J Neurooncol (2010) 99:341–347
DOI 10.1007/s11060-010-0339-x

INVITED REVIEW

Meningiomas and neurofibromatosis

Stéphane Goutagny · Michel Kalamarides

Received: 4 July 2010 / Accepted: 4 August 2010 / Published online: 17 August 2010

Abstract Neurofibromatosis type 2 (NF2) is a rare genetic disorder predisposing to multiple benign tumors of the nervous system. Meningiomas occur in about half of NF2 patients, and are often multiple. Patients harboring seemingly isolated multiple meningiomas should be investigated to diagnose NF2 by careful familial history collection, detailed clinical examination (skin lesions and slit lamp examination of the lens), audiovestibular testing, and fine cranio-spinal Magnetic Resonance Imaging. Somatic mosaicism is frequent in NF2 and may explain a mild phenotype as, e.g. isolated multiple meningiomas. Neurofibromatosis type 1 is not associated with an increased risk of meningioma. Whether meningiomas are part of the schwannomatosis tumor phenotype or not remains debated. Meningiomas in NF2 patients are associated with a higher risk of mortality, and their treatment is challenging, but data about natural history of meningiomas in NF2 patients in the literature are sparse. Thus, knowledge of tumor behavior is essential in slow growing tumors like meningiomas, to balance the risk of treatment against the natural history of the disease, and to evaluate the efficiency of alternative therapeutics (radiation therapy or new drugs).

Keywords NF1 · NF2 · Schwannomatosis · Multiple meningiomas · Meningioangiomatosis

S. Goutagny · M. Kalamarides
INSERM, U674, Paris 75010, France

S. Goutagny · M. Kalamarides
Université Paris 7 – Denis Diderot, Paris 75010, France

S. Goutagny · M. Kalamarides
Assistance Publique-Hôpitaux de Paris, Hôpital Beaujon, Service de Neurochirurgie, Clichy 92110, France

M. Kalamarides (✉)
Department of Neurosurgery, APHP, Hôpital Beaujon, 100 Boulevard du General Leclerc, 92110 Clichy, France
e-mail: michel.kalamarides@bjn.aphp.fr

Meningiomas are found in half of NF2 patients and are frequently multiple

Neurofibromatosis type 2 (NF2, OMIM #101000) is a dominantly inherited tumor predisposition syndrome caused by inactivating mutations of the *NF2* tumor suppressor gene on chromosome 22q12. NF2 is rare genetic disorder with a birth incidence of 1/33,000, and a prevalence of 1/56,161 [1]. NF2 patients are predisposed to develop multiple benign tumors including schwannomas, meningiomas and ependymomas. Half of cases harbor de novo mutation without any family history of NF2, and penetrance is almost 100% by 60 years of age [2, 3]. The cardinal feature of NF2 is the development of schwannomas on the vestibular branches of both eighth cranial nerves. Meningiomas are the second most frequent tumor type in NF2, affecting about half of NF2 patients. Spinal lesions are frequent in NF2, concerning 90% of patients [4], and include schwannomas, meningiomas, and ependymomas. Non-tumoral features of NF2 include polyneuropathy [5], skin and ophthalmic manifestations. About 70% of NF2 patients develop skin lesions: the most frequent are intracutaneous plaque-like lesions, which are slightly raised, pigmented and often hairy; more deep-seated nodular tumors with thickened nerve palpable on either side usually correspond to schwannomas [2]. Ophtalmic examination can show juvenile posterior subcapsular cataracts and epiretinal membranes, highly suggestive of NF2 [6, 7]. Manchester set of diagnostic criteria, widely

Table 1 Manchester clinical diagnostic criteria for Neurofibromatosis type 2

1. Bilateral vestibular schwannomas
2. Family history of NF2 and unilateral vestibular schwannoma or at least 2 of: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities
3. Unilateral vestibular schwannoma and at least 2 of: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities
4. Multiple meningiomas (>1) and unilateral vestibular schwannoma or at least 2 of: schwannoma, glioma, neurofibroma, cataract

Adapted from [2]

used for the diagnosis of NF2 (Table 1), recognizes as NF2 a patient harboring multiple meningiomas when associated with schwannoma, glioma, neurofibroma, or cataract.

The incidence of cranial meningiomas in published cohorts of NF2 patients is about 50%: from 28/74 (38%) in Japan [8], 54/120 (45%) in Manchester [2], 31/63 (49%) in NIH [3] to 28/48 (58%) in Hannover [4], the discrepancy in incidence depending in part on the screening protocols. Meningiomas in NF2 are frequently multiple and occur either in cranial (Fig. 1) or in spinal location (Fig. 2). The female predominance observed in sporadic meningioma cases is also observed in NF2 patients [9], although NF2 affects equally both sexes.

In the pediatric age group, meningiomas are often the first sign of NF2 [10]. In a series of 21 NF2 patients and 18 pediatric cases, 83% of patients with early onset NF2 harbored meningiomas [11]. Furthermore, NF2 has to be ruled out in sporadic pediatric patients harboring meningioma, both multiple and single tumors: NF2 is diagnosed in 10–29% of patients in pediatric meningioma series [12–15].

Meningiomas in NF2 patients are associated with disease severity

Baser et al. [16] analyzed the factors associated with mortality in 368 patients from 261 families in the United Kingdom NF2 registry. Age at diagnosis, intracranial meningiomas, and specialization of treatment center were informative predictors of the risk of mortality. The relative risk of mortality was 2.51-fold greater in people with meningiomas compared with those without meningiomas. Thus, presence of meningiomas in NF2 patients is a marker of disease severity.

Multiple meningiomas is a rare entity largely overlapping NF2

The proportion of patients harboring multiple meningiomas in the literature ranges from 1 to 12% in surgical series, and from 8 to 16% in radiological or autopsy series. Most of the studies refer to cases identified before NIH Consensus Statement on Neurofibromatosis, and NF2 patients are difficult to segregate from other multiple meningiomas patients. Antinheimo et al. [17] analyzed the frequency of multiple meningiomas in a well-defined population of 1,713,000 people in Finland. Seven out of 823 (1%) patients with meningioma had multiple meningiomas in association with NF2, and 29 of 823 (4%) had multiple meningiomas without obvious NF2.

Somatic mosaicism is a pivotal issue in multiple meningiomas patients. Somatic mosaicism is caused by postzygotic mutations in the early stage of embryo development. Only a subpopulation of the normal cells of a mosaic subject carries the constitutional mutation. Therefore, screening of a non-tumor tissue such as leucocytes

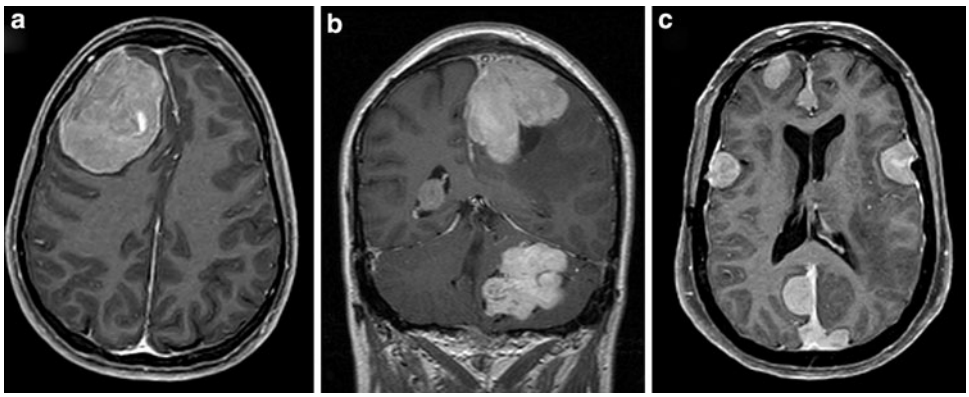

Fig. 1 T1-weighted MRI with Gadolinium enhancement showing aspects of cranial meningiomas in NF2 patients. **a** right frontal convexity meningioma responsible for intra cranial hypertension (**b**) coronal view showing the association of a large left parasagittal meningioma and an intraventricular meningioma. Of note, a large left vestibular schwannoma is also visible (**c**) multiple medium sized meningiomas involving the convexity, the falx cerebri, and sagittal sinus

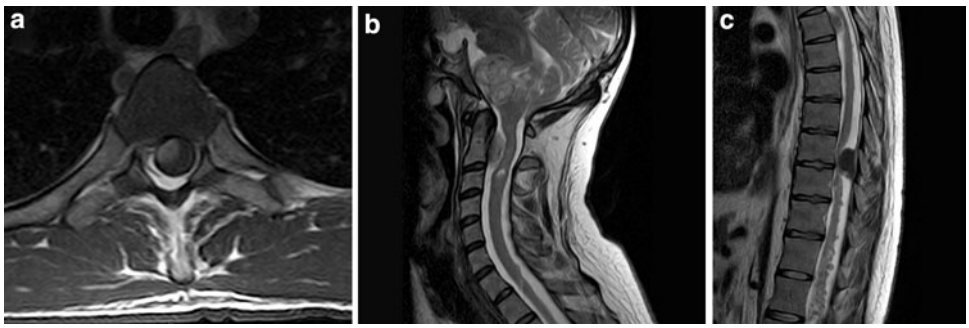

Fig. 2 MRI showing aspects of spinal meningiomas in NF2 patients. **a** axial T1-weighted sequence with Gadolinium enhancement showing a right anterior lateral thoracic meningioma compressing the spinal cord. **b**, **c** sagittal T2-weighted sequence (**b**) anterior C2 meningioma. Of note, an intra spinal cystic tumor corresponding to an associated spinal ependymoma (**c**) two thoracic meningiomas are shown in T5 and T9/10. Of note, multiple schwannomas are visible along the spinal roots

may result in failure of detection when the mutation level of that tissue is low. Somatic mosaicism is of clinical interest because it may correlate with a mild form associated with a favorable course of the disease; it may confound linkage testing of offspring, and decrease genetic risk to the next generation. Somatic mosaicism is frequent in NF2, affecting up to 33% of patients [18, 19], and may explain a mild phenotype in some patients [18, 20]. Risk of transmission to offspring is low in a somatic NF2 patient with a mutation only detectable in tumor [19]. Evans et al. found that 8% of multiple meningiomas in adult patients may be caused by mosaic *NF2* [21].

In contrast to mosaicism, data support the hypothesis that it is not rare that multiple meningiomas in the same patient share the same clonal origin. Larson et al. showed inactivation of the same X chromosome in every sample from the same patient and thus concluded that multiple meningiomas could arise from the uncontrolled spread of a single progenitor cell [22]. Studies addressing only *NF2* somatic mutations cannot differentiate *NF2* mosaicism from clonal spread of a meningioma across the meninges. Somatic mosaicism can be proven if the same *NF2* mutation is identified in two different tumor types (e.g. meningioma and schwannoma) or when the mutation found in a meningioma specimen is detected at a low level in blood sample [18].

Apart from *NF2*, other genes are probably involved in meningioma development. Few familial cases of multiple meningiomas have been reported with an autosomal dominant transmission. Two families with multiple meningiomas have been reported and provide evidence for a locus outside *NF2* involved in multiple meningiomas families. Pulst et al. [23] reported a family with multiple meningiomas and ependymomas in two generations. By linkage analysis with DNA markers known to flank the *NF2* locus, they excluded *NF2* as the candidate locus for the hereditary condition. Maxwell et al. [24] described a family with two members harboring meningiomas; NF2 protein immunoreactivity was present in meningioma samples, suggesting that alternate gene might be involved in tumorigenesis. Shen et al. analyzed by array comparative genomic hybridization the genomic profile of a large series of meningiomas, have recently confirmed this hypothesis. In contrast to sporadic meningiomas, they found that familial multiple meningiomas displayed no chromosomal imbalance events, supporting a distinct mechanism for the origin for these tumors [25]. Similarly to glioblastomas [26], whole genome sequencing of familial multiple meningiomas cases will help uncover new genes involved in meningioma genesis.

The most practical way to diagnose NF2 in multiple meningiomas patients, consist of a careful clinical examination with special emphasize on audiovestibular functions, skin examination, and slit lamp examination of the lens. The family history should be carefully investigated for previous surgery or symptoms suggestive of NF2. Cranial and spinal MRI is required and should include contrast medium injection and thin slices on cerebellopontine angles assessed by an experienced neuroradiologist [27]. Identifying the causative *NF2* mutation by blood or tumor DNA sequencing can definitely be helpful to diagnose NF2 or *NF2* mosaicism [28, 29]. The definitive diagnosis of *NF2* mosaicism requires tumor tissue, underscoring the need to bank tumors for patients who might desire genetic diagnosis in the future.

Meningiomas are rare in Neurofibromatosis type 1 (NF1) and schwannomatosis

NF1 (MIM 162200) is a dominantly inherited disorder characterized by the presence of café au lait spots, peripheral neurofibromas, plexiform neurofibromas, Lisch nodules, axillary freckling, skeletal dysplasia, and optic gliomas. The incidence of meningiomas in NF1 patients seems to be that of general population (1/523 in [30], 2/158 in [31]).

Schwannomatosis (MIM 162091) is characterized by the development of multiple spinal, peripheral, and cranial nerve schwannomas in the absence of vestibular schwannomas (which would otherwise classify patients as NF2) [32]. Although the condition can be difficult to clearly differentiate from NF2 [33], especially in younger patients, where vestibular schwannomas can develop secondarily, often in the second decade of life, few cases of schwannomatosis with associated meningiomas have been reported [34, 35]. Mutation of the *SMARCB1* gene on 22q seems to be responsible for at least one part of familial schwannomatosis [36]. Recently, Bacci et al. [37] reported a family segregating a germline mutation in *SMARCB1* exon 1 in four affected members: one member had multiple schwannomas, one multiple meningiomas and two with both schwannomas and meningiomas. It is therefore possible that meningiomas are an inconstant feature of *SMARCB1* mutation and could be part of the schwannomatosis tumor phenotype. To rule out the implication of *SMARCB1* in multiple meningiomas patients, Hadfield et al. screened the *SMARCB1* gene in a panel of 47 patients with multiple meningiomas unrelated to NF2. No *SMARCB1* germline mutation was found and they concluded that while meningiomas may be associated with the schwannomatosis phenotype, *SMARCB1* is not a major contributor to multiple meningiomas disease [34].

Meningioangiomatosis can occur in association with NF2

Meningioangiomatosis is a rare entity characterized by a plaque-like, cerebral hemispheric mass, most often involving the temporal and/or frontal lobes. Histologically, meningioangiomatosis consists of an intracortical and leptomeningeal collection of small blood vessels with perivascular spindled cells and variable degrees of cellularity, hyalinization, calcification, and even ossification. The intervening glioneuronal parenchyma appears mature but apparently disorganized, and reactive gliosis varies [38]. The majority (75–80% of cases) occurs sporadically and seizures are the most common symptoms. Twenty to 25% of meningioangiomatosis cases occur in association with NF2; they are often multifocal, associated or not with meningioma and are typically asymptomatic, with most cases identified as incidental autopsy finding. They should be considered in the differential diagnosis of cortical lesions in NF2 patients. It might be difficult to differentiate meningioangiomatosis associated with meningioma in NF2 patients from true brain invasion, which has a more severe prognosis in WHO 2007 classification.

Meningiomas can develop throughout the meninges in NF2, but may be less frequent at skull base

Perry et al. [11] reported a series of 53 meningiomas resected in 40 pediatric and/or NF2 patients (including 21 NF2 patients). The sites of origin of meningiomas were convexity and parasagittal in 49%, intraventricular in 13%, skull base in 6%, posterior fossa 9%, orbit/anterior pathways in 8%. Antinheimo et al. [9] reported a series of 39 meningiomas resected in 23 NF2 patients, both from Finland and Hannover. The site of origin of meningiomas was convexity and parasagittal in 38%, skull base in 25%, posterior fossa in 23%, and 2% optic nerve sheath. The higher rate of posterior fossa and skull base meningiomas in this latter series could be biased by specific center recruitment.

Specific locations that seem more frequent in NF2 patients than in sporadic cases include intraventricular meningiomas, usually in close contact with choroid plexus, often in the lateral ventricles, and optic nerve sheath meningiomas [7] that can affect both optic nerves [39].

Eight [11] to 10% [9] of resected meningiomas in NF2 patients are spinal. Spinal meningiomas can be difficult to radiologically distinguish from spinal schwannomas. In the series published by Mautner et al. [4], 89% of NF2 patients harbored spinal tumors on MRI, and 37% (7/19) of intradural extramedullary tumors were meningiomas on pathological examination. These data suggest that 1/3 NF2 patients may have spinal meningiomas.

Meningioma neuropathology might be different in NF2 than in sporadic cases

Data about pathology of NF2 associated meningiomas are sparse, and no specific NF2 features have been identified so far. Perry et al. [11] reported pathological features of 30 NF2 associated meningiomas (15 pediatrics, 15 adults). Nineteen meningiomas (63%) were grade II or III, suggesting that meningiomas associated with NF2 are more aggressive than sporadic meningiomas. The main histological subtypes were transitional (60%), meningothelial (20%), fibroblastic, papillary and rhabdoid (7% each). For comparison, in sporadic meningiomas, the frequencies of histological subtypes have been described as transitional (28%), meningothelial (53%), fibroblastic (8%) [40]. Similarly, search for somatic *NF2* mutations [41] or 22q loss [42] in sporadic meningiomas showed that meningothelial variants are often associated with unaltered *NF2*.

Antinheimo et al. [9] analyzed 35 NF2 patients' meningiomas and compared them to 30 sporadic meningiomas,

matched by age and gender. The most frequent histological subtypes in NF2 patients were transitional (53%), fibroblastic (30%), and meningothelial (17%). The high rate of fibroblastic meningiomas was also observed in the matched control group, suggesting that this difference in meningioma subtypes may reflect age-related differences rather than *NF2* gene-related differences. They did not observe specific histological feature that would distinguish NF2 meningiomas from the sporadic control tumors. They observed a higher proliferation potential of the NF2 meningiomas, suggesting a more aggressive behavior of NF2 tumors. In summary, meningiomas resected in NF2 patients are more frequently of the fibroblastic subtype, and they often display aggressive features on pathological examination. However, these findings are based on the analysis of resected tumors. The majority of meningiomas in NF2 patients remain under surveillance, and these slow growing tumors are probably less histologically aggressive than tumors requiring surgery.

At the molecular level, NF2 associated meningiomas seem to share with sporadic meningiomas a similar spectrum and frequency of allelic deletions. Lamszus et al. studied 30 meningiomas from 22 NF2 patients by microsatellite analysis, and found LOH involving 22q12, 1p, 10q, 6q, 14q, 18q, and 9p in 100, 40, 27, 24, 24, 23, and 17% of the tumors respectively [43].

Treatment of meningiomas in NF2

Data about long-term natural history of meningiomas in NF2 are sparse in the literature. Surgery remains the core of the treatment of growing and/or symptomatic meningiomas in NF2. To our knowledge, no paper focused on meningioma surgery in NF2 in the literature nor described the surgical results in terms of morbidity/mortality and recurrence.

Stereotactic radiosurgery is a controversial treatment of vestibular schwannomas in NF2 [44], and is now being extensively debated. In contrast, stereotactic radiosurgery has rarely been reported for meningiomas in NF2. Kondziolka et al. reported 6 NF2 patients treated by Gamma knife for convexity meningiomas in a larger series of 125 patients. They have found that poorer overall survival was associated with NF2 [45]. Wentworth et al. published a highly controversial paper [46] reporting their experience with radiation therapy in the management of NF2-associated meningiomas. They treated 49 meningiomas in 12 NF2 patients, claming that the majority of their patients presented asymptomatic lesions that showed growth on serial imaging, located in eloquent locations in which further growth would lead to morbidity. A major concern for many physicians is that radiosurgery and radiotherapy may induce malignant transformation and adjacent tumor development in NF2 patients, particularly if used in the case of multiple asymptomatic meningiomas [reviewed in 47].

Finally, Plotkin et al. have reported recently the reduction in the volume of most growing vestibular schwannomas after Bevacizumab in a small series of 10 NF2 patients [48]. No results have been reported regarding the efficiency on meningiomas in this series. New promising drugs have been identified as candidate [49] in NF2 associated meningiomas, and have to be evaluated in clinical trials after validation in preclinical models [50, 51].

Conclusion

Meningiomas occur in about half NF2 patients, and are often multiple. NF2 and somatic mosaic *NF2* should be ruled out in multiple meningiomas patients by detailed clinical and radiological examination; frozen samples should be preserved during tumor removal to search for somatic *NF2* mutation. Meningiomas in NF2 patients are associated with a higher risk of mortality, and their treatment is challenging, but data about natural history of meningiomas in NF2 patients are sparse in the literature. Knowledge of tumor behavior is essential in slow growing tumors like meningiomas, to balance the risk of treatment against the natural history of the disease, and to evaluate the efficiency of alternative therapeutics (radiation therapy or new drugs). Further efforts are needed to delineate the best treatment modality and timing.

References

1. Evans DG, Howard E, Giblin C, Clancy T, Spencer H, Huson SM, Lalloo F (2010) Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service. Am J Med Genet A 152A:327–332
2. Evans DG, Huson SM, Donnai D, Neary W, Blair V, Newton V, Harris R (1992) A clinical study of type 2 neurofibromatosis. Q J Med 84:603–618
3. Parry DM, Eldridge R, Kaiser-Kupfer MI, Bouzas EA, Pikus A, Patronas N (1994) Neurofibromatosis 2 (NF2): clinical characteristics of 63 affected individuals and clinical evidence for heterogeneity. Am J Med Genet 52:450–461
4. Mautner VF, Lindenau M, Baser ME, Hazim W, Tatagiba M, Haase W, Samii M, Wais R, Pulst SM (1996) The neuroimaging and clinical spectrum of neurofibromatosis 2. Neurosurgery 38:880–885
5. Drouet A, Créange A (2005) Polyneuropathy associated with neurofibromatosis. Rev Neurol (Paris) 161:275–283
6. McLaughlin ME, Pepin SM, Maccollin M, Choopong P, Lessell S (2007) Ocular pathologic findings of neurofibromatosis type 2. Arch Ophthalmol 125:389–394
7. Bosch MM, Boltshauser E, Harpes P, Landau K (2006) Ophthalmologic findings and long-term course in patients with neurofibromatosis type 2. Am J Ophthalmol 141:1068–1077

8. Otsuka G, Saito K, Nagatani T, Yoshida J (2003) Age at symptom onset and long-term survival in patients with neurofibromatosis Type 2. J Neurosurg 99:480–483
9. Antinheimo J, Haapasalo H, Haltia M, Tatagiba M, Thomas S, Brandis A, Sainio M, Carpen O, Samii M, Jääskeläinen J (1997) Proliferation potential and histological features in neurofibromatosis 2-associated and sporadic meningiomas. J Neurosurg 87:610–614
10. Ruggieri M, Iannetti P, Polizzi A, Mantia IL, Spalice A, Giliberto O, Platania N, Gabriele AL, Albanese V, Pavone L (2005) Earliest clinical manifestations and natural history of neurofibromatosis type 2 (NF2) in childhood: a study of 24 patients. Neuropediatrics 36:21–34
11. Perry A, Giannini C, Raghavan R, Scheithauer BW, Banerjee R, Margraf L, Bowers DC, Lytle RA, Newsham IF, Gutmann DH (2001) Aggressive phenotypic and genotypic features in pediatric and NF2-associated meningiomas: a clinicopathologic study of 53 cases. J Neuropathol Exp Neurol 60:994–1003
12. Germano IM, Edwards MS, Davis RL, Schiffer D (1994) Intracranial meningiomas of the first two decades of life. J Neurosurg 80:447–453
13. Evans DG, Birch JM, Ramsden RT (1999) Paediatric presentation of type 2 neurofibromatosis. Arch Dis Child 81:496–499
14. Rochat P, Johannesen HH, Gjerris F (2004) Long-term follow up of children with meningiomas in Denmark: 1935 to 1984. J Neurosurg 100:179–182
15. Rushing EJ, Olsen C, Mena H, Rueda M-E, Lee Y-S, Keating RF, Packer RJ, Santi M (2005) Central nervous system meningiomas in the first two decades of life: a clinicopathological analysis of 87 patients. J Neurosurg 103:489–495
16. Baser ME, Friedman JM, Aeschliman D, Joe H, Wallace AJ, Ramsden RT, Evans DGR (2002) Predictors of the risk of mortality in neurofibromatosis 2. Am J Hum Genet 71:715–723
17. Antinheimo J, Sankila R, Carpén O, Pukkala E, Sainio M, Jääskeläinen J (2000) Population-based analysis of sporadic and type 2 neurofibromatosis-associated meningiomas and schwannomas. Neurology 54:71–76
18. Kluwe L, Mautner V, Heinrich B, Dezube R, Jacoby LB, Friedrich RE, MacCollin M (2003) Molecular study of frequency of mosaicism in neurofibromatosis 2 patients with bilateral vestibular schwannomas. J Med Genet 40:109–114
19. Moyhuddin A, Baser ME, Watson C, Purcell S, Ramsden RT, Heiberg A, Wallace AJ, Evans DGR (2003) Somatic mosaicism in neurofibromatosis 2: prevalence and risk of disease transmission to offspring. J Med Genet 40:459–463
20. Evans DG, Wallace AJ, Wu CL, Trueman L, Ramsden RT, Strachan T (1998) Somatic mosaicism: a common cause of classic disease in tumor-prone syndromes? Lessons from type 2 neurofibromatosis. Am J Hum Genet 63:727–736
21. Evans DGR, Watson C, King A, Wallace AJ, Baser ME (2005) Multiple meningiomas: differential involvement of the NF2 gene in children and adults. J Med Genet 42:45–48
22. Larson JJ, Tew JM, Simon M, Menon AG (1995) Evidence for clonal spread in the development of multiple meningiomas. J Neurosurg 83:705–709
23. Pulst SM, Rouleau GA, Marineau C, Fain P, Sieb JP (1993) Familial meningioma is not allelic to neurofibromatosis 2. Neurology 43:2096–2098
24. Maxwell M, Shih SD, Galanopoulos T, Hedley-Whyte ET, Cosgrove GR (1998) Familial meningioma: analysis of expression of neurofibromatosis 2 protein Merlin Report of two cases. J Neurosurg 88:562–569
25. Shen Y, Nunes F, Stemmer-Rachamimov A, James M, Mohapatra G, Plotkin S, Betensky RA, Engler DA, Roy J, Ramesh V, Gusella JF (2009) Genomic profiling distinguishes familial multiple and sporadic multiple meningiomas. BMC Med Genomics 2:42
26. Parsons DW, Jones S, Zhang X, Lin JC-H, Leary RJ, Angenendt P et al (2008) An integrated genomic analysis of human glioblastoma multiforme. Science 321:1807–1812
27. Slattery WH, Lev MH, Fisher LM, Connell SS, Iqbal Z, Go JL (2005) NF2 Natural History Consortium MRI evaluation of neurofibromatosis 2 patients: a standardized approach for accuracy in interpretation. Otol Neurotol 26:733–740
28. Mohyuddin A, Neary WJ, Wallace A, Wu CL, Purcell S, Reid H, Ramsden R, Read A, Black G, Evans DGR (2002) Molecular genetic analysis of the NF2 gene in young patients with unilateral vestibular schwannomas. J Med Genet 39:315–322
29. Evans DGR, Ramsden RT, Gokhale C, Bowers N, Huson SM, Wallace A (2007) Should NF2 mutation screening be undertaken in patients with an apparently isolated vestibular schwannoma? Clin Genet 71:354–358
30. McGaughran JM, Harris DI, Donnai D, Teare D, MacLeod R, Westerbeek R, Kingston H, Super M, Harris R, Evans DG (1999) A clinical study of type 1 neurofibromatosis in north west England. J Med Genet 36:197–203
31. Créange A, Zeller J, Rostaing-Rigattieri S, Brugières P, Degos JD, Revuz J, Wolkenstein P (1999) Neurological complications of neurofibromatosis type 1 in adulthood. Brain 122:473–481
32. MacCollin M, Woodfin W, Kronn D, Short MP (1996) Schwannomatosis: a clinical and pathologic study. Neurology 46:1072–1079
33. MacCollin M, Chiocca EA, Evans DG, Friedman JM, Horvitz R, Jaramillo D, Lev M, Mautner VF, Niimura M, Plotkin SR, Sang CN, Stemmer-Rachamimov A, Roach ES (2005) Diagnostic criteria for schwannomatosis. Neurology 64:1838–1845
34. Hadfield KD, Smith MJ, Trump D, Newman WG, Evans DG (2010) SMARCB1 mutations are not a common cause of multiple meningiomas. J Med Genet. doi:10.1136/jmg.2009.075721
35. Boyd C, Smith MJ, Kluwe L, Balogh A, Maccollin M, Plotkin SR (2008) Alterations in the SMARCB1 (INI1) tumor suppressor gene in familial schwannomatosis. Clin Genet 74:358–366
36. Hulsebos TJM, Plomp AS, Wolterman RA, Robanus-Maandag EC, Baas F, Wesseling P (2007) Germline mutation of INI1/SMARCB1 in familial schwannomatosis. Am J Hum Genet 80:805–810
37. Bacci C, Sestini R, Provenzano A, Paganini I, Mancini I, Porfirio B, Vivarelli R, Genuardi M, Papi L (2010) Schwannomatosis associated with multiple meningiomas due to a familial SMARCB1 mutation. Neurogenetics 11:73–80
38. Perry A, Kurtkaya-Yapicier O, Scheithauer BW, Robinson S, Prayson RA, Kleinschmidt-DeMasters BK, Stemmer-Rachamimov AO, Gutmann DH (2005) Insights into meningioangiomatosis with and without meningioma: a clinicopathologic and genetic series of 24 cases with review of the literature. Brain Pathol 15:55–65
39. Cunliffe IA, Moffat DA, Hardy DG, Moore AT (1992) Bilateral optic nerve sheath meningiomas in a patient with neurofibromatosis type 2. Br J Ophthalmol 76:310–312
40. Kolles H, Niedermayer I, Schmitt C, Henn W, Feld R, Steudel WI, Zang KD, Feiden W (1995) Triple approach for diagnosis and grading of meningiomas: histology morphometry of Ki-67/Feulgen stainings and cytogenetics. Acta Neurochir (Wien) 137:174–181
41. Wellenreuther R, Kraus JA, Lenartz D, Menon AG, Schramm J, Louis DN, Ramesh V, Gusella JF, Wiestler OD, von Deimling A (1995) Analysis of the neurofibromatosis 2 gene reveals molecular variants of meningioma. Am J Pathol 146:827–832
42. Kros J, de Greve K, van Tilborg A, Hop W, Pieterman H, Avezaat C, Deprez RLD, Zwarthoff E (2001) NF2 status of

meningiomas is associated with tumour localization and histology. J Pathol 194:367–372
43. Lamszus K, Vahldiek F, Mautner VF, Schichor C, Tonn J, Stavrou DF et al (2000) Allelic losses in neurofibromatosis 2-associated meningiomas. J Neuropathol Exp Neurol 59:504–512
44. Mathieu D, Kondziolka D, Flickinger JC, Niranjan A, Williamson R, Martin JJ, Lunsford LD (2007) Stereotactic radiosurgery for vestibular schwannomas in patients with neurofibromatosis type 2: an analysis of tumor control complications and hearing preservation rates. Neurosurgery 60:460–470
45. Kondziolka D, Madhok R, Lunsford LD, Mathieu D, Martin JJ, Niranjan A, Flickinger JC (2009) Stereotactic radiosurgery for convexity meningiomas. J Neurosurg 111:458–463
46. Wentworth S, Pinn M, Bourland JD, Deguzman AF, Ekstrand K, Ellis TL, Glazier SS, McMullen KP, Munley M, Stieber VW, Tatter SB, Shaw EG (2009) Clinical experience with radiation therapy in the management of neurofibromatosis-associated central nervous system tumors. Int J Radiat Oncol Biol Phys 73:208–213
47. Evans DGR, Birch JM, Ramsden RT, Sharif S, Baser ME (2006) Malignant transformation and new primary tumours after therapeutic radiation for benign disease: substantial risks in certain tumour prone syndromes. J Med Genet 43:289–294
48. Plotkin SR, Stemmer-Rachamimov AO, Barker FG, Halpin C, Padera TP, Tyrrell A, Sorensen AG, Jain RK, di Tomaso E (2009) Hearing improvement after bevacizumab in patients with neurofibromatosis type 2. N Engl J Med 361:358–367
49. Evans DG, Kalamarides M, Hunter-Schaedle K, Blakeley J, Allen J, Babovic-Vuskanovic D et al (2009) Consensus recommendations to accelerate clinical trials for neurofibromatosis type 2. Clin Cancer Res 15:5032–5039
50. Kalamarides M, Niwa-Kawakita M, Leblois H, Abramowski V, Perricaudet M, Janin A, Thomas G, Gutmann DH, Giovannini M (2002) Nf2 gene inactivation in arachnoidal cells is rate-limiting for meningioma development in the mouse. Genes Dev 16: 1060–1065
51. Kalamarides M, Stemmer-Rachamimov AO, Takahashi M, Han ZY, Chareyre F, Niwa-Kawakita M, Black PM, Carroll RS, Giovannini M (2008) Natural history of meningioma development in mice reveals: a synergy of Nf2 and p16(Ink4a) mutations. Brain Pathol 18:62–70