Vestibular schwannomas (VSs) are benign tumors arising from the sheath of cranial nerve VIII. The pathogenesis underlying most familial and sporadic VSs has been linked to a mutation in a single gene, the neurofibromin 2 (NF2) gene located on chromosome 22, band q11–13.1. In this review, the authors summarized what is known about the epidemiology of NF2 mutations and patients with VSs. The authors also discuss the function of the NF2 gene product, merlin, and describe the known and hypothetical effects of genetic mutations that lead to merlin dysfunction on a broad variety of cellular and histological end points. A better understanding of the molecular pathobiology of VSs may lead to novel therapeutics to augment current modalities of treatment while minimizing morbidity. (DOI: 10.3171/2009.10.JNS091135)

KEY WORDS • vestibular schwannoma • neurofibromatosis Type 2 • merlin

Abbreviations used in this paper: JNK = c-Jun N-terminal kinase; merlin = moesin-ezrin-radixin–like protein; mTOR = mammalian target of rapamycin; NF2 = neurofibromin 2 gene; NF2 = neurofibromatosis Type 2; NF-κB = nuclear factor κB; PI3 = phosphatidylinositol 3′-kinase; pRb-CDK = retinoblastoma protein–cyclin-dependent kinase; STAT = signal transducer and activator of transcription; VEGF = vascular endothelial growth factor; VS = vestibular schwanna.
**Identification and Description of the NF2 Gene**

In 1982 cytogenetic analysis of meningioma samples offered the first clue that the NF2 gene might lie on chromosome 22. In 1987 this broad location was confirmed using linkage analysis. The NF2 gene was further localized to 22q12.2 by genetic linkage analysis and tumor deletion mapping using more precisely localized DNA markers, and the gene itself was then independently isolated by 2 groups using positional cloning techniques. The NF2 gene encodes a 595–amino acid protein named “moesin-ezrin-radixin–like protein,” otherwise known as “merlin” or “schwannomin.” The gene is spread over ~100,000 bases on chromosome 22q12.2 and contains 17 exons.

**The NF2 Gene and Merlin Function**

Sequence alignment showed that merlin exhibits significant homology to a family of proteins including moesin, ezrin, radixin, talin, and members of the protein 4.1 superfamily known as the “ERM family.” The ERM proteins are involved in linking cytoskeletal components with the plasma membrane and are located in actin-rich surface projections such as microvilli, membrane ruffles, and cell contact regions. The N-terminal region of ERM proteins is relatively conserved among this family of proteins and is known as the “FERM region” (the acronym was created from the names of members of this family: F for 4.1 protein, E for ezrin, R for radixin, and M for moesin). The ERM proteins all contain a FERM region, which interacts with a number of components of the plasma membrane, including integral membrane receptors. Note, however, that the merlin molecule contains a unique 7–amino acid domain that has been hypothesized to mediate its unique effects, not found in other members of this family. The C-terminal domain interacts with components of the cytoskeleton including actin. A large alpha helix domain between these 2 domains may serve as a hinge region, allowing either self-association of the merlin molecule in the inactive forms of the molecule or association of this molecule with other members of the ERM family via domains known as ERM-associated domains (known as “N-ERMAD” or “C-ERMAD,” depending on the end of the molecule in which they are located; Fig. 1). While the exact function of merlin is not yet known, available evidence suggests that it is involved in cell-cell or cell-matrix interactions and that it is important for cell movement, cell shape, and communication. There is considerable evidence in both NF2 knockout mice and in vitro schwannoma preparations that functional loss of the merlin protein results in a loss in contact inhibition, which consequently leads to tumorigenesis.

**Genotype-Phenotype Correlations in NF2**

Significant differences in types of NF2 gene mutations have been found among VSs associated with NF2. Approximately 65% of NF2-associated NF2 mutations are nonsense and frameshift mutations, which are expected to cause truncated gene products. Studies aimed at determining the relationship between NF2 gene mutation and clinical severity have established 2 genotype-phenotype correlations: (1) patients with severe clinical disease tend to harbor mutations that produce a truncated protein as a result of insertions or deletions that lead to disruption of the merlin open reading frame (frameshift mutations) or of premature termination codons (nonsense mutations), and (2) patients with milder disease tend to harbor missense mutations or DNA alterations that are not found by conventional mutation detection strategies. Nonsense mutations may result in the production of an unstable truncated protein, leading to a loss of merlin expression from the mutated NF2 allele. Merlin proteins containing missense mutations may be stably expressed but defective in their ability to suppress growth.

**The NF2 Mutations Identified in Sporadic VSs**

The loss of chromosome 22q in up to 45% of sporadic VSs strongly implicates a shared genetic pathogenesis with NF2-associated schwannomas. The NF2 gene mutation and loss of merlin production have also been observed in sporadic VS tissue. This finding strongly argues for the NF2 gene as a critical regulator of Schwann cell growth, with inactivation of the NF2 gene being an essential step in tumorigenesis.
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Using a heteroduplex approach and direct sequencing, Wellin and colleagues\(^\text{70}\) have completed a screen of ~ 88% of the NF2 coding sequence of DNA from 33 schwannomas isolated from patients with NF2 and 29 patients with sporadic schwannomas. Mutations were identified in 66% of sporadic cases but only 33% of NF2 cases, suggesting that there may be different mutational mechanisms involved in the tumorigenesis of unilateral and bilateral schwannomas. Point mutations accounted for 58% of all mutations in the NF2 cases, whereas they accounted for only 19% of unilateral schwannomas. Small deletions accounted for 76% of the mutations in unilateral tumors but were found in only 42% of bilateral tumors. Similar deletion rates of 81%\(^\text{30}\) and 89%\(^\text{60}\) have also been reported in unilateral tumors. The majority of identified mutations (93%) resulted in truncating proteins lacking all or part of the C terminus.

Other Chromosomal Areas in Sporadic VS Formation

Recent screenings of large sporadic VS tumor banks via comparative genomic hybridization have revealed 2 other potential areas of interest. Analysis revealed a copy number addition on chromosome 9q34 in 10% of samples and an addition on chromosome 17q in 5% of samples.\(^\text{59}\) These areas may harbor tumor-forming genes and must be analyzed with more sophisticated methods. These results suggest that NF2 gene inactivation may not be the only determinant of tumorigenesis in patients with NF2.

Mosaicism

Approximately 50–85% of patients with NF2 have no family history of the disease.\(^\text{54}\) Thus, these patients represent new or de novo mutations. Some of these new mutations occur after fertilization, resulting in mosaicism— that is, mixed cell populations with and without mutation in the same individual. In 1998 Kluwe and Mautner\(^\text{15}\) examined the rate of mosaicism in patients with nonfamilial NF2. Mutations were found in 13 (81%) of 16 patients with a family history or affected offspring, but in only 46 (51%) of 91 patients with no affected offspring. Mosaicism may account for the inability to find mutations in some patients with sporadic disease and could partially explain the 30% difference in the rate of mutation detection in inherited and sporadic NF2 cases. Among patients with sporadic NF2, mosaicism may be more common in those with mild phenotypes given that some cases are the result of reduced population sizes of mutation-bearing cells. A higher frequency of mosaicism may partially explain the lower rate of mutations (23%) among patients expressing mild phenotypes compared with those expressing more severe phenotypes (59%).

The exact frequency and nature of mosaicism are difficult to estimate. The difference in the rate of detecting mutations between inherited and sporadic cases ranges from 22 to 30% and to some extent may reflect the frequency of mosaicism in NF2.\(^\text{14}\) Because the cell lineage commitment in the human embryo is not well understood, the effect and outcome of mosaicism is unpredictable.

Gene Array and cDNA Library

Microarray analysis of VS has been performed to identify other potential gene expression levels altered by NF2 gene mutation. Data obtained from these experiments are extensive and often found within significant noise; therefore, making any emphatic interpretation difficult. Nonetheless, an analysis by Wellin and colleagues\(^\text{71}\) of VS tissue with microarrays containing 25,920 known genes has shown significant upregulation of 42 genes (0.2%). Among them was osteonectin, an angiogenesis mediator and glycoprotein that interacts with extracellular matrix to decrease cell adhesion and thus induce a biological state conducive to cell migration, as well as endoglin, transforming growth factor–β receptor, and RhoB GTPase, a protein important in cell signaling. Most of the remaining upregulated genes have unknown functions. Among the underexpressed genes was LUCA-15, an apoptosis-related gene. These analyses suffer from the typical limitations of most gene chip analyses. Although it is an interesting technique for hypothesis generation, it remains a relative comparison of gene expression and does not necessarily imply causation.

Halum and colleagues\(^\text{23,24}\) have used the serial analysis of gene expression (SAGE) technique to determine the qualitative and quantitative evaluations of the NF2 gene transcript from NF2-associated VS specimens. Two transcripts related to apoptosis were identified including Wilms tumor–related protein and Fas-activated serine/threonine (FAST) kinase. Wilms tumor–related protein is thought to act as a tumor suppressor by regulating the expression of several growth-related genes. The Fas-activated serine/threonine kinase is a serine/threonine kinase activated by Fas ligation to phosphorylate T-cell–restricted intracellular antigen–1 (TIA-1), a nuclear RNA-binding protein thought to be an effector of apoptosis.\(^\text{24}\) Two tumor-associated transcripts implicated in tumor angiogenesis were also found, including platelet-derived endothelial cell growth factor (also referred to as “thymidine phosphorylase”) and leptin. Leptin is known to have proliferative effects in some cells. Platelet-derived endothelial cell growth factor is also highly expressed in tumors and functions in angiogenesis by the stimulation of endothelial cell migration. It has also been shown to suppress Fas-induced apoptosis. Thymidine phosphorylase inhibitors have been developed as chemotherapeutic agents for this thymidine phosphorylase–mediated tumor angiogenesis.

Bruder and colleagues\(^\text{7}\) have used an array made with a large number of genes covering ~ 90% of the 22q locus for the NF2 gene. In screening a population of 116 patients with NF2 of variable clinical severity, NF2 gene deletions were detected in 24 patients, although no genotype/phenotype correlation was demonstrated.

Role of Merlin in Schwann Cell Biology and Tumorigenesis

Modulation of Cell Motility

Merlin is believed to act as a link between membrane and cytoskeleton components. Cellular localization stud-
ies have shown that both exogenously and endogenously expressed merlin localizes mainly to areas of membrane remodeling, and prominent staining has been detected in ruffling edges, where F-actin was colocalized. In addition to interacting with F-actin, merlin also associates with the transmembrane protein CD44, β1-integrin, and paxillin. Merlin also interacts indirectly through the ERM proteins or βII-spectrin, which belong to a family of proteins that bind actin, ankyrin, and several other cytoskeletal proteins. The different mechanisms by which merlin and ERM proteins bind to actin may specify their roles in modulating cytoskeletal proteins (Table 1).

The colocalization of merlin and F-actin at membrane ruffles suggests that merlin plays a critical role in maintaining normal cytoskeletal organization and is involved in the regulation of cytoskeleton-associated events such as cell motility because membrane ruffling is a cytoskeletal response associated with cell movement. Several independent observations have supported merlin’s role in actin cytoskeleton-associated processes. First, cancers that arise in NF2 heterozygous (+/−) mice have demonstrated high motility and a propensity for metastasis. Second, cytoskeletal defects, such as increased membrane ruffling, disorganized stress fibers, and altered spreading, have been observed in cells from almost all schwannomas. Third, the loss of merlin in primary schwannoma cell cultures has led to alteration in actin cytoskeleton organization, cell spreading, and cell attachment. The reintroduction of merlin into these NF2-deficient cells has reversed abnormal cell ruffling and spreading. Fourth, the regulated overexpression of merlin in rat schwannoma cells has resulted in the disorganization of the actin cytoskeleton, abnormalities in the initial phases of cell spreading, and reduced cell motility. In contrast, the regulated overexpression of NF2-containing missense mutations has had no effect on actin cytoskeleton function. Thus, while its exact functions remain unclear, perhaps at least one of merlin’s functions is to limit cell motility.

### Suppression of Cell Proliferation

The role of merlin in actin cytoskeleton-associated processes also suggests that merlin may regulate cell growth in response to specific cues from the environment. Studies from several laboratories have demonstrated that merlin has a specific role in growth suppression mediated by the activation of transmembrane proteins (for example, CD44) or cell contact. These results suggest that merlin growth regulation occurs within the context of extracellular interactions provided by normal brain or nerve. The loss of merlin might lead to an impaired ability to respond to these environmental growth regulatory cues and culminate in increased cell growth, tumor formation, and tumor cell infiltration.

Previous studies have shown merlin requires at least 2 important intramolecular associations, including one between its amino and carboxyl terminal domains, to function as a negative growth regulator. A truncated protein product cannot form these intramolecular associations and has been shown to cause a lack of growth suppression. At least one recent study has revealed that intermolecular interactions also play a critical role in merlin tumor suppression. At low cellular density, merlin is phosphorylated and thus is growth permissive and exists in a complex with transmembrane hyaluronate receptor.

### TABLE 1: Summary of known interactions with merlin and the effects in VS*

<table>
<thead>
<tr>
<th>Protein</th>
<th>Effect in VS</th>
<th>Potential Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>actin</td>
<td>loss of cell contact inhibition</td>
<td></td>
</tr>
<tr>
<td>CD44</td>
<td>loss of cell contact inhibition</td>
<td></td>
</tr>
<tr>
<td>β1-integrin</td>
<td>loss of cell contact inhibition</td>
<td></td>
</tr>
<tr>
<td>paxillin</td>
<td>loss of cell contact inhibition</td>
<td></td>
</tr>
<tr>
<td>Rac</td>
<td>disinhibition allows cyclin D dysregulation</td>
<td>temsirolimus</td>
</tr>
<tr>
<td>mTOR</td>
<td>inhibited by merlin, dysregulated in merlin loss</td>
<td></td>
</tr>
<tr>
<td>Akt</td>
<td>inhibited by merlin, inhibits merlin</td>
<td>KP372-1</td>
</tr>
<tr>
<td>STAT3</td>
<td>inhibited by merlin, dysregulated in merlin loss</td>
<td>static</td>
</tr>
<tr>
<td>STAT5</td>
<td>inhibited by merlin, dysregulated in merlin loss</td>
<td>roscovitine</td>
</tr>
<tr>
<td>Ras</td>
<td>inhibited by merlin, dysregulated in merlin loss</td>
<td>farnesylthiosalicylic acid</td>
</tr>
<tr>
<td>MAPK</td>
<td>inhibited by merlin, dysregulated in merlin loss</td>
<td></td>
</tr>
<tr>
<td>NGF receptor</td>
<td>expressed by tumors</td>
<td>AG879</td>
</tr>
<tr>
<td>TGFβ</td>
<td>expressed by tumors</td>
<td>SB-431542</td>
</tr>
<tr>
<td>FGF</td>
<td>expressed by tumors</td>
<td></td>
</tr>
<tr>
<td>interleukin-6</td>
<td>expressed by tumors</td>
<td></td>
</tr>
<tr>
<td>VEGF</td>
<td>induction of angiogenesis</td>
<td>bevacizumab</td>
</tr>
<tr>
<td>FasL</td>
<td>immunoresistance</td>
<td></td>
</tr>
<tr>
<td>Bcl-2</td>
<td>apoptosis resistance</td>
<td></td>
</tr>
<tr>
<td>Bax</td>
<td>maintenance of limited growth rate</td>
<td></td>
</tr>
</tbody>
</table>

* FGF = fibroblast growth factor; MAP = mitogen-activated protein kinase; NGF = nerve growth factor; TGFβ = transforming growth factor β.
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CD44, erzin, and moesin. At high cell density, schwannomin/merlin becomes hyperphosphorylated and inhibits cell growth, again via an interaction with CD44.48 A recent study by Schulze and colleagues62 has demonstrated that merlin inhibits tumor growth in VS tissue. Using oncornovirus–mediated gene transfer, the NF2 gene was introduced into human VS cells. The modified schwannoma cells showed reduced tumor proliferation, increased G0/G1 cell cycle arrest, and increased apoptosis. These experiments highlight the importance of merlin-mediated control of schwannoma growth, suggesting promise for gene or protein therapy as a possible future treatment option.

Merlin and Cell Cycle Regulation

The pRb-CDK Pathway. The mammalian cell cycle is divided into 4 phases: G1, S (DNA replication), G2, and M (mitosis). Progression from phase G1 to S is tightly regulated by the pRb-CDK pathway. Several studies have revealed an interaction between the NF2 gene product and cell cycle regulation via the pRb-CDK pathway.

Merlin functions as a negative regulator of Rac-dependent signaling.45 In addition to regulating cytoskeletal organization, Rac activates an array of intracellular signaling pathways involved in cellular proliferation, transformation, and transcriptional activation. Downstream signaling regulated by Rac includes the JNK, p38, and NF-κB pathways. Activation of the JNK and p38 cascades stimulates the activity of several transcriptional factors such as Jun and activating transcription factor 2 (ATF2).73 Active, dephosphorylated merlin downregulates Rac-induced signaling, whereas inactive, phosphorylated merlin potentiates Rac function.67

Note that Rac functioning is necessary for progression through the G1 phase of the cell cycle, which is attributed to Rac’s ability to stimulate the transcription and translation of cyclin D1, which in turn activates its CDK partners, CDK4 and CDK6, causing phosphorylation and inactivation of the pRb. This cascade is a critical event in the G1 phase that allows cells to pass through the cell cycle checkpoint and enter the S phase.18,64 Given that merlin functions as an inhibitor of Rac signaling, perhaps it plays a role in cell cycle progression by the downregulation of Rac-induced cyclin D1 accumulation in the G1 phase. Importantly, the overexpression of merlin has been shown to induce G0/G1 arrest, identifying a connection between merlin and cyclin D1 regulation.

Lasak and colleagues39 have used microarray technology to study the G1 to S phase cell cycle pathway in VS tissue. Microarray chips with a large number of genes known to be important to the pRb-CDK pathway were generated and hybridized to cDNA from VS, resulting in the decreased function of this pathway in all 8 VS samples. Downregulation of the pRb-CDK pathway may relate to the characteristic slow growth of these tumors.

The PI3K/Akt/mTOR Pathway. Other groups have implicated merlin in the inhibition of cell growth through repression of the cell cycling molecule mTOR. James and colleagues53 have demonstrated excessive mTOR activation in merlin-deficient schwannoma and meningioma cells. Interestingly, they excluded involvement of the PI3K/Akt or the ERK/TSC2 (extracellular signal-regulated kinase/tuberous sclerosis complex 2) pathways in the inactivation of mTOR, suggesting that merlin inhibits mTOR in a novel manner. Note that Akt is a protein kinase that has a variety of proproliferative effects on cell cycle function, most notably the activation of mTOR, and subsequently the nuclear transcription factor NF-κB. Recent data have demonstrated that not only does merlin inhibit Akt function,29 providing at least 2 ways in which merlin inhibits the function of mTOR, but activated Akt reciprocally inhibits merlin function.53 Furthermore, an inhibitor of phosphoinositide-dependent kinase–1 and upstream activator of Akt was recently shown to inhibit schwannoma cell growth in vitro and in vivo.40

Other Pathways. Recent work has implicated the loss of merlin function in the dysregulation of a wide variety of other signaling cascades. For example, merlin mutations have been shown to increase function of the STAT3 and STAT5 signaling cascades66 as well as the mitogen-activated protein kinase62 and Ras pathways.32 The role of merlin in the suppression of nearly every major proproliferative cell signaling pathway possibly explains why a single gene mutation of merlin can initiate and drive tumorigenesis in the absence of other mutations (Fig. 2).

Growth Factor Receptor Expression in VS

A significant proportion of sporadic VSs do not grow at all or grow very slowly, and some even decrease in size. At one center, among 40 sporadic VSs visualized with interval imaging, only 30% of the tumors showed evidence of growth over a 30-month follow-up period. Furthermore, the growth rate in 30% was ~ 1 mm/year.50 The clinical behavior of VS in NF2 is significantly different from that of
sporadic VS. In patients with NF2, 75% of schwannomas show evidence of growth, with an average growth rate of 4.5 mm/year. Mechanisms other than and in addition to NF2 gene inactivation seem to be involved in the initiation and maintenance of VS growth. At present, there is no consensus on the important cellular factors that influence tumor growth in either sporadic VS or NF2. Tumor expression of different cytokines and other factors such as Schwann cell proliferation and tumor growth have been addressed in studies of Ki 67, proliferating cell nuclear antigen, nerve growth factor receptor, transforming growth factor, fibroblast growth factor, interleukin-6, and hormones. Some of these factors have been correlated to in vitro Schwann cell proliferation or to the duration of symptoms. Others have been correlated to the growth rate of either residual tumor or heterotransplanted tumor tissue.

**Angiogenesis Factors**

The growth of any solid tumor with a volume > 2 or 3 mm³ requires angiogenesis for a sufficient supply of oxygen and nutrients through diffusion. Several proangiogenic factors have been implicated in the pathogenesis of VS. Among the most well described and potent is VEGF-A. In VSs, a relationship exists between the number of vessels and the growth rate and size of the tumor. Data from a recent study have demonstrated that VEGF was expressed in VS and that the intensity of immunohistochemical expression correlated positively with the growth rate of the tumor. There was no relationship between the expression of VEGF and tumor size or duration of symptoms. Our own analysis of the clinical history of untreated VSs has revealed that growth rate was the strongest predictor of future hearing loss in patients with VSs, suggesting that tumors with angiogenesis grow faster and behave more aggressively. A recent study in humans has confirmed this hypothesis, as treatment with the anti-VEGF antibody bevacizumab demonstrated a clinical response and hearing improvement in a small cohort of patients with NF2.

**Apoptotic Markers**

A transcription factor, p53 is involved in many cellular pathways responsive to different stressors, including apoptosis. Following ionizing radiation, p53 is stabilized and activated, which leads to the activation of many downstream effectors, including the CDK inhibitor p21. Alterations of the p53 tumor suppressor gene, Fas/FasL system, Bcl-2, and Bax have been studied in VSs. Data from multiple studies have substantiated the absence of significant alterations in the p53 gene in VSs. Mawrin and colleagues have investigated the expression of the Fas/FasL system as well as the proapoptotic factor Bcl-2 and the proapoptotic factor Bax in 14 sporadic VSs and have related the findings to the MIB-1 labeling index as a marker for cell proliferation. Although cytoplasmic Fas expression was seen in only 1 tumor (7%), FasL was found in the nuclei of 12 schwannomas (86%). Expression of Bcl-2 was found in the cytoplasm of 9 tumors (64%), and Bax was found in 10 (71%) of 14 schwannomas. Note, however, that schwannomas expressing Bax tended to show a higher proliferation rate as revealed by the MIB-1 labeling index, suggesting a balance between cell proliferation and cell death.

**Role of Merlin Mutations Beyond NF2 and VS**

Merlin is best known for its association with the NF2 syndrome. In addition to the hallmark presence of bilateral VSs, patients with NF2 often have multiple intracranial meningiomas. Not surprisingly, merlin mutations have been found in up to 60% of sporadic meningiomas. Merlin is highly expressed in cells of the arachnoid villi—thought to be the cell of origin of meningiomas—suggesting that merlin normally plays a critical tumor suppressor role in these cells. Merlin-deficient meningioma cells display a markedly increased size, which may be due to constitutive dis inhibition of the cell signaling molecule mTOR. Furthermore, transfer of the NF2 into meningioma cells using viral vectors has been shown to inhibit meningioma growth in vitro.

The clinical entity of schwannomatosis represents a neurofibromatosis-type syndrome along with multiple schwannomas but lacking the VSs typical of NF2. While the inheritance pattern is unclear, it is unlikely that this syndrome results from inherited NF2 mutations of the germline. Interestingly, although these patients lack germline merlin mutations, schwannomas from these patients have consistently demonstrated truncating mutations of the NF2 gene, suggesting that merlin mutation is an important event in the development of schwannomas regardless of the exact initiating event.

**Conclusions**

Significant advances have been made in understanding the molecular pathophysiology of VSs. Although microsurgery and/or stereotactic radiosurgery represent effective therapies for VSs, they are not entirely benign. Gamma Knife surgery represents a less invasive alternative to open surgery but can be associated with significant morbidity including trigeminal neuropathies, hydrocephalus, and the risk of radiation-induced malignant tumors. Additionally, these tumors are occasionally so large and invasive that complete removal carries the risk of significant morbidity. Future studies are needed to elucidate potential molecular targets that can augment current treatment modalities to address residual disease or radioresistant lesions.

**Disclosure**

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