S.; Biswas, D.; Gadre, R.; Jain, P.; Syed, N.; Stylianou, J.; Zeng, Q.; Mahadevan, A.; Epari, S.; Shetty, P.; et al. Comprehending Meningioma Signaling Cascades Using Multipronged Proteomics Approaches & Targeted Validation of Potential Markers. *Front. Oncol.* 2020, 10, 1600.
185. Gill, C.M.; Loewenstern, J.; Rutland, J.W.; Arib, H.; Pain, M.; Umphlett, M.; Kinoshita, Y.; McBride, R.B.; Bederson, J.; Donovan, M.; et al. SWI/SNF chromatin remodeling complex alterations in meningioma. *J. Cancer Res. Clin. Oncol.* 2021, 147, 3431–3440.
186. Iglesias Gómez, J.C.; Mosquera Orgueira, A. An integrative analysis of meningioma tumors reveals the determinant genes and pathways of malignant transformation. *Front. Oncol.* 2014, 4, 147.
187. Carroll, R.S.; Zhang, J.; Dashner, K.; Black, P.M. Progesterone and glucocorticoid receptor activation in meningiomas. *Neurosurgery* 1995, 37, 92–97.
188. Black, P.; Carroll, R.; Zhang, J. The molecular biology of hormone and growth factor receptors in meningiomas. *Acta Neurochir. Suppl.* 1996, 65, 50–53.

189. Hsu, D.W.; Efird, J.T.; Hedley-Whyte, E.T. Progesterone and estrogen receptors in meningiomas: Prognostic considerations. *J. Neurosurg.* 1997, 86, 113–120.
190. Briscoe, K.; Barrs, V.R.; Foster, D.F.; Beatty, J.A. Hyperaldosteronism and hyperprogesteronism in a cat. *J. Feline Med. Surg.* 2009, 11, 758–762.
191. DeClue, A.E.; Breshears, L.A.; Pardo, I.D.; Kerl, M.E.; Perlis, J.; Cohn, L.A. Hyperaldosteronism and hyperprogesteronism in a cat with an adrenal cortical carcinoma. *J. Vet. Intern. Med.* 2005, 19, 355–358.
192. Shayanfar, N.; Mashayekh, M.; Mohammadpour, M. Expression of progesterone receptor and proliferative marker ki 67 in various grades of meningioma. *Acta Med. Iran.* 2010, 48, 142–147.
193. Maiuri, F.; Mariniello, G.; de Divitiis, O.; Esposito, F.; Guadagno, E.; Teodonno, G.; Barbato, M.; Del Basso De Caro, M. Progesterone Receptor Expression in Meningiomas: Pathological and Prognostic Implications. *Front. Oncol.* 2021, 11, 611218.
194. von Randow, A.J.; Schindler, S.; Tews, D.S. Expression of extracellular matrix-degrading proteins in classic, atypical, and anaplastic meningiomas. *Pathol. Res. Pract.* 2006, 202, 365–372.
195. Barresi, V.; Vitarelli, E.; Tuccari, G.; Barresi, G. MMP-9 expression in meningiomas: A prognostic marker for recurrence risk? *J. Neurooncol.* 2011, 102, 189–196.
196. Pei, J.; Jung, S.; Jin, S.G.; Moon, K.S.; Wen, M.; Li, S.Y.; Jang, W.Y.; Ryu, H.H.; Lee, K.H.; Kim, I.Y.; et al. Possible role of matrix metalloproteinases (MMPs) in hyperostosis of intracranial meningiomas. *Acta Neurochir.* 2012, 154, 611–620; discussion 620.
197. Iwado, E.; Ichikawa, T.; Kosaka, H.; Otsuka, S.; Kambara, H.; Tamiya, T.; Kondo, S.; Date, I. Role of VEGF and matrix metalloproteinase-9 in peritumoral brain edema associated with supratentorial benign meningiomas. *Neuropathology* 2012, 32, 638–646.
198. Mandara, M.T.; Reginato, A.; Foiani, G.; De Luca, S.; Guelfi, G. Gene Expression of Matrix Metalloproteinases and their Inhibitors (TIMPs) in Meningiomas of Dogs. *J. Vet. Intern. Med.* 2017, 31, 1816–1821.
199. Hicks, J.; Platt, S.; Kent, M.; Haley, A. Canine brain tumours: A model for the human disease? *Vet. Comp. Oncol.* 2017, 15, 252–272.
200. Samarani, F.; de la Fuente, C.; Parodi, A.; Mandara, M.T.; Pumarola, M.; Anor, S. Immunohistochemical expression of cyclooxygenase-2 (COX-2) is not associated with tumor grade in feline meningiomas. *Vet. J.* 2018, 241, 20–23.
201. Lin, C.C.; Kenyon, L.; Hyslop, T.; Hammond, E.; Andrews, D.W.; Curran, W.J., Jr.; Dicker, A.P. Cyclooxygenase-2 (COX-2) expression in human meningioma as a function of tumor grade. *Am. J. Clin. Oncol.* 2003, 26, S98–S102.

202. Preusser, M.; Hassler, M.; Birner, P.; Rudas, M.; Acker, T.; Plate, K.H.; Widhalm, G.; Knosp, E.; Breitschopf, H.; Berger, J.; et al. Microvascularization and expression of VEGF and its receptors in recurring meningiomas: Pathobiological data in favor of anti-angiogenic therapy approaches. *Clin. Neuropathol.* 2012, 31, 352–360.
203. Tabernero, M.; Jara-Acevedo, M.; Nieto, A.B.; Caballero, A.R.; Otero, A.; Sousa, P.; Gonçalves, J.; Domingues, P.H.; Orfao, A. Association between mutation of the NF2 gene and monosomy 22 in menopausal women with sporadic meningiomas. *BMC Med. Genet.* 2013, 14, 114.
204. Shimada, S.; Ishizawa, K.; Hirose, T. Expression of E-cadherin and catenins in meningioma: Ubiquitous expression and its irrelevance to malignancy. *Pathol. Int.* 2005, 55, 1–7.
205. Boozer, L.B.; Davis, T.W.; Borst, L.B.; Zseltvay, K.M.; Olby, N.J.; Mariani, C.L. Characterization of immune cell infiltration into canine intracranial meningiomas. *Vet. Pathol.* 2012, 49, 784–795.
206. Rossi, M.L.; Cruz Sanchez, F.; Hughes, J.T.; Esiri, M.M.; Coakham, H.B. Immunocytochemical study of the cellular immune response in meningiomas. *J. Clin. Pathol.* 1988, 41, 314–319.
207. Asai, J.; Suzuki, R.; Fujimoto, T.; Suzuki, T.; Nakagawa, N.; Nagashima, G.; Miyo, T.; Hokaku, H.; Takei, A. Fluorescence automatic cell sorter and immunohistochemical investigation of CD68-positive cells in meningioma. *Clin. Neurol. Neurosurg.* 1999, 101, 229–234.
208. Stavrou, D.; Anzil, A.P.; Weidenbach, W.; Rodt, H. Immunofluorescence study of lymphocytic infiltration in gliomas. Identification of T-lymphocytes. *J. Neurol. Sci.* 1977, 33, 275–282.
209. Bo, L.; Mork, S.J.; Nyland, H. An immunohistochemical study of mononuclear cells in meningiomas. *Neuropathol. Appl. Neurobiol.* 1992, 18, 548–558.

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