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SMARCB1 mutations in schwannomatosis and genotype correlations with rhabdoid tumors

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Mutations in the *SMARCB1* gene are involved in several human tumor-predisposing syndromes. They were established as an underlying cause of the tumor suppressor syndrome schwannomatosis in 2008. There is a much higher rate of mutation detection in familial disease than in sporadic disease. We have performed extensive genetic testing on a cohort of familial and sporadic patients who fulfilled clinical diagnostic criteria for schwannomatosis. In our updated cohort, we identified novel mutations within the *SMARCB1* gene as well as several recurrent mutations. Of the schwannomatosis screens reported to date, including those in our updated cohort, *SMARCB1* mutations have been found in 45% of familial probands and 9% of sporadic patients. The exon 1 mutation, c.41C>A p.Pro14His (10% in our series), and the 3′ untranslated region mutation, c.*82C>T (27%), are the most common changes reported in patients with schwannomatosis to date, indicating the presence of mutation hot spots at both 5′ and 3′ portions of the gene. Comparison with germline *SMARCB1* mutations in patients with rhabdoid tumors showed that the schwannomatosis mutations were significantly more likely to occur at either end of the gene and be nontruncating mutations ($P < 0.0001$). *SMARCB1* mutations are found in a significant proportion of schwannomatosis patients, and an even higher proportion of rhabdoid patients. Whereas *SMARCB1* alone seems to account for rhabdoid disease, there is likely to be substantial heterogeneity in schwannomatosis even for familial disease. There is a clear genotype–phenotype correlation, with germline rhabdoid mutations being significantly more likely to be centrally placed, involve multiple exon deletions, and be truncating mutations.

Keywords *SMARCB1*, *NF2*, rhabdoid, schwannomatosis, mutation

Schwannomatosis is a member of the neurofibromatosis family of inherited tumor predisposition syndromes characterized by the development of multiple nerve sheath tumors. In schwannomatosis, these tumors are benign, nonvestibular, nonintradermal schwannomas, which normally develop in the second or third decade of life (1). The clinical phenotype overlaps with that of neurofibromatosis type 2 (NF2), in which multiple schwannomas also frequently occur on spinal and peripheral nerves. However, the hallmark of NF2 disease is the development of bilateral vestibular schwannomas and intradermal schwannomas (2,3), which are exclusion criteria for a diagnosis of schwannomatosis.

Meningiomas occur in only approximately 5% of patients with schwannomatosis, whereas they occur in over 50% of patients with NF2 disease (4), although meningiomas may be the only, or first, tumor type found in an individual with either syndrome (5,6). Rare cases of other tumors, such as malignant peripheral nerve sheath tumors (MPNSTs) and ependymomas, have also been reported (7,8).

Schwannomatosis normally occurs sporadically, with only approximately 15% of patients inheriting the disease, whereas approximately half of NF2 patients have a family history. Germline *NF2* mutations are identified in the vast majority of NF2 patients (approximately 93%) through clinical diagnostic genetic testing, and acquired second-hit mutations are normally identified in tumors (9,10).

The *SMARCB1* gene, which encodes a subunit of the human SWI/hSNF chromatin remodeling complex, was identified as the cause of schwannomatosis disease in 2007 (11). Germline *SMARCB1* mutations can be found in

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approximately 50% of inherited cases of schwannomatosis but only around 10% of sporadic patients (7,8,12,13).

SMARCB1 mutations are also causative of the highly aggressive pediatric cancer atypical teratoid/rhabdoid tumors (AT/RT) (14,15), which has a much more severe phenotype, in which malignant rhabdoid tumors develop in very young children and normally lead to death within the first few years of life.

It has been reported that in rare cases schwannomatosis can occur in mutation carriers from AT/RT families who have survived to adulthood without developing rhabdoid tumors (16–18), although these tumors seem to be "neuroblastoma-like" schwannomas rather than the classic schwannomas seen in schwannomatosis. It is interesting that mutations in the same gene can lead to these two conditions with such different prognoses, and it is possible that this is due to differences in their mutation spectra and mutation location within the gene. Therefore, we now provide an update on the *SMARCB1* mutations found in schwannomatosis and AT/RT patients screened through the Genomic Diagnostics Laboratory at St. Mary's Hospital in Manchester since 2011 and correlate the mutation spectrum found in the worldwide literature with reports of germline mutations in AT/RT.

Materials and methods

Schwannomatosis and AT/RT patients screened in this study were referred to the Genomic Diagnostics Laboratory at St. Mary's Hospital in Manchester since December 2011 for clinical diagnostic mutation analysis. A total of 30 patients fulfilling clinical diagnostic criteria for schwannomatosis as well as 30 AT/RT patients underwent diagnostic mutation analysis since our previous report (19). All schwannomatosis patients were found to be negative for germline *NF2* mutations in peripheral lymphocyte DNA by direct sequencing of exons 1–15 of the *NF2* gene and by multiplex ligation-dependent probe amplification (MLPA) (MRC-Holland, Amsterdam, The Netherlands) for copy number analysis as previously described (8). The cohort included 25 sporadic patients and five familial schwannomatosis probands. Germline DNA from individuals with either schwannomatosis or AT/RT was analyzed by direct sequencing of all nine *SMARCB1* exons, including the 50–100 bases flanking each exon to ensure coverage of splice donor and acceptor sites. MLPA (MRC-Holland P258-B1 probe set) analysis of *SMARCB1* was used to identify exon deletions and duplications. Tumor DNA was available for testing from seven of the sporadic schwannomatosis patients. DNA from two tumors was available for two of these patients. Similarly, seven tumors were available from AT/RT patients. The study was approved by the North West 7 Research Ethics Committee–GM Central.

Results

Since our previous report in 2012, a total of 30 probands fulfilling the clinical criteria for schwannomatosis have been screened by the Genomic Diagnostics Laboratory for mutations in the *SMARCB1* gene. Of these patients, 25 were cases of sporadic disease and five were from families with familial schwannomatosis.

Tumor DNA was available for seven sporadic disease patients, and two tumors were available for two of these. Neither of these showed evidence of mosaic NF2 disease, although in one patient no *NF2* mutation was found in either tumor and there was no loss of heterozygosity (LOH).

Of the five patients with familial disease whose samples were tested, four were found to have a germline *SMARCB1* mutation (Table 1). The four pathogenic mutations included two patients with the same mutation within the 3′ untranslated region (3′UTR), c.*82C>T, which has been observed previously by Boyd et al. (7). This mutation was originally reported to have unknown pathogenicity: however, it has now been tracked with disease in four separate affected families, it was retained in tumors in combination with loss of the wild-type allele, and it was not found in a cohort of 50 unaffected individuals or in the SNP database, dbSNP (7,20). It has also subsequently been reported that this mutation affects gene expression levels and mRNA stability (21). A frameshift mutation c.38delA in exon 1 was also identified in a patient with familial disease. The patient with the c.38delA mutation developed an MPNST at the age of 52 years. In another of the familial cohort of patients with no pathogenic mutation, we again identified a variant of unknown clinical significance in intron 5, c.628+13C>T, which is likely to be a nonpathogenic rare polymorphism (22).

Of the 25 sporadic disease patients screened, six (24%) were found to have a germline *SMARCB1* mutation. The mutations included an exon 1 in-frame deletion, c.86_91del (p. Gly29_Ser30del), which was reported twice in our original series (8). A single frameshift change, c.1000_1001insG, was found in one patient in exon 8, which introduces a premature stop codon. A missense mutation in exon 1, c.40C>T (p.Pro14Ser), was found in a 38-year-old with two deep-seated schwannomas. We have circumstantial evidence from several sources to suggest that it is pathogenic. First, although we have not observed this mutation previously and to our knowledge it has not been described in the literature, a mutation affecting the same nucleotide, c.40C>T (p.Pro14-His), which segregated with disease, has been seen in two schwannomatosis-affected families (8). The affected amino acid is highly conserved evolutionarily in *SMARCB1,* down to *Caenorhabditis elegans*. In silico analysis with three programs (Align GVGD, SIFT, and PolyPhen) also predicted that c.40C>T (p.Prol4Ser) has a deleterious effect on normal protein function. Two further sporadic disease patients harbored the 3′UTR mutation c.*82C>T, which as evidenced above is thought to be pathogenic. A further 3′UTR variant, c.*70C>T, was found in one sporadic disease patient. In silico analysis of this variant predicted it would create a novel high ranking splice donor site, extremely similar in ranking and position in the *SMARCB1* 3′UTR to the c.*82C>T mutation.

Tumor genotype in new schwannomatosis families

Apart from the two tumors showing no *NF2* involvement in one patient, five tumors showed the typical two hits in the *NF2* gene, with a single point mutation and LOH with a whole gene deletion detected by MLPA in four cases and an exon 2

Table 1 Germline *SMARCB1* alterations identified in the current study

Exon	Mutation	Protein change	Effect	Inheritance
Pathogenic mutations				
1	c.38delA	p.Lys13Serfs*3	Frameshift	Familial
1	c.40C>T	p.Pro14Ser	Missense	Sporadic
1	c.86_91del	p.Gly29_Ser30del	In-frame deletion	Sporadic
8	c.1000_1001insG	p.Pro334Argfs*27	Frameshift	Sporadic
3′UTR	c.*70C>T	N/A	Unknown	Sporadic
3′UTR	c.*82C>T	N/A	Unknown	Familial
3′UTR	c.*82C>T	N/A	Unknown	Familial
3′UTR	c.*82C>T	N/A	Unknown	Sporadic
3′UTR	c.*82C>T	N/A	Unknown	Sporadic
Probable polymorphisms				
5	c.628+13C>T			

deletion and LOH with a whole gene deletion detected by MLPA in a fifth. A sixth tumor simply demonstrated LOH.

Germline mutations in AT/RT

A total of 30 AT/RT patients were screened in this study, and 8 of 30 (27%) of these had germline mutations (Table 2). Seven tumors were available from the 22 individuals without a germline mutation. Both mutational hits were identified in six tumors (four tumors had a point mutation associated with loss of the wild-type allele, and two tumors had homozygous whole gene deletions) and a single point mutation was identified in the seventh. None of the mutations identified in these tumors were present in germline DNA.

Correlations of germline mutations with AT/RT

A total of 48 germline mutations have been identified in schwannomatosis (Table 3), including those documented in the original report (8), and 77 germline AT/RT mutations have been identified, including those in the current report and previous reports of *SMARCB1* screening in two large series (16,23).

Among the reported germline mutations, there were highly significant differences in both position (Table 4) and mutation type (Table 5). Mutations in schwannomatosis clustered around either end of the gene more significantly than in AT/RT ($P < 0.0001$) (Table 4). Mutations in schwannomatosis were more likely to be in the 3′UTR (0 in AT/RT; $P < 0.0001$), missense (0 in AT/RT; $P < 0.0001$), splice site ($P = 0.005$), or in-frame deletion ($P = 0.02$). AT/RT mutations were more likely to be whole gene or multiple exon deletions or duplications, which accounted for 34 of 77 mutations (44%) compared with none in schwannomatosis ($P < 0.0001$) (Tables 4 and 5). They were also more likely to be nonsense mutations ($P = 0.005$) (Table 5). The only mutation type that was not clearly different between phenotypes was frameshift mutation ($P = 0.33$).

Discussion

Since the initial identification of *SMARCB1* mutations as a cause of schwannomatosis, a number of patient cohorts have been screened. The proportion of schwannomatosis patients with identified germline mutations found through these screens is shown in Table 3. From our current and previous reports combined, 13 of 30 patients (43%) with familial schwannomatosis and 15 of 142 patients (10.5%) with sporadic disease had an identifiable *SMARCB1* mutation. We have reclassified one of the sporadic cases from our original report in Table 3 as familial, as the patient's father was found to have been affected with schwannomatosis and have the c.86_91del (p. Gly29_Ser30del) (8). The combined rates of *SMARCB1* mutation in all patient series (without case report studies) are 26 of 54 (48%) for familial and 21 of 215 (9.5%) for sporadic schwannomatosis. Our combined report contributes more than 60% of all reported schwannomatosis series. The exon 1 mutation c.41C>A (p. Pro14-His) (10% of our series) and the 3′UTR mutation c.*82C>T are the most common changes reported in patients with schwannomatosis to date. These constitute 3 of 28 (11%)

Table 2 Germline mutations in AT/RT cases

Lab no.	Mutation	Protein change	Mutation type	Exon
10001222	c.601C>T	p.Arg201*	Nonsense	5
10004960	c.118C>T	p.Arg40*	Nonsense	2
11000880	c.727C>T	p.Gln243*	Nonsense	6
11008560	Exon 1_9del	No protein	Whole gene deletion	
11010297	c.986+2T>A	p.?	Splice site	7
11013808	c.321C>G	p.Tyr107*	Nonsense	3
12000003	Exon 1_9del	No protein	Whole gene deletion	
13007337	Exon 1del	No protein	Large deletion	1

Table 3 Proportion of *SMARCB1* mutation carriers in familial and sporadic schwannomatosis[a]

Familial, no. of carriers/no. of patients (%)	Sporadic, no. of carriers/no. of patients (%)	
3/4	6/25	Current
4/11	8/89	Smith et al. Neurogenet 2012 (19)
0/2	1/19	Sestini et al. Hum Mut 2008 (12)
5/15	2/28[b]	Hadfield et al. J Med Genet 2008 (8)
13/19	–	Boyd et al. Clin Genet 2008 (7)
0/2	5/54	Rousseau et al. BMC Neurol 2011 (13)
25/54[b] (46%)[b]	22/215[b] (10%)[b]	Total

[a] Excludes case reports.
[b] These figures are corrected to 26/54 (48%) for familial and 21/215 (9.5%) for sporadic, when one case was reclassified as familial.

and 8 of 28 (28%) of the mutations identified in our own combined series (8,19).

The mutations found in schwannomatosis patients are predominantly nontruncating mutations, including missense mutations and a common in-frame deletion in exon 1. The most common mutation identified so far is found within the 3′UTR at c.*82C>T. The effect of this alteration is currently unknown, although it does segregate with disease and has not been reported in unaffected individuals. It is possible that this mutation may act by regulating gene expression through alternative splicing within the UTR, although further work is necessary to determine this. The additional exon 1 and exon 8 mutations in the present report, without any additional mutations within the central portion of the gene, further validate the hot spots at either end of the gene in schwannomatosis (Figure 1). This finding is in contrast to the mutations found in AT/RT tumors, which occur mainly in the central exons or which delete all, or large parts, of the coding sequence. The associations reported here are some of the clearest genotype–phenotype correlations reported, with *P* values for many parameters at less than 0.0001. The associations between missense mutations and schwannomatosis and not AT/RT are equally strong; although truncating mutations do occur predominantly in AT/RT, they still occur in schwannomatosis, predominantly in exon 1. This report thus strengthens the hypothesis that AT/RT mutations are associated with a loss of the SMARCB1 protein product, whereas schwannomatosis-associated mutations are much more likely to be hypomorphic, producing the SMARCB1 protein at reduced expression levels or a partial loss of function, as suggested in a recent report on expression of schwannomatosis-associated mutant *SMARCB1* transcripts (21). Nonetheless, an explanation for the truncating mutations that occur frequently in exon 1 in schwannomatosis patients is required to explain why these mutations do not appear to cause AT/RT.

There is a much higher rate of germline mutation detection in familial schwannomatosis patients than in sporadic disease patients (Table 3). It is possible that the proportion of sporadic patients with *SMARCB1* mutations may be higher than currently thought but that some *SMARCB1* mutations are not detected by current screening methods. One possible explanation for this is mosaicism for schwannomatosis, in which the mutation exists at a level that is too low to be detected in blood but is present at a higher level in the affected tissues. It is also possible that some patients

Table 4 Mutation positional differences between schwannomatosis and AT/RT

Exon	Schwannomatosis, no. of carriers/no. of patients	AT/RT no. of carriers/no. of patients	*P* value
Exon 1	16/48	3/77	<0.0001
Exons 2–7	14/48	43/77	0.005
Exon 8	4/48	0/77	0.02
Exon 9 and 3′UTR	14/48	0/77	<0.0001
Whole gene deletion/single or multiexon deletion or duplication	0/48	34/77	<0.0001

Table 5 Differences in germline mutation type between schwannomatosis and AT/RT

Mutation type	Schwannomatosis no. of carriers/no. of patients	AT/RT no. of carriers/no. of patients	*P* value
Nonsense	5/48	25/77	0.005
Frameshift	5/48	15/77	0.2
Splice site	10/48	3/77	0.005
Missense	10/48	0/77	<0.0001
3′UTR	14/48	0/77	<0.0001
In-frame deletion	4/48	0/77	0.02
Whole gene deletion/single or multiexon deletion or duplication	0/48	34/77	<0.0001

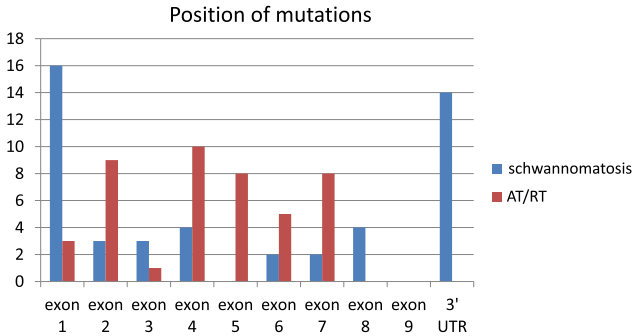

Figure 1 Chart showing the *SMARCB1* gene and distribution of schwannomatosis mutations per exon compared with those of AT/RT.

fulfilling the clinical criteria for schwannomatosis may in fact have mosaic NF2, which cannot be easily distinguished from schwannomatosis and which cannot be detected through genetic testing without at least two tumors available for analysis (9,24,25). Mosaic NF2 represents a particular problem in diagnosing schwannomatosis accurately in sporadic disease cases (26). Another possibility is that additional causative, or modifier, genes are yet to be discovered, which may determine the disease type or severity. The *LZTR1* gene, located centromerically to both *NF2* and *SMARCB1* on chromosome 22, has recently been identified as a second causative gene in schwannomatosis (27). Germline mutations were identified in 80% of a select cohort of schwannomatosis patients who had tested negative for germline *NF2* and *SMARCB1* mutations, but whose tumors all demonstrated loss of heterozygosity on chromosome 22. The overall mutation identification rates and genotype–phenotype correlations have yet to be determined. However, there still remain a significant proportion of schwannomatosis patients with no known underlying cause, including patients with loss of heterozygosity on chromosome 22 with a breakpoint occurring after both the *LZTR1* and *SMARCB1* genes (28).

In addition, previous reports have identified three families with schwannomatosis or AT/RT found in different family members (16,17). Malignant rhabdoid tumors tend to develop at a very early age and are normally lethal, whereas schwannomatosis tends to occur later in life and does not normally shorten life expectancy (1). It may be that different types of mutation can predispose patients to these conditions with differing severity, or that the timing of onset of the disease may be the important factor in determining which disease is expressed. It is likely, therefore, that hypomorphic schwannomatosis mutations may be allowing individuals to escape the highest risk period for AT/RT. The current report is reassuring in that if individuals with schwannomatosis have nontruncating mutations or 3′UTR mutations, their risk of AT/RT will likely not be dramatically increased.

Whereas it is reassuring that AT/RT is relatively uncommon in *SMARCB1* mutation-positive schwannomatosis kindreds, a clear association with MPNST has now emerged (18). In addition to the two cases we previously reported in a single family (19), a further case reported in the present series adds to concern about the risk of this tumor in *SMARCB1*-related schwannomatosis. All four cases reported thus far have point mutations, but there does not appear to be a clear genotype associated with MPNST. The frameshift insertion c.245_246insAT in exon 3 (18) is not a typical schwannomatosis mutation, although the missense mutation we previously reported in exon 7 is more typical (4). In contrast, MPNST is extremely rare in NF2 disease and almost never occurs in the absence of radiation treatment (29).

A combination of specific types of mutations in these and other genes may be responsible for the ultimate expression of specific disease phenotypes. Further work is necessary to identify additional causative genes and to determine their mechanism of action.

A further series of *SMARCB1* mutations reported in the current article, along with eight germline mutations in AT/RT, combined with those mutations reported in the existing literature, show one of the clearest genotype–phenotype correlations in human disease.

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