Familial Syndromes Involving Meningiomas Provide Mechanistic Insight Into Sporadic Disease

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Currently, there is an incomplete understanding of the molecular pathogenesis of meningiomas, the most common primary brain tumor. Several familial syndromes are characterized by increased meningioma risk, and the genetics of these syndromes provides mechanistic insight into sporadic disease. The best defined of these syndromes is neurofibromatosis type 2, which is caused by a mutation in the *NF2* gene and has a meningioma incidence of approximately 50%. This finding led to the subsequent discovery that *NF2* loss-of-function occurs in up to 60% of sporadic tumors. Other important familial diseases with increased meningioma risk include nevoid basal cell carcinoma syndrome, multiple endocrine neoplasia 1 (MEN1), Cowden syndrome, Werner syndrome, BAP1 tumor predisposition syndrome, Rubinstein-Taybi syndrome, and familial meningiomatosis caused by germline mutations in the *SMARCB1* and *SMARCE1* genes. For each of these syndromes, the diagnostic criteria, incidence in the population, and frequency of meningioma are presented to review the relevant clinical information for these conditions. The genetic mutations, molecular pathway derangements, and relationship to sporadic disease for each syndrome are described in detail to identify targets for further investigation. Familial syndromes characterized by meningiomas often affect genes and pathways that are also implicated in a subset of sporadic cases, suggesting key molecular targets for therapeutic intervention. Further studies are needed to resolve the functional relevance of specific genes whose significance in sporadic disease remains to be elucidated.

KEY WORDS: Familial meningioma, Meningioma, Meningioma genetics, Meningioma pathogenesis

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Meningiomas are the most common primary brain tumor reported in the United States, comprising approximately 36% of brain tumors.[1,2] Estimates from recent data predict that more than 20 000 new meningiomas will be diagnosed each year, with an incidence of 7.5 per 100 000.[2] While the majority of these tumors are sporadic, there are many familial syndromes that place a patient at increased risk for meningioma development. The most well characterized and documented of these genetic syndromes is neurofibromatosis type 2 (NF2). Identification of the *NF2* gene led to the investigation of molecular genetic mutations in sporadic meningiomas, in which up to 60% of patients have also been found to have somatic inactivation of *NF2*.[3,4] Recent whole genome sequencing and whole exome sequencing studies in non-*NF2* mutated meningiomas have further delineated additional mutations in *TRAF7*, *KLF4*, *AKT1*, *PI3K*, and *SMO*; however, many sporadic tumors still have not been found to have a genetic basis (Figure 1).[5,6] Greater understanding of the familial syndromes associated with meningiomatosis may elucidate further molecular mechanisms behind the

ABBREVIATIONS: AKT1, v-Akt murine thymoma viral oncogene homolog 1; **BCC,** basal cell carcinoma; **CS,** Cowden syndrome; **IHC,** immunohistochemistry; **KLF4,** Kruppel-like factor 4; **MBAIT,** melanocytic *BAP1*-mutated atypical intradermal tumors; **MEN1,** multiple endocrine neoplasia 1; **NBCCS,** nevoid basal cell carcinoma syndrome; **NF2,** neurofibromatosis type 2; **PHTS,** PTEN hamartoma tumor syndrome; **PI3K,** phosphatidylinositol 3-kinase; **PTEN,** phosphatase and tensin homolog; **SHH,** sonic hedgehog; **SMO,** smoothened; **TRAF7,** TNF receptor-associated factor 7

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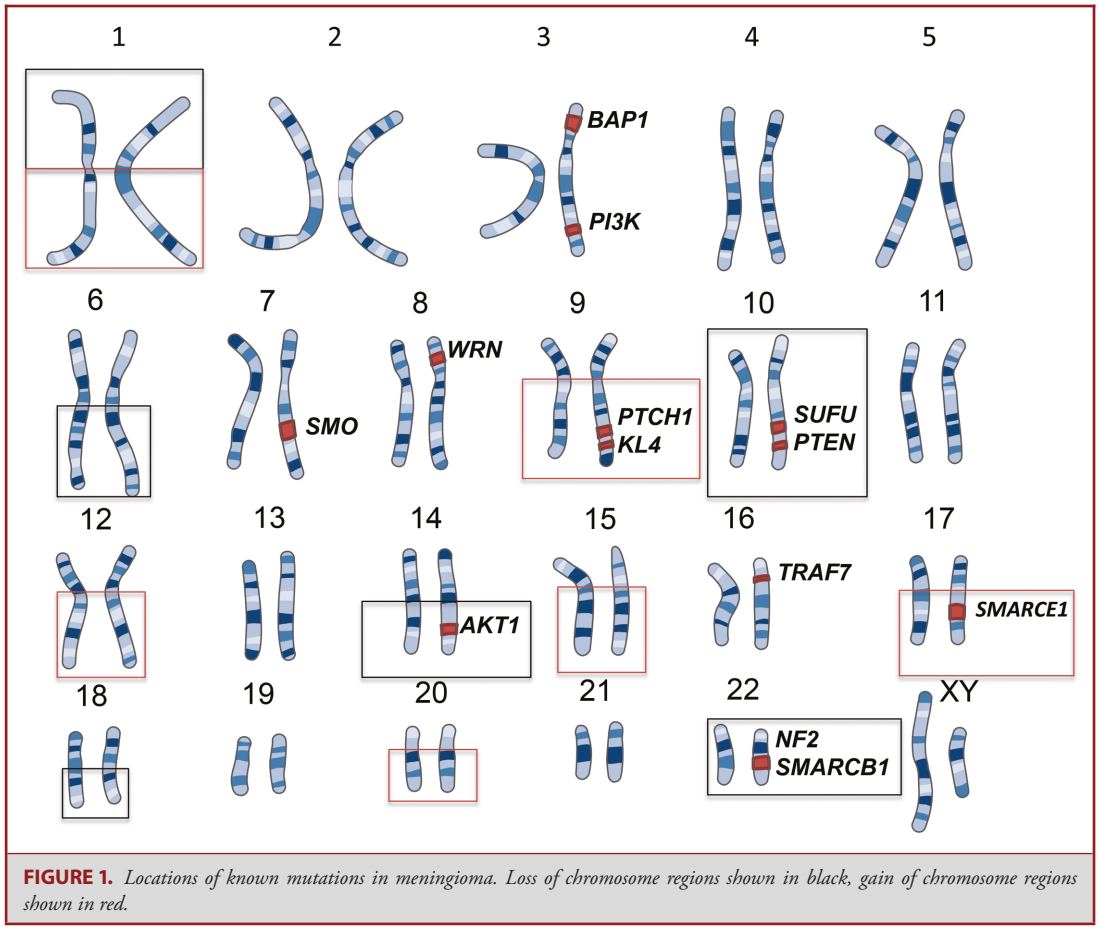

FIGURE 1. *Locations of known mutations in meningioma. Loss of chromosome regions shown in black, gain of chromosome regions shown in red.*

development of sporadic meningiomas. Below, we present a review of familial syndromes associated with meningioma predisposition.

METHODS

A review of the PubMed database was conducted to identify published studies on known familial meningioma syndromes up until June 2017. Combinations of search terms used included "meningioma," "familial meningiomatosis," "familial meningioma," "nevoid basal cell carcinoma syndrome," "Gorlin syndrome," "multiple endocrine neoplasia 1," "Cowden syndrome," "Werner syndrome," "*BAP1* tumor predisposition syndrome," "*SMARCB1*," "*SMARCE1*," "*SUFU*," and "Rubinstein-Taybi syndrome." Only studies available in English were included. All identified abstracts from these searches were analyzed, and those that reviewed or examined familial syndromes associated with meningiomas were included.

RESULTS

A review of PubMed abstracts from the described search criteria resulted in 46 studies that met inclusion (see **Supplemental Digital Content**). The results from these studies are presented below and include NF2, nevoid basal cell carcinoma syndrome (NBCCS, also known as Gorlin syndrome), multiple endocrine neoplasia 1 (MEN1), Cowden syndrome (CS), Werner syndrome, *BAP1* tumor predisposition syndrome, Rubinstein-Taybi syndrome, and familial meningiomatosis caused by germline mutations in the *SMARCB1* and *SMARCE1* genes (Table 1).

Neurofibromatosis Type 2

NF2 is an autosomal dominant, 100% penetrant condition characterized by a constellation of schwannomas and meningiomas.[7] NF2 is clinically diagnosed using the Manchester criteria, the details of which are in Table 2. The overall prevalence of NF2 in the population is approximately 1 in 60 000.[8]

NF2 is caused by germline mutations in the *NF2* tumor suppressor gene, located at 22q12.2. The protein product is called merlin or schwannomin.[9] Within the cell, merlin has been found to interact with several proteins that affect PI3K, YAP/TAZ, and mitogen-activated protein kinase (MAPK) signaling. All 3 pathways are important in cell growth and cellular proliferation.[8,10,11] Given its location at the cell

TABLE 1. List of Syndromes, Mutations, Pathways, and Sporadic Relationships

Syndrome	Mutated gene	Involved pathway	Relationship to sporadic tumors
NF2	NF2 tumor suppressor	EGFR, YAP/TAZ, MAPK, cytoskeletal architecture	Mutated in 40%-60%
Werner	WRN	DNA processing, maintenance and repair	Methylated with decrease in expression
BAP1-TPDS	BAP1	Chromatin Remodeling, DNA repair	Found in high-grade rhabdoid meningiomas
SMARCE1	SMARCE1	Nucleosome remodeling, apoptosis	Found in Clear cell meningiomas
SMARCB1	SMARCB1	Nucleosome remodeling, apoptosis	Mutated in 3%
Gorlin	PTCH1	SHH – PTCH1/SMO/SUFU/GLI-1,2,3	SMO mutated in 5%
Cowden	PTEN	PI3K – RTK/AKT/PI3K/mTOR/PTEN	AKT mutated in 14%; PIK3CA mutated in 7%

TABLE 2. Neurofibromatosis Type 2 Diagnostic Criteria

A diagnosis can be made if an individual meets one of the following:
Bilateral vestibular schwannomas
A first degree relative with NF2 + unilateral vestibular schwannoma or 2 NF2-associated lesions*
Unilateral vestibular schwannoma + 2 NF2-associated lesions*
Multiple meningiomas + unilateral vestibular schwannoma or 2 other NF-2 associated lesions*

*Meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities.

membrane-cytoskeletal interface, several other potential functions have been proposed, including contact-dependent inhibition of EGFR, effects on cell-to-cell adhesion, and regulation of cytoskeletal architecture.[12-14]

The role of *NF2* inactivation in sporadic meningiomas was investigated due to the high frequency of meningiomas in NF2 patients. The frequency of *NF2* inactivation is estimated to be present between in 40% and 60% of cases of sporadic meningiomas based on several studies, and this mutation is thought to be the causative mutation in these cases.[4] Interestingly, *NF2*-mutated meningiomas have certain location predilections.[5] Those with *NF2* mutations and/or chromosome 22 loss were found preferentially in the hemispheres. For meningiomas of the skull base, those located laterally and posteriorly were significantly more likely to have *NF2* mutations and/or chromosome 22 loss, whereas medially located skull base tumors were more commonly non-*NF2* mutated. The work on NF2 has provided an excellent example of how investigating a familial syndrome with meningiomas can lead to establishing the genetic basis for sporadic disease.

Nevoid Basal Cell Carcinoma Syndrome

Nevoid basal cell carcinoma syndrome, also known as basal cell nevus syndrome or Gorlin syndrome, is an autosomal dominant syndrome that is classically characterized by multiple basal cell carcinomas (BCC), jaw keratocysts, and bifid ribs.[15] The complete list of major clinical criteria required for diagnosis and cited by several studies is detailed in Table 3. [16,20] The estimated prevalence is between 1 in 30 000 and 1 in 256 000 and equally affects men and women.[16,17] Additional tumors that are associated with the syndrome include meningiomas and rhabdomyosarcomas.[16,18]

Specifically, meningiomas were reported in 5% of NBCCS patients in 2 studies.[19,20] Given that meningiomas commonly

TABLE 3. Nevoid Basal Cell Carcinoma Syndrome Diagnostic Criteria

A diagnosis can be made if an individual meets 2 major criteria or 1 major + 2 minor criteria

Major criteria	Minor criteria
Basal cell carcinomas: ≥5 in a lifetime or 1 diagnosed before age 30	Childhood medulloblastoma
Lamellar calcification of the falx before the age of 20	Lympho-mesenteric or pleural cysts
Jaw odontogenic keratocyst	Macrocephaly (occipitofrontal circumference (OFC) > 97th percentile)
Palmar or plantar pits: ≥2	Cleft lip/palate
First-degree relative with NBCCS	Vertebral or rib anomalies (bifid/splayed/extra ribs, bifid vertebrae)
	Preaxial or postaxial polydactyly
	Ovarian or cardiac fibromas
	Ocular anomalies (cataract, developmental defects, pigmentary changes of the retinal epithelium)

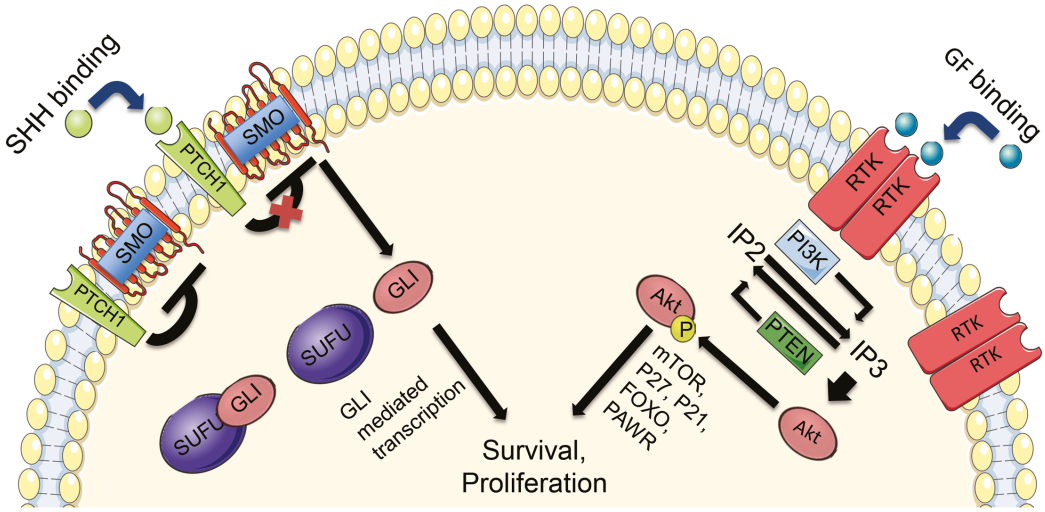

FIGURE 2. *Details of the SHH and Akt pathways. Without SHH binding, PTCH1 renders smoothened (SMO) inactive and inhibits it from signaling downstream targets. When SHH binds to PTCH1, SMO is released from this inhibition, allowing it to interact with SUFU. This results in the activation and nuclear translocation of glioma-associated oncogene homologue 1 (GLI1) and (GLI2), and the degradation of GLI3. In the Akt pathway, PTEN normally targets IP3 to inhibit the phosphorylation of Akt. When growth factor (GF) binding to receptor tyrosine kinases (RTK) occurs, PI3K signaling is increased, leading to IP3 accumulation, phosphorylation of Akt and activation of downstream targets.*

arise from the falx cerebri, it is interesting to note that NBCCS is characterized by prominent calcifications of this area.[16,19] The genetic causes behind NBCCS are pathogenic mutations in genes of the sonic hedgehog (SHH) signaling pathway including *PTCH1*, *PTCH2*, and *SUFU*, located at 9q22.32, 1p34.1, and 10q24.32, respectively, with variations in *PTCH1* being the most common.[21,22] The activation of this pathway drives cell proliferation in both normal neural development and in tumor development.[23] In BCC and a subset of medulloblastoma, the loss of *PTCH1* or *SUFU* and the activation of *SMO* have been implicated in tumor initiation and maintenance.[24,25] In fact, mutations in *PTCH1* or *SMO* are sufficient to drive tumorigenesis in BCC and medulloblastoma mouse models.[23,26,27] The *PTCH1* gene codes for a protein that constitutes the ligand-binding component of the SHH receptor complex. The details of the SHH pathway are depicted in Figure 2.[28,29]

A meningioma has been reported in a patient with NBCCS with a confirmed germline *PTCH1* mutation in which the genetic sequencing of the patient's meningioma revealed an additional somatic mutation in *PTCH1*. Using the Knudson's 2-hit theory, they considered the development of this meningioma to be caused by loss of function of *PTCH1*.[30] Additionally, driver mutations in *SMO* have been identified as one of the most common non-*NF2* mutations in sporadic meningiomas, and have a predilection for the olfactory groove. Meningiomas with an *SMO* mutation in the olfactory groove have been found to have a higher recurrence rate, especially late recurrences (>5 yr). Given this information and the significance with regard to prognostication, surgeons and neuro-oncologists should consider testing olfactory groove meningiomas specifically for *SMO* mutations and adjusting their follow-up schedule accordingly for these lesions, which is currently commercially available at multiple CLIA (Clinical Laboratory Improvement Amendments)-certified laboratories.[5,31]

Patients with NBCCS caused by *SUFU* mutations have been found to be significantly more likely to have a meningioma in comparison to NBCCS patients caused by *PTCH1* or *PTCH2* mutations.[22] *SUFU* mutations have also been investigated in a family with multiple meningiomas and the absence of other features of NBCCS.[32] Genome-wide linkage analysis and exome sequencing in this family found that germline *SUFU* mutations segregated with disease in the family. Functional studies showed that the identified mutation led to significantly increased SHH pathway activation due to loss of the normal suppressor function of SUFU. This group also sequenced the coding exons and exon-intron boundaries of *SUFU* in blood/germline samples of 162 meningiomas (11 of these patients had a familial history of meningiomas and 40 had multiple meningiomas) from a national meningioma database; however, no pathogenic variants of *SUFU* were detected.

TABLE 4. Cowden Syndrome Diagnostic Criteria

A diagnosis can be made if an individual meets 3 major criteria (1 must be macrocephaly, LDD, or GI hamartomas) or 2 major + 3 minor criteria*

Major criteria	Minor criteria
Breast cancer	Autism spectrum disorder
Endometrial cancer (epithelial)	Colon cancer
Thyroid cancer (follicular)	Esophageal glycogenic acanthosis: ≥ 3
Gastrointestinal hamartomas (including ganglioneuromas, but excluding hyperplastic polyps): ≥ 3	Lipomas: ≥ 3
Adult Lhermitte-Duclos disease (LDD)	Intellectual disability (IQ ≤ 75)
Macrocephaly (occipitofrontal circumference (OFC) ≥ 97th percentile)	Renal cell carcinoma
Macular pigmentation of the glans penis	Testicular lipomatosis
Multiple mucocutaneous lesions (any of the following):	Thyroid cancer (papillary or follicular variant of papillary)
Trichilemmomas: ≥ 3, at least one biopsy proven	Thyroid lesions (adenoma, multinodular goiter)
Acral keratoses: ≥ 3 palmoplantar keratotic pits and/or acral hyperkeratotic papules)	Vascular anomalies (including multiple intracranial developmental venous anomalies)
Mucocutaneous neuromas: ≥ 3	
Oral papillomas (particularly on tongue and gingiva): ≥ 3 or 1 biopsy proven/dermatologist diagnosed	

*In an individual who has a relative who meets the above criteria or has a PTEN mutation, a diagnosis can be made if he or she meets 2 major criteria, 1 major + 2 minor criteria, or 3 minor criteria.

The SHH pathway is critical to the formation of meningiomas in some instances. Studies on patients with NBCCS and familial meningiomatosis due to germline *SUFU* mutations have provided important information into the mechanisms by which derangement of the SHH pathway can lead to these tumors. Further research into the other components of this pathway is important.

Cowden Syndrome

Cowden syndrome, part of the *PTEN* hamartoma tumor syndrome (PHTS), is an autosomal dominant disorder caused by germline mutations in phosphatase and tensin homolog (*PTEN*) on chromosome 10q23.31.[33] Its diagnostic criteria include a host of major and minor criteria as well as pathognomonic findings listed in Table 4.[34] CS is estimated to affect between 1 in 200 000 and 1 in 250 000 people.[35,36] Although not part of the major or minor criteria, meningiomas are found in approximately 8% of patients.[37] Other clinical syndromes that are classified as PHTS include Bannayan-Riley-Ruvalcaba and Proteus syndrome.[33] Multiple case reports have also identified meningiomas in patients with Proteus syndrome.[38,39]

The PTEN protein acts as a phosphatase to dephosphorylate various cellular lipids and proteins. Dysfunctional PTEN leads to upregulation of the PI3K-AKT-mTOR (mammalian target of rapamycin) pathway, resulting in increases in cell proliferation, energy metabolism, and survival.[40] It has been found to be important in breast and prostate cancer as well as glioblastoma multiforme.[41] In mouse models of glioma, *PTEN* deletion results in earlier tumor onset and increases tumor grade.[42,43] PTEN targets include phosphatidylinositol trisphosphate and phosphatidylinositol bisphosphate, both products of PI3K. This pathway is illustrated in Figure 2. As part of its protein phosphatase activity, PTEN has been shown to dephosphorylate focal adhesion kinase, which has negative effects on cell migration and cell spreading, as well as MAPK that regulates cell survival.[44,45]

In sporadic meningiomas, higher-grade tumors are associated with progressive changes at the chromosomal level including losses of chromosomes 1p, 9q, 10q, 14q, and 22q.[46] Given this information and *PTEN*'s location at 10q23.3, it was investigated as a candidate gene in sporadic meningiomas.[47] Using a group of 55 WHO grade I, 10 grade II, and 10 grade III meningiomas, Peters et al[47] sequenced the entire coding sequence of the *PTEN* gene in tumor samples. No *PTEN* mutations were seen in the grade I tumors, but 1 grade III tumor harbored a somatic mutation in *PTEN*. These findings led them to hypothesize that mutations in *PTEN* are unlikely to be involved in the initiation and formation of low-grade meningiomas, but may contribute to malignant progression to higher-grade lesions. Such a conclusion supports other work in the chromosomal analysis comparing high-grade and low-grade sporadic meningiomas.[46] This is similar to gliomas in that low-grade gliomas do not have as high of a frequency of *PTEN* loss as high-grade gliomas.[48]

Given *PTEN*'s role in regulation of the PI3K-AKT-mTOR pathway, and evidence of dysregulation of this pathway in many cancers, downstream targets of *PTEN* have also been investigated as potential oncogenic drivers in meningioma.[49]

TABLE 5. Werner Syndrome Diagnostic Criteria

A confirmed diagnosis can be made if an individual has all 6 cardinal signs or a WRN mutation + 3 cardinal signs. A diagnosis is suspected if an individual has 2 cardinal signs or 1 cardinal sign + additional signs

Cardinal signs*	Additional signs
Premature greying or thinning of scalp hair	Abnormal glucose and/or lipid metabolism
Bilateral cataracts	Skeletal abnormalities (osteoporosis)
Characteristic dermatologic changes (atrophic skin, tight skin, clavus, callus, intractable skin ulcers)	Malignant tumors (nonepithelial tumors, thyroid cancer)
Soft-tissue calcification (Achilles tendon)	Parental consanguinity
'Bird-like' facies	Premature atherosclerosis (angina pectoris, myocardial infarction)
Abnormal voice (high pitched, squeaky, hoarse)	Hypogonadism
	Short stature and low bodyweight

*Age of onset between 10-40 years.

Both *AKT* and *PI3KA* mutations have been found in sporadic meningiomas, comprising approximately 9% and 7% of non-*NF2*-mutant meningiomas, respectively.[5,50] The complexity of this pathway suggests ample room for more investigation into the role of both *PTEN* and its downstream targets in meningioma pathogenesis. Previous research in patients with CS has provided some of the framework for our understanding of this pathway's role in cancer.

Werner Syndrome

Werner syndrome, also known as adult progeria, was first described in a set of siblings with short stature, "senile" appearance, premature graying of the hair, early-onset cataracts, dermatologic changes, and muscle atrophy.[51] Biallelic mutations in the *WRN* gene (also known as *RECQL2*) were later established as the cause of the syndrome, which is inherited in an autosomal recessive manner.[52] A set of cardinal and additional signs and symptoms has been designated and was updated most recently in 2013 (Table 5).[53] A definite diagnosis is achieved when all 6 cardinal signs are present or a gene mutation and at least 3 cardinal signs are present. Interestingly, Japan has the highest frequency of carriers, at rates of 6 per 1000, while the disease prevalence in the overall population is estimated to be 1 in 1000 000 individuals based on publically available allele frequency databases.[54,55] A patient with Werner syndrome is approximately 36.2 times Standardized Incidence Ratio (SIR); 95% confidence interval 17.3, 66.5) more likely to develop a meningioma than the general population and are more likely to develop them at a younger age.[56] In addition, the proportion of meningiomas to other brain tumors in the Werner Syndrome is higher than expected.[57]

The *WRN* gene is located on chromosome 8p12 and encodes for a protein with DNA helicase activity that is a member of the RecQ family.[52,58] The WRN protein product uses its helicase function to help resolve intermediate DNA structures generated during DNA metabolism and also functions in DNA repair (specifically base excision repair and double-stranded DNA break repair) replication, transcription, and telomere maintenance.[59] Its loss of function in Werner syndrome patients leads to genomic instability and limited replicative capacity in somatic cells.[60,61] The majority of pathogenic germline mutations leading to Werner syndrome are stop codons, small indels, or splicing mutations that cause loss of the nuclear localization of the protein. Other mutations lead to protein instability and loss of function, but essentially all *WRN* mutations are functional null alleles in Werner syndrome.[62]

Sporadic meningiomas are characterized by a number of chromosomal copy number alterations, and this appears to increase with meningioma grade and tumor progression (Figure 3).[63,64] The most common alteration is monosomy 22, followed by loss of chromosome 1p and 14q. Other chromosomal changes include loss of 6q, 10, and 18q as well as gain of chromosomes 1q, 9q, 12q, 15q, 17q, and 20q.[65] In particular, combined 1p/14q deletions are significantly more likely in higher-grade meningiomas and 14q deletions are more likely in benign recurrent meningiomas.[64] It has been postulated that mutations in *WRN* and other DNA helicases may result in such chromosomal changes, given their role in proper DNA replication and repair. *WRN* silencing through promoter methylation has been investigated.[66] Li et al[66] found that meningiomas had a significantly higher *WRN* methylation rate than did healthy arachnoid control tissue. Subsequently, *WRN* was expressed significantly less in meningioma tissue than in normal arachnoid tissue. *WRN* promoter hypermethylation has been investigated in other cancers, and was found to be most prevalent in colorectal, non-small cell lung, gastric, prostate, and thyroid cancers.[67] In addition, loss of *WRN* function led to chromosomal instability in these cancers. Given that many sporadic meningiomas have DNA changes that could be related to dysfunction of WRN or WRN-like proteins, the role of DNA repair and replication enzymes in sporadic meningiomas may be a relevant topic for further investigation.

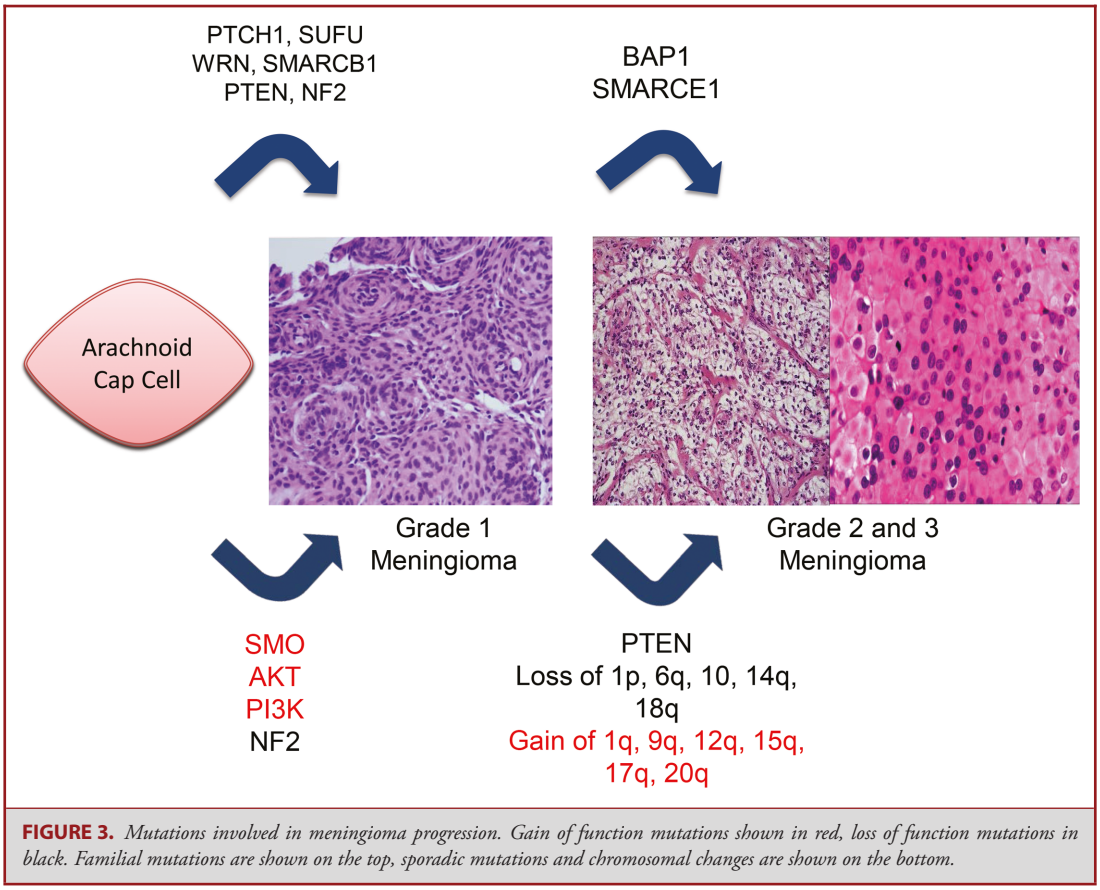

FIGURE 3. *Mutations involved in meningioma progression. Gain of function mutations shown in red, loss of function mutations in black. Familial mutations are shown on the top, sporadic mutations and chromosomal changes are shown on the bottom.*

TABLE 6. Tumors Associated With BAP1 Tumor Predisposition Syndrome

Uveal melanoma
Malignant mesothelioma
Renal cell carcinoma
Cutaneous melanoma
Meningioma
Melanocytic bap1-mutated atypical intradermal tumors

BAP1 Tumor Predisposition Syndrome

The oncogenicity of the *BAP1* gene was originally discovered in the genomic assessment of families with uveal melanoma and malignant mesothelioma.[68] Further studies on *BAP1* indicated that several other neoplasms including meningioma are included in the syndrome (Table 6). A hallmark feature of these patients is the presence of melanocytic *BAP1*-mutated atypical intradermal tumors (MBAITs).[69] MBAITs are skin-colored, dome-shaped papules that appear in up to two-thirds of carriers, typically before other associated malignancies develop. Given that this is a more recently discovered syndrome, prevalence and penetrance data are scarce, and the phenotypic spectrum of associated tumors continues to expand.[68]

BAP1 is located on chromosome 3p21.1 and encodes the *BRCA1*-associated protein 1, which functions in transcription, chromatin modification, and DNA damage response. Part of its tumor suppressive function is related to its interaction with BRCA1, which plays an important role in the repair of double-stranded DNA breaks and has been well described in breast cancer predisposition and development.[68,70]

Meningiomas were identified as part of the *BAP1* tumor predisposition syndrome when examining a group of patients with uveal melanoma.[71] In this study, a germline truncating mutation of *BAP1* was identified in 5 individuals of the same family. One family member had a diagnosis of meningioma, and subsequent tumor tissue analysis revealed biallelic inactivation of *BAP1*. The *BAP1* gene has also been found to be inactivated in a subset of high-grade rhabdoid meningiomas.[72] Initially thought to be sporadic tumors, germline *BAP1* mutations were identified in some of these patients, further supporting meningiomas as part of the *BAP1* tumor predisposition syndrome spectrum. In this series, somatic *BAP1* mutations were a predictor of clinically aggressive tumors, highlighting how genetic characterization

of meningiomas can guide clinical management. It is also recommended that patients with somatic *BAP1*-mutated meningiomas be evaluated for *BAP1* tumor predisposition syndrome, illustrating an instance where genetic testing in meningiomas should be completed. Germline genetic testing for *BAP1* mutations is commercially available. A *BAP1* antibody is available for immunohistochemistry (IHC) testing of patient samples, and in the study listed above all *BAP1* mutants showed loss of *BAP1* expression on IHC.[72]

SMARCE1

Germline mutations of *SMARCE1* have been implicated in several families with familial meningiomatosis.[73,74] *SMARCE1* is also known as *BAF57*, and is thought to be involved in loss of apoptosis in other types of cancer, including breast, ovarian, and prostate.[75] Located on chromosome 17q21, *SMARCE1* encodes for a subunit of the SWI/SNF complex, which regulates chromatin structure by nucleosome remodeling.[76] Specifically, SMARCE1 is responsible for inducing apoptosis by stimulating expression of *CYLD*.[77]

SMARCE1 mutations have been investigated in the germline of families with a history of meningiomas as well as sporadic tumors.[73] Smith et al[73] examined *SMARCE1* mutations in a group of patients with spinal meningiomas and a positive family history of meningiomas that tested negative for germline mutations in *NF2*. Whole exome sequencing with Sanger confirmation revealed heterozygous loss-of-function mutations in *SMARCE1* in these patients. The histology on all of these tumors was of the clear-cell subtype, and the loss of function phenotype was thought to be consistent with a tumor suppressor mechanism. The authors concluded that the SWI/SNF complex plays a key role in the pathogenesis of meningiomas, and that they had identified a new discrete entity with a genetic basis for multiple meningiomas. This work has been further corroborated by the identification of a family with a germline *SMARCE1* mutation and cranial meningiomas.[74] Additionally, in 1 cohort of patients less than 25 years of age with a solitary meningioma, germline *SMARCE1* mutations were identified in 14% (9/63) of patients.[78] All affected individuals also had meningiomas of the clear cell type. These studies have important clinical management implications when a clear cell meningioma is encountered in clinical practice, especially in young patients or those with a family history of meningiomas. Germline genetic testing for *SMARCE1* mutations should be considered in this subset of patients as part of their work-up. Individuals with an identified mutation should be followed more closely given their predilection for multiple lesions, and their family members should be offered predictive genetic testing for risk stratification. IHC investigating the *SMARCE1* status of patient samples has been previously performed, and loss of SMARCE1 protein staining appears specific to clear cell histology.[79,80] However, IHC and genomic profiling of tumor specimens do not routinely include evaluation of *SMARCE1* at this time.

SMARCB1

Similar to *SMARCE1*, *SMARCB1* (also known as *INI1*) encodes a protein that serves as a subunit of the SWI/SNF complex.[81] It is located on chromosome 22q11.23, in close proximity to the *NF2* gene. Germline inactivating mutations of *SMARCB1* have been found to predispose patients to several cancers including malignant rhabdoid tumors and schwannomatosis, both independently and as part of a 4-hit mechanism with NF2.[82-84]

In a study examining a family with schwannomatosis and a germline *SMARCB1* mutation, multiple family members were also noted to have 1 or more meningiomas, independent of an *NF2* mutation.[85] In a similar fashion to schwannomatosis, *SMARCB1* mutations have been described as part of a 4-hit mechanism in a family with multiple meningiomas with a germline *SMARCB1* mutation and somatic *NF2* mutations.[86] In this particular group of patients, this complement of mutations appeared to preferentially produce meningiomas of the falx cerebri. This study also screened newly found carriers of the *SMARCB1* mutation for intracranial lesions by magnetic resonance imaging of the brain and found that 7 of 11 these patients had asymptomatic lesions. All of these lesions appeared to be meningiomas, and all of them were attached to falx. In a patient with a falcine meningioma and a family history of meningioma, germline genetic testing for *SMARCB1* mutations should be considered, which would also allow for the subsequent risk stratification of family members. IHC is also readily available to test tissue samples for loss of *SMARCB1*(*INI1*) expression. However, the identified mutations in the studies above were missense mutations and it is unclear if they will affect overall protein abundance, potentially limiting the value of IHC.

The role of *SMARCB1* has been investigated in sporadic tumors as well. In 1 series of sporadic meningiomas, somatic mutations in exon 9 of *SMARCB1* were noted in 3% of tumors.[87] An insertional mutation in exon 9 of *SMARCB1* was also noted in 1 patient in an 80 patient series of sporadic meningiomas by a separate group.[88]

Other Familial Syndromes

Other syndromes including MEN1 and Rubinstein-Taybi syndrome have been reported to be associated with meningiomas, but have only been demonstrated in case reports and case series.[89,90]

DISCUSSION

A set of common themes emerges when looking at the work done on familial disease and the extension of that work to examine sporadic cases. With the notable exception of *NF2*, most of these genes are not commonly mutated in sporadic disease. However, they are all involved in pathways or processes that appear essential to meningioma formation. These pathways include or involve SHH, AKT-PI3K-mTOR, and YAP/TAZ. SHH pathway

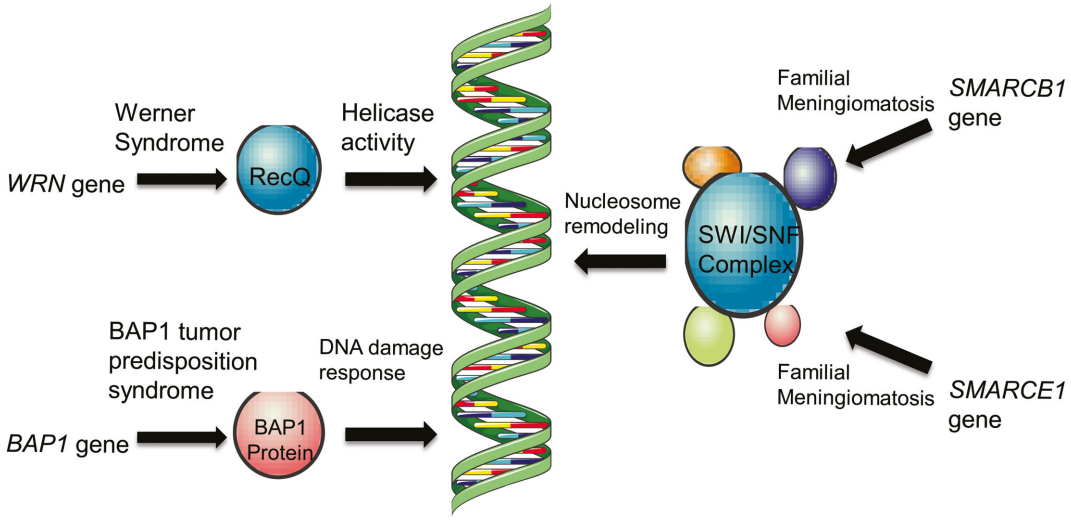

FIGURE 4. *Meningioma-associated mutations in genes involving chromatin structure and the DNA damage response. WRN codes for a protein that is a member of the RecQ family. Its helicase function serves broad functional roles in normal DNA metabolism as well as DNA repair. The BAP1 protein is involved in the DNA damage response, specifically functioning in double-stranded break repair. The SMARCB1 and SMARCE1 genes code for components of the SWI/SNF complex, which participates in chromatin remodeling to regulate transcription.*

mutations lead to uncontrolled cell growth and proliferation in many cancers, while AKT-PI3K-mTOR pathway malfunction leads mainly to increased survival.[23,40] YAP/TAZ signaling dysfunction through merlin mutations produces increased proliferation through the loss of contact inhibition.[12] Merlin is also involved with regulation of the mTOR pathway, a potential point of convergence in these important pathways in meningioma pathogenesis.[91] Another common theme between the familial syndromes presented is that the protein products of the mutated genes commonly function in DNA maintenance and repair (Figure 4). This is particularly interesting given the chromosomal copy number and other large-scale genetic changes that occur in meningioma. These changes are even more prevalent in higher-grade tumors, suggesting an essential role in the pathogenesis of meningioma progression. While it is known that these changes occur, the exact mechanism by which they occur and the ultimate effects of these changes remains to be elucidated.

This work supports the strategy of examining familial syndromes to identify candidate genes and pathways for further study in sporadic cases. The relationship of *SMARCE1* mutations to the clear cell subtype and *BAP1* mutations to the rhabdoid subtype demonstrate how familial studies also provide insight into the specific histopathologic subtypes of meningioma. The histologic grading of meningiomas is challenging given the multitude of types, and the discordance between histology and clinical behavior lessens its utility. Studies in which specific genetic mutations are associated with specific histologies are the beginning of a potential molecular classification of these tumors that could be used to better predict patient outcomes. Epigenetic classification schemes are also a potential method for classification, with a recently proposed scheme based on DNA methylation for meningiomas being an example.[92] The authors found that methylation patterns profiled meningiomas into 2 major groups with several subclasses and that this profiling better predicted recurrence and prognosis than the current WHO classification. The authors included the familial genes *SMARCE1*, *SMARCB1*, *PTEN*, *SUFU*, and *NF2* in their analysis of the subtypes of their classification scheme, with *NF2* and *SUFU* being the only genes that segregated significantly. Investigating the other familial genes discussed in this review could have provided the authors further information. We agree with the authors and WHO that given the complex nature of these tumors, an amalgamated approach combining histology, genetics, epigenetics, and clinical findings will provide the best system for classification. The results of studies on familial syndromes combined with large-scale genetic studies on sporadic meningioma leave up to 20% of meningiomas without a genetic basis. Given the comprehensive examination of the genetic landscape of meningioma that these studies provide, one hypothesis that could be derived is that the remaining causes of meningioma lay outside of genetic mutations. Studies examining gene expression profiles, epigenetic regulation, microRNA, and long noncoding RNA will be important to gain a better understanding of meningioma pathogenesis.

CONCLUSION

Here we present a comprehensive review of the familial syndromes associated with meningiomas. Details of the implicated genes and their associated pathways are given to facilitate further understanding of the molecular pathogenesis of meningiomas and to support future research. As many of the studies on these familial syndromes have shown, the molecular understanding of these syndromes often leads to investigations that broaden our understanding of sporadic disease.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Supplemental Digital Content. Appendix. List of Included Studies. This list provides the studies that were included after the literature review with the provided search terms.

COMMENT

This manuscript presents a summary of known genomic drivers of familial meningiomas and how they help in dissecting the pathogenesis of sporadic cases.

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