Revisiting neurofibromatosis type 2 diagnostic criteria to exclude *LZTR1*-related schwannomatosis

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ABSTRACT

Objective: To determine the specificity of the current clinical diagnostic criteria for neurofibromatosis type 2 (NF2) relative to the requirement for unilateral vestibular schwannoma (VS) and at least 2 other NF2-related tumors.

Methods: We interrogated our Manchester NF2 database, which contained 205 individuals meeting NF2 criteria who initially presented with a unilateral VS. Of these, 83 (40.7%) went on to develop a contralateral VS. We concentrated our genetic analysis on a group of 70 who initially fulfilled NF2 criteria with a unilateral vestibular schwannoma and at least 2 additional nonintra-dermal schwannomas.

Results: Overall, 5/70 (7%) individuals with unilateral VS and at least 2 other schwannomas had a pathogenic or likely pathogenic *LZTR1* mutation. Twenty of the 70 subsequently developed bilateral disease. Of the remaining 50, 5 (10%) had a germline *LZTR1* mutation, equivalent to the number (n = 5) with a germline NF2 mutation.

Conclusions: The most common etiology for unilateral VS and 2 additional NF2-associated tumors in this cohort was mosaic NF2. Germline *LZTR1* and germline NF2 mutations were equally common in our cohort. This indicates that *LZTR1* must be considered when making a diagnosis of NF2 in the presence of unilateral VS in individuals without a germline NF2 mutation. **Neurology® 2017;88:87-92**

GLOSSARY

LOH = loss of heterozygosity; **MLPA** = multiplex ligation-dependent probe amplification; **NF2** = neurofibromatosis type 2; **NGS** = next-generation sequencing; **UVS** = unilateral vestibular schwannoma; **VS** = vestibular schwannoma.

The autosomal dominant tumor suppressor syndromes schwannomatosis and neurofibromatosis type 2 (NF2) both predispose individuals to schwannoma development. Despite their phenotypic similarities, schwannomatosis is genetically distinct from NF2.^{1,2} Clinically, schwannomatosis is mainly discriminated from NF2 by the absence of vestibular schwannomas. In 2007, *SMARCB1*, which lies centromeric to the NF2 gene on chromosome 22q, was identified as a cause of familial schwannomatosis and a minority of sporadic schwannomatosis.³⁻⁶ After identification of *SMARCB1*, we reported that unilateral vestibular schwannoma (VS) occurred in a non-*SMARCB1*-related schwannomatosis family⁷ and a sporadic case where NF2 mutation was excluded as the cause of multiple schwannomas and VS.⁷ As a result of this, a workshop acknowledged that the widely quoted schwannomatosis diagnostic criteria⁸ should not have VS as a complete exclusion criterion for schwannomatosis.⁹ As of yet, no definite VS has occurred in the presence of constitutional *SMARCB1*-related schwannomatosis,¹⁰ although one probable case has been published.¹¹ However, with identification of schwannomatosis-associated mutations in the *LZTR1* gene in 2014,¹² it became clear that VS did occur in the context of *LZTR1*-related schwannomatosis.¹³ This molecular proof for the existence of VS in schwannomatosis raises the reverse question of whether NF2 criteria^{14,15} need to be adjusted to take into account the overlap between the 2 conditions.

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We have assessed the contribution of *LZTR1* mutations to individuals fulfilling Manchester criteria for NF2 with the presence of at least 2 nonintradermal schwannomas in addition to a unilateral VS in our patient cohort.

METHODS One major diagnostic criterion for the clinical diagnosis of NF2 is a unilateral VS and any 2 of the following: meningioma, cataract, glioma, neurofibroma, schwannoma, cerebral calcification. To test the specificity of this criterion, we identified subgroups of patients from our database who initially presented with a unilateral VS to determine their ultimate diagnosis. In particular, we wanted to assess NF2 specificity of patients with a unilateral VS plus ≥ 2 other nonintradermal schwannomas who would potentially meet schwannomatosis criteria were it not for the VS. We interrogated the UK national clinical database to identify patients meeting NF2 criteria who were initially diagnosed with a unilateral VS and no evidence of contralateral VS on first diagnostic MRI, but who also had 2 other nonintradermal schwannomas (presumed or pathologically proven). Individuals going on to develop bilateral VS were included. Patients meeting NF2 diagnostic criteria who were ascertained between 1990 and 2016 were added to the database. Information on laterality of VS at first diagnosis and follow-up extending to 43 years was available for analysis (some patients were diagnosed with unilateral VS before 1990 and developed bilateral VS after 1990). A total of 198 individuals meeting the study criteria underwent *NF2* mutation testing of lymphocyte DNA (and tumor when available) using Sanger sequencing or targeted next-generation sequencing (NGS) and multiplex ligation-dependent probe amplification (MLPA). Eighty of these went on to develop bilateral disease and 118 did not. Patients with no identified

pathogenic germline mutation in blood and without identical mutations found in at least 2 separate NF2 related tumors underwent additional Sanger sequencing or targeted NGS and MLPA analysis for *LZTR1* and *SMARCB1* (P455 and P258 MRC-Holland [Amsterdam, the Netherlands] probe sets, respectively). The *p* values for statistical significance between groups were calculated using the Fisher exact test.

Standard protocol approvals, registrations, and patient consents. Ethical approval for use of anonymized samples and data from a historical, retrospectively collected, archive in this study was obtained from the North West 7–Greater Manchester Central Research Ethics Committee (reference 10/H1008/74).

RESULTS Patients with bilateral vestibular schwannoma at follow-up. A total of 205 of 1,301 (15.8%) patients meeting NF2 criteria initially presented with a unilateral VS. Of these, 83 (40.7%) have gone on to develop a contralateral VS. Time to diagnosis of contralateral VS was a range of 0.5–30 years, mean 6.4 years, median 5 years. In the latter group, 80/83 had undergone mutation testing for NF2 (table 1). Germline mutations were identified in blood in 25/80 (31%) patients with a further 6/80 (7.5%) having low level mosaicism identified on lymphocyte DNA analysis. Fourteen of the remainder had 2 *NF2* mutational events identified on tumor DNA testing with one having an identical *NF2* mutation confirmed in a second tumor. A predisposing *NF2* mutation was therefore found in 32/80 (40%) and overall in 45/80 (56%).

Table 1 Proportion of patients with unilateral vestibular schwannoma (VS) at presentation who have an identifiable *NF2* mutation from blood and tumor testing

	No. (of 198 tested)	Constitutional (germline) <i>NF2</i> mutation	Mosaic <i>NF2</i> confirmed in blood	Identical <i>NF2</i> mutation in 2 tumors	Point mutation and <i>NF2</i> LOH in single tumor	Two point mutations in tumor (neither in blood) and no LOH	No mutation in blood, no tumor analysis	Total with proven <i>NF2</i>
Presented with UVS and had not developed BVS at last follow-up ^a	118	18 (15)	6 (5)	2 (1.7)	18 (15.2) ^{b,c}	3 (2.5)	71 (60.7)	26 (22)
Presented with UVS and went on to develop BVS ^a	80	25 (31)	6 (7.5)	1 (1)	13 (16) ^{b,d}	2 (2.4)	33 (41)	32 (40)
Presented with UVS and ≥ 2 other nonintradermal schwannomas with no BVS at last follow-up	50 ^e	5 (10)	3 (6)	1 (2)	7 (14) ^c	2 (4)	32 ^e (64)	9/50 (18)
Presented with UVS and ≥ 2 other nonintradermal schwannomas and went on to develop BVS	20	12 (60)	2 (10)	2 (10)	0	1 (5)	3 (15)	16 (80)
Presented with UVS and ≥ 2 other nonintradermal schwannomas and did not develop BVS or meningiomas	34	3 (9)	5 (15)	1 (3)	7 (12)	0	18 (53)	9 (26.4)
Presented with UVS did not develop BVS and did not have 2 further schwannomas	68	13 (19)	3 (4.4)	1	14 (20.6)	0	37 (54.4)	17 (25)

Abbreviations: BVS = bilateral vestibular schwannoma; LOH = loss of heterozygosity; NF2 = neurofibromatosis type 2; UVS = unilateral vestibular schwannoma.

Values are n (%).

^aPatients presented with UVS with or without any other signs of NF2: 25 who developed BVS did not have other NF2 features in the interim.

^bFive patients with UVS and 2 patients with BVS had only a single *NF2* event (5 with LOH) identified or no *NF2* hit (n = 2). A total of 35/42 (83%) with tumor analysis had both *NF2* hits identified.

^cTwo patients with UVS had different *NF2* point mutations in 2 separate schwannomas with LOH of the same allele.

^dOne patient with BVS and no other NF2 features had 2 different *NF2* mutations with opposite alleles lost by LOH in his 2 VS, proving he did not have NF2.

^eOne patient had an affected daughter but did not have her mutation detectable in blood and had no tumor available.

Table 2 Age at onset of vestibular schwannoma (VS) and other schwannomas in *LZTR1* mutation heterozygotes

Case	VS age, y	Spinal tumor, age, y (n)	Peripheral nerve tumors, age, y (n)	Other cranial nerve tumor	<i>LZTR1</i> mutation in blood	<i>NF2</i> mutations in tumor
1	33	30 (6)	15 (9)	No	c.1785+2delT	c.165delG p.(Leu56SerfsTer67) and LOH
2	37	30 (1)	24 (3)	No	c.570delT p.(Phe190LeufsTer10)	—
3	34	— (0)	48 (3)	No	c.27delG p.(Gln10ArgfsTer15)	—
4	39	43 (3)	65 (1)	V, IX/X/XI	c.1210 G>A p.(Gly404Arg)	c.448-2A>G and LOH
5	50	56 (1)	48 (1)	No	c.27delG p.(Gln10ArgfsTer15)	c.10delG p.(Ala4ProfsTer6) and LOH

Abbreviation: LOH = loss of heterozygosity.

Mutation nomenclature follows Human Genome Variation Society guidelines using reference sequences *LZTR1* NM_006767.3 and *NF2* NM_000268.3.

Patients without bilateral vestibular schwannoma at follow-up. There were 122 without bilateral disease at last follow-up with a range of 0.4–42 years, mean 8.3 years, median 5.8 years. A total of 118 of 122 had undergone *NF2* mutational analysis. Germline mutations were identified in blood in 18 (15%) patients with a further 6 (5%) having low-level mosaicism identified in lymphocyte DNA. Twenty-one of the remainder had 2 *NF2* mutational events identified in tumor DNA and 3 of these had an identical *NF2* mutation confirmed in a second tumor. A predisposing *NF2* mutation was therefore found in 27/118 (23%). Two people with 2 tumors analyzed had different *NF2* mutations, excluding mosaicism, leaving potential, but unconfirmed, mosaic mutations in 16/118 (14%) and an overall *NF2* mutation detection rate of 43/118 (36.5%).

Bilateral VS alone is a diagnostic criterion for *NF2*. In our cohort, a single patient with bilateral VS and no other *NF2* features in later life had different mutational events in his 2 tumors, proving he had developed these by chance rather than *NF2*, as we have previously reported.¹⁶

Patients with a unilateral vestibular schwannoma and an ependymoma. In a subgroup of patients who presented with unilateral VS and had an ependymoma, 12/20 (60%) developed bilateral VS. Ten of these 12 (82%) had a germline *NF2* mutation and 1 was mosaic for a mutation detectable in blood. Of the 8 who did not develop bilateral VS, 3 had a germline *NF2* mutation. As such, 14/20 (70%) of those with ependymoma had identifiable *NF2* mutations in blood. Individuals with ependymoma were more likely to develop bilateral disease (12/20 vs 68/178; Fisher exact $p = 0.03$) and have an *NF2* mutation identified (14/20 vs 43/178; Fisher exact $p = 0.00006$).

Patients with a unilateral vestibular schwannoma and at least 2 other nonintradermal schwannomas. To test the diagnostic specificity of a unilateral VS plus 2 additional tumors as *NF2* further, we next identified a group of 70 individuals from the original 205 (34%) who initially presented with a unilateral VS

and at least 2 other non-intradermal schwannomas. These individuals would have met diagnostic criteria for schwannomatosis, if they did not have a unilateral VS. In this group, 20/70 (28.5%) have gone on to develop bilateral VS (somewhat fewer than for individuals meeting Manchester criteria due to the presence of other non VS criteria 41/112 [39.2%], and a further 22 who developed bilateral VS without previously meeting Manchester criteria). Of the individuals meeting study criteria who developed bilateral VS, 12/20 (60%) had a germline *NF2* mutation identified in blood. Five additional people had tumor analysis. Two of these had mosaicism for an *NF2* mutation confirmed on targeted NGS analysis of blood, present at 2%–3% mutant allele frequency. Two further patients had an identical mutation found in 2 tumors with no evidence in blood. The fifth individual had 2 mutational events identified in a single tumor with no evidence of either from NGS on blood. As such, 16/20 (80%) had proven *NF2* and 4 had presumed *NF2*.

Of the 50 people without bilateral disease at last follow-up, only 5/50 (10%) had a nonmosaic *NF2* mutation in blood; 3/50 (6%) patients had mosaicism confirmed on blood analysis (2 from targeted NGS of tumor DNA). Seven further patients had a point mutation in *NF2* identified in tumor, in conjunction with loss of heterozygosity (LOH) for the presumed wild-type allele, but no second tumor available for analysis and no evidence on NGS analysis of the point mutation in blood. Two patients had different *NF2* mutations identified in 2 tumors, but each tumor had LOH of the same allele extending at least 6 megabases centromeric of *NF2*. Two patients had 2 separate point mutations in a single tumor and one with no mutation in blood had an affected daughter with a proven point mutation not detectable on NGS. Overall, only 9/50 (18%) had proven *NF2*, with a further 3 having presumed mosaic *NF2*. This left 41 patients (59%) of the original 70 meeting study criteria who went on to have *LZTR1* and *SMARCB1* analysis.

No *SMARCB1* mutation was identified in blood in these 41 patients. Five pathogenic or likely pathogenic *LZTR1* mutations were found, including 3 from our original report.¹³ Two new *LZTR1* mutations were found in isolated cases of unilateral VS in patients who had also developed additional schwannomas (table 2). Case 4 presented with a right-sided VS at age 34 and had 2 thoracic spinal schwannomas removed at age 43. Spinal MRI at age 70 identified a further presumed schwannoma. Cranial MRI showed the presence of a 5th nerve schwannoma and a further schwannoma affecting the 9th/10th/11th cranial nerve has been visible on the right for 15 years. There were no left-sided tumors. Identification of 2 mutational hits in *NF2* in the patient's vestibular schwannoma led to the offer of presymptomatic testing for his 3 children. Two of the children opted for testing and both mutational events, c.448-2A>G and a whole gene deletion, were excluded in blood. DNA from a formalin-fixed spinal tumor from the proband showed loss of the same allele as in the vestibular schwannoma, but no point mutation was seen. Subsequent screening of *LZTR1* identified the presumed pathogenic germline missense mutation, c.1210G>A, p.(Gly404Arg). The patient's son, who had previously been told he did not have NF2, recently presented with a painful L4 schwannoma and screening of his blood showed that he had inherited the presumed pathogenic *LZTR1* mutation from his father.

Case 5 presented at age 47 with a painful peripheral nerve schwannoma. He then went on to develop left-sided hearing loss at age 48 and had a unilateral VS found on MRI at age 50. Spinal MRI showed a single thoracic presumed schwannoma at age 58 years. Analysis of the left VS specimen identified a single base frameshift deletion in *NF2*, c.10delG, p.(Ala4ProfsTer6), and LOH. Neither a large deletion nor the single base deletion mutation was detectable in blood. *LZTR1* analysis identified a pathogenic frameshift mutation c.27delG, p.(Gln10ArgfsTer15) in blood.

All the unilateral VS (UVS) tumors from the 5 *LZTR1* mutation carriers were identified as such at

surgery and none had developed a contralateral VS 10, 12, 16, 21, and 41 years after unilateral VS diagnosis.

Overall, 5/70 (7%) individuals with UVS and at least 2 other schwannomas had an *LZTR1* mutation. This increased to 5/50 (10%) of those who did not go on to develop bilateral VS and 5/34 (14.7%) of those without meningioma disease. In the latter category, only 3/34 (9%) patients had a nonmosaic *NF2* mutation identified. Mosaic mutations were identified by blood DNA analysis of 5/34 (14.7%) and a sixth had an identical mutation in 2 tumors. The likelihood of NF2 or *LZTR1*-related schwannomatosis is shown in table 3.

The results of the remaining 68 patients with NF2 (including 8 with ependymoma) who had undergone mutation analysis who still had UVS but did not meet study criteria are also shown in table 1.

DISCUSSION The Manchester NF2 criteria¹⁵ have been shown to be more sensitive at identifying NF2 at an earlier stage in the disease process as a significant proportion of patients do not present with bilateral VS.¹⁴ However, the identification of *LZTR1* as a cause of schwannomatosis reduces the specificity of these more inclusive criteria and even the presence of bilateral VS is now no longer sufficient to be certain that an individual has NF2.¹⁶ In the past, it had been assumed that the presence of VS plus at least 2 other NF2 clinical criteria, including 2 other schwannomas, was highly specific for an NF2 diagnosis. However, we have identified 5 patients with an NF2 diagnosis based on unilateral VS plus at least 2 other non-VS nonintradural schwannomas who actually have *LZTR1*-associated schwannomatosis. This now questions whether an NF2 diagnosis can be made in this context without first excluding a germline *LZTR1* mutation. We have also shown that the presence of bilateral VS is not sufficient to be certain that an individual has NF2, especially in the elderly, as bilateral VS can occur as 2 random events.¹⁶ We estimated that the presence of bilateral VS >70 has close to a 50% likelihood of being a chance occurrence.¹⁶ The presence of other typical

Table 3 Likelihood of NF2, mosaic NF2, and schwannomatosis in individuals with UVS and 2+ nonintradural schwannomas

	No. of patients	Definite germline NF2, %	Mosaic NF2, %	Probable (unproven) mosaic NF2, %	Schwannomatosis, %
Presenting with UVS and ≥2 other nonintradural schwannomas with no BVS at last follow-up	50	10	8	72	10
Presenting with UVS and ≥2 other nonintradural schwannomas and did not develop BVS or meningiomas	34	9	18	59	15
Presented with UVS and ≥2 other nonintradural schwannomas and went on to develop BVS	20	60	20	30	0

Abbreviations: BVS = bilateral vestibular schwannoma; NF2 = neurofibromatosis type 2; UVS = unilateral vestibular schwannoma.

Table 4 Current and revised Manchester criteria for neurofibromatosis type 2 (NF2)

1. Bilateral vestibular schwannomas <70^a or
2. FDR family history of NF2 and unilateral VS <70^a or
3. FDR family history of NF2 or unilateral VS and 2 of^b meningioma, cataract, glioma, neurofibroma, schwannoma, cerebral calcification (if UVS + ≥2 nonintradermal schwannomas need negative *LZTR1* test^a) or
4. Multiple meningiomas (2 or more) and 2 of unilateral VS, cataract, glioma, neurofibroma, schwannoma, cerebral calcification or
5. Constitutional or mosaic pathogenic *NF2* gene mutation in blood or identical mutations in 2 distinct tumors^a

Abbreviations: FDR = first-degree relative; UVS = unilateral vestibular schwannoma; VS = vestibular schwannoma.

Ideally *LZTR1* testing should be carried out on tumor tissue, but as mosaicism does not appear as common in *LZTR1*-affected individuals, blood will still give a useful result and probably exclude a germline schwannomatosis condition.

^a 2016 suggested revisions.

^b Any 2 includes 2 of any tumor type such as schwannoma.

NF2 features, such as intradermal schwannoma plaques, cataracts, and in particular ependymomas, would make an underlying *NF2* mutation highly probable and *LZTR1* very unlikely. As of yet, we are unaware of any *LZTR1* mutation carrier having any of these features and none of our current 64 identified *LZTR1* mutation carriers has been diagnosed with either ependymoma or cranial meningioma. We would suggest that NF2 diagnosis should not be made until germline testing for *LZTR1* has been carried out in individuals with unilateral VS and other schwannomas unless other NF2 features are present.

The median follow-up time for patients with a unilateral VS was 5.8 years (range 0.4–43 years) and as such it is possible that some of these individuals may go on to develop a contralateral VS or other features. The likelihood of bilateral VS in *LZTR1* is certainly possible although currently only 5/64 (8%) of our *LZTR1* carriers has developed a VS, all of which are unilateral. There is a question as to whether one of the patients in the original *LZTR1* discovery report had developed bilateral VS.¹² Nonetheless, a substantial proportion of those presenting with unilateral VS and other NF2 features go on to develop bilateral disease.^{17,18} This is clearly more likely if a germline *NF2* mutation is found in blood or ependymoma is present. A single case of a unilateral VS in a *SMARCB1*-associated schwannomatosis family has been reported.¹¹ However, the report is inconclusive regarding the link between unilateral VS and *SMARCB1* mutations, as the mutation was not confirmed in the germline of the individual with a VS, and the report lacks evidence to support the diagnosis of schwannomatosis in multiple presumptively affected relatives.

Our current study questions the practice of testing offspring for the mutational events found in a tumor from a patient with a unilateral VS and schwannomas

only, which has become routine practice.^{19,20} In one of our cases, this led to the erroneous exclusion of risk from a male offspring who went on to develop a painful schwannoma.

We have demonstrated that 7% of patients presenting with a unilateral VS and other schwannomas actually have *LZTR1*-associated schwannomatosis, not NF2, and this rises to 15% of those in whom no other NF2 features are present. These findings show further overlap between schwannomatosis and NF2 and raise the question as to whether these conditions should be grouped under a collective title of schwannoma-related disorders.

Continued revision of these criteria will be necessary as we learn more about schwannomatosis and associated disorders. In particular, our findings should change the diagnostic criteria for NF2 to include *LZTR1* mutation testing in individuals with unilateral VS and other schwannomas (table 4) and lead to caution in using *NF2* mutation results from a single tumor to predict schwannoma risk in offspring unless other NF2 features are present. There are clearly very different implications to an individual and their family of having NF2 or *LZTR1*-associated schwannomatosis. We would also suggest the addition of 2 further changes to the criteria (table 4) to include *NF2* mutational testing and insertion of an age limitation of 70 for the development of bilateral VS if no other NF2 features are present.¹⁶

AUTHOR CONTRIBUTIONS

M.J. Smith: study concept and design, acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content. N.L. Bowers: acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content. M. Bulman: analysis and interpretation, critical revision of the manuscript for important intellectual content. C. Gokhale: analysis and interpretation, critical revision of the manuscript for important intellectual content. A.J. Wallace: acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content. A.T. King: analysis and interpretation, critical revision of the manuscript for important intellectual content. S.K.L. Lloyd: analysis and interpretation, critical revision of the manuscript for important intellectual content. S.A. Rutherford: analysis and interpretation, critical revision of the manuscript for important intellectual content. C.L. Hammerbeck-Ward: analysis and interpretation, critical revision of the manuscript for important intellectual content. S.R. Freeman: analysis and interpretation, critical revision of the manuscript for important intellectual content. D.G. Evans: study concept and design, acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content.

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