The Genetics of Vestibular Schwannoma

Adam T. Hexter · D. Gareth Evans

Abstract Vestibular Schwannoma (VS) results from mutations/deletions of both copies of the *NF2* gene on chromosome of 22q12, with lifetime risk estimated at one in 1,000. Bilateral VS is the hallmark of the autosomal dominant inherited tumour predisposition syndrome Neurofibromatosis type 2 (NF2), but the majority of VS are due to sporadic mutations. Estimations indicate that 33 % of de novo patients with bilateral VS and up to 60 % with unilateral VS have mosaicism for an *NF2* mutation. Hundreds of mutations of the *NF2* gene have been described, with truncating mutations (nonsense and frameshifts) leading to a severe phenotype. Despite advances in understanding, the relation between the genotype and phenotype in VS is not fully understood and the mechanisms leading to inactivation of the *NF2* gene have not been fully characterised. As the genetics underlying VS is increasingly demystified targeted therapies offer hope in cases of progressive VS where existing treatment fails.

Keywords Vestibular Schwannoma · Genetics · Neurofibromatosis type 2 · NF2 gene · Mutation · Genotype–phenotype correlation

A. T. Hexter (✉) · D. G. Evans
Department of Genetic Medicine, Manchester Centre for Genomic Medicine, Manchester Academic Health Sciences Centre (MAHSC), University of Manchester, 6th Floor St Mary's Hospital, Oxford Road, Manchester M13 9WL, UK
e-mail: adam.hexter@cmft.nhs.uk

D. G. Evans
e-mail: gareth.evans@cmft.nhs.uk

Introduction

Vestibular Schwannomas (VS) are benign tumours of the Schwann cell sheath arising from the vestibular branch of the eighth cranial nerve [1]. They have previously been referred to as "acoustic neuromas", reflecting the common clinical manifestation of hearing impairment. Nevertheless these lesions are not neuromas and the term VS more accurately reflects the tumour's cell and nerve of origin. There has been debate regarding the exact incidence of VS, and common wisdom is that the recent rising incidence represents improved detection of VS. The population incidence in the North West of England was recently estimated as being between 1 in 80–100,000 per year, representing a lifetime risk of around one in 1,000 [2].

Neurofibromatosis type 2 (NF2), also previously referred to as central neurofibromatosis or bilateral acoustic neurofibromatosis, is an inherited multiple neoplasia syndrome with the hallmark being development of bilateral VS [3]. The birth incidence of NF2 is 1 in 33–40,000 [4]. NF2 patients can develop numerous nervous system tumours including Schwannomas, meningiomas, ependymomas, astrocytomas, and neurofibromas. In addition patients can develop peripheral neuropathy, ophthalmic pathology (cataracts, retinal hamartomas) and cutaneous tumours [5]. NF2, the first case of which was reported in 1822 by Wishart [6], typically presents between the ages of 16–30 as a result of the pressure effects of VS, classically with unilateral hearing impairment, tinnitus or imbalance. However, the presentation of NF2 in childhood is more likely to be related to non-VS lesions [7], such as cutaneous or visual manifestations. Only 5 % of VS cases are associated with NF2 [3], with the vast majority of cases due to sporadic mutations. NF2 remains a devastating diagnosis with substantial morbidity and despite advancements in

imaging modalities and surgical techniques, over 90 % of NF2 patients die early either from the disease or the effects of its treatment [8].

Neurofibromatosis type 1 (NF1), previously known as von Recklinghausen's disease, is a genetically and phenotypically distinct syndrome with autosomal dominance inheritance. NF1 occurs as a result of genetic abnormalities of the *NF1* gene on chromosome 17q11 [9]. Clinical features are diverse and include café-au-lait spots, Lisch nodules, optic pathway gliomas, bony dysplasia and cutaneous neurofibromas. VS do not form part of the NF1 diagnosis and do not occur at increased frequency. In 1987 the formal delineation between NF1 and NF2 was defined at the National Institutes of Health consensus meeting [10].

In this review we discuss current knowledge of the genetics of VS. We focus on recent developments in understanding and explore the controversial discoveries and current hypotheses of interest.

Search for the Gene

The *NF2* gene was first identified in 1993 following extensive genetic mapping. Seizinger et al. [11] studied the DNA of patients with unilateral VS using polymorphic DNA markers and found that loss of constitutional heterozygosity was commonly seen in NF2 patients. Seizinger later reinforced the finding of loss of genes in chromosome 22 in patients with VS and other NF2-related tumours [12]. This led to the subsequent chromosomal localisation of the *NF2* gene to the centre of the long arm of chromosome 22 and then its cloning simultaneously by two separate groups: Trofatter et al. [13] and Rouleau et al. [14]. Specifically the *NF2* gene resides on chromosome 22, band 22q12.2, from nucleotide 29999545 to 30094589. The gene's promoter region and major transcription initiation site have subsequently been described [15].

The gene product is a 69 kDa protein that forms part of the band 4.1 family of cytoskeleton-associated proteins known as ERM proteins [13, 14]. The gene product has most commonly been referred to as Merlin, reflecting an acronym of the first letters of moesin-, ezrin-, radixin-like protein [13]. Merlin has 595 amino acids with three functional domains: an amino terminal domain (exons 1–9), an α helical domain (exons 10–13), and a carboxy terminal domain (exons 14–17) [16]. Hence the *NF2* gene consists of 17 exons and with the effect of alternative splicing it has two predominant isoforms. Merlin is expressed ubiquitously in human tissues, but there is considerable expression in the Schwann cell plasma membrane, meningeal cells and neuronal tissue [17]. Unlike other ERM proteins

that generally function to facilitate growth, Merlin has been shown to have an important suppressive role in the regulation of cell proliferation [18]. The regulation of Merlin itself is by phosphorylation, with phosphorylation by kinases causing inactivation of Merlin; whereas dephosphorylation by phosphatases allows Merlin to adopt its active state [18].

Inheritance Pattern

Gardner and Frazier [19] first demonstrated that NF2 has an autosomal dominant transmission in 1930 in a family of 38 affected members spanning five generations. The *NF2* gene is a tumour suppressor gene and only when both alleles of the gene are inactivated will tumours form. To develop the disease an affected patient only has to have a mutation in one copy of the *NF2* gene because the likelihood of a second hit in a Schwann cell particularly on the vestibular nerve appears extremely high. Patients who develop VS can either have inherited a germline mutation of one affected allele (inherited NF2) or alternatively acquire a de novo mutation of an allele that is not inherited. Tumours occur in cells that experience silencing in both copies of *NF2*, specifically in the wild type *NF2* allele in someone with NF2. The susceptible target organs are those with high Merlin expression. NF2 has extremely high penetrance by 60 years of age [20], which means a patient who inherits an abnormal copy of the *NF2* gene will nearly always develop clinical NF2 by the age of 60. Approximately half of NF2 cases have no family history, and they signify new germline mutations that were not inherited [20]. This has fundamental implications on the risk of vertical transmission. Transmission from parents with an inherited germline mutation has an autosomal dominant inheritance pattern and the likelihood is therefore 50 %. However, the risk of transmission of those with a de novo mutation is substantially lower. In cases of de novo neurofibromatosis type 2 and negative blood mutation analysis, a recent study revealed transmission rates of 1 in 8 for patients with bilateral VS and 1 in 12 for patients with unilateral VS [21]. The risk decreases further if the age of onset of symptoms is older [22]. Unilateral isolated VS are usually due to sporadic mutations whereas bilateral VS are practically always due to NF2. There is nonetheless a 1 in 2 million chance that an individual could develop bilateral VS by chance [23] in their lifetime, equating to approximately 30 people in the UK and 150 in the USA alive today. Sporadic VS tend to grow slowly and has an older age of onset when compared with NF2-associated VS, which occur in younger patients and exhibits faster rates of growth.

Mosaicism

The presence of a mutation or chromosomal abnormality in a subpopulation of cells is referred to as mosaicism [24]. This scenario results from a de novo mutation of an allele at the post-zygotic stage of embryogenesis, thus generating two distinct cell lineages. In 1995 Bourn et al. [25] made the first report of mosaicism in the *NF2* gene. The investigators observed that the mild phenotype was associated with the warm spot alteration 169C>T in approximately 10 % of blood cells of a mosaic patient compared with a non-mosaic patient displaying a severe phenotype with the identical mutation. The clinical severity in mosaic NF2 is related to the time when the mutation took place during development. Early mutations result in more cells being affected and consequently are associated with a more severe phenotype. Generally patients with mosaicism display a mild phenotype, with either localised or mild generalised disease [21].

One of the characteristics of NF2 is the high rate of mosaicism amongst de novo cases. Reports have suggested that 33 % of de novo patients who present with bilateral VS and up to 60 % of such patients who present with unilateral VS have mosaicism [24]. Kluwe et al. [26] showed the rate of mosaicism to be at least 24.8 % in a cohort of 233 NF2 patients with bilateral VS. In approximately half of mosaics the mutation is detectable in blood lymphocytes, whereas in the remainder the genetic abnormality is only detectable upon tumour tissue analysis. The asymmetric presentation of NF2 is a classical feature of mosaicism if the mutation cannot be detected in their blood cells. However, individuals presenting with unilateral VS at a young age might well have mosaicism for NF2 and later go on to develop full-blown NF2 [27, 28]. This is important to bear in mind when counselling patients with unilateral VS about the risks of developing additional tumours.

Unlike germline NF2, the risk of transmitting NF2 in mosaic patients to offspring is negligible. In the unlikely event that an *NF2* mutation is inherited from a mosaic parent the child will host the mutation in all their cells and will develop a severe phenotype. Some reports have suggested a degree of anticipation in NF2 [29]. This most likely represents cases where mosaic patients have transmitted the disease to their offspring, who subsequently develop a severe phenotype. Hence there remains minimal evidence for anticipation in NF2.

Mutational Spectrum of *NF2*

The loss of 22q12 locus harbouring the *NF2* gene is the only genetic alteration reported in both sporadic and NF2-associated VS [13, 14]. The fact that the majority of NF2 cases are sporadic highlights the high mutation rate of *NF2*, a gene also implicated in the tumourigenesis of meningiomas and other non-VS tumours [30, 31]. There has been considerable progression in our understanding of what mutations occur in the *NF2* gene and mutation analysis techniques have identified hundreds of possible mutations [32]. The frequencies of the different types of mutations in our database [33] at the time of writing can be seen in Table 1, with the commonest type being point mutations and complex rearrangements (large single or multi-exon

Table 1 Mutations found in germline and tumour in the Manchester (UK) genetics laboratory

	NF2 VS first hit (germline)	NF2 VS second hit	Sporadic VS first hit	Sporadic VS second hit
Point mutations				
Nonsense	155 (29 %)	3 (2.0 %)	29 (22 %)	3 (2.5 %)
Frameshift insertions/deletions	125 (25 %)	9 (6.0 %)	37 (28 %)	7 (5.5 %)
Missense	24 (4.5 %)	0	1 (7.5 %)	1 (1 %)
In-frame deletions	5 (1.0 %)	0	1 (7.5 %)	0
Splice site	115 (22 %)	5 (3.5 %)	13 (10 %)	3 (2.5 %)
Large rearrangements				
Ring 22	3 (0.5 %)	NA[a]	NA[a]	NA[a]
Chromosome translocation	2 (0.5 %)	NA[a]	NA[a]	NA[a]
MLPA exon/multiexon deletions/duplications	102 (19 %)	3 (2.0 %)	2 (1.5 %)	2 (1.5 %)
Loss of chromosome 22q or most all chromosome	0	80 (55 %)	0	70 (53 %)
Mitotic recombination	0	20 (14 %)	0	9 (7.0 %)
Methylation	0	0	0	0
Total	$n = 531$	$n = 146$	$n = 131$	$n = 131$

[a] Karyotypic analysis is required for this measurement but this has not yet been performed on tumours. The order of mutations in sporadic VS cannot be determined with certainty but is assumed to be a point mutation first if one is present

deletions and duplications). Balanced chromosomal ($n = 2$) translocations that disrupt the *NF2* gene have also been described as causing NF2 but in general such gross chromosomal changes are uncommon [34]. Ring 22 is another inherited defect that can lead to NF2 [34, 35] and it is classically associated with mental retardation. Loss of heterozygosity (LOH) is a common feature found in the majority of sporadic Schwannomas. Loss of function of the second copy of the *NF2* gene may occur by the same point mutations that occur in the germline, by large single or multi-exon deletions or duplications, by loss of the whole chromosome 22 or 22q12 locus, or by mitotic recombination (both the latter events cause LOH) [36].

Genotype–Phenotype Correlations

The disease severity of NF2 has traditionally been divided into subgroups depending on the age of onset of symptoms and the presence of non-VS intracranial and spinal tumours. The age of onset and age of diagnosis have been shown to be the two most important predictors of growth rates of VS in NF2 [8]. The severe "Wishart" form of NF2 is associated with an early age of onset, rapid course and numerous non-VS intracranial and spinal tumours in addition to bilateral VS [6]. The mild "Gardner" form describes a less aggressive type of NF2, associated with a later age of onset and a lower incidence of intracranial tumours [19].

Considerable effort has been made to establish correlations between specific mutations and specific phenotypes (Table 2). Early reports showed that missense mutations, large deletions and in-frame mutations are typically associated with the milder form of disease [37]. Somatic mosaicism is also associated with a mild phenotype. However, frameshift mutations and nonsense mutations that result in truncation of the *NF2* gene product are associated with a more severe phenotype, thought to be due to the formation of a smaller and non-functional protein product [37]. Truncating mutations are seen more frequently in mosaic patients than in inherited cases, something that has been attributed to the reduced genetic fitness of inherited cases. Likewise the so-called milder mutations, such as missense mutations, are rarely seen in mosaic individuals but are relatively frequent in inherited cases [38]. In one of the first large-scale studies [39] into genotype–phenotype correlations 42 patients with classical NF2 resulting from truncating mutations had an average age of onset of symptoms at 19 years and a diagnosis at 22.4 years compared with an average age of onset of symptoms at 27.8 years and a diagnosis at 23.4 years seen

Table 2 Leading reports of genotype–phenotype correlations in NF2

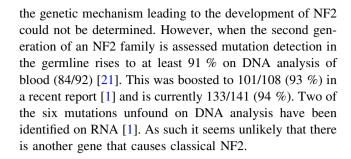| Study	No. NF2 patients	Genotype–phenotype correlation observed
Merel [70]	91 unrelated	Mutations that preserved the carboxy terminal domain were associated with a mild phenotype
Kluwe [71]	59 unrelated	Frameshift and nonsense mutations were associated with a more severe phenotype than missense mutations
Ruttledge [72]	111 (73 families)	Truncating mutations typically exhibited more severe phenotypes and had poorer clinical outcomes
Parry [73]	32 unrelated patients	Nonsense/frameshift mutations were associated with a higher frequency and number of tumours and a younger age at onset and diagnosis
Kluwe [24]	16 inherited, 91 sporadic	Identification of mutations in sporadic NF2 is more likely in patients with severe phenotypes when compared with mild phenotypes ($p = 0.007$)
Kluwe [74]	87 unrelated patients	Mutations downstream from exon 8 in the *NF2* gene were associated with milder phenotypes
Evans [39]	142 families	Truncating mutations demonstrated a younger age at onset ($p < 0.001$) and were more likely to have symptomatic non-VS tumours ($p < 0.001$)
Patronas [40]	49	Nonsense and frameshift mutations were associated with a higher mean frequency of intramedullary and spinal canal tumours ($p < 0.001$)
Baser [75]	18 (inherited)	Growth rates of VS were not affected by mutation type
Baser [8]	368 (261 families)	Constitutional missense mutations were associated with a lower risk of mortality when compared with all other mutation types
Baser [76]	406	Nonsense or frameshift mutations were associated with a higher number of tumours than other mutation types
Baser [41]	831 (528 families)	Splice-site mutations located in exons 1–5 were associated with a more severe phenotype than mutations in exons 11–15
Selvanathan [38]	268	Truncating mutations were associated with a more severe phenotype, reflected by a younger age of VS diagnosis ($p = 0.007$) and a higher prevalence of non-VS tumours ($p < 0.006$)
Smith [31]	411	The position of the NF2 mutation affected occurrence of cranial meningiomas: cumulative risk to age 50 years was 70 % for exons 1–3 compared with 28 % for exons 14–15

in 51 patients with missense, large deletion or splice-site mutations. Truncating mutations have been associated with a higher prevalence of meningioma when compared with missense and splice-site mutations [38]. Patronas et al. [40] found that truncating and nonsense mutations are associated with increased prevalence of spinal tumours when they performed MRI spines in 49 patients with NF2. These genotype–phenotype correlations correspond to the relative risk of mortality for different mutations, with nonsense or frameshift mutations having a higher mortality than missense mutations [8].

Smith et al. [31] investigated the genetic aberrations in a cohort of 411 NF2 patients, which indicated that the location of the mutation in the NF2 gene affected the likelihood of meningioma and this was true across all mutation types. The cumulative risk of cranial meningioma to age 50 years was 70 % for exons 1–3 compared with 28 % for exons 14–15. The authors argued that this positional effect provides evidence that not all truncated products are nonfunctional. Baser et al. [41] evaluated genotype–phenotype correlations in 831 patients from 528 NF2 families with constitutional NF2 mutations and observed a positional effect, with splice-site mutations in exons 11–15 appearing to be associated with less severe disease and younger age at onset of symptoms than mutations in exons 1–5. However, splice-site mutations are generally thought to have a less predictable correlation with phenotype than other types of mutations. Despite these recognised trends, there have been conflicting reports that break the norm. Large deletions that involve the whole NF2 gene have been identified in patients with mild phenotypes yet simple missense and frameshift mutations have been observed in severely affected cases [42]. Hence there is no "one-size-fits-all" rule with genotype–phenotype correlations and other mechanisms must be involved in the inactivation of the NF2 gene and determining the phenotype severity. This notion is further supported by reports of phenotypic variability within NF2 families hosting the same mutation [43] and monozygotic twins harbouring the same mutation but showing distinct variations in phenotype [44]. Bruder et al. [45] proposed the presence of a "modifier gene" being a possible mechanism for inactivation of the NF2 gene, when they observed that deletions in people with the severe form of NF2 often extended onto the telomeric side to the NF2 gene, whereas patients with mild phenotypes had mutations that were limited to the NF2 locus itself.

Is NF2 the Only Gene?

Zucman-Rossi et al. [46] carried out extensive genetic analysis of 19 patients with VS but identified mutations in only 84 % of patients. In the remaining 16 % of patients

the genetic mechanism leading to the development of NF2 could not be determined. However, when the second generation of an NF2 family is assessed mutation detection in the germline rises to at least 91 % on DNA analysis of blood (84/92) [21]. This was boosted to 101/108 (93 %) in a recent report [1] and is currently 133/141 (94 %). Two of the six mutations unfound on DNA analysis have been identified on RNA [1]. As such it seems unlikely that there is another gene that causes classical NF2.

Mechanisms of Gene Inactivation

There are notable similarities and differences between the distribution and type of germline and somatic NF2 mutations (Table 1). The first hit in the germline and in sporadic VS is usually a point mutation (nonsense, frameshift deletion/insertion, splice-site in-frame deletion or missense mutation). However, large single or multi-exon deletions are common, especially in the germline. Second hits are typically chromosome loss events but this can also occur by mitotic recombination without genetic material loss where a mutation is doubled up on each copy of chromosome 22. Finally methylation appears to occur in at least a proportion of sporadic VS.

A recent report showed that nonsense mutations are more common than frameshift mutations by a ratio of 1.3:1 when analysing germline mutations of the NF2 gene. However, analysis of somatic mutations reveals a reversal of this ratio [47]. When considering NF2 nonsense mutations in both scenarios, the most frequently observed single base-pair transitions is C>T. With regards to sporadic meningioma, there is a notable absence of mutations in exons 14 and 15, and mutations in this region correlate with a considerably lower meningioma risk in NF2 [31]. A recently reported mutational mechanism is the increasing change from predominance of nonsense mutations in the germline and early somatic mutations to a preponderance of frameshift mutations in the tumours of older patients with sporadic VS [47]. This age-related shift in the mutation spectra of germline is likely to represent deficiencies in certain DNA repair pathways in older individuals [47]. Although the great majority if not all VS development requires inactivation of the NF2 gene, there has been no report to date that demonstrates 100 % involvement of NF2, with aberrations confirmed in both copies of the gene. One possible reason for this is the heterogeneity of mechanisms that can lead to inactivation of the NF2 gene. Involvement of the NF2 can be detected in approximately 80–90 % of Schwannomas when using conventional approaches of mutational analysis of sequencing and LOH. However, such approaches detect aberrations of both NF2 genes in only 50–60 % of cases. Similarly there are diverse

mechanisms for LOH inactivation, with most instances demonstrating loss of chromosome 22 (or at least its long arm) but some cases have been shown to result from mitotic recombination [36, 47]. Indeed NF2 inactivation in Schwannomatosis is now thought to be partly due to mitotic recombination.

Another hypothesised mechanism for *NF2* inactivation is epigenetic modifications, such as hypermethylation [48, 49]. Gonzalez Gomez et al. [48] examined the DNA methylation profile of Schwannomas in 44 sporadic or NF2-associated Schwannomas using methylation-specific PCR. They identified 5 tumour-related genes most frequently methylated in VS cases that were unaffected in non-VS controls. The finding that the 5′ and 3′ flanking regions of the human *NF2* locus are G/C rich and potential sites for gene methylation and inactivation adds weight to the possibility of epigenetic factors playing a role in VS tumourigenesis. Methylation in a manner such as that described for TP16 could involved both copies of NF2, which would account for the reason why some tumours do not exhibit point mutations or LOH on standard approaches of mutational analysis.

Until recently VS was considered an exclusion criteria for the related condition Schwannomatosis [50]. However, recent evidence suggests that VS can indeed be a feature of Schwannomatosis [51•]. The identification of mutations in the *LZTR1* gene on 22q has now shown that this gene may predispose to the development of VS [52]. Findings such as these make it appear increasingly likely that there are other tumour suppressor genes of 22q that have a role in the formation of VS. Future work must focus on discovering these genes and ascertaining how they play a role in the tumourigenesis of VS and other non-VS tumours.

Although *NF2* loss is the fundamental driver of VS formation it is likely from mouse and human modelling that further hits in other genes are necessary and that a simple two hit cause is insufficient [53]. Chromosome and genomic array studies have shown low levels of loss and gain of material apart from 22q [54] and expression arrays have shown a variety of aberrant expression. MET and associated genes, such as integrin, alpha 4 (ITGA4)/B6, PLEXNB3/SEMA5 and caveolin-1 (CAV1) showed patterns of deregulation in VS. Additionally, androgen receptor (AR) down-regulation may denote a hormonal effect or cause in VS. The osteopontin gene (SPP1), which is involved in merlin protein degradation, was up-regulated in some tumours [55].

Targeted Therapy in VS

With the emergence of the era of targeted therapies in oncology, there has been increasing interest into the molecular mechanisms underlying VS tumourigenesis. The functions of the Merlin are becoming increasingly characterised. Merlin is known to play a role in three important processes: firstly cell-to-cell adhesion via interaction with proteins such as β1 integrin and β catenin; secondly membrane organisation via effects on proteins such as CD44 and the epidermal growth factor receptor (EGFR); and finally influencing intracellular pathways via cytosolic proteins such as phosphatidylinositol 3-kinase [56]. This was demonstrated in mouse models, where overexpression of the *NF2* gene limited cell growth in Schwannoma cells [57]. Distortions in the actin cytoskeleton and abnormalities in cell spreading are seen in Schwannoma cells from NF2 tumours [58]. Welling et al. [59] identified 42 genes that were significantly up-regulated in 6 cases of VS using microarray DNA analysis. These included mediators of angiogenesis and cell migration. At present having knowledge of genotype in VS does not allow reliable prediction of tumour behaviour. However, it is hoped that by identifying the pathways that are abnormal through cDNA microarray analysis it will allow better predictions of clinical behaviour and allow pharmacological targeting of the oncogenic drivers. Proof of concept has been achieved in early clinical trials. Plotkin et al. [60] treated 10 patients with VS that expressed Vascular Endothelial Growth Factor (VEGF) with the anti-VEGF pharmaceutical, Bevacizumab. In nine cases the VS shrank in size, with a median best response being a 26 % volumetric reduction. Follow up of 31 NF2 patients with progressive VS patients has confirmed a benefit of targeted therapy, with Bevacizumab treatment leading to hearing improvement and tumour shrinkage in over 50 % of cases [61•]. However, the same benefit has not been seen with meningiomas associated with NF2, with Bevacizumab treatment achieving only a temporary improvement in tumour size. An explanation for this finding is that VEGF pathways are not the foremost drivers for angiogenesis in meningiomas [62]. In addition to angiogenesis, other signalling pathways have been shown to be important in VS growth. Murine models where the *NF2* genes have been knocked out show lack of contact inhibition. However, when these cells are treated with anti-EGFR therapies contact inhibition is restored [63]. Hence it appears EGFR pathways are involved in VS progression and a recent consensus conference highlighted this family of receptors as attractive targets in cases of progressive VS associated with NF2 [64]. It is likely that more than one pathway is involved in VS tumourigenesis and therefore drugs that target multiple pathways are an attractive proposition. Combination therapy targeting the VEGF and EGFR pathways with VEGFR2/EGFR inhibitors has shown anti-tumour activity in murine models [65]. A recent breakthrough for targeted therapy in VS was when Bevacizumab was approved for the use in strict situations in the English nationally commissioned service [66]. There is need for future clinical trials to determine the optimum doses and

duration of targeted therapies for VSs and other NF2-related tumours, although to date targeted therapies have largely been well tolerated in clinical pilots. Although personalised therapy has not generally translated to clinical practice as yet, it is possible that these new avenues of treatment will provide alternatives to the existing treatment options of untreated observation of tumour growth, stereotactic radiation and surgical intervention. It is hoped that in the future the management of aggressive VS will be based on a molecular classification, whereby the prominent signalling pathways responsible for tumourigenesis are targeted pharmacologically [67]. This personalised approach has been employed with success in other neoplasms, such as leukaemias and solid tumours of the bowel and breast [68, 69].

Conclusion

VS results from genetic aberrations of the *NF2* gene on chromosome of 22q12, most of which are due to sporadic mutations although approximately 5 % occur as part of the tumour predisposition syndrome NF2. Genotype–phenotype correlations have been described, with truncating mutations (the most frequent germline event) being associated a more severe phenotype. Recent progress in cellular research has identified signalling pathways in which the *NF2* gene product is involved. It is hoped new tailored drug therapies will take advantage of the increasing knowledge of the genetics of VS and might revolutionise the management and outcome for the condition.

Compliance with Ethics Guidelines

Conflict of Interest Adam Hexter declares that he has no conflict of interest. D. Gareth Evans declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent Human studies were done by authors. This review article includes some studies with human subjects performed by the authors. This was with research ethics committee approval. With regard to the authors' research cited in this paper, all procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000 and 2008.

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