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NF2-Related Schwannomatosis

Synonyms: Neurofibromatosis 2, Neurofibromatosis Type II

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Summary

Clinical characteristics

NF2-related schwannomatosis (NF2) is characterized by bilateral vestibular schwannomas with associated symptoms of tinnitus, hearing loss, and balance dysfunction. The average age of onset is 18 to 24 years. Almost all affected individuals develop bilateral vestibular schwannomas by age 30 years. Affected individuals may also develop schwannomas of other cranial and peripheral nerves, meningiomas, ependymomas, and (very rarely) low-grade astrocytomas. Because NF2 is considered an adult-onset disease, it may be underrecognized in children, in whom skin tumors and ocular findings (retinal hamartoma, thickened optic nerves, cortical wedge cataracts, third cranial nerve palsy) may be the first manifestations. Mononeuropathy that occurs in childhood is an increasingly recognized finding; it frequently presents as a persistent facial palsy or hand/foot drop.

Diagnosis/testing

The diagnosis of NF2 is established in a proband with bilateral vestibular schwannomas, an identical *NF2* pathogenic variant identified in two or more anatomically distinct NF2-related tumors, or a combination of clinical and molecular criteria that fulfill the consensus diagnostic criteria.

Management

Targeted therapy: The VEGF antibody bevacizumab for rapidly growing vestibular schwannomas; bevacizumab has also shown some clinical benefit in some individuals with ependymoma.

Supportive care: Treatment of vestibular schwannoma is primarily surgical; stereotactic radiosurgery, most commonly with the gamma knife, may be an alternative to surgery. Individuals with vestibular tumors need to be aware of insidious problems with balance and underwater disorientation, which can result in drowning. Cervical spine MRI prior to cranial surgery; lumbosacral MRI prior to regional analgesia. Treatment for hearing loss includes referral to an audiologist, lipreading and sign language instruction, and possibly hearing aids and/or cochlear or brain stem implants. Surgical treatment for infantile cataracts and patching as needed. Management through rehabilitation medicine, physical therapy, and/or occupational therapy should be

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considered for hand or foot drop due to mono- or polyneuropathy. Surgical removal as needed for cutaneous schwannomas that are causing disfigurement and/or pain.

Surveillance: For affected or at-risk individuals, annual neurologic examination by a provider with experience in NF2; annual brain MRI beginning at approximately age ten to 12 years and continuing until at least the fourth decade of life; annual hearing evaluation, including BAER testing; annual complete ophthalmology examination.

Agents/circumstances to avoid: Radiation therapy of NF2-associated tumors, especially in childhood, when malignancy risks are likely to be substantially higher.

Evaluation of relatives at risk: Early identification of relatives who inherited the family-specific *NF2* pathogenic variant allows for appropriate surveillance, resulting in earlier detection and treatment of disease manifestations.

Genetic counseling

NF2 is inherited in an autosomal dominant manner. Approximately 50% of individuals diagnosed with NF2 have an affected parent. Approximately 50% of individuals diagnosed with NF2 have the disorder as the result of a *de novo NF2* pathogenic variant. As many as 25% to 50% of individuals with a *de novo NF2* pathogenic variant have somatic mosaicism for the variant. The possibility that a parent has NF2 can be excluded if the proband is shown to be mosaic. Each child of an individual with NF2 has up to a 50% chance of inheriting the pathogenic variant: offspring of an individual with a germline pathogenic variant have a 50% chance of inheriting the variant, while offspring of an individual who has mosaic NF2 may have a less than 50% risk of inheriting the variant. Once the *NF2* pathogenic variant has been identified in the family, prenatal and preimplantation genetic testing are possible.

Diagnosis

Updated clinical diagnostic criteria for *NF2*-related schwannomatosis (NF2) have been published [Plotkin et al 2022].

Suggestive Findings

NF2 **should be suspected** in probands with the following clinical, laboratory, and family history findings [Halliday et al 2023].

Clinical findings in children (two or more of these findings)

- A schwannoma at any location including intradermal
- Skin plaques present at birth or in early childhood (often plexiform schwannoma on histology)
- A meningioma, particularly non-meningothelial (non-arachnoidal) cell in origin
- A cortical wedge cataract
- A retinal hamartoma
- A mononeuropathy, particularly causing a facial nerve palsy, foot or wrist drop, or third nerve palsy

Clinical findings in adults

- Bilateral vestibular schwannomas
- Unilateral vestibular schwannoma accompanied by ANY TWO of the following: meningioma, schwannoma, glioma, neurofibroma, cataract in the form of subcapsular lenticular opacities or cortical wedge cataract
- Multiple meningiomas accompanied by EITHER of the following:
  - Unilateral vestibular schwannoma

- ANY TWO of the following: schwannoma, ependymoma, cataract in the form of subcapsular lenticular opacities or cortical wedge cataract diagnosed in an individual age <40 years

Laboratory findings. *NF2* pathogenic variant identified on tumor tissue testing

Family history. For individuals of all ages with any of these clinical findings, having a first-degree relative with NF2 increases the likelihood of the disorder being present.

Establishing the Diagnosis

The diagnosis of NF2 **can be established** in a proband with ONE of the following:

- Bilateral vestibular schwannomas
- An identical *NF2* pathogenic variant in two or more anatomically distinct *NF2*-related tumors (schwannoma, meningioma, and/or ependymoma)

  Note: If the variant allele fraction (VAF) in an unaffected tissue (e.g., blood) is clearly <50%, the diagnosis is mosaic NF2.
- Two major criteria
- One major and two minor criteria

Major criteria

- Unilateral vestibular schwannoma
- A first-degree relative other than a sib with NF2
- Two or more meningiomas
- *NF2* pathogenic variant in an unaffected tissue (e.g., blood)

  Note: If the VAF is clearly <50%, the diagnosis is mosaic NF2.

Minor criteria

- Ependymoma, schwannoma (non-vestibular)

  Note: Two ependymomas or two non-vestibular schwannomas count as two minor criteria.
- A single meningioma

  Note: Two meningiomas count as a major criterion.
- Juvenile subcapsular or cortical cataract, retinal hamartoma, epiretinal membrane in a person age <40 years

  Note: Each ocular manifestation that occurs bilaterally only counts as one minor criterion.

Molecular Genetic Testing

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (chromosomal microarray analysis, exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from

many other inherited disorders with neurologic tumors and ocular manifestations are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the clinical findings suggest the diagnosis of NF2, molecular genetic testing approaches can include **single-gene testing**, **chromosomal microarray analysis**, or use of a **multigene panel**.

- **Single-gene testing.** Sequence analysis of *NF2* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.
- **Chromosomal microarray analysis (CMA)** uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *NF2*) that cannot be detected by sequence analysis.
- **A multigene panel** that includes *NF2* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of NF2 is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *NF2*-Related Schwannomatosis

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
NF2	Sequence analysis [3]	75% [4]
	Gene-targeted deletion/duplication analysis [5] or CMA [6]	20% [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Halliday et al [2017]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes may not be detected by these methods.
6. Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *NF2*) that cannot be detected by sequence analysis. The ability to determine the size of the deletion/duplication depends on the type of microarray used and the density of probes in the 22q12.2 region. CMA designs in current clinical use target the 22q12.2 region.
7. Smith et al [2016]

Testing for somatic mosaicism. As many as 25% to 50% of individuals with a *de novo* pathogenic *NF2* variant have somatic mosaicism for the variant [Kluwe et al 2003, Mohyuddin et al 2003, Evans et al 2007b, Evans et al 2013, Evans et al 2020]. Such individuals may have normal molecular genetic testing of *NF2* in unaffected tissue (e.g., leukocytes); thus, molecular genetic testing of tumor tissue may be necessary to establish the presence of somatic mosaicism [Evans et al 2007b, Evans et al 2020, Halliday et al 2023].

When tumor DNA is tested, pathogenic variants in both *NF2* alleles must be identified. This may mean testing for loss (or inactivation) of one *NF2* allele by assessing for loss of heterozygosity. Once both *NF2* pathogenic variants are identified in the tumor, leukocyte DNA can be tested to determine which of the pathogenic variants is constitutional and which is somatic (i.e., present in the tumor only).

Clinical Characteristics

Clinical Description

The average age of onset of findings in individuals with *NF2*-related schwannomatosis (NF2) is 18 to 24 years (onset range: birth to age 70 years). Almost all affected individuals develop bilateral vestibular schwannomas by age 30 years. In addition to vestibular schwannomas, individuals with NF2 develop schwannomas of other cranial and peripheral nerves, meningiomas, ependymomas, and (very rarely) astrocytomas.

Table 2. *NF2*-Related Schwannomatosis: Frequency of Select Features

Feature	% of Persons w/Feature [1]
Bilateral vestibular schwannomas	88%
Meningioma	48%

Table 2. continued from previous page.

Feature	% of Persons w/Feature [1]
Ependymoma	25%

Adapted from Forde et al [2021]
1. Includes percentage of 353 individuals with *NF2*-related schannomatosis assessed annually until death or leaving the study [Forde et al 2021]

Because NF2 is considered an adult-onset disease, it may be underrecognized in children, in whom skin tumors and ocular findings may be the first manifestations [Ruggieri et al 2005, Ruggieri et al 2016, Halliday et al 2019].

Presenting Features of NF2 in Childhood

Skin findings include intradermal plaque-like tumors that often have excess hair and skin pigmentation.

Ocular findings include [Evans et al 2005a, Feucht et al 2008, Ruggieri et al 2016]:

- Retinal hamartoma
- Thickened optic nerves
- Cortical wedge cataracts that may be congenital and associated with amblyopia
- Third cranial nerve palsy
- Epiretinal membranes
- Retinal tufts on optical coherence tomography

Other

- A mononeuropathy (e.g., a facial nerve palsy, foot or wrist drop) with no obvious tumor cause
- An isolated meningioma, or a schwannoma at any site [Pathmanaban et al 2017, Halliday et al 2023]

Details of Typical Clinical Findings in NF2

Vestibular schwannoma. Initial symptoms include tinnitus, hearing loss, and balance dysfunction. Onset of disability is usually insidious, although occasionally hearing loss may occur suddenly, presumably as a result of vascular compromise by the tumor. Affected individuals often report difficulty in using the telephone in one ear or unsteadiness when walking at night or on uneven ground.

With time, vestibular tumors extend medially into the cerebellar pontine angle and, if left untreated, cause compression of the brain stem and hydrocephalus. Significant facial palsy is rare even in individuals with large vestibular schwannomas.

Schwannomas may also develop on other cranial and peripheral nerves, with sensory nerves more frequently affected than motor nerves.

Children and young adults with an apparently isolated vestibular or other cranial nerve schwannoma should be considered at risk for *de novo* and often mosaic NF2 [Pathmanaban et al 2017].

Spinal tumors. At least two thirds of individuals with NF2 develop spinal tumors, which are often the most devastating and difficult tumors to manage [Dow et al 2005]. The most common spinal tumors are schwannomas, which usually originate within the intravertebral canal on the dorsal root and extend both medially and laterally, taking the shape of a "dumbbell." Intramedullary tumors of the spinal cord, such as astrocytoma and ependymoma, occur in 5% to 33% of individuals with NF2. Most persons with spinal cord involvement have multiple tumors. Although multiple tumors are often present on imaging studies, they remain asymptomatic in many individuals.

Meningioma. Approximately half of individuals with NF2 have meningiomas in cross-sectional studies [Goutagny & Kalamarides 2010]; however, lifetime risk may approach 80% [Smith et al 2011]. Most are intracranial, although spinal meningiomas occur. NF2 meningiomas tend to occur less frequently in the skull base than supratentorially and are usually of the fibroblastic variety [Evans et al 2000, Kros et al 2001]. Meningiomas in the orbit may compress the optic nerve and result in visual loss. Those at the skull base may cause cranial neuropathy, brain stem compression, and hydrocephalus.

See Genotype-Phenotype Correlations.

Ocular involvement. One third of individuals with NF2 have decreased visual acuity in one or both eyes. Posterior subcapsular lens opacity – rarely progressing to a visually significant cataract – is the most common ocular finding. Lens opacities may appear prior to the onset of symptoms of vestibular schwannoma and can be seen in children.

Retinal hamartoma and epiretinal membrane are seen in up to one third of individuals. Rarely, other ocular manifestations may occur; persistent hyperplastic primary vitreous has been reported in a father and son [Nguyen et al 2005]. In adulthood, particular issues with the cornea can occur, especially after surgery, resulting in the loss of facial, trigeminal, and intermedius nerve function.

Intracranial and intraorbital tumors may result in decreased visual acuity and diplopia.

Mono- and polyneuropathy. A recognized feature of NF2 is a mononeuropathy occurring particularly in childhood [Evans et al 1999] and frequently presenting as a facial palsy that usually only partially recovers, a squint (third nerve palsy), or a foot or hand drop. The foot drop may mimic polio.

A progressive polyneuropathy of adulthood not directly related to tumor masses is also recognized [Sperfeld et al 2002].

Further evidence for the mononeuropathy of childhood and the polyneuropathy of adulthood has come from sural nerve biopsies [Hagel et al 2002].

Other. Renal vascular disease similar to that occurring in neurofibromatosis type 1 (NF1) has been reported once [Cordeiro et al 2006] but is probably coincidental, as it has not been reported again. However, renal disease does occur with use of bevacizumab (see Targeted Therapy).

Prognosis. Variable expressivity of NF2 among individuals results in varying size, location, and number of tumors. Although these tumors are not malignant, their anatomic location and multiplicity lead to great morbidity and early mortality. The average age of death is 36 years. Actuarial survival from the time of establishing the correct diagnosis has extended from 15 years to more than 30 years. Survival is improving with earlier diagnosis and better treatment in specialty centers [Hexter et al 2015, Forde et al 2021].

Somatic mosaicism for pathogenic variants in *NF2*. Mosaicism has been suspected in individuals with unilateral vestibular schwannoma and multiple other, often ipsilateral, tumors [Mohyuddin et al 2003, Evans et al 2008, Evans et al 2019]. This has now been confirmed for most individuals in which DNA from multiple tumors has been analyzed [Evans et al 2008, Evans et al 2019].

Histopathology. The tumors of NF2 are derived from Schwann cells, meningeal cells, and glial cells. They are uniformly benign. Approximately 40% of NF2 vestibular tumors have a lobular pattern that is uncommon in tumors from individuals without a diagnosis of NF2.

- NF2-associated vestibular schwannomas tend to be more invasive and to have a higher degree of dividing cells than non-NF2 tumors.
- NF2-associated meningiomas have a higher degree of dividing cells than non-NF2 meningiomas. NF2 meningiomas are usually of the fibroblastic variety.

- No histologic differences have been observed between glial tumors in individuals with NF2 and individuals who do not have NF2.

Genotype-Phenotype Correlations

Intrafamilial variability is much lower than interfamilial variability, suggesting a strong effect of the underlying genotype on the resulting phenotype.

Large deletions of *NF2* have been associated with a milder phenotype [Baser et al 2004]; even if quite large, these deletions are not associated with intellectual disability.

The type of *NF2* germline pathogenic variant is an important determinant of the number of NF2-associated intracranial meningiomas, spinal tumors, and peripheral nerve tumors [Evans et al 2019, Forde et al 2021].

- Nonsense and frameshift variants have been associated with severe disease regardless of their position within the gene [Hexter et al 2015, Evans et al 2019, Forde et al 2021].
- Splice site variants have been associated with both mild and severe disease [Kluwe et al 1998, Baser et al 2005] and may be milder if occurring in the 3' half of the gene [Baser et al 2005].
- Missense variants are usually associated with a mild phenotype, often causing the mildest form of NF2 [Evans et al 1998a, Baser et al 2002].
- Truncating variants are associated with earlier onset and greater number of NF2-associated intracranial meningiomas, spinal tumors, and peripheral nerve tumors. In general, truncating variants (frameshift and nonsense) are associated with greater disease-related mortality than missense and splice site variants or deletions [Baser et al 2002, Baser et al 2005]. Truncating variants are also associated with increased prevalence of spinal tumors [Patronas et al 2001, Dow et al 2005]. Although most of these pathogenic variants would be predicted to result in nonsense-mediated decay, and thus no protein product, the apparent dominant-negative effect of these variants requires further investigation.
- Pathogenic variants in the 3' half of *NF2* (especially those in exons 14-16) are associated with lower risk of meningioma than pathogenic variants in the 5' half of the gene [Smith et al 2011] (see Figure 1).

Somatic mosaicism (even when detected in lymphocyte DNA) for typical pathogenic truncating variants that would normally cause severe NF2 may result in a milder phenotype [Evans et al 2013, Evans et al 2019].

Penetrance

Penetrance is close to 100%. Virtually all individuals who have a germline pathogenic variant develop the disease in an average lifetime.

Nomenclature

The term "*NF2*-related schwannomatosis" was proposed by Plotkin et al [2022] to reflect the absence of neurofibroma and glioma (the latter replaced with ependymoma) in current diagnostic criteria and to underscore the importance of molecular testing in diagnosis. Of note, molecular genetic testing is of particular importance for individuals with a unilateral vestibular schwannoma and additional non-vestibular schwannomas in order to distinguish *NF2*-related schwannomatosis and *LZTR1*-related schwannomatosis.

Prevalence

The estimated prevalence of NF2 is 1:50,000 [Evans et al 2010, Evans et al 2018], with a birth incidence of 1:28,000.

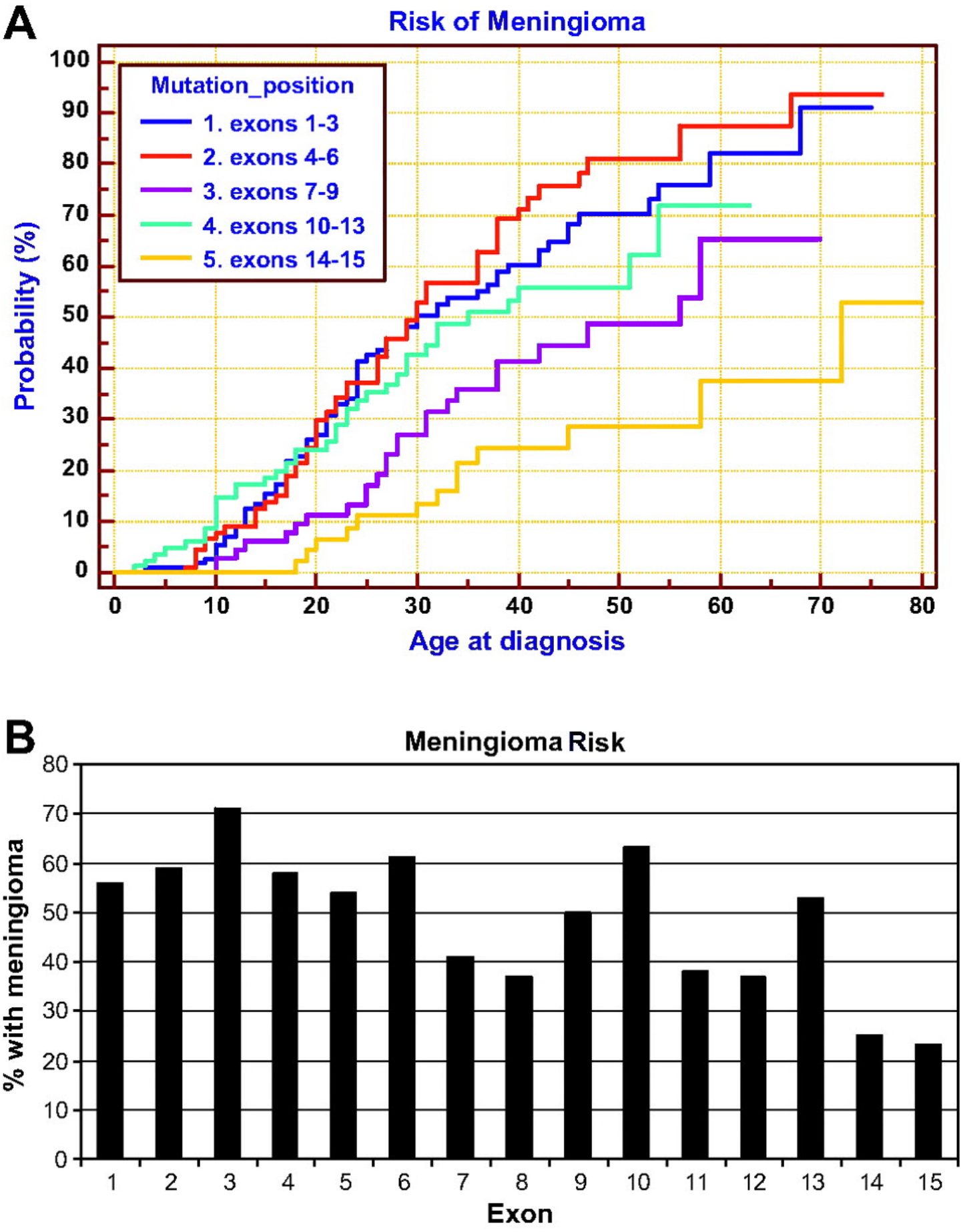

Figure 1. The position of pathogenic variants in *NF2* affects the likelihood of developing a meningioma.

A. The Kaplan-Meier plot shows the risk of meningioma within each functional domain. Gene regions are divided into exons 1-3, 4-6, 7-9, 10-13, and 14-15.

B. The bar graph shows the overall risk for meningioma conferred by pathogenic variants in individual exons. 5' regions confer a higher risk than 3' regions, and exons encoding the junctions between functional domains confer a higher relative risk than the rest of the domain.

Genetically Related (Allelic) Disorders

No other phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *NF2*.

Differential Diagnosis

Table 3. Genes of Interest in the Differential Diagnosis of *NF2*-Related Schwannomatosis

Gene	Disorder	MOI	Clinical Features of Disorder	
			Overlapping w/NF2	Distinguishing from NF2
DGCR8	*DGCR8*-related schwannomatosis [1]	AD	Multiple schwannomas & thyroid adenomas	No vestibular schwannomas
LZTR1 [2]	*LZTR1*-related schwannomatosis	AD	Unilateral vestibular schwannoma & other schwannomas	No intradermal schwannoma plaques, cataract, or ependymoma
NF1	Neurofibromatosis 1	AD	Dumbbell configuration of spinal tumors	Intellectual/learning disability, Lisch nodules, & café au lait macules
SMARCB1	*SMARCB1*-related schwannomatosis	AD	Multiple schwannomas &, less frequently, meningiomas [3]	No vestibular schwannomas; no intradermal schwannoma plaques, cataract, or ependymoma

AD = autosomal dominant; MOI = mode of inheritance; NF2 = *NF2*-related schwannomatosis

1. *DGRC8* has been recognized as a fourth schwannomatosis-related gene [Nogué et al 2022].

2. Smith et al [2017] found that for individuals with a unilateral vestibular schwannoma and additional non-intradermal schwannomas, a constitutional *LZTR1* pathogenic variant is a significant possibility.

3. The great majority of individuals with multiple meningiomas do not have a *SMARCB1* pathogenic variant; likewise, most individuals with a germline *SMARCB1* pathogenic variant do not develop meningiomas [Hadfield et al 2010, Evans et al 2018].

Unilateral vestibular schwannoma. The risk that a unilateral tumor is the first manifestation of *NF2*-related schwannomatosis (NF2) is closely related to the age of the affected individual. Individuals younger than age 30 years with a symptomatic unilateral vestibular schwannoma are at high risk of developing a contralateral tumor and NF2 and should be monitored closely, while individuals older than age 30 years who have a unilateral vestibular schwannoma are at very low risk of developing NF2 [Evans et al 2007a].

Meningioma. Multiple meningiomas typically occur in older adults; thus, the finding of a single meningioma in an individual younger than age 25 years should prompt evaluation for an underlying genetic condition [Evans et al 2005b, Pathmanaban et al 2017].

Management

Clinical practice guidelines for *NF2*-related schwannomatosis (NF2) have been published [Halliday et al 2023]. Evaluation and treatment of individuals with NF2 are best undertaken in an NF2 center experienced in managing the multiple complications of the disease [Baser et al 2002, Evans et al 2005a].

- For NF specialists, see www.ctf.org.
- For NF2 service centers in the UK, see www.nfauk.org.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with NF2, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with *NF2*-Related Schwannomatosis

System/Concern	Evaluation	Comment
Neurologic	Neurologic exam by provider w/experience in NF2	
	Brain MRI	Beginning at age 10-12 yrs
Hearing	Hearing eval, incl BAER)	
Dermatologic	Cutaneous exam	
Eyes	Complete ophthalmology exam	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of NF2 to facilitate medical & personal decision making

BAER = brain stem auditory evoked response; MOI = mode of inheritance; NF2 = *NF2*-related schwannomatosis
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for NF2.

Targeted Therapy

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

The VEGF (vascular endothelial growth factor) antibody bevacizumab has shown promise in the treatment of rapidly growing vestibular schwannomas, with some individuals regaining hearing [Plotkin et al 2009, Morris et al 2016, Halliday et al 2018] (see Supportive Care, **Vestibular schwannoma**).

Bevacizumab has also shown some clinical benefit in some individuals with ependymoma [Farschtschi et al 2016, Morris et al 2017] (see Supportive Care, **Other tumors**).

Supportive Care

Vestibular schwannoma. Untreated tumors may be slow growing and may not require active intervention in the short term [Masuda et al 2004, Slattery et al 2004, Forde et al 2021]. Therapy remains primarily surgical.

- Small vestibular tumors (<1.5 mm) that are completely intracanalicular can often be completely resected, with preservation of both hearing and facial nerve function.
- Larger tumors are probably best managed expectantly, with debulking or decompression carried out only when brain stem compression, deterioration of hearing, and/or facial nerve dysfunction occur [Evans et al 2005a]. However, balancing between early surgery and preservation of facial function and later surgery when an affected individual is still hearing is difficult [Evans et al 2005a].
- Stereotactic radiosurgery, most commonly with the gamma knife, has been offered as an alternative to surgery in select individuals with vestibular schwannoma. However, the outcomes from radiation treatment in individuals with NF2 are not as good as for individuals with sporadic unilateral vestibular schwannoma, with only approximately 60% long-term tumor control [Rowe et al 2003, Chung et al 2018].
- Malignant transformation is a possible (though not common) sequela [Baser et al 2000, Evans et al 2023]; however, it should be noted that tumor development following radiation may take 15 years [Evans et al 2006, Evans et al 2023]. This may involve development of a malignancy within the treated lesion or a new malignancy (e.g., glioblastoma) in the radiation field [Balasubramaniam et al 2007, Halliday et al 2018, Evans et al 2023]. The risk of a malignant progression and/or new central nervous system malignancy has been estimated at 5%-6% in individuals treated with radiation compared to <1% in those not treated with radiation [Evans et al 2023].
- More recently, targeted therapy with the VEGF antibody bevacizumab has shown promise in the treatment of rapidly growing vestibular schwannomas, with some individuals regaining hearing [Plotkin et al 2009, Morris et al 2016, Halliday et al 2018]. Response to treatment occurs in about 60%-70% of individuals; treatment can be sustained over years, although with some concerns regarding renal toxicity [Slusarz et al 2014, Morris et al 2016, Halliday et al 2018].
- There is some promise with targeted therapy with the tyrosine kinase inhibitor brigatinib [Chang et al 2021]; results of a clinical trial with potential effects on NF2-related meningioma are most promising [Chang et al 2021].
- Management of individuals with vestibular tumors should include counseling for insidious problems with balance and underwater disorientation, which can result in drowning.

Considerations prior to surgery

- A cervical spine MRI should be performed before cranial surgery to prevent complications from manipulation under anesthesia [Evans et al 2005a].
- Spinal tumors may make epidural analgesia difficult; therefore, lumbosacral MRI should be performed before regional analgesia is given [Sakai et al 2005, Spiegel et al 2005].

Other tumors. Other intracranial, cranial nerve, or spinal nerve tumors are very slow growing, and surgical intervention for a tumor producing little impairment may cause disability years before it would occur naturally.

- Although ependymoma in individuals without NF2 is optimally treated with complete resection, and occasionally with radiotherapy and chemotherapy, it is unclear whether ependymoma in individuals with NF2 warrants aggressive management. However, bevacizumab has shown some clinical benefit in some individuals [Farschtschi et al 2016, Morris et al 2017].
- Use of radiation therapy for NF2-associated tumors should be carefully considered because radiation exposure may induce, accelerate, or transform tumors in an individual (especially a child) with an inactive tumor suppressor gene [Baser et al 2000, Evans et al 2006].

Hearing. Hearing preservation and augmentation are important in the management of individuals with NF2. All affected individuals and their families should be referred to an audiologist to receive training in optimization of hearing and speech production.

- Lipreading skills may be enhanced by instruction.

- Sign language may often be more effectively acquired before the individual loses hearing.
- Hearing aids may be helpful early in the course of the disease [Evans et al 2005a].
- Auditory habilitation with a cochlear or brain stem implant should be discussed with those who have lost hearing [Evans et al 2005a]. Rarely, individuals who have had vascular insult to the cochlea but are otherwise without nerve damage may benefit from a cochlear implant. Implants can also be used in stable tumors where hearing has been lost but there is evidence of cochlear nerve function [North et al 2016].

Ocular involvement. Early recognition and management of visual impairment from other manifestations of NF2 are extremely important. Most NF2-associated cataracts do not require removal, but particular attention should be paid to cataracts in infancy that may affect vision by causing amblyopia. These may require removal and patching of the unaffected eye.

Mono- and polyneuropathy. Management through rehabilitation medicine, physical therapy, and/or occupational therapy should be considered for hand or foot drop.

Cutaneous involvement. While removal of cutaneous schwannomas is not required, it may be indicated if the schwannomas are causing disfigurement or pain. Removal may also help diagnostically.

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations in affected individuals and at-risk individuals in whom the known pathogenic variant in the family has been identified or whose genetic status cannot be clarified by molecular genetic testing, the evaluations summarized in Table 5 are recommended.

Table 5. Recommended Surveillance for Individuals with *NF2*-Related Schwannomatosis

System/Concern	Evaluation	Frequency
Neurologic	Neurologic exam by provider w/experience in NF2	Annually
	Brain MRI	Annually beginning at age 10-12 yrs until 4th decade of life [1, 2]
Hearing	Hearing eval, incl BAER [3]	Annually
Eyes	Complete ophthalmology exam	

BAER = brain stem auditory evoked response; NF2 = *NF2*-related schwannomatosis

1. Annual brain MRI can start at an older age in individuals from families in which the onset of tumors is known to be later [Evans et al 2005a].

2. It is not clear if earlier surveillance (e.g., brain MRI before age 10 years) is beneficial, and it is not known at what age surveillance by brain MRI can be safely stopped.

3. May be useful in detecting changes in auditory nerve function before changes can be visualized by brain MRI.

Agents/Circumstances to Avoid

Radiotherapy for NF2-associated tumors should be avoided in children when malignancy risks are likely to be substantially higher [Evans et al 2006].

Evaluation of Relatives at Risk

Once the germline *NF2* pathogenic variant has been identified in the proband, it is appropriate to clarify the genetic status of apparently asymptomatic older and younger sibs of a proband and other at-risk relatives in order to identify as early as possible those who would benefit from prompt initiation of appropriate screening (see Surveillance), thus resulting in earlier detection of disease manifestations and improved final outcomes [Halliday et al 2023].

Proband with mosaic NF2. If an *NF2* pathogenic variant is not detected in unaffected tissue (e.g., blood), *NF2* molecular analysis on tumor tissue should be done. Identification of the same *NF2* pathogenic in more than one tumor allows predictive testing in offspring of the proband.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Although there is no convincing evidence that schwannomas increase in size during pregnancy, hormonal effects on meningiomas are possible; therefore, assessment of the potential risk of increased intracranial pressure is important for women considering pregnancy.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

NF2-related schwannomatosis (NF2) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Approximately 50% of individuals diagnosed with NF2 have an affected parent. While there is a strong genotype-phenotype correlation, significant variability within families and even between identical twins can be seen.
- Approximately 50% of individuals diagnosed with NF2 have the disorder as the result of a *de novo NF2* pathogenic variant.
- As many as 25% to 50% of individuals with a *de novo* pathogenic *NF2* variant have somatic mosaicism for the variant [Kluwe et al 2003, Mohyuddin et al 2003, Evans et al 2007b, Evans et al 2013]. The possibility that a parent has NF2 can be excluded if the proband is shown to be mosaic (i.e., the *NF2* pathogenic variant is not detected in an unaffected tissue [e.g., blood] from the proband or the variant allele fraction [VAF] in an unaffected tissue is clearly <50%).
- If the proband is the only family member known to have NF2 and molecular genetic testing does not suggest that the *NF2* pathogenic variant is mosaic, molecular genetic testing is recommended for the parents of the proband to confirm their genetic status. If the pathogenic variant found in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
    - The proband has *de novo* germline pathogenic variant.

- The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism.* Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

  * If the parent is the individual in whom the pathogenic variant first occurred, the parent may have somatic mosaicism for the variant and may be mildly/minimally affected.

- The incidence of pure germline mosaicism in NF2 is extremely low, as thus far all parents having more than one affected child have had a detectable pathogenic variant in *NF2* in DNA extracted from blood and have been clinically affected [Evans et al 2013]. There is one report of two affected children born to apparently unaffected parents before *NF2* testing was available [Parry et al 1996]. However, the low likelihood of sib recurrence of unilateral vestibular schwannoma due to parental germline mosaicism (versus the greater likelihood of unilateral vestibular schwannoma in a sib due to chance) is now recognized by exclusion of a sib in the diagnostic criteria [Evans et al 2019, Plotkin et al 2022].
- Because the age of onset of symptoms is typically consistent within families, it is usually not necessary to offer surveillance to asymptomatic parents.
- The family history of some individuals diagnosed with NF2 may appear to be negative because of failure to recognize the disorder in family members or early death of the parent before the onset of symptoms. Therefore, an apparently negative family history cannot be confirmed unless the proband has mosaic NF2 or molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

Sibs of a proband. The risk to the sibs of a proband depends on the genetic status of the parents:

- If a parent of the proband is affected and/or is known to have the germline *NF2* pathogenic variant identified in the proband, the risk to the sibs is 50%. The age of onset of symptoms within a family is relatively consistent.
- If the proband has a known germline *NF2* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism. Presumed germline mosaicism in a clinically unaffected parent has been reported in one family to date [Parry et al 1994].
- If the proband has a known germline *NF2* pathogenic variant and the parents have not been tested for the pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. The sibs of a proband with clinically unaffected parents are still at increased risk for NF2 because of the possibility of parental germline mosaicism.
- If the proband has mosaic NF2, it is presumed that the parents do not have the *NF2* pathogenic variant identified in the proband and that sibs of the proband are not at risk of inheriting the *NF2* pathogenic variant.

Offspring of a proband. Each child of an individual with NF2 has up to a 50% chance of inheriting the pathogenic variant:

- If the proband has other affected family members, each child of the proband has a 50% chance of inheriting the pathogenic variant.
- If the proband is the only affected individual in the family:
  - The proband may have a *de novo* germline pathogenic variant (i.e., present in the egg or sperm at the time of conception). Each offspring of an individual with a *de novo* germline pathogenic variant has a 50% chance of inheriting the pathogenic variant.

- The proband may have somatic mosaicism for the pathogenic variant. Offspring of an individual who has mosaic NF2 may have a less than 50% risk of inheriting the pathogenic variant.

  Persons with somatic mosaicism and bilateral vestibular tumors have a less than 50% chance of having an affected child [Evans et al 1998b]. If the pathogenic variant is detected in DNA from multiple tumors, but not in DNA from leukocytes, the risk to offspring is probably less than 1% [Evans et al 2019, Halliday et al 2023].

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent is affected, the parent's family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Predictive testing (i.e., testing of asymptomatic at-risk individuals)

- Predictive testing for at-risk asymptomatic family members requires prior identification of the germline *NF2* pathogenic variant in the family.
- Potential consequences of such testing (including, but not limited to, socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.
- Because early detection of at-risk individuals affects medical management, testing of at-risk asymptomatic individuals younger than age 18 years is beneficial. Parents often want to know the genetic status of their children prior to initiating screening in order to avoid unnecessary procedures for a child who has not inherited the pathogenic variant. Special consideration should be given to education of the children and their parents prior to genetic testing. A plan should be established for the manner in which results are to be given to the parents and children.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *NF2* pathogenic variant has been identified in the family, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Children's Tumor Foundation**
  Phone: 800-323-7938
  Email: info@ctf.org
  www.ctf.org
- **MedlinePlus**
  Neurofibromatosis 2
- **NCBI Genes and Disease**
  Neurofibromatosis 2
- **Nerve Tumours UK**
  United Kingdom
  www.nervetumours.org.uk
- **Neurofibromatosis Network**
  Phone: 630-510-1115
  Email: admin@nfnetwork.org
  www.nfnetwork.org
- **Acoustic Neuroma Association**
  Phone: 770-205-8211
  Email: info@anausa.org
  www.anausa.org
- **Children's Tumor Foundation: Schwannomatosis**
  Schwannomatosis
- **NF Registry**
  The NF Registry is for all types of NF (including NF1, NF2, and schwannomatosis).
  Children's Tumor Foundation
  Welcome to the NF Registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. NF2-Related Schwannomatosis: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

NF2	22q12.2	Merlin	NF2 database	NF2	NF2

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for NF2-Related Schwannomatosis (View All in OMIM)

101000	SCHWANNOMATOSIS, VESTIBULAR; SWNV
607379	NF2, MOESIN-EZRIN-RADIXIN-LIKE (MERLIN) TUMOR SUPPRESSOR; NF2

Molecular Pathogenesis

NF2 encodes a large protein containing FERM (4.1 protein, ezrin, radixin, moesin) domains known as merlin (for *m*oesin-*e*zrin-*r*adixin-*l*ike prote*in*). Although the complete function of merlin remains elusive, studies suggest that merlin coordinates growth factor receptor signaling and cell adhesion. Varying use of this organizing activity by different types of cells could provide an explanation for the unique spectrum of tumors associated with merlin deficiency in mammals [McClatchey & Giovannini 2005]. However, the mechanisms by which pathogenic variants in *NF2* cause disease remain unclear due in part to its multiple roles in controlling several signaling pathways, including PI3K-AKT, RAC-PAK, and EGFR-RAS-ERK. More recently, a critical role in the Hippo pathway mediated through suppression of Yap and Taz has also been shown [Reginensi et al 2016].

Abnormal merlin is caused by either somatic or constitutional *NF2* pathogenic variants. Attempts to identify truncated protein product have been unsuccessful, although the non-truncated product from pathogenic missense variants may have partial function. It is thought that nonsense-mediated decay may account for the lack of identifiable product from most variant types; however, this does not explain why phenotypes are more severe for these types of variants compared to whole-gene deletions.

Mechanism of disease causation. Loss of function

***NF2*-specific laboratory technical considerations.** Both germline and mosaic variants are seen in *NF2*. Mosaic genetic variants in *NF2* can have low variant allele frequencies (VAFs) and may therefore elude detection using standard sequencing methods. Using high depth of coverage for sequencing as well as pipelines optimized for the detection of variants with low VAFs is recommended for the detection of mosaic pathogenic *NF2* variants.

Cancer and benign tumors. Sporadic tumors (including schwannomas and meningiomas at any site) occurring as single tumors in the absence of any other findings of *NF2*-related schwannomatosis frequently contain a somatic pathogenic variant in *NF2* that is **not** present in the germline. In these circumstances, predisposition to these tumors is not heritable [Mohyuddin et al 2002, Pathmanaban et al 2017].

Chapter Notes

Author Notes

Professor D Gareth Evans (gareth.evans@mft.nhs.uk) is actively involved in clinical research regarding individuals with NF2. They would be happy to communicate with persons who have any questions regarding diagnosis of NF2 or other considerations.

Contact Dr Miriam J Smith (miriam.smith@manchester.ac.uk) to inquire about review of *NF2* variants of uncertain significance.

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