Neurofibromatosis type 2

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Abstract

Neurofibromatosis type 2 is an often devastating autosomal dominant disorder which, until relatively recently, was confused with its more common namesake neurofibromatosis type 1. Subjects who inherit a mutated allele of the *NF2* gene inevitably develop schwannomas, affecting particularly the superior vestibular branch of the 8th cranial nerve, usually bilaterally. Meningiomas and other benign central nervous system tumours such as ependymomas are other common features. Much of the morbidity from these tumours results from their treatment. It is now possible to identify the *NF2* mutation in most families, although about 20% of apparently sporadic cases are actually mosaic for their mutation. As a classical tumour suppressor, inactivation of the *NF2* gene product, merlin/schwannomin, leads to the development of both NF2 associated and sporadic tumours. Merlin/schwannomin associates with proteins at the cell cytoskeleton near the plasma membrane and it inhibits cell proliferation, adhesion, and migration.

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History

The neurofibromatoses consist of at least two distinct dominantly inherited disorders, neurofibromatosis type 1 (NF1) and neurofibromatosis type 2 (NF2). For many years, these conditions were inextricably linked as part of von Recklinghausen disease. NF2 was first described in 1822 by the Scottish surgeon, Wishart.¹ NF1 was fully delineated in the late nineteenth century by von Recklinghausen.² However, Cushing³ first bracketed them together in 1916 and his standing was such that, despite reports that the conditions were quite different,⁴ another half century elapsed before this was widely recognised. Indeed, publications on neurofibromatosis before 1985 are liberally sprinkled with NF2 cases being described as part of von Recklinghausen disease.⁵ The conditions were eventually recognised as separate entities with the localisation of the respective genes to chromosomes 17 and 22.^{6,7} This was followed by the US National Institutes of Health (NIH) consensus state-

ment in 1987.⁸ Since 1987, it has generally been believed that NF2 is a genetically homogeneous condition, with no evidence of exclusion of classical NF2 (bilateral vestibular schwannomas (VS)) from the *NF2* locus on 22q, in initial studies on small numbers of families.⁹ This has been confirmed in all reports of classical NF2 patients with bilateral VS since the simultaneous isolation of the gene by two groups in 1993.^{10,11} However, the possibility of another closely linked gene that affects the NF2 phenotype cannot be excluded.

Incidence and prevalence

In the UK, the only large population based estimate of birth incidence for NF2 showed that 1 in 33-40 000 people would be born with a mutation in the *NF2* gene.¹² A smaller study in southern Finland estimated a birth incidence of 1 in 87 000.¹³ The only other estimate of birth incidence (1 in 50 000) was made at the 1987 NIH Consensus Conference on the Neurofibromatoses, but a derivation for this figure was not provided.⁸ Initial estimates of prevalence suggested that as few as 1 per million were affected in the USA.¹⁴ The actual diagnostic prevalence from the UK population based study is 1 in 210 000.¹² The annual incidence rate is 1 per 2 355 000, which represents about one new case per year for each Health Region in the UK,¹² or 100 cases per year in the USA. The birth incidence is significantly higher than the diagnostic prevalence because many cases do not develop features of the condition until the third decade or later, and many other cases die before this time. With improvements in early diagnosis and tumour treatment, the prevalence is likely to rise, reflecting an increase from the 15 year survival from diagnosis for UK NF2 patients 10 or more years ago.¹⁵

Genetics

Heredity in NF2 was first reported in 1920 by Feiling and Ward,¹⁶ who described a three generation family with VS. The autosomal dominant transmission was confirmed in a large family reported by Gardner and Frazier.⁴ Subjects who inherit a pathogenic mutation in the *NF2* gene will almost always develop symptoms by 60 years of age¹⁵; very occasionally, patients will have apparent non-penetrance.¹⁷ Although the transmission rate is 50% in the second generation and beyond, the risk of

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Figure 1 MRI scan showing bilateral enhancing masses (VS) in the cerebellopontine angle.

transmission in an apparently sporadic case of NF2 is less than 50% because of mosaicism.¹⁸ There were initial indications of a maternal gene effect, with earlier age at onset in people who had inherited the NF2 from their mother,^{12 14} but this effect is most likely the result of reduced genetic fitness among severely affected males.¹² There is little evidence for anticipation.¹²

Clinical manifestations

The hallmark of NF2 is the development of bilateral VS (fig 1). The other main tumour features are schwannomas of the other cranial, spinal, and peripheral nerves, meningiomas, both intracranial (including optic nerve meningiomas) and intraspinal, and some low grade central nervous system (CNS) malignancies (ependymomas and gliomas). Four large clinical studies have now confirmed this clinical picture^{14 15 19 20} (table 1). Our diagnostic criteria for NF2²¹ are shown in table 2. The original NIH criteria have been expanded to include patients with no family history who have multiple schwannomas/meningiomas, but who

have not yet developed bilateral 8th nerve tumours. Patients may present with cranial meningiomas or a spinal tumour long before the appearance of a VS.^{15 22 23} Since 50% of cases represent new mutations,^{12 24} the criteria are more inclusive but are still extremely unlikely to include chance associations of isolated disease features (see under Genetics).

PRESENTATION

The majority of patients with NF2 present with hearing loss, which is usually unilateral at onset. The hearing loss may be accompanied or preceded by tinnitus. VS may also cause features such as dizziness or imbalance as the first symptom. A significant proportion of cases (20–30%) present with an intracranial meningioma, spinal tumour, or cutaneous tumour.^{14 15 19 25} Indeed, the first sign of more severe multi-tumour disease in early childhood is often a non-8th nerve tumour. Adult presentation is thus quite different from paediatric presentation, in which VS accounts for as little as 15–30% of initial symptoms.²² There also appears to be a tendency to mononeuropathy, particularly affecting the facial nerve, causing a Bell’s-like palsy, which does not fully recover, years before the detection of a VS. Some children present with a polio-like illness with wasting of muscle groups in a lower limb, which again does not fully recover. In adulthood, a more generalised polyneuropathy occurs in about 3–5% of patients, often associated with an “onion bulb” appearance on nerve biopsy.^{12 26} This can progress, leading to severe muscle wasting and even death.

Ophthalmic features are also prominent in NF2. Between 60–80% of patients have cataracts,^{15 27 28} which are usually presenile posterior subcapsular lenticular opacities that rarely require removal. However, cortical wedge opacities may be present from near birth. Optic nerve meningiomas can cause visual loss in the first years of life and extensive retinal hamartomas can also affect vision.^{23 29} Misdiagnosis of both of these abnormalities as retinoblastoma has led to the eye being removed in the first few years of life.

The skin is a useful aid to diagnosis, but cutaneous features in NF2 are much more subtle than in NF1. About 70% of NF2 patients have skin tumours, but only 10% have more than 10 skin tumours.^{15 25} The tumours appear to be of at least three different types. The most frequent type is a plaque-like lesion, which is intracutaneous, slightly raised, and

Table 1 Clinical characteristics of NF2 patients in four studies

Characteristic	Kanter et al ¹⁴	Evans et al ¹⁵	Parry et al ¹⁹	Mautner et al ²⁰
No of cases	73	120	63	48
No of families	17	75	32	44
Sporadic cases	0	45	17	44
Mean age at onset (y)	20 (of 59)	22	20	17
Intracranial meningiomas (%)	18	45	49	58
Spinal tumours (%)	NA	26	67	90
Skin tumours (%)	32 (of 73)	68 (of 100)	67	64
>10 skin tumours (%)	NA	10 (of 100)	NA	NA
Café au lait macules (%)	42 (of 31)	43 (of 100)	47	NA
Cataract (%)	NA	38 (of 90)	81	62
Intracranial astrocytoma (%)	NA	4.1	1.6	NA
Ependymoma (%)	NA	2.5	3.2	6
Optic sheath meningioma (%)*	NA	4.1	4.8	8

*In Mautner et al,²⁰ the frequency of optic nerve sheath tumours is for all histological types (that is, schwannomas and meningiomas).

Table 2 Diagnostic criteria for NF2 (these include the NIH criteria⁸ with additional criteria²¹)

<i>Bilateral vestibular schwannomas or family history of NF2 plus</i>	
(1) Unilateral VS or	
(2) Any two of: meningioma, glioma, neurofibroma, schwannoma, posterior subcapsular lenticular opacities	
<i>Additional criteria</i>	
Unilateral VS plus any two of: meningioma, glioma, neurofibroma, schwannoma, and posterior subcapsular opacities	
or	
Multiple meningioma (two or more) plus unilateral VS or any two of: glioma, neurofibroma, schwannoma, and cataract	

"Any two of" refers to individual tumours or cataract, not to tumour types.

Figure 2 Plaque-like lesions on the chest in a patient with NF2. These are raised, often slightly pigmented lesions that are also frequently hairy.

Figure 3 Subcutaneous schwannoma on a major nerve in the upper arm in a patient with NF2.

more pigmented than surrounding skin, often with excess hair (fig 2). More deep seated subcutaneous nodular tumours can often be felt, sometimes on major peripheral nerves. These tumours occur as a fusiform swelling of the nerve with thickened nerve on either side (fig 3). There are also occasional intracutaneous tumours similar to those in NF1. The great majority of these tumours are schwannomas, but occasional definite neurofibromas do occur.

OUTCOMES

Even with improvements in microsurgery and with use of radiation therapy, the great majority of subjects with NF2 become completely deaf. The tumours in NF2 are more difficult to treat than those of sporadic unilateral VS, as NF2 VS are often multifocal, appearing "like a bunch of grapes"³⁰ around the vestibular nerve in particular. There is evidence for a histological difference, with NF2 VS being more lobular and less vascular than their sporadic counterparts.³¹ Patients may also be severely disabled by a combination of poor balance, visual problems, and weakness owing to spinal tumours. Indeed, many NF2 patients become wheelchair

bound in early adulthood. Loss of facial nerve function is one of the most feared aspects of the condition for many sufferers, although in good surgical hands this complication is now much less common.^{32 33} Many patients with multi-tumour disease die in their twenties and thirties.

RADIOGRAPHIC FINDINGS

NF2 can be diagnosed when the criteria in table 2 are fulfilled. The "gold standard" in terms of diagnostic precision is the magnetic resonance imaging (MRI) scan with gadolinium enhancement, which should include a complete spinal scan as well as a cranial scan. MRI will now detect tumours as small as 1–2 mm in diameter on cranial and spinal nerve roots. Many of these small spinal tumours will never lead to symptoms. Full spinal imaging will detect evidence of spinal tumours in 80–90% of patients,³⁴ but older studies that were done before the widespread use of spinal scanning showed that only 25–30% of NF2 patients had symptomatic spinal tumours.^{15 21} There is also increasing recognition of intramedullary tumours, often associated with a syrinx, which predominate in the upper cervical spine and brainstem. On biopsy these tumours are usually low grade ependymomas. Although these can initially be very worrying for the radiologist or treating clinician, the great majority of these tumours do not progress. Another common finding on MRI is schwannomas on other cranial nerves. These occur most commonly on the 5th nerve,²⁰ but every cranial nerve can be affected in NF2. Nonetheless, it is rare for cranial nerve schwannomas other than VS to grow to a size where removal is necessitated. Meningiomas can easily be detected on MRI as enhanced areas on the meninges around the spinal cord, brain, or optic nerves. These can form confluent areas on scan or "meningioma en plaque". VS growth rates are extremely variable but average 2 mm per year,³⁵ although growth rates are higher in younger patients.³⁶ In contrast, meningiomas characteristically have more rapid growth.

There are several groups of subjects who should be considered at risk and investigated further. These groups include those with a family history of NF2, patients under 30 years presenting with a unilateral VS or meningioma, patients with multiple spinal tumours (schwannomas or meningiomas), and patients with cutaneous schwannomas.^{21 22 37} MRI scanning is vital in their further assessment.

Although CT scans have been largely replaced owing mainly to their poor sensitivity at detecting small VS,¹⁵ a further feature of NF2 can be identified. A proportion of NF2 patients have intracranial calcification from a young age.¹⁵ However, this sign is not useful enough to supplement MRI with CT. Without firm clinical justification, repeated CT scans should be avoided in NF2 owing to the tumour prone nature of the disease.³⁸

Pathology

The main tumour sites, their frequencies, and pathologies are presented in table 1. As previously noted, schwannomas can occur at all locations around the body where there are nerves with Schwann cells. The predilection for the superior vestibular branch of the 8th cranial nerve remains unexplained. Schwannomas are encapsulated tumours of pure Schwann cells that grow around the nerve. They may contain blood vessels and have areas of sheets in inter-twining fascicles (Antoni A) and looser arrangements (Antoni B).³¹ The tumours also stain for S-100 protein and vimentin. In NF2, these tumours can be multifocal and have a more lobular architecture than sporadic tumours.³¹ Spontaneous malignant transformation of these tumours to malignant peripheral nerve sheath tumours (MPNST) does occur, but is more than 10 times as likely to happen after radiation treatment.³⁸ The background rate of 0.5% for CNS malignancy in NF2 is also very much less than for NF1.^{38,39} A small proportion of nerve related tumours in NF2 are pathologically delineated as neurofibroma. In these tumours there is an admixture of cell types (Schwann cells, fibroblasts, and mast cells) and the tumour usually has identifiable axons within it. Neurofibromas mainly occur in the skin²⁵ (where they are still outnumbered by schwannomas by a factor of 5-10), but also on the spinal nerve roots.⁴⁰ Halliday *et al*⁴⁰ showed that, in a series of spinal schwannomas and neurofibromas, all spinal tumours in patients with NF1 were neurofibromas while, with one exception, all spinal tumours in patients with NF2 were schwannomas (one patient had a mixed tumour). Neurofibromas are not a feature in the cranium. There is currently no evidence of histological or molecular differences between neurofibromas in NF1 and NF2. Occasionally tumours are found which show features of both schwannoma and neurofibroma, particularly on spinal nerve roots. In contradistinction to NF2, schwannomas and meningiomas do not occur in excess in NF1.^{39,41}

The second most characteristic tumour of NF2 is meningiomas, which usually occur supratentorially in the falx and around the frontal, temporal, and parietal regions. Meningiomas also occur around the spinal cord, and these can be difficult to remove surgically. Although there are different histological types of meningioma (meningothelial, fibroblastic, and transitional), there is no evidence for a clinical subdivision into NF2 related and non-NF2 related meningiomas.⁴² Collision tumours consisting of a schwannoma and meningioma can occur, particularly in the cerebellopontine angle. Antinheimo *et al*,¹³ in a study of all meningiomas and schwannomas in an 11 year period in the Helsinki area, found that 3% of schwannoma patients and 1% of meningioma patients had NF2. A further 2% of schwannoma patients and 4% of meningioma patients had multiple tumours without fulfilling clinical diagnostic criteria for NF2. Nonetheless, the great majority of NF2 patients do not present with an isolated tumour, and there is only a

small risk of NF2 after a truly isolated VS (no other features of NF2 on clinical examination or scan).⁴³ However, as many as 10% of those presenting in childhood with an apparently isolated meningioma go on to develop NF2.²²

Low grade ependymomas and gliomas occur in NF2 and are now being increasingly recognised. These are very indolent and rarely metastasise around the CNS. The primary location for these tumours is in the cervical spine and brainstem. Malignant progression is sometimes associated with radiotherapy treatment.³⁸

Molecular genetics

Much of the work in isolating the *NF2* gene involved studies of tumour material. Initially, cytogenetic studies of meningiomas highlighted chromosome 22 as the likely location of the *NF2* gene.⁴⁴ Subsequent cytogenetic studies of schwannomas also confirmed that loss of chromosome 22 or its long arm was by far the most frequent event,⁴⁵ which was later confirmed by DNA studies.⁴⁶ Seizinger *et al*⁴⁷ were the first to show loss of constitutional heterozygosity of chromosome 22 DNA markers in tumours from a patient with NF2. Linkage studies then confirmed that all affected members of a large Pennsylvania family⁴ carried the same copy of chromosome 22.⁷ The *NF2* gene was further localised by the discovery of constitutional deletions in NF2 families, one of which involved the neurofilament heavy chain gene.⁴⁸ The *NF2* gene was then isolated by the simultaneous discovery of constitutional and tumour deletions in a cell membrane related gene termed merlin¹⁰ or schwannomin.¹¹

Standard mutation techniques, such as single strand conformational polymorphism analysis or denaturing gradient gel electrophoresis, detect between 35% and 66% of causative mutations.⁴⁹⁻⁵¹ Since the majority of these mutations are truncating mutations, leading to a smaller and probably ineffective protein product, more rapid screening techniques such as the protein truncation test can be used. Early studies suggested that missense mutations (which result in a complete protein product) and large deletions (which result in no protein product) both caused predominantly mild phenotypes.^{48,50,52} Larger studies of detailed genotype/phenotype correlations in multiple families have since been reported.^{51,53,56} The phenotype is more variable in patients with splice site mutations⁵⁷; patients with 5' mutations have more severe disease than patients with 3' mutations.⁵⁸ The more severe phenotype in patients with protein truncating mutations may be because of a dominant negative effect, with mutant protein dimerising with the normal product, leaving less wild type protein for tumour suppression.

Some milder cases have mosaic disease,^{18,59-61} in which only a proportion of cells contain the mutated *NF2* gene. Recent evidence suggests that up to 20% of NF2 cases without a family history of the disease are mosaic, carrying the mutation in too small a proportion of their cells to be detected from a blood sample.^{18,61} This accounts for the milder disease course in many

patients with unfound mutations, and since only a subset of germ cells will carry the mutation, there is less than a 50% risk of transmitting the disease to their offspring.¹⁸ However, if an offspring has inherited the mutation, they will be more severely affected than their parent, since the offspring will carry the mutation in all of their cells.⁶⁰ One of the features that suggested that mosaicism existed in NF2 was that *NF2* mutations were harder to find in blood in sporadic cases than in patients who had inherited the disease from an affected parent.^{18 43 61} Mosaicism may be particularly likely in NF2 if the tumours are predominantly on one side.¹⁸ The mosaic mutation can be detected by analysing tumour material from an affected subject. If an identical mutation is found in two tumours from that subject, their offspring can be tested for the presence of the mutation.

Further causes (apart from mosaicism) of the low detection rate for mutations in blood using standard techniques are large deletions and rearrangements at the *NF2* locus.⁶² However, C>T transitions causing nonsense mutations are the most common mutations in the *NF2* gene.^{50 51 53-56 63}

Diagnostic criteria

Constitutional mutations in the *NF2* gene are found just as frequently in patients who fulfil modified NF2 diagnostic criteria as in sporadic cases with bilateral VS.^{18 43} This justifies future inclusion of these subjects as having "definite" NF2, rather than having only one criterion (bilateral VS) for "definite" NF2.^{8 37} However, the inclusion of criteria for "probable" NF2 (unilateral VS <30 years plus other NF2 criteria, or two or more meningiomas plus other NF2 criteria³⁷) is a helpful addition.

Management

NF2 presents difficult management issues and patients optimally should be managed by a multidisciplinary team consisting of a neurosurgeon, otolaryngologist, audiologist, ophthalmologist, neuroradiologist, and geneticist. Surgical results are certainly far better when managed by an experienced team.^{32 33} It is important to balance the use of microsurgery and radiation treatment, which can have a role in patients who have particularly aggressive tumours, or who are poor surgical risks, or who refuse surgery.⁶⁴ Teams experienced in the positioning of brainstem implants can offer partial auditory rehabilitation to those who are deaf, although results are still behind those achievable for cochlear implants. Although the cochlear nerve may be left initially intact after surgery its blood supply may be damaged; nonetheless a few patients can be rehabilitated successfully with a cochlear implant. Because detection of tumours at an early stage is effective in improving the clinical management of NF2, presymptomatic genetic testing is an integral part of the management of NF2 families.

Predictive diagnosis by linkage analysis using intragenic markers or markers flanking the *NF2* gene is now possible in the great majority

of families with two or more living affected members.^{9 65 66} Once a mutation has been identified in an affected subject, a 100% specific test is available for that family. However, mutation detection is time consuming and expensive, and may not reveal the causative mutation. In most families with more than one affected subject, linkage analysis will still remain the test of choice since it will give >99% certainty of affected status. By combining this with a cumulative age at onset curve,¹⁷ the risk to an unaffected 30 year old with a normal scan and favourable DNA result is infinitesimally small, although 100% confidence can still be attained only with the identification of family specific mutations. Age at onset curves aid genetic counselling; for example, the risk of having inherited NF2 for an asymptomatic at risk subject 25 years of age, before screening, will have dropped to 25%. As more families are followed prospectively, a curve for age at diagnosis with screening will become available. At risk subjects who are shown not to have inherited the mutated *NF2* gene do not need further follow up.

SCREENING PROTOCOL

Children of affected patients should be considered to be at 50% risk of NF2 and screening for NF2 can start at birth.²¹ Cataracts can affect vision in early life and other tumour implications are present in the first 10 years of life.^{22 23 28} Formal screening for VS should start at 10 years, as it is rare for tumours to become symptomatic before that time even in severely affected families. Annual audiological tests including auditory brainstem response are still a useful adjunct to MRI. Surgery is unlikely to be more successful for tumours <6 mm than for tumours sized 6 mm,¹⁷ but VS growth is higher in younger patients,³⁶ so for asymptomatic at risk subjects without tumours, MRI screening every two years for those <20 years old and every three years for those aged >20 years should be sufficient. The initial MRI scan could be at around 12 years of age, or earlier in severely affected families. Once tumours are present, MRI screening should probably be annual. Spinal tumours are found very frequently on MRI, as discussed previously. While only 25-30% of patients with spinal tumours require a spinal operation for a symptomatic tumour,^{15 21} a full annual neurological examination is probably a wise precaution. In most families it is now possible to develop a genetic test so that screening can be targeted to affected subjects only. Uptake of presymptomatic genetic testing in childhood and adult life is high.⁶⁷

Differential diagnosis

The main possible diagnostic dilemma with NF2 occurs in isolated patients with multiple non-cranial schwannomas. Some of these patients may well go on to develop NF2⁶⁸ and all require a cranial MRI scan. Some patients can be proven to be mosaic for an *NF2* mutation.^{18 69} There are nonetheless a small group of patients with tumours largely confined to the skin and spine, with sparing of the 8th nerve,

who can be proven not to have an underlying *NF2* mutation.⁶⁹ These subjects may pass the condition on to their children, and in families where this occurs there is still tight linkage to the *NF2* locus,^{68,69} although *NF2* mutations are found in only a minority of patients with this variant form of the disease.⁷⁰ Confusion with *NF1* is unlikely since only 1–2% of *NF2* patients have six or more café au lait patches^{15,25} and Lisch nodules are rare in *NF2*,²¹ but review of tumour histology is a wise precaution in equivocal cases. The presence of a schwannoma in a patient who does not fulfil NIH criteria for *NF1*⁸ makes *NF1* extremely unlikely, while the presence of multiple neurofibromas makes *NF2* very unlikely.

MODIFYING FACTORS

Early reports suggested that *NF2* was worse if the disease was inherited from the mother^{12,14} but, as previously noted, this may be because of decreased genetic fitness in males. In addition, there is no evidence for genomic imprinting on chromosome 22q. It has also been suggested that the disease course is worse in affected females.^{19,71} However, more recent data indicate that the effect is mainly on meningiomas rather than on schwannoma growth and development.⁷²

On the whole, *NF2* disease course does breed true in families.^{19,54,73} Some families have a mild disease course, with late onset and few if any CNS tumours other than VS. Other families have a more virulent course, with early onset and death owing to multi-tumour disease. The evidence to date of genotype/phenotype correlations is encouraging and may well lend an insight into the disease process. Nonetheless, much will depend on stochastic events, such as loss of the second *NF2* allele, since the disease course is not identical even in monozygotic twins.⁷⁴

NF2 protein

The *NF2* protein, termed merlin or schwannomin by the two groups that identified it independently, is a cell cytoskeleton associating protein of 595 amino acids coded by the 17 exons of the *NF2* gene. The name merlin derived from the sequence homology and shared overall domain structure with ERM (moesin, ezrin, and radixin) superfamily of membrane cytoskeleton linker molecules.¹⁰ Alternative splicing of exon 16 gives rise to two isoforms, which differ by the last C-terminal 11 amino acids. The *NF2* protein is expressed in many tissues including neurones, Schwann cells, and meningeal cells. Normally, it exhibits a linker function by binding transmembrane adhesion molecules such as CD44 (hyaluronate receptor) and cytoskeleton components (F-actin, microtubules, β -spectrin).^{75–77} Accordingly, *NF2* protein impairs cell adhesion, motility, and spreading properties, which are known to be essential for tumour formation.⁷⁹ The *NF2* protein binds to ezrin and thus probably associates also functionally with ERM proteins, which have the ability to oligomerise and bind to each other.⁸⁰ Thus, the *NF2* protein is a unique type of tumour suppressor

protein with an as yet undefined mechanism of action, which may extend to coordination of adhesion and cell signalling pathways, functions recently shown for ERM proteins.⁸¹ ERM proteins associate with Rho and the cAMP dependent protein kinase A (PKA) intracellular signalling pathways and the E-cadherin/ β -catenin complex,⁸² which have a role in control of cell proliferation. Interestingly, also, the *NF2* protein binds to Rho-GDP dissociation inhibitor, a component of the Rho signalling cascade.⁸³ Another mechanism may be that the *NF2* protein and ERM proteins via their interaction with PDZ domain containing molecules (Na^+ -H⁺ exchanger regulatory cofactor, hNE-RF or EBP50) regulate the outside-in signalling events by clustering transmembrane proteins and key components of downstream transduction pathways.⁸⁴ The genotype/phenotype correlation at the protein level arises from the evidence that nonsense mutations result in unstable protein product, while missense mutations that change only one amino acid may give rise to a protein product with defective negative growth regulation.⁷⁸ On the other hand, in experimental models, the potential to inhibit cell growth is associated only with isoform I, but not with isoform II nor C-terminal deletion constructs, both unable to form interdomain head to tail interactions, suggesting that the protein conformation may be relevant for the tumour suppressor function.⁸⁵ However, as yet too little is known about the cellular events that account for the *NF2* gene's ability to suppress growth in Schwann cells nor in other cells. Nonetheless, it is now clear that loss of *NF2* protein is the main and possibly only rate limiting step in the formation of all schwannomas and most meningiomas.^{86,87}

The future

The much awaited step in *NF2* was the localisation and cloning of the gene. This achieved, precise diagnosis is possible if a specific mutation can be found, but this may also allow prediction of the disease course by genotype/phenotype studies. Clinical factors that are closely related to mutation type, such as age at onset or age at diagnosis, may also predict the course of the disease.^{36,88} This may be particularly useful in patients with new mutations, in whom insight into the likely speed of tumour progression and risk of other tumours would be very helpful. Although DNA predictive testing for 70% of families is available with flanking markers or mutation testing,¹⁷ there is currently little demand for prenatal *NF2* diagnosis in the UK (three tests in the last six years). A less controversial option would be preimplantation diagnosis, which is being evaluated in a limited sense for other diseases, such as familial adenomatous polyposis and cystic fibrosis.

The real hope is that the discovery of the gene and its transcriptional protein product, merlin/schwannomin, will lead to the development of somatic gene therapy. Intuitively, the prospects for *NF2* appear promising owing to the relative lack of phenotypic variation in subjects with the same mutation and the paucity of

involvement of other genes in the tumours themselves. Replacement of the tumour suppressor product in the tumours through viral vectors or direct recombination of the *NF2* gene, although requiring great advances in our knowledge, could be very rewarding. Use of newer drugs, particularly anti-angiogenesis agents, may also offer promise.

- 1 Wishart JH. Case of tumours in the skull, dura mater, and brain. *Edinburgh Med Surg J* 1822;18:393-7.
- 2 Von Recklinghausen F. *Ueber die multiplen fibroma der haut und ihre beziehung zu den multiplen neuromen*. Berlin: A Hirschwald, 1882.
- 3 Cushing H. *Tumors of the nervous acusticus and the syndrome of the cerebello-pontine angle*. Philadelphia: WB Saunders, 1917.
- 4 Gardner WJ, Frazier CH. Bilateral acoustic neurofibromas: a clinical study and field survey of a family of five generations with bilateral deafness in thirty eight members. *Arch Neurol Psychiatry* 1930;23:266-302.
- 5 Crowe FW, Schull WJ, Neal JV. *A clinical pathological and genetic study of multiple neurofibromatosis*. Springfield, Illinois: Charles C Thomas, 1956.
- 6 Seizinger BR, Rouleau GA, Ozelius LG, Lane AH, Faryniarz AG, Chao MV, Huson S, Korf BR, Parry DM, Pericak-Vance MA, Collins FS, Hobbs WJ, Falcone BG, Ianazzi JA, Roy JC, St George-Hyslop PH, Tanzi RE, Bothwell MA, Upadhyaya M, Harper PS, Goldstein AE, Hoover DL, Bader JL, Spence MA, Mulvihill JJ, Aylesworth AS, Vance JM, Rossenwasser GOD, Gaskell PC, Roses AD, Martuza RL, Breakfield XO, Gusella JF. Genetic linkage of von Recklinghausen neurofibromatosis to the nerve growth factor receptor gene. *Cell* 1987;49:589-94.
- 7 Rouleau G, Seizinger BR, Wertschek W, Haines JL, Superneau DW, Martuza RL, Gusella JF. Genetic linkage analysis of bilateral acoustic neurofibromatosis to a DNA marker on chromosome 22. *Nature* 1987;329:246-8.
- 8 National Institutes of Health Consensus Development Conference Statement on Neurofibromatosis. *Arch Neurol* 1987;45:575-9.
- 9 Narod SA, Parry DM, Parboosingh J, Lenoir GM, Rutledge M, Fischer G, Eldridge R, Martuza RL, Frontali M, Haines J, Gusella JF, Rouleau GA. Neurofibromatosis type 2 appears to be a genetically homogenous disease. *Am J Hum Genet* 1992;51:486-96.
- 10 Trofatter JA, MacCollin MM, Rutter JL, Murrell JR, Duyao MP, Parry DM, Eldridge R, Kley N, Menon AG, Pulaski K, Haase VH, Ambrose CM, Munroe D, Bove C, Haines JL, Martuza RL, MacDonald ME, Seizinger BR, Short MP, Buckler AJ, Gusella JF. A novel moesin-, ezrin-, radixin-like gene is a candidate for the neurofibromatosis 2 tumor suppressor. *Cell* 1993;72:791-800.
- 11 Rouleau GA, Merel P, Lutchman M, Sanson M, Zucman J, Marineau C, Hoang-Xuan K, Demczuk S, Desmaziere C, Plougastel B, Pulst SM, Lenoir G, Bijsma E, Fashold R, Dumanski J, de Jong P, Parry D, Eldridge R, Aurias A, Delattre O, Thomas G. Alteration in a new gene encoding a putative membrane-organizing protein causes neurofibromatosis type 2. *Nature* 1993;363:515-21.
- 12 Evans DGR, Huson SM, Donnai D, Neary W, Blair V, Teare D, Newton V, Strachan T, Ramsden R, Harris R. A genetic study of type 2 neurofibromatosis in the United Kingdom. I. Prevalence, mutation rate, fitness, and confirmation of maternal transmission effect on severity. *J Med Genet* 1992;29:841-6.
- 13 Antinheimo J, Sankila R, Carpen O, Pukkala E, Sainio M, Jaaskelainen J. Population based analysis of sporadic and NF2-associated meningiomas and schwannomas. *J Neurol* 2000;254:71-6.
- 14 Kanter WR, Eldridge R, Fabricant R, Allen JC, Koerber T. Central neurofibromatosis with bilateral acoustic neuroma. Genetic, clinical and biochemical distinctions from peripheral neurofibromatosis. *Neurology* 1980;30:851-9.
- 15 Evans DGR, Huson SM, Donnai D, Neary W, Blair V, Newton V, Harris R. A clinical study of type 2 neurofibromatosis. *Q J Med* 1992;84:603-18.
- 16 Feiling A, Ward E. A familial form of acoustic tumour. *BMJ* 1920;10:496-7.
- 17 Evans DGR, Newton V, Neary W, Baser ME, Wallace A, MacLeod R, Jenkins JPR, Gillespie J, Ramsden RT. Use of MRI and audiological tests in presymptomatic diagnosis of type 2 neurofibromatosis (NF2). *J Med Genet* 2000;37:944-6.
- 18 Evans DGR, Wallace A, Trueman L, Wu CL, Ramsden RT, Strachan T. Mosaicism in classical neurofibromatosis type 2: a common mechanism for sporadic disease in tumor prone syndromes? *Am J Hum Genet* 1998;63:727-36.
- 19 Parry DM, Eldridge R, Kaiser-Kupfer MI, Bouzas EA, Pikus A, Patronas N. Neurofibromatosis 2 (NF2): clinical characteristics of 63 affected individuals and clinical evidence for heterogeneity. *Am J Med Genet* 1994;52:450-1.
- 20 Mautner VF, Lindenau M, Baser ME, Tatagiba M, Haase W, Samii M, Wais R, Pulst SM. The neuroimaging and clinical spectrum of neurofibromatosis 2. *Neurosurgery* 1996;38:880-5.
- 21 Evans DGR, Huson SM, Donnai D, Neary W, Blair V, Newton V, Strachan T, Harris R. A genetic study of type 2 neurofibromatosis in the United Kingdom. II. Guidelines for genetic counselling. *J Med Genet* 1992;29:847-52.
- 22 Evans DGR, Birch JM, Ramsden R. Paediatric presentation of type 2 neurofibromatosis. *Arch Dis Child* 1998;81:496-9.
- 23 Mautner VF, Tatagiba M, Guthoff R, Samii M, Pulst SM. Neurofibromatosis 2 in the pediatric age group. *Neurosurgery* 1993;33:92-6.
- 24 Baser ME, Evans DGR. Lack of sex-ratio distortion in NF2. *Am J Med Genet* (in press).
- 25 Mautner VF, Lindenau M, Baser ME, Kluwe L, Gottschalk J. Skin abnormalities in neurofibromatosis 2. *Arch Dermatol* 1997;133:1539-43.
- 26 Thomas PK, King RHM, Chiang TR, Scaravilli F, Sharma AK, Downie AW. Neurofibromatous neuropathy. *Muscle Nerve* 1990;13:93-101.
- 27 Kaiser-Kupfer MI, Freidlin V, Datiles MB, Eldridge R. The association of posterior capsular lens opacities with bilateral acoustic neuromas in patients with neurofibromatosis type 2. *Arch Ophthalmol* 1989;107:541-4.
- 28 Ragge NK, Baser ME, Klein J, Nechiporuk A, Sainz J, Pulst SM, Riccardi VM. Ocular abnormalities in neurofibromatosis 2. *Am J Ophthalmol* 1995;120:634-41.
- 29 Bouzas EA, Parry DM, Eldridge R, Kaiser-Kupfer MI. Visual impairment in patients with neurofibromatosis 2. *Neurology* 1993;43:622-3.
- 30 Martuza RL, Ojemann RG. Bilateral acoustic neuromas: clinical aspects, pathogenesis and treatment. *Neurosurgery* 1982;10:1-12.
- 31 Sobel RA, Wang Y. Vestibular (acoustic) schwannomas: histological features in neurofibromatosis 2 and in unilateral cases. *J Neuropathol Exp Neurol* 1993;52:106-13.
- 32 Evans DGR, Ramsden R, Huson SM, Harris R, Lye R, King TT. Type 2 neurofibromatosis: the need for supraregional care? *J Laryngol Otol* 1993;107:401-6.
- 33 Slattery WH, Brackmann DE, Hitselberger W. Hearing preservation in neurofibromatosis type 2. *Am J Otol* 1998;19:638-43.
- 34 Mautner VF, Lindenau M, Baser ME, Hazim W, Tatagiba M, Haase W, Samii M, Wais R, Pulst SM. Spinal tumors in patients with neurofibromatosis type 2: MR imaging study of frequency, multiplicity, and variety (published erratum appears in *AJR* 1996;166:1231). *AJR* 1995;165:951-5.
- 35 Fucci MJ, Buchman CA, Brackmann DE, Berliner KI. Acoustic tumor growth: implications for treatment choices. *Am J Otol* 1999;20:495-9.
- 36 Baser M, Mautner VF, Thakkar SD, Kluwe L. The natural history of neurofibromatosis 2. *Am J Hum Genet* 1998;63(suppl 4):A63.
- 37 Gutmann DH, Aylesworth A, Carey JC, et al. The diagnostic and multi-disciplinary management of neurofibromatosis 1 and neurofibromatosis 2. *JAMA* 1997;278:51-7.
- 38 Baser ME, Evans DGR, Jackler RK, Sujansky E, Rubenstein A. Malignant peripheral nerve sheath tumors, radiotherapy, and neurofibromatosis 2. *Br J Cancer* 2000;82:998.
- 39 McLaughran JM, Harris DI, Donnai D, Teare D, MacLeod R, Westerbeck R, Kingston H, Super M, Harris R, Evans DGR. A clinical study of type 1 neurofibromatosis in north west England. *J Med Genet* 1999;36:197-203.
- 40 Halliday AL, Sobel RA, Martuza RL. Benign spinal nerve sheath tumours. Their occurrence sporadically and in neurofibromatosis types 1 and 2. *J Neurosurg* 1991;74:248-53.
- 41 Huson SM, Harper PS, Compston DAS. Von Recklinghausen neurofibromatosis: a clinical and population based study in south east Wales. *Brain* 1988;111:1355-81.
- 42 Antinheimo J, Haapasalo H, Haltia M, Tatagiba M, Thomas S, Brandis A, Sainio M, Carpen O, Samii M, Jaaskelainen J. Proliferation potential and histological features in neurofibromatosis 2-associated and sporadic meningiomas. *J Neurosurg* 1997;87:610-14.
- 43 Evans DGR, R Lye, Neary W, Black G, Strachan T, Wallace A, Ramsden RT. The probability of bilateral disease in individuals presenting with a unilateral vestibular schwannoma. *J Neurol Neurosurg Psychiatry* 1999;67:64-7.
- 44 Zang KD. Cytological and cytogenetic studies on human meningioma. *Cancer Genet Cytogenet* 1982;6:249-74.
- 45 Wolff RK, Frazer KA, Jackler RK, Lanser MJ, Pitts LH, Cox DR. Analysis of chromosome 22 deletions in neurofibromatosis related tumours. *Am J Hum Genet* 1992;51:478-85.
- 46 Irving RM, Moffat DA, Hardy DG, Barton DE, Xuereb JH, Holland FJ, Maher ER. A molecular, clinical and immunohistochemical study of vestibular schwannoma. *Otolaryngol Head Neck Surg* 1997;116:426-30.
- 47 Seizinger BR, Martuza RL, Gusella JF. Loss of genes on chromosome 22 in tumorigenesis of human acoustic neuroma. *Nature* 1986;322:644-7.
- 48 Watson C, Gaunt L, Evans G, Harris R, Strachan T. A germinal interstitial deletion maps the locus for type 2 neurofibromatosis to the interval between D22S56 and LIF (leukaemia inhibitory factor). *Hum Mol Genet* 1993;2:701-4.
- 49 MacCollin M, Ramesh V, Jacoby LB, Louis DN, Rubio MP, Pulaski K, Trofatter JA, Short MP, Bove C, Eldridge R, Parry DM, Gusella JF. Mutational analysis of patients with neurofibromatosis 2. *Am J Hum Genet* 1994;55:314-20.
- 50 Bourn D, Carter SA, Mason S, Evans DGR, Strachan T. Germline mutations in the neurofibromatosis type 2 tumour suppressor gene. *Hum Mol Genet* 1994;3:813-16.
- 51 Merel P, Hoang-Xuan K, Sanson M, et al. Screening for germline mutations in the NF2 gene. *Genes Chrom Cancer* 1995;12:117-27.
- 52 Evans DGR, Bourn D, Wallace A, Ramsden RT, Mitchell JD, Strachan T. Diagnostic issues in a family with late onset type 2 neurofibromatosis. *J Med Genet* 1995;32:470-4.

- 53 Kluwe L, Bayer S, Baser ME, Hazim W, Haase W, Funsterer C, Mautner VF. Identification of NF2 germline mutations and comparison with neurofibromatosis 2 phenotypes. *Hum Genet* 1996;98:534-8.
- 54 Parry DM, MacCollin M, Kaiser-Kupfer MI, Pulaski K, Nicholson HS, Bolesta M, Eldridge R, Gusella JF. Germ-line mutations in the neurofibromatosis 2 gene: correlations with disease severity and retinal abnormalities. *Am J Hum Genet* 1996;59:529-39.
- 55 Rutledge MH, Andermann AA, Phelan CM, Claudio JO, Han F, Chretien N, Rangaratnam S, MacCollin M, Short P, Parry D, Michels V, Riccardi VM, Weksburg R, Kitamura K, Bradburn JM, Hall BD, Propping P, Rouleau GA. Type of mutation in the neurofibromatosis type 2 gene (NF2) frequently determines severity of disease. *Am J Hum Genet* 1996;59:331-42.
- 56 Evans DGR, Trueman L, Wallace A, Mason S, Strachan T. Genotype/phenotype correlations in type 2 neurofibromatosis: evidence for more severe disease with truncating mutations. *J Med Genet* 1998;35:450-5.
- 57 Kluwe J, MacCollin M, Tatagiba M, et al. Phenotypic variability associated with 14 splice site mutations in the NF2 gene. *Am J Med Genet* 1998;77:228-33.
- 58 Friedman JM, Woods R, Joe H, et al. Germ-line NF2 mutation type, location, and phenotype in neurofibromatosis 2. *Am J Hum Genet* 1999;65(suppl 4):A126.
- 59 Bourn D, Carter SA, Evans DGR, Goodship J, Coakham H, Strachan T. A mutation in the neurofibromatosis type 2 tumour suppressor gene giving rise to widely different clinical phenotypes in two unrelated individuals. *Am J Hum Genet* 1994;55:69-73.
- 60 Biljsma EK, Wallace AJ, Evans DGR. Misleading linkage results in an NF2 presymptomatic test due to mosaicism. *J Med Genet* 1997;34:934-6.
- 61 Kluwe L, Mautner VF. Mosaicism in sporadic neurofibromatosis 2 patients. *Hum Mol Genet* 1998;7:2051-5.
- 62 Zucman-Rossi J, Legoux P, Sarkisian HD, Cheret G, Sor F, Berardi A, Cazes L, Giraud S, Ollagnon E, Lenoir G, Thomas G. NF2 gene in neurofibromatosis type 2 patients. *Hum Mol Genet* 1998;7:2095-101.
- 63 Sainz J, Figueroa K, Baser ME, Mautner VF, Pulst SM. High frequency of nonsense mutations in the NF2 gene caused by C to T transitions in five CGA codons. *Hum Mol Genet* 1995;4:137-9.
- 64 Kondziolka D, Lunsford LD, McLaughlin MR, Flickinger JC. Long-term outcomes after radiosurgery for acoustic neuroma. *N Engl J Med* 1998;339:1426-33.
- 65 Rutledge MH, Narod SA, Dumanski JP, Parry DM, Eldridge R, Wertelecki W, Parboosingh J, Faucher MC, Lenoir GM, Collins VP, Nordenskjold M, Rouleau GA. Presymptomatic diagnosis for neurofibromatosis 2 with chromosome 22 markers. *Neurology* 1993;43:1753-60.
- 66 Baser ME, Mautner VF, Ragge NK, Nechiporuk A, Riccardi VM, Klein J, Sainz J, Pulst SM. Presymptomatic diagnosis of neurofibromatosis 2 using linked genetic markers, neuroimaging, and ocular examinations. *Neurology* 1996;47:1269-77.
- 67 Evans DGR, Maher ER, Macleod R, Davies DR, Craufurd D. Uptake of genetic testing for cancer predisposition. *J Med Genet* 1997;34:746-8.
- 68 Evans DGR, Huson SM, Ponder M, Strachan T, Harding A. Spinal and cutaneous schwannomatosis is a variant form of type 2 neurofibromatosis. *J Neurol Neurosurg Psychiatry* 1997;62:361-6.
- 69 Jacoby L, Jones D, Davis K, Kronn D, Short MP, Gusella J, MacCollin M. Molecular analysis of the NF2 tumor suppressor in schwannomatosis. *Am J Hum Genet* 1997;61:1293-302.
- 70 Honda M, Arai E, Sawada S, Ohta A, Niihara M. Neurofibromatosis 2 and neurilemmomatosis gene are identical. *J Invest Dermatol* 1995;104:74-7.
- 71 Allen J, Eldridge R, Koerber T. Acoustic neuroma in the last months of pregnancy. *Am J Obstet Gynecol* 1974;9:516-20.
- 72 Evans DGR, Blair V, Strachan T, Lye RH, Ramsden RT. Variation in expression of the gene for type 2 neurofibromatosis: absence of a gender effect on vestibular schwannoma. *J Laryngol Otol* 1995;9:830-5.
- 73 Kumar RA, Baser ME, Evans DGR, Wallace A, Mautner VF, Kluwe L, Rouleau G, Joe H, Friedman JM. Intrafamilial correlation of clinical manifestations in neurofibromatosis 2 (NF2). *Am J Hum Genet* 1999;65(suppl 4):A155.
- 74 Baser ME, Ragge N, Riccardi V, Gantz B, Janus T, Pulst S. Phenotypic variability in monozygotic twins with neurofibromatosis 2. *Am J Med Genet* 1996;64:563-7.
- 75 Sainio M, Zhao F, Heiska L, Turunen O, den Bakker M, Zwarthoff E, Lutchman M, Rouleau G, Jaaskelainen J, Vaheri A, Carpen O. Neurofibromatosis 2 tumor suppressor protein colocalizes with ezrin and CD44 and associates with actin-containing cytoskeleton. *J Cell Sci* 1997;10:2249-60.
- 76 Gonzalez-Agosti C, Xu L, Pinney D, Beauchamp R, Hobbs W, Gusella J, Ramesh V. The merlin tumor suppressor localizes preferentially in membrane ruffles. *Oncogene* 1996;13:1339-47.
- 77 Xu HM, Gutmann DH. Merlin differentially associates with the microtubule and actin cytoskeleton. *J Neurosci Res* 1998;51:403-15.
- 78 Gutmann DH, Geist RT, Xu H, Kim JS, Saporito-Irwin S. Defects in neurofibromatosis 2 protein function can arise at multiple levels. *Hum Mol Genet* 1998;7:335-45.
- 79 Gutmann DH, Sherman L, Seftor L, Haipke C, Lu KH, Hendrix M. Increased expression of the NF2 tumor suppressor gene product, merlin, impairs cell motility, adhesion and spreading. *Hum Mol Genet* 1999;8:267-75.
- 80 Grönholm M, Sainio M, Zhao F, Heiska L, Vaheri A, Carpen O. Homotypic and heterotypic interaction of the neurofibromatosis 2 tumor suppressor protein merlin and the ERM protein ezrin. *J Cell Sci* 1999;112:895-904.
- 81 Tsukita S, Yonemura S. Cortical actin organization: lessons from ERM (ezrin/radixin/moesin) proteins. *J Biol Chem* 1999;274:34507-10.
- 82 Hiscox S, Jiang WG. Ezrin regulates cell-cell and cell-matrix adhesion, a possible role with E-cadherin/beta-catenin. *J Cell Sci* 1999;112:3081-90.
- 83 Maeda M, Matsui T, Imamura M, Tsukita S, Tsukita S. Expression level, subcellular distribution and rho-GDI binding affinity of merlin in comparison with ezrin/radixin/moesin proteins. *Oncogene* 1999;18:4788-97.
- 84 Bretscher A. Regulation of cortical structure by the ezrin-radixin-moesin protein family. *Curr Opin Cell Biol* 1999;11:109-16.
- 85 Sherman L, Xu HM, Geist RT, Saporito-Irwin S, Howells N, Ponta H, Herrlich P, Gutmann DH. Interdomain binding mediates tumor growth suppression by the NF2 gene product. *Oncogene* 1997;15:2505-9.
- 86 Gutmann DH, Giordano MJ, Fishback AS, Guha A. Loss of merlin expression in sporadic meningiomas, ependymomas and schwannomas. *Neurology* 1997;49:267-70.
- 87 Huynh DP, Mautner V, Baser ME, Stavrou D, Pulst SM. Immunohistochemical detection of schwannomin and neurofibromin in vestibular schwannomas, ependymomas and meningiomas. *J Neuropathol Exp Neurol* 1997;56:382-90.
- 88 Baser ME, Friedman JM, Evans DGR. Predictors of survival in neurofibromatosis 2. *Am J Hum Genet* 1999;65(suppl 4):A61.

NOTICE

Inherited Disorders and their Genes in Different European Populations

A conference on "Inherited Disorders and their Genes in Different European Populations: Exploring Human Genetic Variability" (Chair: Peter De Knijff, Leiden) will be held in San Feliu de Guixols, Spain on 15-19 November 2001. For further information contact Dr J

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CORRECTION

In the paper by Evans *et al* "Neurofibromatosis type 2" (*J Med Genet* 2000;37:897-904), it

was erroneously stated that linkage studies confirmed that all affected members of a large Pennsylvania family carried the same copy of chromosome 22. Linkage to chromosome 22 was confirmed in a different family described by Wertelecki *et al* in their paper "Neurofibromatosis 2: clinical and DNA linkage studies of a large kindred" (*N Engl J Med* 1988;319:278-83).