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REVIEW ARTICLE

Germline and somatic mutations in meningiomas

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Meningiomas arise from the arachnoid layer of the meninges that surround the brain and spine. They account for over one third of all primary central nervous system tumors in adults and confer a significant risk of location-dependent morbidity due to compression or displacement. A significant increase in risk of meningiomas is associated with neurofibromatosis type 2 (NF2) disease through mutation of the *NF2* gene. In addition, approximately 5% of individuals with schwannomatosis disease develop meningiomas, through mutation of the SWI/SNF chromatin remodeling complex subunit, *SMARCB1*. Recently, a second SWI/SNF complex subunit, *SMARCE1*, was identified as a cause of clear cell meningiomas, indicating a wider role for this complex in meningioma disease. The sonic hedgehog (SHH)-GLI1 signaling pathway gene, *SUFU*, has also been identified as the cause of hereditary multiple meningiomas in a large Finnish family. The recent identification of somatic mutations in components of the SHH-GLI1 and AKT1-MTOR signaling pathways indicates the potential for cross talk of these pathways in the development of meningiomas. This review describes the known meningioma predisposition genes and their links to the recently identified somatic mutations.

Keywords *SMARCB1*, *SMARCE1*, *SUFU*, *AKT1*, meningioma

Meningiomas are the most common primary central nervous system tumors in adults (1). Over 90% of meningiomas are single and sporadic. Fewer than 2% of meningiomas are classed as malignant; however, 20–35% of meningiomas, initially classed as benign, have been reclassified as atypical since the World Health Organization (WHO) grading system changed in 2007 (2). These tumors tend to occur at an earlier age and have a seven-to eightfold increased rate of recurrence. Atypical meningiomas also confer a reduced survival rate with an approximately twofold increased risk of death by 3–5 years after diagnosis (3).

Benign meningiomas carry a significant risk of location-dependent morbidity due to compression or displacement. Spinal meningiomas can cause back pain and numbness and weakness of the arms or legs, suprasellar and intraorbital meningiomas can cause vision problems and swelling or bulging of the eye, and olfactory groove meningiomas can cause loss of sense of smell. Intraventricular meningiomas may cause headaches and changes in mental function due to increased pressure resulting from reduced flow of cerebrospinal fluid, whereas meningiomas within the convexity can cause various focal neurological deficits that are restricted to a specific region, such as weakness or paresthesia in one side of the face, or one arm or leg.

Many meningiomas are well-delineated tumors that respond well to surgical excision, although meningiomas that occur in the skull base can be difficult to access and remove. Meningioma growth can be unpredictable. Some meningiomas show a linear growth pattern that may be fast or slow and may be dependent on the level of calcification (4), whereas others show a saltatory growth pattern with variable periods of quiescence (5). There are many histologic subtypes of meningioma. Meningothelial, fibroblastic, and transitional meningiomas, as well as the psammomatous, secretory, microcystic, angiomatous, lymphoplasmacyte-rich, and metaplastic variants are all classed as grade I. Clear cell, chordoid and atypical subtypes are classed as grade II, whereas the anaplastic, rhabdoid, and papillary variants are all classed as grade III. Most meningiomas have a mixed histology and are categorized by the dominant component.

Of the known causes for sporadic meningiomas, ionizing radiation is probably the most common. A hormonal aspect to meningioma development has also been suggested, as there is a 2.3:1 overall female/male ratio for meningiomas (6), and even higher ratios, of between 4:1 and 9:1, have been reported for spinal meningiomas (7–10). It has also been observed that the gender bias is reversed in

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meningiomas that develop before 20 years of age (11,12) and that the appearance of meningiomas in women can correlate with, or worsen during, pregnancy (13,14). There is no definitive evidence for this hormonal influence and although the accelerated growth of meningiomas during pregnancy has been attributed to raised progesterone levels (15), the proportion of meningiomas expressing progesterone receptors is not significantly different between males and females (16) and a recent study has shown that the effects of pregnancy on meningioma growth may be more likely to be due to temporary hemodynamic changes (14).

The most common genetic cause of meningiomas is mutation of the *NF2* gene. Germline mutations of *NF2* cause the tumor suppressor syndrome neurofibromatosis type 2 (NF2), which predisposes individuals to schwannomas and ependymomas as well as meningiomas. Other individuals without a family history of NF2 disease harbor multiple meningiomas that are likely to be caused by an underlying genetic cause. Cases with more than one meningioma, but no other clinical features of NF2 or schwannomatosis, may arise because of independent sporadic tumors (17), mosaic NF2 with no mutation identified in the blood (18), or clonal spread of a single sporadic tumor (19,20). The identification of different *NF2* mutations in each tumor indicates that the tumors arose independently. Identical, biallelic *NF2* mutations in each tumor indicates mosaic NF2 or clonal spread. Identical somatic mutations in other genes or X-inactivation of the same X chromosome (19) indicates clonal spread of a single tumor. Rare families also exist with a history of meningiomas, inherited in an autosomal dominant fashion, outside of the context of NF2 disease (13,21).

Two of the SWI/SNF chromatin remodeling complex subunits, SMARCB1 (22) and SMARCE1 (13), have been implicated in meningioma disease. Germline mutations of *SMARCB1* confer a risk of meningiomas as part of the schwannomatosis phenotype. More recently, loss-of-function mutations in *SMARCE1* were found to specifically predispose carriers to clear cell meningiomas (13,23).

The human SWI/SNF chromatin remodeling complex is made up of between 9 and 12 subunits (24), which work together to activate or repress genes throughout the genome. Each complex includes one of the two ATPase subunits, *SMARCA2* or *SMARCA4*; the evolutionarily conserved core subunits, *SMARCB1*, *SMARCC1*, and *SMARCC2*; and additional complex-specific variant subunits (24) (Figure 1A and B). *SMARCE1* is not conserved in lower eukaryotes, but it has been found to exist in all mammalian forms of the complex (25). Several reports have found associations between the SWI/SNF complex and various forms of cancer (26). For example, somatic *SMARCA4* mutations have been found in medulloblastomas of the wingless-related integration site (WNT) and sonic hedgehog (SHH) subtypes (27). In addition to *SMARCE1*, other SWI/SNF subunits have recently been associated with clear cell tumors. Somatic *ARID1A* mutations are associated with ovarian clear cell carcinomas (28), and somatic *PBRM1* mutations are associated with clear cell renal cell carcinomas (29).

Mutations of *SMARCB1* have been associated with several forms of cancer (30). Germline *SMARCB1* mutations are known to cause the highly aggressive pediatric cancer atypical teratoid/rhabdoid tumors (AT/RT) (31), as well as the benign tumor predisposition syndrome schwannomatosis (32). The type of *SMARCB1* mutation and its location within the gene are significantly different between these two syndromes (33), indicating different mechanisms of tumor development in different syndromes caused by the same gene.

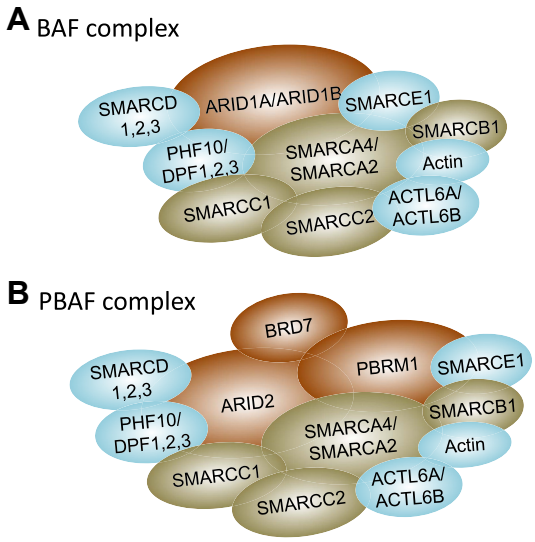

Figure 1 Schematic diagram of the human SWI/SNF chromatin remodeling complex: (A) a BAF complex containing either an ARID1A or an ARID1B subunit and (B) a PBAF complex containing a PBRM1 subunit.

A nontruncating mutation in the Shh-Gli1 pathway gene, *SUFU*, was identified as the cause of multiple meningiomas in a single large Finnish family (21). SUFU, SMARCB1, and SMARCE1 have all been associated with a predisposition to meningiomas and are all known to bind the Shh pathway transcription factor, Gli1 (34). Somatic mutations identified in the Shh-Gli and Akt1-mTor signaling pathways in non-NF2-associated meningiomas (35,36) indicate the potential for cross talk of these pathways in the development of meningioma tumors.

Genetic risk factors

NF2-associated meningiomas

NF2

Germline mutation of the *NF2* gene is the most commonly identified genetic risk factor for multiple meningioma disease. Multiple meningiomas often occur as part of the NF2 tumor suppressor syndrome. Germline *NF2* mutations are detectable in over 90% of all cases of nonmosaic NF2 disease and confer a significant risk of meningiomas, with approximately 50% of people with NF2 developing at least one intracranial meningioma during their lifetime. The presence of intracranial meningiomas in NF2 is associated with the likelihood of disease mortality.

The risk of meningiomas in NF2 disease has been demonstrated to correlate with the type and location of mutations within the gene, with a greater risk of developing a meningioma associated with truncating mutations than