Neurofibromatosis: emerging phenotypes, mechanisms and management

Susan Huson MD FRCP, Consultant Clinical Geneticist, *Medical Genetics Research Group and Regional Genetics Service, University of Manchester and Central Manchester and Manchester Children's University Hospitals NHS Trust*

Clin Med 2008;8:611–17

Neurofibromatosis (NF) was for many years regarded as a medical curiosity and nothing more. However, progress in understanding has been rapid following diagnostic criteria for the two main types agreed at a National Institutes of Health (NIH) consensus conference in 1987.[1–6] The following decade saw the identification of the *NF1* and *NF2* genes and the development of animal models.[7,8] Clinically useful genotype-phenotype correlations are now emerging and pathogenesis-based treatment trials underway.[9–11] This review highlights the likely presentations of NF1 and NF2 in adult life and gives an overview of management, recently delineated subtypes and current understanding of disease pathogenesis.

Definition of neurofibromatoses

The delineation of the different types of NF is important as their natural history and management are quite different. The key features of NF1, NF2 and related disorders are summarised in Tables 1(a) and 1(b).[12] They can usually be distinguished by the type and distribution of nervous system tumours, the presence or absence of café au lait spots (CAL)± skinfold freckling and the ophthalmic examination. In most cases the type of NF is obvious after clinical assessment. With the availability of cranial imaging, NF1 and NF2 are now rarely confused.

Neurofibromatosis type one

Diagnosis

In most adult patients the combination of CAL spots/freckling and dermal neurofibromas (Fig 1) makes the diagnosis of NF1 straightforward. The NIH diagnostic criteria[1] are clinically useful, with two provisos:

1 Patients with *segmental NF1* may satisfy the criteria but have limited body involvement. In this form of NF1 there is a somatic mutation of the *NF1* gene with a much lower risk of complications and of transmitting NF1 to offspring.[13] Identification of mutations in affected tissue is now possible.[14]

2 The recently recognised phenotype of *mismatch repair deficiency* syndrome (MMR-D) means that the term 'first-degree relative' can be misleading.[15,16] In typical NF1, clinically normal parents with two affected children are rarely seen. Individuals with MMR-D develop early-onset haematological malignancies and/or central nervous system tumours. Some have CAL-like lesions (often with very irregular outlines) though others appear to have typical NF1. An *NF1* mutation has been reported in one case and it is likely that *NF1* is a target for mismatch repair.[17] Inheritance is recessive, so siblings may be diagnosed as NF1 and the wider implications of MMR-D may not be appreciated. The parents and heterozygote siblings are at risk of hereditary non-polyposis colon cancer, and children with MMR-D are at risk of malignancies not usually seen in NF1.

Management

Many complications are associated with NF1 and their occurrence cannot be predicted even within families. Those that can present in adults are summarised in Table 2. None occurs sufficiently frequently to warrant screening asymptomatic patients but there should be a low threshold for investigating relevant symptoms. Conversely, in assessing a patient with an NF1-related complication it is important to examine carefully the skin for NF1. The diagnosis in some patients is not obvious on routine examination because CAL spots tend to fade with age and some people have very few neurofibromas.

There are published consensus guidelines on NF1 management.[5] The minimum recommendations for adults with NF1 are annual blood pressure checks and to seek advice if symptoms develop that could be NF1 related.

Recent clinical developments

Some new clinical associations have recently emerged:

- Women under 50 with NF1 have a fivefold relative risk of breast cancer and are therefore eligible for

Key Points

- **The correct diagnosis of the different types of neurofibromatosis (NF) is critical to appropriate management and genetic counselling**
- **NF1 is a common genetic condition and patients can present to almost any medical specialty**
- **Gastrointestinal stromal tumours, glomus tumours of the nailbeds and breast cancer in women aged under 50 years have recently been shown to be associated with NF1**
- **Patients with NF2 are best managed in specialist multidisciplinary clinics**
- **Genetic testing is now clinically useful for both NF1 and NF2**

KEY WORDS: diagnosis, genetics, management, neurofibromatosis types one (NF1) and 2 (NF2)

mammographic screening from the age of 40.[18]

- Lesions previously diagnosed as gastrointestinal (GI) neurofibromas in the NF1 population are now recognised histologically to be GI stromal tumours (GISTs).[19,20] NF1-associated GISTs tend to be multicentric, occur predominantly in the small bowel and follow a more benign course than sporadic GISTs. It remains to be determined whether imatinib is as effective for treating NF1-related GISTs as for the sporadic counterpart.
- The use of positron emission tomography (PET) computed tomography (CT) has greatly improved the diagnosis of malignant peripheral nerve tumours.[21] These usually arise through malignant change in an existing plexiform neurofibroma. PET CT is sensitive and specific in distinguishing benign and malignant change. It also localises the area for biopsy.

Table 1(a). Summary of the different types of neurofibromatoses (NF): NF1 and related disorders (adapted with permission from S Karger AG, Basel).[12]

NF type	Previous names	Disease frequency	Gene/ chromosome	CAL spots	Skinfold freckling	Peripheral nerve tumours	Eye findings	Other frequent clinical features
NF1	Von Recklinghausen or peripheral NF	1/3,000 (birth incidence)	*NF1*/17	≥6	Yes	Dermal, nodular and plexiform neurofibromas	LNs and ONGs	Learning and behaviour problems. Predisposition to certain malignancies and numerous other complications (see Table 2)
A1 NF1 microdeletions	Accounted for at least some designated NF-Noonan syndrome	1/60,000 (assuming accounts for 5% NF1 mutations)	*NF1*/17	Clinical features of NF1 with tendency to excessive numbers of dermal neurofibromas, more severe learning problems, increased frequency of certain NF1 complications, including cardiovascular and MPNST. In addition, microdeletion cases usually have specific craniofacial dysmorphism and a tendency to be taller than average rather than shorter				
A2 Del AAT exon 17	AD CAL spots only	?	*NF1*/17	≥6	Yes	None reported to date	LN less frequent than usual	Most reported families have pigmentary features only with lower frequency of all complications except pulmonary stenosis
A3 Watson syndrome	NA	Very rare	*NF1*/17	≥6	Yes	Adults have few, if any, dermal NFs. Other kinds of neurofibromas not reported	LN less frequent than normal. No ONGs reported	Mild learning problems more frequent than usual, as is pulmonary stenosis. Other complications not reported
A4 Localised segmental/ NF1	Segmental NF1	1/36,000–40,000 (prevalence)	Somatic *NF1* mutations	Cutaneous features of NF1 (pigmentation and/or neurofibromas) limited to one or more segments of body. Associated NF1 complications relatively uncommon (combined frequency 5.6% in one large series[3])				
A5 Spinal NF (Fig 2)	NA	?	*NF1*/17 – one family not linked to 17	Very few, if any, pigmentary changes and no dermal neurofibromas but with multiple spinal tumours often with neurofibromas of major peripheral nerves (Fig 2). Those with NF1 mutations have over-representation of missense and splice mutations (Ludwine Messiaen, personal communication)				
NA1 SPRED1 phenotype	AD CAL spots only	?	*SPRED1*/15	≥6	Yes	None	None	Only one series published to date:[11] main other NF1 feature in most people was macrocephaly. A few had learning problems, two ADHD and several lipoma

A = allelic; ADHD = attention deficit-hyperactivity disorder; BVS = bilateral vestibular schwannomas; CAL = café au lait; LN = Lisch nodules; MPNST = malignant peripheral nerve sheath tumour; NA = non-allelic; ONG = optic nerve glioma.

- The association of glomus tumours in the nailbeds of the fingers or toes.[22] These benign tumours cause severe pain, particularly when touched or on exposure to hot/cold.
- Bone issues: localised NF1-related skeletal problems (including scoliosis and long bone pseudarthrosis) have long been recognised. Recent studies have pointed to a more generalised bone abnormality,[23] with NF1 patients having decreased bone mineral density. Studies of fracture risk are awaited.

Genetics and pathogenesis

NF1 is one of the most common autosomal dominant disorders, with a birth incidence of one in 3,000. About 50% of cases represent new gene mutations. The *NF1* tumour suppressor gene (TSG) maps to chromosome 17q11.2 and encodes neurofibromin.[6,7] Neurofibromin is widely expressed, with the highest concentrations

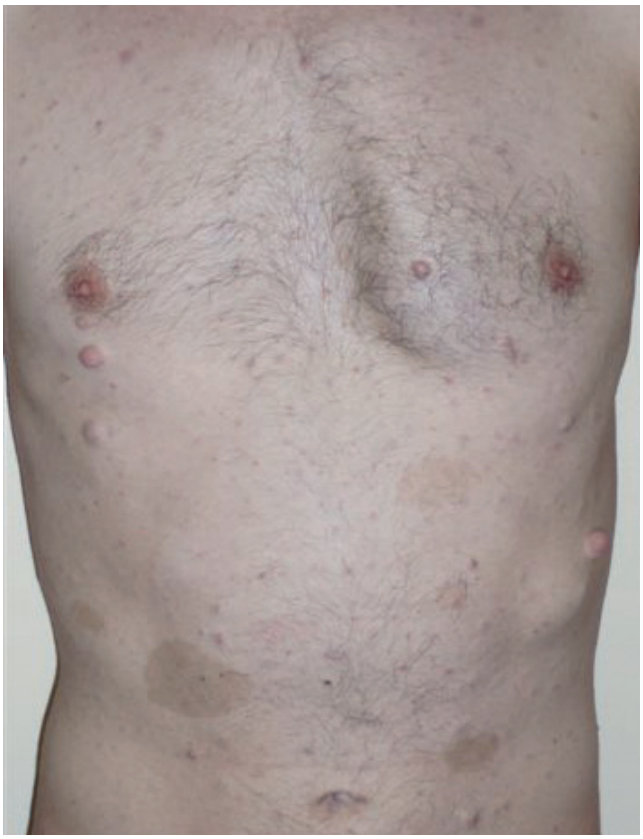

Fig 1. A 29-year-old man with typical neurofibromatosis type one showing café au lait spots and multiple dermal neurofibromas.

Table 1(b). Summary of the different types of neurofibromatoses (NF): NF2 and related disorders (adapted with permission from S Karger AG, Basel).[12]

NF type	Previous names	Disease frequency	Gene/ chromosome	CAL spots	Skinfold freckling	Peripheral nerve tumours	Eye findings	Other frequent clinical features
NF2	Central or Wishart	1/25,000 (birth incidence)	*NF2*/22	≤6 but occur at higher frequency than in general population	No	Predominantly schwannomas histologically but neurofibromas can occur. Clinically, only NF2 plaques are distinguishable from dermal/ nodular/plexiform neurofibromas	Juvenile posterior subcapsular lens opacity/ cortical cataract in 70–80%. Retinal abnormalities in 22%	BVS the most frequent feature. Meningiomas, other cranial nerve and spinal root schwannomas, ependymomas
A1 localised/ segmental NF2	NA	1/80,000	*NF2*/22	NF2 associated cranial tumours localised to one half of brain. When patients have spinal or peripheral nerve schwannomas localised to one part of body, impossible to know clinically if this is a form of NF2 or schwannomatosis				
NA1 schwannomatosis	NA	?	*IN11/SMARCB1*/22	None	None	Peripheral nerve and spinal root schwannomas	None	None

A = allelic; ADHD = attention deficit-hyperactivity disorder; BVS = bilateral vestibular schwannomas; CAL = café au lait; LN = Lisch nodules; MPNST = malignant peripheral nerve sheath tumour; NA = non-allelic; ONG = optic nerve glioma.

in the nervous system. Neurofibromin negatively regulates RAS by acting as a guanosine triphosphatase activating protein (GAP). Haploid insufficiency or complete *NF1* deficiency results in a dose-dependent rise in RAS activity, which in turn activates a variety of signalling pathways that affect cell proliferation and differentiation in a cell-specific way. Neurofibromin also has a non-RAS-GAP function involving regulation of cyclic adenosine monophosphate.

Treatment prospects

The RAS pathway can be targeted by many licensed drugs. The effect of rapamycin and imatinib on the growth of plexiform neurofibromas in NF1 is under investigation in human trials in the USA. In a mouse model of NF1,[24] impaired cognition was related to excessive RAS activity and increased gamma-aminobutyric acid inhibition; it was reversed by reduction in RAS activity by lovastatin through its inhibition of p21 RAS/mitogen-activated protein kinase activity. Clinical trials are underway.[25]

Genetic testing

Using up-to-date laboratory techniques, the *NF1* mutation can be identified in 95% of cases. Some clinically useful genotype-phenotype correlations are emerging:

- Patients with a microdeletion of the

Table 2. Neurofibromatosis (NF) type one: the frequency of different types of neurofibromas and disease complications presenting in adults.[1,12]

Disease feature	Frequency (%)	Comments re presentation/management
Dermal neurofibromas	>95 of adults	Present in nearly all adult patients but in greatly varying numbers. NOT associated with malignant change but can be major cosmetic burden
Nodular neurofibromas	ca 5%	Develop on major peripheral nerves; can be painful. Patients with multiple lesions at increased risk of MPNST
Plexiform neurofibromas:		
All lesions	30.0	Can be a major cause of morbidity. Most MPNSTs arise in pre-existing plexiforms, particularly those with deep involvement. Patients can also present acutely because of sudden major haemorrhage into lesion
Large lesions of head and neck	1.2	
Limbs/trunk lesions associated with hypertrophy	5.2	
Intellectual handicap:		
Severe	0.8	Severe problems unusual in NF1. A further 20% of children have specific learning problems. There is a greatly increased risk of ADHD
Moderate	2.4	
Minimal	29.8	
Epilepsy:		
No known cause	4.4	NF1 patients should always have a scan at presentation to exclude an underlying cause
Secondary to disease complications	2.2	
CNS tumours:		
Optic glioma (symptomatic)	1.5	Most present in childhood
Other gliomas	1.5	Can develop at any age
Spinal neurofibromas	1.5	Can develop at any age
Aqueductal stenosis	1.5	Usually presents <30 years
Malignancy: MPNST	1.5 prevalence but lifetime risk ca 10%	Most present at 20–40 years with pain, neurological deficit, change in pre-existing plexiform or as rapidly growing mass
GISTs	2.2	May be multiple. Follow a more benign course than sporadic GISTs
Renal artery stenosis	1.5	Usually presents <20 years
Vascular disease elsewhere	<1	Very rare, but case reports of sudden haemorrhage from vessel rupture with underlying aneurysm/AVM
Phaeochromocytoma	0.7	When occurs, need to check for carcinoid
Duodenal carcinoid	1.5	When occurs, need to check for phaeochromocytoma
Lateral meningocele	<1	Usually asymptomatic
Glomus tumours of nailbed	<1	Usually in adults
Breast cancer in women	8.4	Relative risk x5 for those <50 years; 8.4% is cumulative risk to age 50 (compared with 2% for general population)
Pulmonary fibrosis/HOCM	Significantly <1 (may not be true association)	Some case reports, but not reported in large NF1 cohorts

ADHD = attention deficit-hyperactivity disorder; AVM = arteriovenous malformation; GIST = gastrointestinal stromal tumour; HOCM = hypertrophic obstructive cardiomyopathy; MPNST = malignant peripheral nerve sheath tumour.

NF1 region are known to have a more severe phenotype with an increased risk of malignant peripheral nerve sheath tumour.[9]

- In some families, CAL spots ± freckling are present, but neither neurofibromas nor major complications develop apart from mild learning problems. Some of these families arise from a specific mutation in exon 17 of the *NF1* gene[10] and others from a mutation in the *SPRED1* gene on chromosome 15.[11]

Indications for genetic testing

1 Those who may have deletions on clinical grounds.
2 Those with an atypical phenotype for diagnostic clarification, although review in a specialist NF clinic may be a useful preliminary.
3 Families with two or more generations with isolated pigmentary changes.
4 Children with no family history and isolated pigmentary changes.
5 Prenatal/pre-implantation diagnosis.

Neurofibromatosis type two

Diagnosis

In contrast to NF1, the causes of severe morbidity and mortality in NF2 are limited to the nervous system and eye.[3] The major feature of NF2 is bilateral vestibular schwannomas (BVS) which usually cause hearing-related symptoms in the late teens/early 20s. Many patients also develop other cranial and spinal nerve root schwannomas, cranial/spinal meningiomas and ependymomas (usually spinal). In families with 'mild NF2' the only tumour burden may be BVS with no skin tumours or ocular signs. In contrast, those with 'severe NF2' tend to present in childhood with eye problems (retinal hamartomas/cataracts), loss of use of a muscle group due to focal amyotrophy or NF2-related skin lesions. Although histologically the peripheral tumours are usually schwannomas, clinically they are often indistinguishable from NF1 neurofibromas. The one distinct lesion is the NF2 plaque which appears as a raised area of roughened skin with an orange-brown colour associated with hypertrichosis.[3]

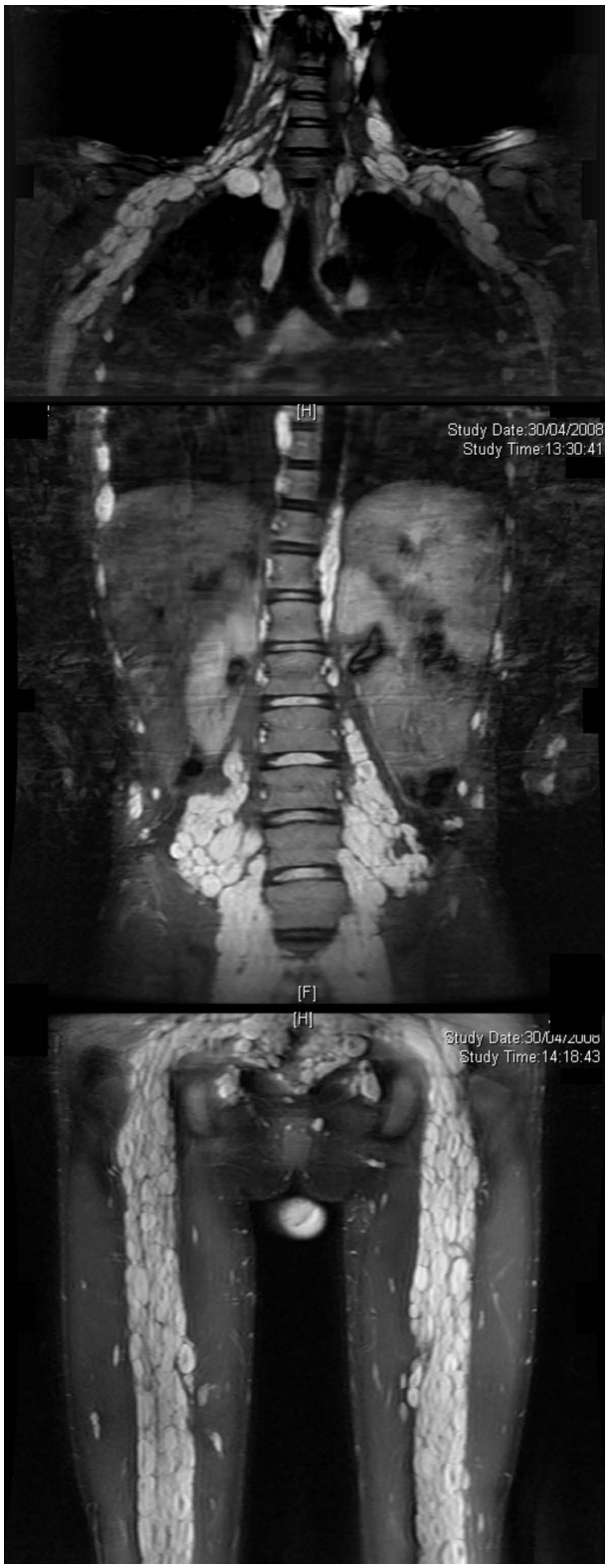

Fig 2. Composite image of coronal short tau inversion recovery sequences through the neck and thorax, abdomen and thighs of a 17-year-old with atypical neurofibromatosis type one (spinal variant). He has only two café au lait spots, no dermal but multiple nodular neurofibromas. The scan, done to check for internal involvement, shows multiple neurofibromas on spinal roots and major peripheral nerves.

Management

The management of NF2 is complex (detailed discussion of the management options is beyond the scope of this article). Consensus guidelines recommend follow-up in a multidisciplinary clinic.[2,3] There have been major improvements in postoperative auditory rehabilitation in the last two decades with improved surgical outcomes and with the introduction of a brain stem implant for patients where the eighth nerve is damaged at surgery. Despite this, the non-VS tumour burden in some patients is huge and repeated surgery results in increasing disability, which may be compounded by an associated polyneuropathy.

Genetics and pathogenesis

NF2 is caused by mutations in the *NF2* TSG on chromosome 22. Inheritance is autosomal dominant, with approximately 50% of cases the result of new mutations. The gene encodes the protein merlin which has an important role in the co-ordination of two inter-dependent processes: cellular adhesion and growth factor receptor response.[8,26] Both *in vitro* and mouse models of schwannoma growth are being tested for response to drugs that target the relevant pathways.

Indications for genetic testing

In contrast to NF1, genetic testing is now a routine part of diagnosis and genetic counselling in NF2. Genetic testing is possible for most families and usually discussed from around the age of 10 years. Some couples opt for prenatal or pre-implantation genetic diagnosis. There is genotype-phenotype correlation, with nonsense and frameshift mutations associated with severe disease.[27]

Mosaicism and neurofibromatosis type two

There is evidence that 20–30% of sporadic patients are mosaics, the mutation having arisen after conception leading to two separate cell lineages.[27] In most cases, the mutation is not detected on lymphocyte analysis and it is necessary to perform mutation analysis on tumours. Occasionally, there is clinical suggestion of mosaicism with the scan showing unilateral VS and multiple meningiomas. Mosaic patients have a lower risk of transmitting the disease but when they do the children, who have the mutation in all their cells, tend to be more severely affected. However, in the second and subsequent generations of a family NF2 tends to 'breed true'.

Schwannomatosis

Schwannomatosis overlaps with NF2 at both the clinical and molecular level,[28,29] but these patients are mainly at risk of developing peripheral nerve and spinal root schwannomas. Cranial nerve involvement is rare. There is no eye involvement, ependymomas have not been seen and meningiomas occur very rarely. The appearance of the tumours is clinically and radiologically the same as in NF2 but the tumours are associated with more pain. Currently, schwannomatosis is a diagnosis made after exclusion of NF2 by eye examination, neuraxis imaging and genetic testing.

Genetics and pathogenesis

Most cases of schwannomatosis are sporadic, with some patients having localised lesions suggestive of mosaicism. The risk to offspring of sporadic cases is much less than 50%. In familial cases inheritance is dominant but expression is variable and incomplete penetrance is recorded.[28]

The genetic mechanisms underlying schwannomatosis are still being elucidated.[29,30] The gene has been localised to chromosome 22 proximal to *NF2* and mutations in the *INI1/SMARCB1* TSG were reported in one family last year.[30] Subsequent reports suggest that a third of familial cases and 7% of sporadic cases have germline *INI1* mutations. Mutations in the same gene also cause inherited predisposition to rhabdoid tumours which develop after a somatic 'second hit'.[29,31]

The major question therefore is why mutations in the same gene cause such different phenotypes. Early work from two groups suggests a complex mechanism of tumorigenesis in schwannomatosis which requires somatic mutation in both copies of the *NF2* gene as well as in *INI1*.[29,31]

Acknowledgement

I am grateful to Dr Rick Whitehouse for compiling Fig 2.

References

1 Neurofibromatosis. Conference statement. National Institutes of Health Consensus Development Conference. *Arch Neurol* 1988;45:575–8.
2 Gutmann DH, Aylsworth A, Carey JC *et al.* The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. *JAMA* 1997;278:51–7.
3 Evans DG, Baser ME, O'Reilly B *et al.* Management of the patient and family with neurofibromatosis 2. Review. *Br J Neurosurg* 2005;19:5–12.
4 Korf BR, Rubenstein AE. *Neurofibromatosis: a handbook for patients, families, and health care professionals.* New York: Thieme Medical Publishers, 2005.
5 Ferner RE, Huson SM, Thomas N *et al.* Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. *J Med Genet* 2007; 44:81–8.
6 Kaufmann D (ed). Neurofibromatoses. *Monographs in human genetics,* vol 16. Basel: S Karger AG, 2008.
7 Le LQ, Parada LF. Tumor microenvironment and neurofibromatosis type 1: connecting the GAPs. Review. *Oncogene* 2007;26:4609–16.
8 Curto M, McClatchey AI. *NF2*/merlin: a coordinator of receptor signalling and intercellular contact. *Br J Cancer* 2008; 98:256–62.
9 Tinschert S. Clinical phenotypes in patients with *NF1* microdeletions. In: Kaufmann D (ed). Neurofibromatoses. *Monographs in human genetics* 2008;16:78–88.
10 Upadhyaya M, Huson SM, Davies M *et al.* An absence of cutaneous neurofibromas associated with a 3-bp inframe deletion in exon 17 of the NF1 gene (c.2970–2972 delAAT): evidence of a clinically significant NF1 genotype-phenotype correlation. *Am J Hum Genet* 2007;80:140–51.
11 Brems H, Chmara M, Sahbatou M *et al.* Germline loss-of-function mutations in SPRED1 cause a neurofibromatosis 1-like phenotype. *Nat Genet* 2007;39:1120–6.
12 Huson SM. The neurofibromatoses: classification, clinical features and genetic counselling. In: Kaufmann D (ed) Neurofibromatoses. *Monographs in human genetics* 2008;16:1–20.
13 Ruggieri M, Huson SM. The clinical and diagnostic implications of mosaicism in the

neurofibromatoses. *Neurology* 2001;56: 1433–43.
14 Maertens O, De Schepper S, Vandesompele J *et al.* Molecular dissection of isolated disease features in mosaic neurofibromatosis type 1. *Am J Hum Genet* 2007; 81:243–51.
15 Bandipalliam P. Syndrome of early onset colon cancers, hematologic malignancies and features of neurofibromatosis in HNPCC families with homozygous mismatch repair gene mutations. *Fam Cancer* 2005;4:323–33.
16 Scott RH, Mansour S, Pritchard-Jones K *et al.* Medulloblastoma, acute myelocytic leukaemia and colonic carcinomas in a child with biallelic *MSH6* mutations. *Nat Clin Pract Oncol* 2007;4:130–4.
17 Alotaibi H, Ricciardone MD, Ozturk M. Homozygosity at variant *MLH1* can lead to secondary mutation in *NF1*, neurofibromatosis type 1 and early onset leukaemia. *Mutat Res* 2008;637:209–14.
18 Sharif S, Moran A, Huson SM *et al.* Women with neurofibromatosis 1 are at moderately increased risk of developing breast cancer and should be considered for early screening. *J Med Genet* 2007;44: 481–4.
19 Maertens O, Prenen H, Debiec-Rychter M *et al.* Molecular pathogenesis of multiple gastrointestinal stromal tumors in NF1 patients. *Hum Mol Genet* 2006;15:1015–23.
20 Andersson J, Sihto H, Meis-Kindblom JM *et al.* NF1-associated gastrointestinal stromal tumors have unique clinical, phenotypic, and genotypic characteristics. *Am J Surg Pathol* 2005;29:1170–6.
21 Ferner RE, Golding JF, Smith M *et al.* [18F]2-fluoro-deoxy-D-glucose positron emission tomography (FDG PET) as a diagnostic tool for neurofibromatosis 1 (NF1) associated malignant peripheral nerve sheath tumours (MPNSTs): a long-term clinical study. *Ann Oncol* 2008;19: 390–4.
22 De Smet L, Sciot R, Legius E. Multifocal glomus tumours in the fingers in two patients with neurofibromatosis type 1. *J Med Genet* 2002;39:e45.
23 Schindeler A, Little DG. Recent insights into bone development, homeostasis, and repair in type 1 neurofibromatosis (NF1). *Bone* 2008;42:616–22.
24 Li W, Cui Y, Kushner SA *et al.* The HMG-CoA reductase inhibitor lovastatin reverses the learning and attention deficits in a mouse model of neurofibromatosis type 1. *Curr Biol* 2005;15:1961–7.
25 Krab LC, de Goede-Bolder A, Aarsen FK *et al.* Effect of simvastatin on cognitive functioning in children with neurofibromatosis type 1: a randomized controlled trial. JAMA 2008;300:287–94.
26 Hanemann CO. Magic but treatable? Tumours due to loss of merlin. *Brain* 2008;131(Pt 3):606–15.
27 Evans DG, Wallace A. NF2: mutations and management of disease. In: Kaufmann D (ed). Neurofibromatoses. *Monographs in human genetics.* Basel: Karger, 2008;16: 154–66.
28 MacCollin M, Chiocca EA, Evans DG *et al.* Diagnostic criteria for schwannomatosis. *Neurology* 2005;64:1838–45.
29 Hadfield KD, Newman WG, Bowers NL *et al.* Molecular characterisation of SMARCB1 and NF2 in familial and sporadic schwannomatosis. *J Med Genet* 2008;45:332–9.
30 Hulsebos TJ, Plomp AS, Wolterman RA *et al.* Germline mutation of INI1/SMARCB1 in familial schwannomatosis. *Am J Hum Genet* 2007;80:805–10.
31 Sestini R, Bacci C, Provenzano A, Genuardi M, Papi L. Evidence of a four-hit mechanism involving SMARCB1 and NF2 in schwannomatosis-associated schwannomas. *Hum Mut* 2007;29:227–31.