Spinal and cutaneous schwannomatosis is a variant form of type 2 neurofibromatosis: a clinical and molecular study

D Gareth R Evans, Susan Mason, Susan M Huson, Margaret Ponder, the late A E Harding, Thomas Strachan

Abstract

Objective—To delineate the clinical phenotype, molecular basis, and implications for screening in patients and families with multiple schwannomas not generally involving the cranium.

Methods—As part of a United Kingdom clinical and genetic study of type 2 neurofibromatosis (NF2) patients and families with multiple schwannomas who do not fulfil diagnostic criteria for NF2 have been identified. The clinical phenotype was studied in the extended families and molecular analysis was carried out at the NF2 gene locus on chromosome 22.

Results—Patterns of inheritance in five families with schwannomatosis are consistent with inheritance of an autosomal dominant gene. The consistency of phenotype, with relative sparing of the cranium, is constant in these families. However, families which initially seem to be indicative of schwannomatosis may develop into classic NF2 as shown by a sixth family. Many of the tumours found in these families were referred to as "neurofibroma" when they were clearly schwannomas. This difference in classification has major implications for the relative risk of each particular type of neurofibromatosis and neuropathological review may be important in some cases. Genetic linkage analysis in the two largest families is entirely consistent with primary involvement of the NF2 gene.

Conclusions—Variant forms of neurofibromatosis have presented a dilemma in classification and determination of recurrence risks in families. Previous reports have suggested that schwannomatosis is a sporadic non-hereditary condition. Patients with multiple schwannomas are likely to have a variant form of NF2 and up to a 50% risk of passing on a gene predisposing to multiple schwannoma.

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The neurofibromatoses consist of at least two distinct dominantly inherited disorders: neurofibromatosis type 1 (NF1) and NF2. These conditions were eventually recognised as separate entities with the localisation of the respective genes to chromosome 17 and 22, and with

Table 1 Diagnostic criteria for NF1 and NF2

NF1 (≥ 2 must be present):

- (1) Six or more café au lait macules, the greatest diameter of which is more than 5 mm in prepubertal patients and more than 15 mm in postpubertal patients
- (2) Two or more neurofibromas of any type or one plexiform neurofibroma
- (3) Axillary or inguinal freckling
- (4) Optic glioma
- (5) Two or more Lisch nodules
- (6) A distinctive osseous lesion such as sphenoid dysplasia or pseudarthrosis
- (7) A first degree relative with NF1 according to the preceding criteria

NF2:

- Bilateral acoustic neuromas or family history of NF2 plus
- (1) unilateral acoustic or (2) any two of: meningioma, glioma, neurofibroma, schwannoma, posterior subcapsular lenticular opacities

the NIH consensus statement in 1987.¹⁻³ None the less there are many patients and indeed some families who do not fulfil NIH criteria for NF1 or NF2 (table 1). This has led various authors to speculate on there being up to six other types of neurofibromatosis.^{4,5} Two entities which have been suggested as separate forms of NF are: familial spinal NF, NF4 and schwannomatosis.^{4,5} Most reports of patients with multiple cutaneous and or spinal schwannomas emphasise that these cases are usually sporadic,^{4,6} and that indeed they may not represent a hereditary condition. Our experience with six families and seven sporadic cases of schwannomatosis leads us to think that this is a true genetic entity and that it is likely in most instances to be a variant form of NF2. We present here the clinical features and molecular analysis of these families and sporadic cases.

Case reports

FAMILIAL CASES

Figures 1 and 2 show the pedigrees of the two largest families and table 2 shows a clinical summary.

Family M (fig 1)

The proband II-3 presented aged 25 years with a subcutaneous lump which was removed. He underwent three further excisions of subcutaneous tumours between 50 and 54 years of age. He then presented with foot drop and was found to have two tumours at L4-5. Both these proved to be schwannomas. Finally aged 65 years he had a schwannoma removed from his left hand. His brother II-1 has had six subcutaneous tumours removed at various intervals from the age of 21 years. Several of these were associated with major nerves (femoral, brachial plexus). All were reported as neurilemmoma or neurilemmoma.

Department of Medical Genetics, St Mary's Hospital, Manchester M13 0JH, UK

D G R Evans

Clinical Genetics Department, Oxford Radcliffe Hospital Trust, the Churchill, Oxford OX3 7LJ, UK
S M Huson

CRC Human Cancer Genetics Research Group, Addenbrookes Hospital, Cambridge CB2 2QQ, UK
M Ponder

Division of Human Genetics, University of Newcastle upon Tyne NE2 4AA, UK
S Mason
T Strachan

Neurogenetics Section, Institute of Neurology, Queen Square, London WC1N 3BG, UK
A E Harding

Correspondence to: Dr D Gareth R Evans, Department of Medical Genetics, St Mary's Hospital, Hathersage Road, Manchester M13 0JH, UK.

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Figure 1 Haplotype analysis of schwannomatosis family M. Shaded boxes represent a haplotype that is inferred to segregate with the disease.

noma. Proband II-1 has complained of hearing loss for several years, but this improved substantially after stapedectomy. All three of II-3's sons had had a cutaneous schwannoma/neurilemmoma removed. In addition III-3 had an S1 schwannoma removed when aged 31. More recently he complained of unilateral tinnitus and MRI showed a right sided vestibular schwannoma, but no evidence of contralateral disease. Patients II-1 and III-1 were found to have lenticular opacities on ophthalmoscopy and I-2 was known to have had a longstanding cataract.

Family C (fig 2)

The proband CII-2 presented aged 33 with a lump in her right ankle. She underwent routine preoperative chest radiography, which showed a right sided mediastinal mass. At thoracotomy a cystic mass was removed posteriorly. This mass and the ankle tumour were reported as "neurilemmoma". Three years later two tumours were removed from the left sternomastoid, which were reported as "neurofibromata", yet the report states that they were "very similar" to the previous specimens. She had no further problems until the age of 61 when she developed tingling and weakness in her lower limbs. A myelogram showed a tumour at L1 which was excised (schwannoma). However, her symptoms remained and she underwent a further myelogram which showed cord compression from C5-T1. Exploration disclosed an inoperable meningioma encircling the cord, with an adjacent schwannoma. She died 12 months after her final spinal surgery. She had two deep subcutaneous tumours in her right forearm and left heel consistent with schwannomas. There were no other cutaneous findings and she had no cataracts or Lisch nodules on slit lamp examination.

The father of II-2 died aged 62 having had spinal tumours and an intrathoracic tumour removed. His death certificate stated that he had "multiple neurofibromata". A paternal uncle and aunt were also said to have had spinal tumours removed. Family members II-3, II-5, and II-7 all had spinal tumours diagnosed and all had deep cutaneous tumours. Patient II-3 presented aged 37 with deafness and headache and had a left cerebellopontine angle tumour removed. This came from the spinal accessory nerve and was reported as a "neurofibroma". Three years later he underwent removal of a further "neurofibroma" at L1-2 and aged 64 had a schwannoma removed from C5-6. Finally a schwannoma was removed from T12 when he was aged 65. Although he has recently complained of deafness cranial CT was normal. Patient II-5 had three small asymptomatic spinal tumours on MRI and three large subcutaneous tumours.

Figure 1 Haplotype analysis of schwannomatosis family C. The haplotypes shown are for the polymorphic DNA markers D22S275, NF2CA3, NF2TET, D22S268, D22S430, D22S273, D22S280, and D22S281. Shaded boxes represent a haplotype inferred to segregate with the disease.

Table 2 Onset of symptoms and site of tumours in familial cases of schwannomatosis

Case	Age (y)		Schwannomas (n)			Deafness	Cranial scan	Cataract	Cal
	Now	Symptoms	Spinal	Cutaneous	Cranial				
CI-1	≥ 62	NK	≥ 2	1‡	NK	No	No	No	NK
CII-2	≥ 65	33	3†	6‡	No	No	No	No	No
CII-3	67	37	2	4	1	Yes	Yes	No	No
					IX				
CII-5	61	59	3	4	No	No	No	No	No
CII-7	58	54	2	1	No	No	Yes	No	No
CIII-3	30	No	1	0	No	No	Yes	No	No
CIII-7	35	No	0	1	No	No	No	No	No
MI-2	≥ 93	NK	NK	≥ 1*	No	Yes	No	Yes	NK
MII-1	62	21	0	6	No	Yes	No	Yes	No
MII-3	64	25	2	4	No	No	No	No	No
MIII-1	37	24	1	4	1	No	Yes	No	No
					VIII				
MIII-2	39	23	0	1	0	No	No	Yes	1
MIII-3	33	19	0	1	0	No	No	No	No
D101	68	16	3	0	0	No	Yes	No	No
D201	31	18	1	0	0	No	Yes	No	No
S201	45	23	0	3	0	No	Yes	No	No
S202	58	22	4	2	1	No	Yes	No	No
					IX				
S203	≥ 33	20	7	NK	0	No	No	NK	NK
S204	≥ 37	NK	1	NK	0	No	No	NK	NK
Ma101	37	20	6+	10	0	No	No	NK	2
Ma202	20	18	1	1	0	No	Yes	NK	No

*No historical confirmation available; †meningioma; ‡extraspinal intrathoracic tumour requiring thoracotomy; VIII and IX = cranial nerve schwannoma; NK = not known; Cal = café au lait patches.

Patient II-7 had two spinal schwannomas removed, but recent cranial MRI was normal. There were no intracutaneous tumours in any member of the family and no evidence of Lisch nodules or cataract on slit lamp examination.

Families D, S, and Ma

Table 2 shows the summaries of these families. Family D consists of an affected father and son, family S contains four affected siblings, and family Ma an affected mother and son. The pattern of tumours in these families was very similar to families M and C. Again some confusion existed over the terminology of the tumours removed. These ranged from neurofibroma through neurilemmoma to schwannoma.

Family V

The proband presented aged 17 with muscle wasting. She has since had four spinal schwannomas and a cervical spinal ependymoma removed surgically. She denied hearing loss when aged 38, but had no cranial imaging for more than 10 years. Her brother presented aged 27 in the same year as his sister with numbness and pain in his left leg. Eventually five years later a large tumour attached to the sciatic nerve was removed and reported as a neurilemmoma. Four years later he had a thoracotomy for two opacities noticed on chest

radiography. Both tumours were reported as neurilemmoma. He then presented aged 41 years with a tumour at T11, which again proved to be neurilemmoma. It was not until the age of 44 years that he noticed some hearing loss and one year later bilateral vestibular schwannoma were diagnosed.

His son had undergone craniotomy aged 10 for a cranial meningioma which induced seizures. After his father's diagnosis he underwent MRI when aged 22 which showed bilateral vestibular schwannoma and a further meningioma. There was a suggestive history of NF2 in the father of the proband as he had three skin lumps and unilateral hearing loss before his death from lung cancer aged 57 years. The paternal uncle was also deaf and the paternal grandmother was said to have died from a brain tumour at the age of 30 years. All the living affected cases had easily identifiable lens opacities, but no café au lait patches or Lisch nodules. It is clear that this family has classic NF2. However, between the diagnosis of the original tumours in the proband and her brother and the diagnosis of bilateral vestibular schwannoma in the brother some 19 years later their disorder could have been classified as schwannomatosis.

SPORADIC CASES

Table 3 shows seven sporadic cases with three

Table 3 Onset of symptoms and site of tumours in sporadic cases of schwannomatosis

Case	Age (y)		Schwannomas (n)			Deafness	Cranial scan	Cataract	Cal
	Now	Symptoms	Spinal	Cutaneous	Cranial				
1	64	54	1	4	0	No	Yes	Yes	1
2	43	23	0	4‡	0	No	Yes	No	1
3	39	19	0	≥ 3	0	No	Yes	No	0
4	54	12	3	6	0	No	Yes	No	0
5	40	38	3	1	0	No	Yes	No	0
6	41	29	> 10	0	0	No	Yes	NK	0
7	55	42	2+	0	0	No	Yes	NK	0

*Footnotes as for table 2.

or more schwannomas, but insufficient criteria for NF2. There are no features suggestive of schwannomatosis in any other family member.

Methods for molecular analysis

Genomic DNA was prepared from blood samples using standard methods.⁷ Radioactive polymerase chain reaction (PCR) was performed on 50–200 ng of genomic DNA from each family member, to amplify individual microsatellite markers. The markers were D22S275,⁸ NF2CA3,⁹ NF2TET (previously unpublished tetranucleotide {AAAG} marker in intron 1 of the NF2 gene (forward primer-ACCACTGCACTCCAGCCTGG; reverse primer-TATGCCATGTTCTTGTGAAGG; product size 160–174 bp)), D22S273,⁸ D22S268,¹⁰ D22S430,¹¹ D22S281,⁸ D22S280.⁸ The forward primer was radioactively labelled at the 5' terminus with γ -³²P ATP using standard procedures and PCR reactions were carried out in a reaction volume of 10 μ l Tbr polymerase (NBL Gene Sciences) according to the manufacturer's instructions. Samples were thermocycled on a PCR480 Perkin Elmer Cetus thermal cycler machine for 30 cycles of 95°C for one minute, annealing at the appropriate temperature^{8–11} for one minute, and 72°C for one minute followed by a final elongation step at 72°C for 10 minutes. With the exception of D22S430, which was denatured and annealed for 30 seconds and extended for 90 seconds and NF2TET which was denatured and annealed for 90 seconds and an extension of 30 seconds. Products from PCR were electrophoresed on 6% denaturing polyacrylamide gels and viewed by autoradiography on Kodak X-Omat AR film.

Linkage analysis was performed with data management package LINKSYS in conjunction with the computer programme LINK-

AGE version 5.1. The penetrance values used in linkage were as follows: 20% at 30 years; 35% at 35 years; 85% at 55 years; 93% at 60 years; and 95% at 70 years.

Results

Figures 1 and 2 show the results of linkage analysis in the two large multigenerational families (M and C). All affected people in both families shared the inferred disease haplotype, with no recombination between any of the markers. Individuals III-1 and III-11 in family C, however, have inherited the "disease" haplotype but are phenotypically normal. If they carry the disease gene they have as yet failed to manifest any signs of the disorder and are clear on craniospinal MRI. Both are comparatively young (38 and 37 years) and the penetrance values for this age range are assumed to be relatively low (see methods).

The two point linkage analysis between chromosome 22q12.2 markers and the schwannomatosis families are consistent with the possibility that the disorder in these families is linked to the NF2 locus (table 4). For all markers analysed $Z_{\max}$ is at zero recombination. The maximum lod score was obtained with the intragenic marker NF2TET ($Z_{\max} = 2.88$). Although the significant lod score of +3.00 was not achieved, by using a candidate gene, significance is likely with a lod score in excess of +2.00.

Discussion

Distinguishing the different forms of neurofibromatosis is not merely an academic exercise: their natural history, and, therefore, management, are quite different. The patients presented here raise the question as to whether schwannomatosis is actually a distinct entity from NF2 or part of an extended phenotype.

SCHWANNOMA VERSUS NEUROFIBROMA

One of the problems in answering this question by reviewing of patients' case notes, was the loose use of terminology with respect to their tumours—we often found tumours reported as schwannoma but referred to in a clinician's letter as neurofibroma. The histological term is interchangeable with neurilemmoma,⁵ which it has now largely replaced. Although clinically spinal schwannomas and neurofibromas can appear similar radiologically and at operation, histologically they are quite distinct. Schwannomas are a pure growth of Schwann cells containing few if any other cell types, whereas a neurofibroma contains Schwann cells, fibroblasts, and mast cells and the axons are often seen running through the tumour, rather than around it as occurs in a schwannoma.¹² Despite this, in some of our cases, histologists had reported tumours as neurofibromas, but review by an experienced neuropathologist as part of the study showed the lesions to be schwannomas. The importance of this distinction is that schwannomas do not occur in excess in NF1, but are the prominent feature of NF2. A review of

Table 4 Lod score table for two point linkage analysis of families with Schwannomatosis and chromosome 22q12.2 markers

Locus	Family	Recombination fraction Θ						
		0.0	0.01	0.05	0.1	0.2	0.3	0.4
D22S275	C	1.45	1.42	1.29	1.13	0.79	0.42	0.11
	M	0.90	0.89	0.84	0.77	0.61	0.44	0.24
	C+M	2.35	2.31	2.13	1.90	1.40	0.86	0.35
NF2CA3	C	0.78	0.76	0.68	0.58	0.38	0.19	0.05
	M	1.20	1.18	1.09	0.98	0.75	0.50	0.25
	C+M	1.99	1.95	1.78	1.56	1.13	0.69	0.30
NF2TET	C	1.68	1.65	1.51	1.34	0.95	0.53	0.15
	M	1.20	1.18	1.09	0.98	0.75	0.50	0.25
	C+M	2.88	2.83	2.61	2.32	1.70	1.03	0.40
D22S268	C	0.57	0.56	0.51	0.44	0.30	0.16	0.05
	M	0.82	0.80	0.72	0.62	0.41	0.21	0.06
	C+M	1.40	1.36	1.23	1.06	0.71	0.37	0.11
D22S430	C	1.38	1.35	1.23	1.08	0.75	0.40	0.11
	M	1.20	1.18	1.09	0.98	0.75	0.50	0.25
	C+M	2.58	2.53	2.33	2.06	1.50	0.91	0.36
D22S273	C	1.38	1.35	1.23	1.08	0.75	0.40	0.11
	M	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	C+M	1.38	1.35	1.23	1.08	0.75	0.40	0.11
D22S280	C	1.45	1.42	1.29	1.13	0.79	0.42	0.11
	M	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	C+M	1.45	1.42	1.29	1.13	0.79	0.42	0.11
D22S281	C	1.68	1.65	1.51	1.34	0.95	0.53	0.15
	M	1.20	1.18	1.09	0.98	0.75	0.50	0.25
	C+M	2.88	2.83	2.61	2.32	1.70	1.03	0.40

Values represent pairwise lod scores between disease and indicated marker locus: linkage analysis was performed with the data management package LINKSYS in conjunction with the computer program LINKAGE version 5.1: genetic distances between the 22q12.2 markers were taken to be as follows: D22S275-1 cM - D22S273 - 2cM - D22S280 - 1cM - D22S281; NF2CA3 and NF2TET are located within intron 1 of the NF2 gene; D22S268 and D22S430 are located in a 160 kb contig, approximately 300 kb telomeric to the NF2 gene.

patients with spinal nerve tumours¹³ showed that of 68 patients, 40 had a sporadic schwannoma, two had a sporadic neurofibroma, with 14 patients having NF1 and seven NF2. Of the patients with NF1 all had neurofibromas only, whereas six of seven patients with NF2 had schwannomas only. The remaining patient with NF2 had features of both types. A further five patients had either more than one schwannoma or a schwannoma and other CNS tumours. It could be argued that at least three of these patients had schwannomatosis.

SCHWANNOMATOSIS

Schwannomatosis or neurilemmomatosis has been proposed as a separate entity to NF1 and NF2.^{6,14,15} This classification is made largely on the basis of an extensive Japanese literature and 35 cases were reviewed in 1984.¹⁴ Of 13 definite cases, seven had eighth nerve symptomatology highly suggestive of vestibular schwannoma, three patients were children, and the other three only in their 20s. Of the four definite new cases reported by Shishiba *et al.*¹⁴ one had bilateral vestibular schwannoma, two were only 8 and 13 years old and although one patient was 45 years old, no radiological exclusion of vestibular schwannoma was performed. Of the remaining 16 probable cases, nine had eighth nerve symptomatology, three were prepubertal, and one was 18 years old with evidence of intracranial disease. Only three patients were over the average age of presentation for vestibular schwannoma in NF2 (20–22 years)^{16,17} and all of these were in the pre-CT era. Shishiba *et al.*¹⁴ reported an overall rate for eighth nerve tumour of 15 of 33 and it is highly likely that these patients represented new mutations for classic NF2. The type and range of skin lesions reported were identical with those occurring in NF2.¹⁶ It is also of note that the incidence of glioma in their report was identical to that found in large NF2 series.^{16,17} A more recent report of two cases⁶ contained one clear case of NF2. This patient had bilateral vestibular schwannoma, typical intracranial calcification, ependymomas, and a trigeminal tumour. A rather spurious argument was made that this case lacked the other “cardinal” features of NF and therefore this precluded a diagnosis of NF2. The second case had multiple intracranial meningiomas and although CT of the auditory meatuses were normal the patient was only 20 years old. This patient would therefore fulfil our modified criteria for NF2,¹⁸ and we think it very likely she would go on to develop bilateral vestibular schwannoma. A further American patient aged 60 years with multiple neurilemmomas has been reported, but, there were insufficient clinical data to determine the context in which these tumours occurred.¹⁹ A more convincing recent report of 14 patients with schwannomatosis, who were carefully excluded as having NF2 (no vestibular schwannoma, cataracts, or meningioma) also identified this condition as being distinct from NF2. However, three of the patients were still very young and many others had very localised disease.

Most previous cases of schwannomatosis have been isolated; this report has clearly outlined autosomal dominant inheritance of a tendency to develop multiple schwannomas. This has also been reported by Riccardi⁴ and Shishiba *et al.*¹⁴ The question is whether this entity is distinct from NF2. One of the patients from Shishiba *et al.* from the 1984 report^{5,14} has gone on to develop more classic NF2. The diagnosis of schwannomatosis relies heavily on exclusion of NF2 by the NIH criteria (table 1).¹ These criteria rely on the presence of bilateral vestibular schwannoma or a family history. As 50% of people with NF2 are new mutations²⁰ and at least 20% present initially with spinal or cutaneous tumours¹⁷ most, if not all, of the eight patients aged 16 years or under in Shishiba's review¹⁴ are likely to develop classic NF2. This is further borne out by our family V, who for many years would have been considered a classic schwannomatosis family until bilateral vestibular schwannoma were diagnosed in two family members. It is therefore likely that the great majority of all the previous cases of schwannomatosis actually represent new mutations for NF2. It is possible that some patients may represent somatic mutations in whom the mutation in the NF2 gene has occurred postzygotically, but may still mean that a significant proportion of cells contains the mutation. This could mean that tumours may be confined to one part of the spine or skin for instance, such as in the study of MacCollin *et al.*¹⁵ There is a good precedent for this “mosaicism” in NF1 where there are clear patients in whom only part of the body is affected and yet there may still be a risk of transmission to the offspring if the gonads are involved.⁵ None the less if the patient is young, a diagnosis of classic NF2 is still highly likely and even if they are old and vestibular schwannoma have been excluded on MRI, caution must be exercised about the risks of transmission.

Previous analysis of families with familial spinal neurofibromatosis found linkage to the NF1 locus in one family who also had café au lait patches, but exclusion in a second family without other corroborating features of NF1.²¹ There was insufficient information to assess linkage to the NF2 locus. These families are likely to be distinct from those exhibiting multiple schwannomas. The first family clearly had NF1 with spinal neurofibromas and therefore linkage at this locus was not surprising.

No single family member fulfils the NIH diagnostic criteria for NF1 or NF2 in five of the families reported here. Although at least one family member has developed a cranial nerve schwannoma in three of them. It is likely that the reliance on bilateral vestibular schwannoma as the sole diagnostic criteria for NF2 in sporadic cases has biased all reported cases, leading us to think that there is virtual complete penetrance of this disease feature in NF2. However, even in classic families there are often patients who do not develop vestibular schwannoma late into life.^{18,22} The premise that vestibular schwannoma reaches full penetrance in NF2 would seem to be a false one. It

is therefore possible that certain mutations in the NF2 gene, or in a closely linked gene predispose to a different pattern of tumours, with sparse cranial involvement, but many spinal and cutaneous tumours. In some families such as the five we have presented it may be possible to counsel on the basis of a lower risk of cranial tumours, but it would be dangerous to do so in isolated patients with multiple schwannomas. It is likely that there is still an increased risk of eighth nerve tumours in all these families.

We have found no evidence for exclusion of any of these families from the NF2 locus using linked and intragenic markers and indeed have generated a near significant lod score to support involvement of the NF2 gene. Coupled with the recent identification of a germline mutation in the NF2 gene in a 42 year old with schwannomatosis,²³ and a 163 base pair deletion in another patient with multiple schwannomas,²⁴ we think that, even in the families in which there would seem to be a schwannomatosis phenotype distinct from classic NF2, the causative mutation may well be in the NF2 gene. We have not as yet isolated a mutation in these families using single strand conformation polymorphism (SSCP) and heteroduplex analysis, but these methods have a relatively low success rate in identifying mutations in the NF2 gene.²⁵ As mutation screening techniques of the NF2 gene^{26,27} improve it will soon be possible to determine whether there is a molecular basis for isolated and familial cases of schwannomatosis, when there is cranial sparing. An intriguing possibility has been raised by the differential expression of two isoforms of the NF2 protein in adult rat brain and spinal cord.²⁷ Mutations which interfere with normal splicing of exon 16 to create the type 1 isoform could give rise to a form of the disease confined to the spine.

Conclusions

When an individual presents with a spinal tumour at a young age, or they develop multiple tumours, NF2 must be considered. It is important that the difference between neurofibroma and schwannoma is established and that cranial imaging is also performed. Our families suggest that a spinal form of NF is probably not a distinct disorder, but a variant of NF2. Only in families with an established pattern of spinal and cutaneous tumours and absence of cranial tumours is it possible to relax screening for vestibular schwannoma. Patients presenting at a young age with a spinal or cutaneous schwannoma or at any age with multiple schwannomas should still be screened for the development of cranial tumours. Although bilateral vestibular schwannoma will occur in most cases of NF2

this manifestation should no longer be thought of as the "hallmark" of the disease.

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